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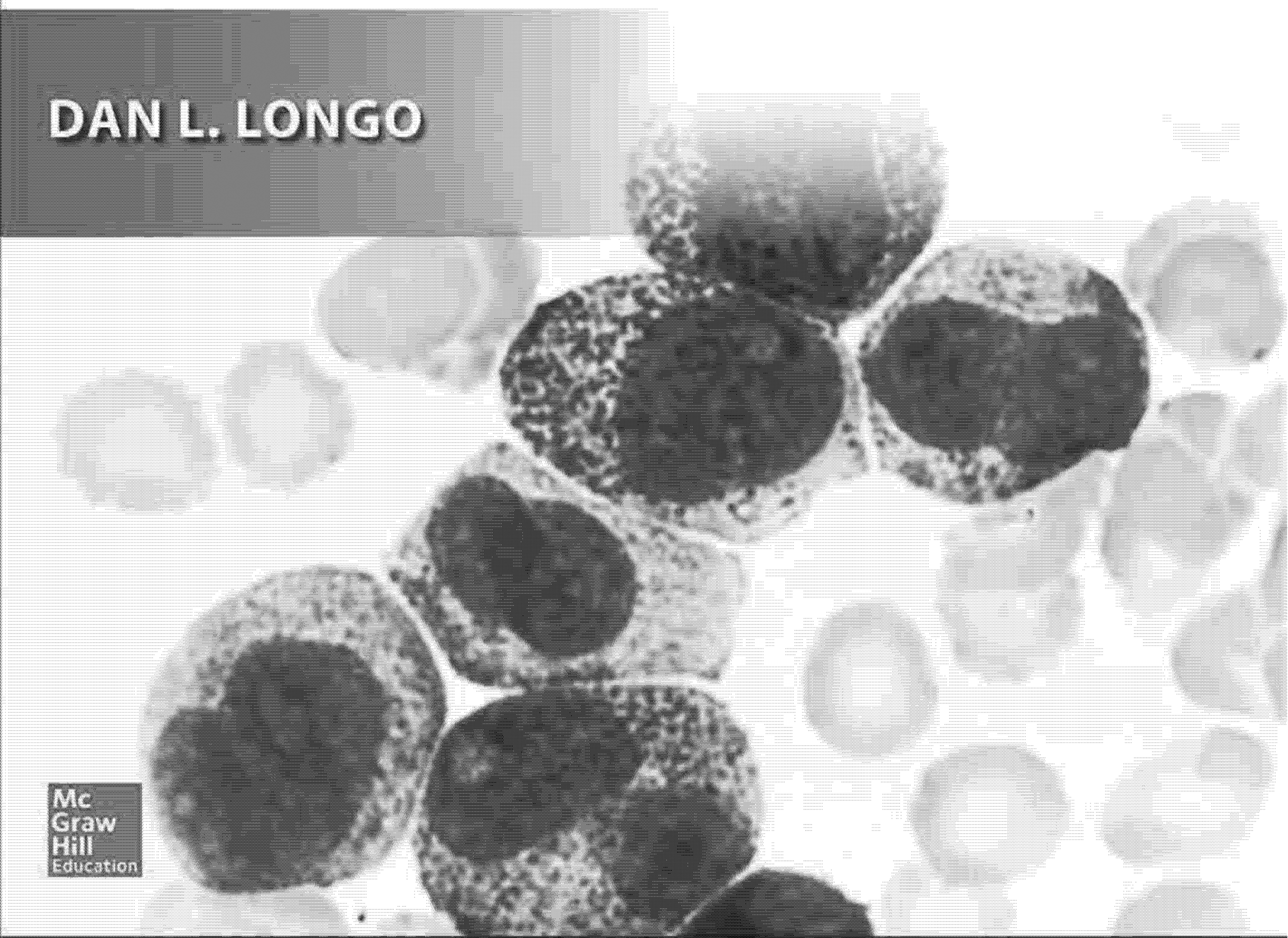
HEMATOLOGY AND ONCOLOGY

DAN L. LONGO



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3rd Edition

HARRISON'S™

HEMATOLOGY AND ONCOLOGY

Derived from Harrison's Principles of Internal Medicine, 19th Edition

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PREFACE

Harrison's Principles *of* Internal Medicine has a long and distinguished tradition in the field of hematology. Maxwell Wintrobe, whose work actually established hematology as a distinct subspecialty of medicine, was a founding editor of the book and participated in the first seven editions, taking over for Tinsley Harrison as editor-in-chief on the sixth and seventh editions. Wintrobe, born in 1901, began his study of blood in earnest in 1927 as an assistant in medicine at Tulane University in New Orleans. He continued his studies at Johns Hopkins from 1930 to 1943 and moved to the University of Utah in 1943, where he remained until his death in 1986. He invented a variety of the measures that are routinely used to characterize red blood cell abnormalities, including the hematocrit, the red cell indices, and erythrocyte sedimentation rate, and defined the normal and abnormal values for these parameters, among many other important contributions in a 50-year career.

Oncology began as a subspecialty much later. It came to life as a specific subdivision within hematology. A subset of hematologists with a special interest in hematologic malignancies began working with chemotherapeutic agents to treat leukemia and lymphoma in the mid-1950s and early 1960s. As new agents were developed and the principles of clinical trial research were developed, the body of knowledge of oncology began to become larger and mainly independent from hematology. Informed by the laboratory study of cancer biology and an expansion in focus beyond hematologic neoplasms to tumors of all organ systems, oncology developed as a separable discipline from hematology. T is separation was also fueled by the expansion of the body of knowledge about clotting and its disorders, which became a larger part of hematology.

In most academic medical centers, hematology and oncology remain connected. However, conceptual distinctions between hematology and oncology have been made. Differences are reinforced by separate fellowship training programs (although many joint training programs remain), separate board certification examinations, separate professional organizations, and separate textbooks describing separate bodies of knowledge. In some academic medical centers, oncology is not merely a separate subspecialty division in a Department of Medicine but is an entirely distinct department in the medical school with the same standing as the Department of Medicine. Economic forces are also at work to separate hematology and oncology.

Perhaps I am only ref ecting the biases of an old dog, but I am unenthusiastic about the increasing fractionation of medicine subspecialties. T ere are now invasive and noninvasive cardiologists, gastroenterologists who do and others who do not use endoscopes, and organ- or individual disease-focused subspecialists (diabetologists, thyroidologists) instead of organ system–focused subspecialists (endocrinologists). T is fractionation has also begun within hematology and oncology. Some oncologists specialize in a single type of cancer and divisions of hematology have designated experts in clotting. At a time when the body of knowledge that must be mastered is increasing dramatically, the duration of training has not been increased to accommodate the additional learning that is necessary to become highly skilled. Extraordinary attention has been focused on the hours that trainees work. Apparently, the administrators are more concerned about undocumented adverse effects of every third night call on trainees than they are about the well-documented adverse effects on patients of frequent handoffs of patient responsibility to multiple caregivers.

Despite the sub-sub-subspecialization that is pervasive in modern medicine, students, trainees, general internists, family medicine physicians, physicians' assistants, nurse practitioners, and specialists in nonmedicine specialties still require access to information in hematology and oncology that can assist them in meeting the needs of their patients. Given the paucity of single sources of integrated information on hematology and oncology, the editors of Harrison's Principles *of* Internal Medicine decided to pull together the chapters in the "mother book" related to hematology and oncology and bind them together in a subspecialty themed book called Harrison's Hematology and Oncology. T e first edition of this book appeared in 2010 and was based on the 17th edition of Harrison's Principles *of* Internal Medicine. A second edition based on 18th edition of Harrison's Principles *of* Internal Medicine appeared in 2013. T is third edition is derived from the 19th edition of Harrison's Principles *of* Internal Medicine. T e book contains 57 chapters organized into 12 sections: (I) T e Cellular Basis of Hematopoiesis, (II) Cardinal Manifestations of Hematologic Diseases, (III) Anemias, (IV) Myeloproliferative Disorders, (V) Hematologic Malignancies, (VI) Disorders of Hemostasis, (VII) Biology of Cancer, (VIII) Principles of Cancer Prevention and Treatment, (IX) Neoplastic Disorders, (X) Endocrine Neoplasia, (XI) Remote Effects of Cancer, and (XII) Oncologic Emergencies and Late Effects and Complications of Cancer and Its Treatment.

T e chapters have been written by physicians who have made seminal contributions to the body of knowledge in their areas of expertise. T e information is authoritative and as current as we can make it, given the time requirements of producing books. Each contains the relevant information on the genetics, cell biology, pathophysiology, and treatment of specific disease entities. In addition, separate chapters on hematopoiesis, cancer cell biology, and cancer prevention ref ect the rapidly growing body of knowledge in these areas that are the underpinning of our current concepts of diseases in hematology and oncology. In addition to the factual information presented in the chapters, a section of test questions and answers is provided to reinforce important principles. A narrative explanation of what is wrong with the wrong answers should be of further value in the preparation of the reader for board examinations.

T e bringing together of hematology and oncology in a single text is unusual and we hope it is useful. Like many areas of medicine, the body of knowledge relevant to the practice of hematology and oncology is expanding rapidly. New discoveries with clinical impact are being made at an astounding rate; nearly constant effort is required to try to keep pace. It is our hope that this book is helpful to you in the struggle to master the daunting volume of new findings relevant to the care of your patients.

We are extremely grateful to Kim Davis and James Shanahan at McGraw-Hill for their invaluable assistance in the preparation of this book.

Dan L. Longo, MD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. T e authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. T is recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Houston B (eds). Harrison's Self-Assessment and Board Review, 19th ed. New York, McGraw-Hill, 2017, ISBN 978-1-259-64288-3.

T e global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

T e genetic icons identify a clinical issue with an explicit genetic relationship.

SECTION I

THE CELLULAR BASIS OF HEMATOPOIESIS

CHAPTER 1

HEMATOPOIETIC STEM CELLS

David T. Scadden ■ Dan L. Longo

All of the cell types in the peripheral blood and some cells in every tissue of the body are derived from hematopoietic (hemo: blood; poiesis: creation) stem cells. If the hematopoietic stem cell is damaged and can no longer function (e.g., due to a nuclear accident), a person would survive 2–4 weeks in the absence of extraordinary support measures. With the clinical use of hematopoietic stem cells, tens of thousands of lives are saved each year **(Chap. 31)**. Stem cells produce hundreds of billions of blood cells daily from a stem cell pool that is estimated to be only in the tens of thousands. How stem cells do this, how they persist for many decades despite the production demands, and how they may be better used in clinical care are important issues in medicine.

T e study of blood cell production has become a paradigm for how other tissues may be organized and regulated. Basic research in hematopoiesis includes defining stepwise molecular changes accompanying functional changes in maturing cells, aggregating cells into functional subgroups, and demonstrating hematopoietic stem cell regulation by a specialized microenvironment; these concepts are worked out in hematology, but they offer models for other tissues. Moreover, these concepts may not be restricted to normal tissue function but extend to malignancy. Stem cells are rare cells among a heterogeneous population of cell types, and their behavior is assessed mainly in experimental animal models involving reconstitution of hematopoiesis. T us, much of what we know about stem cells is imprecise and based on inferences from genetically manipulated animals.

CARDINAL FUNCTIONS OF HEMATOPOIETIC STEM CELLS

All stem cell types have two cardinal functions: self-renewal and differentiation **(Fig. 1-1)**. Stem cells exist to generate, maintain, and repair tissues. T ey function successfully if they can replace a wide variety of shorter-lived mature cells over prolonged periods. T e process of self-renewal (see below) assures that a stem cell population can be sustained over time. Without self-renewal, the stem cell pool would become exhausted and tissue maintenance would not be possible. T e process of differentiation leads to production of the effectors of tissue function: mature cells. Without proper differentiation, the integrity of tissue function would be compromised and organ failure or neoplasia would ensue.

In the blood, mature cells have variable average life spans, ranging from 7 h for mature neutrophils to a few months for red blood cells to many years for memory lymphocytes. However, the stem cell pool is the central, durable source of all blood and immune cells, maintaining a capacity to produce a broad range of cells from a single cell source, yet keeping itself vigorous over decades of life. As an individual stem cell divides, it has the capacity to accomplish one of three division outcomes: two stem cells, two cells destined for differentiation, or one stem cell and one differentiating cell. T e former two outcomes are the result of symmetric cell division, whereas the latter indicates a different outcome for the two daughter cells—an event termed asymmetric cell division. T e relative balance for these types of outcomes may change during development and under particular kinds of demands on the stem cell pool.

DEVELOPMENTAL BIOLOGY OF HEMATOPOIETIC STEM CELLS

During development, blood cells are produced at different sites. Initially, the yolk sac provides oxygen-carrying red blood cells, and then the placenta and several sites of intraembryonic blood cell production become involved. T ese intraembryonic sites engage in sequential order, moving from the genital ridge at a site where the aorta, gonadal tissue, and mesonephros

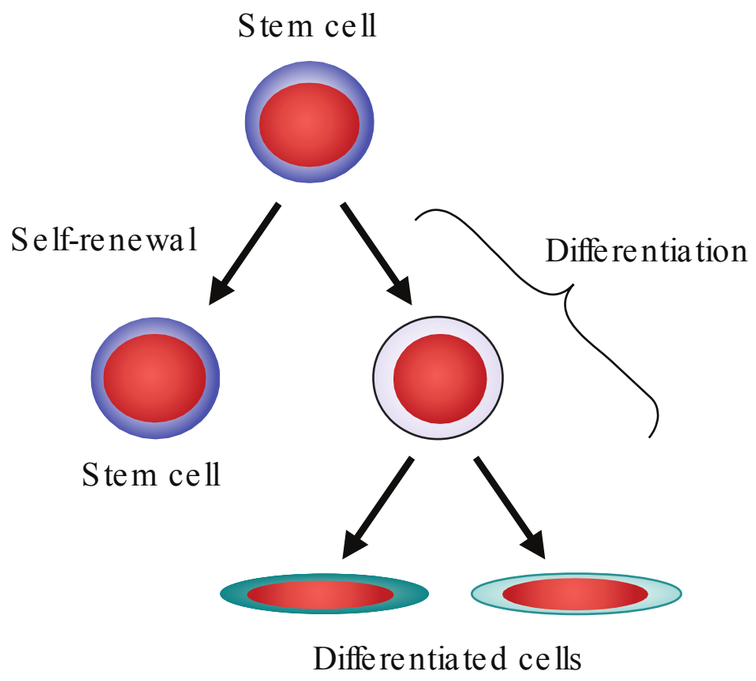

FIGURE 1-1
Signature characteristics of the stem cell. Stem cells have two essential features: the capacity to differentiate into a variety of mature cell types and the capacity for self-renewal. Intrinsic factors associated with self-renewal include expression of Bmi-1, Gf-1, PTEN, STAT5, Tel/Atv6, p21, p18, MCL-1, Mel-18, RAE28, and HoxB4. Extrinsic signals for self-renewal include Notch, Wnt, SHH, and Tie2/Ang-1. Based mainly on murine studies, hematopoietic stem cells express the following cell surface molecules: CD34, Thy-1 (CD90), c-Kit receptor (CD117), CD133, CD164, and c-Mpl (CD110, also known as the thrombopoietin receptor).

are emerging to the fetal liver and then, in the second trimester, to the bone marrow and spleen. As the location of stem cells changes, the cells they produce also change. The yolk sac provides red cells expressing embryonic hemoglobins while intraembryonic sites of hematopoiesis generate red cells, platelets, and the cells of innate immunity. The production of the cells of adaptive immunity occurs when the bone marrow is colonized and the thymus forms. Stem cell proliferation remains high, even in the bone marrow, until shortly after birth, when it appears to dramatically decline. The cells in the bone marrow are thought to arrive by the bloodborne transit of cells from the fetal liver after calcification of the long bones has begun. The presence of stem cells in the circulation is not unique to a time window in development; however, hematopoietic stem cells appear to circulate throughout life. The time that cells spend freely circulating appears to be brief (measured in minutes in the mouse), but the cells that do circulate are functional and can be used for transplantation. The number of stem cells that circulate can be increased in a number of ways to facilitate harvest and transfer to the same or a different host.

MOBILITY OF HEMATOPOIETIC STEM CELLS

Cells entering and exiting the bone marrow do so through a series of molecular interactions. Circulating stem cells (through CD162 and CD44) engage the lectins (carbohydrate binding proteins) P- and E-selectin on the endothelial surface to slow the movement of the cells to a rolling phenotype. Stem cell integrins are then activated and accomplish firm adhesion between the stem cell and vessel wall, with a particularly important role for stem cell VCAM-1 engaging endothelial VLA-4. The chemokine CXCL12 (SDF1) interacting with stem cell CXCR4 receptors and ionic calcium interacting with the calcium sensing receptor appear to be important in the process of stem cells getting from the circulation to where they engraft in the bone marrow. This is particularly true in the developmental move from fetal liver to bone marrow.

However, the role for CXCR4 in adults appears to be more related to retention of stem cells in the bone marrow rather than the process of getting them there. Interrupting that retention process through either specific molecular blockers of the CXCR4/CXCL12 interaction, cleavage of CXCL12, or downregulation of the CXCR4 receptor can all result in the release of stem cells into the circulation. This process is an increasingly important aspect of recovering stem cells for therapeutic use as it has permitted the harvesting process to be done by leukapheresis rather than bone marrow punctures in the operating room. Granulocyte colony-stimulating factor and plerixafor, a macrocyclic compound that can block CXCR4, are both used clinically to mobilize marrow hematopoietic stem cells for transplant. Refining our knowledge of how stem cells get into and out of the bone marrow may improve our ability to obtain stem cells and make them more efficient at finding their way to the specific sites for blood cell production, the so-called stem cell niche.

HEMATOPOIETIC STEM CELL MICROENVIRONMENT

The concept of a specialized microenvironment, or stem cell niche, was first proposed to explain why cells derived from the bone marrow of one animal could be used in transplantation and again be found in the bone marrow of the recipient. This niche is more than just a housing site for stem cells, however. It is an anatomic location where regulatory signals are provided that allow the stem cells to thrive, to expand if needed, and to provide varying amounts of descendant daughter cells. In addition, unregulated growth of stem cells may be problematic based on their undifferentiated state and self-renewal capacity. Thus, the niche must also regulate the number of stem cells produced. In this manner, the niche has the dual function of serving as a site of nurture but imposing limits for stem cells: in effect, acting as both a nutritive and constraining home.

The niche for blood stem cells changes with each of the sites of blood production during development, but for most of human life it is located in the bone marrow. Within the bone marrow, the perivascular space

particularly in regions of trabecular bone serves as a niche. T e mesenchymal and endothelial cells of the marrow microvessels produce kit ligand and CXCL12, both known to be important for hematopoietic stem cells. Other cell types, such as sympathetic neurons, nonmyelinating Schwann cells, macrophages, osteoclasts, and osteoblasts, have been shown to regulate stem cells, but it is unclear whether their effects are direct or indirect. Extracellular matrix proteins like osteopontin also affect stem cell function. T e endosteal region is particularly important for transplanted cells, suggesting that there may be distinctive features of that region that are yet to be defined that are important mediators of stem cell engraftment. T e functioning of the niche as a supportive context for stem cells is of obvious importance for maintaining hematopoiesis and in transplantation. An active area of study involves determining whether the niche is altered in disease and whether drugs can modify niche function to improve transplantation or normal stem cell function in hematologic disease.

EXCESS CAPACITY OF HEMATOPOIETIC STEM CELLS

In the absence of disease, one never runs out of hematopoietic stem cells. Indeed, serial transplantation studies in mice suggest that sufficient stem cells are present to reconstitute several animals in succession, with each animal having normal blood cell production. T e fact that allogeneic stem cell transplant recipients also never run out of blood cells in their life span, which can extend for decades, argues that even the limiting numbers of stem cells provided to them are sufficient. How stem cells respond to different conditions to increase or decrease their mature cell production remains poorly understood. Clearly, negative feedback mechanisms affect the level of production of most of the cells, leading to the normal tightly regulated blood cell counts. However, many of the regulatory mechanisms that govern production of more mature progenitor cells do not apply or apply differently to stem cells. Similarly, most of the molecules shown to be able to change the size of the stem cell pool have little effect on more mature blood cells. For example, the growth factor erythropoietin, which stimulates red blood cell production from more mature precursor cells, has no effect on stem cells. Similarly, granulocyte colony-stimulating factor drives the rapid proliferation of granulocyte precursors but has little or no effect on the cell cycling of stem cells. Rather, it changes the location of stem cells by indirect means, altering molecules such as CXCL12 that tether stem cells to their niche. Molecules shown to be important for altering the proliferation, self-renewal, or survival of stem cells, such as cyclin-dependent kinase inhibitors, transcription factors like Bmi-1, or microRNA-processing enzymes like Dicer, have little or different effects on progenitor cells. Hematopoietic stem cells have governing mechanisms that are distinct from the cells they generate.

HEMATOPOIETIC STEM CELL DIFFERENTIATION

Hematopoietic stem cells sit at the base of a branching hierarchy of cells culminating in the many mature cell types that compose the blood and immune system **(Fig. 1-2)**. T e maturation steps leading to terminally differentiated and functional blood cells take place both as a consequence of intrinsic changes in gene expression and niche-directed and cytokine-directed changes in the cells. Our knowledge of the details remains incomplete. As stem cells mature to progenitors, precursors, and, finally, mature effector cells, they undergo a series of functional changes. T ese include the obvious acquisition of functions defining mature blood cells, such as phagocytic capacity or hemoglobin synthesis. T ey also include the progressive loss of plasticity (i.e., the ability to become other cell types). For example, the myeloid progenitor can make all cells in the myeloid series but none in the lymphoid series. As common myeloid progenitors mature, they become precursors for either monocytes and granulocytes or erythrocytes and megakaryocytes, but not both. Some amount of reversibility of this process may exist early in the differentiation cascade, but that is lost beyond a distinct stage in normal physiologic conditions. With genetic interventions, however, blood cells, like other somatic cells, can be reprogrammed to become a variety of cell types.

As cells differentiate, they may also lose proliferative capacity **(Fig. 1-3)**. Mature granulocytes are incapable of proliferation and only increase in number by increased production from precursors. T e exceptions to the rule are some resident macrophages, which appear capable of proliferation, and lymphoid cells. Lymphoid cells retain the capacity to proliferate but have linked their proliferation to the recognition of particular proteins or peptides by specific antigen receptors on their surface. Like many tissues with short-lived mature cells such as the skin and intestine, blood cell proliferation is largely accomplished by a more immature progenitor population. In general, cells within the highly proliferative progenitor cell compartment are also relatively short-lived, making their way through the differentiation process in a defined molecular program involving the sequential activation of particular sets of genes. For any particular cell type, the differentiation program is difficult to speed up. T e time it takes for hematopoietic progenitors to become mature cells is ~10–14 days in humans, evident clinically by the

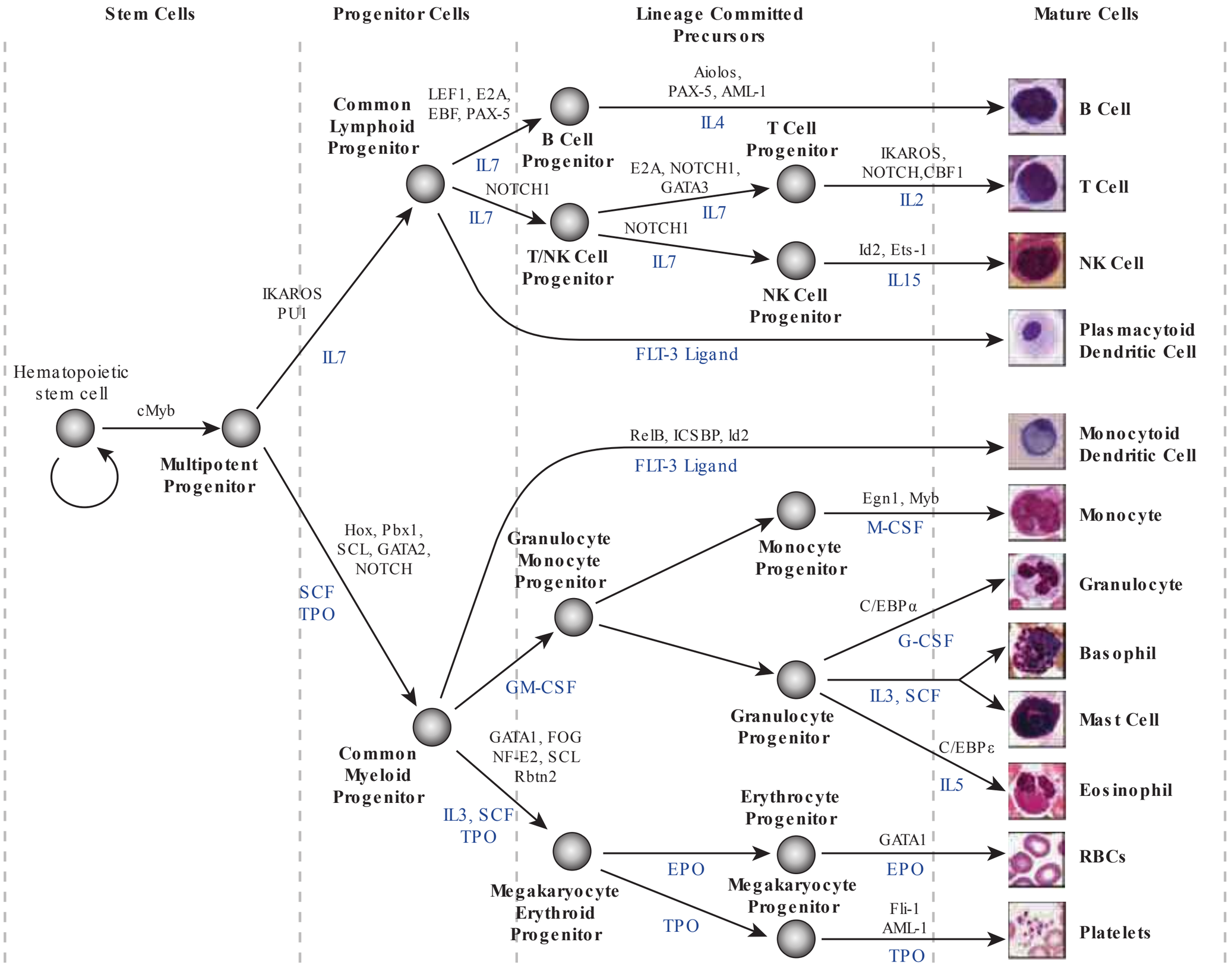

FIGURE 1-2

Hierarchy of hematopoietic differentiation. Stem cells are multipotent cells that are the source of all descendant cells and have the capacity to provide either long-term (measured in years) or short-term (measured in months) cell production. Progenitor cells have a more limited spectrum of cells they can produce and are generally a short-lived, highly proliferative population also known as transient amplifying cells. Precursor cells are cells committed to a single blood cell lineage but with a continued ability to proliferate; they do not have all the features of a fully mature cell. Mature cells are the terminally differentiated product of the differentiation process and are the effector cells of specific activities of the blood and immune system. Progress through the pathways is mediated by alterations in gene expression. The regulation of the differentiation by soluble factors and cell-cell communications within the bone marrow niche are still being defined. The transcription factors that characterize particular cell transitions are illustrated on the arrows; the soluble factors that contribute to the differentiation process are in blue. This picture is a simplification of the process. Active research is revealing multiple discrete cell types in the maturation of B cells and T cells and has identified cells that are biased toward one lineage or another (rather than uncommitted) in their differentiation. EPO, erythropoietin; RBC, red blood cell; SCF, stem cell factor; TPO, thrombopoietin.

interval between cytotoxic chemotherapy and blood count recovery in patients.

Although hematopoietic stem cells are generally thought to have the capacity to form all cells of the blood, it is becoming clear that individual stem cells may not be equal in their differentiation potential. That is, some stem cells are "biased" to become mature cells of a particular type. In addition, the general concept of cells having a binary choice of lymphoid or myeloid differentiation is not entirely accurate. A cell population with limited myeloid (monocyte and granulocyte) and lymphoid potential is now added to the commitment steps stem cells may undergo.

SELF-RENEWAL

The hematopoietic stem cell must balance its three potential fates: apoptosis, self-renewal, and differentiation.

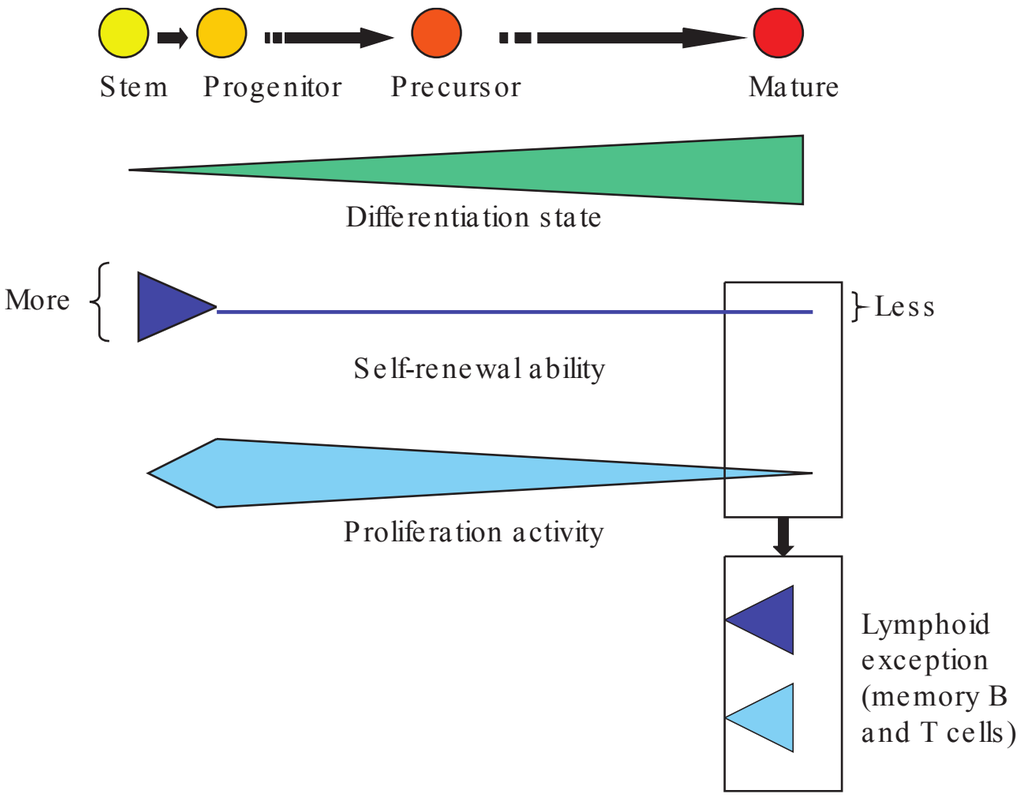

FIGURE 1-3
Relative function of cells in the hematopoietic hierarchy. The boxes represent distinct functional features of cells in the myeloid (upper box) versus lymphoid (lower box) lineages.

The proliferation of cells is generally not associated with the ability to undergo a self-renewing division except among memory T and B cells and among stem cells. Self-renewal capacity gives way to differentiation as the only option after cell division when cells leave the stem cell compartment, until they have the opportunity to become memory lymphocytes. In addition to this self-renewing capacity, stem cells have an additional feature characterizing their proliferation machinery. Stem cells in many mature adult tissues may be heterogeneous with some being deeply quiescent, serving as a deep reserve, whereas others are more proliferative and replenish the short-lived progenitor population. In the hematopoietic system, stem cells are generally cytokine-resistant, remaining dormant even when cytokines drive bone marrow progenitors to proliferation rates measured in hours. Stem cells, in contrast, are thought to divide at far longer intervals, measured in months to years, for the most quiescent cells. This quiescence is difficult to overcome in vitro, limiting the ability to effectively expand human hematopoietic stem cells. The process may be controlled by particularly high levels of cyclin-dependent kinase inhibitors like p57 or CDKN1c that restrict entry of stem cells into the cell cycle, blocking the G_1-S transition. Exogenous signals from the niche also appear to enforce quiescence, including the activation of the tyrosine kinase receptor Tie2 on stem cells by angiopoietin 1 on niche cells.

The regulation of stem cell proliferation also appears to change with age. In mice, the cyclin-dependent kinase inhibitor p16INK4a accumulates in stem cells in older animals and is associated with a change in five different stem cell functions, including cell cycling. Lowering expression of p16INK4a in older animals improves stem cell cycling and capacity to reconstitute hematopoiesis in adoptive hosts, making them similar to younger animals. Mature cell numbers are unaffected. Therefore, molecular events governing the specific functions of stem cells are being gradually made clear and offer the potential of new approaches to changing stem cell function for therapy. One critical stem cell function that remains poorly defined is the molecular regulation of self-renewal.

For medicine, self-renewal is perhaps the most important function of stem cells because it is critical in regulating the number of stem cells. Stem cell number is a key limiting parameter for both autologous and allogeneic stem cell transplantation. Were we to have the ability to use fewer stem cells or expand limited numbers of stem cells ex vivo, it might be possible to reduce the morbidity and expense of stem cell harvests and enable use of other stem cell sources. Specifically, umbilical cord blood is a rich source of stem cells. However, the volume of cord blood units is extremely small, and therefore, the total number of hematopoietic stem cells that can be obtained in any single cord blood unit is generally only sufficient to transplant an individual of <40 kg. This limitation restricts what would otherwise be an extremely promising source of stem cells. Two features of cord blood stem cells are particularly important. (1) They are derived from a diversity of individuals that far exceeds the adult donor pool and therefore can overcome the majority of immunologic cross-matching obstacles. (2) Cord blood stem cells have a large number of T cells associated with them, but (paradoxically) they appear to be associated with a lower incidence of graft-versus-host disease when compared with similarly mismatched stem cells from other sources. If stem cell expansion by self-renewal could be achieved, the number of cells available might be sufficient for use in larger adults. An alternative approach to this problem is to improve the efficiency of engraftment of donor stem cells. Graft engineering is exploring methods of adding cell components that may enhance engraftment. Furthermore, at least some data suggest that depletion of host NK (natural killer) cells may lower the number of stem cells necessary to reconstitute hematopoiesis.

Some limited understanding of self-renewal exists and, intriguingly, implicates gene products that are associated with the chromatin state, a high-order organization of chromosomal DNA that influences transcription. These include members of the polycomb family, a group of zinc finger–containing transcriptional regulators that interact with the chromatin structure, contributing to the accessibility of groups of genes for transcription. One member, Bmi-1, is important in enabling hematopoietic stem cell self-renewal through modification of cell cycle regulators such as the cyclin-dependent kinase inhibitors. In the absence of Bmi-1 or of the transcriptional regulator, Gfi-1, hematopoietic

stem cells decline in number and function. In contrast, dysregulation of Bmi-1 has been associated with leukemia; it may promote leukemic stem cell self-renewal when it is overexpressed. Other transcription regulators have also been associated with self-renewal, particularly homeobox, or "hox," genes. T ese transcription factors are named for their ability to govern large numbers of genes, including those determining body patterning in invertebrates. HoxB4 is capable of inducing extensive self-renewal of stem cells through its DNA-binding motif. Other members of the hox family of genes have been noted to affect normal stem cells, but they are also associated with leukemia. External signals that may inf uence the relative self-renewal versus differentiation outcomes of stem cell cycling include specific Wnt ligands. Intracellular signal transducing intermediates are also implicated in regulating self-renewal. T ey include PTEN, an inhibitor of the AKT pathway, and STAT5, both of which are downstream of activated growth factor receptors and necessary for normal stem cell functions including self-renewal, at least in mouse models. T e connections between these molecules remain to be defined, and their role in physiologic regulation of stem cell self-renewal is still poorly understood.

CANCER IS SIMILAR TO AN ORGAN WITH SELF-RENEWING CAPACITY

T e relationship of stem cells to cancer is an important evolving dimension of adult stem cell biology. Cancer may share principles of organization with normal tissues. Cancer cells are heterogeneous even within a given patient and may have a hierarchical organization of cells with a base of stem-like cells capable of the signature stem cell features: self-renewal and differentiation. T ese stem-like cells might be the basis for perpetuation of the tumor and represent a slowly dividing, rare population with distinct regulatory mechanisms, including a relationship with a specialized microenvironment. A subpopulation of self-renewing cells has been defined for some, but not all, cancers. A more sophisticated understanding of the stem cell organization of cancers may lead to improved strategies for developing new therapies for the many common and difficult-to-treat types of malignancies that have been relatively refractory to interventions aimed at dividing cells.

Does the concept of cancer stem cells provide insight into the cellular origin of cancer? T e fact that some cells within a cancer have stem cell–like properties does not necessarily mean that the cancer arose in the stem cell itself. Rather, more mature cells could have acquired the self-renewal characteristics of stem cells. Any single genetic event is unlikely to be sufficient to enable full transformation of a normal cell to a frankly malignant one. Rather, cancer is a multistep process, and for the multiple steps to accumulate, the cell of origin must be able to persist for prolonged periods. It must also be able to generate large numbers of daughter cells. T e normal stem cell has these properties and, by virtue of its having intrinsic self-renewal capability, may be more readily converted to a malignant phenotype. T is hypothesis has been tested experimentally in the hematopoietic system. Taking advantage of the cell-surface markers that distinguish hematopoietic cells of varying maturity, stem cells, progenitors, precursors, and mature cells can be isolated. Powerful transforming gene constructs were placed in these cells, and it was found that the cell with the greatest potential to produce a malignancy was dependent on the transforming gene. In some cases, it was the stem cell, but in others, the progenitor cell functioned to initiate and perpetuate the cancer. T is shows that cells can acquire stem cell–like properties in malignancy.

WHAT ELSE CAN HEMATOPOIETIC STEM CELLS DO?

Some experimental data have suggested that hematopoietic stem cells or other cells mobilized into the circulation by the same factors that mobilize hematopoietic stem cells are capable of playing a role in healing the vascular and tissue damage associated with stroke and myocardial infarction. T ese data are controversial, and the applicability of a stem cell approach to nonhematopoietic conditions remains experimental. However, reprogramming technology offers the potential for using the readily obtained hematopoietic stem cell as a source for cells with other capabilities.

T e stem cell, therefore, represents a true dual-edged sword. It has tremendous healing capacity and is essential for life. Uncontrolled, it can threaten the life it maintains. Understanding how stem cells function, the signals that modify their behavior, and the tissue niches that modulate stem cell responses to injury and disease are critical for more effectively developing stem cell–based medicine. T at aspect of medicine will include the use of the stem cells and the use of drugs to target stem cells to enhance repair of damaged tissues. It will also include the careful balance of interventions to control stem cells where they may be dysfunctional or malignant.

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SECTION II

CARDINAL MANIFESTATIONS OF HEMATOLOGIC DISEASE

CHAPTER 2

ANEMIA AND POLYCYTHEMIA

John W. Adamson ■ Dan L. Longo

HEMATOPOIESIS AND THE PHYSIOLOGIC BASIS OF RED CELL PRODUCTION

Hematopoiesis is the process by which the formed elements of blood are produced. T e process is regulated through a series of steps beginning with the hematopoietic stem cell. Stem cells are capable of producing red cells, all classes of granulocytes, monocytes, platelets, and the cells of the immune system. T e precise molecular mechanism—either intrinsic to the stem cell itself or through the action of extrinsic factors—by which the stem cell becomes committed to a given lineage is not fully defined. However, experiments in mice suggest that erythroid cells come from a common erythroid/megakaryocyte progenitor that does not develop in the absence of expression of the GATA-1 and FOG-1 (friend of GATA-1) transcription factors **(Chap. 1)**. Following lineage commitment, hematopoietic progenitor and precursor cells come increasingly under the regulatory influence of growth factors and hormones. For red cell production, erythropoietin (EPO) is the primary regulatory hormone. EPO is required for the maintenance of committed erythroid progenitor cells that, in the absence of the hormone, undergo programmed cell death (apoptosis). T e regulated process of red cell production is erythropoiesis, and its key elements are illustrated in **Fig. 2-1**.

In the bone marrow, the first morphologically recognizable erythroid precursor is the pronormoblast. T is cell can undergo four to five cell divisions, which result in the production of 16–32 mature red cells. With increased EPO production, or the administration of EPO as a drug, early progenitor cell numbers are amplified and, in turn, give rise to increased numbers of erythrocytes. T e regulation of EPO production itself is linked to tissue oxygenation.

In mammals, O_2 is transported to tissues bound to the hemoglobin contained within circulating red cells. T e mature red cell is 8 μm in diameter, anucleate, discoid in shape, and extremely pliable in order to traverse the microcirculation successfully; its membrane integrity is maintained by the intracellular generation of ATP. Normal red cell production results in the daily replacement of 0.8–1% of all circulating red cells in the body, since the average red cell lives 100–120 days. T e organ responsible for red cell production is called the erythron. T e erythron is a dynamic organ made up of a rapidly proliferating pool of marrow erythroid precursor cells and a large mass of mature circulating red blood cells. T e size of the red cell mass reflects the balance of red cell production and destruction. T e physiologic basis of red cell production and destruction provides an understanding of the mechanisms that can lead to anemia.

T e physiologic regulator of red cell production, the glycoprotein hormone EPO, is produced and released by peritubular capillary lining cells within the kidney. T ese cells are highly specialized epithelial-like cells. A small amount of EPO is produced by hepatocytes. T e fundamental stimulus for EPO production is the availability of O_2 for tissue metabolic needs. Key to EPO gene regulation is hypoxia-inducible factor (HIF)-1α. In the presence of O_2, HIF-1α is hydroxylated at a key proline, allowing HIF-1α to be ubiquitinated and degraded via the proteasome pathway. If O_2 becomes limiting, this critical hydroxylation step does not occur, allowing HIF-1α to partner with other proteins, translocate to the nucleus, and upregulate the expression of the EPO gene, among others.

Impaired O_2 delivery to the kidney can result from a decreased red cell mass (anemia), impaired O_2 loading of the hemoglobin molecule or a high O_2 affinity mutant hemoglobin (hypoxemia), or, rarely, impaired blood flow to the kidney (renal artery stenosis). EPO governs the day-to-day production of red cells, and ambient levels of the hormone can be measured in the plasma by sensitive immunoassays—the normal level

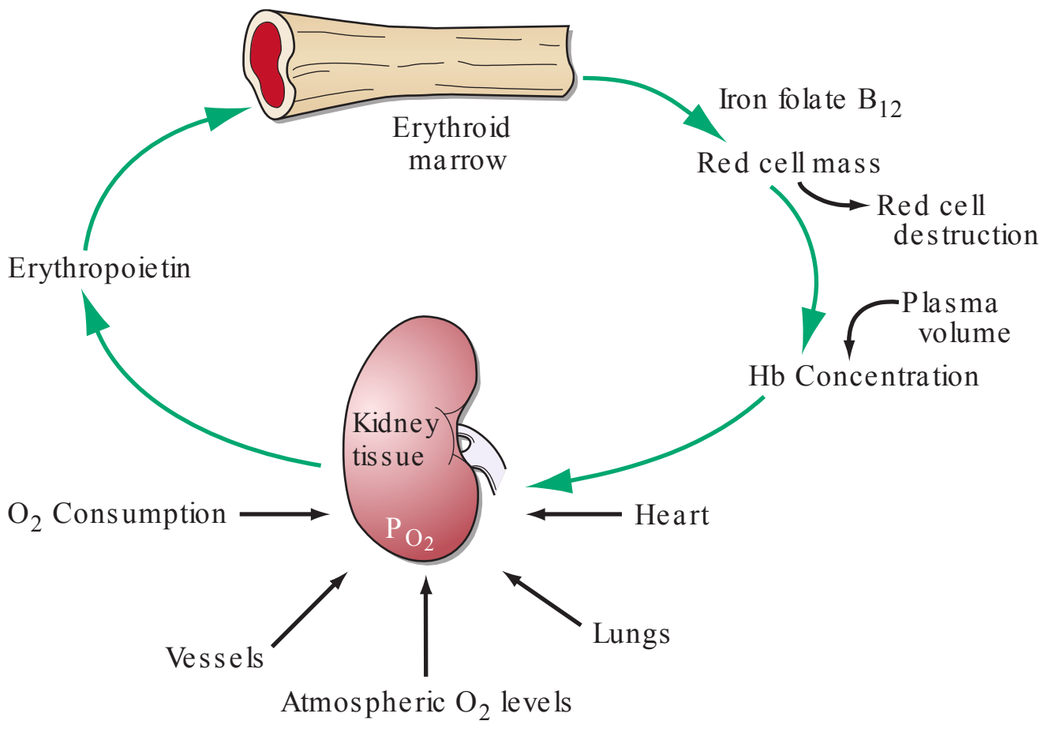


FIGURE 2-1
The physiologic regulation of red cell production by tissue oxygen tension. Hb, hemoglobin.

being 10–25 U/L. When the hemoglobin concentration falls below 100–120 g/L (10–12 g/dL), plasma EPO levels increase in proportion to the severity of the anemia **(Fig. 2-2)**. In circulation, EPO has a half-clearance time of 6–9 h. EPO acts by binding to specific receptors on the surface of marrow erythroid precursors, inducing them to proliferate and to mature. With EPO stimulation, red cell production can increase four- to fivefold within a 1- to 2-week period, but only in the presence of adequate nutrients, especially iron. The functional capacity of the erythron, therefore, requires normal renal production of EPO, a functioning erythroid marrow, and

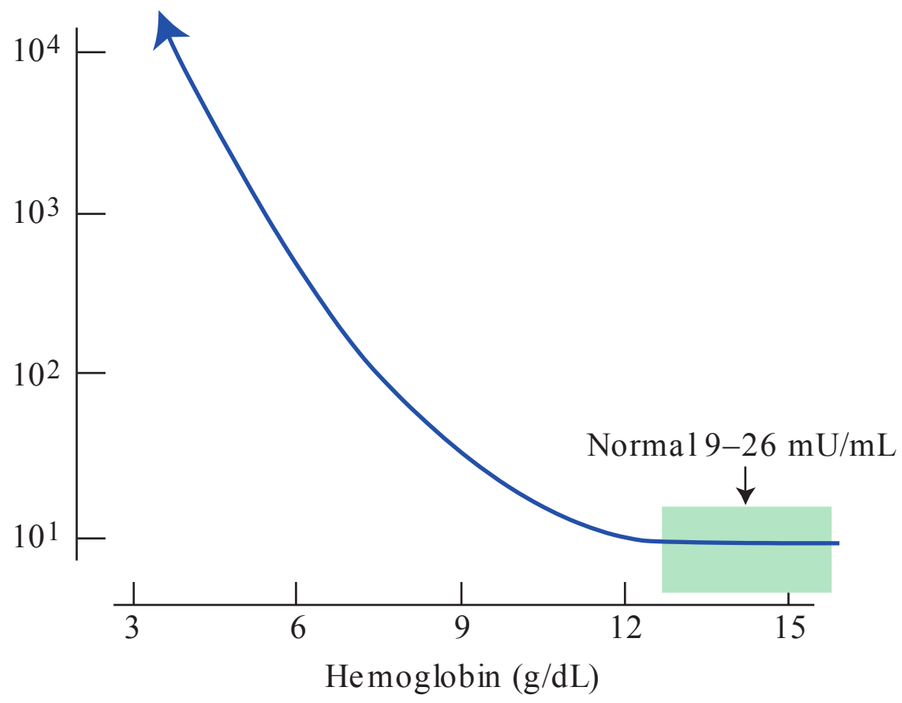


FIGURE 2-2
Erythropoietin (EPO) levels in response to anemia. When the hemoglobin level falls to 120 g/L (12 g/dL), plasma EPO levels increase logarithmically. In the presence of chronic kidney disease or chronic inflammation, EPO levels are typically lower than expected for the degree of anemia. As individuals age, the level of EPO needed to sustain normal hemoglobin levels appears to increase. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

an adequate supply of substrates for hemoglobin synthesis. A defect in any of these key components can lead to anemia. Generally, anemia is recognized in the laboratory when a patient's hemoglobin level or hematocrit is reduced below an expected value (the normal range). The likelihood and severity of anemia are defined based on the deviation of the patient's hemoglobin/hematocrit from values expected for age- and sex-matched normal subjects. The hemoglobin concentration in adults has a Gaussian distribution. The mean hematocrit value for adult males is 47% (standard deviation, ±7%) and that for adult females is 42% (±5%). Any single hematocrit or hemoglobin value carries with it a likelihood of associated anemia. Thus, a hematocrit of <39% in an adult male or <35% in an adult female has only about a 25% chance of being normal. Hematocrit levels are less useful than hemoglobin levels in assessing anemia because they are calculated rather than measured directly. Suspected low hemoglobin or hematocrit values are more easily interpreted if previous values for the same patient are known for comparison. The World Health Organization (WHO) defines anemia as a hemoglobin level <130 g/L (13 g/dL) in men and <120 g/L (12 g/dL) in women.

The critical elements of erythropoiesis—EPO production, iron availability, the proliferative capacity of the bone marrow, and effective maturation of red cell precursors—are used for the initial classification of anemia (see below).

ANEMIA

CLINICAL PRESENTATION OF ANEMIA

Signs and symptoms

Anemia is most often recognized by abnormal screening laboratory tests. Patients less commonly present with advanced anemia and its attendant signs and symptoms. Acute anemia is due to blood loss or hemolysis. If blood loss is mild, enhanced O_2 delivery is achieved through changes in the O_2–hemoglobin dissociation curve mediated by a decreased pH or increased CO_2 (Bohr effect). With acute blood loss, hypovolemia dominates the clinical picture, and the hematocrit and hemoglobin levels do not reflect the volume of blood lost. Signs of vascular instability appear with acute losses of 10–15% of the total blood volume. In such patients, the issue is not anemia but hypotension and decreased organ perfusion. When >30% of the blood volume is lost suddenly, patients are unable to compensate with the usual mechanisms of vascular contraction and changes in regional blood flow. The patient prefers to remain supine and will show postural hypotension and tachycardia. If the volume of blood lost is >40% (i.e., >2 L in the average-sized adult), signs of hypovolemic shock

including confusion, dyspnea, diaphoresis, hypotension, and tachycardia appear **(Chap. 10)**. Such patients have significant deficits in vital organ perfusion and require immediate volume replacement.

With acute hemolysis, the signs and symptoms depend on the mechanism that leads to red cell destruction. Intravascular hemolysis with release of free hemoglobin may be associated with acute back pain, free hemoglobin in the plasma and urine, and renal failure. Symptoms associated with more chronic or progressive anemia depend on the age of the patient and the adequacy of blood supply to critical organs. Symptoms associated with moderate anemia include fatigue, loss of stamina, breathlessness, and tachycardia (particularly with physical exertion). However, because of the intrinsic compensatory mechanisms that govern the O_2–hemoglobin dissociation curve, the gradual onset of anemia—particularly in young patients—may not be associated with signs or symptoms until the anemia is severe (hemoglobin <70–80 g/L [7–8 g/dL]). When anemia develops over a period of days or weeks, the total blood volume is normal to slightly increased, and changes in cardiac output and regional blood flow help compensate for the overall loss in O_2-carrying capacity. Changes in the position of the O_2–hemoglobin dissociation curve account for some of the compensatory response to anemia. With chronic anemia, intracellular levels of 2,3-bisphosphoglycerate rise, shifting the dissociation curve to the right and facilitating O_2 unloading. This compensatory mechanism can only maintain normal tissue O_2 delivery in the face of a 20–30 g/L (2–3 g/dL) deficit in hemoglobin concentration. Finally, further protection of O_2 delivery to vital organs is achieved by the shunting of blood away from organs that are relatively rich in blood supply, particularly the kidney, gut, and skin.

Certain disorders are commonly associated with anemia. Chronic inflammatory states (e.g., infection, rheumatoid arthritis, cancer) are associated with mild to moderate anemia, whereas lymphoproliferative disorders, such as chronic lymphocytic leukemia and certain other B cell neoplasms, may be associated with autoimmune hemolysis.

APPROACH TO THE PATIENT: Anemia

The evaluation of the patient with anemia requires a careful history and physical examination. Nutritional history related to drugs or alcohol intake and family history of anemia should always be assessed. Certain geographic backgrounds and ethnic origins are associated with an increased likelihood of an inherited disorder of the hemoglobin molecule or intermediary metabolism. Glucose-6-phosphate dehydrogenase (G6PD) deficiency and certain hemoglobinopathies are seen more commonly in those of Middle Eastern or African origin, including African Americans who have a high frequency of G6PD deficiency. Other information that may be useful includes exposure to certain toxic agents or drugs and symptoms related to other disorders commonly associated with anemia. These include symptoms and signs such as bleeding, fatigue, malaise, fever, weight loss, night sweats, and other systemic symptoms. Clues to the mechanisms of anemia may be provided on physical examination by findings of infection, blood in the stool, lymphadenopathy, splenomegaly, or petechiae. Splenomegaly and lymphadenopathy suggest an underlying lymphoproliferative disease, whereas petechiae suggest platelet dysfunction. Past laboratory measurements are helpful to determine a time of onset.

In the anemic patient, physical examination may demonstrate a forceful heartbeat, strong peripheral pulses, and a systolic "flow" murmur. The skin and mucous membranes may be pale if the hemoglobin is <80–100 g/L (8–10 g/dL). This part of the physical examination should focus on areas where vessels are close to the surface such as the mucous membranes, nail beds, and palmar creases. If the palmar creases are lighter in color than the surrounding skin when the hand is hyperextended, the hemoglobin level is usually <80 g/L (8 g/dL).

LABORATORY EVALUATION **Table 2-1** lists the tests used in the initial workup of anemia. A routine complete blood count (CBC) is required as part of the evaluation and includes the hemoglobin, hematocrit, and red cell indices: the mean cell volume (MCV) in femtoliters, mean cell hemoglobin (MCH) in picograms per cell, and mean concentration of hemoglobin per volume of red cells (MCHC) in grams per liter (non-SI: grams per deciliter). The red cell indices are calculated as shown in **Table 2-2**, and the normal variations in the hemoglobin and hematocrit with age are shown in **Table 2-3**. A number of physiologic factors affect the CBC, including age, sex, pregnancy, smoking, and altitude. High-normal hemoglobin values may be seen in men and women who live at altitude or smoke heavily. Hemoglobin elevations due to smoking reflect normal compensation due to the displacement of O_2 by CO in hemoglobin binding. Other important information is provided by the reticulocyte count and measurements of iron supply including serum iron, total iron-binding capacity (TIBC; an indirect measure of serum transferrin), and serum *f*erritin. Marked alterations in the red cell indices usually reflect disorders of maturation or iron deficiency. A careful evaluation of the peripheral blood smear is important, and clinical laboratories often provide a description of both the red and white cells, a white cell differential count, and the platelet count. In patients with severe anemia and abnormalities in red blood cell morphology and/or low reticulocyte counts, a

TABLE 2-1

LABORATORY TESTS IN ANEMIA DIAGNOSIS

I. Complete blood count (CBC)
  A. Red blood cell count
    1. Hemoglobin
    2. Hematocrit
    3. Reticulocyte count
  B. Red blood cell indices
    1. Mean cell volume (MCV)
    2. Mean cell hemoglobin (MCH)
    3. Mean cell hemoglobin concentration (MCHC)
    4. Red cell distribution width (RDW)
  C. White blood cell count
    1. Cell differential
    2. Nuclear segmentation of neutrophils
  D. Platelet count
  E. Cell morphology
    1. Cell size
    2. Hemoglobin content
    3. Anisocytosis
    4. Poikilocytosis
    5. Polychromasia
II. Iron supply studies
  A. Serum iron
  B. Total iron-binding capacity
  C. Serum ferritin
III. Marrow examination
  A. Aspirate
    1. M/E ratio[a]
    2. Cell morphology
    3. Iron stain
  B. Biopsy
    1. Cellularity
    2. Morphology

[a]M/E ratio, ratio of myeloid to erythroid precursors.

bone marrow aspirate or biopsy can assist in the diagnosis. Other tests of value in the diagnosis of specific anemias are discussed in chapters on specific disease states.

The components of the CBC also help in the classification of anemia. Microcytosis is reflected by a lower than normal MCV (<80), whereas high values (>100) reflect macrocytosis. The MCH and MCHC reflect defects in

TABLE 2-2

RED BLOOD CELL INDICES

INDEX	NORMAL VALUE
Mean cell volume (MCV) = (hematocrit × 10)/(red cell count × 10^6)	90 ± 8 fL
Mean cell hemoglobin (MCH) = (hemoglobin × 10)/(red cell count × 10^6)	30 ± 3 pg
Mean cell hemoglobin concentration = (hemoglobin × 10)/hematocrit, or MCH/MCV	33 ± 2%

TABLE 2-3

CHANGES IN NORMAL HEMOGLOBIN/HEMATOCRIT VALUES WITH AGE, SEX, AND PREGNANCY

AGE/SEX	HEMOGLOBIN, g/dL	HEMATOCRIT, %
At birth	17	52
Childhood	12	36
Adolescence	13	40
Adult man	16 (±2)	47 (±6)
Adult woman (menstruating)	13 (±2)	40 (±6)
Adult woman (postmenopausal)	14 (±2)	42 (±6)
During pregnancy	12 (±2)	37 (±6)

Source: From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.

hemoglobin synthesis (hypochromia). Automated cell counters describe the red cell volume distribution width (RDW). The MCV (representing the peak of the distribution curve) is insensitive to the appearance of small populations of macrocytes or microcytes. An experienced laboratory technician will be able to identify minor populations of large or small cells or hypochromic cells before the red cell indices change.

Peripheral Blood Smear The peripheral blood smear provides important information about defects in red cell production **(Chap. 6)**. As a complement to the red cell indices, the blood smear also reveals variations in cell size (anisocytosis) and shape (poikilocytosis). The degree of anisocytosis usually correlates with increases in the RDW or the range of cell sizes. Poikilocytosis suggests a defect in the maturation of red cell precursors in the bone marrow or fragmentation of circulating red cells. The blood smear may also reveal polychromasia—red cells that are slightly larger than normal and grayish blue in color on the Wright-Giemsa stain. These cells are reticulocytes that have been prematurely released from the bone marrow, and their color represents residual amounts of ribosomal RNA. These cells appear in circulation in response to EPO stimulation or to architectural damage of the bone marrow (fibrosis, infiltration of the marrow by malignant cells, etc.) that results in their disordered release from the marrow. The appearance of nucleated red cells, Howell-Jolly bodies, target cells, sickle cells, and others may provide clues to specific disorders **(Figs. 2-3 to 2-11)**.

Reticulocyte Count An accurate reticulocyte count is key to the initial classification of anemia. Reticulocytes are red cells that have been recently released from the bone marrow. They are identified by staining with a supravital dye that precipitates the ribosomal RNA **(Fig. 2-12)**. These precipitates appear as blue or black punctate spots and can be counted manually or, currently, by fluorescent emission

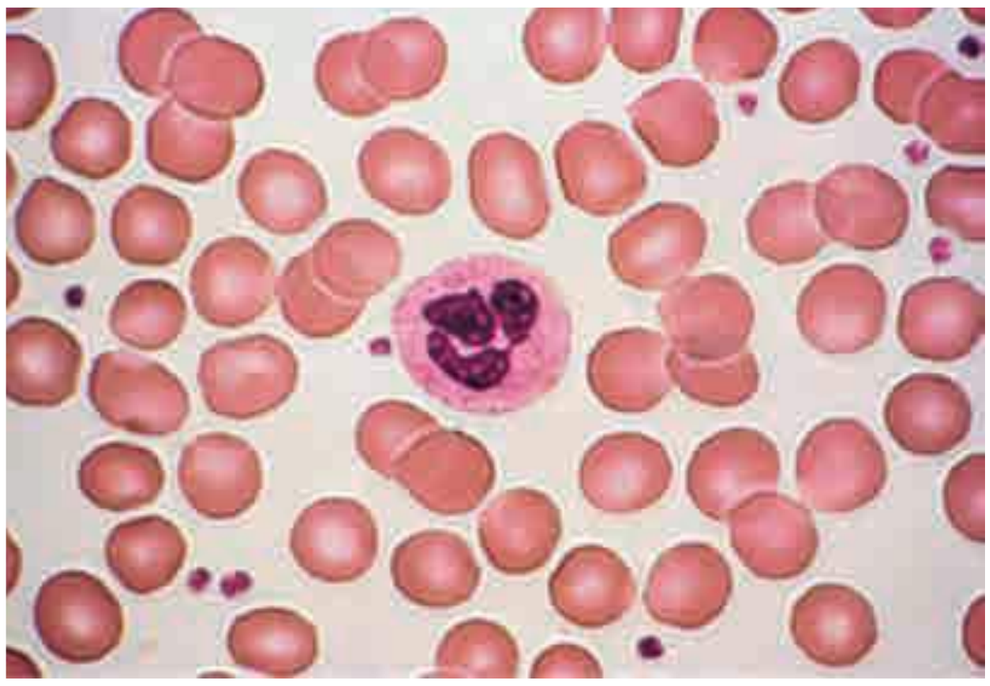


FIGURE 2-3
Normal blood smear (Wright stain). High-power field showing normal red cells, a neutrophil, and a few platelets. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

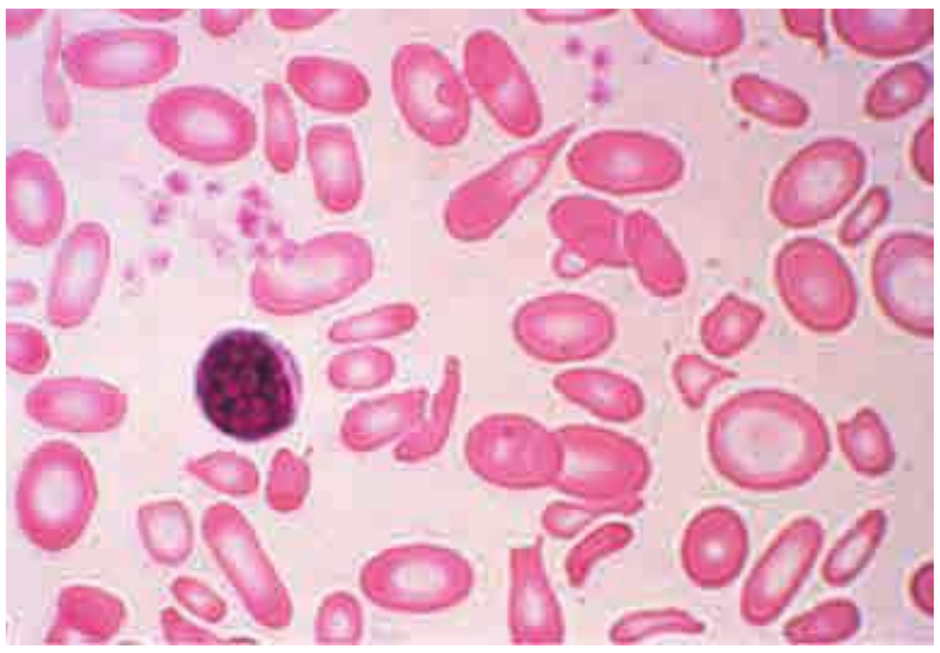


FIGURE 2-4
Severe iron-deficiency anemia. Microcytic and hypochromic red cells smaller than the nucleus of a lymphocyte associated with marked variation in size (anisocytosis) and shape (poikilocytosis). (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

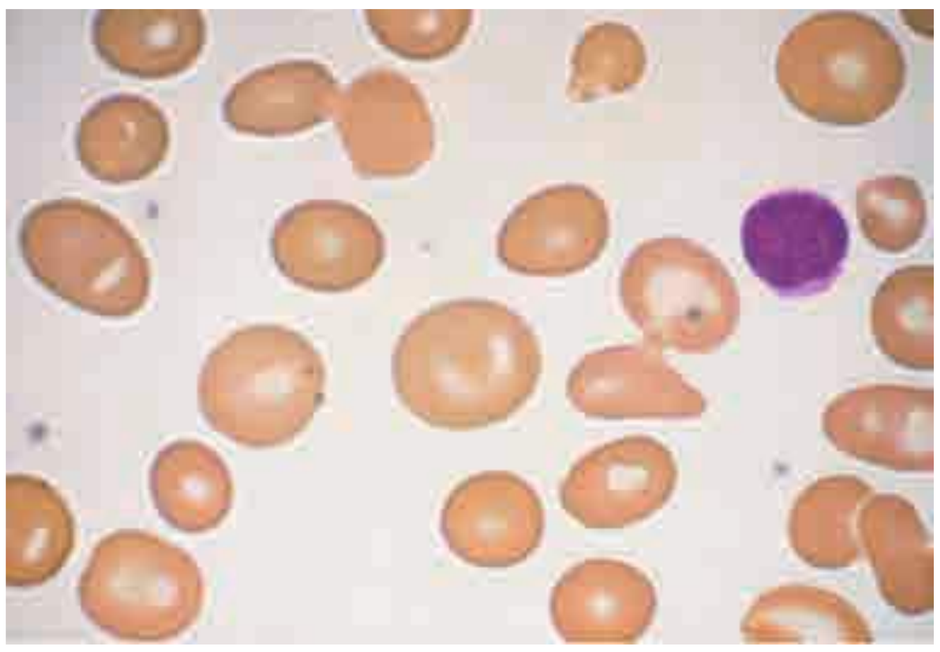


FIGURE 2-5
Macrocytosis. Red cells are larger than a small lymphocyte and well hemoglobinized. Often macrocytes are oval shaped (macro-ovalocytes).

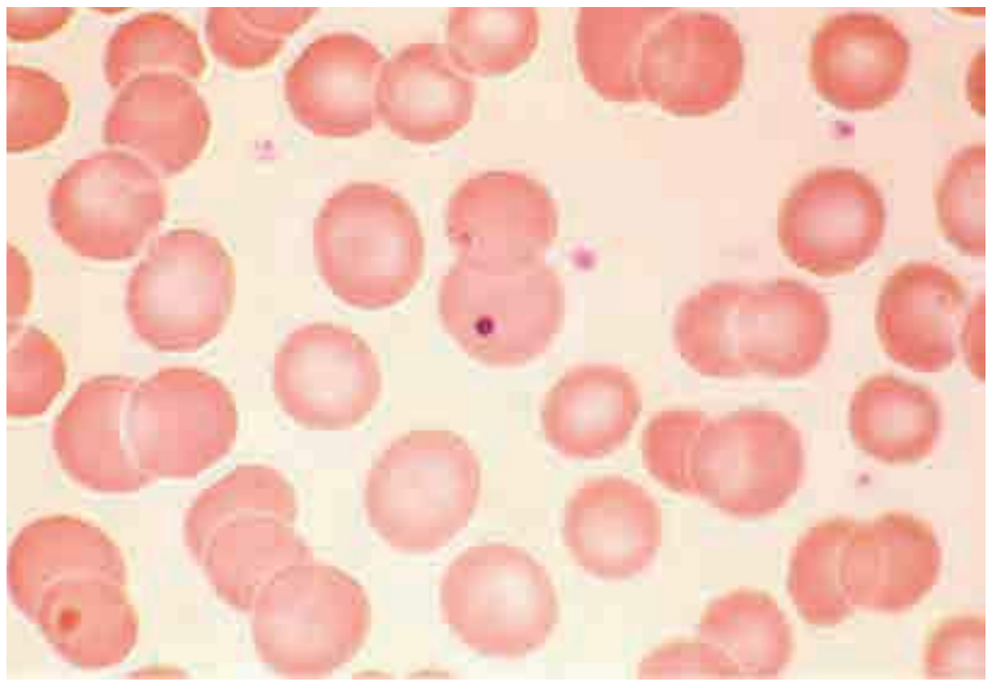


FIGURE 2-6
Howell-Jolly bodies. In the absence of a functional spleen, nuclear remnants are not culled from the red cells and remain as small homogeneously staining blue inclusions on Wright stain. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

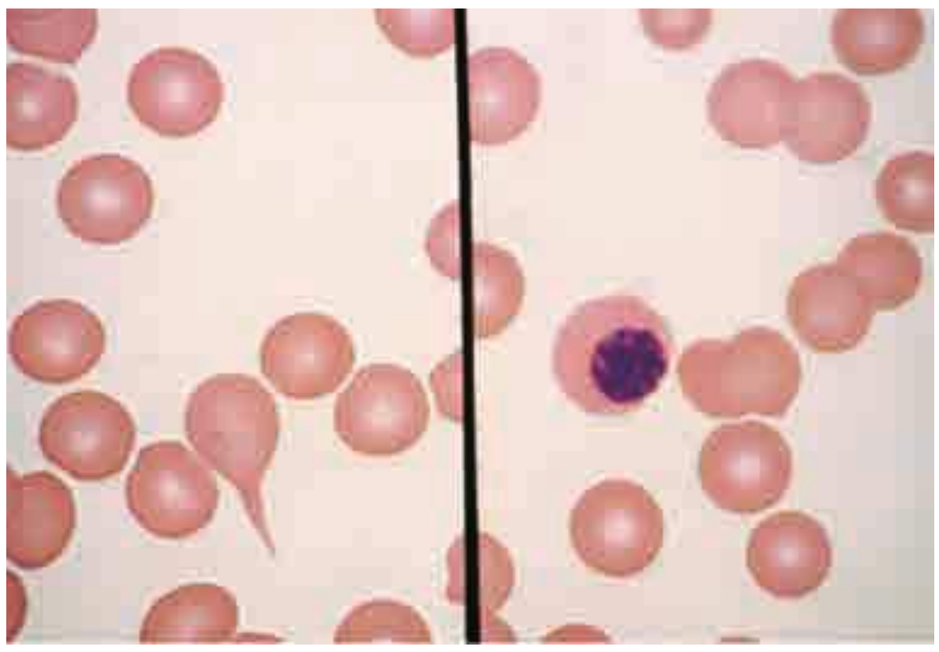


FIGURE 2-7
Red cell changes in myelofibrosis. The left panel shows a teardrop-shaped cell. The right panel shows a nucleated red cell. These forms can be seen in myelofibrosis.

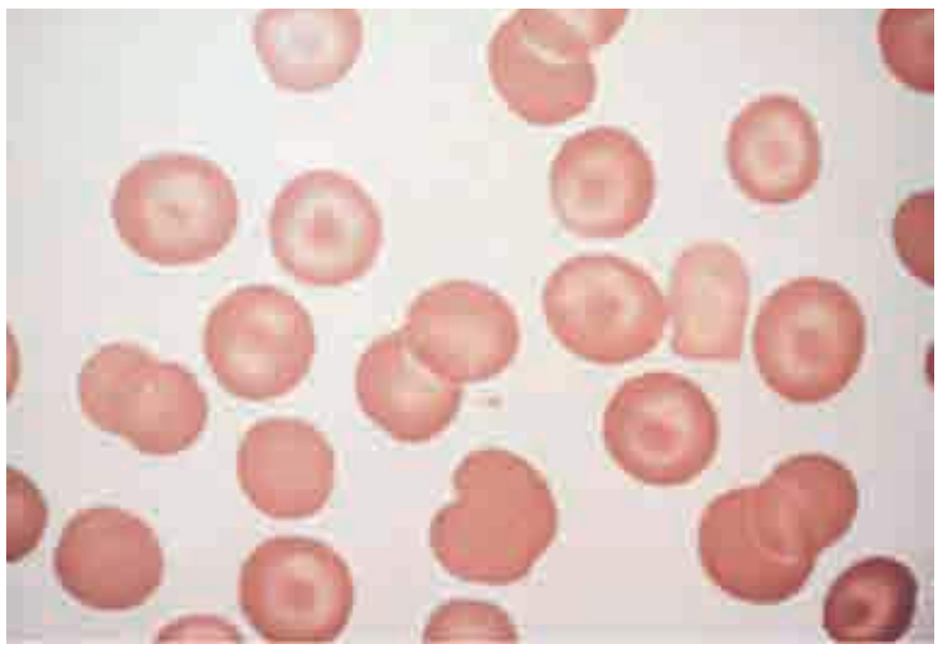


FIGURE 2-8
Target cells. Target cells have a bull's-eye appearance and are seen in thalassemia and in liver disease. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

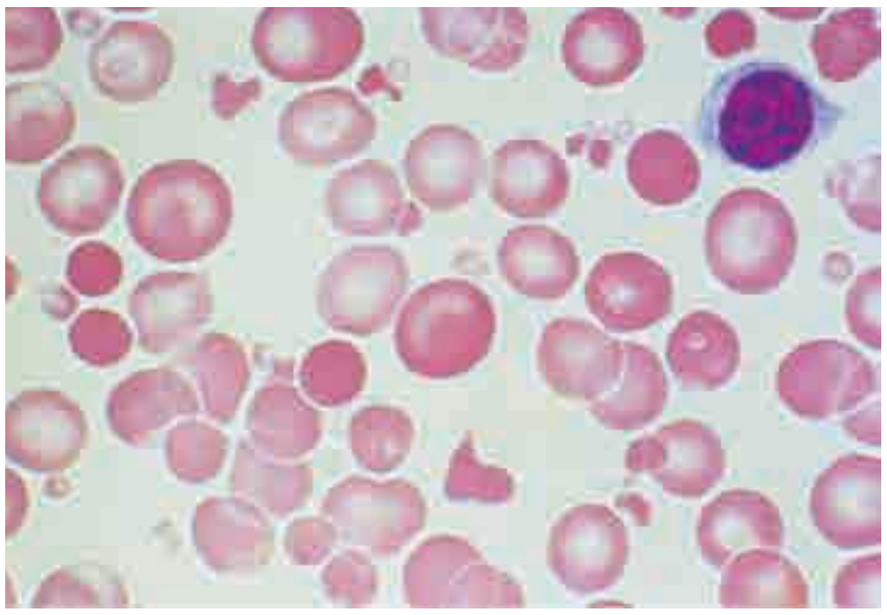


FIGURE 2-9
Red cell fragmentation. Red cells may become fragmented in the presence of foreign bodies in the circulation, such as mechanical heart valves, or in the setting of thermal injury. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

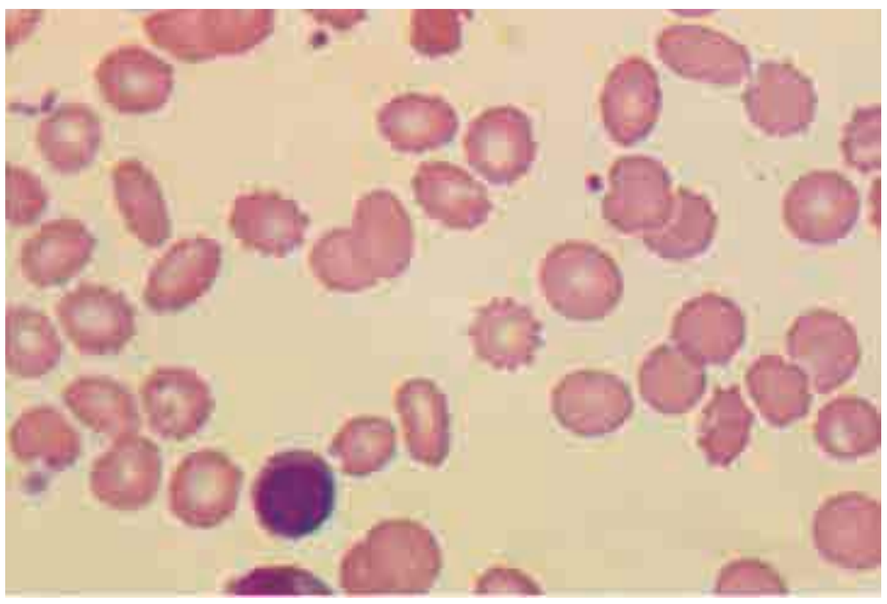


FIGURE 2-10
Uremia. The red cells in uremia may acquire numerous regularly spaced, small, spiny projections. Such cells, called burr cells or echinocytes, are readily distinguishable from irregularly spiculated acanthocytes shown in Fig. 2-11.

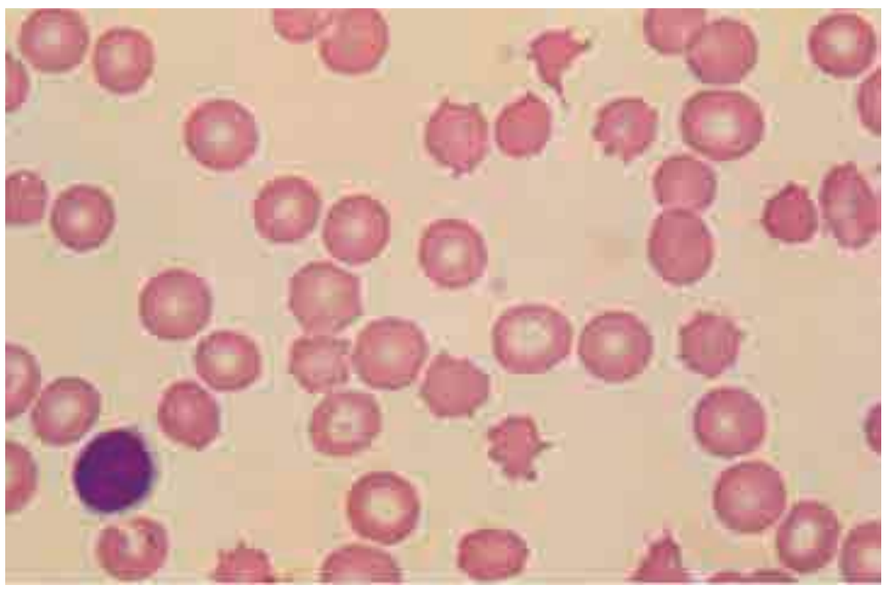


FIGURE 2-11
Spur cells. Spur cells are recognized as distorted red cells containing several irregularly distributed thornlike projections. Cells with this morphologic abnormality are also called acanthocytes. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

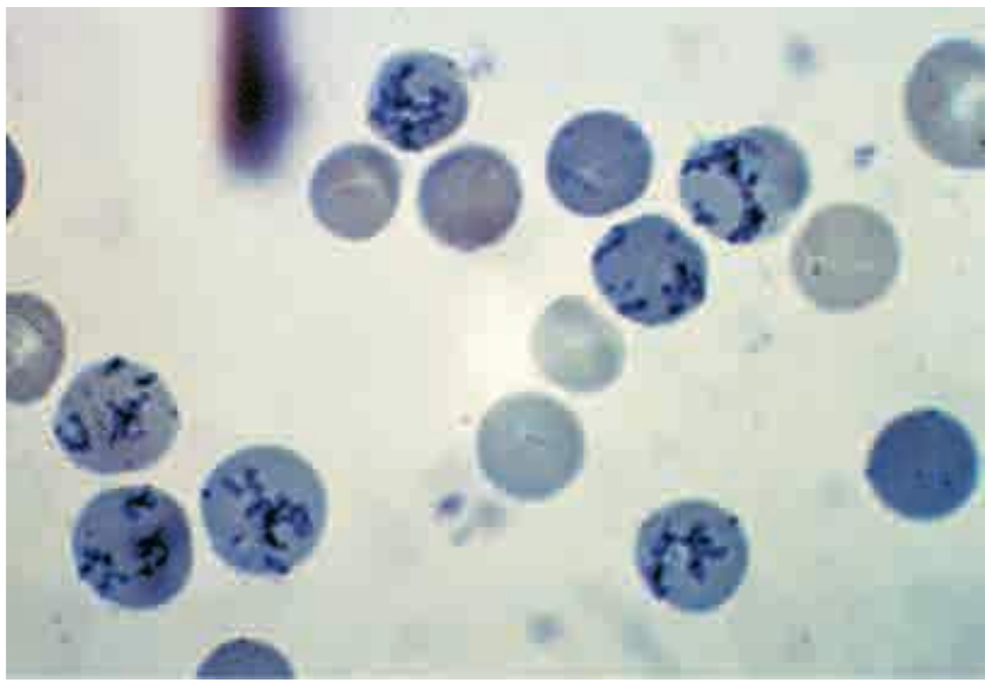


FIGURE 2-12
Reticulocytes. Methylene blue stain demonstrates residual RNA in newly made red cells. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

of dyes that bind to RNA. T is residual RNA is metabolized over the first 24–36 h of the reticulocyte's life span in circulation. Normally, the reticulocyte count ranges from 1 to 2% and reflects the daily replacement of 0.8–1.0% of the circulating red cell population. A corrected reticulocyte count provides a reliable measure of effective red cell production.

In the initial classification of anemia, the patient's reticulocyte count is compared with the expected reticulocyte response. In general, if the EPO and erythroid marrow responses to moderate anemia [hemoglobin <100 g/L (10 g/dL)] are intact, the red cell production rate increases to two to three times normal within 10 days following the onset of anemia. In the face of established anemia, a reticulocyte response less than two to three times normal indicates an inadequate marrow response.

To use the reticulocyte count to estimate marrow response, two corrections are necessary. T e first correction adjusts the reticulocyte count based on the reduced number of circulating red cells. With anemia, the percentage of reticulocytes may be increased while the absolute number is unchanged. To correct for this effect, the reticulocyte percentage is multiplied by the ratio of the patient's hemoglobin or hematocrit to the expected hemoglobin/hematocrit for the age and sex of the patient **(Table 2-4)**. T is provides an estimate of the reticulocyte count corrected for anemia. To convert the corrected reticulocyte count to an index of marrow production, a further correction is required, depending on whether some of the reticulocytes in circulation have been released from the marrow prematurely. For this second correction, the peripheral blood smear is examined to see if there are polychromatophilic macrocytes present.

T ese cells, representing prematurely released reticulocytes, are referred to as "shif " cells, and the relationship

TABLE 2-4

CALCULATION OF RETICULOCYTE PRODUCTION INDEX

Correction #1 for Anemia:
This correction produces the corrected reticulocyte count.
In a person whose reticulocyte count is 9%, hemoglobin 7.5 g/dL, and hematocrit 23%, the absolute reticulocyte count = 9 × (7.5/15) [or × (23/45)] = 4.5%
Note. This correction is not done if the reticulocyte count is reported in absolute numbers (e.g., 50,000/μL of blood)

Correction #2 for Longer Life of Prematurely Released Reticulocytes in the Blood:
This correction produces the reticulocyte production index.
In a person whose reticulocyte count is 9%, hemoglobin 7.5 gm/dL, and hematocrit 23%, the reticulocyte production index

$$= 9 \times \frac{(7.5/15)(\text{hemoglobin correction})}{2(\text{maturation time correction})} = 2.25$$

between the degree of shif and the necessary shif correction factor is shown in **Fig. 2-13**. T e correction is necessary because these prematurely released cells survive as reticulocytes in circulation for >1 day, thereby providing a falsely high estimate of daily red cell production. If polychromasia is increased, the reticulocyte count, already corrected for anemia, should be divided again by 2 to account for the prolonged reticulocyte maturation time. T e second correction factor varies from 1 to 3 depending on the

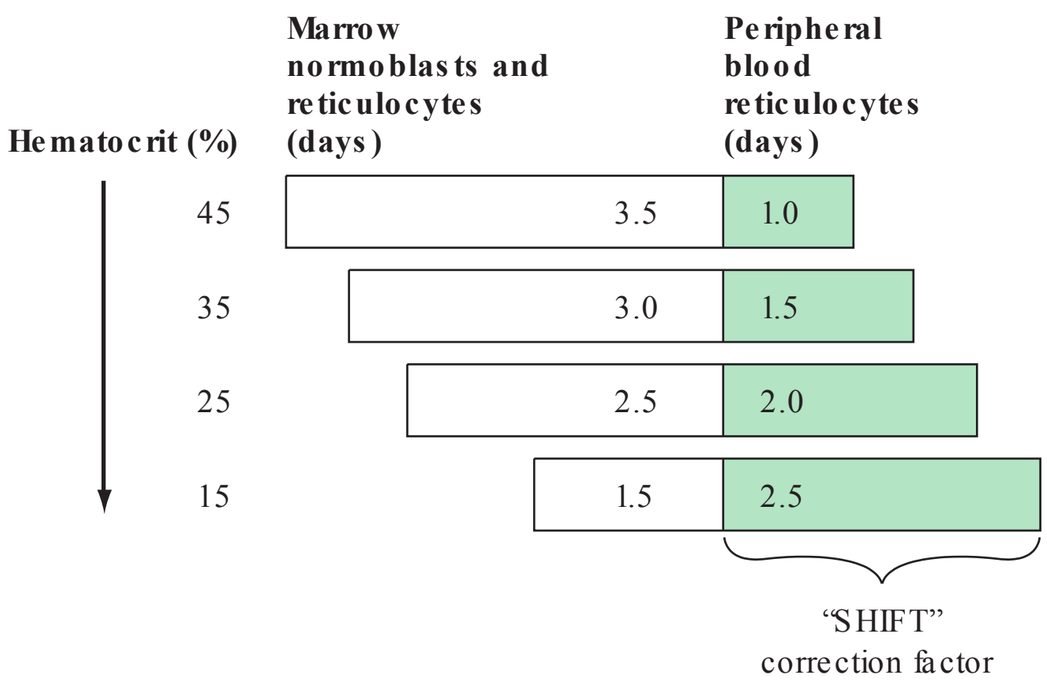


FIGURE 2-13
Correction of the reticulocyte count. To use the reticulocyte count as an indicator of effective red cell production, the reticulocyte percentage must be corrected based on the level of anemia and the circulating life span of the reticulocytes. Erythroid cells take ~4.5 days to mature. At a normal hemoglobin, reticulocytes are released to the circulation with ~1 day left as reticulocytes. However, with different levels of anemia, reticulocytes (and even earlier erythroid cells) may be released from the marrow prematurely. Most patients come to clinical attention with hematocrits in the mid-20s, and thus a correction factor of 2 is commonly used because the observed reticulocytes will live for 2 days in the circulation before losing their RNA.

TABLE 2-5

NORMAL MARROW RESPONSE TO ANEMIA

HEMOGLOBIN	PRODUCTION INDEX	RETICULOCYTE COUNT
15 g/dL	1	50,000/μL
11 g/dL	2.0–2.5	100–150,000/μL
8 g/dL	3.0–4.0	300–400,000/μL

severity of anemia. In general, a correction of 2 is simply used. An appropriate correction is shown in Table 2-4. If polychromatophilic cells are not seen on the blood smear, the second correction is not required. T e now doubly corrected reticulocyte count is the reticulocyte production index, and it provides an estimate of marrow production relative to normal. In many hospital laboratories, the reticulocyte count is reported not only as a percentage but also in absolute numbers. If so, no correction for dilution is required. A summary of the appropriate marrow response to varying degrees of anemia is shown in **Table 2-5**.

Premature release of reticulocytes is normally due to increased EPO stimulation. However, if the integrity of the bone marrow release process is lost through tumor infiltration, fibrosis, or other disorders, the appearance of nucleated red cells or polychromatophilic macrocytes should still invoke the second reticulocyte correction. T e shif correction should always be applied to a patient with anemia and a very high reticulocyte count to provide a true index of effective red cell production. Patients with severe chronic hemolytic anemia may increase red cell production as much as six- to sevenfold. T is measure alone confirms the fact that the patient has an appropriate EPO response, a normally functioning bone marrow, and sufficient iron available to meet the demands for new red cell formation. If the reticulocyte production index is <2 in the face of established anemia, a defect in erythroid marrow proliferation or maturation must be present.

Tests of Iron Supply and Storage T e laboratory measurements that reflect the availability of iron for hemoglobin synthesis include the serum iron, the TIBC, and the percent transferrin saturation. T e percent transferrin saturation is derived by dividing the serum iron level (× 100) by the TIBC. T e normal serum iron ranges from 9 to 27 μmol/L (50–150 μg/dL), whereas the normal TIBC is 54–64 μmol/L (300–360 μg/dL); the normal transferrin saturation ranges from 25 to 50%. A diurnal variation in the serum iron leads to a variation in the percent transferrin saturation. T e serum ferritin is used to evaluate total body iron stores. Adult males have serum ferritin levels that average ~100 μg/L, corresponding to iron stores of ~1 g. Adult females have lower serum ferritin levels averaging 30 μg/L, reflecting lower iron stores (~300 mg). A serum ferritin level of 10–15 μg/L indicates depletion of body iron stores. However, ferritin is also an acute-phase reactant

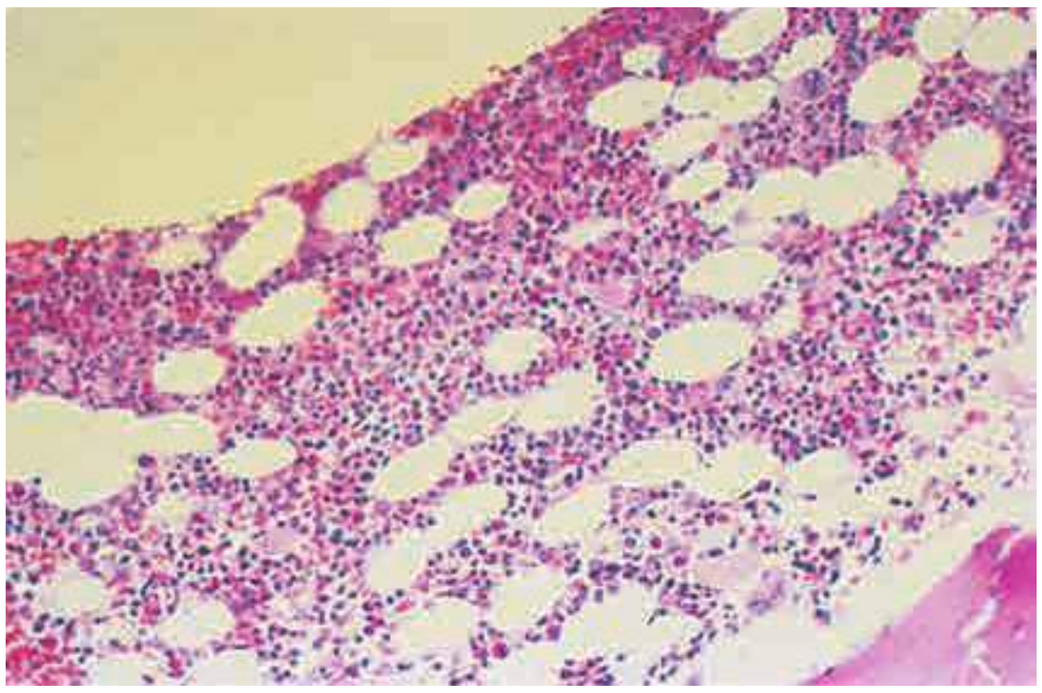


FIGURE 2-14
Normal bone marrow. This is a low-power view of a section of a normal bone marrow biopsy stained with hematoxylin and eosin (H&E). Note that the nucleated cellular elements account for ~40–50% and the fat (clear areas) accounts for ~50–60% of the area. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

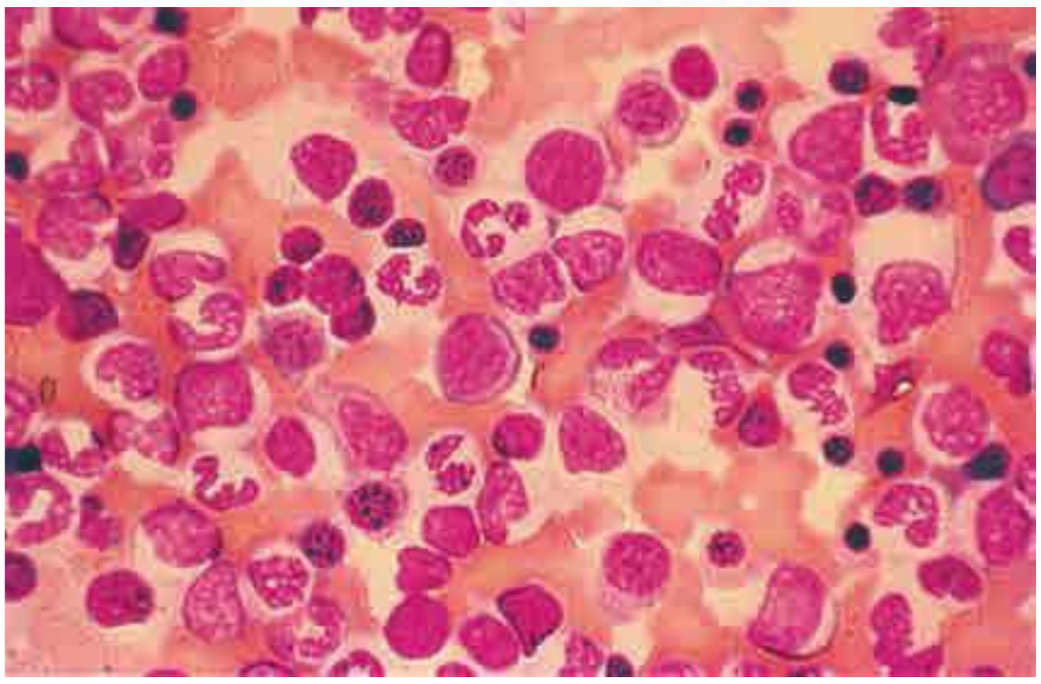


FIGURE 2-16
Myeloid hyperplasia. This marrow shows an increase in the fraction of cells in the myeloid or granulocytic lineage as might be seen in a normal marrow responding to infection. The myeloid/erythroid (M/E) ratio is >3:1. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

and, in the presence of acute or chronic inflammation, may rise several-fold above baseline levels. As a rule, a serum ferritin >200 μg/L means there is at least some iron in tissue stores.

Bone Marrow Examination A bone marrow aspirate and smear or a needle biopsy can be useful in the evaluation of some patients with anemia. In patients with hypoproliferative anemia and normal iron status, a bone marrow is indicated. Marrow examination can diagnose primary marrow disorders such as myelofibrosis, a red cell maturation defect, or an infiltrative disease **(Figs. 2-14 to 2-16)**. The increase or decrease of one cell lineage (myeloid vs erythroid) compared to another is obtained by a differential count of nucleated cells in a bone marrow smear (the myeloid/erythroid [M/E] ratio). A patient with a hypoproliferative anemia (see below) and a reticulocyte production index <2 will demonstrate an M/E ratio of 2 or 3:1. In contrast, patients with hemolytic disease and a production index >3 will have an M/E ratio of at least 1:1. Maturation disorders are identified from the discrepancy between the M/E ratio and the reticulocyte production index (see below). Either the marrow smear or biopsy can be stained for the presence of iron stores or iron in developing red cells. The storage iron is in the form of ferritin or hemosiderin. On carefully prepared bone marrow smears, small ferritin granules can normally be seen under oil immersion in 20–40% of developing erythroblasts. Such cells are called sideroblasts.

OTHER LABORATORY MEASUREMENTS Additional laboratory tests may be of value in confirming specific diagnoses. **For details of these tests and how they are applied in individual disorders, see Chaps. 7 to 11**.

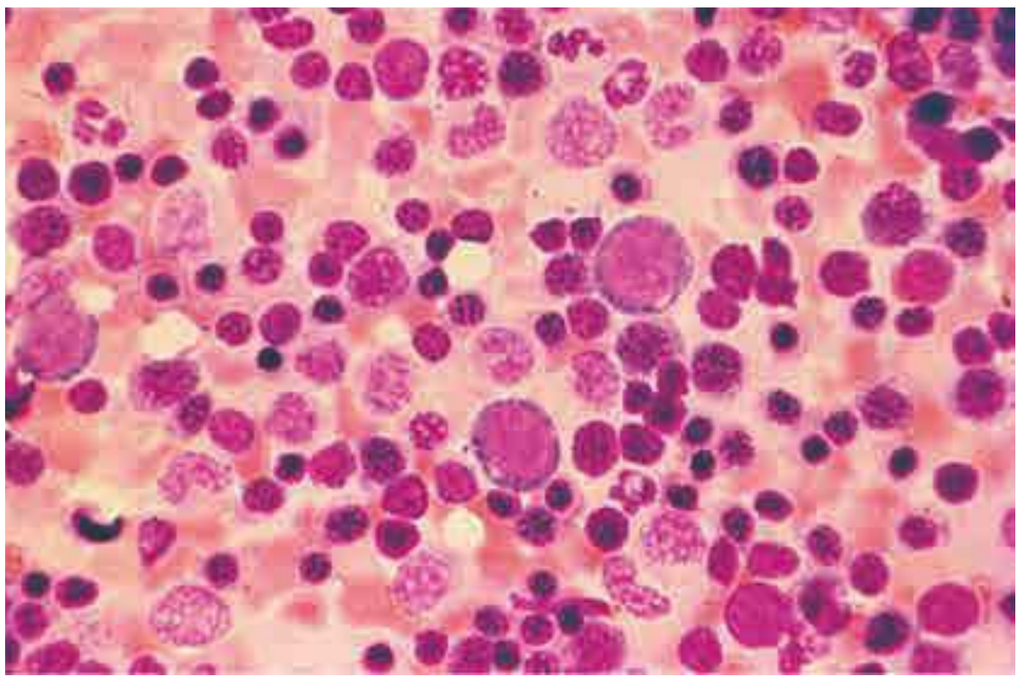


FIGURE 2-15
Erythroid hyperplasia. This marrow shows an increase in the fraction of cells in the erythroid lineage as might be seen when a normal marrow compensates for acute blood loss or hemolysis. The myeloid/erythroid (M/E) ratio is about 1:1. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

DEFINITION AND CLASSIFICATION OF ANEMIA

Initial classification of anemia

The functional classification of anemia has three major categories. These are (1) marrow production defects (hypoproliferation), (2) red cell maturation defects (ineffective erythropoiesis), and (3) decreased red cell survival (blood loss/hemolysis). The classification is shown in **Fig. 2-17**. A hypoproliferative anemia is typically seen with a low reticulocyte production index together with little or no change in red cell morphology (a normocytic, normochromic anemia) **(Chap. 7)**. Maturation disorders typically have a slight to moderately elevated

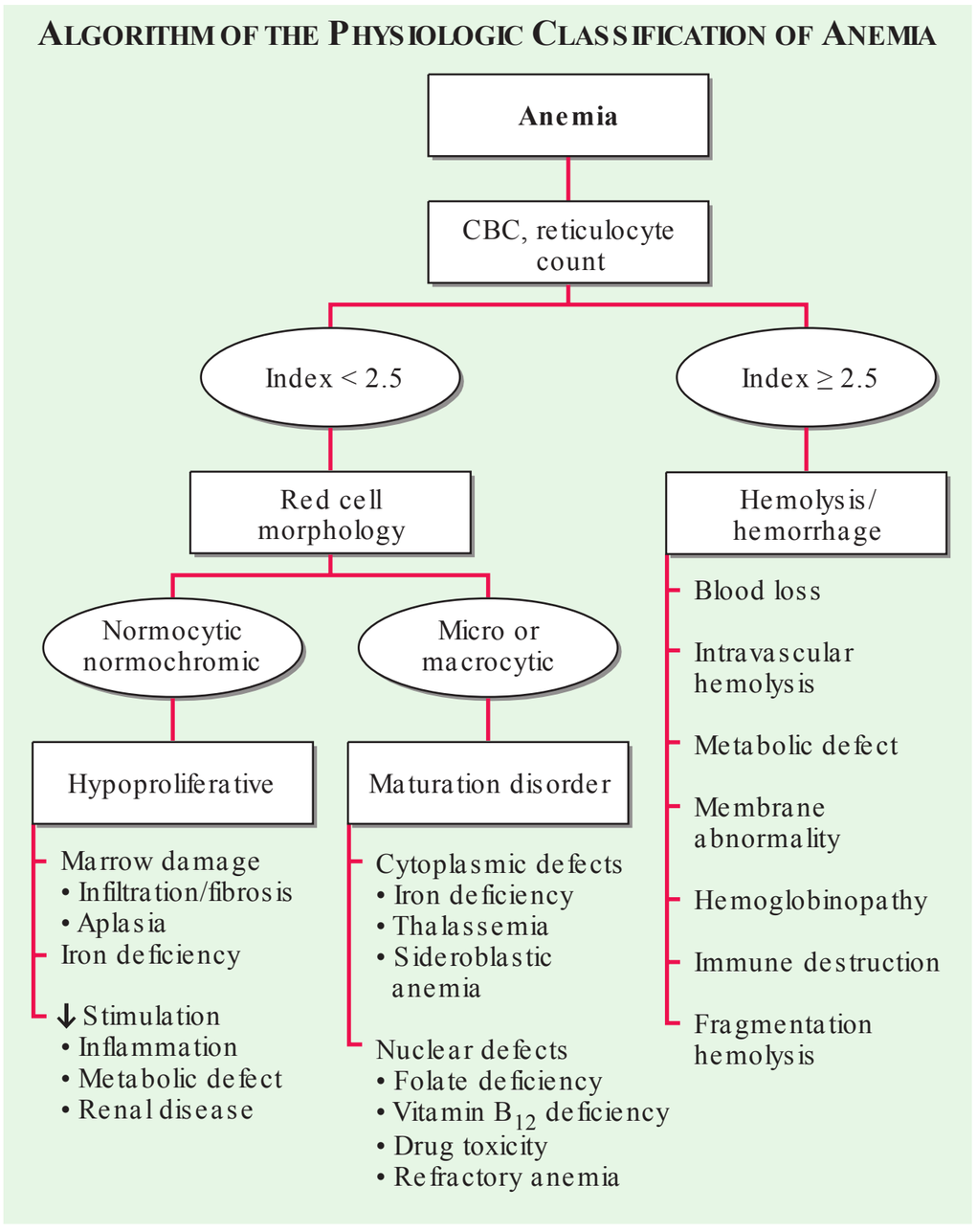


FIGURE 2-17
The physiologic classification of anemia. CBC, complete blood count.

reticulocyte production index that is accompanied by either macrocytic **(Chap. 9)** or microcytic **(Chaps. 7, 8)** red cell indices. Increased red blood cell destruction secondary to hemolysis results in an increase in the reticulocyte production index to at least three times normal **(Chap. 10)**, provided sufficient iron is available. Hemorrhagic anemia does not typically result in production indices of more than 2.0–2.5 times normal because of the limitations placed on expansion of the erythroid marrow by iron availability.

In the first branch point of the classification of anemia, a reticulocyte production index >2.5 indicates that hemolysis is most likely. A reticulocyte production index <2 indicates either a hypoproliferative anemia or maturation disorder. The latter two possibilities can often be distinguished by the red cell indices, by examination of the peripheral blood smear, or by a marrow examination. If the red cell indices are normal, the anemia is almost certainly hypoproliferative in nature. Maturation disorders are characterized by ineffective red cell production and a low reticulocyte production index. Bizarre red cell shapes—macrocytes or hypochromic microcytes—are seen on the peripheral blood smear. With a hypoproliferative anemia, no erythroid hyperplasia is noted in the marrow, whereas patients with ineffective red cell production have erythroid hyperplasia and an M/E ratio <1:1.

Hypoproliferative anemias

At least 75% of all cases of anemia are hypoproliferative in nature. A hypoproliferative anemia reflects absolute or relative marrow failure in which the erythroid marrow has not proliferated appropriately for the degree of anemia. The majority of hypoproliferative anemias are due to mild to moderate iron deficiency or inflammation. A hypoproliferative anemia can result from marrow damage, iron deficiency, or inadequate EPO stimulation. The last may reflect impaired renal function, suppression of EPO production by inflammatory cytokines such as interleukin 1, or reduced tissue needs for O_2 from metabolic disease such as hypothyroidism. Only occasionally is the marrow unable to produce red cells at a normal rate, and this is most prevalent in patients with renal failure. With diabetes mellitus or myeloma, the EPO deficiency may be more marked than would be predicted by the degree of renal insufficiency. In general, hypoproliferative anemias are characterized by normocytic, normochromic red cells, although microcytic, hypochromic cells may be observed with mild iron deficiency or long-standing chronic inflammatory disease. The key laboratory tests in distinguishing between the various forms of hypoproliferative anemia include the serum iron and iron-binding capacity, evaluation of renal and thyroid function, a marrow biopsy or aspirate to detect marrow damage or infiltrative disease, and serum ferritin to assess iron stores. An iron stain of the marrow will determine the pattern of iron distribution. Patients with the anemia of acute or chronic inflammation show a distinctive pattern of serum iron (low), TIBC (normal or low), percent transferrin saturation (low), and serum ferritin (normal or high). These changes in iron values are brought about by hepcidin, the iron regulatory hormone that is produced by the liver and is increased in inflammation **(Chap. 7)**. A distinct pattern of results is noted in mild to moderate iron deficiency (low serum iron, high TIBC, low percent transferrin saturation, low serum ferritin) **(Chap. 7)**. Marrow damage by drugs, infiltrative disease such as leukemia or lymphoma, or marrow aplasia is diagnosed from the peripheral blood and bone marrow morphology. With infiltrative disease or fibrosis, a marrow biopsy is required.

Maturation disorders

The presence of anemia with an inappropriately low reticulocyte production index, macro- or microcytosis on smear, and abnormal red cell indices suggests a maturation disorder. Maturation disorders are divided into two categories: nuclear maturation defects, associated with macrocytosis, and cytoplasmic maturation defects, associated with microcytosis and hypochromia usually

from defects in hemoglobin synthesis. T e inappropriately low reticulocyte production index is a reflection of the ineffective erythropoiesis that results from the destruction within the marrow of developing erythroblasts. Bone marrow examination shows erythroid hyperplasia.

Nuclear maturation defects result from vitamin B_{12} or folic acid deficiency, drug damage, or myelodysplasia. Drugs that interfere with cellular DNA synthesis, such as methotrexate or alkylating agents, can produce a nuclear maturation defect. Alcohol, alone, is also capable of producing macrocytosis and a variable degree of anemia, but this is usually associated with folic acid deficiency. Measurements of folic acid and vitamin B_{12} are critical not only in identifying the specific vitamin deficiency but also because they reflect different pathogenetic mechanisms **(Chap. 9)**.

Cytoplasmic maturation defects result from severe iron deficiency or abnormalities in globin or heme synthesis. Iron deficiency occupies an unusual position in the classification of anemia. If the iron-deficiency anemia is mild to moderate, erythroid marrow proliferation is blunted and the anemia is classified as hypoproliferative. However, if the anemia is severe and prolonged, the erythroid marrow will become hyperplastic despite the inadequate iron supply, and the anemia will be classified as ineffective erythropoiesis with a cytoplasmic maturation defect. In either case, an inappropriately low reticulocyte production index, microcytosis, and a classic pattern of iron values make the diagnosis clear and easily distinguish iron deficiency from other cytoplasmic maturation defects such as the thalassemias. Defects in heme synthesis, in contrast to globin synthesis, are less common and may be acquired or inherited. Acquired abnormalities are usually associated with myelodysplasia, may lead to either a macro- or microcytic anemia, and are frequently associated with mitochondrial iron loading. In these cases, iron is taken up by the mitochondria of the developing erythroid cell but not incorporated into heme. T e iron-encrusted mitochondria surround the nucleus of the erythroid cell, forming a ring. Based on the distinctive finding of so-called ringed sideroblasts on the marrow iron stain, patients are diagnosed as having a sideroblastic anemia—almost always reflecting myelodysplasia. Again, studies of iron parameters are helpful in the differential diagnosis of these patients.

Blood loss/hemolytic anemia

In contrast to anemias associated with an inappropriately low reticulocyte production index, hemolysis is associated with red cell production indices ≥2.5 times normal. T e stimulated erythropoiesis is reflected in the blood smear by the appearance of increased numbers of polychromatophilic macrocytes. A marrow examination is rarely indicated if the reticulocyte production index is increased appropriately. T e red cell indices are typically normocytic or slightly macrocytic, reflecting the increased number of reticulocytes. Acute blood loss is not associated with an increased reticulocyte production index because of the time required to increase EPO production and, subsequently, marrow proliferation. Subacute blood loss may be associated with modest reticulocytosis. Anemia from chronic blood loss presents more of en as iron deficiency than with the picture of increased red cell production.

T e evaluation of blood loss anemia is usually not difficult. Most problems arise when a patient presents with an increased red cell production index from an episode of acute blood loss that went unrecognized. T e cause of the anemia and increased red cell production may not be obvious. T e confirmation of a recovering state may require observations over a period of 2–3 weeks, during which the hemoglobin concentration will rise and the reticulocyte production index fall **(Chap. 10)**.

Hemolytic disease, while dramatic, is among the least common forms of anemia. T e ability to sustain a high reticulocyte production index reflects the ability of the erythroid marrow to compensate for hemolysis and, in the case of extravascular hemolysis, the efficient recycling of iron from the destroyed red cells to support red cell production. With intravascular hemolysis, such as paroxysmal nocturnal hemoglobinuria, the loss of iron may limit the marrow response. T e level of response depends on the severity of the anemia and the nature of the underlying disease process.

Hemoglobinopathies, such as sickle cell disease and the thalassemias, present a mixed picture. T e reticulocyte index may be high but is inappropriately low for the degree of marrow erythroid hyperplasia **(Chap. 8)**.

Hemolytic anemias present in different ways. Some appear suddenly as an acute, self-limited episode of intravascular or extravascular hemolysis, a presentation pattern of en seen in patients with autoimmune hemolysis or with inherited defects of the Embden-Meyerhof pathway or the glutathione reductase pathway. Patients with inherited disorders of the hemoglobin molecule or red cell membrane generally have a lifelong clinical history typical of the disease process. T ose with chronic hemolytic disease, such as hereditary spherocytosis, may actually present not with anemia but with a complication stemming from the prolonged increase in red cell destruction such as symptomatic bilirubin gallstones or splenomegaly. Patients with chronic hemolysis are also susceptible to aplastic crises if an infectious process interrupts red cell production.

T e differential diagnosis of an acute or chronic hemolytic event requires the careful integration of family history, the pattern of clinical presentation,

and—whether the disease is congenital or acquired—careful examination of the peripheral blood smear. Precise diagnosis may require more specialized laboratory tests, such as hemoglobin electrophoresis or a screen for red cell enzymes. Acquired defects in red cell survival are of en immunologically mediated and require a direct or indirect antiglobulin test or a cold agglutinin titer to detect the presence of hemolytic antibodies or complement-mediated red cell destruction **(Chap. 10)**.

TREATMENT Anemia

An overriding principle is to initiate treatment of mild to moderate anemia only when a specific diagnosis is made. Rarely, in the acute setting, anemia may be so severe that red cell transfusions are required before a specific diagnosis is available. Whether the anemia is of acute or gradual onset, the selection of the appropriate treatment is determined by the documented cause(s) of the anemia. Of en, the cause of the anemia is multifactorial. For example, a patient with severe rheumatoid arthritis who has been taking anti-inflammatory drugs may have a hypoproliferative anemia associated with chronic inflammation as well as chronic blood loss associated with intermittent gastrointestinal bleeding. In every circumstance, it is important to evaluate the patient's iron status fully before and during the treatment of any anemia. **Transfusion is discussed in Chap. 12; iron therapy is discussed in Chap. 7; treatment of megaloblastic anemia is discussed in Chap. 9; treatment of other entities is discussed in their respective chapters (sickle cell anemia, Chap. 8; hemolytic anemias, Chap. 10; aplastic anemia and myelodysplasia, Chap. 11).**

T erapeutic options for the treatment of anemias have expanded dramatically during the past 30 years. Blood component therapy is available and safe. Recombinant EPO as an adjunct to anemia management has transformed the lives of patients with chronic renal failure on dialysis and reduced transfusion needs of anemic cancer patients receiving chemotherapy. Eventually, patients with inherited disorders of globin synthesis or mutations in the globin gene, such as sickle cell disease, may benefit from the successful introduction of targeted genetic therapy.

POLYCYTHEMIA

Polycythemia is defined as an increase in the hemoglobin above normal. T is increase may be real or only apparent because of a decrease in plasma volume (spurious or relative polycythemia). T e term erythrocytosis may be used interchangeably with polycythemia, but some draw a distinction between them: erythrocytosis implies documentation of increased red cell mass, whereas polycythemia refers to any increase in red cells. Of en patients with polycythemia are detected through an incidental finding of elevated hemoglobin or hematocrit levels. Concern that the hemoglobin level may be abnormally high is usually triggered at 170 g/L (17 g/dL) for men and 150 g/L (15 g/dL) for women. Hematocrit levels >50% in men or >45% in women may be abnormal. Hematocrits >60% in men and >55% in women are almost invariably associated with an increased red cell mass. Given that the machine that quantitates red cell parameters actually measures hemoglobin concentrations and calculates hematocrits, hemoglobin levels may be a better index.

Features of the clinical history that are useful in the differential diagnosis include smoking history; current living at high altitude; or a history of congenital heart disease, sleep apnea, or chronic lung disease.

Patients with polycythemia may be asymptomatic or experience symptoms related to the increased red cell mass or the underlying disease process that leads to the increased red cell mass. T e dominant symptoms from an increased red cell mass are related to hyperviscosity and thrombosis (both venous and arterial), because the blood viscosity increases logarithmically at hematocrits >55%. Manifestations range from digital ischemia to Budd-Chiari syndrome with hepatic vein thrombosis. Abdominal vessel thromboses are particularly common. Neurologic symptoms such as vertigo, tinnitus, headache, and visual disturbances may occur. Hypertension is of en present. Patients with polycythemia vera may have aquagenic pruritus and symptoms related to hepatosplenomegaly. Patients may have easy bruising, epistaxis, or bleeding from the gastrointestinal tract. Peptic ulcer disease is common. Patients with hypoxemia may develop cyanosis on minimal exertion or have headache, impaired mental acuity, and fatigue.

T e physical examination usually reveals a ruddy complexion. Splenomegaly favors polycythemia vera as the diagnosis **(Chap. 13)**. T e presence of cyanosis or evidence of a right-to-lef shunt suggests congenital heart disease presenting in the adult, particularly tetralogy of Fallot or Eisenmenger's syndrome. Increased blood viscosity raises pulmonary artery pressure; hypoxemia can lead to increased pulmonary vascular resistance. Together, these factors can produce cor pulmonale.

Polycythemia can be spurious (related to a decrease in plasma volume; Gaisbock's syndrome), primary, or secondary in origin. T e secondary causes are all associated with increases in EPO levels: either a physiologically adapted appropriate elevation based on tissue hypoxia (lung disease, high altitude, CO poisoning, high-affinity hemoglobinopathy) or an abnormal overproduction (renal cysts, renal artery stenosis, tumors with ectopic EPO production). A rare familial form of polycythemia is associated with normal EPO levels but hyperresponsive EPO receptors due to mutations.

APPROACH TO THE PATIENT: Polycythemia

As shown in **Fig. 2-18**, the first step is to document the presence of an increased red cell mass using the principle of isotope dilution by administering ^{51}Cr-labeled autologous red blood cells to the patient and sampling blood radioactivity over a 2-h period. If the red cell mass is normal (<36 mL/kg in men, <32 mL/kg in women), the patient has spurious or relative polycythemia. If the red cell mass is increased (>36 mL/kg in men, >32 mL/kg in women), serum EPO levels should be measured. If EPO levels are low or unmeasurable, the patient most likely has polycythemia vera. A mutation in JAK2 (Val617Phe), a key member of the cytokine intracellular signaling pathway, can be found in 90–95% of patients with polycythemia vera. Many of those without this particular JAK2 mutation have mutations in exon 12. As a practical matter, few centers assess red cell mass in the setting of an increased hematocrit. T e short workup is to measure EPO levels, check for JAK2 mutation, and perform an abdominal ultrasound to assess spleen size. Tests that support the diagnosis of polycythemia vera include elevated white blood cell count, increased absolute basophil count, and thrombocytosis.

If serum EPO levels are elevated, one needs to distinguish whether the elevation is a physiologic response to hypoxia or related to autonomous EPO production. Patients with low arterial O_2 saturation (<92%) should be further evaluated for the presence of heart or lung disease, if they are not living at high altitude. Patients with normal O_2 saturation who are smokers may have elevated EPO levels because of CO displacement of O_2. If carboxyhemoglobin (COHb) levels are high, the diagnosis is "smoker's polycythemia." Such patients should be urged to stop smoking. T ose who cannot stop smoking require phlebotomy to control their polycythemia. Patients with normal O_2 saturation who do not smoke either have an abnormal hemoglobin that does not deliver O_2 to the tissues (evaluated by finding elevated O_2–hemoglobin affinity) or have a source of EPO production that is not responding to the normal feedback inhibition. Further workup is dictated by the differential diagnosis of EPO-producing neoplasms. Hepatoma, uterine leiomyoma, and renal cancer or cysts are all detectable with abdominopelvic computed tomography scans. Cerebellar hemangiomas may produce EPO, but they present with localizing neurologic signs and symptoms rather than polycythemia-related symptoms.

AN APPROACH TO DIAGNOSING PATIENTS WITH POLYCYTHEMIA

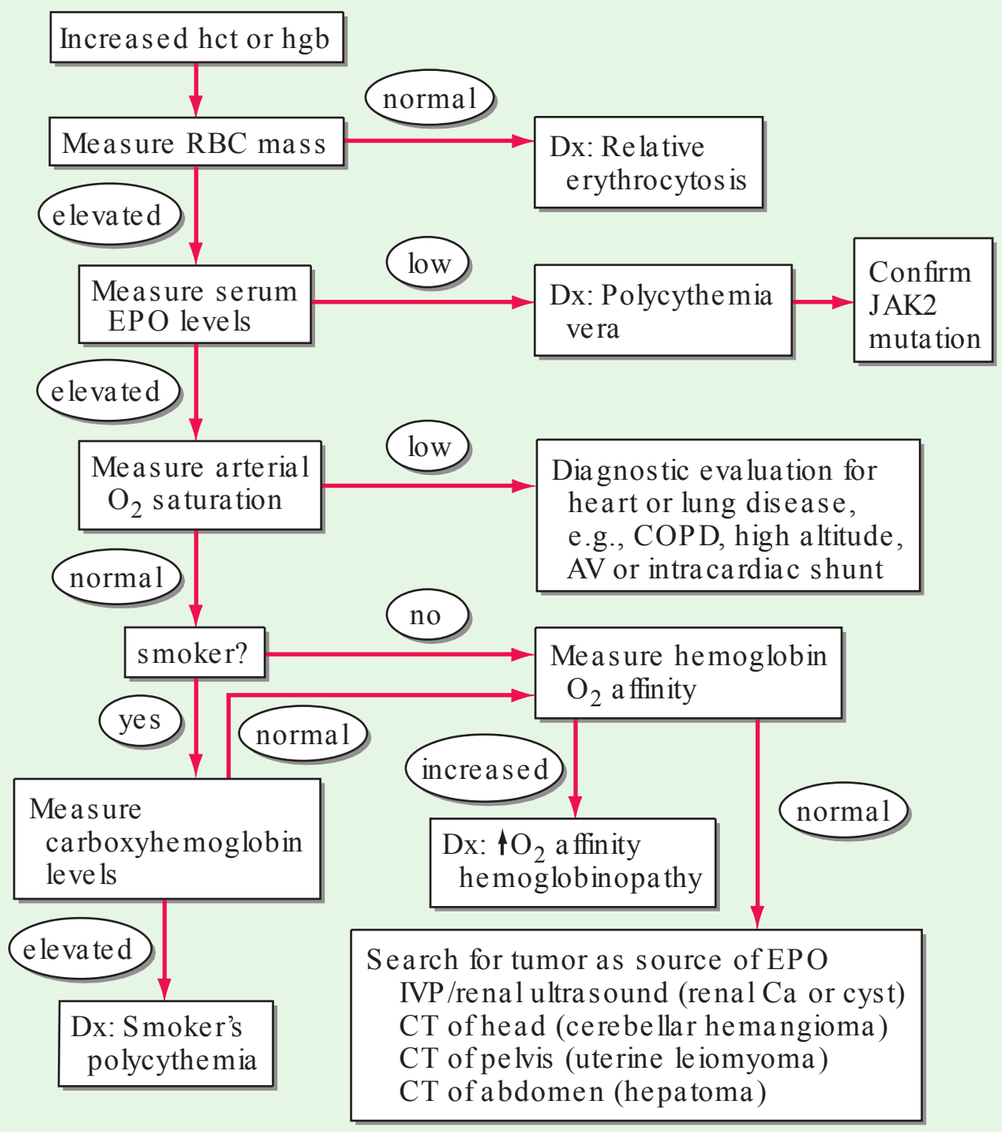


FIGURE 2-18
An approach to the dif erential diagnosis of patients with an elevated hemoglobin (possible polycythemia). AV, atrioventricular; COPD, chronic obstructive pulmonary disease; CT, computed tomography; EPO, erythropoietin; hct, hematocrit; hgb, hemoglobin; IVP, intravenous pyelogram; RBC, red blood cell.

CHAPTER 3

BLEEDING AND THROMBOSIS

Barbara A. Konkle

The human hemostatic system provides a natural balance between procoagulant and anticoagulant forces. The procoagulant forces include platelet adhesion and aggregation and fibrin clot formation; anticoagulant forces include the natural inhibitors of coagulation and fibrinolysis. Under normal circumstances, hemostasis is regulated to promote blood flow; however, it is also prepared to clot blood rapidly to arrest blood flow and prevent exsanguination. After bleeding is successfully halted, the system remodels the damaged vessel to restore normal blood flow. The major components of the hemostatic system, which function in concert, are (1) platelets and other formed elements of blood, such as monocytes and red cells; (2) plasma proteins (the coagulation and fibrinolytic factors and inhibitors); and (3) the vessel wall.

STEPS OF NORMAL HEMOSTASIS

PLATELET PLUG FORMATION

On vascular injury, platelets adhere to the site of injury, usually the denuded vascular intimal surface. Platelet adhesion is mediated primarily by Von Willebrand factor (VWF), a large multimeric protein present in both plasma and the extracellular matrix of the subendothelial vessel wall, which serves as the primary "molecular glue," providing sufficient strength to withstand the high levels of shear stress that would tend to detach them with the flow of blood. Platelet adhesion is also facilitated by direct binding to subendothelial collagen through specific platelet membrane collagen receptors.

Platelet adhesion results in subsequent platelet activation and aggregation. This process is enhanced and amplified by humoral mediators in plasma (e.g., epinephrine, thrombin); mediators released from activated platelets (e.g., adenosine diphosphate, serotonin); and vessel wall extracellular matrix constituents that come in contact with adherent platelets (e.g., collagen, VWF). Activated platelets undergo the release reaction, during which they secrete contents that further promote aggregation and inhibit the naturally anticoagulant endothelial cell factors. During platelet aggregation (platelet-platelet interaction), additional platelets are recruited from the circulation to the site of vascular injury, leading to the formation of an occlusive platelet thrombus. The platelet plug is anchored and stabilized by the developing fibrin mesh.

The platelet glycoprotein (Gp) IIb/IIIa ($\alpha_{IIb}\beta_3$) complex is the most abundant receptor on the platelet surface. Platelet activation converts the normally inactive Gp IIb/IIIa receptor into an active receptor, enabling binding to fibrinogen and VWF. Because the surface of each platelet has about 50,000 Gp IIb/IIIa–binding sites, numerous activated platelets recruited to the site of vascular injury can rapidly form an occlusive aggregate by means of a dense network of intercellular fibrinogen bridges. Because this receptor is the key mediator of platelet aggregation, it has become an effective target for antiplatelet therapy.

FIBRIN CLOT FORMATION

Plasma coagulation proteins (clotting factors) normally circulate in plasma in their inactive forms. The sequence of coagulation protein reactions that culminate in the formation of fibrin was originally described as a waterfall or a cascade. Two pathways of blood coagulation have been described in the past: the so-called extrinsic, or tissue factor, pathway and the so-called intrinsic, or contact activation, pathway. We now know that coagulation is normally initiated through tissue factor (TF) exposure and activation through the classic extrinsic pathway but with critically important amplification through elements of the classic intrinsic pathway, as illustrated in **Fig. 3-1**. These reactions take place on phospholipid surfaces, usually the activated platelet surface. Coagulation testing in the laboratory can reflect other

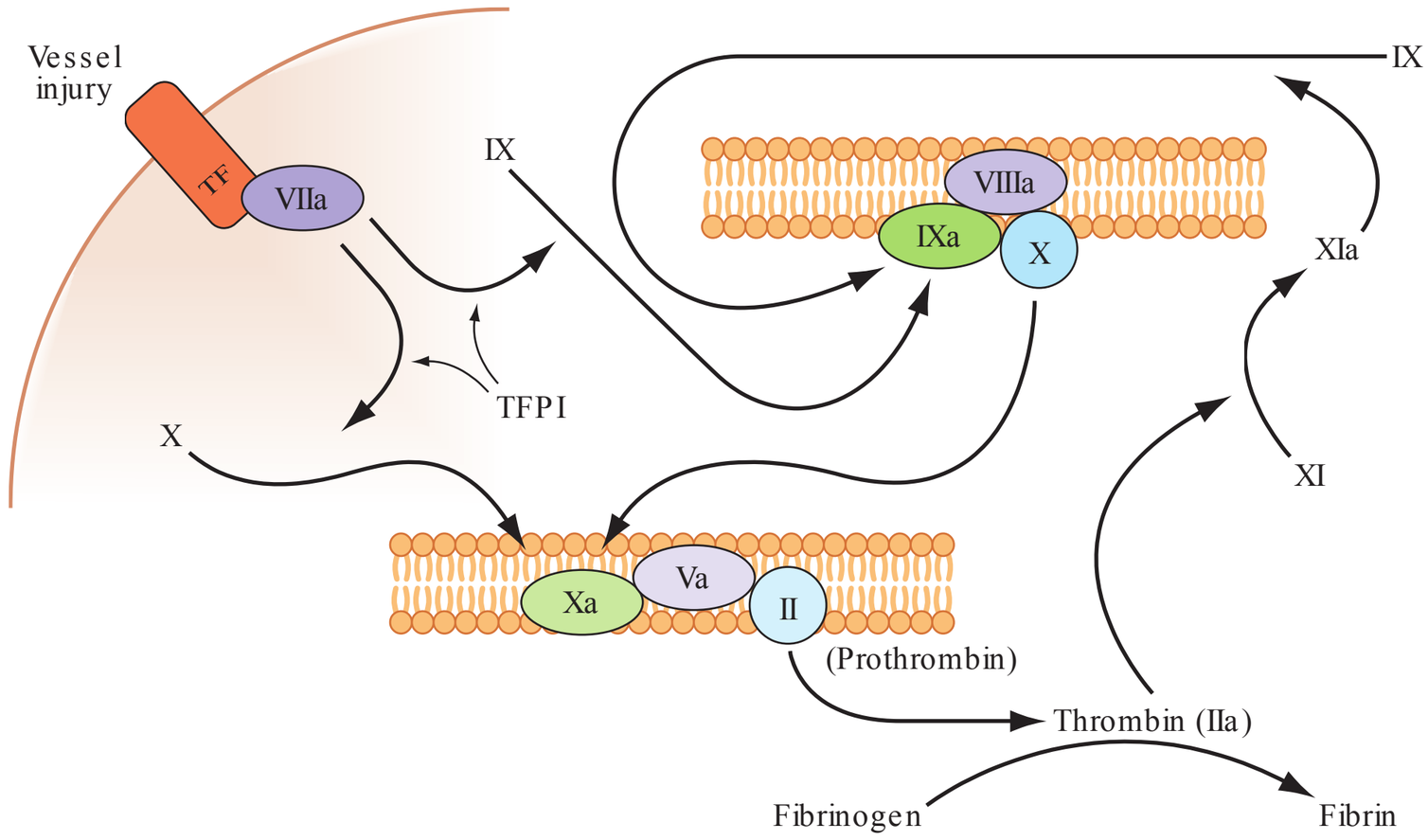


FIGURE 3-1
Coagulation is initiated by tissue factor (TF) exposure, which, with factor (F) VIIa, activates FIX and FX, which in turn, with FVIII and FV as cofactors, respectively, results in thrombin formation and subsequent conversion of fibrinogen to fibrin. Thrombin activates FXI, FVIII, and FV, amplifying the coagulation signal. Once the TF/FVIIa/FXa complex is formed, tissue factor pathway inhibitor (TFPI) inhibits the TF/FVIIa pathway, making coagulation dependent on the amplification loop through FIX/FVIII. Coagulation requires calcium (not shown) and takes place on phospholipid surfaces, usually the activated platelet membrane.

influences due to the artificial nature of the in vitro systems used (see below).

The immediate trigger for coagulation is vascular damage that exposes blood to TF that is constitutively expressed on the surfaces of subendothelial cellular components of the vessel wall, such as smooth muscle cells and fibroblasts. TF is also present in circulating microparticles, presumably shed from cells including monocytes and platelets. TF binds the serine protease factor VIIa; the complex activates factor X to factor Xa. Alternatively, the complex can indirectly activate factor X by initially converting factor IX to factor IXa, which then activates factor X. The participation of factor XI in hemostasis is not dependent on its activation by factor XIIa but rather on its positive feedback activation by thrombin. Thus, factor XIa functions in the propagation and amplification, rather than in the initiation, of the coagulation cascade.

Factor Xa can be formed through the actions of either the TF/factor VIIa complex or factor IXa (with factor VIIIa as a cofactor) and converts prothrombin to thrombin, the pivotal protease of the coagulation system. The essential cofactor for this reaction is factor Va. Like the homologous factor VIIIa, factor Va is produced by thrombin-induced limited proteolysis of factor V. Thrombin is a multifunctional enzyme that converts soluble plasma fibrinogen to an insoluble fibrin matrix. Fibrin polymerization involves an orderly process of intermolecular associations **(Fig. 3-2)**. Thrombin also activates factor XIII (fibrin-stabilizing factor) to factor

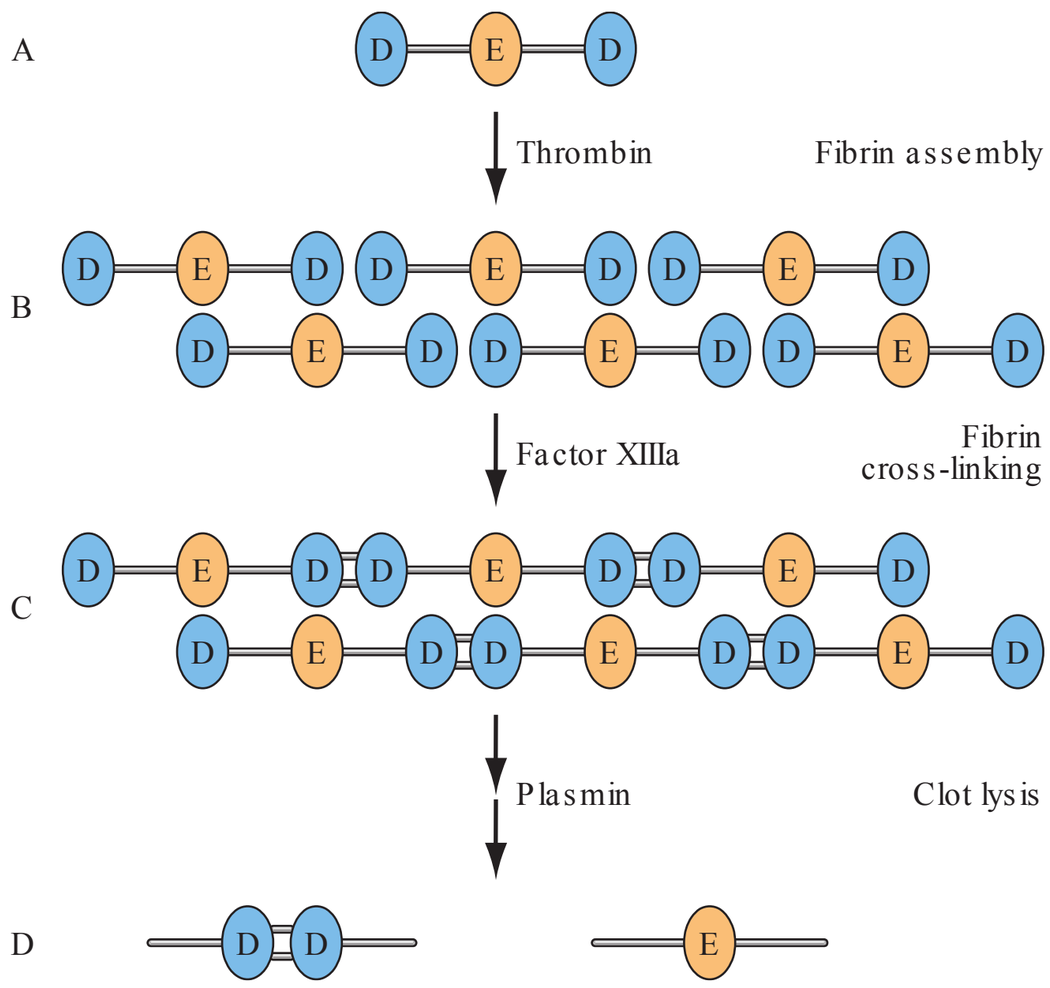


FIGURE 3-2
Fibrin formation and dissolution. A Fibrinogen is a trinodular structure consisting of two D domains and one E domain. Thrombin activation results in an ordered lateral assembly of protofibrils B with noncovalent associations. Factor XIIIa cross-links the D domains on adjacent molecules C. Fibrin and fibrinogen (not shown) lysis by plasmin occurs at discrete sites and results in intermediary fibrin(ogen) degradation products (not shown). d-Dimers are the product of complete lysis of fibrin D, maintaining the cross-linked D domains.

XIIIa, which covalently cross-links and thereby stabilizes the fibrin clot.

The assembly of the clotting factors on activated cell membrane surfaces greatly accelerates their reaction rates and also serves to localize blood clotting to sites of vascular injury. The critical cell membrane components, acidic phospholipids, are not normally exposed on resting cell membrane surfaces. However, when platelets, monocytes, and endothelial cells are activated by vascular injury or inflammatory stimuli, the procoagulant head groups of the membrane anionic phospholipids become translocated to the surfaces of these cells or released as part of microparticles, making them available to support and promote the plasma coagulation reactions.

ANTITHROMBOTIC MECHANISMS

Several physiologic antithrombotic mechanisms act in concert to prevent clotting under normal circumstances. These mechanisms operate to preserve blood fluidity and to limit blood clotting to specific focal sites of vascular injury. Endothelial cells have many antithrombotic effects. They produce prostacyclin, nitric oxide, and ectoADPase/CD39, which act to inhibit platelet binding, secretion, and aggregation. Endothelial cells produce anticoagulant factors including heparan proteoglycans, antithrombin, TF pathway inhibitor, and thrombomodulin. They also activate fibrinolytic mechanisms through the production of tissue plasminogen activator 1, urokinase, plasminogen activator inhibitor, and annexin-2. The sites of action of the major physiologic antithrombotic pathways are shown in **Fig. 3-3**.

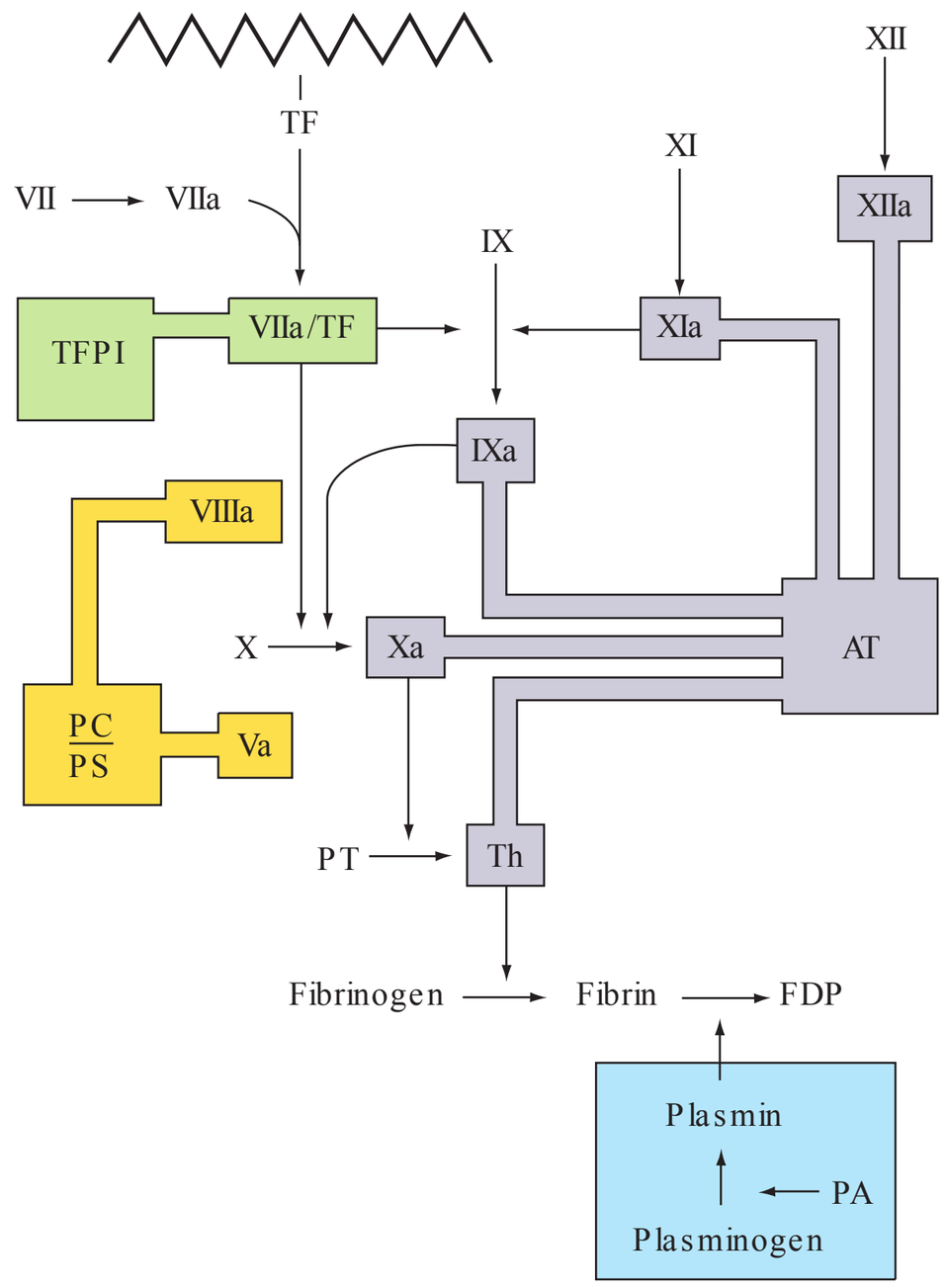


FIGURE 3-3
Sites of action of the four major physiologic antithrombotic pathways: antithrombin (AT); protein C/S (PC/PS); tissue factor pathway inhibitor (TFPI); and the fibrinolytic system, consisting of plasminogen, plasminogen activator (PA), and plasmin. PT, prothrombin; Th, thrombin; FDP, fibrin(ogen) degradation products. (Modified from BA Konkle, AI Schafer, in DP Zipes et al [eds]: Braunwald's Heart Disease, 7th ed. Philadelphia, Saunders, 2005.)

Antithrombin (or antithrombin III) is the major plasma protease inhibitor of thrombin and the other clotting factors in coagulation. Antithrombin neutralizes thrombin and other activated coagulation factors by forming a complex between the active site of the enzyme and the reactive center of antithrombin. The rate of formation of these inactivating complexes increases by a factor of several thousand in the presence of heparin. Antithrombin inactivation of thrombin and other activated clotting factors occurs physiologically on vascular surfaces, where glycosoaminoglycans, including heparan sulfates, are present to catalyze these reactions. Inherited quantitative or qualitative deficiencies of antithrombin lead to a lifelong predisposition to venous thromboembolism.

Protein C is a plasma glycoprotein that becomes an anticoagulant when it is activated by thrombin. The thrombin-induced activation of protein C occurs physiologically on thrombomodulin, a transmembrane proteoglycan-binding site for thrombin on endothelial cell surfaces. The binding of protein C to its receptor on endothelial cells places it in proximity to the thrombin-thrombomodulin complex, thereby enhancing its activation efficiency. Activated protein C acts as an anticoagulant by cleaving and inactivating activated factors V and VIII. This reaction is accelerated by a cofactor, protein S, which, like protein C, is a glycoprotein that undergoes vitamin K–dependent posttranslational modification. Quantitative or qualitative deficiencies of protein C or protein S, or resistance to the action of activated protein C by a specific mutation at its target cleavage site in factor Va (factor V Leiden), lead to hypercoagulable states.

Tissue factor pathway inhibitor (TFPI) is a plasma protease inhibitor that regulates the TF-induced extrinsic pathway of coagulation. TFPI inhibits the TF/factor VIIa/factor Xa complex, essentially turning of the TF/factor VIIa initiation of coagulation, which then becomes dependent on the "amplification loop" via factor XI and factor VIII activation by thrombin. TFPI is bound to lipoprotein and can also be released by heparin from endothelial cells, where it

is bound to glycosaminoglycans, and from platelets. The heparin-mediated release of TFPI may play a role in the anticoagulant effects of unfractionated and low-molecular-weight heparins.

THE FIBRINOLYTIC SYSTEM

Any thrombin that escapes the inhibitory effects of the physiologic anticoagulant systems is available to convert fibrinogen to fibrin. In response, the endogenous fibrinolytic system is then activated to dispose of intravascular fibrin and thereby maintain or reestablish the patency of the circulation. Just as thrombin is the key protease enzyme of the coagulation system, plasmin is the major protease enzyme of the fibrinolytic system, acting to digest fibrin to fibrin degradation products. The general scheme of fibrinolysis and its control is shown in **Fig. 3-4**.

The plasminogen activators, tissue type plasminogen activator (tPA) and the urokinase-type plasminogen activator (uPA), cleave the Arg560-Val561 bond of plasminogen to generate the active enzyme plasmin. The lysine-binding sites of plasmin (and plasminogen) permit it to bind to fibrin, so that physiologic fibrinolysis is "fibrin specific." Both plasminogen (through its lysine-binding sites) and tPA possess specific affinity for fibrin and thereby bind selectively to clots. The assembly of a ternary complex, consisting of fibrin, plasminogen, and tPA, promotes the localized interaction between plasminogen and tPA and greatly accelerates the rate of plasminogen activation to plasmin. Moreover, partial degradation of fibrin by plasmin exposes new plasminogen and tPA-binding sites in carboxy-terminus lysine residues of fibrin fragments to enhance these reactions further. This creates a highly efficient mechanism to generate plasmin focally on the fibrin clot, which then becomes plasmin's substrate for digestion to fibrin degradation products.

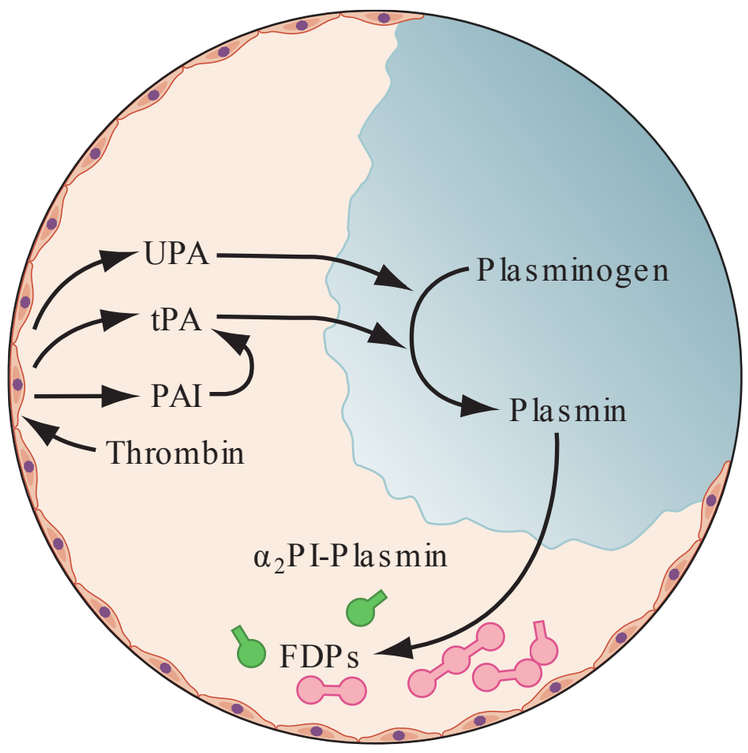


FIGURE 3-4
A schematic diagram of the fibrinolytic system. Tissue plasminogen activator (tPA) is released from endothelial cells, binds the fibrin clot, and activates plasminogen to plasmin. Excess fibrin is degraded by plasmin to distinct degradation products (FDPs). Any free plasmin is complexed with α_2-antiplasmin (α_2PI). PAI, plasminogen activator inhibitor; UPA, urokinase-type plasminogen activator.

Plasmin cleaves fibrin at distinct sites of the fibrin molecule, leading to the generation of characteristic fibrin fragments during the process of fibrinolysis (Fig. 3-2). The sites of plasmin cleavage of fibrin are the same as those in fibrinogen. However, when plasmin acts on covalently cross-linked fibrin, d-dimers are released; hence, d-dimers can be measured in plasma as a relatively specific test of fibrin (rather than fibrinogen) degradation. d-Dimer assays can be used as sensitive markers of blood clot formation and have been validated for clinical use to exclude the diagnosis of deep venous thrombosis (DVT) and pulmonary embolism in selected populations. In addition, d-dimer measurement can be used to stratify patients, particularly women, for risk of recurrent venous thromboembolism (VTE) when measured 1 month after discontinuation of anticoagulation given for treatment of an initial idiopathic event. d-Dimer levels may be elevated in the absence of VTE in elderly people.

Physiologic regulation of fibrinolysis occurs primarily at three levels: (1) plasminogen activator inhibitors (PAIs), specifically PAI-1 and PAI-2, inhibit the physiologic plasminogen activators; (2) the thrombin-activatable fibrinolysis inhibitor (TAFI) limits fibrinolysis; and (3) α_2-antiplasmin inhibits plasmin. PAI-1 is the primary inhibitor of tPA and uPA in plasma. TAFI cleaves the N-terminal lysine residues of fibrin, which aid in localization of plasmin activity. α_2-Antiplasmin is the main inhibitor of plasmin in human plasma, inactivating any nonfibrin clot-associated plasmin.

APPROACH TO THE PATIENT: Bleeding and Thrombosis

CLINICAL PRESENTATION Disorders of hemostasis may be either inherited or acquired. A detailed personal and family history is key in determining the chronicity of symptoms and the likelihood of the disorder being inherited, as well as providing clues to underlying conditions that have contributed to the bleeding or thrombotic state. In addition, the history can give clues as to the etiology by determining (1) the bleeding (mucosal and/or joint) or thrombosis (arterial and/or venous) site and (2) whether an underlying bleeding or clotting tendency was enhanced by another medical condition or the introduction of medications or dietary supplements.

History of Bleeding A history of bleeding is the most important predictor of bleeding risk. In evaluating a patient for a bleeding disorder, a history of at-risk situations, including the response to past surgeries, should be assessed. Does the patient have a history of spontaneous or trauma/surgery-induced bleeding? Spontaneous hemarthroses are a hallmark of moderate and severe factor VIII and IX deficiency and, in rare circumstances, of other clotting factor deficiencies. Mucosal bleeding symptoms are more suggestive of underlying platelet disorders or Von Willebrand disease (VWD), termed disorders of primary hemostasis or platelet plug formation. Disorders af ecting primary hemostasis are shown in **Table 3-1**.

A bleeding score has been validated as a tool to predict patients more likely to have type 1 VWD (International Society on T rombosis and Haemostasis Bleeding Assessment Tool [www.isth.org/resource/resmgr/ssc/isth-ssc_bleeding_assessment.pdf]). T is is most useful tool in excluding the diagnosis of a bleeding disorder, and thus avoiding unnecessary testing. One study found that a low bleeding score (≤3) and a normal activated partial thromboplastin time (aPTT) had 99.6% negative predictive value for the diagnosis of VWD. Bleeding symptoms that appear to be more common in patients with bleeding disorders include prolonged bleeding with surgery, dental procedures and extractions, and/or trauma, menorrhagia or postpartum hemorrhage, and large bruises (often described with lumps).

TABLE 3-1

PRIMARY HEMOSTATIC (PLATELET PLUG) DISORDERS
Defects of Platelet Adhesion
Von Willebrand disease
Bernard-Soulier syndrome (absence or dysfunction of platelet Gp Ib-IX-V)
Defects of Platelet Aggregation
Glanzmann's thrombasthenia (absence or dysfunction of platelet glycoprotein [Gp] IIb/IIIa)
Afibrinogenemia
Defects of Platelet Secretion
Decreased cyclooxygenase activity
Drug-induced (aspirin, nonsteroidal anti-inflammatory agents, thienopyridines)
Inherited
Granule storage pool defects
Inherited
Acquired
Nonspecific inherited secretory defects
Nonspecific drug ef ects
Uremia
Platelet coating (e.g., paraprotein, penicillin)
Defect of Platelet Coagulant Activity
Scott's syndrome

Easy bruising and menorrhagia are common complaints in patients with and without bleeding disorders. Easy bruising can also be a sign of medical conditions in which there is no identifiable coagulopathy; instead, the conditions are caused by an abnormality of blood vessels or their supporting tissues. In Ehlers-Danlos syndrome, there may be posttraumatic bleeding and a history of joint hyperextensibility. Cushing's syndrome, chronic steroid use, and aging result in changes in skin and subcutaneous tissue, and subcutaneous bleeding occurs in response to minor trauma. T e latter has been termed senile purpura.

Epistaxis is a common symptom, particularly in children and in dry climates, and may not reflect an underlying bleeding disorder. However, it is the most common symptom in hereditary hemorrhagic telangiectasia and in boys with VWD. Clues that epistaxis is a symptom of an underlying bleeding disorder include lack of seasonal variation and bleeding that requires medical evaluation or treatment, including cauterization. Bleeding with eruption of primary teeth is seen in children with more severe bleeding disorders, such as moderate and severe hemophilia. It is uncommon in children with mild bleeding disorders. Patients with disorders of primary hemostasis (platelet adhesion) may have increased bleeding after dental cleanings and other procedures that involve gum manipulation.

Menorrhagia is defined quantitatively as a loss of >80 mL of blood per cycle, based on the quantity of blood loss required to produce iron-deficiency anemia. A complaint of heavy menses is subjective and has a poor correlation with excessive blood loss. Predictors of menorrhagia include bleeding resulting in iron-deficiency anemia or a need for blood transfusion, passage of clots >1 inch in diameter, and changing a pad or tampon more than hourly. Menorrhagia is a common symptom in women with underlying bleeding disorders and is reported in the majority of women with VWD, women with factor XI deficiency, and symptomatic carriers of hemophilia. Women with underlying bleeding disorders are more likely to have other bleeding symptoms, including bleeding after dental extractions, postoperative bleeding, and postpartum bleeding, and are much more likely to have menorrhagia beginning at menarche than women with menorrhagia due to other causes.

Postpartum hemorrhage (PPH) is a common symptom in women with underlying bleeding disorders. In women with type 1 VWD and symptomatic carriers of hemophilia A in whom levels of VWF and factor VIII usually normalize during pregnancy, PPH may be delayed. Women with a history of PPH have a high risk of recurrence with subsequent pregnancies. Rupture of ovarian cysts with intraabdominal hemorrhage has also been reported in women with underlying bleeding disorders.

Tonsillectomy is a major hemostatic challenge, because intact hemostatic mechanisms are essential to prevent

excessive bleeding from the tonsillar bed. Bleeding may occur early after surgery or after approximately 7 days postoperatively, with loss of the eschar at the operative site. Similar delayed bleeding is seen after colonic polyp resection. Gastrointestinal (GI) bleeding and hematuria are usually due to underlying pathology, and procedures to identify and treat the bleeding site should be undertaken, even in patients with known bleeding disorders. VWD, particularly types 2 and 3, has been associated with angiodysplasia of the bowel and GI bleeding.

Hemarthroses and spontaneous muscle hematomas are characteristic of moderate or severe congenital factor VIII or IX deficiency. T ey can also be seen in moderate and severe deficiencies of fibrinogen, prothrombin, and factors V, VII, and X. Spontaneous hemarthroses occur rarely in other bleeding disorders except for severe VWD, with associated factor VIII levels <5%. Muscle and soft tissue bleeds are also common in acquired factor VIII deficiency. Bleeding into a joint results in severe pain and swelling, as well as loss of function, but is rarely associated with discoloration from bruising around the joint. Life-threatening sites of bleeding include bleeding into the oropharynx, where bleeding can obstruct the airway, into the central nervous system, and into the retroperitoneum. Central nervous system bleeding is the major cause of bleeding-related deaths in patients with severe congenital factor deficiencies.

Prohemorrhagic Effects of Medications and Dietary Supplements Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase 1 impair primary hemostasis and may exacerbate bleeding from another cause or even unmask a previously occult mild bleeding disorder such as VWD. All NSAIDs, however, can precipitate GI bleeding, which may be more severe in patients with underlying bleeding disorders. The aspirin effect on platelet function as assessed by aggregometry can persist for up to 7 days, although it has frequently returned to normal by 3 days after the last dose. The effect of other NSAIDs is shorter, as the inhibitor effect is reversed when the drug is removed. Thienopyridines (clopidogrel and prasugrel) inhibit ADP-mediated platelet aggregation and, like NSAIDs, can precipitate or exacerbate bleeding symptoms.

Many herbal supplements can impair hemostatic function **(Table 3-2)**. Some are more convincingly associated with a bleeding risk than others. Fish oil or concentrated omega-3 fatty acid supplements impair platelet function. T ey alter platelet biochemistry to produce more PGI_3, a more potent platelet inhibitor than prostacyclin (PGI_2), and more thromboxane A_3, a less potent platelet activator than thromboxane A_2. In fact, diets naturally rich in omega-3 fatty acids can result in a prolonged bleeding time and abnormal platelet aggregation studies, but the actual associated bleeding risk is unclear. Vitamin E appears to inhibit protein kinase C–mediated platelet aggregation and nitric oxide production. In patients with unexplained bruising or bleeding, it is prudent to review any new medications or supplements and discontinue those that may be associated with bleeding.

TABLE 3-2

HERBAL SUPPLEMENTS ASSOCIATED WITH INCREASED BLEEDING

Herbs with Potential Antiplatelet Activity
Ginkgo (Ginkgo biloba L.)
Garlic (Allium sativum)
Bilberry (Vaccinium myrtillus)
Ginger (Gingiber of cinale)
Dong quai (Angelica sinensis)
Feverfew (Tanacetum parthenium)
Asian ginseng (Panax ginseng)
American ginseng (Panax quinque*f*olius)
Siberian ginseng/eleuthero (Eleutherococcus senticosus)
Turmeric (Circuma longa)
Meadowsweet (Filipendula ulmaria)
Willow (Salix spp.)
Coumarin-Containing Herbs
Motherwort (Leonurus cardiaca)
Chamomile (Matricaria recutita, Chamaemelum mobile)
Horse chestnut (Aesculus hippocastanum)
Red clover (Tri*f*olium pratense)
Fenugreek (Trigonella *f*oenum-graecum)

Underlying Systemic Diseases That Cause or Exacerbate a Bleeding Tendency Acquired bleeding disorders are commonly secondary to, or associated with, systemic disease. The clinical evaluation of a patient with a bleeding tendency must therefore include a thorough assessment for evidence of underlying disease. Bruising or mucosal bleeding may be the presenting complaint in liver disease, severe renal impairment, hypothyroidism, paraproteinemias or amyloidosis, and conditions causing bone marrow failure. All coagulation factors are synthesized in the liver, and hepatic failure results in combined factor deficiencies. This is often compounded by thrombocytopenia from splenomegaly due to portal hypertension. Coagulation factors II, VII, IX, and X and proteins C, S, and Z are dependent on vitamin K for posttranslational modification. Although vitamin K is required in both procoagulant and anticoagulant processes, the phenotype of vitamin K deficiency or the warfarin effect on coagulation is bleeding.

T e normal blood platelet count is 150,000–450,000/μL. T rombocytopenia results from decreased production, increased destruction, and/or sequestration. Although the bleeding risk varies somewhat by the reason for the thrombocytopenia, bleeding rarely occurs in isolated thrombocytopenia at counts <50,000/μL and usually not until <10,000–20,000/μL. Coexisting coagulopathies, as is seen in liver failure or disseminated coagulation; infection; platelet-inhibitory drugs; and underlying medical

conditions can all increase the risk of bleeding in the thrombocytopenic patient. Most procedures can be performed in patients with a platelet count of 50,000/μL. The level needed for major surgery will depend on the type of surgery and the patient's underlying medical state, although a count of approximately 80,000/μL is likely sufficient.

HISTORY OF THROMBOSIS The risk of thrombosis, like that of bleeding, is influenced by both genetic and environmental influences. The major risk factor for arterial thrombosis is atherosclerosis, whereas for venous thrombosis, the risk factors are immobility, surgery, underlying medical conditions such as malignancy, medications such as hormonal therapy, obesity, and genetic predispositions. Factors that increase risks for venous and for both venous and arterial thromboses are shown in **Table 3-3**.

The most important point in a history related to venous thrombosis is determining whether the thrombotic event was idiopathic (meaning there was no clear precipitating factor) or was a precipitated event. In patients without underlying malignancy, having an idiopathic event is the strongest predictor of recurrence of VTE. In patients who have a vague history of thrombosis, a history of being treated with warfarin suggests a past DVT. Age is an important risk factor for venous thrombosis—the risk of DVT increases per decade, with an approximate incidence of 1/100,000 per year in early childhood to 1/200 per year among octogenarians. Family history is helpful in determining if there is a genetic predisposition and how strong that predisposition appears to be. A genetic thrombophilia that confers a relatively small increased risk, such as being a heterozygote for the prothrombin G20210A or factor V Leiden mutation, may be a minor determinant of risk in an elderly individual undergoing a high-risk surgical procedure. As illustrated in **Fig. 3-5**, a thrombotic event usually has more than one contributing factor. Predisposing factors must be carefully assessed to determine the risk of recurrent thrombosis and, with consideration of the patient's bleeding risk, determine the length of anticoagulation. Similar consideration should be given in determining the need, if any, to test the patient and family members for thrombophilias.

LABORATORY EVALUATION Careful history taking and clinical examination are essential components in the assessment of bleeding and thrombotic risk. The use of laboratory

TABLE 3-3

RISK FACTORS FOR THROMBOSIS

VENOUS	VENOUS AND ARTERIAL
Inherited	**Inherited**
Factor V Leiden	Homocystinuria
Prothrombin G20210A	Dysfibrinogenemia
Antithrombin deficiency	**Mixed (inherited and acquired)**
Protein C deficiency	Hyperhomocysteinemia
Protein S deficiency	**Acquired**
Elevated factor VIII	Malignancy
Acquired	Antiphospholipid antibody syndrome
Age	Hormonal therapy
Previous thrombosis	Polycythemia vera
Immobilization	Essential thrombocythemia
Major surgery	Paroxysmal nocturnal hemoglobinuria
Pregnancy and puerperium	Thrombotic thrombocytopenic purpura
Hospitalization	Heparin-induced thrombocytopenia
Obesity	Disseminated intravascular coagulation
Infection	
APC resistance, nongenetic	
Smoking	
Unknown[a]	
Elevated factor II, IX, XI	
Elevated TAFI levels	
Low levels of TFPI	

[a]Unknown whether risk is inherited or acquired.

Abbreviations: APC, activated protein C; TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor.

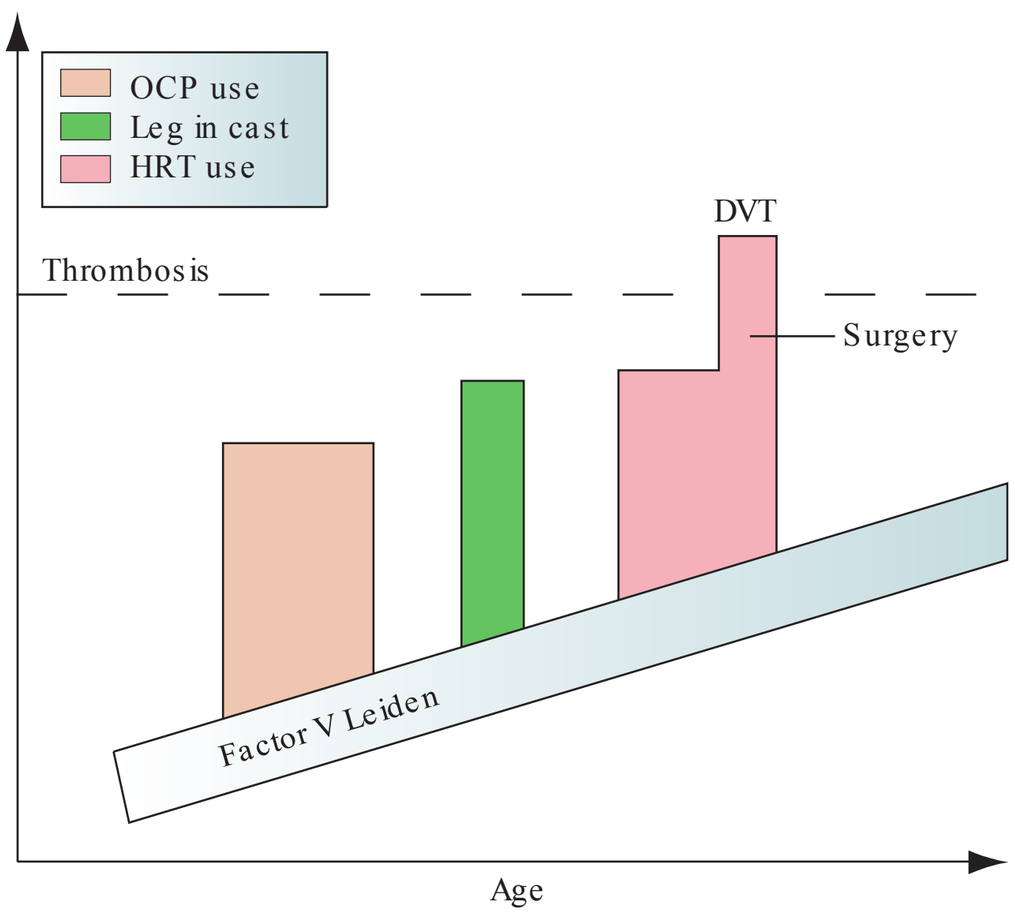


FIGURE 3-5

Thrombotic risk over time. Shown schematically is an individual's thrombotic risk over time. An underlying factor V Leiden mutation provides a "theoretically" constant increased risk. The thrombotic risk increases with age and, intermittently, with oral contraceptive (OCP) or hormone replacement therapy (HRT) use; other events may increase the risk further. At some point, the cumulative risk may increase to the threshold for thrombosis and result in deep venous thrombosis (DVT). Note: The magnitude and duration of risk portrayed in the figure are meant for example only and may not precisely reflect the relative risk determined by clinical study. (From BA Konkle, A Schafer, in DP Zipes et al [eds]: Braunwald's Heart Disease, 7th ed. Philadelphia, Saunders, 2005; modified with permission from FR Rosendaal: Venous thrombosis: A multicausal disease. Lancet 353:1167, 1999.)

tests of coagulation complement, but cannot substitute for, clinical assessment. No test exists that provides a global assessment of hemostasis. The bleeding time has been used to assess bleeding risk; however, it does not predict bleeding risk with surgery and it is not recommended for this indication. The PFA-100, an instrument that measures platelet-dependent coagulation under flow conditions, is more sensitive and specific for VWD than the bleeding time; however, it is not sensitive enough to rule out mild bleeding disorders. PFA-100 closure times are prolonged in patients with some, but not all, inherited platelet disorders. Also, its utility in predicting bleeding risk has not been determined.

For routine preoperative and preprocedure testing, an abnormal prothrombin time (PT) may detect liver disease or vitamin K deficiency that had not been previously appreciated. Studies have not confirmed the usefulness of an aPTT in preoperative evaluations in patients with a negative bleeding history. T e primary use of coagulation testing should be to confirm the presence and type of bleeding disorder in a patient with a suspicious clinical history.

Because of the nature of coagulation assays, proper sample acquisition and handling is critical to obtaining valid results. In patients with abnormal coagulation assays who have no bleeding history, repeat studies with attention to these factors frequently results in normal values. Most coagulation assays are performed in sodium citrate anticoagulated plasma that is recalcified for the assay. Because the anticoagulant is in liquid solution and needs to be added to blood in proportion to the plasma volume, incorrectly filled or inadequately mixed blood collection tubes will give erroneous results. Vacutainer tubes should be filled to >90% of the recommended fill, which is usually denoted by a line on the tube. An elevated hematocrit (>55%) can result in a false value due to a decreased plasma-to-anticoagulant ratio.

Screening Assays The most commonly used screening tests are the PT, aPTT, and platelet count. The PT assesses the factors I (fibrinogen), II (prothrombin), V, VII, and X **(Fig. 3-6)**. The PT measures the time for clot formation of the citrated plasma after recalcification and addition of thromboplastin, a mixture of TF and phospholipids. The sensitivity of the assay varies by the source of thromboplastin. The relationship between defects in secondary hemostasis (fibrin formation) and coagulation test abnormalities is shown in **Table 3-4**. To adjust for this variability, the overall sensitivity of different thromboplastins to reduction of the vitamin K–dependent clotting factors II, VII, IX, and X in anticoagulation patients is now expressed as the International Sensitivity Index (ISI). An inverse relationship exists between ISI and thromboplastin sensitivity. The international normalized ratio (INR) is then determined based on the formula: $INR = (PT_{patient}/PT_{normal\ mean})^{ISI}$.

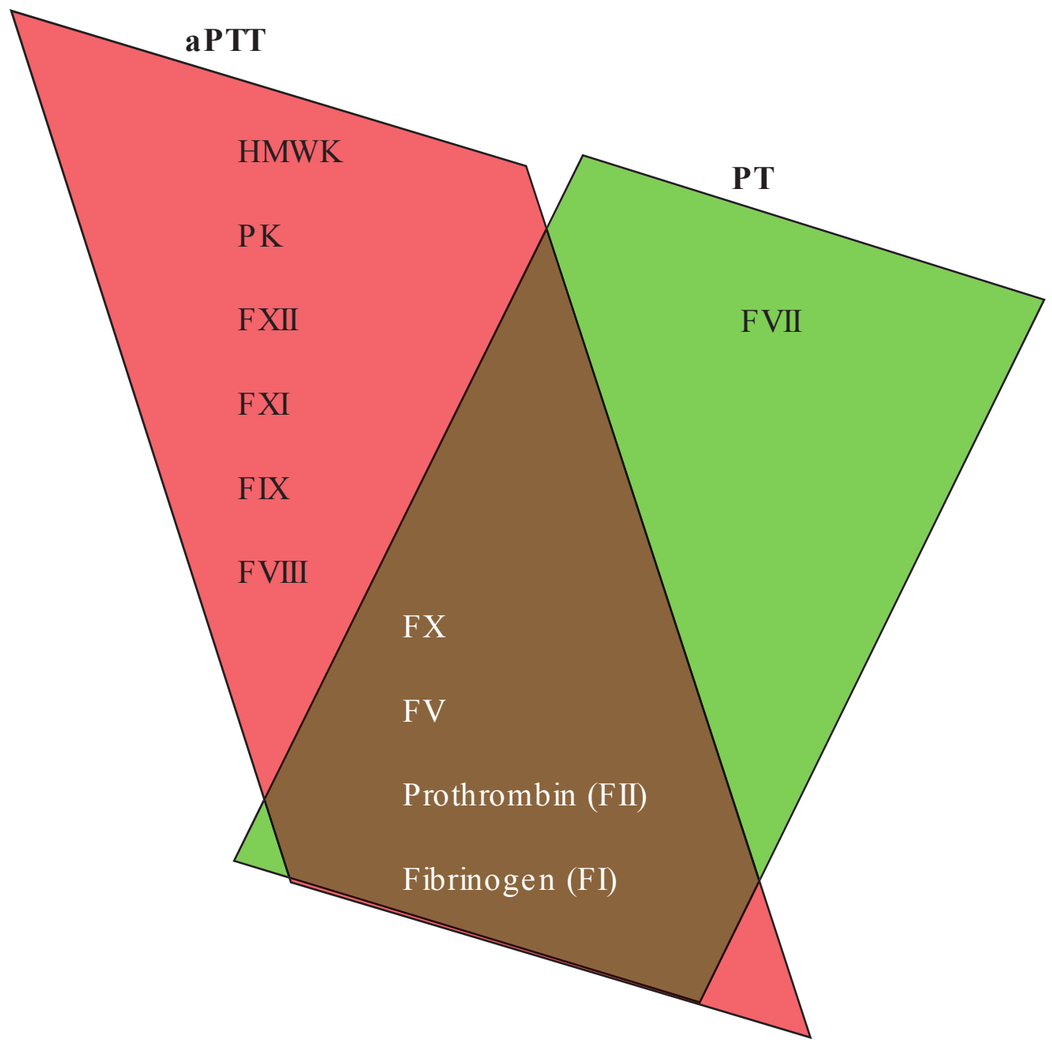


FIGURE 3-6
Coagulation factor activity tested in the activated partial thromboplastin time (aPTT) in red and prothrombin time (PT) in green, or both. F, factor; HMWK, high-molecular-weight kininogen; PK, prekallikrein.

T e INR was developed to assess stable anticoagulation due to reduction of vitamin K–dependent coagulation factors; it is commonly used in the evaluation of patients with liver disease. Although it does allow comparison between laboratories, reagent sensitivity as used to determine the ISI is not the same in liver disease as with warfarin anticoagulation. In addition, progressive liver failure is associated with variable changes in coagulation factors; the degree of prolongation of either the PT or the INR only roughly predicts the bleeding risk. T rombin generation has been shown to be normal in many patients with mild to moderate liver dysfunction. Because the PT only measures one aspect of hemostasis af ected by liver dysfunction, we likely overestimate the bleeding risk of a mildly elevated INR in this setting.

T e aPTT assesses the intrinsic and common coagulation pathways; factors XI, IX, VIII, X, V, and II; fibrinogen; prekallikrein; high-molecular-weight kininogen; and factor XII (Fig. 3-6). T e aPTT reagent contains phospholipids derived from either animal or vegetable sources that function as a platelet substitute in the coagulation pathways and includes an activator of the intrinsic coagulation system, such as nonparticulate ellagic acid or the particulate activators kaolin, celite, or micronized silica.

T e phospholipid composition of aPTT reagents varies, which influences the sensitivity of individual reagents to clotting factor deficiencies and to inhibitors such as heparin and lupus anticoagulants. T us, aPTT results will vary

TABLE 3-4

HEMOSTATIC DISORDERS AND COAGULATION TEST ABNORMALITIES
Prolonged Activated Partial Thromboplastin Time (aPTT)
No clinical bleeding—↓ factor XII, high-molecular-weight kininogen, prekallikrein
Variable, but usually mild, bleeding—↓ factor XI, mild ↓ factor VIII and factor IX
Frequent, severe bleeding—severe deficiencies of factors VIII and IX
Heparin and direct thrombin inhibitors
Prolonged Prothrombin Time (PT)
Factor VII deficiency
Vitamin K deficiency—early
Warfarin anticoagulation
Direct Xa inhibitors (rivaroxaban, apixaban)
Prolonged aPTT and PT
Factor II, V, X, or fibrinogen deficiency
Vitamin K deficiency—late
Direct thrombin inhibitors
Prolonged Thrombin Time
Heparin or heparin-like inhibitors
Direct thrombin inhibitors (e.g., dabigatran, argatroban, bivalirudin)
Mild or no bleeding—dysfibrinogenemia
Frequent, severe bleeding—afibrinogenemia
Prolonged PT and/or aPTT Not Corrected with Mixing with Normal Plasma
Bleeding—specific factor inhibitor
No symptoms, or clotting and/or pregnancy loss—lupus anticoagulant
Disseminated intravascular coagulation
Heparin or direct thrombin inhibitor
Abnormal Clot Solubility
Factor XIII deficiency
Inhibitors or defective cross-linking
Rapid Clot Lysis
Deficiency of α_2-antiplasmin or plasminogen activator inhibitor 1
Treatment with fibrinolytic therapy

from one laboratory to another, and the normal range in the laboratory where the testing occurs should be used in the interpretation. Local laboratories can relate their aPTT values to the therapeutic heparin anticoagulation by correlating aPTT values with direct measurements of heparin activity (anti-Xa or protamine titration assays) in samples from heparinized patients, although correlation between these assays is often poor. The aPTT reagent will vary in sensitivity to individual factor deficiencies and usually becomes prolonged with individual factor deficiencies of 30–50%.

Mixing Studies Mixing studies are used to evaluate a prolonged aPTT or, less commonly PT, to distinguish between a factor deficiency and an inhibitor. In this assay, normal plasma and patient plasma are mixed in a 1:1 ratio, and the aPTT or PT is determined immediately and after incubation at 37°C for varying times, typically 30, 60, and/or 120 min. With isolated factor deficiencies, the aPTT will correct with mixing and stay corrected with incubation. With aPTT prolongation due to a lupus anticoagulant, the mixing and incubation will show no correction. In acquired neutralizing factor antibodies, notably an acquired factor VIII inhibitor, the initial assay may or may not correct immediately after mixing but will prolong or remain prolonged with incubation at 37°C. Failure to correct with mixing can also be due to the presence of other inhibitors or interfering substances such as heparin, fibrin split products, and paraproteins.

Specific Factor Assays Decisions to proceed with specific clotting factor assays will be influenced by the clinical situation and the results of coagulation screening tests. Precise diagnosis and effective management of inherited and acquired coagulation deficiencies necessitate quantitation of the relevant factors. When bleeding is severe, specific assays are urgently required to guide appropriate therapy. Individual factor assays are usually performed as modifications of the mixing study, where the patient's plasma is mixed with plasma deficient in the factor being studied. This will correct all factor deficiencies to >50%, thus making prolongation of clot formation due to a factor deficiency dependent on the factor missing from the added plasma.

Testing for Antiphospholipid Antibodies Antibodies to phospholipids (cardiolipin) or phospholipid-binding proteins (β_2-microglobulin and others) are detected by enzyme-linked immunosorbent assay (ELISA). When these antibodies interfere with phospholipid-dependent coagulation tests, they are termed lupus anticoagulants. The aPTT has variability sensitivity to lupus anticoagulants, depending in part on the aPTT reagents used. An assay using a sensitive reagent has been termed an LA-PTT. The dilute Russell viper venom test (dRVVT) and the tissue thromboplastin inhibition (TTI) test are modifications of standard tests with the phospholipid reagent decreased, thus increasing the sensitivity to antibodies that interfere with the phospholipid component. The tests, however, are not specific for lupus anticoagulants, because factor deficiencies or other inhibitors will also result in prolongation. Documentation of a lupus anticoagulant requires not only prolongation of a phospholipid-dependent coagulation test but also lack of correction when mixed with normal plasma and correction with the addition of activated platelet membranes or certain phospholipids (e.g., hexagonal phase).

Other Coagulation Tests The thrombin time and the reptilase time measure fibrinogen conversion to fibrin and are prolonged when the fibrinogen level is low (usually <80–100 mg/dL) or qualitatively abnormal, as seen in

inherited or acquired dysfibrinogenemias, or when fibrin/fibrinogen degradation products interfere. The thrombin time, but not the reptilase time, is prolonged in the presence of heparin. The thrombin time is markedly prolonged in the presence of the direct thrombin inhibitor, dabigatran; a dilute thrombin time can be used to assess drug activity. Measurement of anti–factor Xa plasma inhibitory activity is a test frequently used to assess low-molecular-weight heparin (LMWH) levels, as a direct measurement of unfractionated heparin (UFH) activity, or to assess activity of the new direct Xa inhibitors rivaroxaban or apixaban. Drug in the patient sample inhibits the enzymatic conversion of an Xa-specific chromogenic substrate to colored product by factor Xa. Standard curves are created using multiple concentrations of drug and are used to calculate the concentration of anti-Xa activity in the patient plasma.

Laboratory Testing for Thrombophilia Laboratory assays to detect thrombophilic states include molecular diagnostics and immunologic and functional assays. These assays vary in their sensitivity and specificity for the condition being tested. Furthermore, acute thrombosis, acute illnesses, inflammatory conditions, pregnancy, and medications affect levels of many coagulation factors and their inhibitors. Antithrombin is decreased by heparin and in the setting of acute thrombosis. Protein C and S levels may be increased in the setting of acute thrombosis and are decreased by warfarin. Antiphospholipid antibodies are frequently transiently positive in acute illness. Testing for genetic thrombophilias should, in general, only be performed when there is a strong family history of thrombosis and results would affect clinical decision making.

Because thrombophilia evaluations are usually performed to assess the need to extend anticoagulation, testing should be performed in a steady state, remote from the acute event. In most instances, warfarin anticoagulation can be stopped after the initial 3–6 months of treatment, and testing can be performed at least 3 weeks later. As a sensitive marker of coagulation activation, the quantitative d-dimer assay, drawn 4 weeks after stopping anticoagulation, can be used to stratify risk of recurrent thrombosis in patients who have an idiopathic event.

Measures of Platelet Function The bleeding time has been used to assess bleeding risk; however, it has not been found to predict bleeding risk with surgery, and it is not recommended for use for this indication. The PFA-100 and similar instruments that measure platelet-dependent coagulation under flow conditions are generally more sensitive and specific for platelet disorders and VWD than the bleeding time; however, data are insufficient to support their use to predict bleeding risk or monitor response to therapy, and they will be normal in some patients with platelet disorders or mild VWD. When they are used in the evaluation of a patient with bleeding symptoms, abnormal results, as with the bleeding time, require specific testing, such as VWF assays and/or platelet aggregation studies. Because all of these "screening" assays may miss patients with mild bleeding disorders, further studies are needed to define their role in hemostasis testing.

For classic platelet aggregometry, various agonists are added to the patient's platelet-rich plasma and platelet aggregation is measured. Tests of platelet secretion in response to agonists can also be measured. These tests are affected by many factors, including numerous medications, and the association between minor defects in aggregation or secretion in these assays and bleeding risk is not clearly established.

Acknowledgment

Robert I. Handin, MD, contributed this chapter in the 16th edition, and some material from that chapter has been retained here.

CHAPTER 4

ENLARGEMENT OF LYMPH NODES AND SPLEEN

Patrick H. Henry ■ Dan L. Longo

This chapter is intended to serve as a guide to the evaluation of patients who present with enlargement of the lymph nodes (lymphadenopathy) or the spleen (splenomegaly). Lymphadenopathy is a rather common clinical finding in primary care settings, whereas palpable splenomegaly is less so.

LYMPHADENOPATHY

Lymphadenopathy may be an incidental finding in patients being examined for various reasons, or it may be a presenting sign or symptom of the patient's illness. The physician must eventually decide whether the lymphadenopathy is a normal finding or one that requires further study, up to and including biopsy. Soft, flat, submandibular nodes (<1 cm) are often palpable in healthy children and young adults; healthy adults may have palpable inguinal nodes of up to 2 cm, which are considered normal. Further evaluation of these normal nodes is not warranted. In contrast, if the physician believes the node(s) to be abnormal, then pursuit of a more precise diagnosis is needed.

APPROACH TO THE PATIENT: Lymphadenopathy

Lymphadenopathy may be a primary or secondary manifestation of numerous disorders, as shown in **Table 4-1**. Many of these disorders are infrequent causes of lymphadenopathy. In primary care practice, more than two-thirds of patients with lymphadenopathy have nonspecific causes or upper respiratory illnesses (viral or bacterial), and <1% have a malignancy. In one study, 84% of patients referred for evaluation of lymphadenopathy had a "benign" diagnosis. The remaining 16% had a malignancy (lymphoma or metastatic adenocarcinoma). Of the patients with benign lymphadenopathy, 63% had a nonspecific or reactive etiology (no causative agent found), and the remainder had a specific cause demonstrated, most commonly infectious mononucleosis, toxoplasmosis, or tuberculosis. Thus, the vast majority of patients with lymphadenopathy will have a nonspecific etiology requiring few diagnostic tests.

CLINICAL ASSESSMENT The physician will be aided in the pursuit of an explanation for the lymphadenopathy by a careful medical history, physical examination, selected laboratory tests, and perhaps an excisional lymph node biopsy.

The medical history should reveal the setting in which lymphadenopathy is occurring. Symptoms such as sore throat, cough, fever, night sweats, fatigue, weight loss, or pain in the nodes should be sought. The patient's age, sex, occupation, exposure to pets, sexual behavior, and use of drugs such as diphenylhydantoin are other important historic points. For example, children and young adults usually have benign (i.e., nonmalignant) disorders that account for the observed lymphadenopathy such as viral or bacterial upper respiratory infections; infectious mononucleosis; toxoplasmosis; and, in some countries, tuberculosis. In contrast, after age 50, the incidence of malignant disorders increases and that of benign disorders decreases.

The physical examination can provide useful clues such as the extent of lymphadenopathy (localized or generalized), size of nodes, texture, presence or absence of nodal tenderness, signs of inflammation over the node, skin lesions, and splenomegaly. A thorough ear, nose, and throat (ENT) examination is indicated in adult patients with cervical adenopathy and a history of tobacco use. Localized or regional adenopathy implies involvement of a single anatomic area. Generalized adenopathy has been defined as involvement of three or more noncontiguous lymph node areas. Many of the causes of lymphadenopathy (Table 4-1) can produce localized or generalized adenopathy, so this distinction is of limited utility in the differential diagnosis. Nevertheless, generalized lymphadenopathy is frequently associated with nonmalignant disorders such as infectious mononucleosis (Epstein-Barr

TABLE 4-1

DISEASES ASSOCIATED WITH LYMPHADENOPATHY

1. Infectious diseases
   a. Viral—infectious mononucleosis syndromes (EBV, CMV), infectious hepatitis, herpes simplex, herpesvirus-6, varicella-zoster virus, rubella, measles, adenovirus, HIV, epidemic keratoconjunctivitis, vaccinia, herpesvirus-8
   b. Bacterial—streptococci, staphylococci, cat-scratch disease, brucellosis, tularemia, plague, chancroid, melioidosis, glanders, tuberculosis, atypical mycobacterial infection, primary and secondary syphilis, diphtheria, leprosy, Bartonella
   c. Fungal—histoplasmosis, coccidioidomycosis, paracoccidioidomycosis
   d. Chlamydial—lymphogranuloma venereum, trachoma
   e. Parasitic—toxoplasmosis, leishmaniasis, trypanosomiasis, filariasis
   f. Rickettsial—scrub typhus, rickettsialpox, Q fever
2. Immunologic diseases
   a. Rheumatoid arthritis
   b. Juvenile rheumatoid arthritis
   c. Mixed connective tissue disease
   d. Systemic lupus erythematosus
   e. Dermatomyositis
   f. Sjögren's syndrome
   g. Serum sickness
   h. Drug hypersensitivity—diphenylhydantoin, hydralazine, allopurinol, primidone, gold, carbamazepine, etc.
   i. Angioimmunoblastic lymphadenopathy
   j. Primary biliary cirrhosis
   k. Graft-versus-host disease
   l. Silicone-associated
   m. Autoimmune lymphoproliferative syndrome
   n. IgG4-related disease
   o. Immune reconstitution inflammatory syndrome (IRIS)
3. Malignant diseases
   a. Hematologic—Hodgkin's disease, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, hairy cell leukemia, malignant histiocytosis, amyloidosis
   b. Metastatic—from numerous primary sites
4. Lipid storage diseases—Gaucher's, Niemann-Pick, Fabry, Tangier
5. Endocrine diseases—hyperthyroidism
6. Other disorders
   a. Castleman's disease (giant lymph node hyperplasia)
   b. Sarcoidosis
   c. Dermatopathic lymphadenitis
   d. Lymphomatoid granulomatosis
   e. Histiocytic necrotizing lymphadenitis (Kikuchi's disease)
   f. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)
   g. Mucocutaneous lymph node syndrome (Kawasaki's disease)
   h. Histiocytosis X
   i. Familial Mediterranean fever
   j. Severe hypertriglyceridemia
   k. Vascular transformation of sinuses
   l. Inflammatory pseudotumor of lymph node
   m. Congestive heart failure

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus.

virus [EBV] or cytomegalovirus [CMV]), toxoplasmosis, AIDS, other viral infections, systemic lupus erythematosus (SLE), and mixed connective tissue disease. Acute and chronic lymphocytic leukemias and malignant lymphomas also produce generalized adenopathy in adults.

The site of localized or regional adenopathy may provide a useful clue about the cause. Occipital adenopathy often reflects an infection of the scalp, and preauricular adenopathy accompanies conjunctival infections and cat-scratch disease. The most frequent site of regional adenopathy is the neck, and most of the causes are benign—upper respiratory infections, oral and dental lesions, infectious mononucleosis, or other viral illnesses. The chief malignant causes include metastatic cancer from head and neck, breast, lung, and thyroid primaries. Enlargement of supraclavicular and scalene nodes is always abnormal. Because these nodes drain regions of the lung and retroperitoneal space, they can reflect lymphomas, other cancers, or infectious processes arising in these areas. Virchow's node is an enlarged left supraclavicular node infiltrated with metastatic cancer from a gastrointestinal primary. Metastases to supraclavicular nodes also occur from lung, breast, testis, or ovarian cancers. Tuberculosis, sarcoidosis, and toxoplasmosis are nonneoplastic causes of supraclavicular adenopathy. Axillary adenopathy is usually due to injuries or localized infections of the ipsilateral upper extremity. Malignant causes include melanoma or lymphoma and, in women, breast cancer. Inguinal lymphadenopathy is usually secondary to infections or trauma of the lower extremities and may accompany sexually transmitted diseases such as lymphogranuloma venereum, primary syphilis, genital herpes, or chancroid. These nodes may also be involved by lymphomas and metastatic cancer from primary lesions of the rectum, genitalia, or lower extremities (melanoma).

The size and texture of the lymph node(s) and the presence of pain are useful parameters in evaluating a patient with lymphadenopathy. Nodes <1.0 cm^2 in area (1.0 cm × 1.0 cm or less) are almost always secondary to benign, nonspecific reactive causes. In one retrospective analysis of younger patients (9–25 years) who had a lymph node biopsy, a maximum diameter of >2 cm served as one discriminant for predicting that the biopsy would reveal malignant or granulomatous disease. Another study showed that a lymph node size of 2.25 cm^2 (1.5 cm × 1.5 cm) was the best size limit for distinguishing malignant or granulomatous lymphadenopathy from other causes of lymphadenopathy. Patients with node(s) ≤ 1.0 cm^2 should be observed after excluding infectious mononucleosis and/or toxoplasmosis unless there are symptoms and signs of an underlying systemic illness.

The texture of lymph nodes may be described as soft, firm, rubbery, hard, discrete, matted, tender, movable, or fixed. Tenderness is found when the capsule is stretched during rapid enlargement, usually secondary to an inflammatory process. Some malignant diseases such as acute

leukemia may produce rapid enlargement and pain in the nodes. Nodes involved by lymphoma tend to be large, discrete, symmetric, rubbery, firm, mobile, and nontender. Nodes containing metastatic cancer are often hard, nontender, and nonmovable because of fixation to surrounding tissues. T e coexistence of splenomegaly in the patient with lymphadenopathy implies a systemic illness such as infectious mononucleosis, lymphoma, acute or chronic leukemia, SLE, sarcoidosis, toxoplasmosis, cat-scratch disease, or other less common hematologic disorders. T e patient's story should provide helpful clues about the underlying systemic illness.

Nonsuperficial presentations (thoracic or abdominal) of adenopathy are usually detected as the result of a symptom-directed diagnostic workup. T oracic adenopathy may be detected by routine chest radiography or during the workup for superficial adenopathy. It may also be found because the patient complains of a cough or wheezing from airway compression; hoarseness from recurrent laryngeal nerve involvement; dysphagia from esophageal compression; or swelling of the neck, face, or arms secondary to compression of the superior vena cava or subclavian vein. T e differential diagnosis of mediastinal and hilar adenopathy includes primary lung disorders and systemic illnesses that characteristically involve mediastinal or hilar nodes. In the young, mediastinal adenopathy is associated with infectious mononucleosis and sarcoidosis. In endemic regions, histoplasmosis can cause unilateral paratracheal lymph node involvement that mimics lymphoma. Tuberculosis can also cause unilateral adenopathy. In older patients, the differential diagnosis includes primary lung cancer (especially among smokers), lymphomas, metastatic carcinoma (usually lung), tuberculosis, fungal infection, and sarcoidosis.

Enlarged intraabdominal or retroperitoneal nodes are usually malignant. Although tuberculosis may present as mesenteric lymphadenitis, these masses usually contain lymphomas or, in young men, germ cell tumors.

LABORATORY INVESTIGATION The laboratory investigation of patients with lymphadenopathy must be tailored to elucidate the etiology suspected from the patient's history and physical findings. One study from a family practice clinic evaluated 249 younger patients with "enlarged lymph nodes, not infected" or "lymphadenitis." No laboratory studies were obtained in 51%. When studies were performed, the most common were a complete blood count (CBC) (33%), throat culture (16%), chest x-ray (12%), or monospot test (10%). Only eight patients (3%) had a node biopsy, and half of those were normal or reactive. The CBC can provide useful data for the diagnosis of acute or chronic leukemias, EBV or CMV mononucleosis, lymphoma with a leukemic component, pyogenic infections, or immune cytopenias in illnesses such as SLE. Serologic studies may demonstrate antibodies specific to components of EBV, CMV, HIV, and other viruses; Toxoplasma gondii; Brucella; and so on. If SLE is suspected, antinuclear and anti-DNA antibody studies are warranted.

T e chest x-ray is usually negative, but the presence of a pulmonary infiltrate or mediastinal lymphadenopathy would suggest tuberculosis, histoplasmosis, sarcoidosis, lymphoma, primary lung cancer, or metastatic cancer and demands further investigation.

A variety of imaging techniques (computed tomography [CT], magnetic resonance imaging [MRI], ultrasound, color Doppler ultrasonography) have been used to differentiate benign from malignant lymph nodes, especially in patients with head and neck cancer. CT and MRI are comparably accurate (65–90%) in the diagnosis of metastases to cervical lymph nodes. Ultrasonography has been used to determine the long axis, short axis, and a ratio of long to short (L/S) axis in cervical nodes. An L/S ratio of <2.0 has a sensitivity and a specificity of 95% for distinguishing benign and malignant nodes in patients with head and neck cancer. T is ratio has greater specificity and sensitivity than palpation or measurement of either the long or the short axis alone.

T e indications for lymph node biopsy are imprecise, yet it is a valuable diagnostic tool. T e decision to biopsy may be made early in a patient's evaluation or delayed for up to 2 weeks. Prompt biopsy should occur if the patient's history and physical findings suggest a malignancy; examples include a solitary, hard, nontender cervical node in an older patient who is a chronic user of tobacco; supraclavicular adenopathy; and solitary or generalized adenopathy that is firm, movable, and suggestive of lymphoma. If a primary head and neck cancer is suspected as the basis of a solitary, hard cervical node, then a careful ENT examination should be performed. Any mucosal lesion that is suspicious for a primary neoplastic process should be biopsied first. If no mucosal lesion is detected, an excisional biopsy of the largest node should be performed. Fine-needle aspiration should not be performed as the first diagnostic procedure. Most diagnoses require more tissue than such aspiration can provide, and it often delays a definitive diagnosis. Fine-needle aspiration should be reserved for thyroid nodules and for confirmation of relapse in patients whose primary diagnosis is known. If the primary physician is uncertain about whether to proceed to biopsy, consultation with a hematologist or medical oncologist should be helpful. In primary care practices, <5% of lymphadenopathy patients will require a biopsy. T at percentage will be considerably larger in referral practices, i.e., hematology, oncology, or ENT.

Two groups have reported algorithms that they claim will identify more precisely those lymphadenopathy patients who should have a biopsy. Both reports were retrospective analyses in referral practices. T e first study involved patients 9–25 years of age who had a node biopsy performed. T ree variables were identified that predicted

those young patients with peripheral lymphadenopathy who should undergo biopsy; lymph node size >2 cm in diameter and abnormal chest x-ray had positive predictive values, whereas recent ENT symptoms had negative predictive values. T e second study evaluated 220 lymphadenopathy patients in a hematology unit and identified five variables (lymph node size, location [supraclavicular or nonsupraclavicular], age [>40 years or <40 years], texture [nonhard or hard], and tenderness) that were used in a mathematical model to identify patients requiring a biopsy. Positive predictive value was found for age >40 years, supraclavicular location, node size >2.25 cm^2, hard texture, and lack of pain or tenderness. Negative predictive value was evident for age <40 years, node size <1.0 cm^2, nonhard texture, and tender or painful nodes. Ninety-one percent of those who required biopsy were correctly classified by this model. Because both of these studies were retrospective analyses and one was limited to young patients, it is not known how useful these models would be if applied prospectively in a primary care setting.

Most lymphadenopathy patients do not require a biopsy, and at least half require no laboratory studies. If the patient's history and physical findings point to a benign cause for lymphadenopathy, careful follow-up at a 2- to 4-week interval can be used. T e patient should be instructed to return for reevaluation if there is an increase in the size of the nodes. Antibiotics are not indicated for lymphadenopathy unless strong evidence of a bacterial infection is present. Glucocorticoids should not be used to treat lymphadenopathy because their lympholytic effect obscures some diagnoses (lymphoma, leukemia, Castleman's disease), and they contribute to delayed healing or activation of underlying infections. An exception to this statement is the life-threatening pharyngeal obstruction by enlarged lymphoid tissue in Waldeyer's ring that is occasionally seen in infectious mononucleosis.

SPLENOMEGALY

STRUCTURE AND FUNCTION OF THE SPLEEN

T e spleen is a reticuloendothelial organ that has its embryologic origin in the dorsal mesogastrium at about 5 weeks of gestation. It arises in a series of hillocks, migrates to its normal adult location in the left upper quadrant (LUQ), and is attached to the stomach via the gastrolienal ligament and to the kidney via the lienorenal ligament. When the hillocks fail to unify into a single tissue mass, accessory spleens may develop in around 20% of persons. T e function of the spleen has been elusive. Galen believed it was the source of "black bile" or melancholia, and the word hypochondria (literally, beneath the ribs) and the idiom "to vent one's spleen" attest to the beliefs that the spleen had an important influence on the psyche and emotions. In humans, its normal physiologic roles seem to be the following:

1. Maintenance of quality control over erythrocytes in the red pulp by removal of senescent and defective red blood cells. T e spleen accomplishes this function through a unique organization of its parenchyma and vasculature **(Fig. 4-1)**.

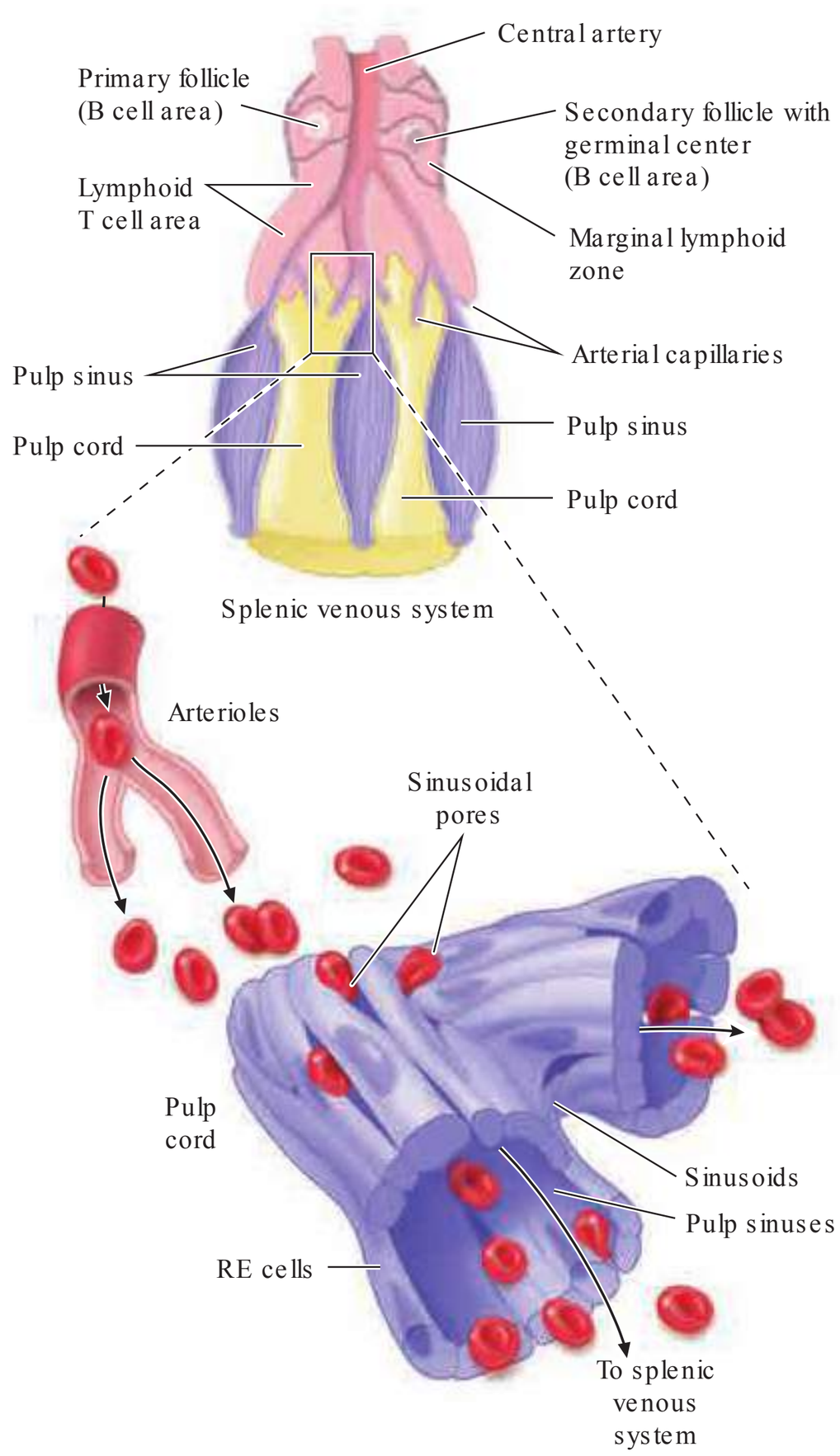


FIGURE 4-1
Schematic spleen structure. The spleen comprises many units of red and white pulp centered around small branches of the splenic artery, called central arteries. White pulp is lymphoid in nature and contains Bcell follicles, a marginal zone around the follicles, and Tcell–rich areas sheathing arterioles. The red pulp areas include pulp sinuses and pulp cords. The cords are dead ends. In order to regain access to the circulation, red blood cells must traverse tiny openings in the sinusoidal lining. Stif , damaged, or old red cells cannot enter the sinuses. RE, reticuloendothelial. (Bottom portion of f gure from RS Hillman, KA Ault: Hematology in Clinical Practice, 4th ed. New York, McGraw-Hill, 2005.)

2. Synthesis of antibodies in the white pulp.
3. T e removal of antibody-coated bacteria and antibody-coated blood cells from the circulation.

An increase in these normal functions may result in splenomegaly.

T e spleen is composed of red pulp and white pulp, which are Malpighi's terms for the red blood–filled sinuses and reticuloendothelial cell–lined cords and the white lymphoid follicles arrayed within the red pulp matrix. T e spleen is in the portal circulation. T e reason for this is unknown but may relate to the fact that lower blood pressure allows less rapid flow and minimizes damage to normal erythrocytes. Blood flows into the spleen at a rate of about 150 mL/min through the splenic artery, which ultimately ramifies into central arterioles. Some blood goes from the arterioles to capillaries and then to splenic veins and out of the spleen, but the majority of blood from central arterioles flows into the macrophage-lined sinuses and cords. T e blood entering the sinuses reenters the circulation through the splenic venules, but the blood entering the cords is subjected to an inspection of sorts. To return to the circulation, the blood cells in the cords must squeeze through slits in the cord lining to enter the sinuses that lead to the venules. Old and damaged erythrocytes are less deformable and are retained in the cords, where they are destroyed and their components recycled. Red cell–inclusion bodies such as parasites, nuclear residua (Howell-Jolly bodies, **see Fig. 2-6**), or denatured hemoglobin (Heinz bodies) are pinched off in the process of passing through the slits, a process called pitting. T e culling of dead and damaged cells and the pitting of cells with inclusions appear to occur without significant delay because the blood transit time through the spleen is only slightly slower than in other organs.

T e spleen is also capable of assisting the host in adapting to its hostile environment. It has at least three adaptive functions: (1) clearance of bacteria and particulates from the blood, (2) the generation of immune responses to certain pathogens, and (3) the generation of cellular components of the blood under circumstances in which the marrow is unable to meet the needs (i.e., extramedullary hematopoiesis). T e latter adaptation is a recapitulation of the blood-forming function the spleen plays during gestation. In some animals, the spleen also serves a role in the vascular adaptation to stress because it stores red blood cells (often hemoconcentrated to higher hematocrits than normal) under normal circumstances and contracts under the influence of β-adrenergic stimulation to provide the animal with an autotransfusion and improved oxygen-carrying capacity. However, the normal human spleen does not sequester or store red blood cells and does not contract in response to sympathetic stimuli. T e normal human spleen contains approximately one-third of the total body platelets and a significant number of marginated neutrophils. T ese sequestered cells are available when needed to respond to bleeding or infection.

APPROACH TO THE PATIENT: Splenomegaly

CLINICAL ASSESSMENT T e most common symptoms produced by diseases involving the spleen are pain and a heavy sensation in the LUQ. Massive splenomegaly may cause early satiety. Pain may result from acute swelling of the spleen with stretching of the capsule, infarction, or inflammation of the capsule. For many years, it was believed that splenic infarction was clinically silent, which, at times, is true. However, Soma Weiss, in his classic 1942 report of the self-observations by a Harvard medical student on the clinical course of subacute bacterial endocarditis, documented that severe LUQ and pleuritic chest pain may accompany thromboembolic occlusion of splenic blood flow. Vascular occlusion, with infarction and pain, is commonly seen in children with sickle cell crises. Rupture of the spleen, from either trauma or infiltrative disease that breaks the capsule, may result in intraperitoneal bleeding, shock, and death. T e rupture itself may be painless.

A palpable spleen is the major physical sign produced by diseases affecting the spleen and suggests enlargement of the organ. T e normal spleen weighs <250 g, decreases in size with age, normally lies entirely within the rib cage, has a maximum cephalocaudad diameter of 13 cm by ultrasonography or maximum length of 12 cm and/or width of 7 cm by radionuclide scan, and is usually not palpable. However, a palpable spleen was found in 3% of 2200 asymptomatic, male, freshman college students. Follow-up at 3 years revealed that 30% of those students still had a palpable spleen without any increase in disease prevalence. Ten-year follow-up found no evidence for lymphoid malignancies. Furthermore, in some tropical countries (e.g., New Guinea), the incidence of splenomegaly may reach 60%. T us, the presence of a palpable spleen does not always equate with presence of disease. Even when disease is present, splenomegaly may not reflect the primary disease but rather a reaction to it. For example, in patients with Hodgkin's disease, only two-thirds of the palpable spleens show involvement by the cancer.

Physical examination of the spleen uses primarily the techniques of palpation and percussion. Inspection may reveal fullness in the LUQ that descends on inspiration, a finding associated with a massively enlarged spleen. Auscultation may reveal a venous hum or friction rub.

Palpation can be accomplished by bimanual palpation, ballotment, and palpation from above (Middleton maneuver). For bimanual palpation, which is at least as reliable as the other techniques, the patient is supine with flexed knees. T e examiner's left hand is placed on the lower rib

cage and pulls the skin toward the costal margin, allowing the fingertips of the right hand to feel the tip of the spleen as it descends while the patient inspires slowly, smoothly, and deeply. Palpation is begun with the right hand in the left lower quadrant with gradual movement toward the left costal margin, thereby identifying the lower edge of a massively enlarged spleen. When the spleen tip is felt, the finding is recorded as centimeters below the left costal margin at some arbitrary point, i.e., 10–15 cm, from the midpoint of the umbilicus or the xiphisternal junction. T is allows other examiners to compare findings or the initial examiner to determine changes in size over time. Bimanual palpation in the right lateral decubitus position adds nothing to the supine examination.

Percussion for splenic dullness is accomplished with any of three techniques described by Nixon, Castell, or Barkun:

1. Nixon's method: T e patient is placed on the right side so that the spleen lies above the colon and stomach. Percussion begins at the lower level of pulmonary resonance in the posterior axillary line and proceeds diagonally along a perpendicular line toward the lower midanterior costal margin. T e upper border of dullness is normally 6–8 cm above the costal margin. Dullness >8 cm in an adult is presumed to indicate splenic enlargement.
2. Castell's method: With the patient supine, percussion in the lowest intercostal space in the anterior axillary line (eighth or ninth) produces a resonant note if the spleen is normal in size. T is is true during expiration or full inspiration. A dull percussion note on full inspiration suggests splenomegaly.
3. Percussion *of* Traube's semilunar space: T e borders of Traube's space are the sixth rib superiorly, the left midaxillary line laterally, and the left costal margin inferiorly. T e patient is supine with the left arm slightly abducted. During normal breathing, this space is percussed from medial to lateral margins, yielding a normal resonant sound. A dull percussion note suggests splenomegaly.

Studies comparing methods of percussion and palpation with a standard of ultrasonography or scintigraphy have revealed sensitivity of 56–71% for palpation and 59–82% for percussion. Reproducibility among examiners is better for palpation than percussion. Both techniques are less reliable in obese patients or patients who have just eaten. T us, the physical examination techniques of palpation and percussion are imprecise at best. It has been suggested that the examiner perform percussion first and, if positive, proceed to palpation; if the spleen is palpable, then one can be reasonably confident that splenomegaly exists. However, not all LUQ masses are enlarged spleens; gastric or colon tumors and pancreatic or renal cysts or tumors can mimic splenomegaly.

T e presence of an enlarged spleen can be more precisely determined, if necessary, by liver-spleen radionuclide scan, CT, MRI, or ultrasonography. T e latter technique is the current procedure of choice for routine assessment of spleen size (normal = a maximum cephalocaudad diameter of 13 cm) because it has high sensitivity and specificity and is safe, noninvasive, quick, mobile, and less costly. Nuclear medicine scans are accurate, sensitive, and reliable but are costly, require greater time to generate data, and use immobile equipment. T ey have the advantage of demonstrating accessory splenic tissue. CT and MRI provide accurate determination of spleen size, but the equipment is immobile and the procedures are expensive. MRI appears to offer no advantage over CT. Changes in spleen structure such as mass lesions, infarcts, inhomogeneous infiltrates, and cysts are more readily assessed by CT, MRI, or ultrasonography. None of these techniques is very reliable in the detection of patchy infiltration (e.g., Hodgkin's disease).

DIFFERENTIAL DIAGNOSIS Many of the diseases associated with splenomegaly are listed in **Table 4-2**. They are grouped according to the presumed basic mechanisms responsible for organ enlargement:

1. Hyperplasia or hypertrophy related to a particular splenic function such as reticuloendothelial hyperplasia (work hypertrophy) in diseases such as hereditary spherocytosis or thalassemia syndromes that require removal of large numbers of defective red blood cells; immune hyperplasia in response to systemic infection (infectious mononucleosis, subacute bacterial endocarditis) or to immunologic diseases (immune thrombocytopenia, SLE, Felty's syndrome).
2. Passive congestion due to decreased blood flow from the spleen in conditions that produce portal hypertension (cirrhosis, Budd-Chiari syndrome, congestive heart failure).
3. Infiltrative diseases of the spleen (lymphomas, metastatic cancer, amyloidosis, Gaucher's disease, myeloproliferative disorders with extramedullary hematopoiesis).

T e differential diagnostic possibilities are much fewer when the spleen is "massively enlarged," palpable more than 8 cm below the left costal margin or has a drained weight of ≥1000 g **(Table 4-3)**. T e vast majority of such patients will have non-Hodgkin's lymphoma, chronic lymphocytic leukemia, hairy cell leukemia, chronic myeloid leukemia, myelofibrosis with myeloid metaplasia, or polycythemia vera.

LABORATORY ASSESSMENT The major laboratory abnormalities accompanying splenomegaly are determined by the underlying systemic illness. Erythrocyte counts may be normal, decreased (thalassemia major syndromes, SLE, cirrhosis with portal hypertension), or increased (polycythemia vera). Granulocyte counts may be normal, decreased (Felty's syndrome, congestive splenomegaly, leukemias), or increased (infections or inflammatory disease,

TABLE 4-2

DISEASES ASSOCIATED WITH SPLENOMEGALY GROUPED BY PATHOGENIC MECHANISM	
Enlargement Due to Increased Demand for Splenic Function	
Reticuloendothelial system hyperplasia (for removal of defective erythrocytes)	Leishmaniasis
Spherocytosis	Trypanosomiasis
Early sickle cell anemia	Ehrlichiosis
Ovalocytosis	Disordered immunoregulation
Thalassemia major	Rheumatoid arthritis (Felty's syndrome)
Hemoglobinopathies	Systemic lupus erythematosus
Paroxysmal nocturnal hemoglobinuria	Collagen vascular diseases
Pernicious anemia	Serum sickness
Immune hyperplasia	Immune hemolytic anemias
Response to infection (viral, bacterial, fungal, parasitic)	Immune thrombocytopenias
Infectious mononucleosis	Immune neutropenias
AIDS	Drug reactions
Viral hepatitis	Angioimmunoblastic lymphadenopathy
Cytomegalovirus	Sarcoidosis
Subacute bacterial endocarditis	Thyrotoxicosis (benign lymphoid hypertrophy)
Bacterial septicemia	Interleukin 2 therapy
Congenital syphilis	Extramedullary hematopoiesis
Splenic abscess	Myelofibrosis
Tuberculosis	Marrow damage by toxins, radiation, strontium
Histoplasmosis	Marrow infiltration by tumors, leukemias, Gaucher's disease
Malaria	
Enlargement Due to Abnormal Splenic or Portal Blood Flow	
Cirrhosis	Splenic artery aneurysm
Hepatic vein obstruction	Hepatic schistosomiasis
Portal vein obstruction, intrahepatic or extrahepatic	Congestive heart failure
Cavernous transformation of the portal vein	Hepatic echinococcosis
Splenic vein obstruction	Portal hypertension (any cause including the above): "Banti's disease"
Infiltration of the Spleen	
Intracellular or extracellular depositions	Hodgkin's disease
Amyloidosis	Myeloproliferative syndromes (e.g., polycythemia vera, essential thrombocytosis)
Gaucher's disease	Angiosarcomas
Niemann-Pick disease	Metastatic tumors (melanoma is most common)
Tangier disease	Eosinophilic granuloma
Hurler's syndrome and other mucopolysaccharidoses	Histiocytosis X
Hyperlipidemias	Hamartomas
Benign and malignant cellular infiltrations	Hemangiomas, fibromas, lymphangiomas
Leukemias (acute, chronic, lymphoid, myeloid, monocytic)	Splenic cysts
Lymphomas	
Unknown Etiology	
Idiopathic splenomegaly	Iron-deficiency anemia
Berylliosis	

TABLE 4-3

DISEASES ASSOCIATED WITH MASSIVE SPLENOMEGALY[a]	
Chronic myeloid leukemia	Gaucher's disease
Lymphomas	Chronic lymphocytic leukemia
Hairy cell leukemia	Sarcoidosis
Myelofibrosis with myeloid metaplasia	Autoimmune hemolytic anemia
Polycythemia vera	Diffuse splenic hemangiomatosis

[a]The spleen extends >8 cm below the left costal margin and/or weighs >1000 g.

myeloproliferative disorders). Similarly, the platelet count may be normal, decreased when there is enhanced sequestration or destruction of platelets in an enlarged spleen (congestive splenomegaly, Gaucher's disease, immune thrombocytopenia), or increased in the myeloproliferative disorders such as polycythemia vera.

T e CBC may reveal cytopenia of one or more blood cell types, which should suggest hypersplenism. T is condition is characterized by splenomegaly, cytopenia(s), normal or hyperplastic bone marrow, and a response to splenectomy. T e latter characteristic is less precise because reversal of cytopenia, particularly granulocytopenia, is sometimes not sustained after splenectomy. T e cytopenias result from increased destruction of the cellular elements secondary to reduced flow of blood through enlarged and congested cords (congestive splenomegaly) or to immune-mediated mechanisms. In hypersplenism, various cell types usually have normal morphology on the peripheral blood smear, although the red cells may be spherocytic due to loss of surface area during their longer transit through the enlarged spleen. T e increased marrow production of red cells should be reflected as an increased reticulocyte production index, although the value may be less than expected due to increased sequestration of reticulocytes in the spleen.

T e need for additional laboratory studies is dictated by the differential diagnosis of the underlying illness of which splenomegaly is a manifestation.

SPLENECTOMY

Splenectomy is infrequently performed for diagnostic purposes, especially in the absence of clinical illness or other diagnostic tests that suggest underlying disease. More often, splenectomy is performed for symptom control in patients with massive splenomegaly, for disease control in patients with traumatic splenic rupture, or for correction of cytopenias in patients with hypersplenism or immune-mediated destruction of one or more cellular blood elements. Splenectomy is necessary for staging of patients with Hodgkin's disease only in those with clinical stage I or II disease in whom radiation therapy alone is contemplated as the treatment. Noninvasive staging of the spleen in Hodgkin's disease is not a suf ciently reliable basis for treatment decisions because one-third of normal-sized spleens will be involved with Hodgkin's disease and one-third of enlarged spleens will be tumor-free. T e widespread use of systemic therapy to test all stages of Hodgkin's disease has made staging laparotomy with splenectomy unnecessary. Although splenectomy in chronic myeloid leukemia (CML) does not affect the natural history of disease, removal of the massive spleen usually makes patients significantly more comfortable and simplifies their management by significantly reducing transfusion requirements. T e improvements in therapy of CML have reduced the need for splenectomy for symptom control. Splenectomy is an effective secondary or tertiary treatment for two chronic B cell leukemias, hairy cell leukemia and prolymphocytic leukemia, and for the very rare splenic mantle cell or marginal zone lymphoma. Splenectomy in these diseases may be associated with significant tumor regression in bone marrow and other sites of disease. Similar regressions of systemic disease have been noted after splenic irradiation in some types of lymphoid tumors, especially chronic lymphocytic leukemia and prolymphocytic leukemia. T is has been termed the abscopal *eff*ect. Such systemic tumor responses to local therapy directed at the spleen suggest that some hormone or growth factor produced by the spleen may affect tumor cell proliferation, but this conjecture is not yet substantiated. A common therapeutic indication for splenectomy is traumatic or iatrogenic splenic rupture. In a fraction of patients with splenic rupture, peritoneal seeding of splenic fragments can lead to splenosis—the presence of multiple rests of spleen tissue not connected to the portal circulation. T is ectopic spleen tissue may cause pain or gastrointestinal obstruction, as in endometriosis. A large number of hematologic, immunologic, and congestive causes of splenomegaly can lead to destruction of one or more cellular blood elements. In the majority of such cases, splenectomy can correct the cytopenias, particularly anemia and thrombocytopenia. In a large series of patients seen in two tertiary care centers, the indication for splenectomy was diagnostic in 10% of patients, therapeutic in 44%, staging for Hodgkin's disease in 20%, and incidental to another procedure in 26%. Perhaps the only contraindication to splenectomy is the presence of marrow failure, in which the enlarged spleen is the only source of hematopoietic tissue.

T e absence of the spleen has minimal long-term effects on the hematologic profile. In the immediate postsplenectomy period, leukocytosis (up to 25,000/μL) and thrombocytosis (up to 1×10^6/μL) may develop, but within 2–3 weeks, blood cell counts and survival of each cell lineage are usually normal. T e chronic manifestations of splenectomy are marked variation in size and shape of erythrocytes (anisocytosis, poikilocytosis) and the presence of Howell-Jolly bodies (nuclear remnants), Heinz bodies (denatured hemoglobin), basophilic stippling, and an occasional nucleated erythrocyte in the peripheral blood. When such erythrocyte abnormalities appear in a patient whose spleen has not been removed, one should suspect splenic infiltration by tumor that has interfered with its normal culling and pitting function.

T e most serious consequence of splenectomy is increased susceptibility to bacterial infections, particularly those with capsules such as Streptococcus pneumoniae, Haemophilus inf uenzae, and some gram-negative enteric organisms. Patients under age 20 years

are particularly susceptible to overwhelming sepsis with S. pneumoniae, and the overall actuarial risk of sepsis in patients who have had their spleens removed is about 7% in 10 years. T e case–fatality rate for pneumococcal sepsis in splenectomized patients is 50–80%. About 25% of patients without spleens will develop a serious infection at some time in their life. T e frequency is highest within the first 3 years after splenectomy. About 15% of the infections are polymicrobial, and lung, skin, and blood are the most common sites. No increased risk of viral infection has been noted in patients who have no spleen. T e susceptibility to bacterial infections relates to the inability to remove opsonized bacteria from the bloodstream and a defect in making antibodies to T cell–independent antigens such as the polysaccharide components of bacterial capsules. Pneumococcal vaccine should be administered to all patients 2 weeks before elective splenectomy. T e Advisory Committee on Immunization Practices recommends that these patients receive repeat vaccination 5 years after splenectomy. Ef cacy has not been proven for this group, and the recommendation discounts the possibility that administration of the vaccine may actually lower the titer of specific pneumococcal antibodies. A more effective pneumococcal conjugate vaccine that involves T cells in the response is now available (Prevenar, 7-valent). T e vaccine to Neisseria meningitidis should also be given to patients in whom elective splenectomy is planned. Although ef cacy data for H. infuenzae type b vaccine are not available for older children or adults, it may be given to patients who have had a splenectomy.

Splenectomized patients should be educated to consider any unexplained fever as a medical emergency. Prompt medical attention with evaluation and treatment of suspected bacteremia may be life-saving. Routine chemoprophylaxis with oral penicillin can result in the emergence of drug-resistant strains and is not recommended.

In addition to an increased susceptibility to bacterial infections, splenectomized patients are also more susceptible to the parasitic disease babesiosis. T e splenectomized patient should avoid areas where the parasite Babesia is endemic (e.g., Cape Cod, MA).

Surgical removal of the spleen is an obvious cause of hyposplenism. Patients with sickle cell disease often suffer from autosplenectomy as a result of splenic destruction by the numerous infarcts associated with sickle cell crises during childhood. Indeed, the presence of a palpable spleen in a patient with sickle cell disease after age 5 suggests a coexisting hemoglobinopathy, e.g., thalassemia or hemoglobin C. In addition, patients who receive splenic irradiation for a neoplastic or autoimmune disease are also functionally hyposplenic. T e term hyposplenism is preferred to asplenism in referring to the physiologic consequences of splenectomy because asplenia is a rare, specific, and fatal congenital abnormality in which there is a failure of the left side of the coelomic cavity (which includes the splenic anlagen) to develop normally. Infants with asplenia have no spleens, but that is the least of their problems. T e right side of the developing embryo is duplicated on the left so there is liver where the spleen should be, there are two right lungs, and the heart comprises two right atria and two right ventricles.

CHAPTER 5

DISORDERS OF GRANULOCYTES AND MONOCYTES

Steven M. Holland ■ John I. Gallin

Leukocytes, the major cells comprising inflammatory and immune responses, include neutrophils, T and B lymphocytes, natural killer (NK) cells, monocytes, eosinophils, and basophils. T ese cells have specific functions, such as antibody production by B lymphocytes or destruction of bacteria by neutrophils, but in no single infectious disease is the exact role of the cell types completely established. T us, whereas neutrophils are classically thought to be critical to host defense against bacteria, they may also play important roles in defense against viral infections.

T e blood delivers leukocytes to the various tissues from the bone marrow, where they are produced. Normal blood leukocyte counts are 4.3–10.8 × 10^9/L, with neutrophils representing 45–74% of the cells, bands 0–4%, lymphocytes 16–45%, monocytes 4–10%, eosinophils 0–7%, and basophils 0–2%. Variation among individuals and among different ethnic groups can be substantial, with lower leukocyte numbers for certain African-American ethnic groups. T e various leukocytes are derived from a common stem cell in the bone marrow. T ree-fourths of the nucleated cells of bone marrow are committed to the production of leukocytes. Leukocyte maturation in the marrow is under the regulatory control of a number of different factors, known as colony-stimulating factors (CSFs) and interleukins (ILs). Because an alteration in the number and type of leukocytes is often associated with disease processes, total white blood cell (WBC) count (cells per μL) and differential counts are informative. T is chapter focuses on neutrophils, monocytes, and eosinophils.

NEUTROPHILS

MATURATION

Important events in neutrophil life are summarized in **Fig. 5-1**. In normal humans, neutrophils are produced only in the bone marrow. T e minimum number of stem cells necessary to support hematopoiesis is estimated to be 400–500 at any one time. Human blood monocytes, tissue macrophages, and stromal cells produce CSFs, hormones required for the growth of monocytes and neutrophils in the bone marrow. T e hematopoietic system not only produces enough neutrophils (~1.3 × 10^{11} cells per 80-kg person per day) to carry out physiologic functions but also has a large reserve stored in the marrow, which can be mobilized in response to inflammation or infection. An increase in the number of blood neutrophils is called neutrophilia, and the presence of immature cells is termed a sh*ift* to the le*ft*. A decrease in the number of blood neutrophils is called neutropenia.

Neutrophils and monocytes evolve from pluripotent stem cells under the influence of cytokines and CSFs **(Fig. 5-2)**. T e proliferation phase through the metamyelocyte takes about 1 week, while the maturation phase from metamyelocyte to mature neutrophil takes another week. T e myeloblast is the first recognizable precursor cell and is followed by the promyelocyte. T e promyelocyte evolves when the classic lysosomal granules, called the primary, or azurophil, granules are produced. T e primary granules contain hydrolases, elastase, myeloperoxidase, cathepsin G, cationic proteins, and bactericidal/permeability-increasing protein, which is important for killing gram-negative bacteria. Azurophil granules also contain de*f*ensins, a family of cysteine-rich polypeptides with broad antimicrobial activity against bacteria, fungi, and certain enveloped viruses. T e promyelocyte divides to produce the myelocyte, a cell responsible for the synthesis of the speci*f*ic, or secondary, granules, which contain unique (specific) constituents such as lactoferrin, vitamin B_{12}–binding protein, membrane components of the reduced nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase required for hydrogen peroxide production, histaminase, and receptors for certain chemoattractants and adherence-promoting factors (CR3)

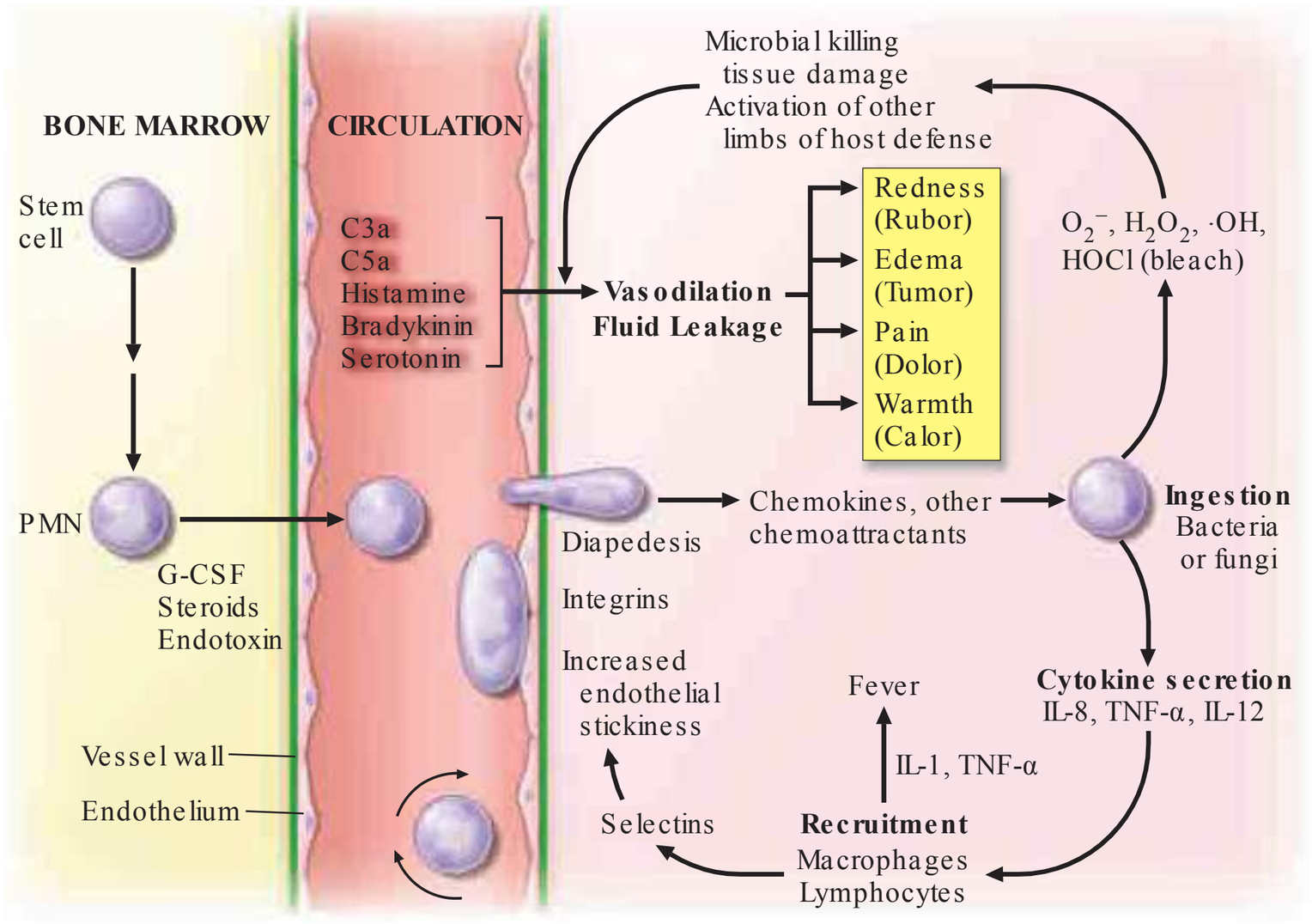
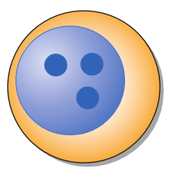
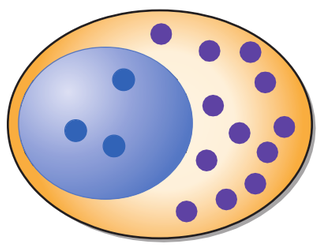
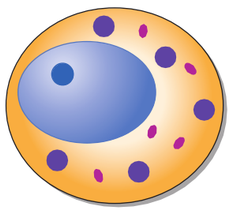
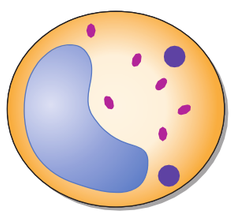
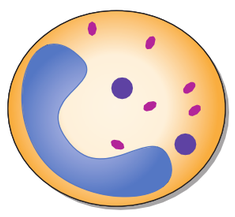
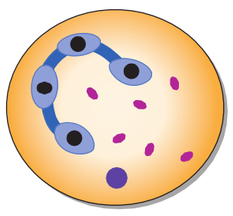


FIGURE 5-1
Schematic events in neutrophil production, recruitment, and inflammation. The four cardinal signs of inflammation (rubor, tumor, calor, dolor) are indicated, as are the interactions of neutrophils with other cells and cytokines. G-CSF, granulocyte colony-stimulating factor; IL, interleukin; PMN, polymorphonuclear leukocyte; TNF-α, tumor necrosis factor α.

Cell	Stage	Surface Markers[a]	Characteristics
	MYELOBLAST	CD33, CD13, CD15	Prominent nucleoli
	PROMYELOCYTE	CD33, CD13, CD15	Large cell Primary granules appear
	MYELOCYTE	CD33, CD13, CD15, CD14, CD11b	Secondary granules appear
	METAMYELOCYTE	CD33, CD13, CD15, CD14, CD11b	Kidney bean–shaped nucleus
	BAND FORM	CD33, CD13, CD15, CD14, CD11b CD10, CD16	Condensed, band–shaped nucleus
	NEUTROPHIL	CD33, CD13, CD15, CD14, CD11b CD10, CD16	Condensed, multilobed nucleus

[a]CD = Cluster Determinant; ● Nucleolus; ● Primary granule; ● Secondary granule.

FIGURE 5-2
Stages of neutrophil development shown schematically. Granulocyte colony-stimulating factor (G-CSF)and granulocyte-macrophage colony-stimulating factor (GM-CSF) are critical to this process. Identifying cellular characteristics and specific cell-surface markers are listed for each maturational stage.

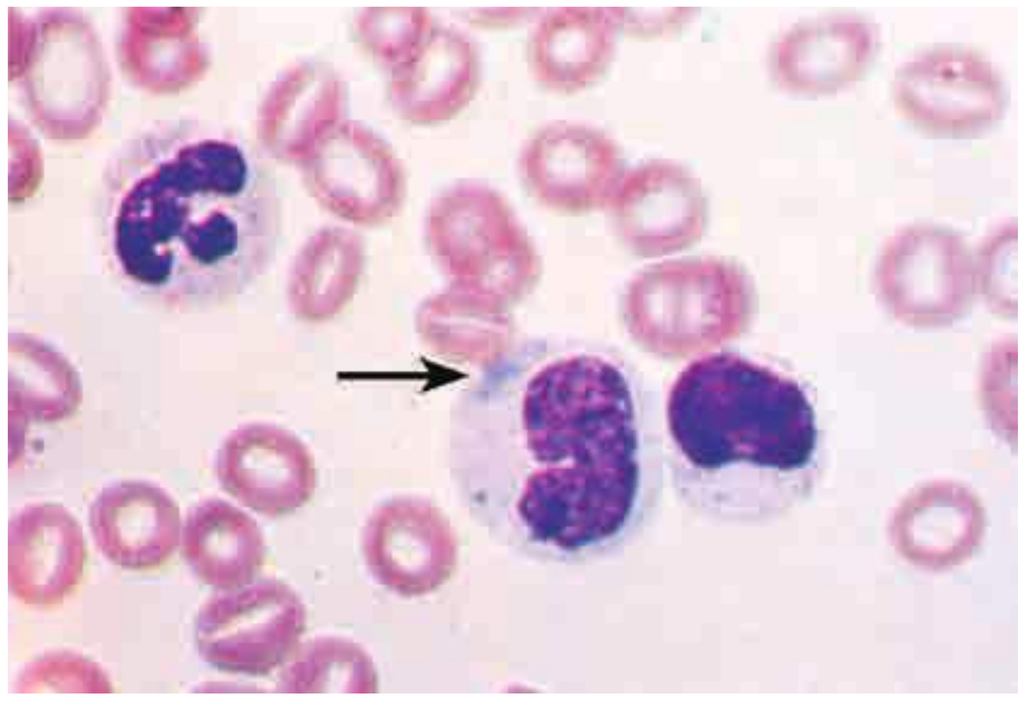


FIGURE 5-3
Neutrophil band with Döhle body. The neutrophil with a sausage-shaped nucleus in the center of the field is a band form. Döhle bodies are discrete, blue-staining, nongranular areas found in the periphery of the cytoplasm of the neutrophil in infections and other toxic states. They represent aggregates of rough endoplasmic reticulum.

as well as receptors for the basement membrane component, laminin. T e secondary granules do not contain acid hydrolases and therefore are not classic lysosomes. Packaging of secondary granule contents during myelopoiesis is controlled by CCAAT/enhancer binding protein-ε. Secondary granule contents are readily released extracellularly, and their mobilization is important in modulating inflammation. During the final stages of maturation, no cell division occurs, and the cell passes through the metamyelocyte stage and then to the band neutrophil with a sausage-shaped nucleus **(Fig. 5-3)**. As the band cell matures, the nucleus assumes a lobulated configuration. T e nucleus of neutrophils normally contains up to four segments **(Fig. 5-4)**. Excessive segmentation (more than five nuclear lobes) may be a manifestation of folate or vitamin B_{12} deficiency or the congenital neutropenia syndrome of warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) described below. T e Pelger-Hüet anomaly **(Fig. 5-5)**, an infrequent dominant benign inherited trait, results in neutrophils with distinctive bilobed nuclei that must be distinguished from band forms. Acquired bilobed nuclei, pseudo Pelger-Hüet anomaly, can occur with acute infections or in myelodysplastic syndromes. T e physiologic role of the normal multilobed nucleus of neutrophils is unknown, but it may allow great deformation of neutrophils during migration into tissues at sites of inflammation.

In severe acute bacterial infection, prominent neutrophil cytoplasmic granules, called toxic granulations, are occasionally seen. Toxic granulations are immature or abnormally staining azurophil granules. Cytoplasmic

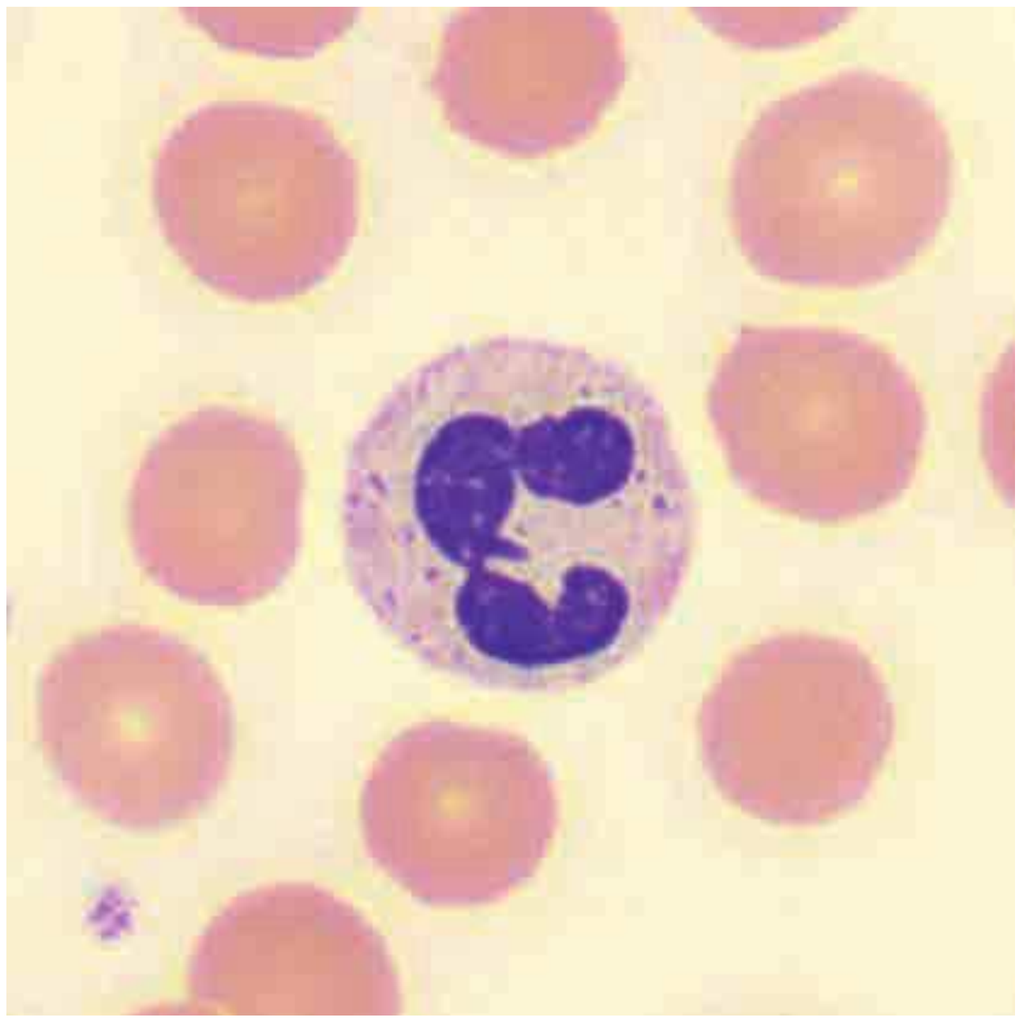


FIGURE 5-4
Normal granulocyte. The normal granulocyte has a segmented nucleus with heavy, clumped chromatin; fine neutrophilic granules are dispersed throughout the cytoplasm.

inclusions, also called Döhle bodies (Fig. 5-3), can be seen during infection and are fragments of ribosome-rich endoplasmic reticulum. Large neutrophil vacuoles are often present in acute bacterial infection and probably represent pinocytosed (internalized) membrane.

Neutrophils are heterogeneous in function. Monoclonal antibodies have been developed that recognize only a subset of mature neutrophils. T e meaning of neutrophil heterogeneity is not known.

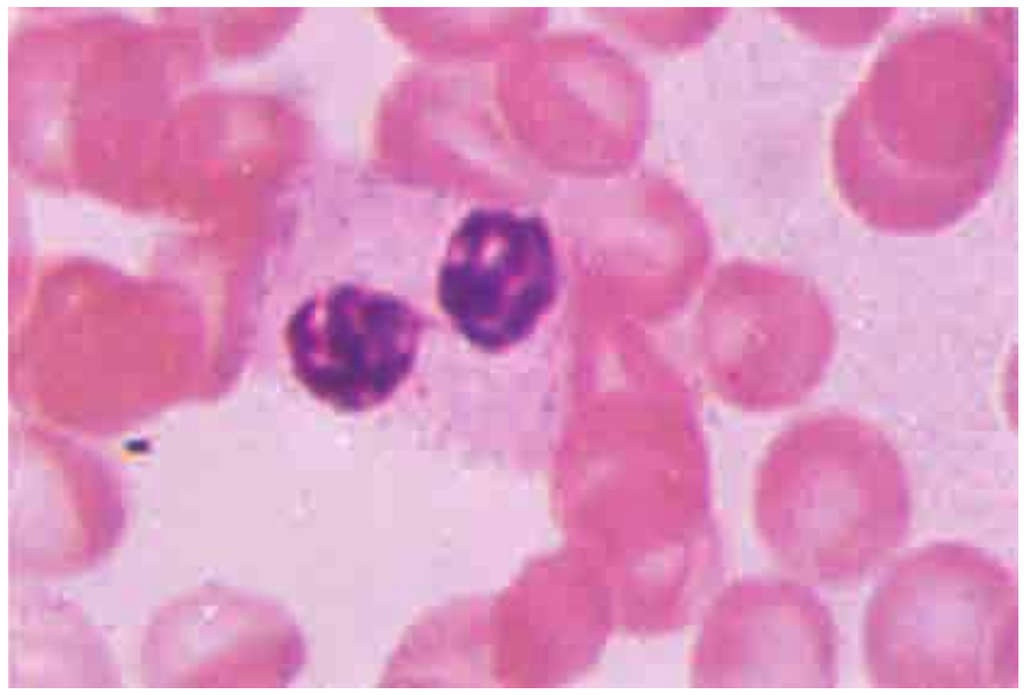


FIGURE 5-5
Pelger-Hüet anomaly. In this benign disorder, the majority of granulocytes are bilobed. The nucleus frequently has a spectacle-like, or "pince-nez," configuration.

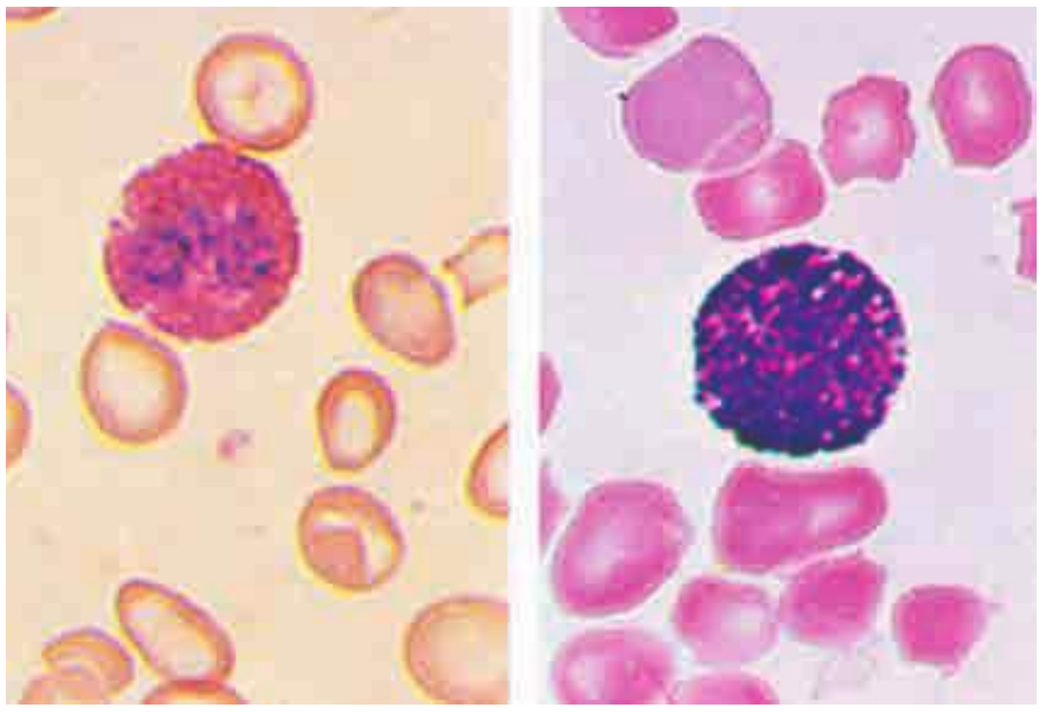


FIGURE 5-6
Normal eosinophil (left) and basophil (right). The eosinophil contains large, bright orange granules and usually a bilobed nucleus. The basophil contains large purple-black granules that fill the cell and obscure the nucleus.

The morphology of eosinophils and basophils is shown in **Fig. 5-6**.

MARROW RELEASE AND CIRCULATING COMPARTMENTS

Specific signals, including IL-1, tumor necrosis factor α (TNF-α), the CSFs, complement fragments, and chemokines, mobilize leukocytes from the bone marrow and deliver them to the blood in an unstimulated state. Under normal conditions, ~90% of the neutrophil pool is in the bone marrow, 2–3% in the circulation, and the remainder in the tissues **(Fig. 5-7)**.

The circulating pool exists in two dynamic compartments: one freely flowing and one marginated. The freely flowing pool is about one-half the neutrophils in the basal state and is composed of those cells that are in the blood and not in contact with the endothelium. Marginated leukocytes are those that are in close physical contact with the endothelium **(Fig. 5-8)**. In the pulmonary circulation, where an extensive capillary bed (~1000 capillaries per alveolus) exists, margination occurs because the capillaries are about the same size as a mature neutrophil. Therefore, neutrophil fluidity and deformability are necessary to make the transit through the pulmonary bed. Increased neutrophil rigidity and decreased deformability lead to augmented neutrophil trapping and margination in the lung. In contrast, in the systemic postcapillary venules, margination is mediated by the interaction of specific cell-surface molecules called selectins. Selectins are glycoproteins expressed on neutrophils and endothelial cells, among others, that cause a low-affinity interaction, resulting in "rolling" of the neutrophil along the endothelial

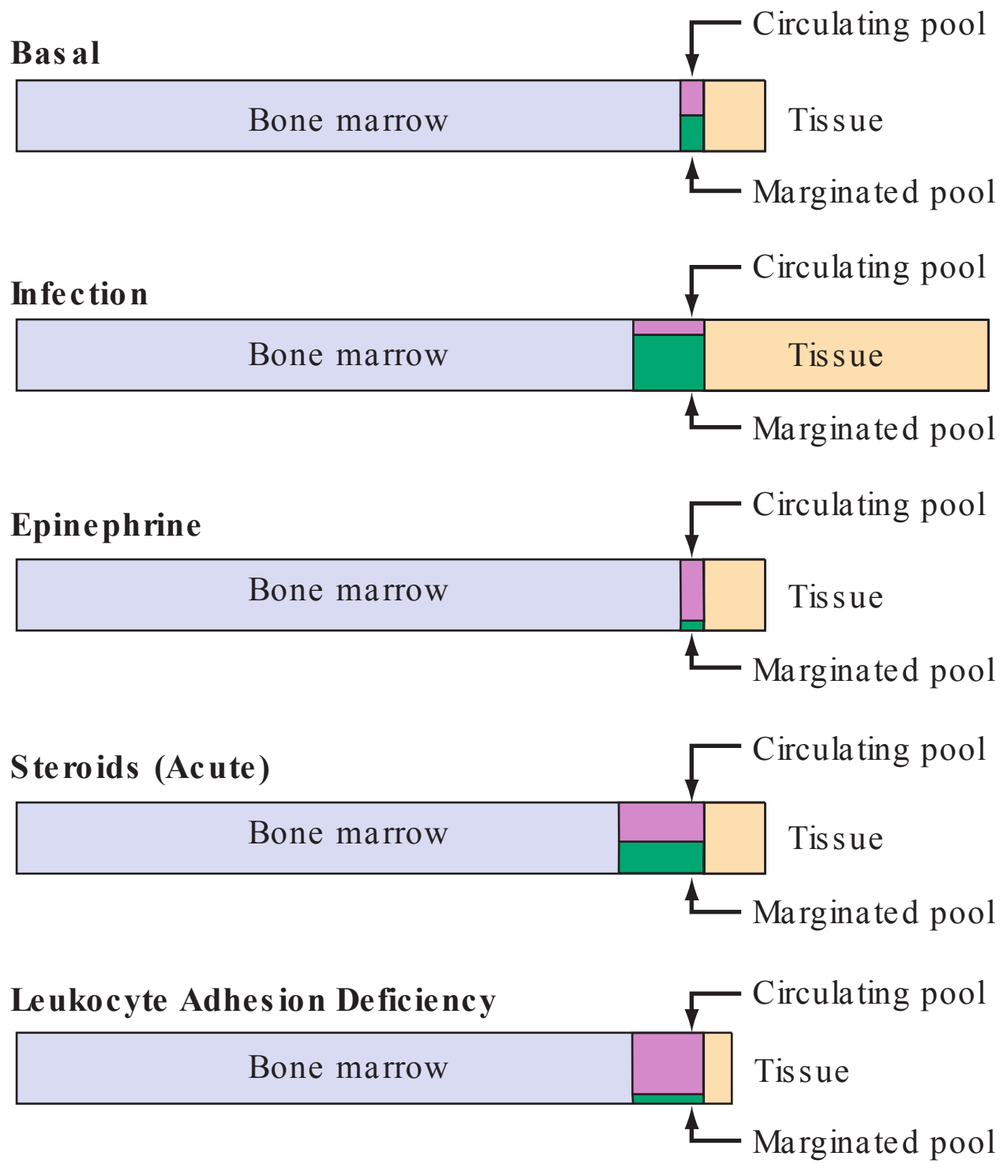


FIGURE 5-7
Schematic neutrophil distribution and kinetics between the different anatomic and functional pools.

surface. On neutrophils, the molecule L-selectin (cluster determinant [CD] 62L) binds to glycosylated proteins on endothelial cells (e.g., glycosylation-dependent cell adhesion molecule [GlyCAM1] and CD34). Glycoproteins on neutrophils, most importantly sialyl-Lewis^x (SLe^x, CD15s), are targets for binding of selectins expressed on endothelial cells (E-selectin [CD62E] and P-selectin [CD62P]) and other leukocytes. In response to chemotactic stimuli from injured tissues (e.g., complement product C5a, leukotriene B_4, IL-8) or bacterial products (e.g., N-formylmethionylleucylphenylalanine [f-met-leu-phe]), neutrophil adhesiveness increases through mobilization of intracellular adhesion proteins stored in specific granules to the cell surface, and the cells "stick" to the endothelium through integrins. The integrins are leukocyte glycoproteins that exist as complexes of a common CD18 β chain with CD11a (LFA-1), CD11b (called Mac-1, CR3, or the C3bi receptor), and CD11c (called p150,95 or CR4). CD11a/CD18 and CD11b/CD18 bind to specific endothelial receptors (intercellular adhesion molecules [ICAM] 1 and 2).

On cell stimulation, L-selectin is shed from neutrophils, and E-selectin increases in the blood, presumably because it is shed from endothelial cells; receptors for chemoattractants and opsonins are mobilized; and the phagocytes orient toward the chemoattractant source in the extravascular space, increase their motile activity (chemokinesis), and migrate directionally (chemotaxis) into tissues. The process of migration into tissues is

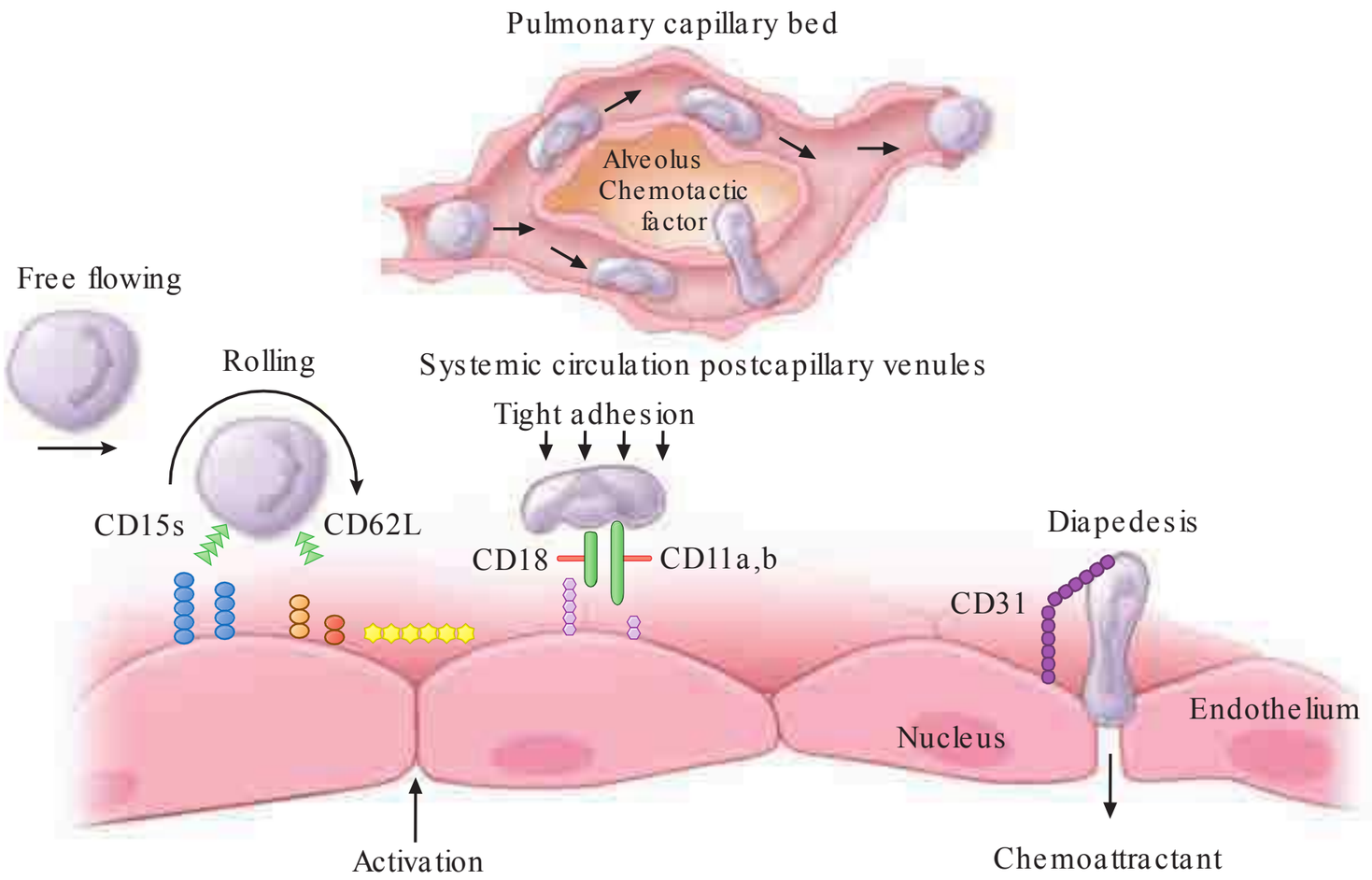


FIGURE 5-8

Neutrophil travel through the pulmonary capillaries is dependent on neutrophil deformability. Neutrophil rigidity (e.g., caused by C5a) enhances pulmonary trapping and response to pulmonary pathogens in a way that is not so dependent on cell-surface receptors. Intraalveolar chemotactic factors, such as those caused by certain bacteria (e.g., Streptococcus pneumoniae), lead to diapedesis of neutrophils from the pulmonary capillaries into the alveolar space. Neutrophil interaction with the endothelium of the systemic postcapillary venules is dependent on molecules of attachment. The neutrophil "rolls" along the endothelium using selectins: neutrophil CD15s (sialyl-Lewis^x) binds to CD62E (E-selectin) and CD62P (P-selectin) on endothelial cells; CD62L (L-selectin) on neutrophils binds to CD34 and other molecules (e.g., GlyCAM-1) expressed on endothelium. Chemokines or other activation factors stimulate integrin-mediated "tight adhesion": CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1, CR3) bind to CD54 (ICAM-1) and CD102 (ICAM-2) on the endothelium. Diapedesis occurs between endothelial cells: CD31 (PECAM-1) expressed by the emigrating neutrophil interacts with CD31 expressed at the endothelial cell-cell junction. CD, cluster determinant; GlyCAM, glycosylation-dependent cell adhesion molecule; ICAM, intercellular adhesion molecule; PECAM, platelet/endothelial cell adhesion molecule.

called diapedesis and involves the crawling of neutrophils between postcapillary endothelial cells that open junctions between adjacent cells to permit leukocyte passage. Diapedesis involves platelet/endothelial cell adhesion molecule (PECAM) 1 (CD31), which is expressed on both the emigrating leukocyte and the endothelial cells. The endothelial responses (increased blood flow from increased vasodilation and permeability) are mediated by anaphylatoxins (e.g., C3a and C5a) as well as vasodilators such as histamine, bradykinin, serotonin, nitric oxide, vascular endothelial growth factor (VEGF), and prostaglandins E and I. Cytokines regulate some of these processes (e.g., TNF-α induction of VEGF, interferon [IFN] γ inhibition of prostaglandin E).

In the healthy adult, most neutrophils leave the body by migration through the mucous membrane of the gastrointestinal tract. Normally, neutrophils spend a short time in the circulation (half-life, 6–7 h). Senescent neutrophils are cleared from the circulation by macrophages in the lung and spleen. Once in the tissues, neutrophils release enzymes, such as collagenase and elastase, which may help establish abscess cavities. Neutrophils ingest pathogenic materials that have been opsonized by IgG and C3b. Fibronectin and the tetrapeptide tuftsin also facilitate phagocytosis.

With phagocytosis comes a burst of oxygen consumption and activation of the hexose-monophosphate shunt. A membrane-associated NADPH oxidase, consisting of membrane and cytosolic components, is assembled and catalyzes the univalent reduction of oxygen to superoxide anion, which is then converted by superoxide dismutase to hydrogen peroxide and other toxic oxygen products (e.g., hydroxyl radical). Hydrogen peroxide + chloride + neutrophil myeloperoxidase generate hypochlorous acid (bleach), hypochlorite, and chlorine. These products oxidize and halogenate microorganisms and tumor cells and, when uncontrolled, can damage host tissue. Strongly cationic proteins, defensins, elastase, cathepsins, and probably nitric oxide also participate in microbial killing. Lactoferrin chelates iron, an important growth factor for microorganisms, especially fungi. Other enzymes, such as lysozyme and acid proteases, help digest microbial debris. After 1–4 days in tissues, neutrophils die. The apoptosis of neutrophils is also cytokine-regulated; granulocyte colony-stimulating factor (G-CSF) and IFN-γ prolong their life

span. Under certain conditions, such as in delayed-type hypersensitivity, monocyte accumulation occurs within 6–12 h of initiation of inflammation. Neutrophils, monocytes, microorganisms in various states of digestion, and altered local tissue cells make up the inflammatory exudate, pus. Myeloperoxidase confers the characteristic green color to pus and may participate in turning off the inflammatory process by inactivating chemoattractants and immobilizing phagocytic cells.

Neutrophils respond to certain cytokines (IFN-γ, granulocyte-macrophage colony-stimulating factor [GM-CSF], IL-8) and produce cytokines and chemotactic signals (TNF-α, IL-8, macrophage inflammatory protein [MIP] 1) that modulate the inflammatory response. In the presence of fibrinogen, f-met-leu-phe or leukotriene B_4 induces IL-8 production by neutrophils, providing autocrine amplification of inflammation. Chemokines (chemoattractant cytokines) are small proteins produced by many different cell types, including endothelial cells, fibroblasts, epithelial cells, neutrophils, and monocytes, that regulate neutrophil, monocyte, eosinophil, and lymphocyte recruitment and activation. Chemokines transduce their signals through heterotrimeric G protein–linked receptors that have seven cell membrane–spanning domains, the same type of cell-surface receptor that mediates the response to the classic chemoattractants f-met-leu-phe and C5a. Four major groups of chemokines are recognized based on the cysteine structure near the N terminus: C, CC, CXC, and CXXXC. T e CXC cytokines such as IL-8 mainly attract neutrophils; CC chemokines such as MIP-1 attract lymphocytes, monocytes, eosinophils, and basophils; the C chemokine lymphotactin is T cell tropic; the CXXXC chemokine fractalkine attracts neutrophils, monocytes, and T cells. T ese molecules and their receptors not only regulate the trafficking and activation of inflammatory cells, but specific chemokine receptors also serve as co-receptors for HIV infection **(Chap. 226)** and have a role in other viral infections such as West Nile infection and atherogenesis.

NEUTROPHIL ABNORMALITIES

Defects in the neutrophil life cycle can lead to dysfunction and compromised host defenses. Inflammation is often depressed, and the clinical result is often recurrent, severe bacterial and fungal infections. Aphthous ulcers of mucous membranes (gray ulcers without pus) and gingivitis and periodontal disease suggest a phagocytic cell disorder. Patients with congenital phagocyte defects can have infections within the first few days of life. Skin, ear, upper and lower respiratory tract, and bone infections are common. Sepsis and meningitis are rare. In some disorders, the frequency of infection is variable, and patients can go for months or even years without major infection. Aggressive management of these congenital diseases has extended the life span of patients well beyond 30 years.

Neutropenia

T e consequences of absent neutrophils are dramatic. Susceptibility to infectious diseases increases sharply when neutrophil counts fall below 1000 cells/μL. When the absolute neutrophil count (ANC; band forms and mature neutrophils combined) falls to <500 cells/μL, control of endogenous microbial flora (e.g., mouth, gut) is impaired; when the ANC is <200/μL, the local inflammatory process is absent. Neutropenia can be due to depressed production, increased peripheral destruction, or excessive peripheral pooling. A falling neutrophil count or a significant decrease in the number of neutrophils below steady-state levels, together with a failure to increase neutrophil counts in the setting of infection or other challenge, requires investigation. Acute neutropenia, such as that caused by cancer chemotherapy, is more likely to be associated with increased risk of infection than neutropenia of long duration (months to years) that reverses in response to infection or carefully controlled administration of endotoxin (see "Laboratory Diagnosis and Management," below).

Some causes of inherited and acquired neutropenia are listed in **Table 5-1**. T e most common neutropenias are iatrogenic, resulting from the use of cytotoxic or immunosuppressive therapies for malignancy or control of autoimmune disorders. T ese drugs cause neutropenia because they result in decreased production of rapidly growing progenitor (stem) cells of the marrow. Certain antibiotics such as chloramphenicol, trimethoprim-sulfamethoxazole, flucytosine, vidarabine, and the antiretroviral drug zidovudine may cause neutropenia by inhibiting proliferation of myeloid precursors. Azathioprine and 6-mercaptopurine are metabolized by the enzyme thiopurine methyltransferase (TPMT), hypofunctional polymorphisms in which are found in 11% of whites and can lead to accumulation of 6-thioguanine and profound marrow toxicity. T e marrow suppression is generally dose-related and dependent on continued administration of the drug. Cessation of the offending agent and recombinant human G-CSF usually reverse these forms of neutropenia.

Another important mechanism for iatrogenic neutropenia is the effect of drugs that serve as immune haptens and sensitize neutrophils or neutrophil precursors to immune-mediated peripheral destruction. T is form of drug-induced neutropenia can be seen within 7 days of exposure to the drug; with previous drug exposure, resulting in preexisting antibodies, neutropenia may occur a few hours after administration of the

TABLE 5-1

CAUSES OF NEUTROPENIA

Decreased Production
Drug-induced—alkylating agents (nitrogen mustard, busulfan, chlorambucil, cyclophosphamide); antimetabolites (methotrexate, 6-mercaptopurine, 5-flucytosine); noncytotoxic agents (antibiotics [chloramphenicol, penicillins, sulfonamides], phenothiazines, tranquilizers [meprobamate], anticonvulsants [carbamazepine], antipsychotics [clozapine], certain diuretics, anti-inflammatory agents, antithyroid drugs, many others)
Hematologic diseases—idiopathic, cyclic neutropenia, Chédiak-Higashi syndrome, aplastic anemia, infantile genetic disorders (see text)
Tumor invasion, myelofibrosis
Nutritional deficiency—vitamin B_{12}, folate (especially alcoholics)
Infection—tuberculosis, typhoid fever, brucellosis, tularemia, measles, infectious mononucleosis, malaria, viral hepatitis, leishmaniasis, AIDS
Peripheral Destruction
Antineutrophil antibodies and/or splenic or lung trapping
Autoimmune disorders—Felty's syndrome, rheumatoid arthritis, lupus erythematosus
Drugs as haptens—aminopyrine, α-methyldopa, phenylbutazone, mercurial diuretics, some phenothiazines
Granulomatosis with polyangiitis (Wegener's)
Peripheral Pooling (Transient Neutropenia)
Overwhelming bacterial infection (acute endotoxemia)
Hemodialysis
Cardiopulmonary bypass

drug. Although any drug can cause this form of neutropenia, the most frequent causes are commonly used antibiotics, such as sulfa-containing compounds, penicillins, and cephalosporins. Fever and eosinophilia may also be associated with drug reactions, but often these signs are not present. Drug-induced neutropenia can be severe, but discontinuation of the sensitizing drug is sufficient for recovery, which is usually seen within 5–7 days and is complete by 10 days. Readministration of the sensitizing drug should be avoided, because abrupt neutropenia will often result. For this reason, diagnostic challenge should be avoided.

Autoimmune neutropenias caused by circulating antineutrophil antibodies are another form of acquired neutropenia that results in increased destruction of neutrophils. Acquired neutropenia may also be seen with viral infections, including infection with HIV. Acquired neutropenia may be cyclic in nature, occurring at intervals of several weeks. Acquired cyclic or stable neutropenia may be associated with an expansion of large granular lymphocytes (LGLs), which may be T cells, NK cells, or NK-like cells. Patients with large granular lymphocytosis may have moderate blood and bone marrow lymphocytosis, neutropenia, polyclonal hypergammaglobulinemia, splenomegaly, rheumatoid arthritis, and absence of lymphadenopathy. Such patients may have a chronic and relatively stable course. Recurrent bacterial infections are frequent. Benign and malignant forms of this syndrome occur. In some patients, a spontaneous regression has occurred even after 11 years, suggesting an immunoregulatory defect as the basis for at least one form of the disorder. Glucocorticoids, cyclosporine, and methotrexate are commonly used to manage these cytopenias.

Hereditary neutropenias

Hereditary neutropenias are rare and may manifest in early childhood as a profound constant neutropenia or agranulocytosis. Congenital forms of neutropenia include Kostmann's syndrome (neutrophil count <100/μL), which is often fatal and due to mutations in the anti-apoptosis gene HAX-1; severe chronic neutropenia (neutrophil count of 300–1500/μL) due to mutations in neutrophil elastase (ELANE); hereditary cyclic neutropenia, or, more appropriately, cyclic hematopoiesis, also due to mutations in neutrophil elastase (ELANE); the cartilage-hair hypoplasia syndrome due to mutations in the mitochondrial RNA-processing endoribonuclease RMRP; Shwachman-Diamond syndrome associated with pancreatic insufficiency due to mutations in the Shwachman-Bodian-Diamond syndrome gene SBDS; the WHIM (warts, hypogammaglobulinemia, infections, myelokathexis [retention of WBCs in the marrow]) syndrome, characterized by neutrophil hypersegmentation and bone marrow myeloid arrest due to mutations in the chemokine receptor CXCR4; and neutropenias associated with other immune defects, such as X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and CD40 ligand deficiency. Mutations in the G-CSF receptor can develop in severe congenital neutropenia and are linked to leukemia. Absence of both myeloid and lymphoid cells is seen in reticular dysgenesis, due to mutations in the nuclear genome-encoded mitochondrial enzyme adenylate kinase-2 (AK2).

Maternal factors can be associated with neutropenia in the newborn. Transplacental transfer of IgG directed against antigens on fetal neutrophils can result in peripheral destruction. Drugs (e.g., thiazides) ingested during pregnancy can cause neutropenia in the newborn by either depressed production or peripheral destruction.

In Felty's syndrome—the triad of rheumatoid arthritis, splenomegaly, and neutropenia—spleen-produced antibodies can shorten neutrophil life span, while large granular lymphocytes can attack marrow neutrophil precursors. Splenectomy may increase the neutrophil count in Felty's syndrome and lower serum neutrophil-binding IgG. Some Felty's syndrome patients also have neutropenia associated with an increased number of LGLs.

Splenomegaly with peripheral trapping and destruction of neutrophils is also seen in lysosomal storage diseases and in portal hypertension.

Neutrophilia

Neutrophilia results from increased neutrophil production, increased marrow release, or defective margination **(Table 5-2)**. The most important acute cause of neutrophilia is infection. Neutrophilia from acute infection represents both increased production and increased marrow release. Increased production is also associated with chronic inflammation and certain myeloproliferative diseases. Increased marrow release and mobilization of the marginated leukocyte pool are induced by glucocorticoids. Release of epinephrine, as with vigorous exercise, excitement, or stress, will demarginate neutrophils in the spleen and lungs and double the neutrophil count in minutes. Cigarette smoking can elevate neutrophil counts above the normal range. Leukocytosis with cell counts of 10,000–25,000/μL occurs in response to infection and other forms of acute inflammation and results from both release of the marginated pool and mobilization of marrow reserves. Persistent neutrophilia with cell counts of ≥30,000–50,000/μL is called a leukemoid reaction, a term often used to distinguish this degree of neutrophilia from leukemia. In a leukemoid reaction, the circulating neutrophils are usually mature and not clonally derived.

TABLE 5-2

CAUSES OF NEUTROPHILIA
Increased Production
Idiopathic
Drug-induced—glucocorticoids, G-CSF
Infection—bacterial, fungal, sometimes viral
Inflammation—thermal injury, tissue necrosis, myocardial and pulmonary infarction, hypersensitivity states, collagen vascular diseases
Myeloproliferative diseases—myelocytic leukemia, myeloid metaplasia, polycythemia vera
Increased Marrow Release
Glucocorticoids
Acute infection (endotoxin)
Inflammation—thermal injury
Decreased or Defective Margination
Drugs—epinephrine, glucocorticoids, nonsteroidal anti-inflammatory agents
Stress, excitement, vigorous exercise
Leukocyte adhesion deficiency type 1 (CD18); leukocyte adhesion deficiency type 2 (selectin ligand, CD15s); leukocyte adhesion deficiency type 3 (FERMT3)
Miscellaneous
Metabolic disorders—ketoacidosis, acute renal failure, eclampsia, acute poisoning
Drugs—lithium
Other—metastatic carcinoma, acute hemorrhage or hemolysis

Abbreviation: G-CSF, granulocyte colony-stimulating factor.

Abnormal neutrophil function

Inherited and acquired abnormalities of phagocyte function are listed in **Table 5-3**. The resulting diseases are best considered in terms of the functional defects of adherence, chemotaxis, and microbicidal activity. The distinguishing features of the important inherited disorders of phagocyte function are shown in **Table 5-4**.

Disorders of adhesion

Three main types of leukocyte adhesion deficiency (LAD) have been described. All are autosomal recessive and result in the inability of neutrophils to exit the circulation to sites of infection, leading to leukocytosis and increased susceptibility to infection (Fig. 5-8). Patients with LAD 1 have mutations in CD18, the common component of the integrins LFA-1, Mac-1, and p150,95, leading to a defect in tight adhesion between neutrophils and the endothelium. The heterodimer formed by CD18/CD11b (Mac-1) is also the receptor for the complement-derived opsonin C3bi (CR3). The CD18 gene is located on distal chromosome 21q. The severity of the defect determines the severity of clinical disease. Complete lack of expression of the leukocyte integrins results in a severe phenotype in which inflammatory stimuli do not increase the expression of leukocyte integrins on neutrophils or activated T and B cells. Neutrophils (and monocytes) from patients with LAD 1 adhere poorly to endothelial cells and protein-coated surfaces and exhibit defective spreading, aggregation, and chemotaxis. Patients with LAD 1 have recurrent bacterial infections involving the skin, oral and genital mucosa, and respiratory and intestinal tracts; persistent leukocytosis (resting neutrophil counts of 15,000–20,000/μL) because cells do not marginate; and, in severe cases, a history of delayed separation of the umbilical stump. Infections, especially of the skin, may become necrotic with progressively enlarging borders, slow healing, and development of dysplastic scars. The most common bacteria are Staphylococcus aureus and enteric gram-negative bacteria. LAD 2 is caused by an abnormality of fucosylation of SLe^x (CD15s), the ligand on neutrophils that interacts with selectins on endothelial cells and is responsible for neutrophil rolling along the endothelium. Infection susceptibility in LAD 2 appears to be less severe than in LAD 1. LAD 2 is also known as congenital disorder of glycosylation IIc (CDGIIc) due to mutation in a GDP-fucose transporter (SLC35C1). LAD 3 is characterized by infection susceptibility, leukocytosis, and petechial hemorrhage due to impaired integrin activation caused by mutations in the gene FERMT3.

TABLE 5-3

TYPES OF GRANULOCYTE AND MONOCYTE DISORDERS

	CAUSE OF INDICATED DYSFUNCTION		
FUNCTION	DRUG-INDUCED	ACQUIRED	INHERITED
Adherence-aggregation	Aspirin, colchicine, alcohol, glucocorticoids, ibuprofen, piroxicam	Neonatal state, hemodialysis	Leukocyte adhesion deficiency types 1, 2, and 3
Deformability		Leukemia, neonatal state, diabetes mellitus, immature neutrophils	
Chemokinesis-chemotaxis	Glucocorticoids (high dose), auranofin, colchicine (weak effect), phenylbutazone, naproxen, indomethacin, interleukin 2	Thermal injury, malignancy, malnutrition, periodontal disease, neonatal state, systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, sepsis, influenza virus infection, herpes simplex virus infection, acrodermatitis enteropathica, AIDS	Chédiak-Higashi syndrome, neutrophil-specific granule deficiency, hyper IgE–recurrent infection (Job's) syndrome (in some patients), Down's syndrome, α-mannosidase deficiency, leukocyte adhesion deficiencies, Wiskott-Aldrich syndrome
Microbicidal activity	Colchicine, cyclophosphamide, glucocorticoids (high dose), TNF-α-blocking antibodies	Leukemia, aplastic anemia, certain neutropenias, tuftsin deficiency, thermal injury, sepsis, neonatal state, diabetes mellitus, malnutrition, AIDS	Chédiak-Higashi syndrome, neutrophil-specific granule deficiency, chronic granulomatous disease, defects in IFNγ/IL-12 axis

Abbreviations: IFNγ, interferon γ; IL, interleukin; TNF-α, tumor necrosis factor alpha.

TABLE 5-4

INHERITED DISORDERS OF PHAGOCYTE FUNCTION: DIFFERENTIAL FEATURES

CLINICAL MANIFESTATIONS	CELLULAR OR MOLECULAR DEFECTS	DIAGNOSIS
Chronic Granulomatous Diseases (70% X-Linked, 30% Autosomal Recessive)		
Severe infections of skin, ears, lungs, liver, and bone with catalase-positive microorganisms such as Staphylococcus aureus, Burkholderia cepacia complex, Aspergillus spp., Chromobacterium violaceum; often hard to culture organism; excessive inflammation with granulomas, frequent lymph node suppuration; granulomas can obstruct GI or GU tracts; gingivitis, aphthous ulcers, seborrheic dermatitis	No respiratory burst due to the lack of one of five NADPH oxidase subunits in neutrophils, monocytes, and eosinophils	DHR or NBT test; no superoxide and H_2O_2 production by neutrophils; immunoblot for NADPH oxidase components; genetic detection
Chédiak-Higashi Syndrome (Autosomal Recessive)		
Recurrent pyogenic infections, especially with S. aureus; many patients get lymphoma-like illness during adolescence; periodontal disease; partial oculocutaneous albinism, nystagmus, progressive peripheral neuropathy, mental retardation in some patients	Reduced chemotaxis and phagolysosome fusion, increased respiratory burst activity, defective egress from marrow, abnormal skin window; defect in CHS1	Giant primary granules in neutrophils and other granule-bearing cells (Wright's stain); genetic detection
Specific Granule Deficiency (Autosomal Recessive and Dominant)		
Recurrent infections of skin, ears, and sinopulmonary tract; delayed wound healing; decreased inflammation; bleeding diathesis	Abnormal chemotaxis, impaired respiratory burst and bacterial killing, failure to upregulate chemotactic and adhesion receptors with stimulation, defect in transcription of granule proteins; defect in CEBPE	Lack of secondary (specific) granules in neutrophils (Wright's stain), no neutrophil-specific granule contents (i.e., lactoferrin), no defensins, platelet α granule abnormality; genetic detection

(continued)

TABLE 5-4

INHERITED DISORDERS OF PHAGOCYTE FUNCTION: DIFFERENTIAL FEATURES (CONTINUED)

CLINICAL MANIFESTATIONS	CELLULAR OR MOLECULAR DEFECTS	DIAGNOSIS
Myeloperoxidase Deficiency (Autosomal Recessive)		
Clinically normal except in patients with underlying disease such as diabetes mellitus; then candidiasis or other fungal infections	No myeloperoxidase due to pre- and posttranslational defects in myeloperoxidase deficiency	No peroxidase in neutrophils; genetic detection
Leukocyte Adhesion Deficiency		
Type 1: Delayed separation of umbilical cord, sustained neutrophilia, recurrent infections of skin and mucosa, gingivitis, periodontal disease	Impaired phagocyte adherence, aggregation, spreading, chemotaxis, phagocytosis of C3bi-coated particles; defective production of CD18 subunit common to leukocyte integrins	Reduced phagocyte surface expression of the CD18-containing integrins with monoclonal antibodies against LFA-1 (CD18/CD11a), Mac-1 or CR3 (CD18/CD11b), p150,95 (CD18/CD11c); genetic detection
Type 2: Mental retardation, short stature, Bombay (hh) blood phenotype, recurrent infections, neutrophilia	Impaired phagocyte rolling along endothelium; due to defects in fucose transporter	Reduced phagocyte surface expression of Sialyl-Lewis^x, with monoclonal antibodies against CD15s; genetic detection
Type 3: Petechial hemorrhage, recurrent infections	Impaired signaling for integrin activation resulting in impaired adhesion due to mutation in FERMT3	Reduced signaling for adhesion through integrins; genetic detection
Phagocyte Activation Defects (X-Linked and Autosomal Recessive)		
NEMO deficiency: mild hypohidrotic ectodermal dysplasia; broad-based immune defect: pyogenic and encapsulated bacteria, viruses, Pneumocystis, mycobacteria; X-linked	Impaired phagocyte activation by IL-1, IL-18, TLR, CD40L, TNF-α leading to problems with inflammation and antibody production	Poor in vitro response to endotoxin; impaired NF-κB activation; genetic detection
IRAK4 and MyD88 deficiency: susceptibility to pyogenic bacteria such as staphylococci, streptococci, clostridia; resistant to Candida; autosomal recessive	Impaired phagocyte activation by endotoxin through TLR and other pathways; TNF-α signaling preserved	Poor in vitro response to endotoxin; lack of NF-κB activation by endotoxin; genetic detection
Hyper IgE–Recurrent Infection Syndrome (Autosomal Dominant) (Job's Syndrome)		
Eczematoid or pruritic dermatitis, "cold" skin abscesses, recurrent pneumonias with S. aureus with bronchopleural fistulae and cyst formation, mild eosinophilia, mucocutaneous candidiasis, characteristic facies, restrictive lung disease, scoliosis, delayed primary dental deciduation	Reduced chemotaxis in some patients, reduced memory T and B cells; mutation in STAT3	Somatic and immune features involving lungs, skeleton, and immune system; serum IgE >2000 IU/mL; genetic testing
DOCK8 deficiency (autosomal recessive), severe eczema, atopic dermatitis, cutaneous abscesses, HSV, HPV, and molluscum infections, severe allergies, cancer	Impaired T cell proliferation to mitogens; mutation in DOCK8	Severe allergies, viral infections, high IgE, eosinophilia, low IgM, progressive lymphopenia, genetic detection
Mycobacteria Susceptibility (Autosomal Dominant and Recessive Forms)		
Severe extrapulmonary or disseminated infections with bacille Calmette-Guérin (BCG), nontuberculous mycobacteria, salmonella, histoplasmosis, coccidioidomycosis, poor granuloma formation	Inability to kill intracellular organisms due to low IFN-γ production or response; mutations in IFN-γ receptors, IL-12 receptors, IL-12 p40, STAT1, NEMO, ISG15, GATA2	Abnormally low or very high levels of IFN-γ receptor 1; functional assays of cytokine production and response; genetic detection
GATA2 Deficiency (Autosomal Dominant)		
Persistent or disseminated warts, disseminated mycobacterial disease, low monocytes, NK cells, B cells; hypoplastic myelodysplasia, leukemia, cytogenetic abnormalities, pulmonary alveolar proteinosis	Impaired macrophage activity, cytopenias; mutations in GATA2	Profound circulating monocytopenia, NK and B cell cytopenias; genetic detection

Abbreviations: C/EBPε, CCAAT/enhancer binding protein-ε; DHR, dihydrorhodamine (oxidation test); DOCK8, dedicator of cytokinesis 8; GI, gastrointestinal; GU, genitourinary; HPV, human papilloma virus; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; IRAK4, IL-1 receptor–associated kinase 4; LFA-1, leukocyte function–associated antigen 1; MyD88, myeloid differentiation primary response gene 88; NADPH, nicotinamide–adenine dinueleotide phosphate; NBT, nitroblue tetrazolium (dye test); NEMO, NF-κB essential modulator; NF-κB, nuclear factor-κB; NK, natural killer; STAT1–3, signal transducer and activator of transcription 1–3; TLR, Toll-like receptor; TNF, tumor necrosis factor.

Disorders of neutrophil granules

The most common neutrophil defect is myeloperoxidase deficiency, a primary granule defect inherited as an autosomal recessive trait; the incidence is ~1 in 2000 persons. Isolated myeloperoxidase deficiency is not associated with clinically compromised defenses, presumably because other defense systems such as hydrogen peroxide generation are amplified. Microbicidal activity of neutrophils is delayed but not absent. Myeloperoxidase deficiency may make other acquired host defense defects more serious, and patients with myeloperoxidase deficiency and diabetes are more susceptible to Candida infections. An acquired form of myeloperoxidase deficiency occurs in myelomonocytic leukemia and acute myeloid leukemia.

Chédiak-Higashi syndrome (CHS) is a rare disease with autosomal recessive inheritance due to defects in the lysosomal transport protein LYST, encoded by the gene CHS1 at 1q42. This protein is required for normal packaging and disbursement of granules. Neutrophils (and all cells containing lysosomes) from patients with CHS characteristically have large granules **(Fig. 5-9)**, making it a systemic disease. Patients with CHS have nystagmus, partial oculocutaneous albinism, and an increased number of infections resulting from many bacterial agents. Some CHS patients develop an "accelerated phase" in childhood with a hemophagocytic syndrome and an aggressive lymphoma requiring bone marrow transplantation. CHS neutrophils and monocytes have impaired chemotaxis and abnormal rates of microbial killing due to slow rates of fusion of the lysosomal granules with phagosomes. NK cell function is also impaired. CHS patients may develop a severe disabling peripheral neuropathy in adulthood that can lead to bed confinement.

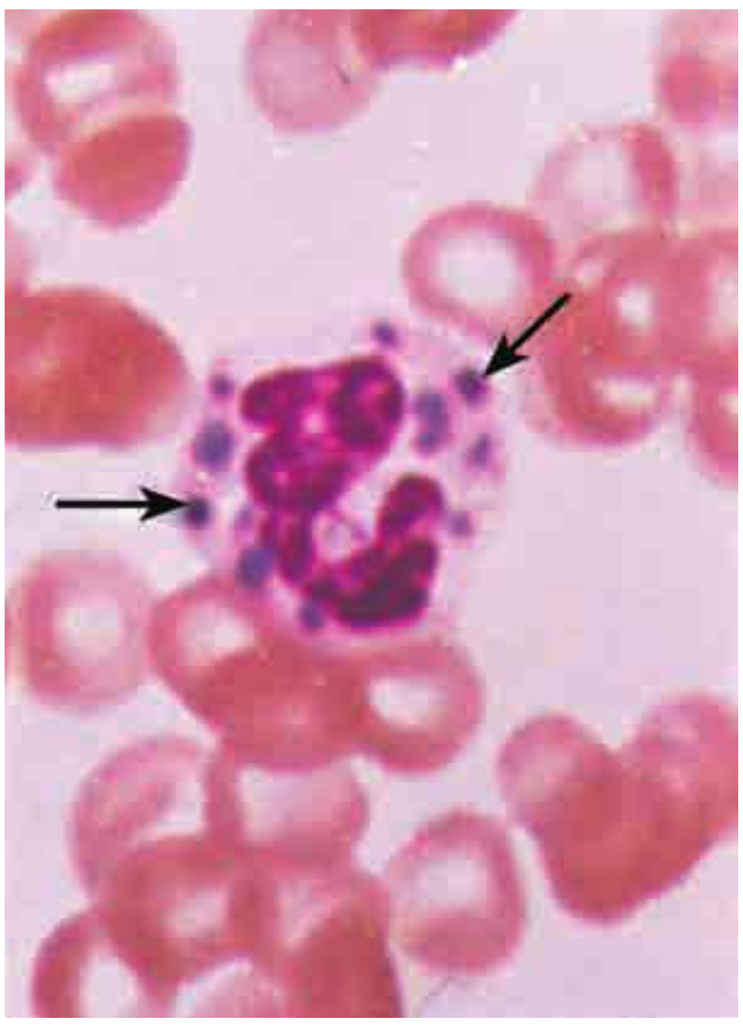


FIGURE 5-9
Chédiak-Higashi syndrome. The granulocytes contain huge cytoplasmic granules formed from aggregation and fusion of azurophilic and specific granules. Large abnormal granules are found in other granule-containing cells throughout the body.

Specific granule deficiency is a rare autosomal recessive disease in which the production of secondary granules and their contents, as well as the primary granule component defensins, is defective. The defect in killing leads to severe bacterial infections. One type of specific granule deficiency is due to a mutation in the CCAAT/enhancer binding protein-ε, a regulator of expression of granule components. A dominant mutation in C/EBP-ε has also been described.

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is a group of disorders of granulocyte and monocyte oxidative metabolism. Although CGD is rare, with an incidence of ~1 in 200,000 individuals, it is an important model of defective neutrophil oxidative metabolism. In about two-thirds of patients, CGD is inherited as an X-linked recessive trait; 30% of patients inherit the disease in an autosomal recessive pattern. Mutations in the genes for the five proteins that assemble at the plasma membrane account for all patients with CGD. Two proteins (a 91-kDa protein, abnormal in X-linked CGD, and a 22-kDa protein, absent in one form of autosomal recessive CGD) form the heterodimer cytochrome b-558 in the plasma membrane. Three other proteins (40, 47, and 67 kDa, abnormal in the other autosomal recessive forms of CGD) are cytoplasmic in origin and interact with the cytochrome after cell activation to form NADPH oxidase, required for hydrogen peroxide production. Leukocytes from patients with CGD have severely diminished hydrogen peroxide production. The genes involved in each of the defects have been cloned and sequenced and the chromosome locations identified. Patients with CGD characteristically have increased numbers of infections due to catalase-positive microorganisms (organisms that destroy their own hydrogen peroxide) such as S. aureus, Burkholderia cepacia, and Aspergillus species. When patients with CGD become infected, they often have extensive inflammatory reactions, and lymph node suppuration is common despite the administration of appropriate antibiotics. Aphthous ulcers and chronic inflammation of the nares are often present. Granulomas are frequent and can obstruct the gastrointestinal or genitourinary tracts. The excessive inflammation is due to failure to downregulate inflammation, reflecting failure to inhibit the synthesis of, degradation of, or response to chemoattractants or residual antigens, leading to persistent neutrophil accumulation. Impaired killing of intracellular microorganisms by macrophages may lead to persistent cell-mediated immune activation and granuloma formation.

Autoimmune complications such as immune thrombocytopenic purpura and juvenile rheumatoid arthritis are also increased in CGD. In addition, for unexplained reasons, discoid lupus is more common in X-linked carriers. Late complications, including nodular regenerative hyperplasia and portal hypertension, are increasingly recognized in long-term survivors of severe CGD.

Disorders of phagocyte activation

Phagocytes depend on cell-surface stimulation to induce signals that evoke multiple levels of the inflammatory response, including cytokine synthesis, chemotaxis, and antigen presentation. Mutations affecting the major pathway that signals through NF-κB have been noted in patients with a variety of infection susceptibility syndromes. If the defects are at a very late stage of signal transduction, in the protein critical for NF-κB activation known as the NF-κB essential modulator (NEMO), then affected males develop ectodermal dysplasia and severe immune deficiency with susceptibility to bacteria, fungi, mycobacteria, and viruses. If the defects in NF-κB activation are closer to the cell-surface receptors, in the proteins transducing Toll-like receptor signals, IL-1 receptor–associated kinase 4 (IRAK4), and myeloid differentiation primary response gene 88 (MyD88), then children have a marked susceptibility to pyogenic infections early in life but develop resistance to infection later.

MONONUCLEAR PHAGOCYTES

T e mononuclear phagocyte system is composed of monoblasts, promonocytes, and monocytes, in addition to the structurally diverse tissue macrophages that make up what was previously referred to as the reticuloendothelial system. Macrophages are long-lived phagocytic cells capable of many of the functions of neutrophils. T ey are also secretory cells that participate in many immunologic and inflammatory processes distinct from neutrophils. Monocytes leave the circulation by diapedesis more slowly than neutrophils and have a half-life in the blood of 12–24 h.

After blood monocytes arrive in the tissues, they differentiate into macrophages (“big eaters”) with specialized functions suited for specific anatomic locations. Macrophages are particularly abundant in capillary walls of the lung, spleen, liver, and bone marrow, where they function to remove microorganisms and other noxious elements from the blood. Alveolar macrophages, liver Kupffer cells, splenic macrophages, peritoneal macrophages, bone marrow macrophages, lymphatic macrophages, brain microglial cells, and dendritic macrophages all have specialized functions. Macrophage-secreted products include lysozyme, neutral proteases, acid hydrolases, arginase, complement components, enzyme inhibitors (plasmin, α_2-macroglobulin), binding proteins (transferrin, fibronectin, transcobalamin II), nucleosides, and cytokines (TNF-α; IL-1, -8, -12, -18). IL-1 has many functions, including initiating fever in the hypothalamus, mobilizing leukocytes from the bone marrow, and activating lymphocytes and neutrophils. TNF-α is a pyrogen that duplicates many of the actions of IL-1 and plays an important role in the pathogenesis of gram-negative shock. TNF-α stimulates production of hydrogen peroxide and related toxic oxygen species by macrophages and neutrophils. In addition, TNF-α induces catabolic changes that contribute to the profound wasting (cachexia) associated with many chronic diseases.

Other macrophage-secreted products include reactive oxygen and nitrogen metabolites, bioactive lipids (arachidonic acid metabolites and platelet-activating factors), chemokines, CSFs, and factors stimulating fibroblast and vessel proliferation. Macrophages help regulate the replication of lymphocytes and participate in the killing of tumors, viruses, and certain bacteria (Mycobacterium tuberculosis and Listeria monocytogenes). Macrophages are key effector cells in the elimination of intracellular microorganisms. T eir ability to fuse to form giant cells that coalesce into granulomas in response to some inflammatory stimuli is important in the elimination of intracellular microbes and is under the control of IFN-γ. Nitric oxide induced by IFN-γ is an important effector against intracellular parasites, including tuberculosis and Leishmania.

Macrophages play an important role in the immune response. T ey process and present antigen to lymphocytes and secrete cytokines that modulate and direct lymphocyte development and function. Macrophages participate in autoimmune phenomena by removing immune complexes and other substances from the circulation. Polymorphisms in macrophage receptors for immunoglobulin (FcγRII) determine susceptibility to some infections and autoimmune diseases. In wound healing, they dispose of senescent cells, and they contribute to atheroma development. Macrophage elastase mediates development of emphysema from cigarette smoking.

DISORDERS OF THE MONONUCLEAR PHAGOCYTE SYSTEM

Many disorders of neutrophils extend to mononuclear phagocytes. Monocytosis is associated with tuberculosis, brucellosis, subacute bacterial endocarditis, Rocky Mountain spotted fever, malaria, and visceral leishmaniasis (kala azar). Monocytosis also occurs with malignancies, leukemias, myeloproliferative syndromes, hemolytic anemias, chronic idiopathic neutropenias, and granulomatous diseases such as sarcoidosis, regional enteritis, and some collagen vascular diseases.

Patients with LAD, hyperimmunoglobulin E–recurrent infection (Job's) syndrome, CHS, and CGD all have defects in the mononuclear phagocyte system.

Monocyte cytokine production or response is impaired in some patients with disseminated nontuberculous mycobacterial infection who are not infected with HIV. Genetic defects in the pathways regulated by IFN-γ and IL-12 lead to impaired killing of intracellular bacteria, mycobacteria, salmonellae, and certain viruses **(Fig. 5-10)**.

Certain viral infections impair mononuclear phagocyte function. For example, influenza virus infection causes abnormal monocyte chemotaxis. Mononuclear phagocytes can be infected by HIV using CCR5, the chemokine receptor that acts as a co-receptor with CD4 for HIV. T lymphocytes produce IFN-γ, which induces FcR expression and phagocytosis and stimulates hydrogen peroxide production by mononuclear phagocytes and neutrophils. In certain diseases, such as AIDS, IFN-γ production may be deficient, whereas in other diseases, such as T cell lymphomas, excessive release of IFN-γ may be associated with erythrophagocytosis by splenic macrophages.

Autoinflammatory diseases are characterized by abnormal cytokine regulation, leading to excess inflammation in the absence of infection. T ese diseases can mimic infectious or immunodeficient syndromes. Gain-of-function mutations in the TNF-α receptor cause TNF-α receptor–associated periodic syndrome (TRAPS), which is characterized by recurrent fever in the absence of infection, due to persistent stimulation of the TNF-α receptor. Diseases with abnormal IL-1 regulation leading to fever include familial Mediterranean fever due to mutations in PYRIN. Mutations in cold-induced autoinf ammatory syndrome 1 (CIAS1) lead to neonatal-onset multisystem autoinflammatory disease, familial cold urticaria, and Muckle-Wells syndrome. T e syndrome of pyoderma gangrenosum, acne, and sterile pyogenic arthritis (PAPA syndrome) is caused by mutations in PSTPIP1. In contrast to these syndromes of overexpression of proinflammatory cytokines, blockade of TNF-α by the antagonists infliximab, adalimumab, certolizumab, golimumab, or etanercept has been associated with severe infections due to tuberculosis, nontuberculous mycobacteria, and fungi.

Monocytopenia occurs with acute infections, with stress, and after treatment with glucocorticoids. Drugs that suppress neutrophil production in the bone marrow can cause monocytopenia. Persistent severe circulating monocytopenia is seen in GATA2 deficiency, even though macrophages are found at the sites of inflammation. Monocytopenia also occurs in aplastic anemia, hairy cell leukemia, acute myeloid leukemia, and as a direct result of myelotoxic drugs.

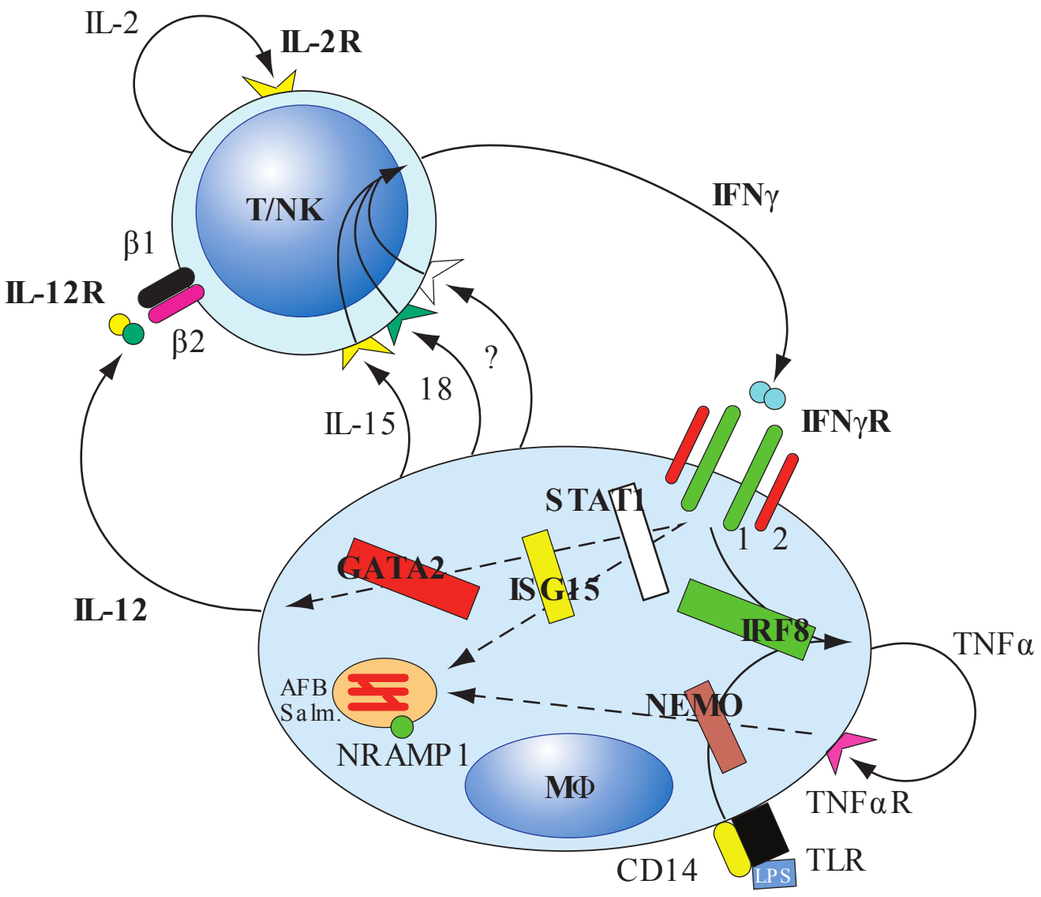


FIGURE 5-10

Lymphocyte-macrophage interactions underlying resistance to mycobacteria and other intracellular pathogens such as Salmonella, Histoplasma, and Coccidioides. Mycobacteria (and others) infect macrophages, leading to the production of IL-12, which activates T or NK cells through its receptor, leading to production of IL-2 and IFN-γ. IFN-γ acts through its receptor on macrophages to upregulate TNF-γ and IL-12 and kill intracellular pathogens. Other critical interacting molecules include signal transducer and activator of transcription 1 (STAT1), interferon regulatory factor 8 (IRF8), GATA2, and ISG15. Mutant forms of the cytokines and receptors shown in bold type have been found in severe cases of nontuberculous mycobacterial infection, salmonellosis and other intracellular pathogens. AFB, acid-fast bacilli; IFN, interferon; IL, interleukin; NEMO, nuclear factor-κB essential modulator; NK, natural killer; TLR, Toll-like receptor; TNF, tumor necrosis factor.

EOSINOPHILS

Eosinophils and neutrophils share similar morphology, many lysosomal constituents, phagocytic capacity, and oxidative metabolism. Eosinophils express a specific chemoattractant receptor and respond to a specific chemokine, eotaxin, but little is known about their required role. Eosinophils are much longer lived than neutrophils, and unlike neutrophils, tissue eosinophils can recirculate. During most infections, eosinophils appear unimportant. However, in invasive helminthic infections, such as hookworm, schistosomiasis, strongyloidiasis, toxocariasis, trichinosis, filariasis, echinococcosis, and cysticercosis, the eosinophil plays a central role in host defense. Eosinophils are associated with bronchial asthma, cutaneous allergic reactions, and other hypersensitivity states.

T e distinctive feature of the red-staining (Wright's stain) eosinophil granule is its crystalline core consisting of an arginine-rich protein (major basic protein) with histaminase activity, important in host defense

against parasites. Eosinophil granules also contain a unique eosinophil peroxidase that catalyzes the oxidation of many substances by hydrogen peroxide and may facilitate killing of microorganisms.

Eosinophil peroxidase, in the presence of hydrogen peroxide and halide, initiates mast cell secretion in vitro and thereby promotes inflammation. Eosinophils contain cationic proteins, some of which bind to heparin and reduce its anticoagulant activity. Eosinophil-derived neurotoxin and eosinophil cationic protein are ribonucleases that can kill respiratory syncytial virus. Eosinophil cytoplasm contains Charcot-Leyden crystal protein, a hexagonal bipyramidal crystal first observed in a patient with leukemia and then in sputum of patients with asthma; this protein is lysophospholipase and may function to detoxify certain lysophospholipids.

Several factors enhance the eosinophil's function in host defense. T cell–derived factors enhance the ability of eosinophils to kill parasites. Mast cell–derived eosinophil chemotactic factor of anaphylaxis (ECFa) increases the number of eosinophil complement receptors and enhances eosinophil killing of parasites. Eosinophil CSFs (e.g., IL-5) produced by macrophages increase eosinophil production in the bone marrow and activate eosinophils to kill parasites.

EOSINOPHILIA

Eosinophilia is the presence of >500 eosinophils per μL of blood and is common in many settings besides parasite infection. Significant tissue eosinophilia can occur without an elevated blood count. A common cause of eosinophilia is allergic reaction to drugs (iodides, aspirin, sulfonamides, nitrofurantoin, penicillins, and cephalosporins). Allergies such as hay fever, asthma, eczema, serum sickness, allergic vasculitis, and pemphigus are associated with eosinophilia. Eosinophilia also occurs in collagen vascular diseases (e.g., rheumatoid arthritis, eosinophilic fasciitis, allergic angiitis, and periarteritis nodosa) and malignancies (e.g., Hodgkin's disease; mycosis fungoides; chronic myeloid leukemia; and cancer of the lung, stomach, pancreas, ovary, or uterus), as well as in Job's syndrome, DOCK8 deficiency (see below), and CGD. Eosinophilia is commonly present in helminthic infections. IL-5 is the dominant eosinophil growth factor. T erapeutic administration of the cytokines IL-2 or GM-CSF frequently leads to transient eosinophilia. T e most dramatic hypereosinophilic syndromes are Loef er's syndrome, tropical pulmonary eosinophilia, Loef er's endocarditis, eosinophilic leukemia, and idiopathic hypereosinophilic syndrome (50,000–100,000/μL). IL-5 is the dominant eosinophil growth factor and can be specifically inhibited with the monoclonal antibody mepolizumab.

T e idiopathic hypereosinophilic syndrome represents a heterogeneous group of disorders with the common feature of prolonged eosinophilia of unknown cause and organ system dysfunction, including the heart, central nervous system, kidneys, lungs, gastrointestinal tract, and skin. T e bone marrow is involved in all affected individuals, but the most severe complications involve the heart and central nervous system. Clinical manifestations and organ dysfunction are highly variable. Eosinophils are found in the involved tissues and likely cause tissue damage by local deposition of toxic eosinophil proteins such as eosinophil cationic protein and major basic protein. In the heart, the pathologic changes lead to thrombosis, endocardial fibrosis, and restrictive endomyocardiopathy. T e damage to tissues in other organ systems is similar. Some cases are due to mutations involving the platelet-derived growth factor receptor, and these are extremely sensitive to the tyrosine kinase inhibitor imatinib. Glucocorticoids, hydroxyurea, and IFN-α each have been used successfully, as have therapeutic antibodies against IL-5. Cardiovascular complications are managed aggressively.

T e eosinophilia-myalgia syndrome is a multisystem disease, with prominent cutaneous, hematologic, and visceral manifestations, that frequently evolves into a chronic course and can occasionally be fatal. T e syndrome is characterized by eosinophilia (eosinophil count >1000/μL) and generalized disabling myalgias without other recognized causes. Eosinophilic fasciitis, pneumonitis, and myocarditis; neuropathy culminating in respiratory failure; and encephalopathy may occur. T e disease is caused by ingesting contaminants in L-tryptophan–containing products. Eosinophils, lymphocytes, macrophages, and fibroblasts accumulate in the affected tissues, but their role in pathogenesis is unclear. Activation of eosinophils and fibroblasts and the deposition of eosinophil-derived toxic proteins in affected tissues may contribute. IL-5 and transforming growth factor β have been implicated as potential mediators. Treatment is withdrawal of products containing L-tryptophan and the administration of glucocorticoids. Most patients recover fully, remain stable, or show slow recovery, but the disease can be fatal in up to 5% of patients.

Eosinophilic neoplasms are discussed in Chapter 17.

EOSINOPENIA

Eosinopenia occurs with stress, such as acute bacterial infection, and after treatment with glucocorticoids. T e mechanism of eosinopenia of acute bacterial infection is unknown but is independent of endogenous glucocorticoids, because it occurs in animals after total adrenalectomy. T ere is no known adverse effect of eosinopenia.

HYPERIMMUNOGLOBULIN E–RECURRENT INFECTION SYNDROME

The hyperimmunoglobulin E–recurrent infection syndrome, or Job's syndrome, is a rare multisystem disease in which the immune and somatic systems are affected, including neutrophils, monocytes, T cells, B cells, and osteoclasts. Autosomal dominant mutations in signal transducer and activator of transcription 3 (STAT3) lead to inhibition of normal STAT signaling with broad and profound effects. Patients have characteristic facies with broad nose, kyphoscoliosis, and eczema. The primary teeth erupt normally but do not deciduate, often requiring extraction. Patients develop recurrent sinopulmonary and cutaneous infections that tend to be much less inflamed than appropriate for the degree of infection and have been referred to as "cold abscesses." Characteristically, pneumonias cavitate, leading to pneumatoceles. Coronary artery aneurysms are common, as are cerebral demyelinated plaques that accumulate with age. Importantly, IL-17–producing T cells, which are thought responsible for protection against extracellular and mucosal infections, are profoundly reduced in Job's syndrome. Despite very high IgE levels, these patients do not have elevated levels of allergy. An important syndrome with clinical overlap with STAT3 deficiency is due to autosomal recessive defects in dedicator of cytokinesis 8 (DOCK8). In DOCK8 deficiency, IgE elevation is joined to severe allergy, viral susceptibility, and increased rates of cancer.

LABORATORY DIAGNOSIS AND MANAGEMENT

Initial studies of WBC and differential and often a bone marrow examination may be followed by assessment of bone marrow reserves (steroid challenge test), marginated circulating pool of cells (epinephrine challenge test), and marginating ability (endotoxin challenge test) (Fig. 5-7). In vivo assessment of inflammation is possible with a Rebuck skin window test or an in vivo skin blister assay, which measures the ability of leukocytes and inflammatory mediators to accumulate locally in the skin. In vitro tests of phagocyte aggregation, adherence, chemotaxis, phagocytosis, degranulation, and microbicidal activity (for S. aureus) may help pinpoint cellular or humoral lesions. Deficiencies of oxidative metabolism are detected with either the nitroblue tetrazolium (NBT) dye test or the dihydrorhodamine (DHR) oxidation test. These tests are based on the ability of products of oxidative metabolism to alter the oxidation states of reporter molecules so that they can be detected microscopically (NBT) or by flow cytometry (DHR). Qualitative studies of superoxide and hydrogen peroxide production may further define neutrophil oxidative function.

Patients with leukopenias or leukocyte dysfunction often have delayed inflammatory responses. Therefore, clinical manifestations may be minimal despite overwhelming infection, and unusual infections must always be suspected. Early signs of infection demand prompt, aggressive culturing for microorganisms, use of antibiotics, and surgical drainage of abscesses. Prolonged courses of antibiotics are often required. In patients with CGD, prophylactic antibiotics (trimethoprim-sulfamethoxazole) and antifungals (itraconazole) markedly diminish the frequency of life-threatening infections. Glucocorticoids may relieve gastrointestinal or genitourinary tract obstruction by granulomas in patients with CGD. Although TNF-α-blocking agents may markedly relieve inflammatory bowel symptoms, extreme caution must be exercised in their use in CGD inflammatory bowel disease, because it profoundly increases these patients' already heightened susceptibility to infection. Recombinant human IFN-γ, which nonspecifically stimulates phagocytic cell function, reduces the frequency of infections in patients with CGD by 70% and reduces the severity of infection. The effect of IFN-γ in CGD is additive to the effect of prophylactic antibiotics. The recommended dose is 50 μg/m^2 subcutaneously three times weekly. IFN-γ has also been used successfully in the treatment of leprosy, nontuberculous mycobacteria, and visceral leishmaniasis.

Rigorous oral hygiene reduces but does not eliminate the discomfort of gingivitis, periodontal disease, and aphthous ulcers; chlorhexidine mouthwash and tooth brushing with a hydrogen peroxide–sodium bicarbonate paste help many patients. Oral antifungal agents (fluconazole, itraconazole, voriconazole, posaconazole) have reduced mucocutaneous candidiasis in patients with Job's syndrome. Androgens, glucocorticoids, lithium, and immunosuppressive therapy have been used to restore myelopoiesis in patients with neutropenia due to impaired production. Recombinant G-CSF is useful in the management of certain forms of neutropenia due to depressed neutrophil production, including those related to cancer chemotherapy. Patients with chronic neutropenia with evidence of a good bone marrow reserve need not receive prophylactic antibiotics. Patients with chronic or cyclic neutrophil counts <500/μL may benefit from prophylactic antibiotics and G-CSF during periods of neutropenia. Oral trimethoprim-sulfamethoxazole (160/800 mg) twice daily can prevent infection. Increased numbers of fungal infections are not seen in patients with CGD on this regimen. Oral quinolones such as levofloxacin and ciprofloxacin are alternatives.

In the setting of cytotoxic chemotherapy with severe, persistent lymphocyte dysfunction, trimethoprim-sulfamethoxazole prevents Pneumocystis jiroveci pneumonia.

T ese patients, and patients with phagocytic cell dysfunction, should avoid heavy exposure to airborne soil, dust, or decaying matter (mulch, manure), which are often rich in Nocardia and the spores of Aspergillus and other fungi. Restriction of activities or social contact has no proven role in reducing risk of infection for phagocyte defects.

Although aggressive medical care for many patients with phagocytic disorders can allow them to go for years without a life-threatening infection, there may still be delayed effects of prolonged antimicrobials and other inflammatory complications. Cure of most congenital phagocyte defects is possible by bone marrow transplantation, and rates of success are improving **(Chap. 31)**. T e identification of specific gene defects in patients with LAD 1, CGD, and other immunodeficiencies has led to gene therapy trials in a number of genetic white cell disorders.

CHAPTER 6

ATLAS OF HEMATOLOGY AND ANALYSIS OF PERIPHERAL BLOOD SMEARS

Dan L. Longo

Some of the relevant findings in peripheral blood, enlarged lymph nodes, and bone marrow are illustrated in this chapter. Systematic histologic examination of the bone marrow and lymph nodes is beyond the scope of a general medicine textbook. However, every internist should know how to examine a peripheral blood smear.

The examination of a peripheral blood smear is one of the most informative exercises a physician can perform. Although advances in automated technology have made the examination of a peripheral blood smear by a physician seem less important, the technology is not a completely satisfactory replacement for a blood smear interpretation by a trained medical professional who also knows the patient's clinical history, family history, social history, and physical findings. It is useful to ask the laboratory to generate a Wright's-stained peripheral blood smear and examine it.

The best place to examine blood cell morphology is the feathered edge of the blood smear where red cells lie in a single layer, side by side, just barely touching one another but not overlapping. The author's approach is to look at the smallest cellular elements, the platelets, first and work his way up in size to red cells and then white cells.

Using an oil immersion lens that magnifies the cells 100-fold, one counts the platelets in five to six fields, averages the number per field, and multiplies by 20,000 to get a rough estimate of the platelet count. The platelets are usually 1–2 μm in diameter and have a blue granulated appearance. There is usually 1 platelet for every 20 or so red cells. Of course, the automated counter is much more accurate, but gross disparities between the automated and manual counts should be assessed. Large platelets may be a sign of rapid platelet turnover, as young platelets are often larger than old ones; alternatively, certain rare inherited syndromes can produce large platelets. Platelet clumping visible on the smear can be associated with falsely low automated platelet counts. Similarly, neutrophil fragmentation can be a source of falsely elevated automated platelet counts.

Next one examines the red blood cells. One can gauge their size by comparing the red cell to the nucleus of a small lymphocyte. Both are normally about 8 μm wide. Red cells that are smaller than the small lymphocyte nucleus may be microcytic; those larger than the small lymphocyte nucleus may be macrocytic. Macrocytic cells also tend to be more oval than spherical in shape and are sometimes called macroovalocytes. The automated mean corpuscular volume (MCV) can assist in making a classification. However, some patients may have both iron and vitamin B_{12} deficiency, which will produce an MCV in the normal range but wide variation in red cell size. When the red cells vary greatly in size, anisocytosis is said to be present. When the red cells vary greatly in shape, poikilocytosis is said to be present. The electronic cell counter provides an independent assessment of variability in red cell size. It measures the range of red cell volumes and reports the results as "red cell distribution width" (RDW). This value is calculated from the MCV; thus, cell width is not being measured but cell volume is. The term is derived from the curve displaying the frequency of cells at each volume, also called the distribution. The width of the red cell volume distribution curve is what determines the RDW. The RDW is calculated as follows: RDW = (standard deviation of MCV ÷ mean MCV) × 100. In the presence of morphologic anisocytosis, RDW (normally 11–14%) increases to 15–18%. The RDW is useful in at least two clinical settings. In patients with microcytic anemia, the differential diagnosis is generally between iron deficiency and thalassemia. In thalassemia, the small red cells are generally of uniform size with a normal small RDW. In iron deficiency, the size variability and the RDW are large. In addition, a large

RDW can suggest a dimorphic anemia when a chronic atrophic gastritis can produce both vitamin B_{12} malabsorption to produce macrocytic anemia and blood loss to produce iron deficiency. In such settings, RDW is also large. An elevated RDW also has been reported as a risk factor for all-cause mortality in population-based studies (Patel KV et al: Arch Intern Med 169:515, 2009), a finding that is unexplained currently.

After red cell size is assessed, one examines the hemoglobin content of the cells. They are either normal in color (normochromic) or pale in color (hypochromic). They are never "hyperchromic." If more than the normal amount of hemoglobin is made, the cells get larger—they do not become darker. In addition to hemoglobin content, the red cells are examined for inclusions. Red cell inclusions are the following:

1. Basophilic stippling—diffuse fine or coarse blue dots in the red cell usually representing RNA residue—especially common in lead poisoning
2. Howell-Jolly bodies—dense blue circular inclusions that represent nuclear remnants—their presence implies defective splenic function
3. Nuclei—red cells may be released or pushed out of the marrow prematurely before nuclear extrusion—often implies a myelophthisic process or a vigorous narrow response to anemia, usually hemolytic anemia
4. Parasites—red cell parasites include malaria and babesia
5. Polychromatophilia—the red cell cytoplasm has a bluish hue, reflecting the persistence of ribosomes still actively making hemoglobin in a young red cell

Vital stains are necessary to see precipitated hemoglobin called Heinz bodies.

Red cells can take on a variety of different shapes. All abnormally shaped red cells are poikilocytes. Small red cells without the central pallor are spherocytes; they can be seen in hereditary spherocytosis, hemolytic anemias of other causes, and clostridial sepsis. Dacrocytes are teardrop-shaped cells that can be seen in hemolytic anemias, severe iron deficiency, thalassemias, myelofibrosis, and myelodysplastic syndromes. Schistocytes are helmet-shaped cells that reflect microangiopathic hemolytic anemia or fragmentation on an artificial heart valve. Echinocytes are spiculated red cells with the spikes evenly spaced; they can represent an artifact of abnormal drying of the blood smear or reflect changes in stored blood. They also can be seen in renal failure and malnutrition and are often reversible. Acanthocytes are spiculated red cells with the spikes irregularly distributed. This process tends to be irreversible and reflects underlying renal disease, abetalipoproteinemia, or splenectomy. Elliptocytes are elliptical-shaped red cells that can reflect an inherited defect in the red cell membrane, but they also are seen in iron deficiency, myelodysplastic syndromes, megaloblastic anemia, and thalassemias. Stomatocytes are red cells in which the area of central pallor takes on the morphology of a slit instead of the usual round shape. Stomatocytes can indicate an inherited red cell membrane defect and also can be seen in alcoholism. Target cells have an area of central pallor that contains a dense center, or bull's-eye. These cells are seen classically in thalassemia, but they are also present in iron deficiency, cholestatic liver disease, and some hemoglobinopathies. They also can be generated artifactually by improper slide making.

One last feature of the red cells to assess before moving to the white blood cells is the distribution of the red cells on the smear. In most individuals, the cells lie side by side in a single layer. Some patients have red cell clumping (called agglutination) in which the red cells pile upon one another; it is seen in certain paraproteinemias and autoimmune hemolytic anemias. Another abnormal distribution involves red cells lying in single cell rows on top of one another like stacks of coins. This is called rouleaux formation and reflects abnormal serum protein levels.

Finally, one examines the white blood cells. Three types of granulocytes are usually present: neutrophils, eosinophils, and basophils, in decreasing frequency. Neutrophils are generally the most abundant white cell. They are round, are 10–14 μm wide, and contain a lobulated nucleus with two to five lobes connected by a thin chromatin thread. Bands are immature neutrophils that have not completed nuclear condensation and have a U-shaped nucleus. Bands reflect a left shift in neutrophil maturation in an effort to make more cells more rapidly. Neutrophils can provide clues to a variety of conditions. Vacuolated neutrophils may be a sign of bacterial sepsis. The presence of 1- to 2-μm blue cytoplasmic inclusions, called Döhle bodies, can reflect infections, burns, or other inflammatory states. If the neutrophil granules are larger than normal and stain a darker blue, "toxic granulations" are said to be present, and they also suggest a systemic inflammation. The presence of neutrophils with more than five nuclear lobes suggests megaloblastic anemia. Large misshapen granules may reflect the inherited Chédiak-Higashi syndrome.

Eosinophils are slightly larger than neutrophils, have bilobed nuclei, and contain large red granules. Diseases of eosinophils are associated with too many of them rather than any morphologic or qualitative change. They normally total less than one-thirtieth the number of neutrophils. Basophils are even rarer than eosinophils in the blood. They have large dark blue granules and may be increased as part of chronic myeloid leukemia.

Lymphocytes can be present in several morphologic forms. Most common in healthy individuals are small lymphocytes with a small dark nucleus and scarce cytoplasm. In the presence of viral infections, more of the

lymphocytes are larger, about the size of neutrophils, with abundant cytoplasm and a less condensed nuclear chromatin. T ese cells are called reactive lymphocytes. About 1% of lymphocytes are larger and contain blue granules in a light blue cytoplasm; they are called large granular lymphocytes. In chronic lymphoid leukemia, the small lymphocytes are increased in number, and many of them are ruptured in making the blood smear, leaving a smudge of nuclear material without a surrounding cytoplasm or cell membrane; they are called smudge cells and are rare in the absence of chronic lymphoid leukemia.

Monocytes are the largest white blood cells, ranging from 15 to 22 μm in diameter. T e nucleus can take on a variety of shapes but usually appears to be folded; the cytoplasm is gray.

Abnormal cells may appear in the blood. Most often the abnormal cells originate from neoplasms of bone marrow–derived cells, including lymphoid cells, myeloid cells, and occasionally red cells. More rarely, other types of tumors can get access to the bloodstream, and rare epithelial malignant cells may be identified. T e chances of seeing such abnormal cells is increased by examining blood smears made from buffy coats, the layer of cells that is visible on top of sedimenting red cells when blood is left in the test tube for an hour. Smears made from finger sticks may include rare endothelial cells.

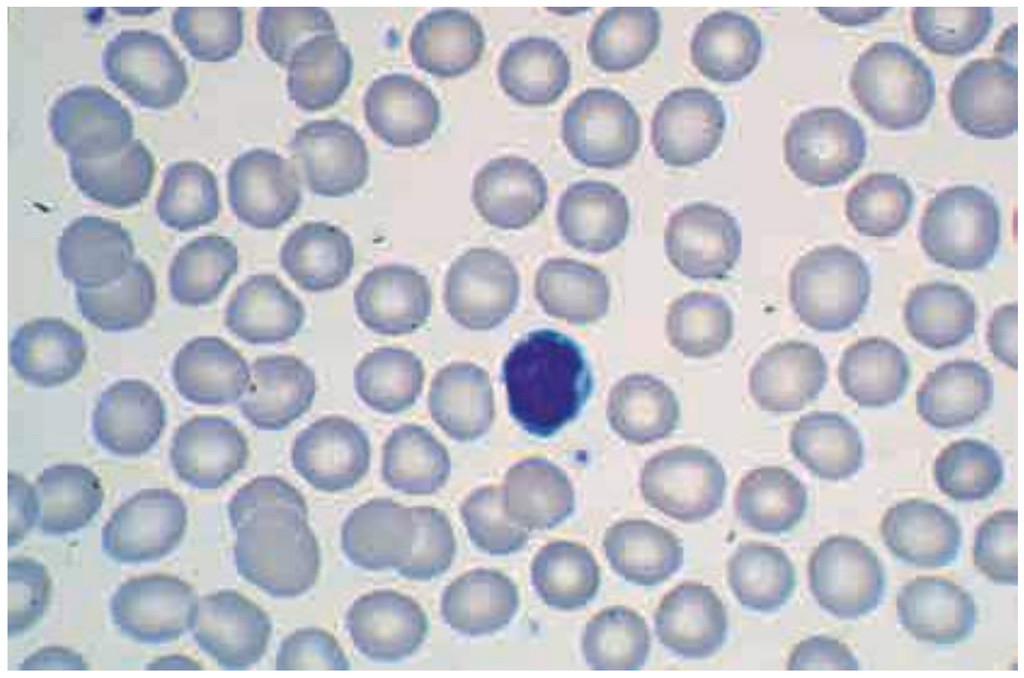


FIGURE 6-1
Normal peripheral blood smear. Small lymphocyte in center of field. Note that the diameter of the red blood cell is similar to the diameter of the small lymphocyte nucleus.

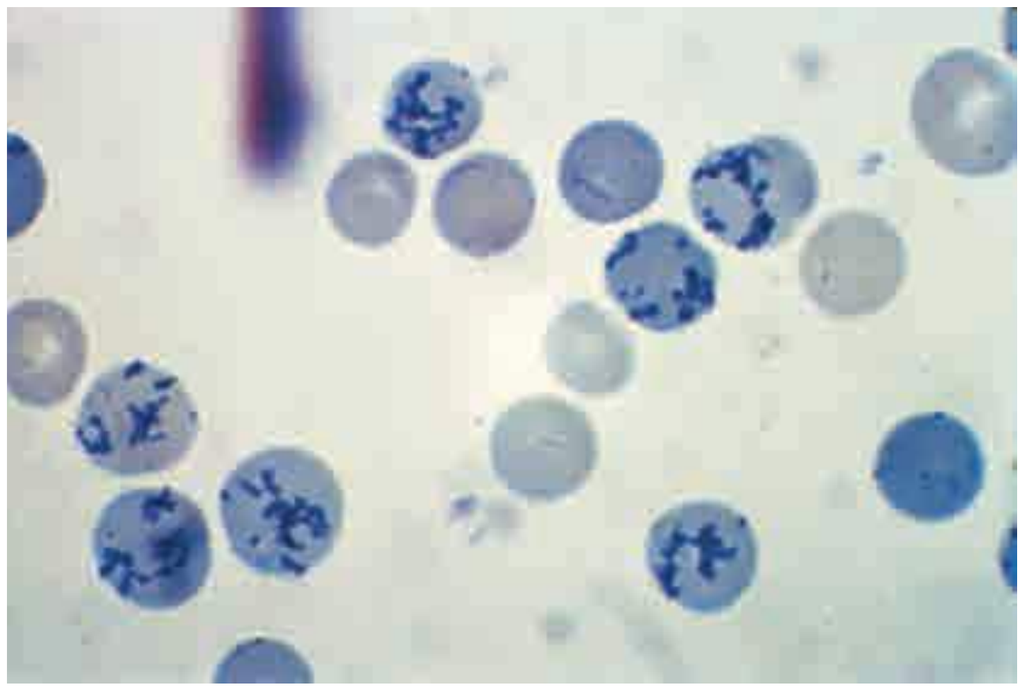


FIGURE 6-2
Reticulocyte count preparation. This new methylene blue–stained blood smear shows large numbers of heavily stained reticulocytes (the cells containing the dark blue–staining RNA precipitates).

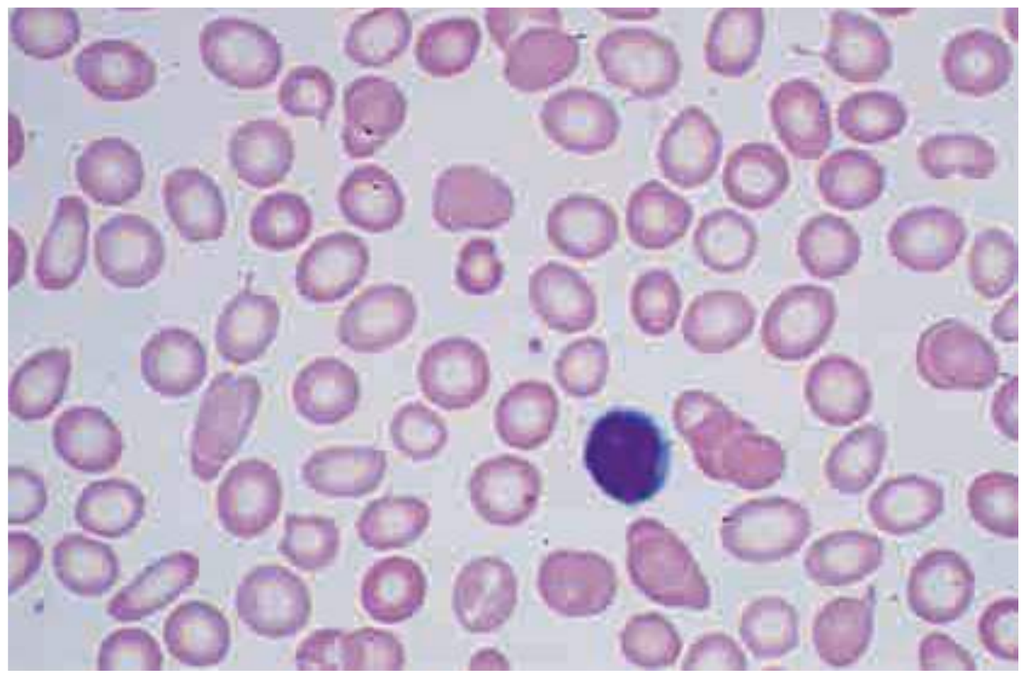


FIGURE 6-3
Hypochromic microcytic anemia of iron deficiency. Small lymphocyte in field helps assess the red blood cell size.

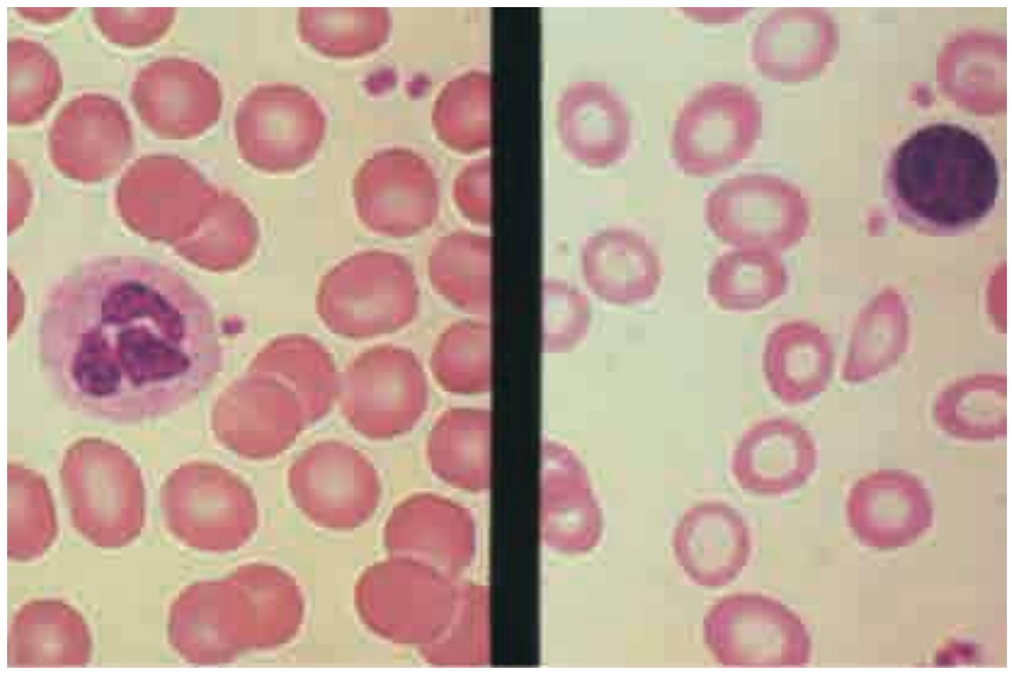


FIGURE 6-4
Iron deficiency anemia next to normal red blood cells. Microcytes (right panel) are smaller than normal red blood cells (cell diameter <7 μm) and may or may not be poorly hemoglobinized (hypochromic).

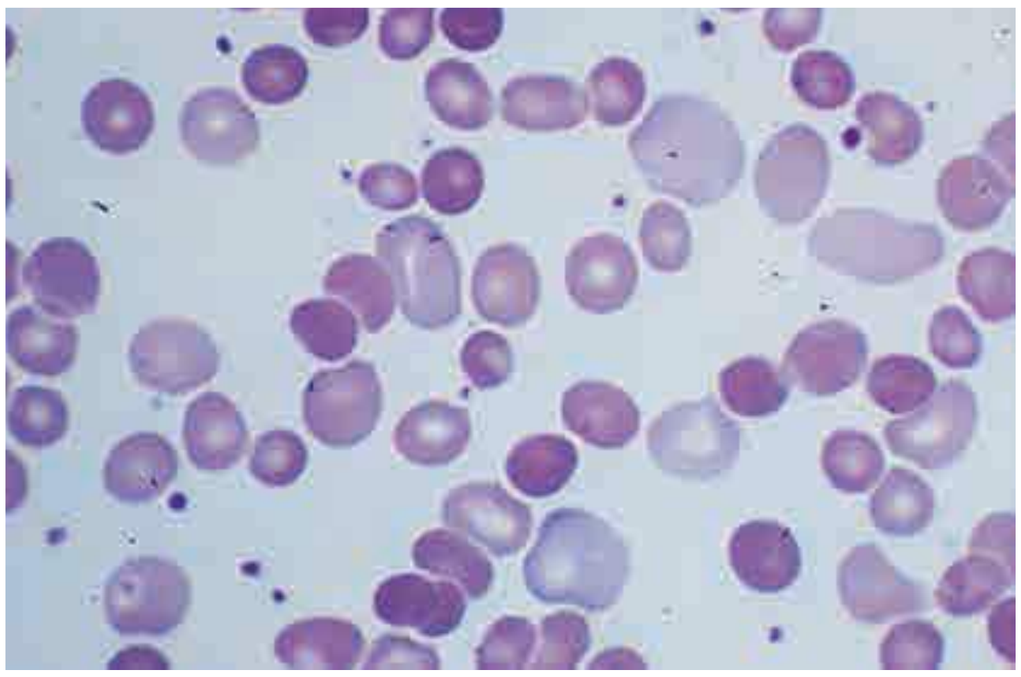


FIGURE 6-5
Polychromatophilia. Note large red cells with light purple coloring.

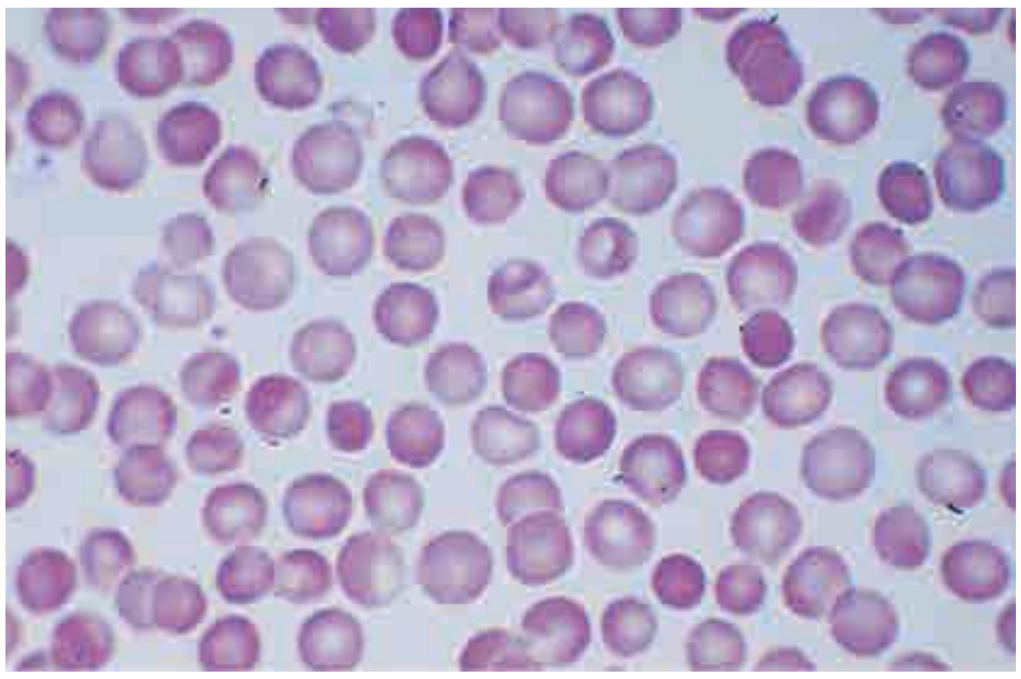


FIGURE 6-8
Spherocytosis. Note small hyperchromatic cells without the usual clear area in the center.

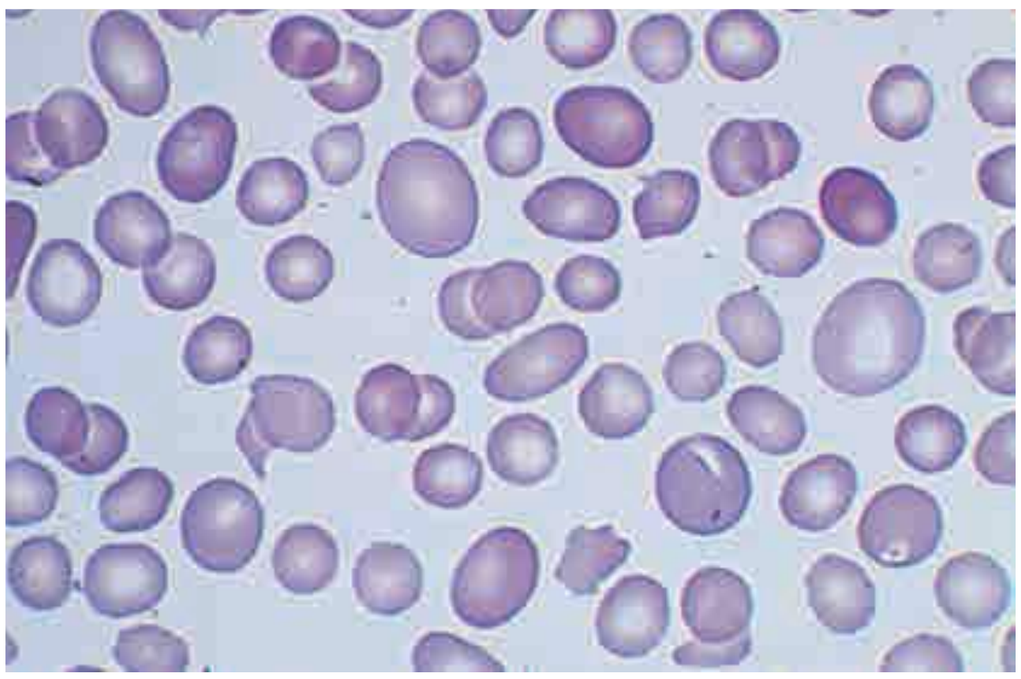


FIGURE 6-6
Macrocytosis. These cells are both larger than normal (mean corpuscular volume >100) and somewhat oval in shape. Some morphologists call these cells macroovalocytes.

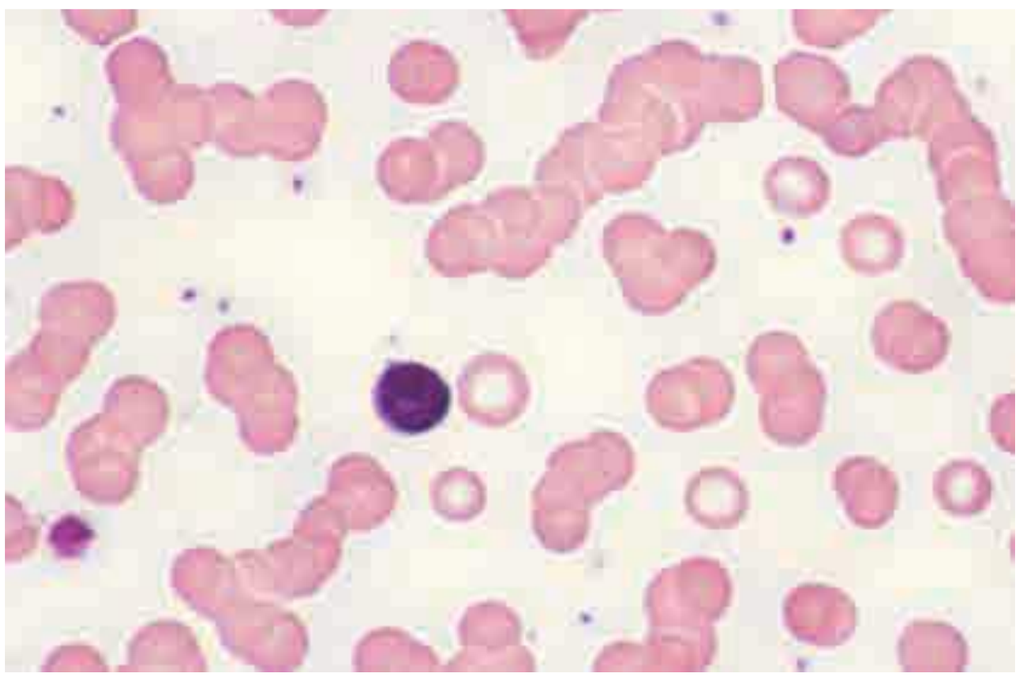


FIGURE 6-9
Rouleaux formation. Small lymphocyte in center of field. These red cells align themselves in stacks and are related to increased serum protein levels.

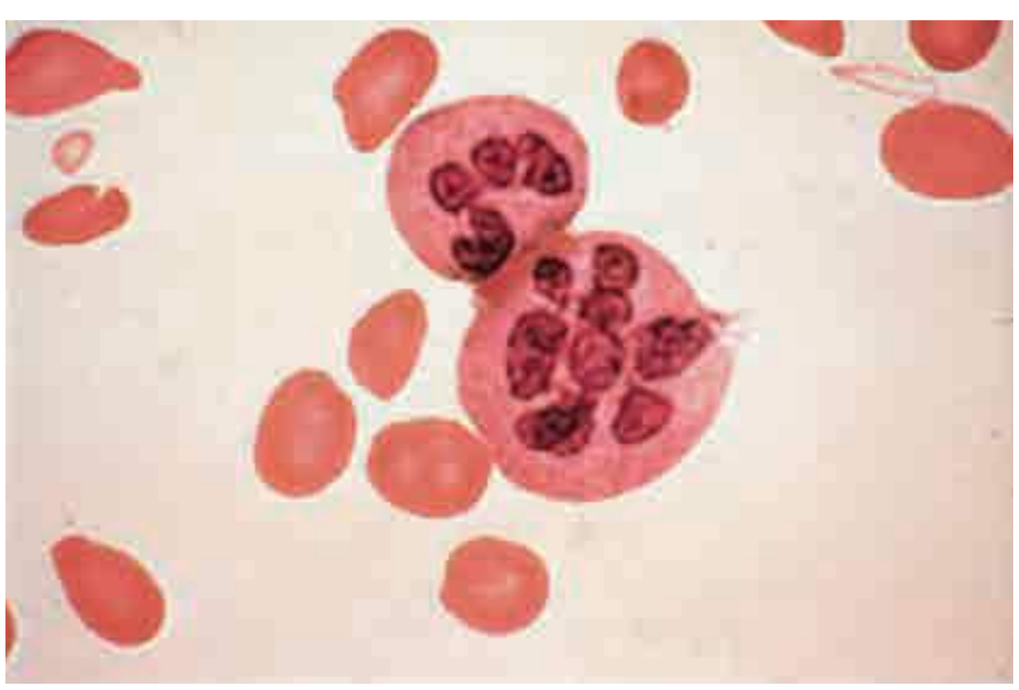


FIGURE 6-7
Hypersegmented neutrophils. Hypersegmented neutrophils (multilobed polymorphonuclear leukocytes) are larger than normal neutrophils with five or more segmented nuclear lobes. They are commonly seen with folic acid or vitamin B_{12} deficiency.

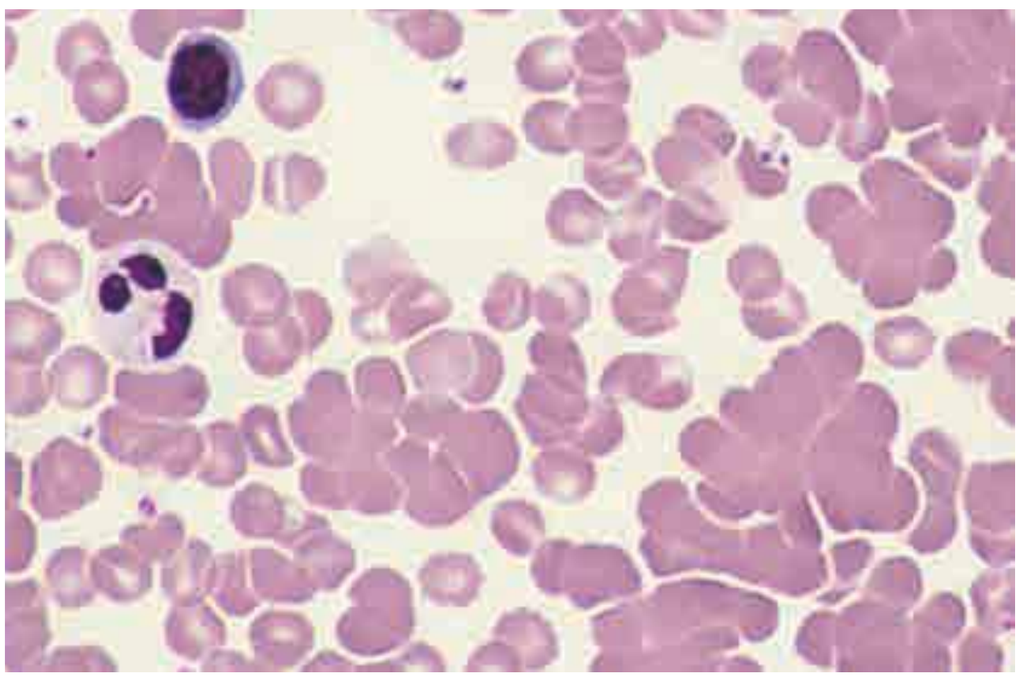


FIGURE 6-10
Red cell agglutination. Small lymphocyte and segmented neutrophil in upper left center. Note irregular collections of aggregated red cells.

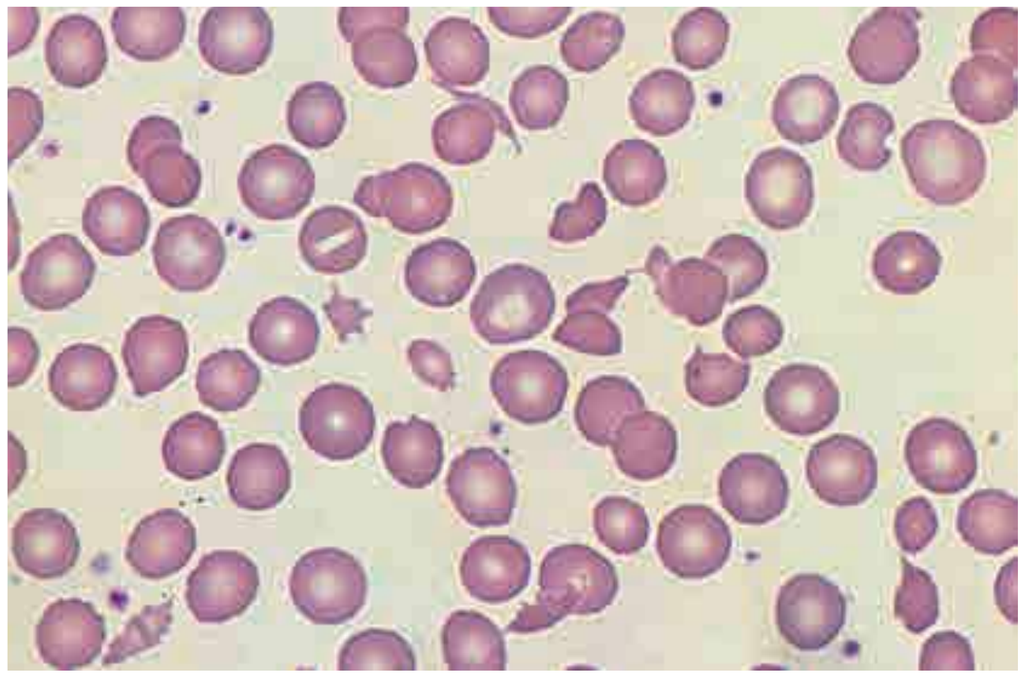


FIGURE 6-11
Fragmented red cells. Heart valve hemolysis.

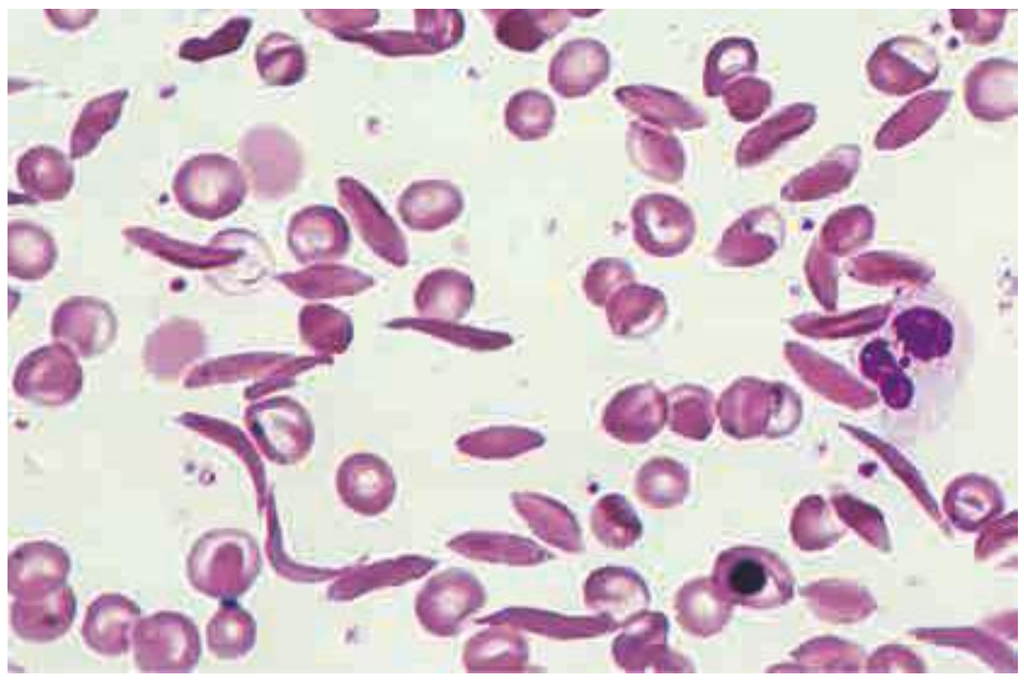


FIGURE 6-12
Sickle cells. Homozygous sickle cell disease. A nucleated red cell and neutrophil are also in the field.

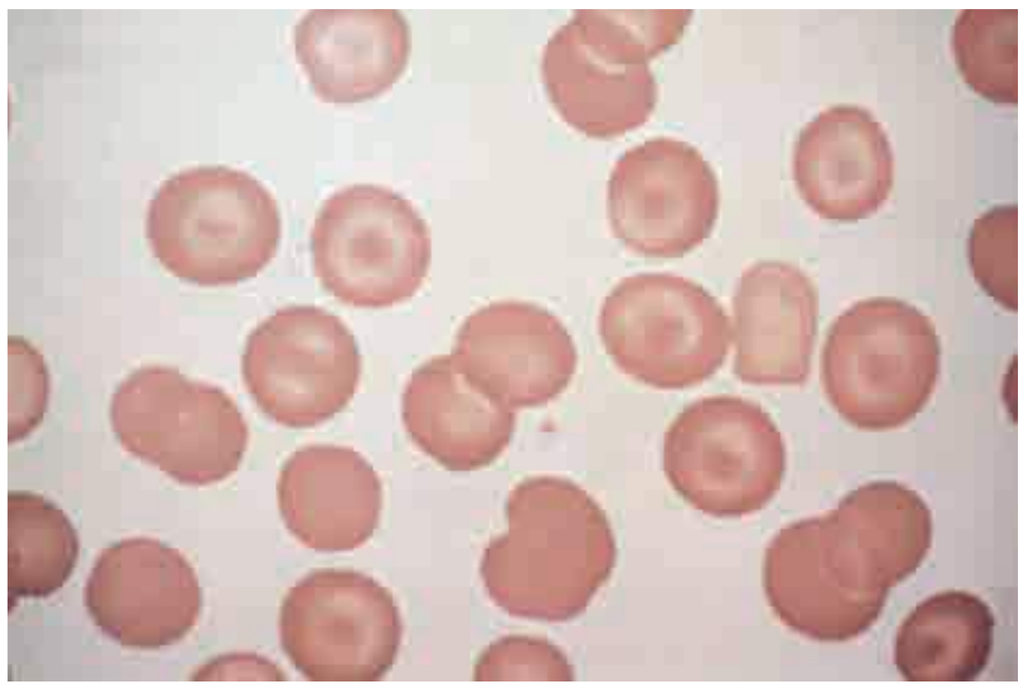


FIGURE 6-13
Target cells. Target cells are recognized by the bull's-eye appearance of the cell. Small numbers of target cells are seen with liver disease and thalassemia. Larger numbers are typical of hemoglobin C disease.

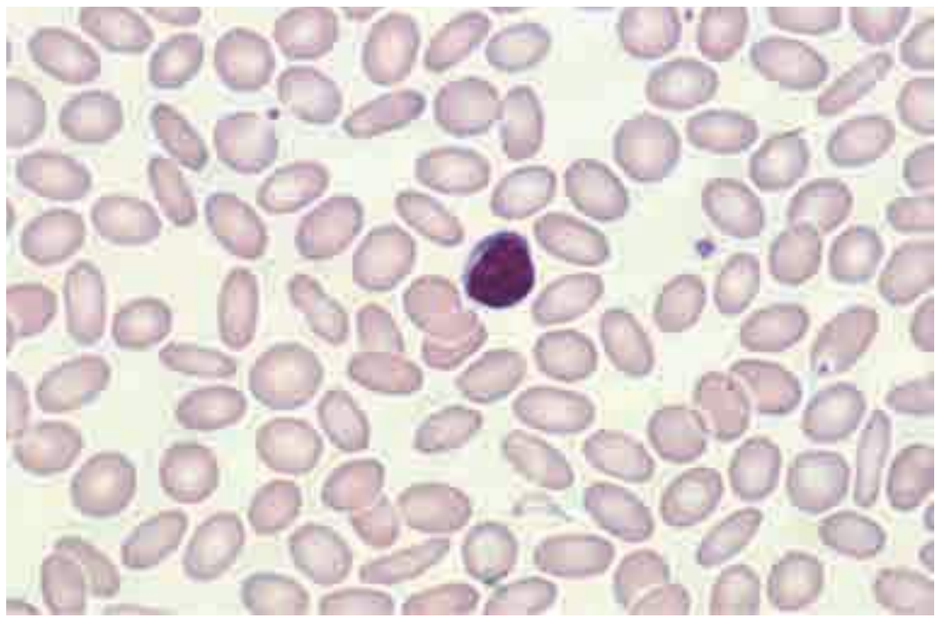


FIGURE 6-14
Elliptocytosis. Small lymphocyte in center of field. Elliptical shape of red cells is related to weakened membrane structure, usually due to mutations in spectrin.

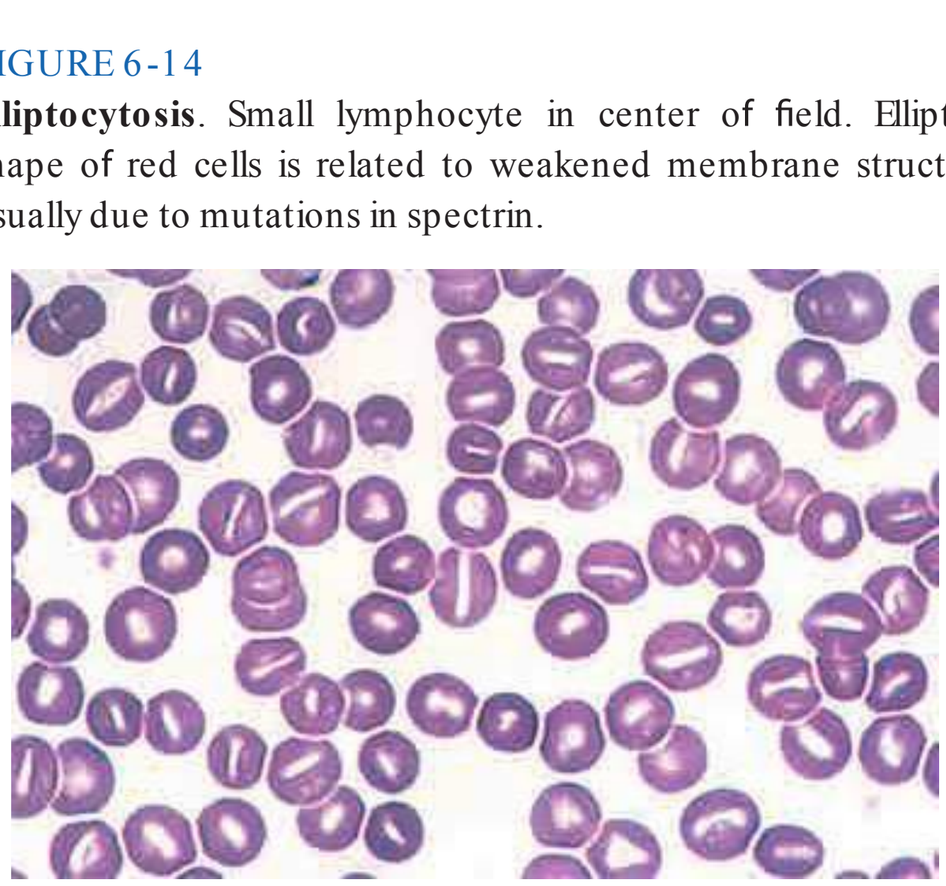


FIGURE 6-15
Stomatocytosis. Red cells characterized by a wide transverse slit or stoma. This often is seen as an artifact in a dehydrated blood smear. These cells can be seen in hemolytic anemias and in conditions in which the red cell is overhydrated or dehydrated.

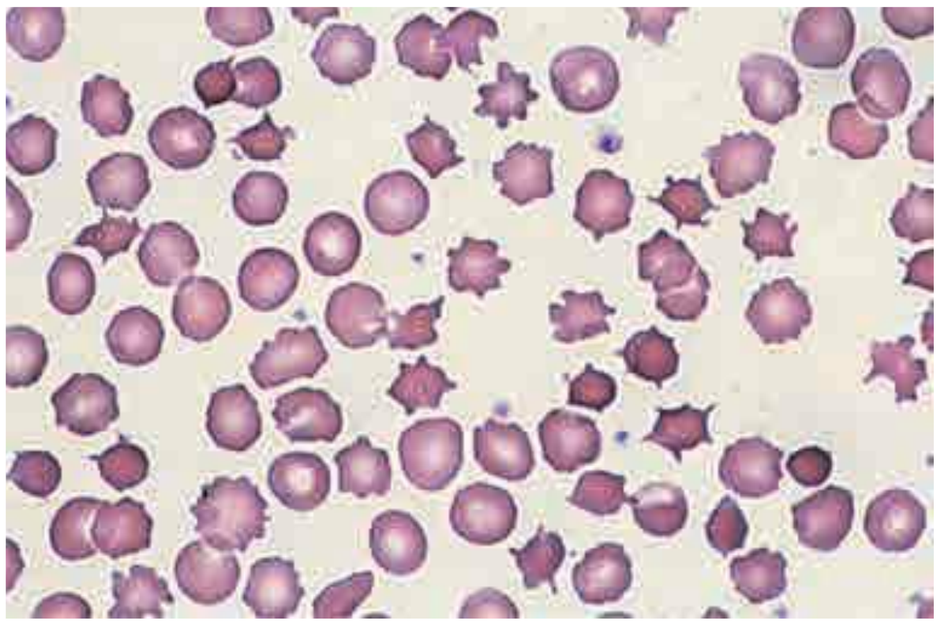


FIGURE 6-16
Acanthocytosis. Spiculated red cells are of two types: acanthocytes are contracted dense cells with irregular membrane projections that vary in length and width; echinocytes have small, uniform, and evenly spaced membrane projections. Acanthocytes are present in severe liver disease, in patients with abetalipoproteinemia, and in rare patients with McLeod blood group. Echinocytes are found in patients with severe uremia, in glycolytic red cell enzyme defects, and in microangiopathic hemolytic anemia.

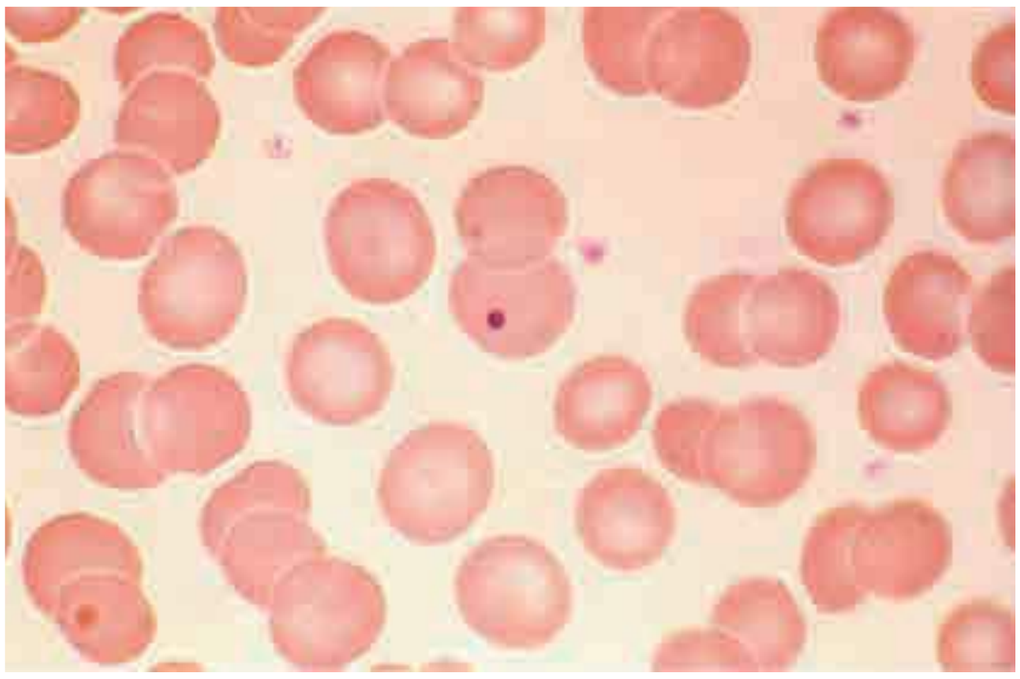


FIGURE 6-17
Howell-Jolly bodies. Howell-Jolly bodies are tiny nuclear remnants that normally are removed by the spleen. They appear in the blood after splenectomy (defect in removal) and with maturation/dysplastic disorders (excess production).

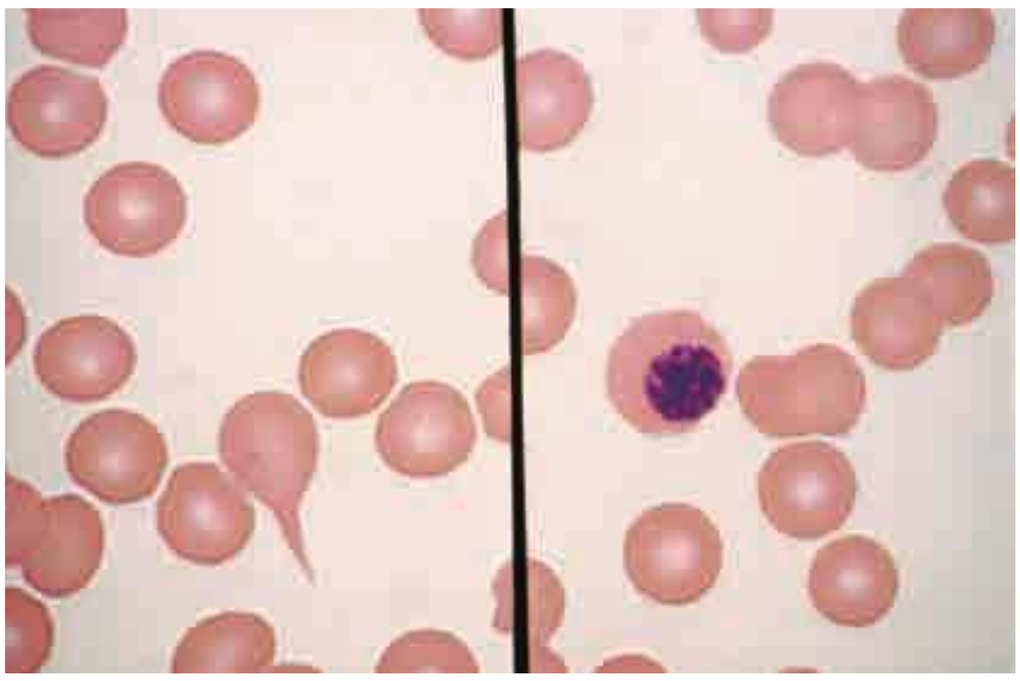


FIGURE 6-18
Teardrop cells and nucleated red blood cells characteristic of myelofibrosis. A teardrop-shaped red blood cell (left panel) and a nucleated red blood cell (right panel) as typically seen with myelofibrosis and extramedullary hematopoiesis.

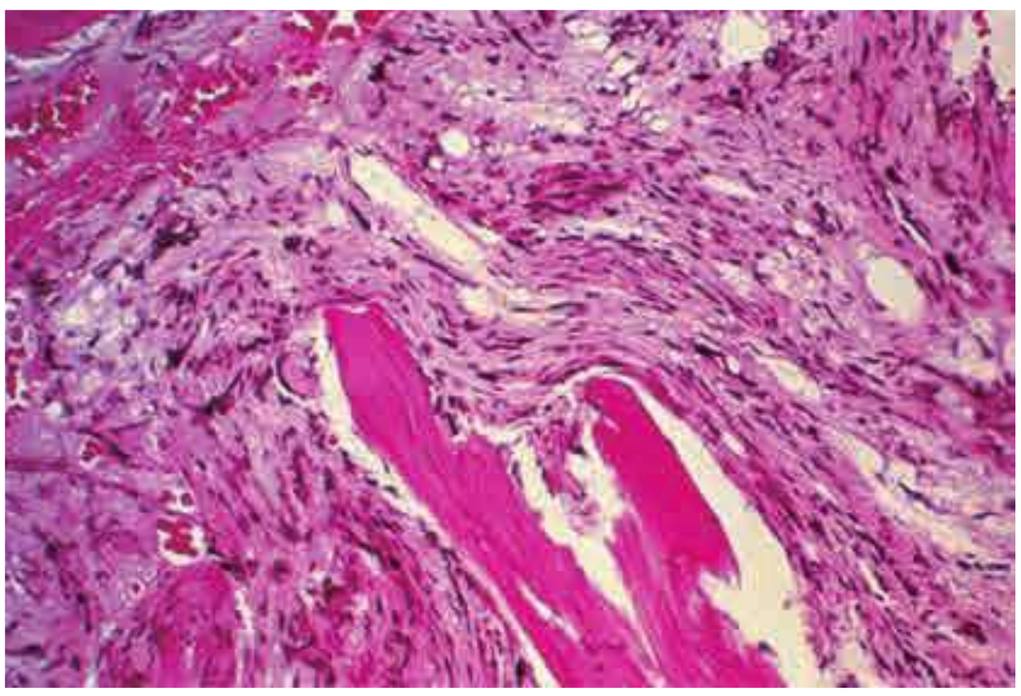


FIGURE 6-19
Myelofibrosis of the bone marrow. Total replacement of marrow precursors and fat cells by a dense infiltrate of reticulin fibers and collagen (H&E stain).

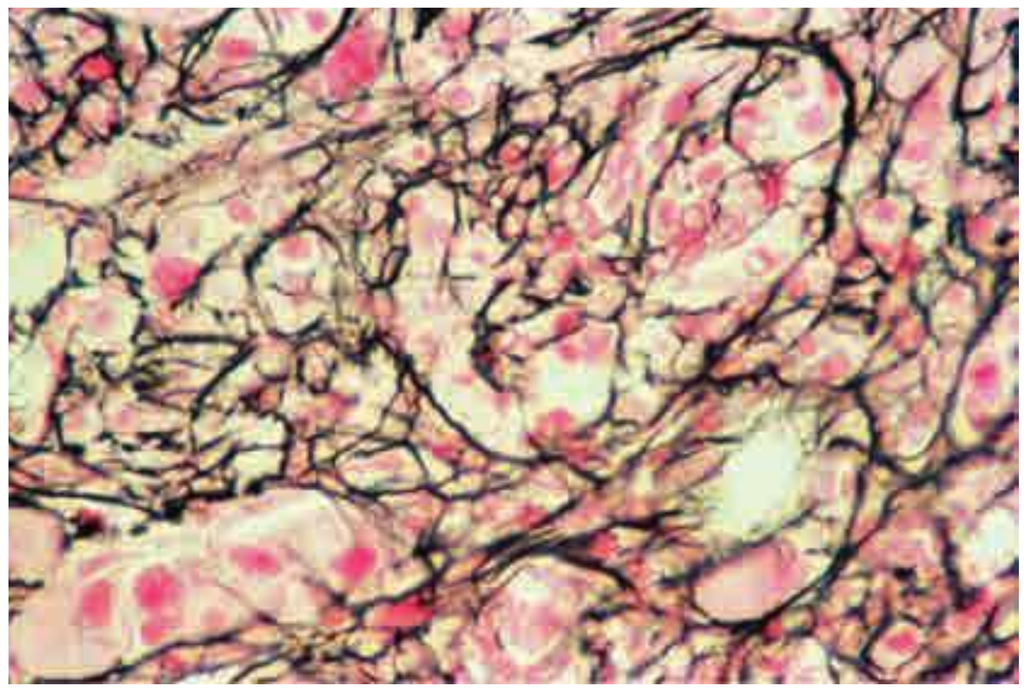


FIGURE 6-20
Reticulin stain of marrow myelofibrosis. Silver stain of a myelofibrotic marrow showing an increase in reticulin fibers (black-staining threads).

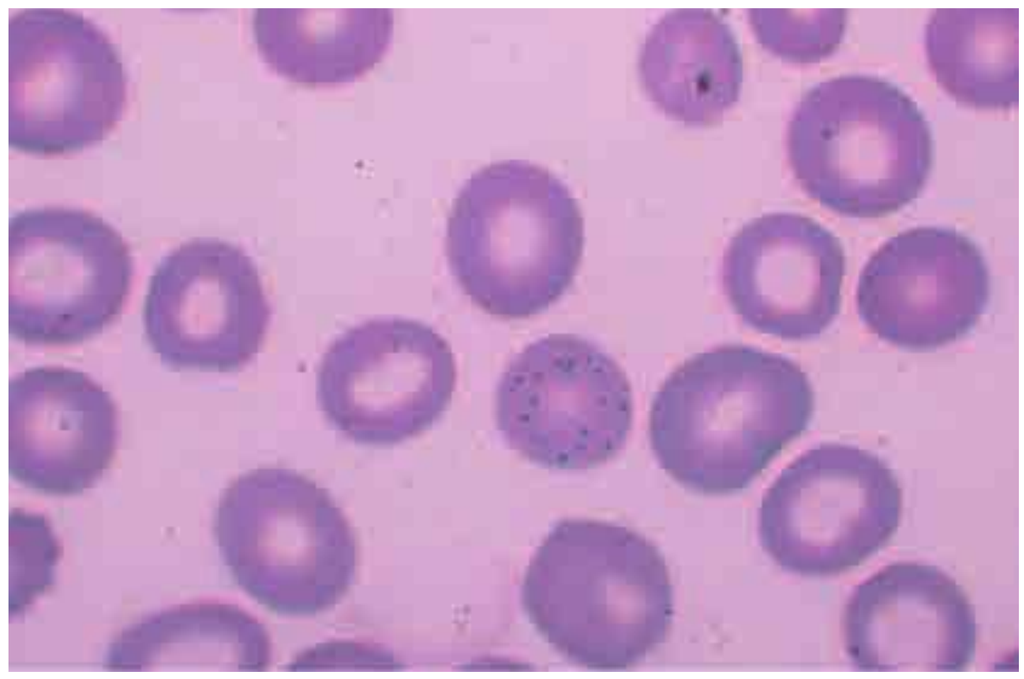


FIGURE 6-21
Stippled red cell in lead poisoning. Mild hypochromia. Coarsely stippled red cell.

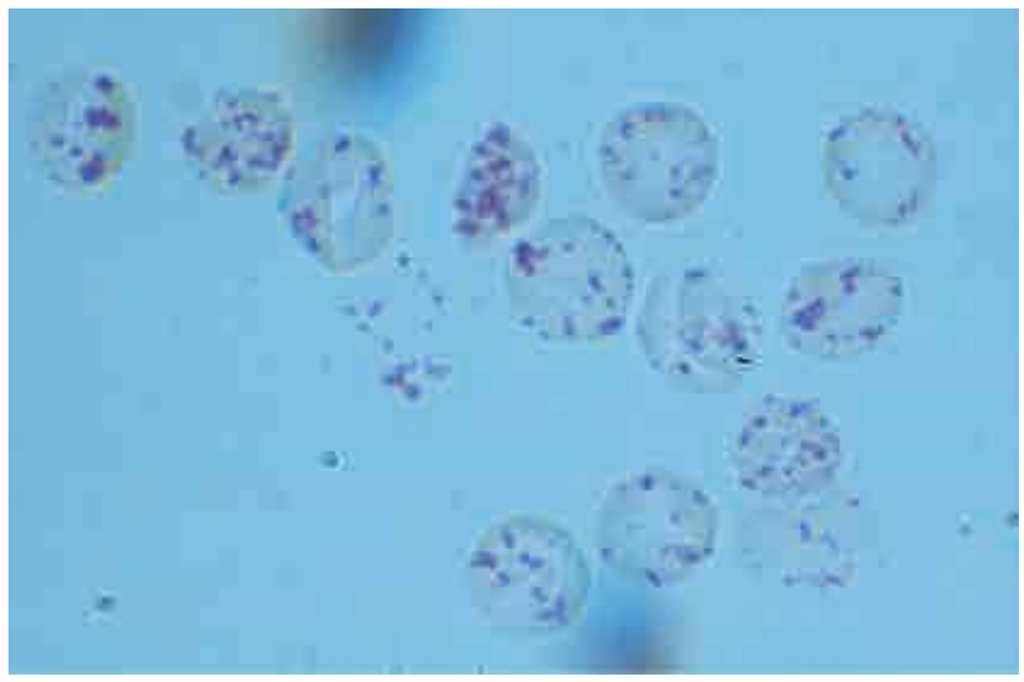


FIGURE 6-22
Heinz bodies. Blood mixed with hypotonic solution of crystal violet. The stained material is precipitates of denatured hemoglobin within cells.

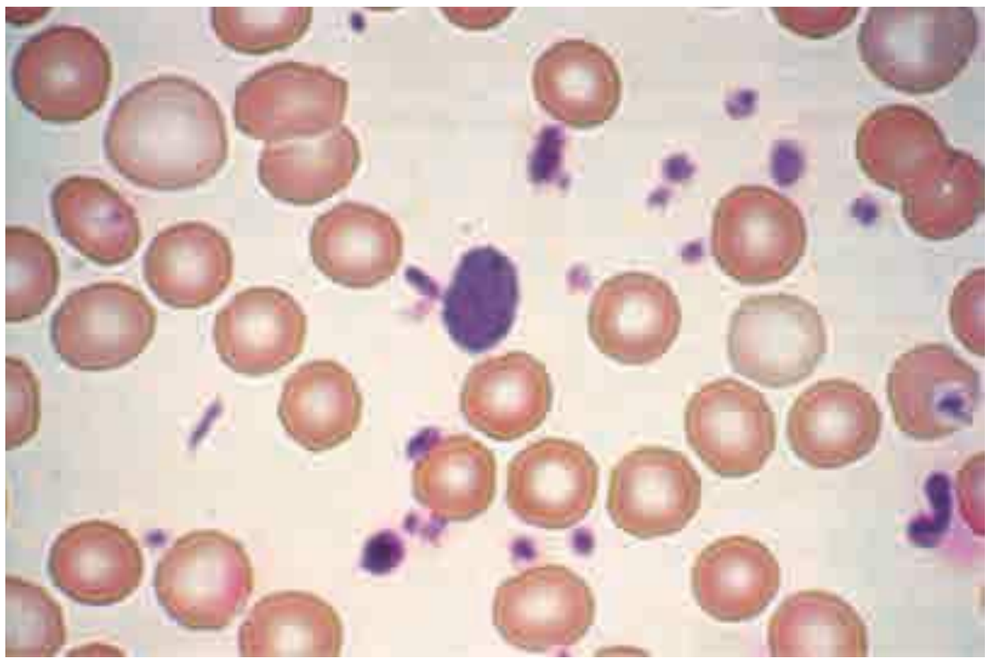


FIGURE 6-23
Giant platelets. Giant platelets, together with a marked increase in the platelet count, are seen in myeloproliferative disorders, especially primary thrombocythemia.

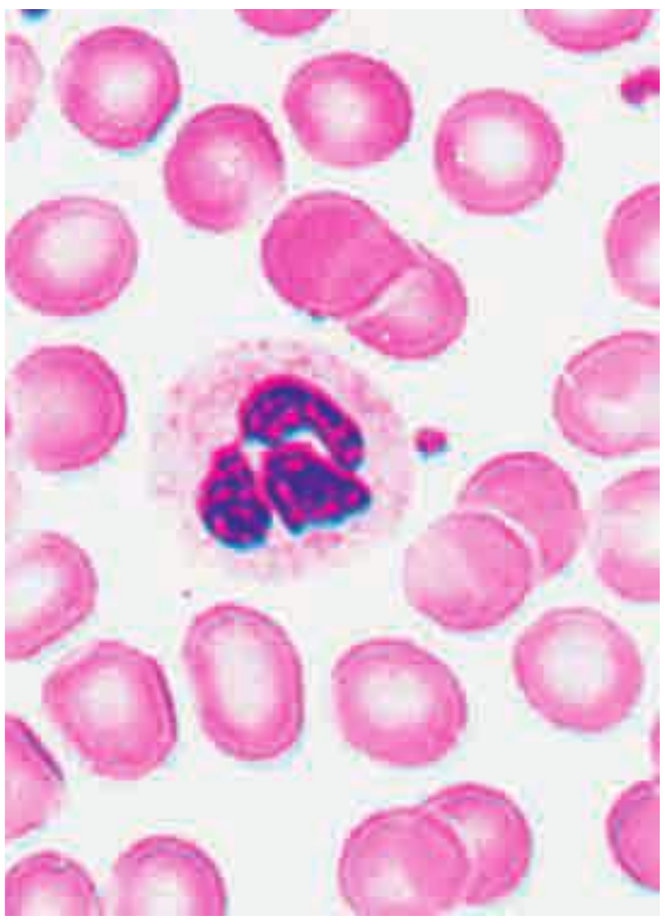


FIGURE 6-24
Normal granulocytes. The normal granulocyte has a segmented nucleus with heavy, clumped chromatin; fine neutrophilic granules are dispersed throughout the cytoplasm.

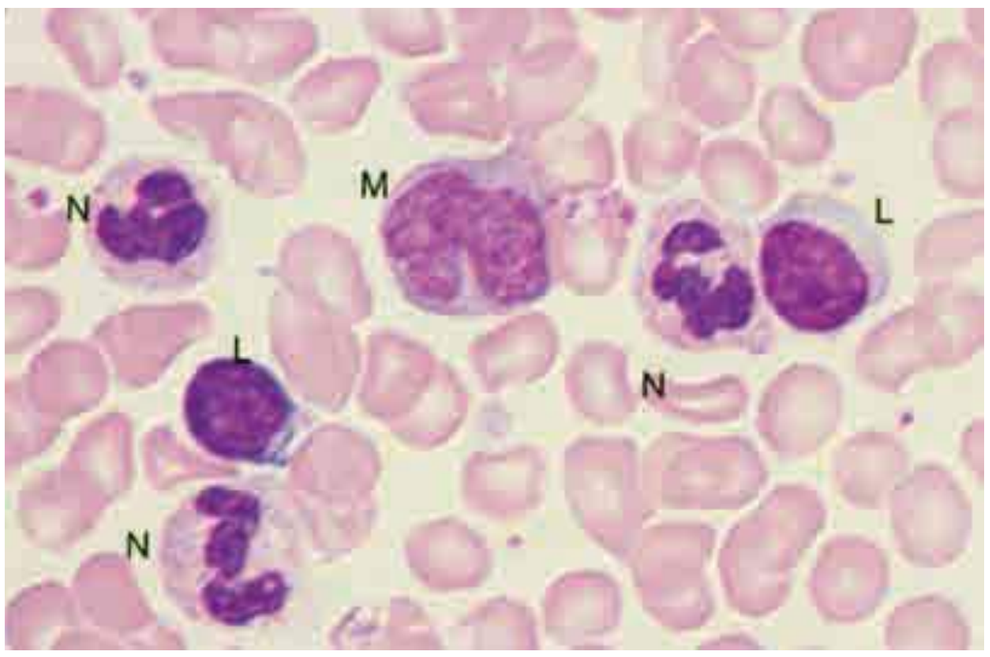


FIGURE 6-25
Normal monocytes. The film was prepared from the buffy coat of the blood from a normal donor. L, lymphocyte; M, monocyte; N, neutrophil.

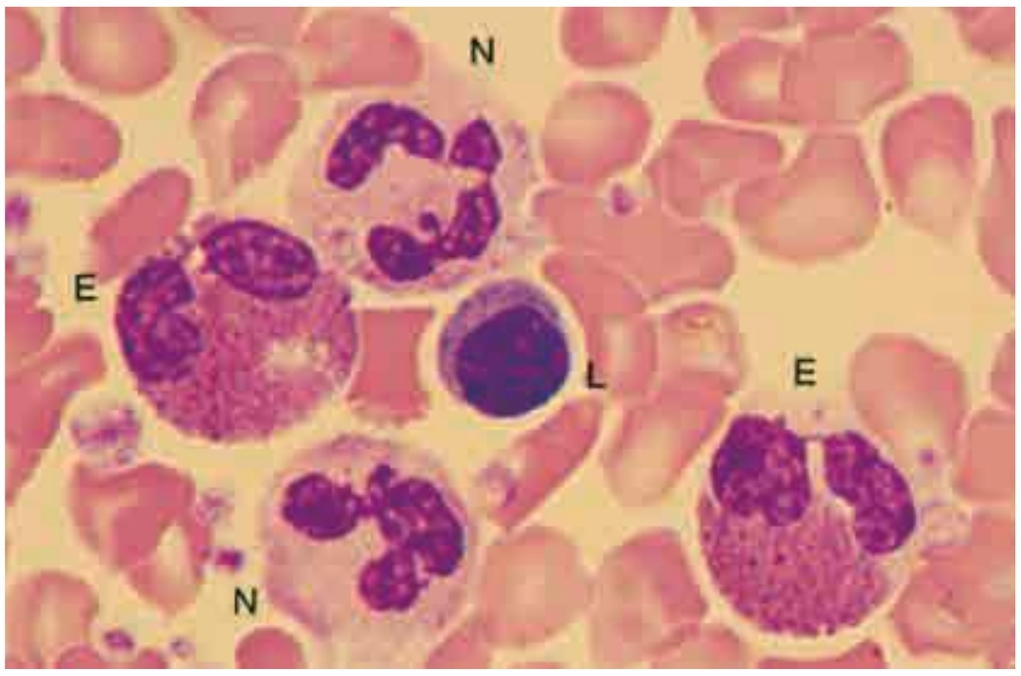


FIGURE 6-26
Normal eosinophils. The film was prepared from the buffy coat of the blood from a normal donor. E, eosinophil; L, lymphocyte; N, neutrophil.

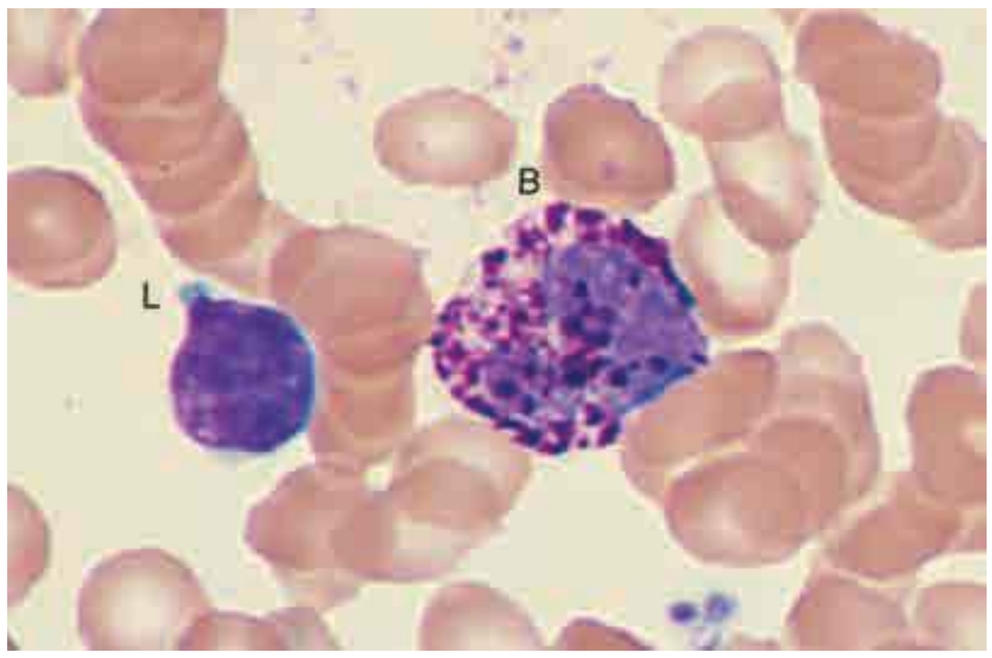


FIGURE 6-27
Normal basophil. The film was prepared from the buffy coat of the blood from a normal donor. B, basophil; L, lymphocyte.

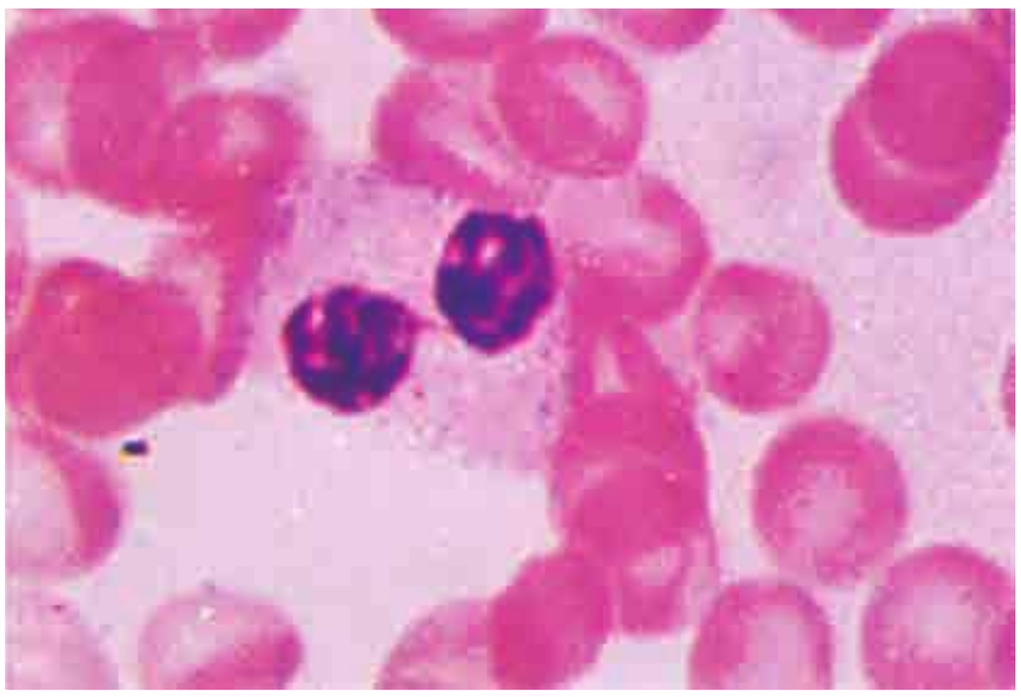


FIGURE 6-28
Pelger-Hüet anomaly. In this benign disorder, the majority of granulocytes are bilobed. The nucleus frequently has a spectacle-like, or "pince-nez," configuration.

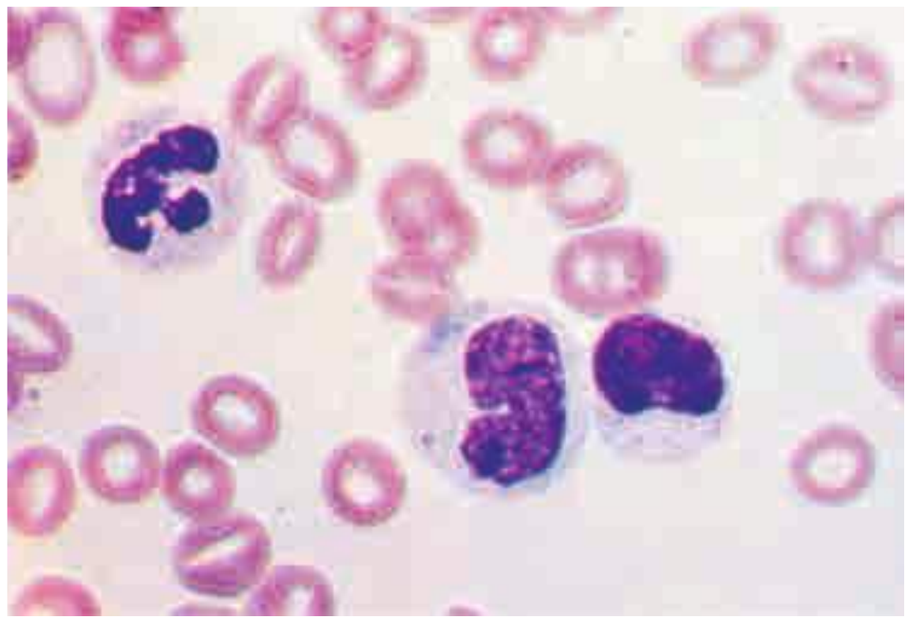


FIGURE 6-29
Döhle body. Neutrophil band with Döhle body. The neutrophil with a sausage-shaped nucleus in the center of the field is a band form. Döhle bodies are discrete, blue-staining nongranular areas found in the periphery of the cytoplasm of the neutrophil in infections and other toxic states. They represent aggregates of rough endoplasmic reticulum.

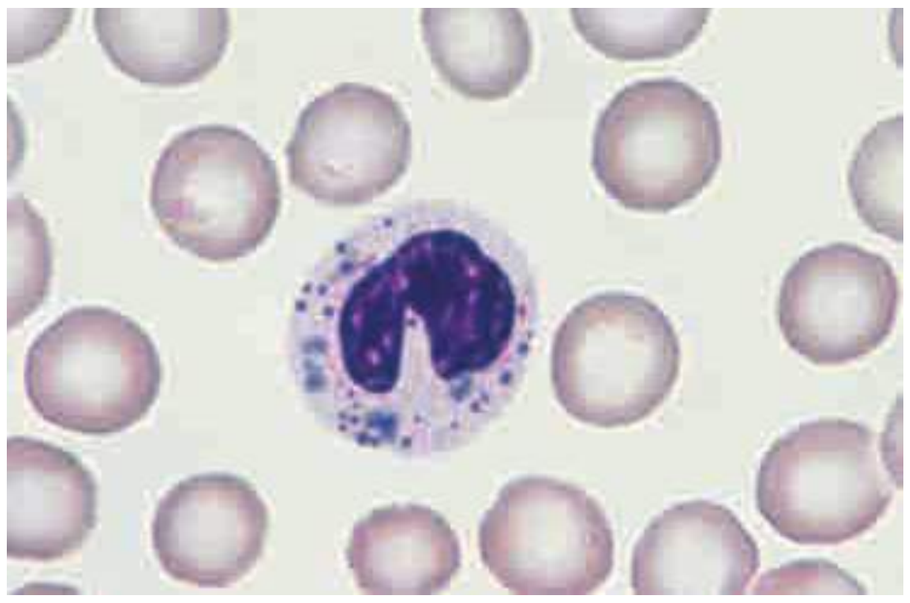


FIGURE 6-30
Chédiak-Higashi disease. Note giant granules in neutrophil.

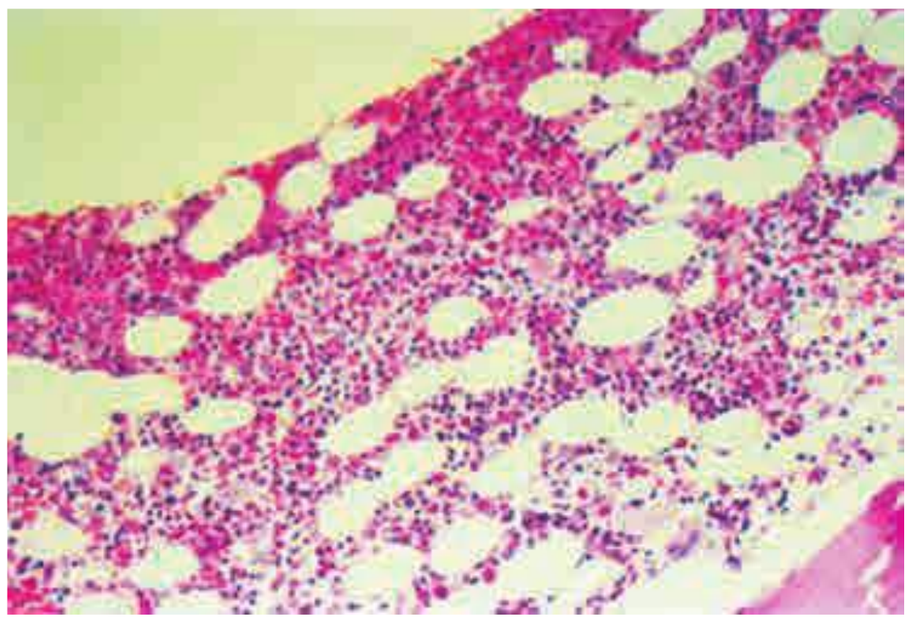


FIGURE 6-31
Normal bone marrow. Low-power view of normal adult marrow (hematoxylin and eosin [H&E] stain), showing a mix of fat cells (clear areas) and hematopoietic cells. The percentage of the space that consists of hematopoietic cells is referred to as marrow cellularity. In adults, normal marrow cellularity is 35–40%. If demands for increased marrow production occur, cellularity may increase to meet the demand. As people age, the marrow cellularity decreases and the marrow fat increases. Patients >70 years old may have a 20–30% marrow cellularity.

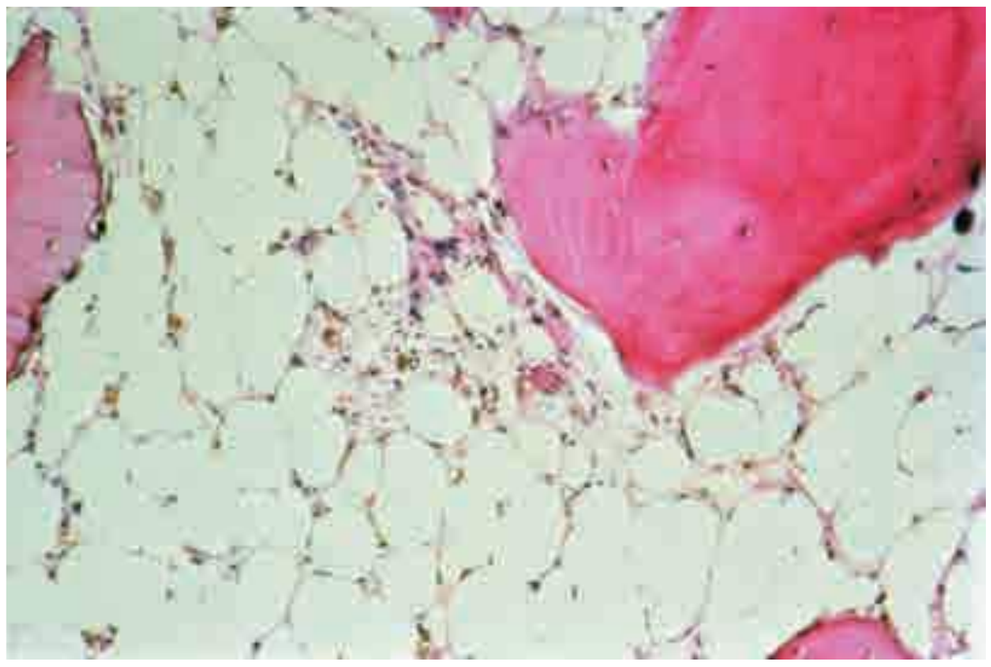


FIGURE 6-32
Aplastic anemia bone marrow. Normal hematopoietic precursor cells are virtually absent, leaving behind fat cells, reticuloendothelial cells, and the underlying sinusoidal structure.

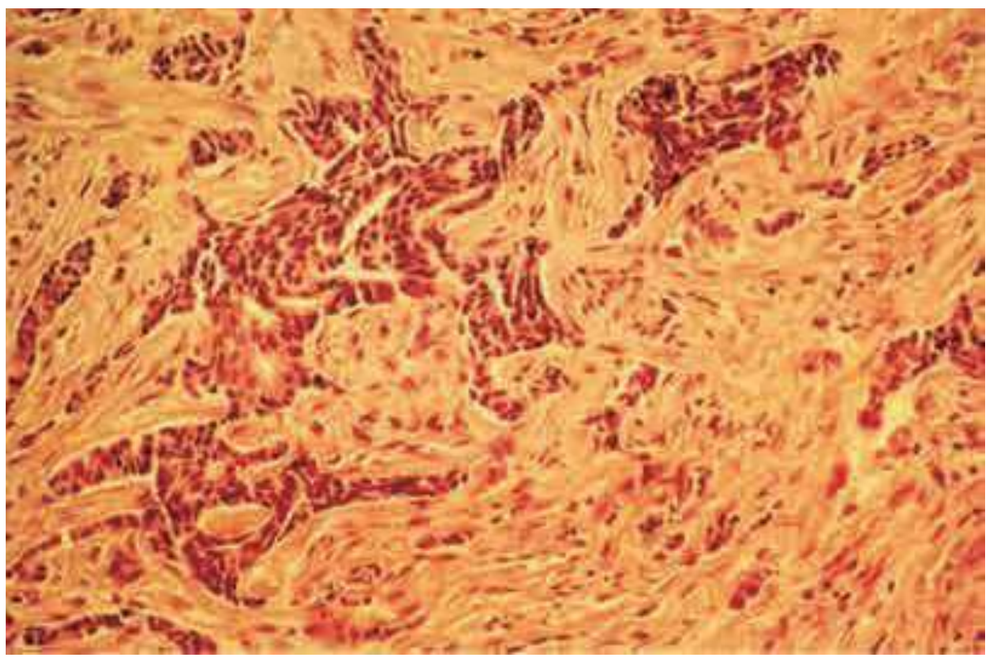


FIGURE 6-33
Metastatic cancer in the bone marrow. Marrow biopsy specimen infiltrated with metastatic breast cancer and reactive fibrosis (H&E stain).

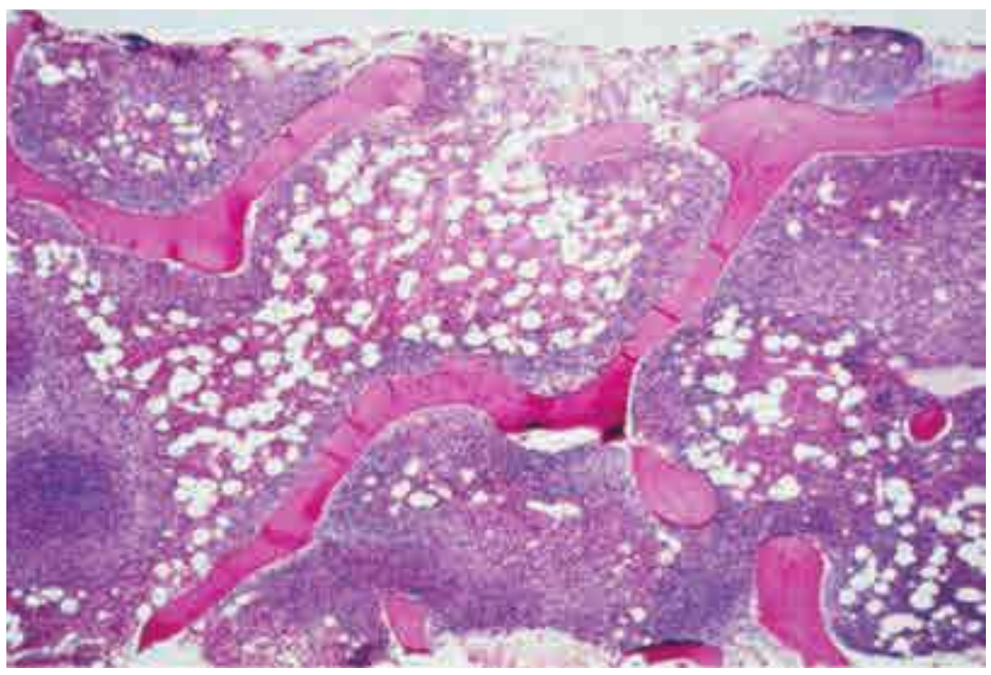


FIGURE 6-34
Lymphoma in the bone marrow. Nodular (follicular) lymphoma infiltrate in a marrow biopsy specimen. Note the characteristic paratrabecular location of the lymphoma cells.

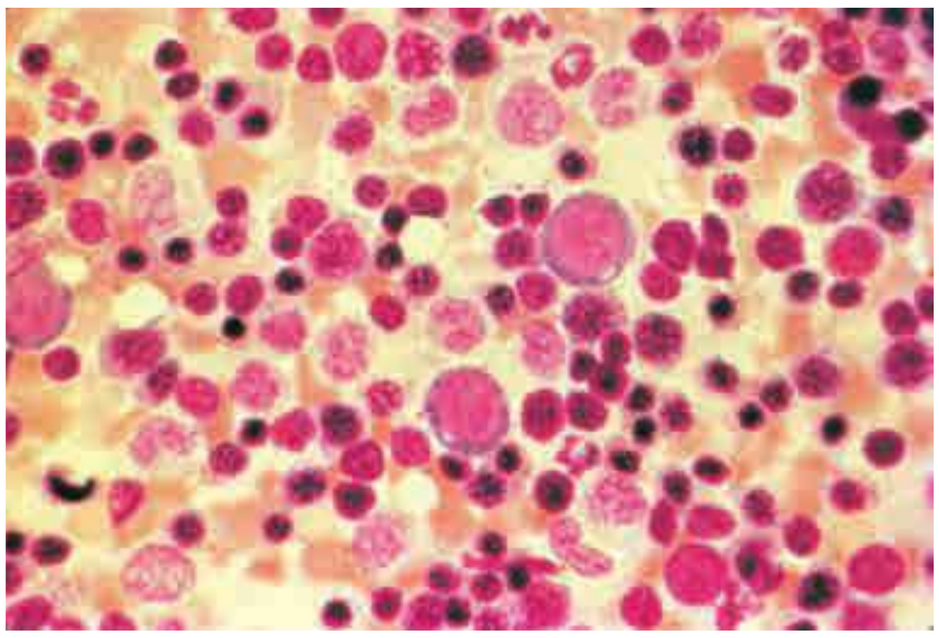


FIGURE 6-35
Erythroid hyperplasia of the marrow. Marrow aspirate specimen with a myeloid/erythroid ratio (M/E ratio) of 1:1–2, typical for a patient with a hemolytic anemia or one recovering from blood loss.

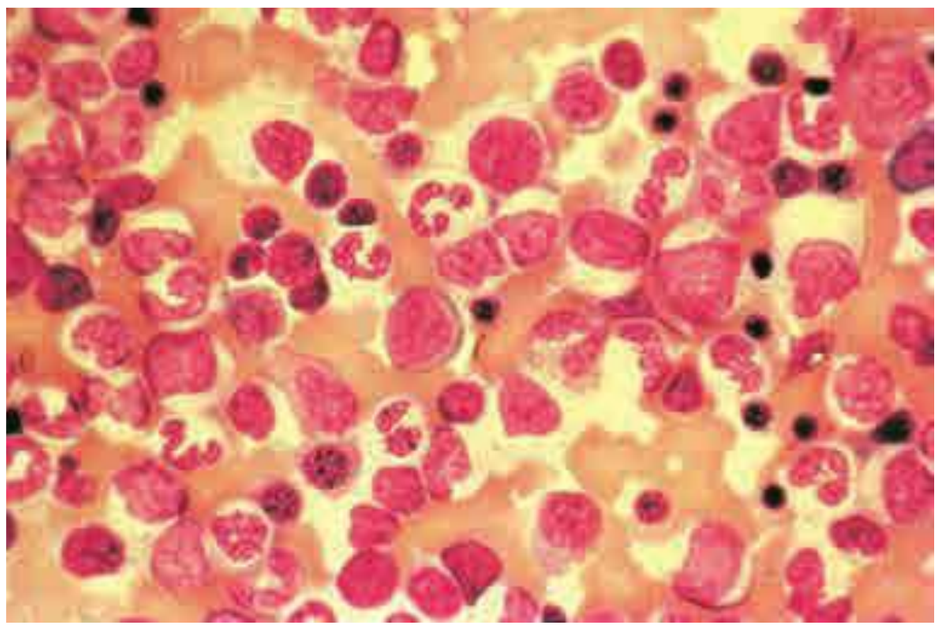


FIGURE 6-36
Myeloid hyperplasia of the marrow. Marrow aspirate specimen showing a myeloid/erythroid ratio of ≥3:1, suggesting either a loss of red blood cell precursors or an expansion of myeloid elements.

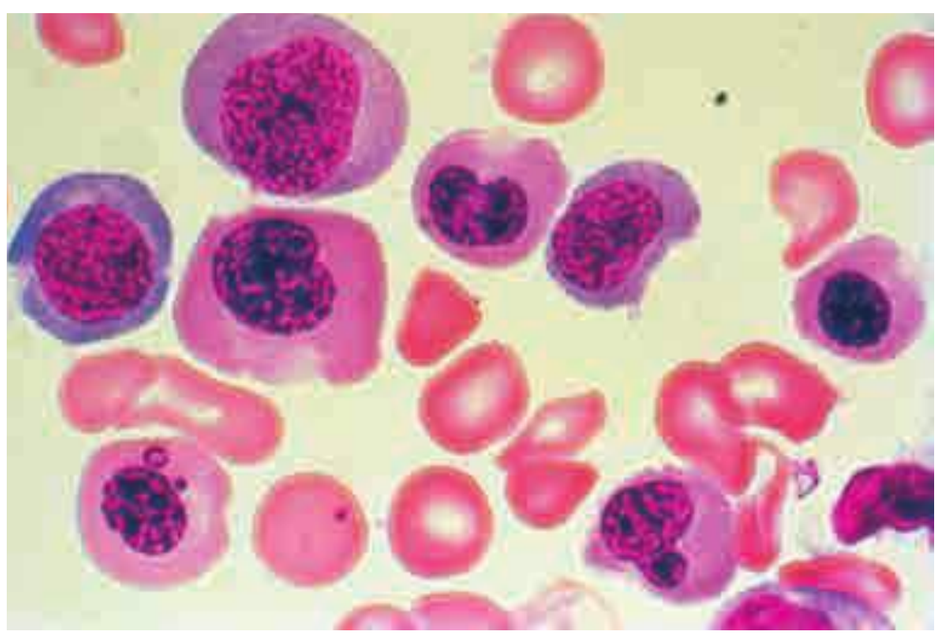


FIGURE 6-37
Megaloblastic erythropoiesis. High-power view of megaloblastic red blood cell precursors from a patient with a macrocytic anemia. Maturation is delayed, with late normoblasts showing a more immature-appearing nucleus with a lattice-like pattern with normal cytoplasmic maturation.

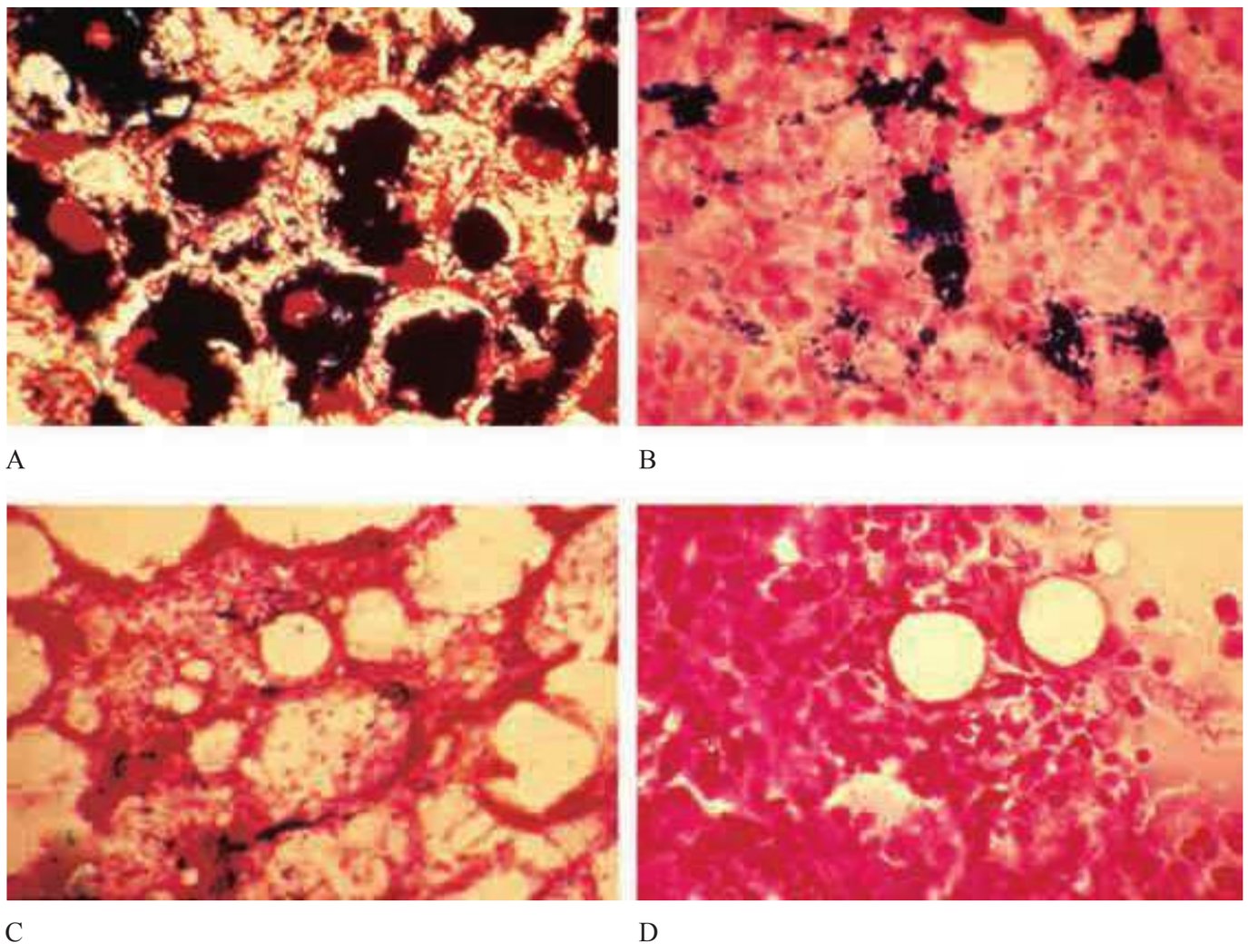


FIGURE 6-38
Prussian blue staining of marrow iron stores. Iron stores can be graded on a scale of 0 to 4+. A. A marrow with excess iron stores (>4+); B. normal stores (2–3+); C. minimal stores (1+); and D. absent iron stores (0).

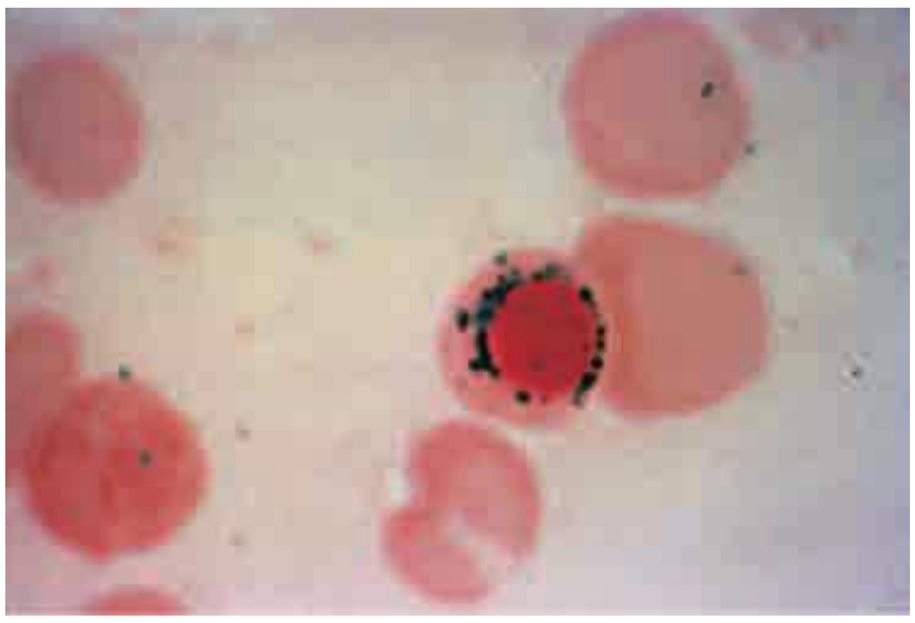


FIGURE 6-39
Ringed sideroblast. An orthochromatic normoblast with a collar of blue granules (mitochondria encrusted with iron) surrounding the nucleus.

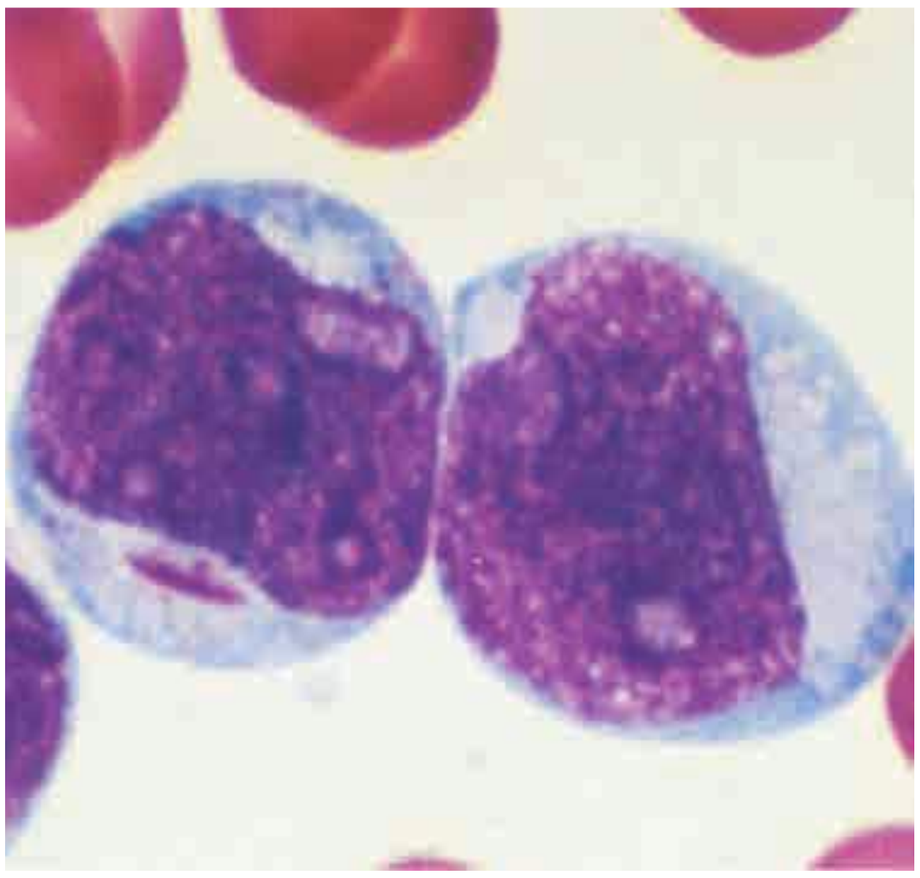


FIGURE 6-40
Acute myeloid leukemia. Leukemic myeloblast with an Auer rod. Note two to four large, prominent nucleoli in each cell.

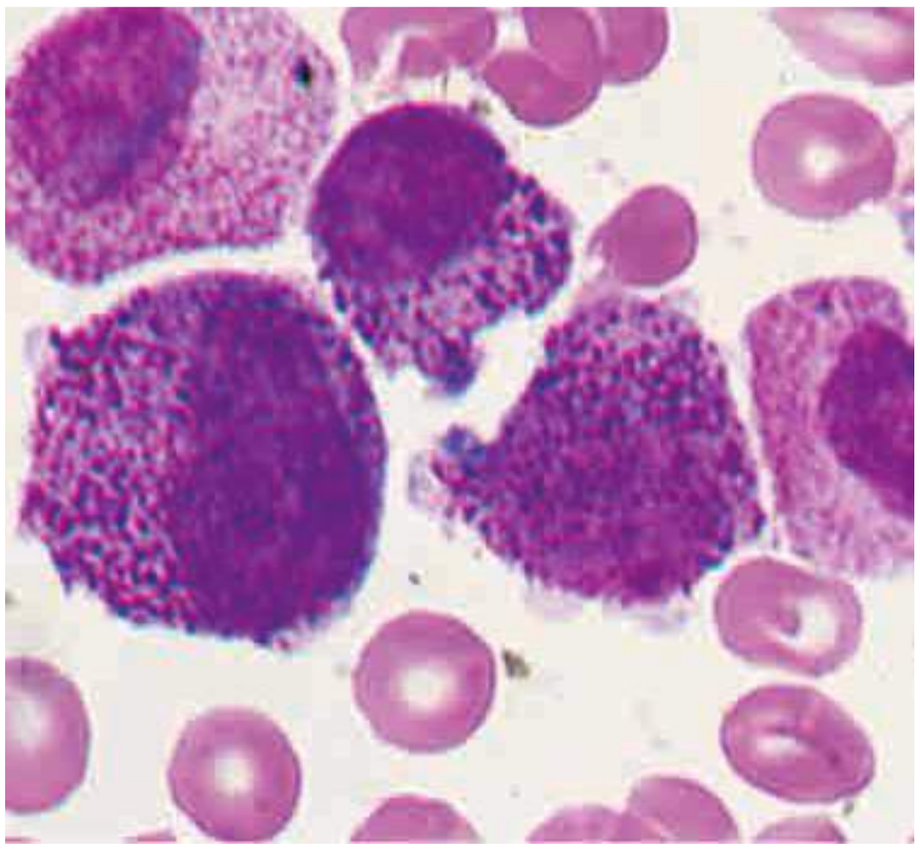


FIGURE 6-41
Acute promyelocytic leukemia. Note prominent cytoplasmic granules in the leukemia cells.

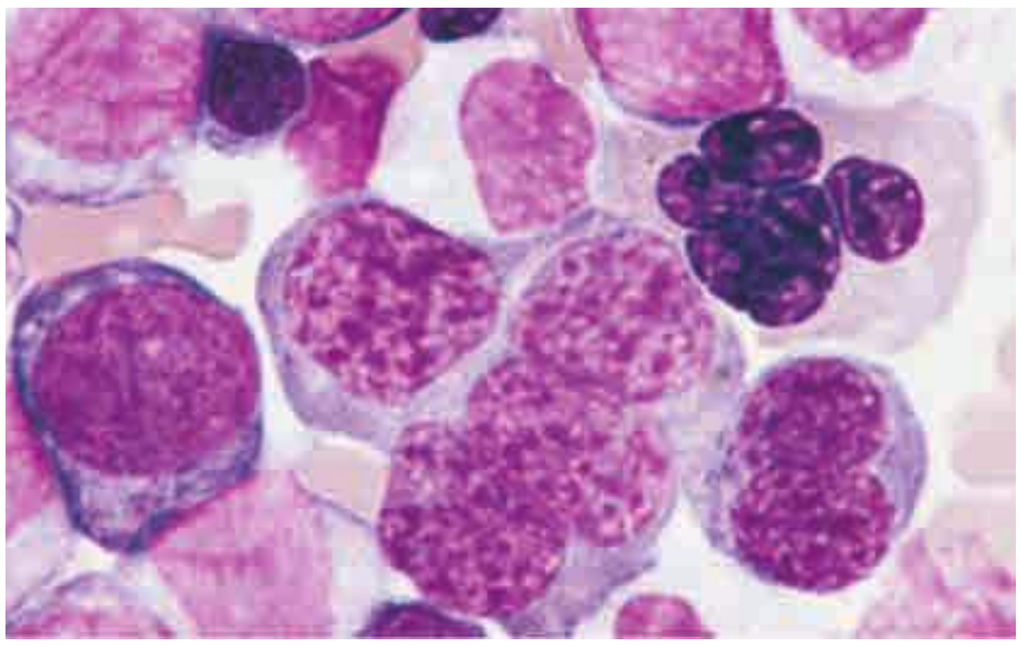


FIGURE 6-42
Acute erythroleukemia. Note giant dysmorphic erythroblasts; two are binucleate, and one is multinucleate.

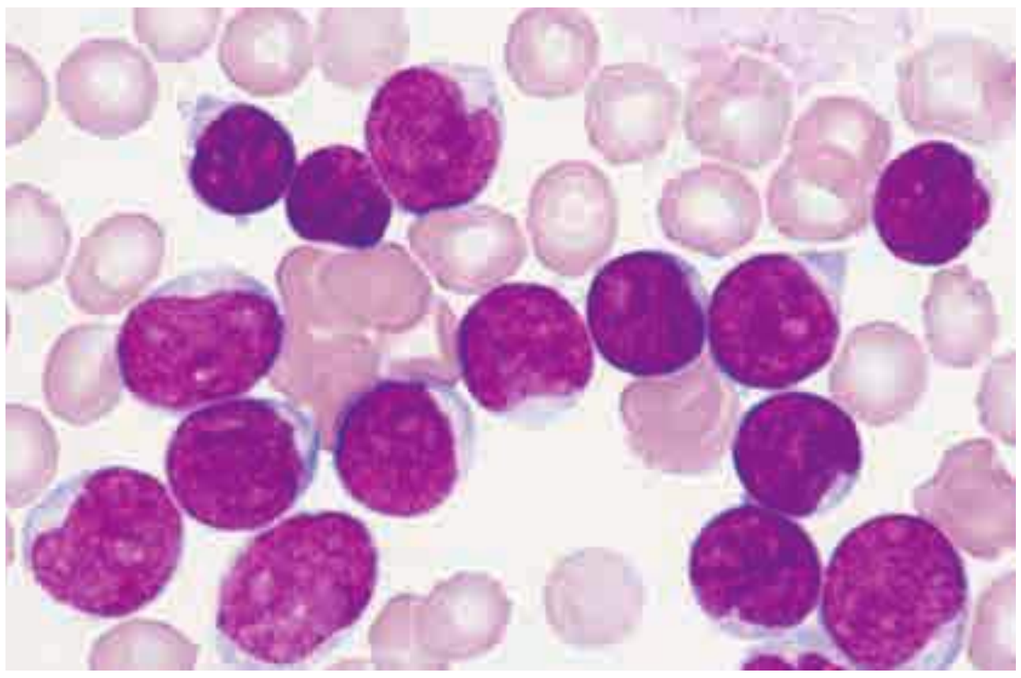


FIGURE 6-43
Acute lymphoblastic leukemia.

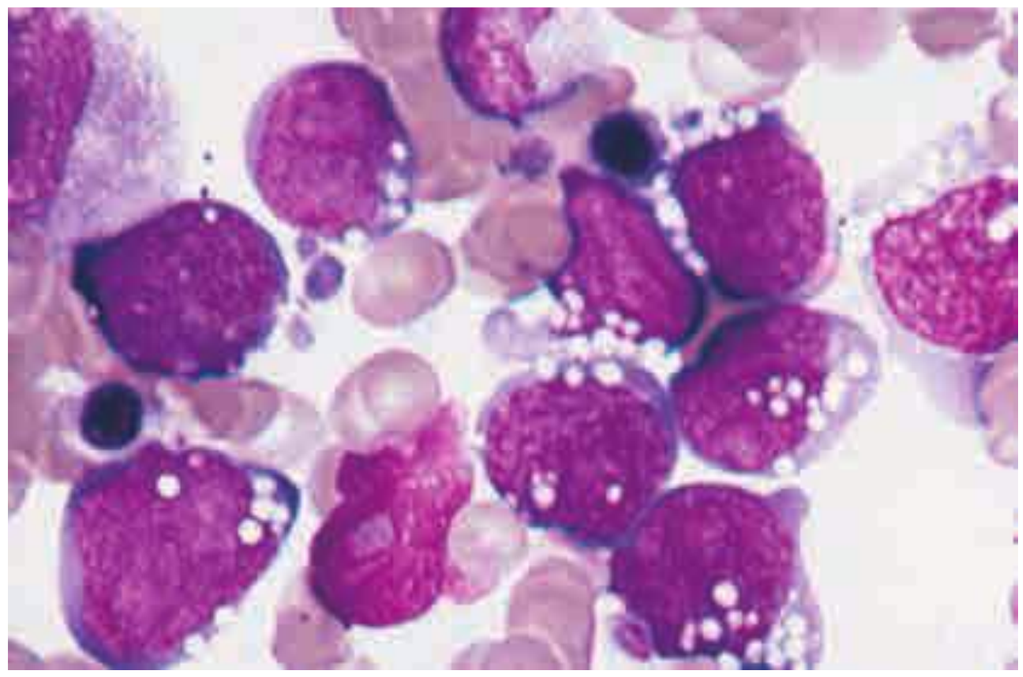


FIGURE 6-44
Burkitt's leukemia, acute lymphoblastic leukemia.

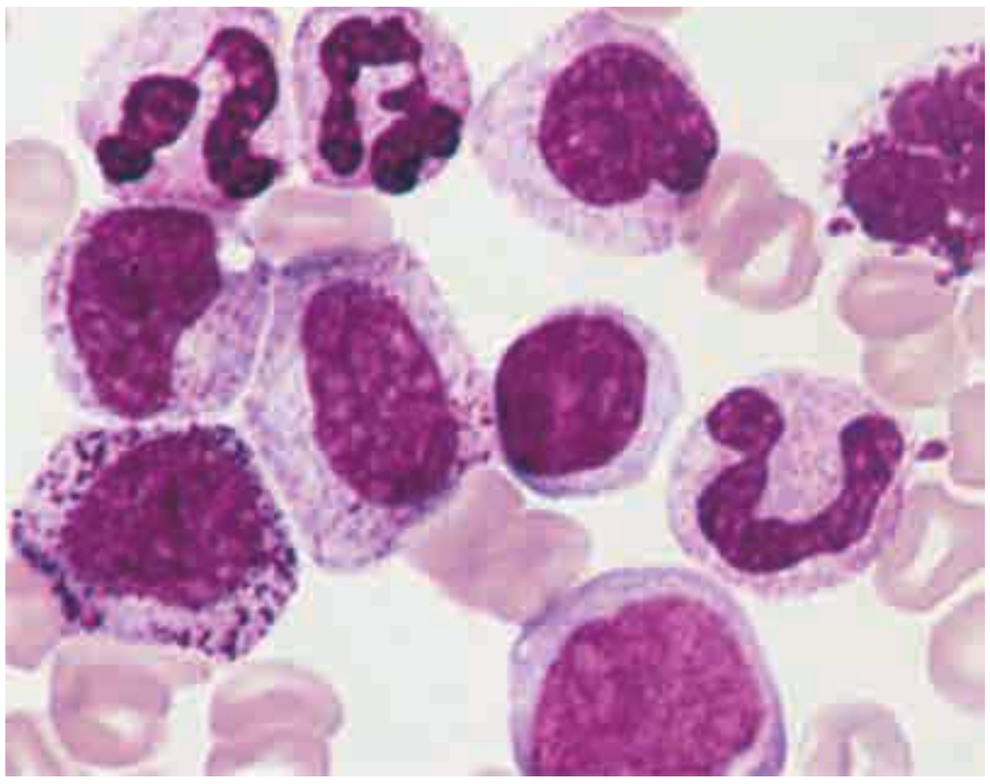


FIGURE 6-45
Chronic myeloid leukemia in the peripheral blood.

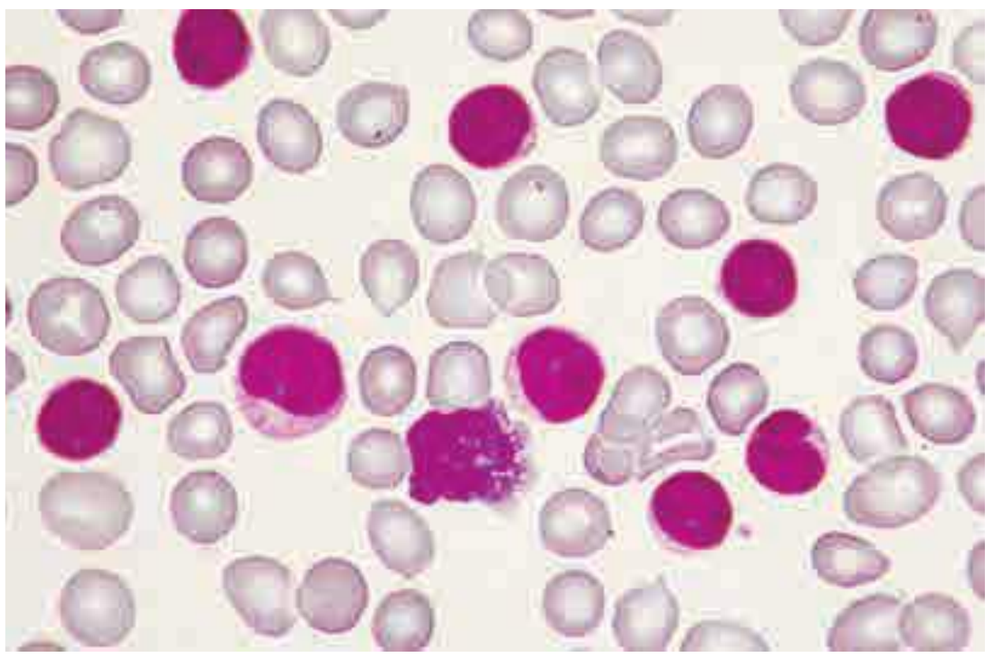


FIGURE 6-46
Chronic lymphoid leukemia in the peripheral blood.

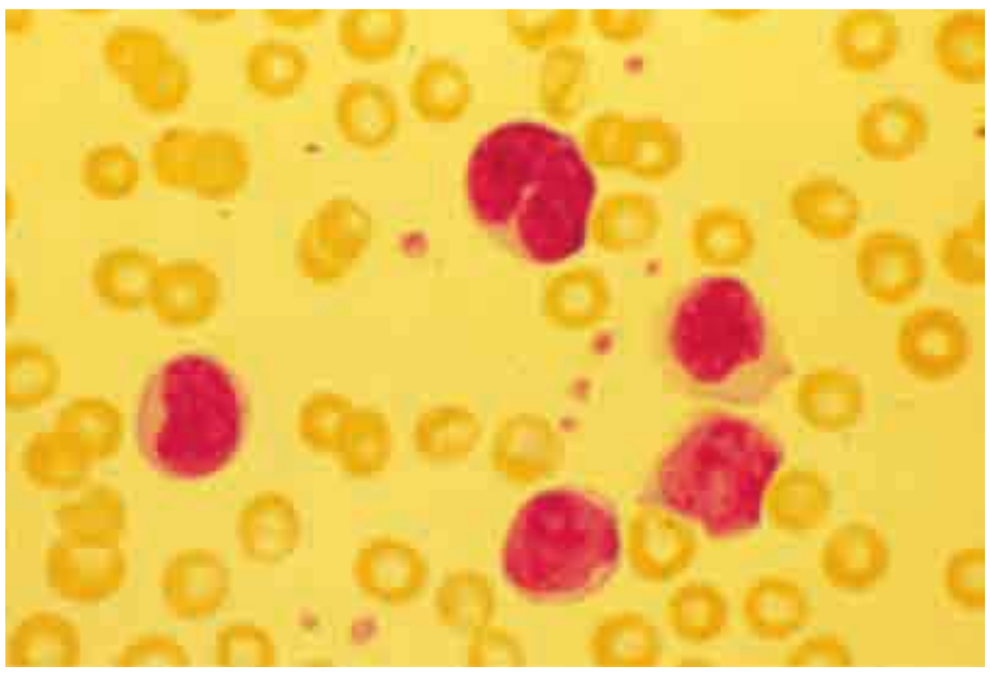


FIGURE 6-47
Sézary's syndrome. Lymphocytes with frequently convoluted nuclei (Sézary cells) in a patient with advanced mycosis fungoides.

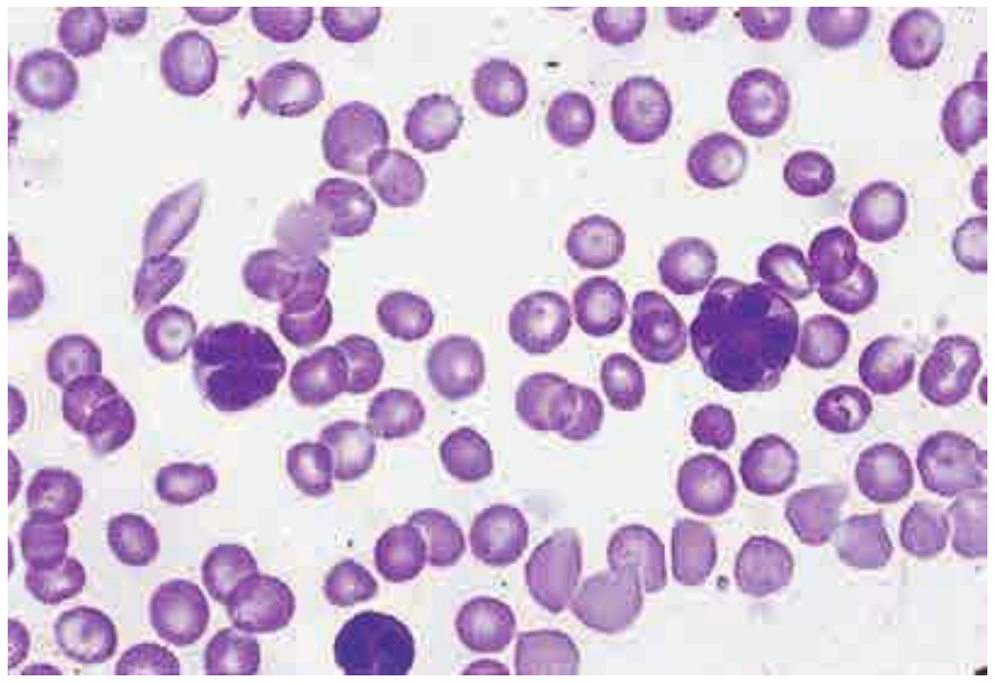


FIGURE 6-48
Adult T cell leukemia. Peripheral blood smear showing leukemia cells with typical "flower-shaped" nucleus.

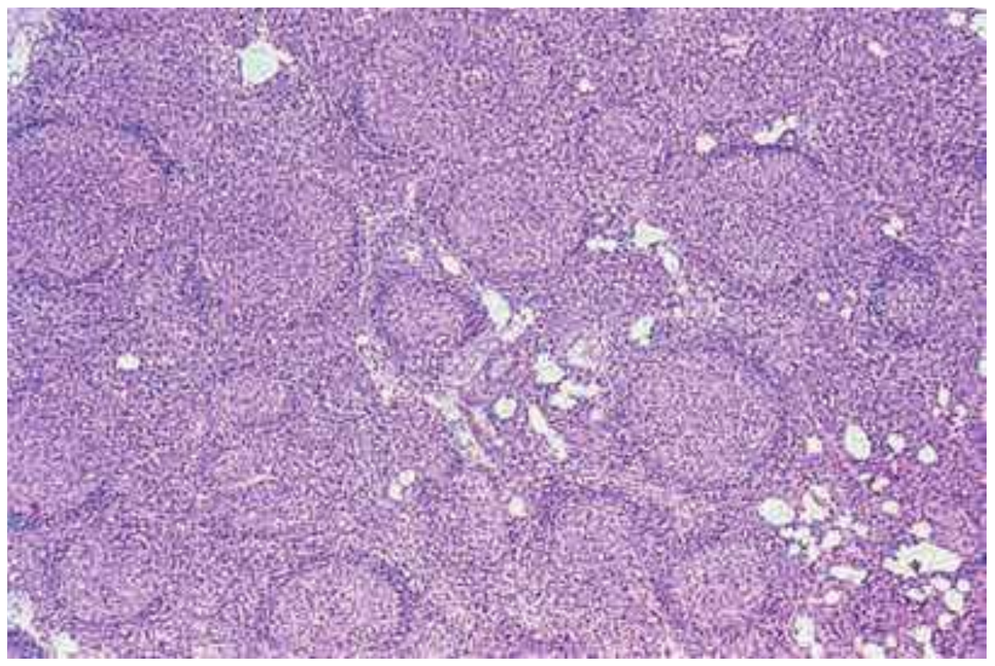


FIGURE 6-49
Follicular lymphoma in a lymph node. The normal nodal architecture is effaced by nodular expansions of tumor cells. Nodules vary in size and contain predominantly small lymphocytes with cleaved nuclei along with variable numbers of larger cells with vesicular chromatin and prominent nucleoli.

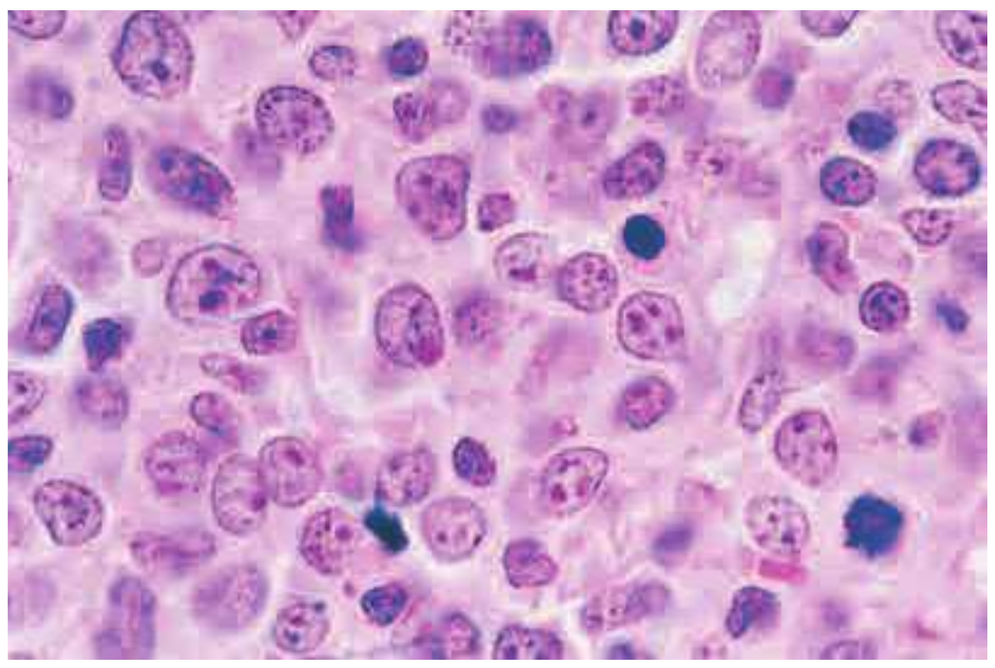


FIGURE 6-50
Diffuse large B cell lymphoma in a lymph node. The neoplastic cells are heterogeneous but predominantly large cells with vesicular chromatin and prominent nucleoli.

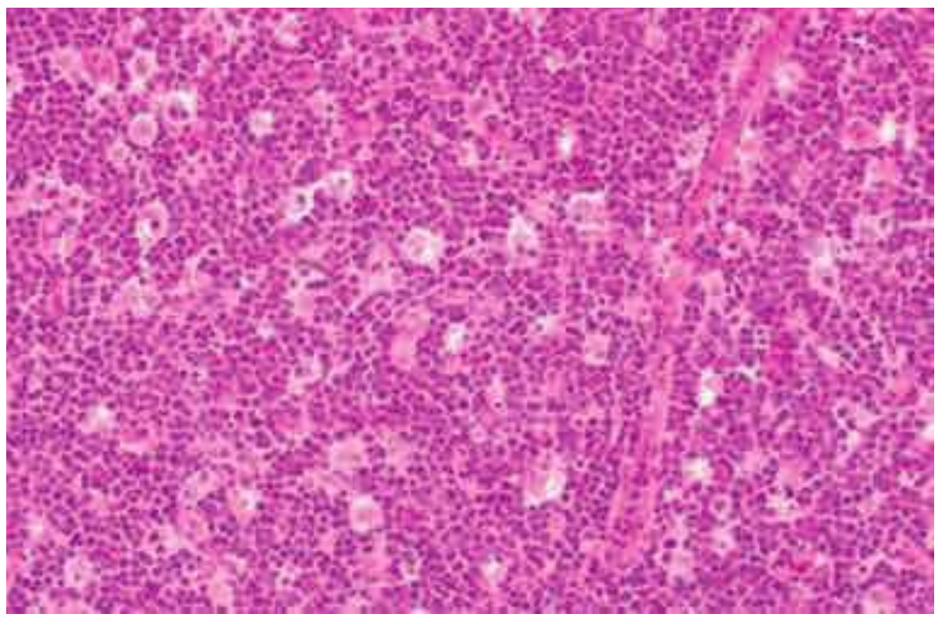


FIGURE 6-51
Burkitt's lymphoma in a lymph node. Burkitt's lymphoma with starry-sky appearance. The lighter areas are macrophages attempting to clear dead cells.

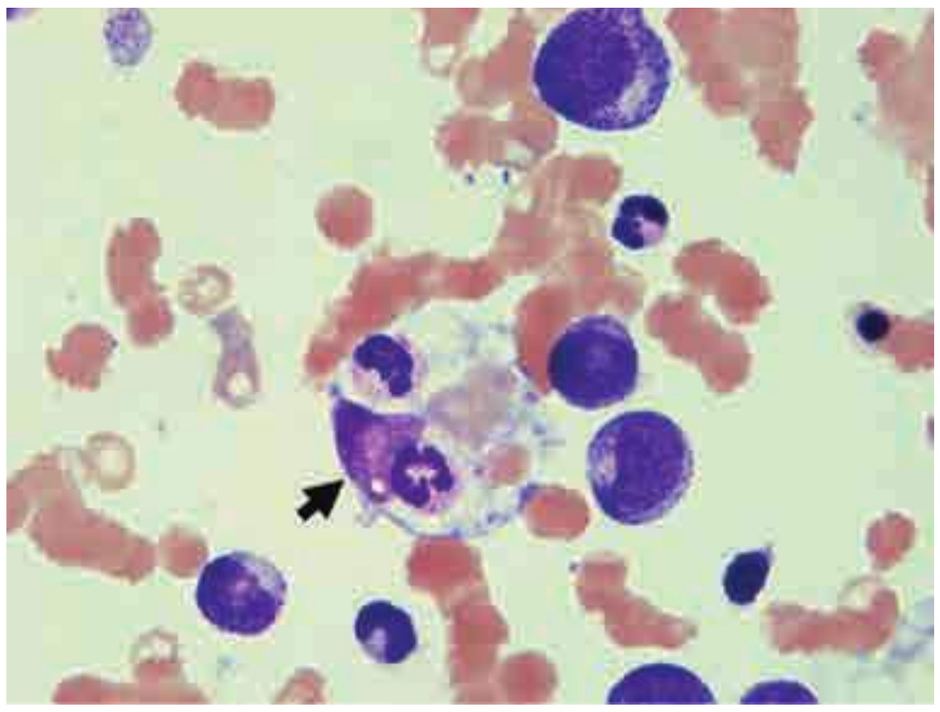


FIGURE 6-52
Erythrophagocytosis accompanying aggressive lymphoma. The central macrophage is ingesting red cells, neutrophils, and platelets. (Courtesy of Dr. Kiyomi Tsukimori, Kyushu University, Fukuoka, Japan.)

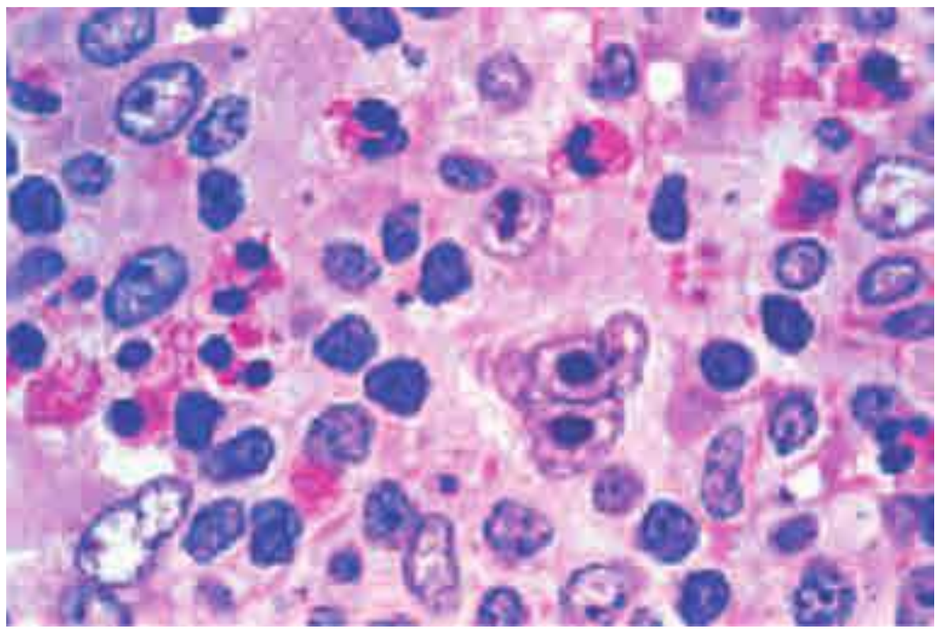


FIGURE 6-53
Hodgkin's disease. A Reed-Sternberg cell is present near the center of the field; a large cell with a bilobed nucleus and prominent nucleoli giving an "owl's eyes" appearance. The majority of the cells are normal lymphocytes, neutrophils, and eosinophils that form a pleiomorphic cellular infiltrate.

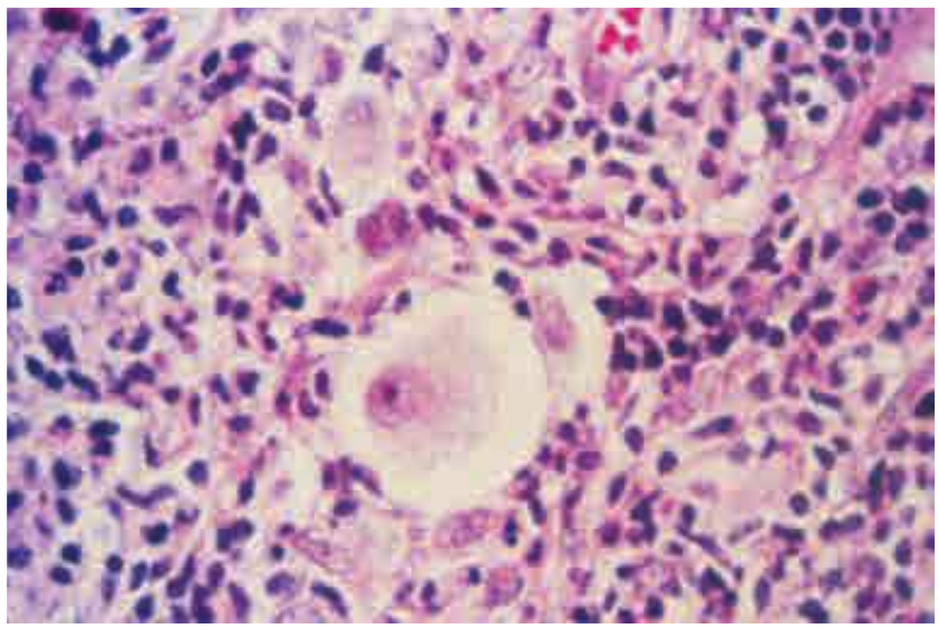


FIGURE 6-54
Lacunar cell; Reed-Sternberg cell variant in nodular sclerosing Hodgkin's disease. High-power view of single mononuclear lacunar cell with retracted cytoplasm in a patient with nodular sclerosing Hodgkin's disease.

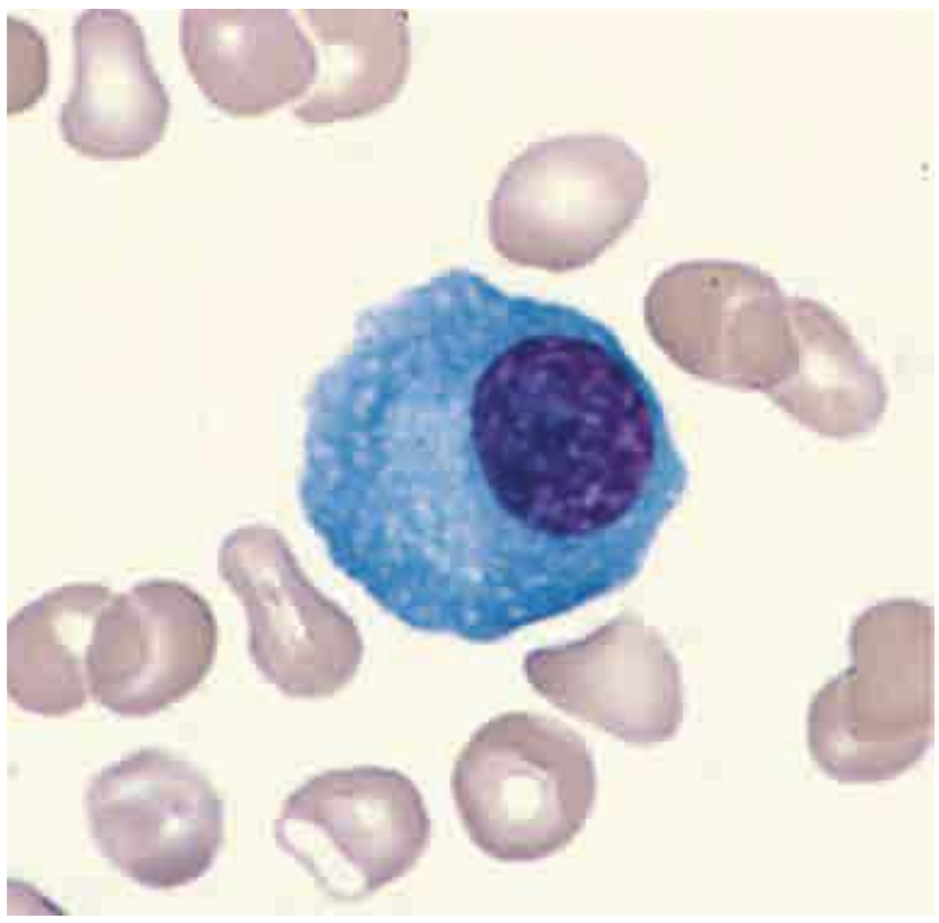


FIGURE 6-55
Normal plasma cell.

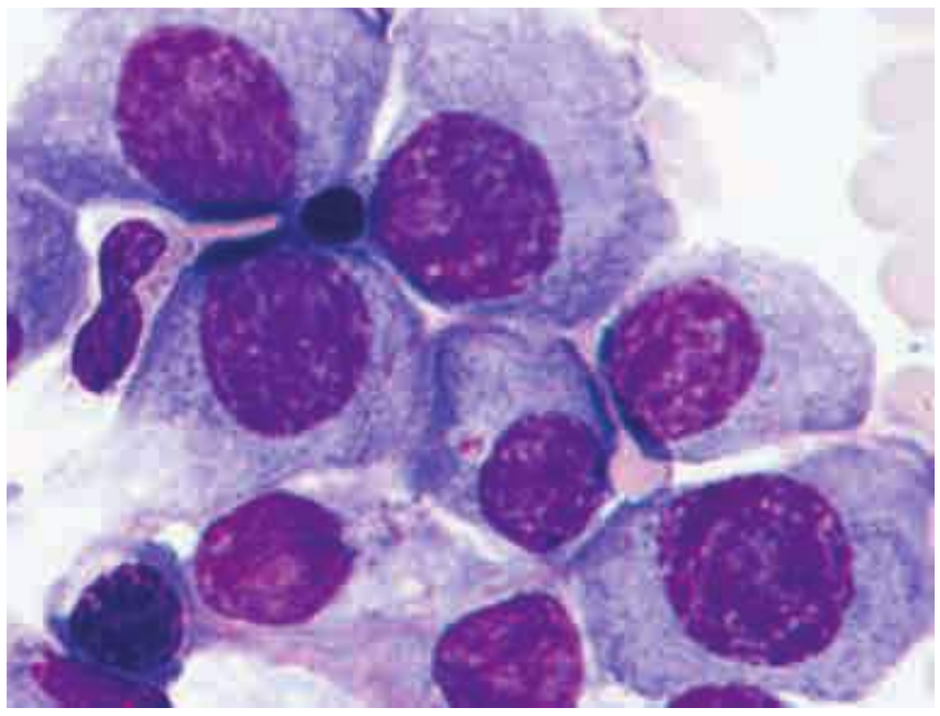


FIGURE 6-56
Multiple myeloma.

FIGURE 6-57

Serum color in hemoglobinemia. The distinctive red coloration of plasma (hemoglobinemia) in a spun blood sample in a patient with intravascular hemolysis.

Acknowledgment

Figures in this e-chapter were borrowed from Williams Hematology, 7th edition, M Lichtman et al (eds). New York, McGraw-Hill, 2005; Hematology in General Practice, 4th edition, RS Hillman, KA Ault, New York, McGraw-Hill, 2005.

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SECTION III

ANEMIAS

CHAPTER 7

IRON DEFICIENCY AND OTHER HYPOPROLIFERATIVE ANEMIAS

John W. Adamson

Anemias associated with normocytic and normochromic red cells and an inappropriately low reticulocyte response (reticulocyte index <2–2.5) are hypoproliferative anemias. This category includes early iron deficiency (before hypochromic microcytic red cells develop), acute and chronic inflammation (including many malignancies), renal disease, hypometabolic states such as protein malnutrition and endocrine deficiencies, and anemias from marrow damage. **Marrow damage states are discussed in Chap. 11.**

Hypoproliferative anemias are the most common anemias, and in the clinic, iron deficiency anemia is the most common of these followed by the anemia of inflammation. The anemia of inflammation, similar to iron deficiency, is related in part to abnormal iron metabolism. The anemias associated with renal disease, inflammation, cancer, and hypometabolic states are characterized by a suboptimal erythropoietin response to the anemia.

IRON METABOLISM

Iron is a critical element in the function of all cells, although the amount of iron required by individual tissues varies during development. At the same time, the body must protect itself from free iron, which is highly toxic in that it participates in chemical reactions that generate free radicals such as singlet O_2 or OH^-. Consequently, elaborate mechanisms have evolved that allow iron to be made available for physiologic functions while at the same time conserving this element and handling it in such a way that toxicity is avoided.

The major role of iron in mammals is to carry O_2 as part of hemoglobin. O_2 is also bound by myoglobin in muscle. Iron is a critical element in iron-containing enzymes, including the cytochrome system in mitochondria. Iron distribution in the body is shown in **Table 7-1**. Without iron, cells lose their capacity for electron transport and energy metabolism. In erythroid cells, hemoglobin synthesis is impaired, resulting in anemia and reduced O_2 delivery to tissue.

THE IRON CYCLE IN HUMANS

Figure 7-1 outlines the major pathways of internal iron exchange in humans. Iron absorbed from the diet or released from stores circulates in the plasma bound to transferrin, the iron transport protein. Transferrin is a bilobed glycoprotein with two iron binding sites. Transferrin that carries iron exists in two forms—monoferric (one iron atom) or diferric (two iron atoms). The turnover (half-clearance time) of transferrin-bound iron is very rapid—typically 60–90 min. Because almost all of the iron transported by transferrin is delivered to the erythroid marrow, the clearance time of transferrin-bound iron from the circulation is affected most by the plasma iron level and the erythroid marrow activity. When erythropoiesis is markedly stimulated, the pool of erythroid cells requiring iron increases and the clearance time of iron from the circulation decreases. The half-clearance time of iron in the presence of iron deficiency is as short as 10–15 min. With suppression of

TABLE 7-1

BODY IRON DISTRIBUTION

	IRON CONTENT, mg	
	ADULT MALE, 80 kg	ADULT FEMALE, 60 kg
Hemoglobin	2500	1700
Myoglobin/enzymes	500	300
Transferrin iron	3	3
Iron stores	600–1000	0–300

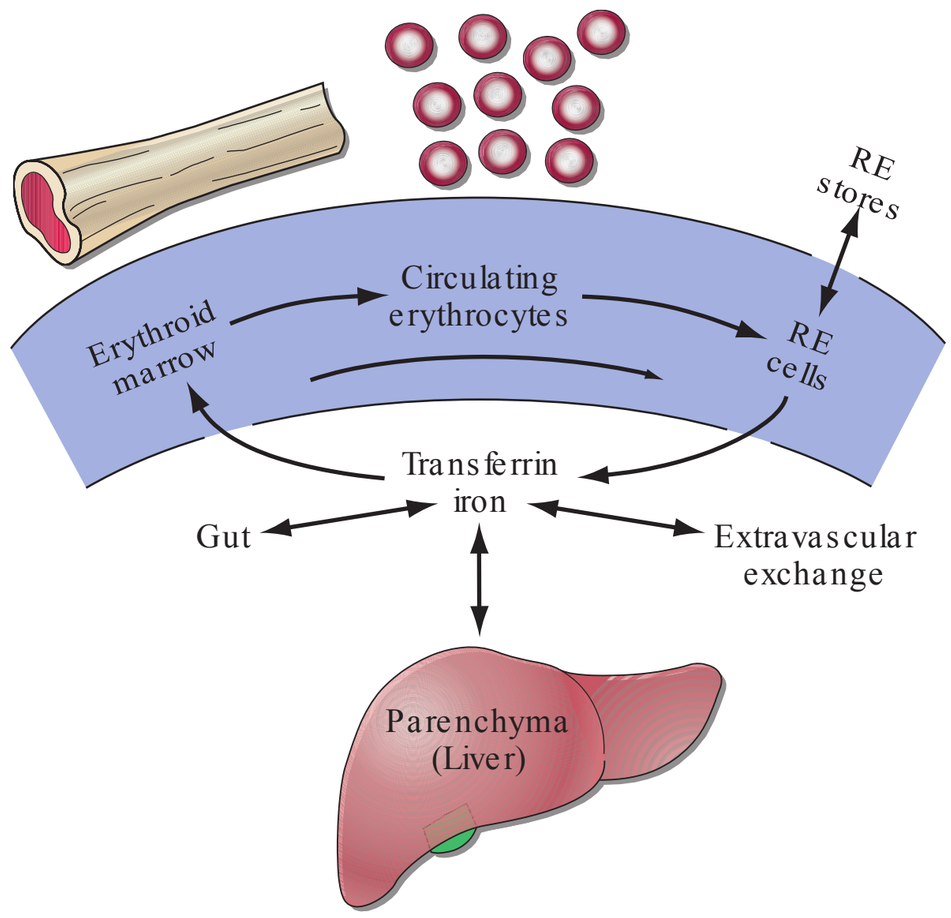


FIGURE 7-1
Internal iron exchange. Normally 80% of iron passing through the plasma transferrin pool is recycled from senescent red cells. Absorption of approximately 1 mg/d is required from the diet in men, and 1.4 mg/d in women to maintain homeostasis. As long as transferrin saturation is maintained between 20 and 60% and erythropoiesis is not increased, use of iron stores is not required. However, in the event of blood loss, dietary iron deficiency, or inadequate iron absorption, up to 40 mg/d of iron can be mobilized from stores. RE, reticuloendothelial.

erythropoiesis, the plasma iron level typically increases and the half-clearance time may be prolonged to several hours. Normally, the iron bound to transferrin turns over 6–8 times per day. Assuming a normal plasma iron level of 80–100 μg/dL, the amount of iron passing through the transferrin pool is 20–24 mg/d.

The iron-transferrin complex circulates in the plasma until it interacts with specific transferrin receptors on the surface of marrow erythroid cells. Diferric transferrin has the highest affinity for transferrin receptors; apotransferrin (not carrying iron) has very little affinity. Although transferrin receptors are found on cells in many tissues within the body—and all cells at some time during development will display transferrin receptors—the cell having the greatest number of receptors (300,000–400,000/cell) is the developing erythroblast.

Once the iron-bearing transferrin interacts with its receptor, the complex is internalized via clathrin-coated pits and transported to an acidic endosome, where the iron is released at the low pH. The iron is then made available for heme synthesis while the transferrin-receptor complex is recycled to the surface of the cell, where the bulk of the transferrin is released back into circulation and the transferrin receptor reanchors into the cell membrane. At this point a certain amount of the transferrin receptor protein may be released into circulation and can be measured as soluble transferrin receptor protein. Within the erythroid cell, iron in excess of the amount needed for hemoglobin synthesis binds to a storage protein, apoferritin, forming ferritin. This is mechanism of iron exchange also takes place in other cells of the body expressing transferrin receptors, especially liver parenchymal cells where the iron can be incorporated into heme-containing enzymes or stored. The iron incorporated into hemoglobin subsequently enters the circulation as new red cells are released from the bone marrow. The iron is then part of the red cell mass and will not become available for reutilization until the red cell dies.

In a normal individual, the average red cell life span is 120 days. Thus, 0.8–1% of red cells are replaced each day. At the end of its life span, the red cell is recognized as senescent by the cells of the reticuloendothelial (RE) system, and the red cell undergoes phagocytosis. Once within the RE cell, the ingested hemoglobin is broken down, the globin and other proteins are returned to the amino acid pool, and the iron is shuttled back to the surface of the RE cell, where it is presented to circulating transferrin. It is the efficient and highly conserved recycling of iron from senescent red cells that supports steady-state (and even mildly accelerated) erythropoiesis.

Because each milliliter of red cells contains 1 mg of elemental iron, the amount of iron needed to replace those red cells lost through senescence amounts to 20 mg/d (assuming an adult with a red cell mass of 2 L). Any additional iron required for daily red cell production comes from the diet. Normally, an adult male will need to absorb at least 1 mg of elemental iron daily to meet needs, while females in the childbearing years will need to absorb an average of 1.4 mg/d. However, to achieve a maximum proliferative erythroid marrow response to anemia, additional iron must be available. With markedly stimulated erythropoiesis, demands for iron are increased by as much as six- to eightfold. With extravascular hemolytic anemia, the rate of red cell destruction is increased, but the iron recovered from the red cells is efficiently reutilized for hemoglobin synthesis. In contrast, with intravascular hemolysis or blood loss anemia, the rate of red cell production is limited by the amount of iron that can be mobilized from stores. Typically, the rate of mobilization under these circumstances will not support red cell production more than 2.5 times normal. If the delivery of iron to the stimulated marrow is suboptimal, the marrow's proliferative response is blunted, and hemoglobin synthesis is impaired. The result is a hypoproliferative marrow accompanied by microcytic, hypochromic anemia.

Whereas blood loss or hemolysis places a demand on the iron supply, inflammatory conditions interfere with iron release from stores and can result in a rapid decrease in the serum iron (see below).

NUTRITIONAL IRON BALANCE

T e balance of iron in humans is tightly controlled and designed to conserve iron for reutilization. T ere is no regulated excretory pathway for iron, and the only mechanisms by which iron is lost are blood loss (via gastrointestinal bleeding, menses, or other forms of bleeding) and the loss of epithelial cells from the skin, gut, and genitourinary tract. Normally, the only route by which iron comes into the body is via absorption from food or from medicinal iron taken orally. Iron may also enter the body through red cell transfusions or injection of iron complexes. T e margin between the amount of iron available for absorption and the requirement for iron in growing infants and the adult female is narrow; this accounts for the great prevalence of iron deficiency worldwide—currently estimated at one-half billion people.

T e amount of iron required from the diet to replace losses averages approximately 10% of body iron content a year in men and 15% in women of childbearing age. Dietary iron content is closely related to total caloric intake (approximately 6 mg of elemental iron per 1000 calories). Iron bioavailability is affected by the nature of the foodstuff, with heme iron (e.g., red meat) being most readily absorbed. In the United States, the average iron intake in an adult male is 15 mg/d with 6% absorption; for the average female, the daily intake is 11 mg/d with 12% absorption. An individual with iron deficiency can increase iron absorption to approximately 20% of the iron present in a meat-containing diet but only 5–10% of the iron in a vegetarian diet. As a result, one-third of the female population in the United States has virtually no iron stores. Vegetarians are at an additional disadvantage because certain foodstuffs that include phytates and phosphates reduce iron absorption by approximately 50%. When ionizable iron salts are given together with food, the amount of iron absorbed is reduced. When the percentage of iron absorbed from individual food items is compared with the percentage for an equivalent amount of ferrous salt, iron in vegetables is only about one-twentieth as available, egg iron one-eighth, liver iron one-half, and heme iron one-half to two-thirds.

Infants, children, and adolescents may be unable to maintain normal iron balance because of the demands of body growth and lower dietary intake of iron. During the last two trimesters of pregnancy, daily iron requirements increase to 5–6 mg, and iron supplements are strongly recommended for pregnant women in developed countries.

Iron absorption takes place largely in the proximal small intestine and is a carefully regulated process. For absorption, iron must be taken up by the luminal cell. T at process is facilitated by the acidic contents of the stomach, which maintains the iron in solution. At the brush border of the absorptive cell, the ferric iron is converted to the ferrous form by a ferrireductase. Transport across the membrane is accomplished by divalent metal transporter type 1 (DMT-1, also known as natural resistance macrophage-associated protein type 2 [Nramp 2] or DCT-1). DMT-1 is a general cation transporter. Once inside the gut cell, iron may be stored as ferritin or transported through the cell to be released at the basolateral surface to plasma transferrin through the membrane-embedded iron exporter, ferroportin. T e function of ferroportin is negatively regulated by hepcidin, the principal iron regulatory hormone. In the process of release, iron interacts with another ferroxidase, hephaestin, which oxidizes the iron to the ferric form for transferrin binding. Hephaestin is similar to ceruloplasmin, the copper-carrying protein.

Iron absorption is influenced by a number of physiologic states. Erythroid hyperplasia stimulates iron absorption even in the face of normal or increased iron stores, and hepcidin levels are inappropriately low. T us, patients with anemias associated with high levels of ineffective erythropoiesis absorb excess amounts of dietary iron. T e molecular mechanism underlying this relationship is not known. Over time, this may lead to iron overload and tissue damage. In iron deficiency, hepcidin levels are also low and iron is much more efficiently absorbed; the contrary is true in states of secondary iron overload. T e normal individual can reduce iron absorption in situations of excessive intake or medicinal iron intake; however, while the percentage of iron absorbed goes down, the absolute amount goes up. T is accounts for the acute iron toxicity occasionally seen when children ingest large numbers of iron tablets. Under these circumstances, the amount of iron absorbed exceeds the transferrin binding capacity of the plasma, resulting in free iron that affects critical organs such as cardiac muscle cells.

IRON-DEFICIENCY ANEMIA

Iron deficiency is one of the most prevalent forms of malnutrition. Globally, 50% of anemia is attributable to iron deficiency and accounts for approximately 841,000 deaths annually worldwide. Africa and parts of Asia bear 71% of the global mortality burden; North America represents only 1.4% of the total morbidity and mortality associated with iron deficiency.

STAGES OF IRON DEFICIENCY

T e progression to iron deficiency can be divided into three stages **(Fig. 7-2)**. T e first stage is negative iron balance, in which the demands for (or losses of) iron

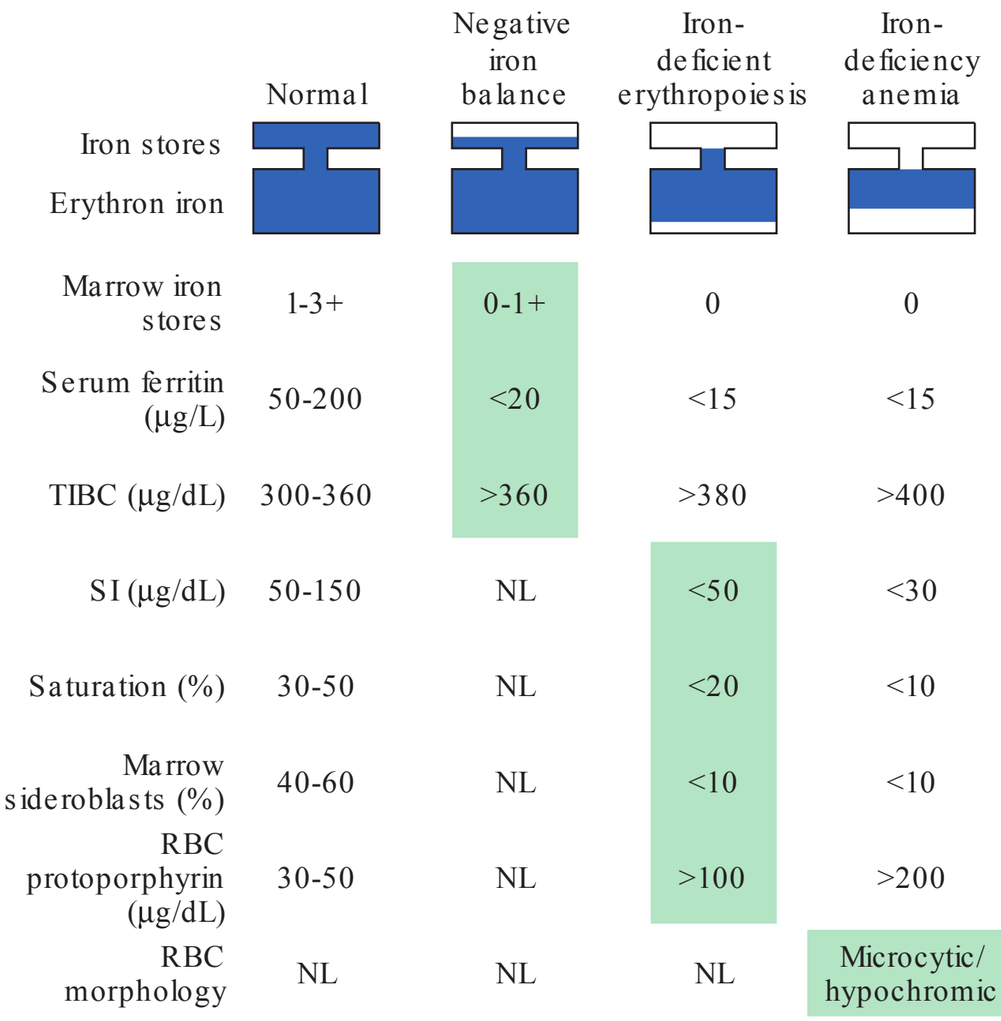


FIGURE 7-2
Laboratory studies in the evolution of iron deficiency. Measurements of marrow iron stores, serum ferritin, and total iron-binding capacity (TIBC) are sensitive to early iron-store depletion. Iron-deficient erythropoiesis is recognized from additional abnormalities in the serum iron (SI), percent transferrin saturation, the pattern of marrow sideroblasts, and the red blood cell (RBC) protoporphyrin level. Patients with iron-deficiency anemia demonstrate all the same abnormalities plus hypochromic microcytic anemia. (From RS Hillman, CA Finch: The Red Cell Manual, 7th ed. Philadelphia, F.A.Davis and Co., 1996, with permission.)

exceed the body's ability to absorb iron from the diet. This stage results from a number of physiologic mechanisms, including blood loss, pregnancy (in which the demands for red cell production by the fetus outstrip the mother's ability to provide iron), rapid growth spurts in the adolescent, or inadequate dietary iron intake. Blood loss in excess of 10–20 mL of red cells per day is greater than the amount of iron that the gut can absorb from a normal diet. Under these circumstances, the iron deficit must be made up by mobilization of iron from RE storage sites. During this period, iron stores—reflected by the serum ferritin level or the appearance of stainable iron on bone marrow aspirations—decrease. As long as iron stores are present and can be mobilized, the serum iron, total iron-binding capacity (TIBC), and red cell protoporphyrin levels remain within normal limits. At this stage, red cell morphology and indices are normal.

When iron stores become depleted, the serum iron begins to fall. Gradually, the TIBC increases, as do red cell protoporphyrin levels. By definition, marrow iron stores are absent when the serum ferritin level is <15 µg/L. As long as the serum iron remains within the normal range, hemoglobin synthesis is unaffected despite the dwindling iron stores. Once the transferrin saturation falls to 15–20%, hemoglobin synthesis becomes impaired. This is a period of iron-deficient erythropoiesis. Careful evaluation of the peripheral blood smear reveals the first appearance of microcytic cells, and if the laboratory technology is available, one finds hypochromic reticulocytes in circulation. Gradually, the hemoglobin and hematocrit begin to fall, reflecting iron-deficiency anemia. The transferrin saturation at this point is 10–15%.

When moderate anemia is present (hemoglobin 10–13 g/dL), the bone marrow remains hypoproliferative. With more severe anemia (hemoglobin 7–8 g/dL), hypochromia and microcytosis become more prominent, target cells and misshapen red cells (poikilocytes) appear on the blood smear as cigar- or pencil-shaped forms, and the erythroid marrow becomes increasingly ineffective. Consequently, with severe prolonged iron-deficiency anemia, erythroid hyperplasia of the marrow develops, rather than hypoproliferation.

CAUSES OF IRON DEFICIENCY

Conditions that increase demand for iron, increase iron loss, or decrease iron intake or absorption can produce iron deficiency **(Table 7-2)**.

CLINICAL PRESENTATION OF IRON DEFICIENCY

Certain clinical conditions carry an increased likelihood of iron deficiency. Pregnancy, adolescence, periods of rapid growth, and an intermittent history of blood loss of any kind should alert the clinician to possible iron deficiency. A cardinal rule is that the appearance of iron deficiency in an adult male means

TABLE 7-2

CAUSES OF IRON DEFICIENCY
Increased Demand for Iron
Rapid growth in infancy or adolescence
Pregnancy
Erythropoietin therapy
Increased Iron Loss
Chronic blood loss
Menses
Acute blood loss
Blood donation
Phlebotomy as treatment for polycythemia vera
Decreased Iron Intake or Absorption
Inadequate diet
Malabsorption from disease (sprue, Crohn's disease)
Malabsorption from surgery (gastrectomy and some forms of bariatric surgery)
Acute or chronic inflammation

gastrointestinal blood loss until proven otherwise. Signs related to iron deficiency depend on the severity and chronicity of the anemia in addition to the usual signs of anemia—fatigue, pallor, and reduced exercise capacity. Cheilosis (fissures at the corners of the mouth) and koilonychia (spooning of the fingernails) are signs of advanced tissue iron deficiency. The diagnosis of iron deficiency is typically based on laboratory results.

LABORATORY IRON STUDIES

Serum iron and total iron-binding capacity

The serum iron level represents the amount of circulating iron bound to transferrin. The TIBC is an indirect measure of the circulating transferrin. The normal range for the serum iron is 50–150 μg/dL; the normal range for TIBC is 300–360 μg/dL. Transferrin saturation, which is normally 25–50%, is obtained by the following formula: serum iron × 100 ÷ TIBC. Iron-deficiency states are associated with saturation levels below 20%. There is a diurnal variation in the serum iron. A transferrin saturation % >50% indicates that a disproportionate amount of the iron bound to transferrin is being delivered to nonerythroid tissues. If this persists for an extended time, tissue iron overload may occur.

Serum ferritin

Free iron is toxic to cells, and the body has established an elaborate set of protective mechanisms to bind iron in various tissue compartments. Within cells, iron is stored complexed to protein as ferritin or hemosiderin. Apoferritin binds to free ferrous iron and stores it in the ferric state. As ferritin accumulates within cells of the RE system, protein aggregates are formed as hemosiderin. Iron in ferritin or hemosiderin can be extracted for release by the RE cells, although hemosiderin is less readily available. Under steady-state conditions, the serum ferritin level correlates with total body iron stores; thus, the serum ferritin level is the most convenient laboratory test to estimate iron stores. The normal value for ferritin varies according to the age and gender of the individual **(Fig. 7-3)**. Adult males have serum ferritin values averaging 100 μg/L, while adult females have levels averaging 30 μg/L. As iron stores are depleted, the serum ferritin falls to <15 μg/L. Such levels are diagnostic of absent body iron stores.

Evaluation of bone marrow iron stores

Although RE iron stores can be estimated from the iron stain of a bone marrow aspirate or biopsy, the measurement of serum ferritin has largely supplanted these procedures for determination of storage iron **(Table 7-3)**. The serum ferritin level is a better indicator of iron overload than the marrow iron stain.

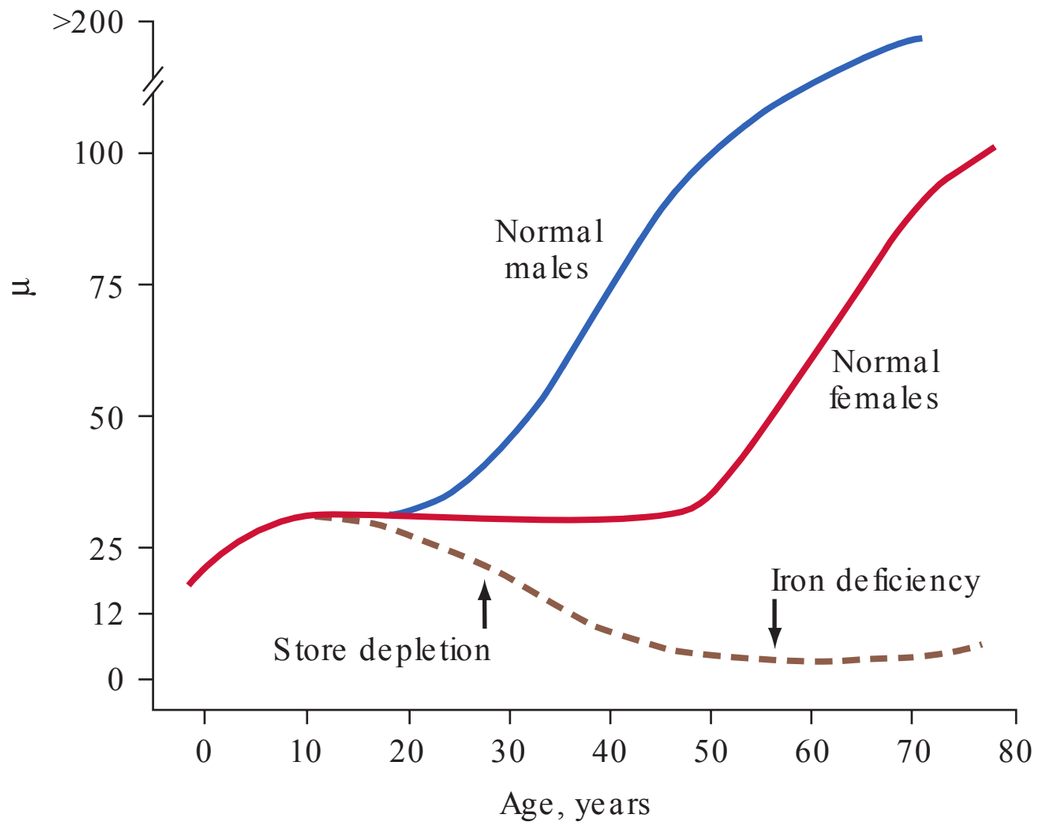


FIGURE 7-3
Serum ferritin levels as a function of sex and age. Iron store depletion and iron deficiency are accompanied by a decrease in serum ferritin level below 20 μg/L. (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2011, with permission.)

However, in addition to storage iron, the marrow iron stain provides information about the effective delivery of iron to developing erythroblasts. Normally, when the marrow smear is stained for iron, 20–40% of developing erythroblasts—called sideroblasts—will have visible ferritin granules in their cytoplasm. This represents iron in excess of that needed for hemoglobin synthesis. In states in which release of iron from storage sites is blocked, RE iron will be detectable, and there will be few or no sideroblasts. In the myelodysplastic syndromes, mitochondrial dysfunction can occur, and accumulation of iron in mitochondria appears in a necklace fashion around the nucleus of the erythroblast. Such cells are referred to as ringed sideroblasts.

Red cell protoporphyrin levels

Protoporphyrin is an intermediate in the pathway to heme synthesis. Under conditions in which heme synthesis is impaired, protoporphyrin accumulates within

TABLE 7-3
IRON STORE MEASUREMENTS

IRON STORES	MARROW IRON STAIN, 0–4+	SERUM FERRITIN, μg/L
0	0	<15
1–300 mg	Trace to 1+	15–30
300–800 mg	2+	30–60
800–1000 mg	3+	60–150
1–2 g	4+	>150
Iron overload	—	>500–1000

the red cell. This reflects an inadequate iron supply to erythroid precursors to support hemoglobin synthesis. Normal values are <30 μg/dL of red cells. In iron deficiency, values in excess of 100 μg/dL are seen. The most common causes of increased red cell protoporphyrin levels are absolute or relative iron deficiency and lead poisoning.

Serum levels of transferrin receptor protein

Because erythroid cells have the highest numbers of transferrin receptors of any cell in the body, and because transferrin receptor protein (TRP) is released by cells into the circulation, serum levels of TRP reflect the total erythroid marrow mass. Another condition in which TRP levels are elevated is absolute iron deficiency. Normal values are 4–9 μg/L determined by immunoassay. This is laboratory test is becoming increasingly available and, along with the serum ferritin, has been proposed to distinguish between iron deficiency and the anemia of inflammation (see below).

DIFFERENTIAL DIAGNOSIS

Other than iron deficiency, only three conditions need to be considered in the differential diagnosis of a hypochromic microcytic anemia **(Table 7-4)**. The first is an inherited defect in globin chain synthesis: the thalassemias. These are differentiated from iron deficiency most readily by serum iron values; normal or increased serum iron levels and transferrin saturation are characteristic of the thalassemias. In addition, the red blood cell distribution width (RDW) index is generally normal in thalassemia and elevated in iron deficiency.

The second condition is the anemia of inflammation (AI; also referred to as the anemia of chronic disease) with inadequate iron supply to the erythroid marrow. The distinction between true iron-deficiency anemia and AI is among the most common diagnostic problems encountered by clinicians (see below). Usually, AI is normocytic and normochromic. The iron values usually make the differential diagnosis clear, as the ferritin level is normal or increased and the percent transferrin saturation and TIBC are typically below normal.

Finally, the myelodysplastic syndromes represent the third and least common condition. Occasionally, patients with myelodysplasia have impaired hemoglobin synthesis with mitochondrial dysfunction, resulting in impaired iron incorporation into heme. The iron values again reveal normal stores and more than an adequate supply to the marrow, despite the microcytosis and hypochromia.

TREATMENT Iron-Deficiency Anemia

The severity and cause of iron-deficiency anemia will determine the appropriate approach to treatment. As an example, symptomatic elderly patients with severe iron-deficiency anemia and cardiovascular instability may require red cell transfusions. Younger individuals who have compensated for their anemia can be treated more conservatively with iron replacement. The foremost issue for the latter patient is the precise identification of the cause of the iron deficiency.

For the majority of cases of iron deficiency (pregnant women, growing children and adolescents, patients with infrequent episodes of bleeding, and those with inadequate dietary intake of iron), oral iron therapy will suffice. For patients with unusual blood loss or malabsorption, specific diagnostic tests and appropriate therapy take priority. Once the diagnosis of iron-deficiency anemia and its cause is made, there are three major therapeutic approaches.

RED CELL TRANSFUSION Transfusion therapy is reserved for individuals who have symptoms of anemia, cardiovascular instability, and continued and excessive blood loss from whatever source and who require immediate intervention. The management of these patients is less related to the iron

TABLE 7-4

DIAGNOSIS OF MICROCYTIC ANEMIA

TESTS	IRON DEFICIENCY	INFLAMMATION	THALASSEMIA	SIDEROBLASTIC ANEMIA
Smear	Micro/hypo	Normal micro/hypo	Micro/hypo with targeting	Variable
Serum iron (μg/dL)	<30	<50	Normal to high	Normal to high
TIBC (μg/dL)	>360	<300	Normal	Normal
Percent saturation	<10	10–20	30–80	30–80
Ferritin (μg/L)	<15	30–200	50–300	50–300
Hemoglobin pattern on electrophoresis	Normal	Normal	Abnormal with β thalassemia; can be normal with α thalassemia	Normal

Abbreviation: TIBC, total iron-binding capacity.

deficiency than it is to the consequences of the severe anemia. Not only do transfusions correct the anemia acutely, but the transfused red cells provide a source of iron for reutilization, assuming they are not lost through continued bleeding. Transfusion therapy will stabilize the patient while other options are reviewed.

ORAL IRON THERAPY In the asymptomatic patient with established iron-deficiency anemia, treatment with oral iron is usually adequate. Multiple preparations are available, ranging from simple iron salts to complex iron compounds designed for sustained release throughout the small intestine **(Table 7-5)**. Although the various preparations contain different amounts of iron, they are generally all absorbed well and are effective in treatment. Some come with other compounds designed to enhance iron absorption, such as ascorbic acid. It is not clear whether the benefits of such compounds justify their costs. Typically, for iron replacement therapy, up to 200 mg of elemental iron per day is given, usually as three or four iron tablets (each containing 50–65 mg elemental iron) given over the course of the day. Ideally, oral iron preparations should be taken on an empty stomach, since food may inhibit iron absorption. Some patients with gastric disease or prior gastric surgery require special treatment with iron solutions, because the retention capacity of the stomach may be reduced. The retention capacity is necessary for dissolving the shell of the iron tablet before the release of iron. A dose of 200 mg of elemental iron per day should result in the absorption of iron up to 50 mg/d. This supports a red cell production level of two to three times normal in an individual with a normally functioning marrow and appropriate erythropoietin stimulus. However, as the hemoglobin level rises, erythropoietin stimulation decreases, and the amount of iron absorbed is reduced. The goal of therapy in individuals with iron-deficiency anemia is not only to repair the anemia, but also to provide stores of at least 0.5–1 g of iron. Sustained treatment for a period of 6–12 months after correction of the anemia will be necessary to achieve this.

Of the complications of oral iron therapy, gastrointestinal distress is the most prominent and is seen in 15–20% of patients. Abdominal pain, nausea, vomiting, or constipation may lead to noncompliance. Although small doses of iron or iron preparations with delayed release may help somewhat, the gastrointestinal side effects are a major impediment to the effective treatment of a number of patients.

The response to iron therapy varies, depending on the erythropoietin stimulus and the rate of absorption. Typically, the reticulocyte count should begin to increase within 4–7 days after initiation of therapy and peak at 1–1½ weeks. The absence of a response may be due to poor absorption, noncompliance (which is common), or a confounding diagnosis. A useful test in the clinic to determine the patient's ability to absorb iron is the iron tolerance test. Two iron tablets are given to the patient on an empty stomach, and the serum iron is measured serially over the subsequent 2 h. Normal absorption will result in an increase in the serum iron of at least 100 μg/dL. If iron deficiency persists despite adequate treatment, it may be necessary to switch to parenteral iron therapy.

PARENTERAL IRON THERAPY Intravenous iron can be given to patients who are unable to tolerate oral iron; whose needs are relatively acute; or who need iron on an ongoing basis, usually due to persistent gastrointestinal blood loss. Parenteral iron use has been increasing rapidly in the last several years with the recognition that recombinant erythropoietin (EPO) therapy induces a large demand for iron—a demand that frequently cannot be met through the physiologic release of iron from RE sources or oral iron absorption. The safety of parenteral iron—particularly iron dextran—has been a concern. The serious adverse reaction rate to intravenous high-molecular-weight iron dextran is 0.7%. Fortunately, newer iron complexes are available in the United States, such as ferumoxytol (Feraheme), sodium ferric gluconate (Ferrlecit), iron sucrose (Venofer), and ferric carboxymaltose (Injectafer), that have much lower rates of adverse effects. Ferumoxytol delivers 510 mg of iron per injection; ferric gluconate 125 mg per injection, ferric carboxymaltose 750 mg per injection, and iron sucrose 200 mg per injection.

Parenteral iron is used in two ways: one is to administer the total dose of iron required to correct the hemoglobin deficit and provide the patient with at least 500 mg of iron stores; the second is to give repeated small doses of parenteral iron over a protracted period. The latter approach is common in dialysis centers, where it is not unusual for 100 mg of elemental iron to be given weekly for 10 weeks to augment the response to recombinant EPO therapy. The amount of iron needed by an individual patient is calculated by the following formula:

$$\text{Body weight (kg)} \times 2.3 \times (15 - \text{patient's hemoglobin, g/dL}) + 500 \text{ or } 1000 \text{ mg (for stores)}.$$

In administering intravenous iron dextran, anaphylaxis is a concern. Anaphylaxis is much rarer with the newer preparations. The factors that have correlated with an anaphylactic-like reaction include a history of multiple allergies or a prior allergic reaction to dextran (in the case of iron dextran).

TABLE 7-5

ORAL IRON PREPARATIONS

GENERIC NAME	TABLET (IRON CONTENT), mg	ELIXIR (IRON CONTENT), mg IN 5 mL
Ferrous sulfate	325 (65)	300 (60)
	195 (39)	90 (18)
Extended release	525 (105)	
Ferrous fumarate	325 (107)	
	195 (64)	100 (33)
Ferrous gluconate	325 (39)	300 (35)
Polysaccharide iron	150 (150)	100 (100)
	50 (50)	

Generalized symptoms appearing several days after the infusion of a large dose of iron can include arthralgias, skin rash, and low-grade fever. These may be dose-related, but they do not preclude the further use of parenteral iron in the patient. To date, patients with sensitivity to iron dextran have been safely treated with other parenteral iron preparations. If a large dose of iron dextran is to be given (>100 mg), the iron preparation should be diluted in 5% dextrose in water or 0.9% NaCl solution. The iron solution can then be infused over a 60- to 90-min period (for larger doses) or at a rate convenient for the attending nurse or physician. Although a test dose (25 mg) of parenteral iron dextran is recommended, in reality a slow infusion of a larger dose of parenteral iron solution will afford the same kind of early warning as a separately injected test dose. Early in the infusion of iron, if chest pain, wheezing, a fall in blood pressure, or other systemic symptoms occur, the infusion of iron should be stopped immediately.

OTHER HYPOPROLIFERATIVE ANEMIAS

In addition to mild to moderate iron-deficiency anemia, the hypoproliferative anemias can be divided into four categories: (1) chronic inflammation, (2) renal disease, (3) endocrine and nutritional deficiencies (hypometabolic states), and (4) marrow damage **(Chap. 11)**. With chronic inflammation, renal disease, or hypometabolism, endogenous EPO production is inadequate for the degree of anemia observed. For the anemia of chronic inflammation, the erythroid marrow also responds inadequately to stimulation, due in part to defective iron reutilization. As a result of the lack of adequate EPO stimulation, an examination of the peripheral blood smear will disclose only an occasional polychromatophilic ("shift") reticulocyte. In cases of iron deficiency or marrow damage, appropriate elevations in endogenous EPO levels are typically found, and shift reticulocytes will be present on the blood smear.

ANEMIA OF ACUTE AND CHRONIC INFLAMMATION/INFECTION (AI)

AI—which encompasses inflammation, infection, tissue injury, and conditions (such as cancer) associated with the release of proinflammatory cytokines—is one of the most common forms of anemia seen clinically. It is the most important anemia in the differential diagnosis of iron deficiency, because many of the features of the anemia are brought about by inadequate iron delivery to the marrow, despite the presence of normal or increased iron stores. This is reflected by a low serum iron, increased red cell protoporphyrin, a hypoproliferative marrow, transferrin saturation in the range of 15–20%, and a normal or increased serum ferritin. The serum ferritin values are often the most distinguishing features between true iron-deficiency anemia and the iron-restricted erythropoiesis associated with inflammation. Typically, serum ferritin values increase threefold over basal levels in the face of inflammation. These changes are due to the effects of inflammatory cytokines and hepcidin, the key iron regulatory hormone, acting at several levels of erythropoiesis **(Fig. 7-4)**.

Interleukin 1 (IL-1) directly decreases EPO production in response to anemia. IL-1, acting through accessory cell release of interferon γ (IFN-γ), suppresses the response of the erythroid marrow to EPO—an effect that can be overcome by EPO administration in vitro and in vivo. In addition, tumor necrosis factor (TNF), acting through the release of IFN-γ by marrow stromal cells, also suppresses the response to EPO. Hepcidin, made by the liver, is increased in inflammation via an IL-6 mediated pathway, and acts to suppress iron absorption and iron release from storage sites. The overall result is a chronic hypoproliferative anemia with classic changes in iron metabolism. The anemia is further compounded by a mild to moderate shortening in red cell survival.

With chronic inflammation, the primary disease will determine the severity and characteristics of the anemia. For example, many patients with cancer also have anemia that is typically normocytic and normochromic. In contrast, patients with long-standing active rheumatoid arthritis or chronic infections such as tuberculosis will have a microcytic, hypochromic anemia. In both cases, the bone marrow is hypoproliferative, but the differences in red cell indices reflect differences in the

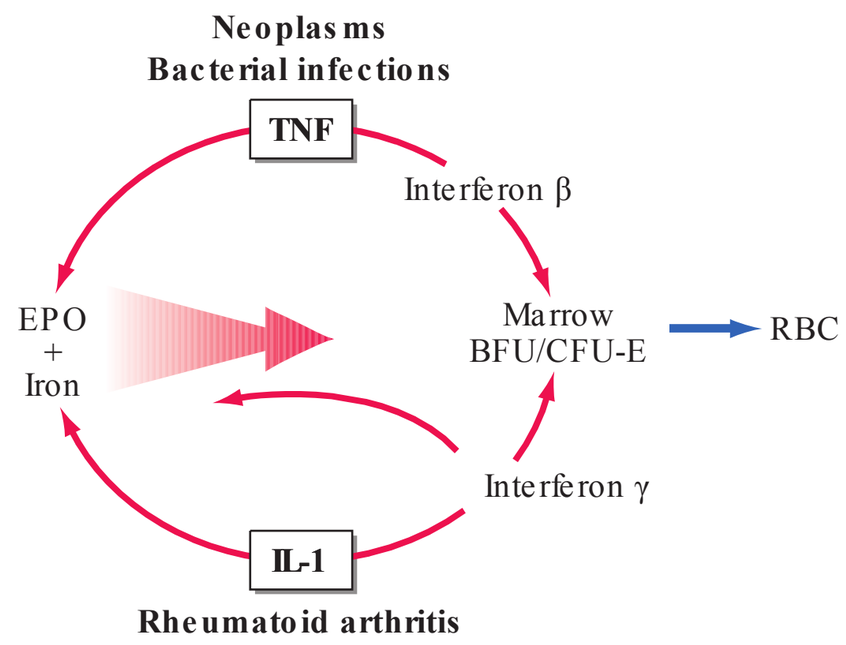


FIGURE 7-4
Suppression of erythropoiesis by inflammatory cytokines. Through the release of tumor necrosis factor (TNF) and interferon γ (IFN-γ), neoplasms and bacterial infections suppress erythropoietin (EPO) production and the proliferation of erythroid progenitors (erythroid burst-forming units and erythroid colony-forming units [BFU/CFU-E]). The mediators in patients with vasculitis and rheumatoid arthritis include interleukin 1 (IL-1) and IFN-γ. The red arrows indicate sites of inflammatory cytokine inhibitory effects. RBC, red blood cell.

availability of iron for hemoglobin synthesis. Occasionally, conditions associated with chronic inflammation are also associated with chronic blood loss. Under these circumstances, a bone marrow aspirate stained for iron may be necessary to rule out absolute iron deficiency. However, the administration of iron in this case will correct the iron deficiency component of the anemia and leave the inflammatory component unaffected.

The anemia associated with acute infection or inflammation is typically mild but becomes more pronounced over time. Acute infection can produce a decrease in hemoglobin levels of 2–3 g/dL within 1 or 2 days; this is largely related to the hemolysis of red cells near the end of their natural life span. The fever and cytokines released exert a selective pressure against cells with more limited capacity to maintain the red cell membrane. In most individuals, the mild anemia is reasonably well tolerated, and symptoms, if present, are associated with the underlying disease. Occasionally, in patients with preexisting cardiac disease, moderate anemia (hemoglobin 10–11 g/dL) may be associated with angina, exercise intolerance, and shortness of breath. The erythropoietic profile that distinguishes the anemia of inflammation from the other causes of hypoproliferative anemias is shown in **Table 7-6**.

ANEMIA OF CHRONIC KIDNEY DISEASE (CKD)

Progressive CKD is usually associated with a moderate to severe hypoproliferative anemia; the level of the anemia correlates with the stage of CKD. Red cells are typically normocytic and normochromic, and reticulocytes are decreased. The anemia is primarily due to a failure of EPO production by the diseased kidney and a reduction in red cell survival. In certain forms of acute renal failure, the correlation between the anemia and renal function is weaker. Patients with the hemolytic-uremic syndrome increase erythropoiesis in response to the hemolysis, despite renal failure requiring dialysis. Polycystic kidney disease also shows a smaller degree of EPO deficiency for a given level of renal failure. By contrast, patients with diabetes or myeloma have more severe EPO deficiency for a given level of renal failure.

Assessment of iron status provides information to distinguish the anemia of CKD from the other forms of hypoproliferative anemia (Table 7-6) and to guide management. Patients with the anemia of CKD usually present with normal serum iron, TIBC, and ferritin levels. However, those maintained on chronic hemodialysis may develop iron deficiency from blood loss through the dialysis procedure. Iron must be replenished in these patients to ensure an adequate response to EPO therapy (see below).

ANEMIA IN HYPOMETABOLIC STATES

Patients who are starving, particularly for protein, and those with a variety of endocrine disorders that produce lower metabolic rates, may develop a mild to moderate hypoproliferative anemia. The release of EPO from the kidney is sensitive to the need for O_2, not just O_2 levels. Thus, EPO production is triggered at lower levels of blood O_2 content in disease states (such as hypothyroidism and starvation) where metabolic activity, and thus O_2 demand, is decreased.

Endocrine deficiency states

The difference in the levels of hemoglobin between men and women is related to the effects of androgen and estrogen on erythropoiesis. Testosterone and anabolic steroids augment erythropoiesis; castration and estrogen administration to males decrease erythropoiesis. Patients who are hypothyroid or have deficits in pituitary hormones also may develop a mild anemia. Pathogenesis may be complicated by other nutritional deficiencies because iron and folic acid absorption can be affected by these disorders. Usually, correction of the hormone deficiency reverses the anemia.

TABLE 7-6

DIAGNOSIS OF HYPOPROLIFERATIVE ANEMIAS

TESTS	IRON DEFICIENCY	INFLAMMATION	RENAL DISEASE	HYPOMETABOLIC STATES
Anemia	Mild to severe	Mild	Mild to severe	Mild
MCV (fL)	60–90	80–90	90	90
Morphology	Normo-microcytic	Normocytic	Normocytic	Normocytic
SI (µg/dL)	<30	<50	Normal	Normal
TIBC (µg/dL)	>360	<300	Normal	Normal
Saturation (%)	<10	10–20	Normal	Normal
Serum ferritin (µg/L)	<15	30–200	115–150	Normal
Iron stores	0	2–4+	1–4+	Normal

Abbreviations: MCV, mean corpuscular volume; SI, serum iron; TIBC, total iron-binding capacity.

Anemia may be more severe in Addison's disease, depending on the level of thyroid and androgen hormone dysfunction; however, anemia may be masked by decreases in plasma volume. Once such patients are given cortisol and volume replacement, the hemoglobin level may fall rapidly. Mild anemia complicating hyperparathyroidism may be due to decreased EPO production as a consequence of the renal effects of hypercalcemia or to impaired proliferation of erythroid progenitors.

Protein starvation

Decreased dietary intake of protein may lead to mild to moderate hypoproliferative anemia; this form of anemia may be prevalent in the elderly. The anemia can be more severe in patients with a greater degree of starvation. In marasmus, where patients are both protein and calorie deficient, the release of EPO is impaired in proportion to the reduction in metabolic rate; however, the degree of anemia may be masked by volume depletion and becomes apparent after refeeding. Deficiencies in other nutrients (iron, folate) may also complicate the clinical picture but may not be apparent at diagnosis. Changes in the erythrocyte indices on refeeding should prompt evaluation of iron, folate, and B_{12} status.

Anemia in liver disease

A mild hypoproliferative anemia may develop in patients with chronic liver disease from nearly any cause. The peripheral blood smear may show spur cells and stomatocytes from the accumulation of excess cholesterol in the membrane from a deficiency of lecithin-cholesterol acyltransferase. Red cell survival is shortened, and the production of EPO is inadequate to compensate. In alcoholic liver disease, nutritional deficiencies are common and complicate the management. Folate deficiency from inadequate intake, as well as iron deficiency from blood loss and inadequate intake, can alter the red cell indices.

TREATMENT Hypoproliferative Anemias

Many patients with hypoproliferative anemias experience recovery of normal hemoglobin levels when the underlying disease is appropriately treated. For those in whom such reversals are not possible—such as patients with end-stage kidney disease, cancer, and chronic inflammatory diseases—symptomatic anemia requires treatment. The two major forms of treatment are transfusions and EPO.

TRANSFUSIONS Thresholds for transfusion should be determined based on the patient's symptoms. In general, patients without serious underlying cardiovascular or pulmonary disease can tolerate hemoglobin levels above 7–8 g/dL and do not require intervention until the hemoglobin falls below that level. Patients with more physiologic compromise may need to have their hemoglobin levels kept above 11 g/dL. Usually, a unit of packed red cells increases the hemoglobin level by 1 g/dL. Transfusions are associated with certain infectious risks **(Chap. 12)**, and chronic transfusions can produce iron overload. Importantly, the liberal use of blood has been associated with increased morbidity and mortality, particularly in the intensive care setting. Therefore, in the absence of documented tissue hypoxia, a conservative approach to the use of red cell transfusions is preferable.

ERYTHROPOIETIN (EPO) EPO is particularly useful in anemias in which endogenous EPO levels are inappropriately low, such as CKD or AI. Iron status must be evaluated and iron replaced to obtain optimal effects from EPO. In patients with CKD, the usual dose of EPO is 50–150 U/kg three times a week intravenously. Hemoglobin levels of 10–12 g/dL are usually reached within 4–6 weeks if iron levels are adequate; 90% of these patients respond. Once a target hemoglobin level is achieved, the EPO dose can be decreased. A decrease in hemoglobin level occurring in the face of EPO therapy usually signifies the development of an infection or iron depletion. Aluminum toxicity and hyperparathyroidism can also compromise the response to EPO. When an infection intervenes, it is best to interrupt the EPO therapy and rely on transfusions to correct the anemia until the infection is adequately treated. The dose of EPO needed to correct chemotherapy-induced anemia in patients with cancer is higher, up to 300 U/kg three times a week, and only approximately 60% of patients respond. Because of evidence that there is an increased risk of thromboembolic complications and tumor progression with EPO administration, the risks and benefits of using EPO in such patients must be weighed carefully, and the target hemoglobin should be that necessary to avoid transfusions.

Longer-acting preparations of EPO can reduce the frequency of injections. Darbepoetin alfa, a molecularly modified EPO with additional carbohydrate, has a half-life in the circulation that is three to four times longer than recombinant human EPO, permitting weekly or every other week dosing.

CHAPTER 8

DISORDERS OF HEMOGLOBIN

Edward J. Benz, Jr.

Hemoglobin is critical for normal oxygen delivery to tissues; it is also present in erythrocytes in such high concentrations that it can alter red cell shape, deformability, and viscosity. Hemoglobinopathies are disorders affecting the structure, function, or production of hemoglobin. T ese conditions are usually inherited and range in severity from asymptomatic laboratory abnormalities to death in utero. Different forms may present as hemolytic anemia, erythrocytosis, cyanosis, or vaso-occlusive stigmata.

PROPERTIES OF THE HUMAN HEMOGLOBINS

HEMOGLOBIN STRUCTURE

Different hemoglobins are produced during embryonic, fetal, and adult life **(Fig. 8-1)**. Each consists of a tetramer of globin polypeptide chains: a pair of α-like chains 141 amino acids long and a pair of β-like chains 146 amino acids long. T e major adult hemoglobin, HbA, has the structure $\alpha_2\beta_2$. HbF ($\alpha_2\gamma_2$) predominates during most of gestation, and HbA_2 ($\alpha_2\delta_2$) is minor adult hemoglobin. Embryonic hemoglobins need not be considered here.

Each globin chain enfolds a single heme moiety, consisting of a protoporphyrin IX ring complexed with a single iron atom in the ferrous state (Fe^{2+}). Each heme moiety can bind a single oxygen molecule; a molecule of hemoglobin can transport up to four oxygen molecules.

T e amino acid sequences of the various globins are highly homologous to one another. Each has a highly helical secondary structure. T eir globular tertiary structures cause the exterior surfaces to be rich in polar (hydrophilic) amino acids that enhance solubility, and the interior to be lined with nonpolar groups, forming a hydrophobic pocket into which heme is inserted. T e tetrameric quaternary structure of HbA contains two αβ dimers. Numerous tight interactions (i.e., $\alpha_1\beta_1$ contacts) hold the α and β chains together. T e complete tetramer is held together by interfaces (i.e., $\alpha_1\beta_2$ contacts) between the α-like chain of one dimer and the non-α chain of the other dimer.

T e hemoglobin tetramer is highly soluble, but individual globin chains are insoluble. Unpaired globin precipitates, forming inclusions that damage the cell and can trigger apoptosis. Normal globin chain synthesis is balanced so that each newly synthesized α or non-α globin chain will have an available partner with which to pair.

Solubility and reversible oxygen binding are the key properties deranged in hemoglobinopathies. Both depend most on the hydrophilic surface amino acids, the hydrophobic amino acids lining the heme pocket, a key histidine in the F helix, and the amino acids forming the $\alpha_1\beta_1$ and $\alpha_1\beta_2$ contact points. Mutations in these strategic regions tend to be the ones that alter oxygen affinity or solubility.

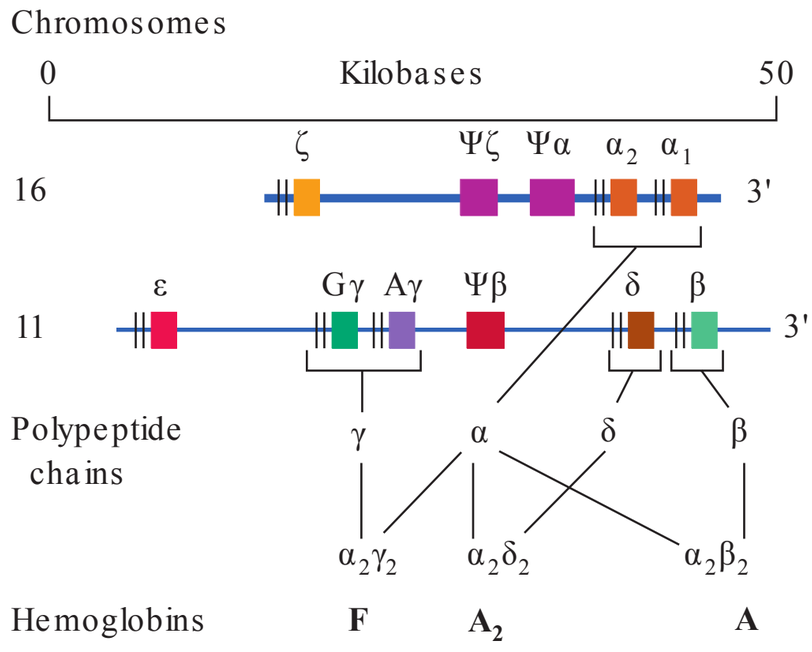


FIGURE 8-1

The globin genes. The α-like genes (α, ζ) are encoded on chromosome 16; the β-like genes (β, γ, δ, ε) are encoded on chromosome 11. The ζ and ε genes encode embryonic globins.

FUNCTION OF HEMOGLOBIN

To support oxygen transport, hemoglobin must bind O_2 efficiently at the partial pressure of oxygen (Po_2) of the alveolus, retain it in the circulation, and release it to tissues at the Po_2 of tissue capillary beds. Oxygen acquisition and delivery over a relatively narrow range of oxygen tensions depend on a property inherent in the tetrameric arrangement of heme and globin subunits within the hemoglobin molecule called cooperativity or heme-heme interaction.

At low oxygen tensions, the hemoglobin tetramer is fully deoxygenated **(Fig. 8-2)**. Oxygen binding begins slowly as O_2 tension rises. However, as soon as some oxygen has been bound by the tetramer, an abrupt increase occurs in the slope of the curve. T us, hemoglobin molecules that have bound some oxygen develop a higher oxygen affinity, greatly accelerating their ability to combine with more oxygen. T is S-shaped oxygen equilibrium curve (Fig. 8-2), along which substantial amounts of oxygen loading and unloading can occur over a narrow range of oxygen tensions, is physiologically more useful than the high-affinity hyperbolic curve of individual monomers.

Oxygen affinity is modulated by several factors. T e Bohr effect is the ability of hemoglobin to deliver more oxygen to tissues at low pH. It arises from the stabilizing action of protons on deoxyhemoglobin, which binds protons more readily than oxyhemoglobin because the latter is a weaker acid (Fig. 8-2). T us, hemoglobin has a lower oxygen affinity at low pH. T e major small molecule that alters oxygen affinity in humans is 2,3-bisphosphoglycerate (2,3-BPG; formerly 2,3-DPG), which lowers oxygen affinity when bound to hemoglobin. HbA has a reasonably high affinity for 2,3-BPG. HbF does not bind 2,3-BPG, so it tends to have a higher oxygen affinity in vivo. Hemoglobin also binds nitric oxide reversibly; this interaction influences vascular tone, but its clinical relevance remains incompletely understood.

Proper oxygen transport depends on the tetrameric structure of the proteins, the proper arrangement of hydrophilic and hydrophobic amino acids, and interaction with protons or 2,3-BPG.

DEVELOPMENTAL BIOLOGY OF HUMAN HEMOGLOBINS

Red cells first appearing at about 6 weeks af er conception contain the embryonic hemoglobins Hb Portland ($\zeta_2\gamma_2$), Hb Gower I ($\zeta_2\varepsilon_2$), and Hb Gower II ($\alpha_2\varepsilon_2$). At 10–11 weeks, fetal hemoglobin (HbF; $\alpha_2\gamma_2$) becomes predominant. T e switch to nearly exclusive synthesis of adult hemoglobin (HbA; $\alpha_2\beta_2$) occurs at about 38 weeks (Fig. 8-1). Fetuses and newborns therefore require α-globin but not β-globin for normal gestation. A major advance in understanding the HbF to

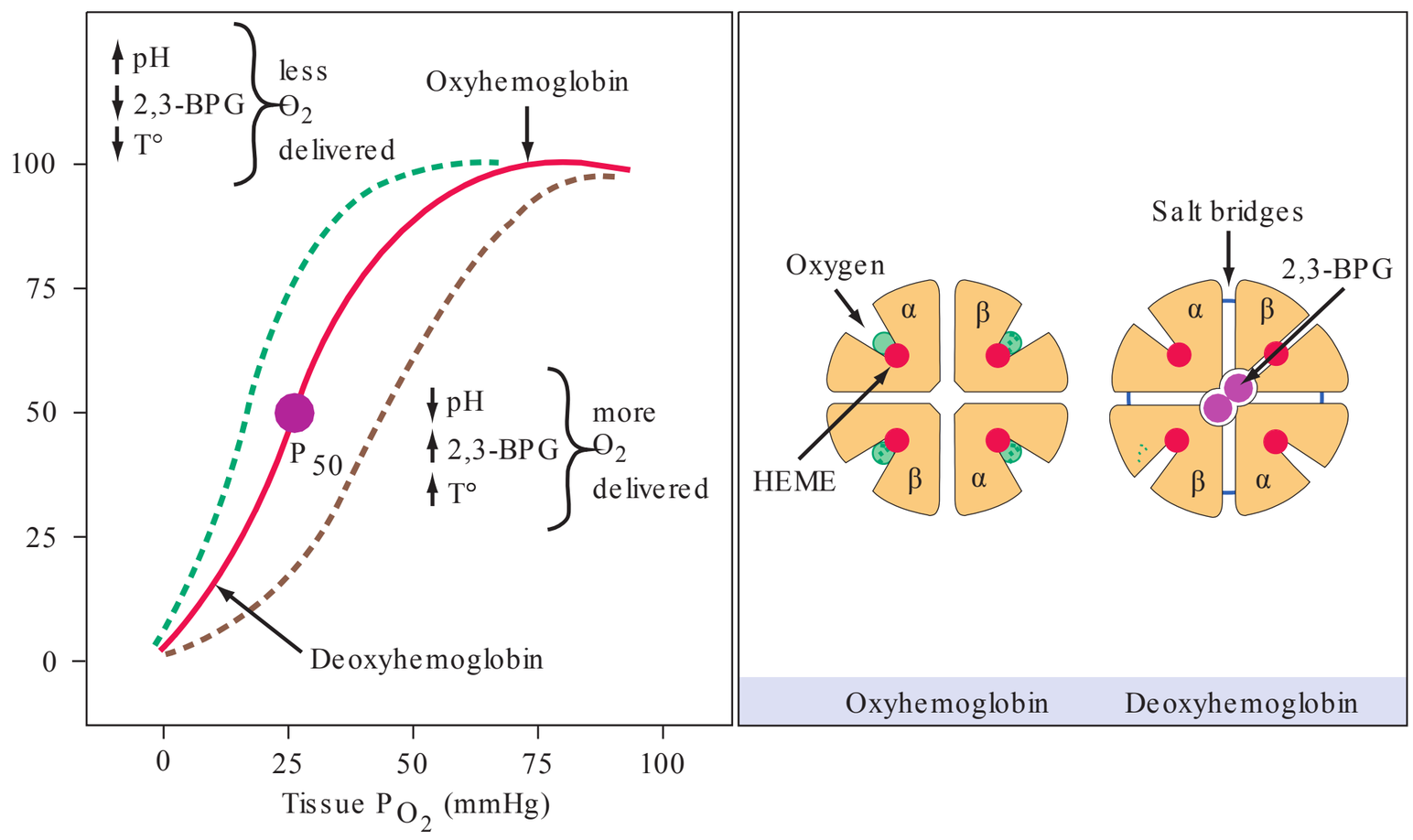


FIGURE 8-2

Hemoglobin-oxygen dissociation curve. The hemoglobin tetramer can bind up to four molecules of oxygen in the iron-containing sites of the heme molecules. As oxygen is bound, 2,3-bisphosphoglycerate (2,3-BPG) and carbon dioxide (CO_2) are expelled. Salt bridges are broken, and each of the globin molecules changes its conformation to facilitate oxygen binding. Oxygen release to the tissues is the reverse process, with salt bridges being formed and 2,3-BPG and CO_2 bound. Deoxyhemoglobin does not bind oxygen efficiently until the cell returns to conditions of higher pH, the most important modulator of O_2 affinity (Bohr effect). When acid is produced in the tissues, the dissociation curve shifts to the right, facilitating oxygen release and CO_2 binding. Alkalosis has the opposite effect, reducing oxygen delivery.

HbA transition has been the demonstration that the transcription factor Bcl11a plays a pivotal role in its regulation. Small amounts of HbF are produced during postnatal life. A few red cell clones called F cells are progeny of a small pool of immature committed erythroid precursors (BFU-e) that retain the ability to produce HbF. Profound erythroid stresses, such as severe hemolytic anemias, bone marrow transplantation, or cancer chemotherapy, cause more of the F-potent BFU-e to be recruited. HbF levels thus tend to rise in some patients with sickle cell anemia or thalassemia. This phenomenon probably explains the ability of hydroxyurea to increase levels of HbF in adults. Agents such as butyrate and histone deacetylase inhibitors can also activate fetal globin genes partially after birth.

GENETICS AND BIOSYNTHESIS OF HUMAN HEMOGLOBIN

The human hemoglobins are encoded in two tightly linked gene clusters; the α-like globin genes are clustered on chromosome 16 and the β-like genes on chromosome 11 (Fig. 8-1). The α-like cluster consists of two α-globin genes and a single copy of the ζ gene. The non-α gene cluster consists of a single ε gene, the Gγ and Aγ fetal globin genes, and the adult δ and β genes.

Important regulatory sequences flank each gene. Immediately upstream are typical promoter elements needed for the assembly of the transcription initiation complex. Sequences in the 5′ flanking region of the γ and the β genes appear to be crucial for the correct developmental regulation of these genes, whereas elements that function like classic enhancers and silencers are in the 3′ flanking regions. The locus control region (LCR) elements located far upstream appear to control the overall level of expression of each cluster. These elements achieve their regulatory effects by interacting with trans-acting transcription factors. Some of these factors are ubiquitous (e.g., Sp1 and YY1), while others are more or less limited to erythroid cells or hematopoietic cells (e.g., GATA-1, NFE-2, and EKLF). The LCR controlling the α-globin gene cluster is modulated by a SWI/SNF-like protein called ATRX; this protein appears to influence chromatin remodeling and DNA methylation. The association of α thalassemia with mental retardation and myelodysplasia in some families appears to be related to mutations in the ATRX pathway. This pathway also modulates genes specifically expressed during erythropoiesis, such as those that encode the enzymes for heme biosynthesis. Normal red blood cell (RBC) differentiation requires the coordinated expression of the globin genes with the genes responsible for heme and iron metabolism. RBC precursors contain a protein, α-hemoglobin-stabilizing protein (AHSP), that enhances the folding and solubility of α globin, which is otherwise easily denatured, leading to insoluble precipitates. These precipitates play an important role in the thalassemia syndromes and certain unstable hemoglobin disorders. Polymorphic variation in the amounts and/or functional capacity of AHSP might explain some of the clinical variability seen in patients inheriting identical thalassemia mutations.

CLASSIFICATION OF HEMOGLOBINOPATHIES

There are five major classes of hemoglobinopathies **(Table 8-1)**. Structural hemoglobinopathies occur when mutations alter the amino acid sequence of a globin chain, altering the physiologic properties of the variant hemoglobins and producing the characteristic clinical abnormalities. The most clinically relevant variant hemoglobins polymerize abnormally, as in sickle cell anemia, or exhibit altered solubility or oxygen-binding affinity. Thalassemia syndromes arise from mutations that impair production or translation of globin mRNA, leading to deficient globin chain biosynthesis. Clinical

TABLE 8-1

CLASSIFICATION OF HEMOGLOBINOPATHIES

I. Structural hemoglobinopathies—hemoglobins with altered amino acid sequences that result in deranged function or altered physical or chemical properties
   - A. Abnormal hemoglobin polymerization—HbS, hemoglobin sickling
   - B. Altered O_2 affinity
     1. High affinity—polycythemia
     2. Low affinity—cyanosis, pseudoanemia
   - C. Hemoglobins that oxidize readily
     1. Unstable hemoglobins—hemolytic anemia, jaundice
     2. Mhemoglobins—methemoglobinemia, cyanosis

II. Thalassemias—defective biosynthesis of globin chains
   - A. α Thalassemias
   - B. β Thalassemias
   - C. δβ, γδβ, αβ Thalassemias

III. Thalassemic hemoglobin variants—structurally abnormal Hb associated with coinherited thalassemic phenotype
   - A. HbE
   - B. Hb Constant Spring
   - C. Hb Lepore

IV. Hereditary persistence of fetal hemoglobin—persistence of high levels of HbF into adult life

V. Acquired hemoglobinopathies
   - A. Methemoglobin due to toxic exposures
   - B. Sulfhemoglobin due to toxic exposures
   - C. Carboxyhemoglobin
   - D. HbH in erythroleukemia
   - E. Elevated HbF in states of erythroid stress and bone marrow dysplasia

abnormalities are attributable to the inadequate supply of hemoglobin and the imbalances in the production of individual globin chains, leading to premature destruction of erythroblasts and RBC. T alassemic hemoglobin variants combine features of thalassemia (e.g., abnormal globin biosynthesis) and of structural hemoglobinopathies (e.g., an abnormal amino acid sequence). Hereditary persistence o*f* *f*etal hemoglobin (HPFH) is characterized by synthesis of high levels of fetal hemoglobin in adult life. Acquired hemoglobinopathies include modifications of the hemoglobin molecule by toxins (e.g., acquired methemoglobinemia) and clonal abnormalities of hemoglobin synthesis (e.g., high levels of HbF production in preleukemia and α thalassemia in myeloproliferative disorders).

EPIDEMIOLOGY

Hemoglobinopathies are especially common in areas in which malaria is endemic. T is clustering of hemoglobinopathies is assumed to reflect a selective survival advantage for the abnormal RBC, which presumably provides a less hospitable environment during the obligate RBC stages of the parasitic life cycle. Very young children with α thalassemia are more susceptible to infection with the nonlethal Plasmodium vivax. T alassemia might then favor a natural protection against infection with the more lethal Plasmodium *f*alciparum.

T alassemias are the most common genetic disorders in the world, affecting nearly 200 million people worldwide. About 15% of African Americans are silent carriers for α thalassemia; α thalassemia trait (minor) occurs in 3% of African American and in 1–15% of persons of Mediterranean origin. β T alassemia has a 10–15% incidence in individuals from the Mediterranean and Southeast Asia and 0.8% in African Americans. T e number of severe cases of thalassemia in the United States is about 1000. Sickle cell disease is the most common structural hemoglobinopathy, occurring in heterozygous form in ~8% of African Americans and in homozygous form in 1 in 400. Between 2 and 3% of African Americans carry a hemoglobin C allele.

INHERITANCE AND ONTOGENY

Hemoglobinopathies are autosomal codominant traits—thus, compound heterozygotes who inherit a different abnormal mutant allele from each parent exhibit composite features of each. For example, patients inheriting sickle β thalassemia exhibit features of β thalassemia and sickle cell anemia. T e α chain is present in HbA, HbA_2, and HbF; α-chain mutations thus cause abnormalities in all three. T e α-globin hemoglobinopathies are symptomatic in utero and af er birth because normal function of the α-globin gene is required throughout gestation and adult life. In contrast, infants with β-globin hemoglobinopathies tend to be asymptomatic until 3–9 months of age, when HbA has largely replaced HbF. Prevention or partial reversion of the switch should thus be an effective therapeutic strategy for β-chain hemoglobinopathies.

DETECTION AND CHARACTERIZATION OF HEMOGLOBINOPATHIES–GENERAL METHODS

Electrophoretic techniques are still widely used for hemoglobin analysis. Electrophoresis at pH 8.6 on cellulose acetate membranes is especially simple, inexpensive, and reliable for initial screening. Agar gel electrophoresis at pH 6.1 in citrate buffer is of en used as a complementary method because each method detects different variants. Some important variants are electrophoretically silent. T ese mutant hemoglobins can usually be characterized by more specialized techniques such as mass spectroscopy, which is rapidly replacing electrophoresis for initial analysis.

Quantitation of the hemoglobin profile is of en desirable. HbA_2 is frequently elevated in β thalassemia trait and depressed in iron deficiency. HbF is elevated in HPFH, some β thalassemia syndromes, and occasional periods of erythroid stress or marrow dysplasia. For characterization of sickle cell trait, sickle thalassemia syndromes, or HbSC disease, and for monitoring the progress of exchange transfusion therapy to lower the percentage of circulating HbS, quantitation of individual hemoglobins is also required. In most laboratories, quantitation is performed only if the test is specifically ordered. Complete characterization, including amino acid sequencing or gene cloning and sequencing, is readily available from several reference laboratories.

Because some variants can comigrate with HbA or HbS (sickle hemoglobin), electrophoretic assessment should always be regarded as incomplete unless functional assays for hemoglobin sickling, solubility, or oxygen affinity are also performed, as dictated by the clinical presentation. T e best sickling assays involve measurement of the degree to which the hemoglobin sample becomes insoluble, or gelated, as it is deoxygenated (i.e., sickle solubility test). Unstable hemoglobins are detected by their precipitation in isopropanol or af er heating to 50°C. High-O_2 affinity and low-O_2 affinity variants are detected by quantitating the P_{50}, the partial pressure of oxygen at which the hemoglobin sample becomes 50% saturated with oxygen. Direct tests for the percent carboxyhemoglobin and methemoglobin, using spectrophotometric techniques, can readily be obtained from most clinical laboratories on an urgent basis.

Laboratory evaluation remains an adjunct, rather than the sole diagnostic aid. Diagnosis is best established by recognition of a characteristic history, physical findings, peripheral blood smear morphology, and abnormalities of the complete blood cell count (e.g., profound microcytosis with minimal anemia in thalassemia trait).

STRUCTURALLY ABNORMAL HEMOGLOBINS

SICKLE CELL SYNDROMES

The sickle cell syndromes are caused by a mutation in the β-globin gene that changes the sixth amino acid from glutamic acid to valine. HbS ($\alpha_2\beta_2^{6\ Glu\rightarrow Val}$) polymerizes reversibly when deoxygenated to form a gelatinous network of fibrous polymers that stiffen the RBC membrane, increase viscosity, and cause dehydration due to potassium leakage and calcium influx **(Fig. 8-3)**. These changes also produce the sickle shape. Sickled cells lose the pliability needed to traverse small capillaries. They possess altered "sticky" membranes that are abnormally adherent to the endothelium of small venules. These abnormalities provoke unpredictable episodes of microvascular vasoocclusion and premature RBC destruction (hemolytic anemia). Hemolysis occurs because the spleen destroys the abnormal RBC. The rigid adherent cells clog small capillaries and venules, causing tissue ischemia, acute pain, and gradual end-organ damage. This is venoocclusive component usually dominates the clinical course. Prominent manifestations include episodes of ischemic pain (i.e., painful crises) and ischemic malfunction or frank infarction in the spleen, central nervous system, bones, joints, liver, kidneys, and lungs (Fig. 8-3).

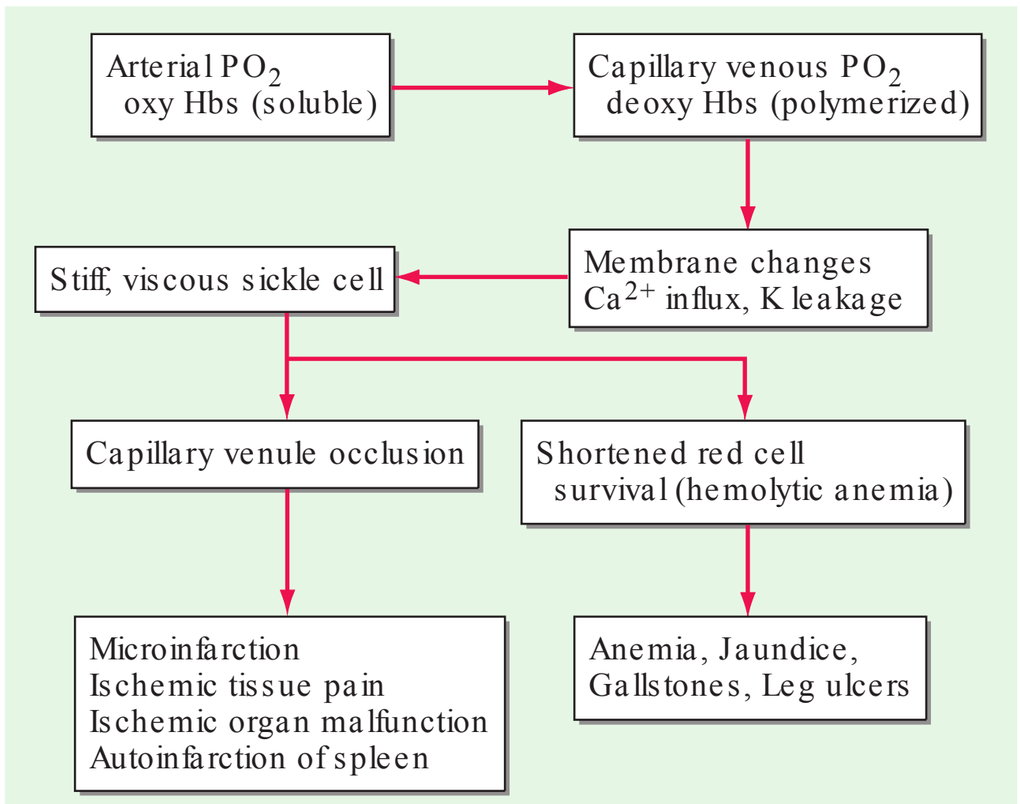


FIGURE 8-3
Pathophysiology of sickle cell crisis.

Several sickle syndromes occur as the result of inheritance of HbS from one parent and another hemoglobinopathy, such as β thalassemia or HbC ($\alpha_2\beta_2^{6\ Glu\rightarrow Lys}$), from the other parent. The prototype disease, sickle cell anemia, is the homozygous state for HbS **(Table 8-2)**.

Clinical manifestations of sickle cell anemia

Most patients with sickling syndromes suffer from hemolytic anemia, with hematocrits from 15 to 30%, and significant reticulocytosis. Anemia was once thought to exert protective effects against vasoocclusion by reducing blood viscosity. However, natural history and drug therapy trials suggest that an increase in the hematocrit and feedback inhibition of reticulocytosis might be beneficial, even at the expense of increased blood viscosity. The role of adhesive reticulocytes in vasoocclusion might account for these paradoxical effects.

Granulocytosis is common. The white count can fluctuate substantially and unpredictably during and between painful crises, infectious episodes, and other intercurrent illnesses.

Vasoocclusion causes protean manifestations. Intermittent episodes of vasoocclusion in connective and musculoskeletal structures produce ischemia manifested by acute pain and tenderness, fever, tachycardia, and anxiety. These recurrent episodes, called pain*ful* crises, are the most common clinical manifestation. Their frequency and severity vary greatly. Pain can develop almost anywhere in the body and may last from a few hours to 2 weeks. Repeated crises requiring hospitalization (>3 episodes per year) correlate with reduced survival in adult life, suggesting that these episodes are associated with accumulation of chronic end-organ damage. Provocative factors include infection, fever, excessive exercise, anxiety, abrupt changes in temperature, hypoxia, or hypertonic dyes.

Repeated microinfarction can destroy tissues having microvascular beds prone to sickling. Thus, splenic function is frequently lost within the first 18–36 months of life, causing susceptibility to infection, particularly by pneumococci. Acute venous obstruction of the spleen (splenic sequestration crisis), a rare occurrence in early childhood, may require emergency transfusion and/or splenectomy to prevent trapping of the entire arterial output in the obstructed spleen. Occlusion of retinal vessels can produce hemorrhage, neovascularization, and eventual detachments. Renal papillary necrosis invariably produces isosthenuria. More widespread renal necrosis leads to renal failure in adults, a common late cause of death. Bone and joint ischemia can lead to aseptic necrosis, especially of the femoral or humeral heads; chronic arthropathy; and unusual susceptibility to osteomyelitis, which may be caused by organisms, such as Salmonella, rarely encountered in other settings. The hand-*foot* syndrome is caused by painful infarcts of

TABLE 8-2

CLINICAL FEATURES OF SICKLE HEMOGLOBINOPATHIES

CONDITION	CLINICAL ABNORMALITIES	HEMOGLOBIN LEVEL, g/L (g/dL)	MCV, fL	HEMOGLOBIN ELECTROPHORESIS
Sickle cell trait	None; rare painless hematuria	Normal	Normal	HbS/A: 40/60
Sickle cell anemia	Vasoocclusive crises with infarction of spleen, brain, marrow, kidney, lung; aseptic necrosis of bone; gallstones; priapism; ankle ulcers	70–100 (7–10)	80–100	HbS/A: 100/0 HbF: 2–25%
S/β° thalassemia	Vasoocclusive crises; aseptic necrosis of bone	70–100 (7–10)	60–80	HbS/A: 100/0 HbF: 1–10%
S/β+ thalassemia	Rare crises and aseptic necrosis	100–140 (10–14)	70–80	HbS/A: 60/40
Hemoglobin SC	Rare crises and aseptic necrosis; painless hematuria	100–140 (10–14)	80–100	HbS/A: 50/0 HbC: 50%

the digits and dactylitis. Stroke is especially common in children; a small subset tends to suffer repeated episodes. Stroke is less common in adults and is often hemorrhagic. A particularly painful complication in males is priapism, due to infarction of the penile venous outflow tracts; permanent impotence is a frequent consequence. Chronic lower leg ulcers probably arise from ischemia and superinfection in the distal circulation.

Acute chest syndrome is a distinctive manifestation characterized by chest pain, tachypnea, fever, cough, and arterial oxygen desaturation. It can mimic pneumonia, pulmonary emboli, bone marrow infarction and embolism, myocardial ischemia, or in situ lung infarction. Acute chest syndrome is thought to reflect in situ sickling within the lung, producing pain and temporary pulmonary dysfunction. Often it is difficult or impossible to distinguish among other possibilities. Pulmonary infarction and pneumonia are the most frequent underlying or concomitant conditions in patients with this syndrome. Repeated episodes of acute chest pain correlate with reduced survival. Acutely, reduction in arterial oxygen saturation is especially ominous because it promotes sickling on a massive scale. Chronic acute or subacute pulmonary crises lead to pulmonary hypertension and cor pulmonale, an increasingly common cause of death as patients survive longer. Considerable controversy exists about the possible role played by free plasma HbS in scavenging nitrogen dioxide (NO_2), thus raising pulmonary vascular tone. Trials of sildenafil to restore NO_2 levels were terminated because of adverse effects.

Chronic subacute central nervous system damage in the absence of an overt stroke is a distressingly common phenomenon beginning in early childhood. Modern functional imaging techniques have pinpointed circulatory dysfunction due to a likely CNS sickle vasculopathy; these changes correlate with an array of cognitive and behavioral abnormalities in children and young adults. It is important to be aware of these often subtle changes because they can complicate clinical management or be misinterpreted as "difficult patient" behaviors.

Sickle cell syndromes are remarkable for their clinical heterogeneity. Some patients remain virtually asymptomatic into or even through adult life, while others suffer repeated crises requiring hospitalization from early childhood. Patients with sickle thalassemia and sickle-HbE tend to have similar, slightly milder symptoms, perhaps because of the ameliorating effects of production of other hemoglobins within the RBC. Hemoglobin SC disease, one of the more common variants of sickle cell anemia, is frequently marked by lesser degrees of hemolytic anemia and a greater propensity for the development of retinopathy and aseptic necrosis of bones. In most respects, however, the clinical manifestations resemble sickle cell anemia. Some rare hemoglobin variants actually aggravate the sickling phenomenon.

The clinical variability in different patients inheriting the same disease-causing mutation (sickle hemoglobin) has made sickle cell disease the focus of efforts to identify modifying genetic polymorphisms in other genes that might account for the heterogeneity. The complexity of the data obtained thus far has dampened the expectation that genome-wide analysis will yield individualized profiles that predict a patient's clinical course. Nevertheless, a number of interesting patterns have emerged from these modifying gene analyses. For example, genes affecting the inflammatory response or cytokine expression appear to be modifying candidates. Genes that affect transcriptional regulation of lymphocytes may also be involved.

Clinical manifestations of sickle cell trait

Sickle cell trait is often asymptomatic. Anemia and painful crises are rare. An uncommon but highly distinctive symptom is painless hematuria often occurring in adolescent males, probably due to papillary necrosis. Isosthenuria is a more common manifestation of the

same process. Sloughing of papillae with urethral obstruction has been reported, as have isolated cases of massive sickling or sudden death due to exposure to high altitudes or extremes of exercise and dehydration. Avoidance of dehydration or extreme physical stress should be advised.

Diagnosis

Sickle cell syndromes are suspected on the basis of hemolytic anemia, RBC morphology **(Fig. 8-4)**, and intermittent episodes of ischemic pain. Diagnosis is confirmed by hemoglobin electrophoresis, mass spectroscopy, and the sickling tests already discussed. Thorough characterization of the exact hemoglobin profile of the patient is important, because sickle thalassemia and hemoglobin SC disease have distinct prognoses or clinical features. Diagnosis is usually established in childhood, but occasional patients, often with compound heterozygous states, do not develop symptoms until the onset of puberty, pregnancy, or early adult life. Genotyping of family members and potential parental partners is critical for genetic counseling. Details of the childhood history establish prognosis and need for aggressive or experimental therapies. Factors associated with increased morbidity and reduced survival include more than three crises requiring hospitalization per year, chronic neutrophilia, a history of splenic sequestration or hand-foot syndrome, and second episodes of acute chest syndrome. Patients with a history of cerebrovascular accidents are at higher risk for repeated episodes and require partial exchange transfusion and especially close monitoring using Doppler carotid flow measurements. Patients with severe or repeated episodes of acute chest syndrome may need lifelong transfusion support, using partial exchange transfusion, if possible.

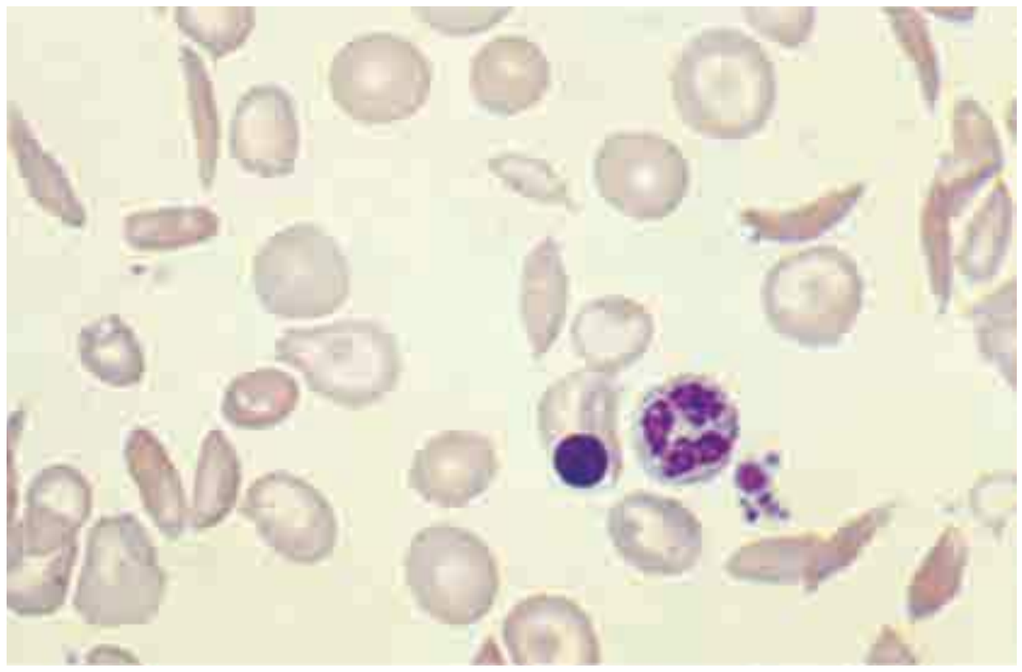


FIGURE 8-4
Sickle cell anemia. The elongated and crescent-shaped red blood cells seen on this smear represent circulatingirreversibly sickled cells. Target cells and a nucleated red blood cell are also seen.

TREATMENT Sickle Cell Syndromes

Patients with sickle cell syndromes require ongoing continuity of care. Familiarity with the pattern of symptoms provides the best safeguard against excessive use of the emergency room, hospitalization, and habituation to addictive narcotics. Additional preventive measures include regular slit-lamp examinations to monitor development of retinopathy; antibiotic prophylaxis appropriate for splenectomized patients during dental or other invasive procedures; and vigorous oral hydration during or in anticipation of periods of extreme exercise, exposure to heat or cold, emotional stress, or infection. Pneumococcal and Haemophilus in*fl*uenzae vaccines are less effective in splenectomized individuals. Thus, patients with sickle cell anemia should be vaccinated early in life.

The management of an acute painful crisis includes vigorous hydration, thorough evaluation for underlying causes (such as infection), and aggressive analgesia administered by a standing order and/or patient-controlled analgesia (PCA) pump. Morphine (0.1–0.15 mg/kg every 3–4 h) should be used to control severe pain. Bone pain may respond as well to ketorolac (30–60 mg initial dose, then 15–30 mg every 6–8 h). Inhalation of nitrous oxide can provide short-term pain relief, but great care must be exercised to avoid hypoxia and respiratory depression. Nitrous oxide also elevates O_2 affinity, reducing O_2 delivery to tissues. Its use should be restricted to experts. Many crises can be managed at home with oral hydration and oral analgesia. Use of the emergency room should be reserved for especially severe symptoms or circumstances in which other processes, e.g., infection, are strongly suspected. Nasal oxygen should be used as appropriate to protect arterial saturation. Most crises resolve in 1–7 days. Use of blood transfusion should be reserved for extreme cases: transfusions do not shorten the duration of the crisis.

No tests are definitive to diagnose acute painful crisis. Critical to good management is an approach that recognizes that most patients reporting crisis symptoms do indeed have crisis or another significant medical problem. Diligent diagnostic evaluation for underlying causes is imperative, even though these are found infrequently. In adults, the possibility of aseptic necrosis or sickle arthropathy must be considered, especially if pain and immobility become repeated or chronic at a single site. Nonsteroidal anti-inflammatory agents are often effective for sickle cell arthropathy.

Acute chest syndrome is a medical emergency that may require management in an intensive care unit. Hydration should be monitored carefully to avoid the development of pulmonary edema, and oxygen therapy should be especially vigorous for protection of arterial saturation. Diagnostic evaluation for pneumonia and pulmonary embolism should be especially thorough, since these may occur with atypical symptoms. Critical interventions are transfusion to maintain a hematocrit >30, and emergency exchange transfusion if arterial saturation drops to <90%. As patients with sickle

cell syndrome increasingly survive into their fif h and sixth decades, end-stage renal failure and pulmonary hypertension are becoming increasingly prominent causes of end-stage morbidity. A sickle cell cardiomyopathy and/or premature coronary artery disease may compromise cardiac function in later years. Sickle cell patients have received kidney transplants, but they of en experience an increase in the frequency and severity of crises, possibly due to increased infection as a consequence of immunosuppression.

T e most significant advance in the therapy of sickle cell anemia has been the introduction of hydroxyurea as a mainstay of therapy for patients with severe symptoms. Hydroxyurea (10–30 mg/kg per day) increases fetal hemoglobin and may also exert beneficial effects on RBC hydration, vascular wall adherence, and suppression of the granulocyte and reticulocyte counts; dosage is titrated to maintain a white cell count between 5000 and 8000/μL. White cells and reticulocytes may play a major role in the pathogenesis of sickle cell crisis, and their suppression may be an important side benefit of hydroxyurea therapy.

Hydroxyurea should be considered in patients experiencing repeated episodes of acute chest syndrome or with more than three crises per year requiring hospitalization. T e utility of this agent for reducing the incidence of other complications (priapism, retinopathy) is under evaluation, as are the long-term side effects. To date, however, minimal risk of bone marrow dyscrasias or other neoplasms has been documented. Hydroxyurea offers broad benefits to most patients whose disease is severe enough to impair their functional status, and it may improve survival. HbF levels increase in most patients within a few months.

T e antitumor drug 5-azacytidine was the first agent found to elevate HbF. It never achieved widespread use because of concerns about acute toxicity and carcinogenesis. However, low doses of the related agent 5-deoxyazacytidine (decitabine) can elevate HbF with more acceptable toxicity.

Bone marrow transplantation can provide definitive cures but is known to be effective and safe only in children. Clinical trials studying partially myeloablative conditioning regimens ("mini" transplants) are likely to support more widespread use of this modality in older patients. Prognostic features justifying bone marrow transplant are the presence of repeated crises early in life, a high neutrophil count, or the development of hand-foot syndrome. Children at risk for stroke can now be identified through the use of Doppler ultrasound techniques. Prophylactic exchange transfusion appears to substantially reduce the risk of stroke in this population. Children who do suffer a cerebrovascular accident should be maintained for at least 3–5 years on a program of vigorous exchange transfusion, as the risk of second strokes is extremely high.

Gene therapy for sickle cell anemia is being intensively pursued, but no safe measures are currently available. T e development of newer methods of direct gene correction in situ (e.g., zinc finger nucleases, or "CRISPR" [clustered regularly interspaced short palindromic repeats] technology) could well find clinical use in these patients. Experimental methods of derepressing HbF by interfering with Bcl11a are also being explored.

UNSTABLE HEMOGLOBINS

Amino acid substitutions that reduce solubility or increase susceptibility to oxidation result in unstable hemoglobins that precipitate, forming inclusion bodies injurious to the RBC membrane. Representative mutations are those that interfere with contact points between the α and β subunits (e.g., Hb Philly [$\beta^{35Tyr\rightarrow Phe}$]), alter the helical segments (e.g., Hb Genova [$\beta^{28Leu\rightarrow Pro}$]), or disrupt interactions of the hydrophobic pockets of the globin subunits with heme (e.g., Hb Köln [$\beta^{98Val\rightarrow Met}$]) **(Table 8-3)**. T e inclusions, called Heinz bodies, are clinically detectable by staining with supravital dyes such as crystal violet. Removal of these inclusions by the spleen generates pitted, rigid cells that have shortened life spans, producing hemolytic anemia of variable severity, sometimes requiring chronic transfusion support. Splenectomy may be needed to correct the anemia. Leg ulcers and premature gallbladder disease due to bilirubin loading are frequent stigmata.

Unstable hemoglobins occur sporadically, of en by spontaneous new mutations. Heterozygotes are of en symptomatic because a significant Heinz body burden can develop even when the unstable variant accounts for only a portion of the total hemoglobin. Symptomatic unstable hemoglobins tend to be β-globin variants,

TABLE 8-3

REPRESENTATIVE ABNORMAL HEMOGLOBINS WITH ALTERED SYNTHESIS OR FUNCTION

DESIGNATION	MUTATION	POPULATION	MAIN CLINICAL EFFECTS[a]
Sickle or S	$\beta^{6Glu\rightarrow Val}$	African	Anemia, ischemic infarcts
C	$\beta^{6Glu\rightarrow Lys}$	African	Mild anemia; interacts with HbS
E	$\beta^{26Glu\rightarrow Lys}$	Southeast Asian	Microcytic anemia, splenomegaly, thalassemic phenotype
Köln	$\beta^{98Val\rightarrow Met}$	Sporadic	Hemolytic anemia, Heinz bodies when splenectomized
Yakima	$\beta^{99Asp\rightarrow His}$	Sporadic	Polycythemia
Kansas	$\beta^{102Asn\rightarrow Lys}$	Sporadic	Mild anemia
M Iwata	$\beta^{87His\rightarrow Tyr}$	Sporadic	Methemoglobinemia

[a]See text for details.

because sporadic mutations affecting only one of the four α globins alleles would generate only 20–30% abnormal hemoglobin.

HEMOGLOBINS WITH ALTERED OXYGEN AFFINITY

High-af nity hemoglobins (e.g., Hb Yakima [$\beta^{99Asp\rightarrow His}$]) bind oxygen more readily but deliver less O_2 to tissues at normal capillary Po_2 levels (Fig. 8-2). Mild tissue hypoxia ensues, stimulating RBC production and erythrocytosis (Table 8-3). In extreme cases, the hematocrits can rise to 60–65%, increasing blood viscosity and producing typical symptoms (headache, somnolence, or dizziness). Phlebotomy may be required. Typical mutations alter interactions within the heme pocket or disrupt the Bohr effect or salt-bond site. Mutations that impair the interaction of HbA with 2,3-BPG can increase O_2 affinity because 2,3-BPG binding lowers O_2 affinity.

Low-af nity hemoglobins (e.g., Hb Kansas [$\beta^{102Asn\rightarrow Lys}$]) bind sufficient oxygen in the lungs, despite their lower oxygen affinity, to achieve nearly full saturation. At capillary oxygen tensions, they lose sufficient amounts of oxygen to maintain homeostasis at a low hematocrit (Fig. 8-2) (pseudoanemia). Capillary hemoglobin desaturation can also be sufficient to produce clinically apparent cyanosis. Despite these findings, patients usually require no specific treatment.

METHEMOGLOBINEMIAS

Methemoglobin is generated by oxidation of the heme iron moieties to the ferric state, causing a characteristic bluish-brown muddy color resembling cyanosis. Methemoglobin has such high oxygen affinity that virtually no oxygen is delivered. Levels >50–60% are of en fatal.

Congenital methemoglobinemia arises from globin mutations that stabilize iron in the ferric state (e.g., HbM Iwata [$\alpha^{87His\rightarrow Tyr}$], Table 8-3) or from mutations that impair the enzymes that reduce methemoglobin to hemoglobin (e.g., methemoglobin reductase, NADP diaphorase). Acquired methemoglobinemia is caused by toxins that oxidize heme iron, notably nitrate and nitrite-containing compounds, including drugs commonly used in cardiology and anesthesiology.

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE HEMOGLOBINS, HIGH-AFFINITY HEMOGLOBINS, AND METHEMOGLOBINEMIA

Unstable hemoglobin variants should be suspected in patients with nonimmune hemolytic anemia, jaundice, splenomegaly, or premature biliary tract disease. Severe hemolysis usually presents during infancy as neonatal jaundice or anemia. Milder cases may present in adult life with anemia or only as unexplained reticulocytosis, hepatosplenomegaly, premature biliary tract disease, or leg ulcers. Because spontaneous mutation is common, family history of anemia may be absent. T e peripheral blood smear of en shows anisocytosis, abundant cells with punctate inclusions, and irregular shapes (i.e., poikilocytosis).

T e two best tests for diagnosing unstable hemoglobins are the Heinz body preparation and the isopropanol or heat stability test. Many unstable Hb variants are electrophoretically silent. A normal electrophoresis does not rule out the diagnosis. Mass spectroscopy or direct gene analysis will provide a definitive diagnosis.

Severely affected patients may require transfusion support for the first 3 years of life, because splenectomy before age 3 is associated with a significantly higher immune deficit. Splenectomy is usually effective thereaf er, but occasional patients may require lifelong transfusion support. Af er splenectomy, patients can develop cholelithiasis and leg ulcers, hypercoagulable states, and susceptibility to overwhelming sepsis. Splenectomy should thus be avoided or delayed unless it is the only alternative. Precipitation of unstable hemoglobins is aggravated by oxidative stress, e.g., infection and antimalarial drugs, which should be avoided where possible.

High-O_2 af nity hemoglobin variants should be suspected in patients with erythrocytosis. T e best test for confirmation is measurement of the P_{50}. A high-O_2 affinity hemoglobin causes a significant lef shif (i.e., lower numeric value of the P_{50}); confounding conditions, e.g., tobacco smoking or carbon monoxide exposure, can also lower the P_{50}.

High-affinity hemoglobins are of en asymptomatic; rubor or plethora may be telltale signs. When the hematocrit approaches 60%, symptoms of high blood viscosity and sluggish flow (headache, lethargy, dizziness, etc.) may be present. T ese persons may benefit from judicious phlebotomy. Erythrocytosis represents an appropriate attempt to compensate for the impaired oxygen delivery by the abnormal variant. Overzealous phlebotomy may stimulate increased erythropoiesis or aggravate symptoms by thwarting this compensatory mechanism. T e guiding principle of phlebotomy should be to improve oxygen delivery by reducing blood viscosity and increasing blood flow rather than restoration of a normal hematocrit. Phlebotomy-induced modest iron deficiency may aid in control.

Low-af nity hemoglobins should be considered in patients with cyanosis or a low hematocrit with no other reason apparent af er thorough evaluation. T e P_{50} test confirms the diagnosis. Counseling and reassurance are the interventions of choice.

Methemoglobin should be suspected in patients with hypoxic symptoms who appear cyanotic but have a Pao_2

sufficiently high that hemoglobin should be fully saturated with oxygen. A history of nitrite or other oxidant ingestions may not always be available; some exposures may be inapparent to the patient, and others may result from suicide attempts. The characteristic muddy appearance of freshly drawn blood can be a critical clue. The best diagnostic test is methemoglobin assay, which is usually available on an emergency basis.

Methemoglobinemia often causes symptoms of cerebral ischemia at levels >15%; levels >60% are usually lethal. Intravenous injection of 1 mg/kg of methylene blue is effective emergency therapy. Milder cases and follow-up of severe cases can be treated orally with methylene blue (60 mg three to four times each day) or ascorbic acid (300–600 mg/d).

THALASSEMIA SYNDROMES

The thalassemia syndromes are inherited disorders of α- or β-globin biosynthesis. The reduced supply of globin diminishes production of hemoglobin tetramers, causing hypochromia and microcytosis. Unbalanced accumulation of α and β subunits occurs because the synthesis of the unaffected globins proceeds at a normal rate. Unbalanced chain accumulation dominates the clinical phenotype. Clinical severity varies widely, depending on the degree to which the synthesis of the affected globin is impaired, altered synthesis of other globin chains, and coinheritance of other abnormal globin alleles.

CLINICAL MANIFESTATIONS OF β THALASSEMIA SYNDROMES

Mutations causing thalassemia can affect any step in the pathway of globin gene expression: transcription, processing of the mRNA precursor, translation, and posttranslational metabolism of the β-globin polypeptide chain. The most common forms arise from mutations that derange splicing of the mRNA precursor or prematurely terminate translation of the mRNA.

Hypochromia and microcytosis characterize all forms of β thalassemia because of the reduced amounts of hemoglobin tetramers **(Fig. 8-5)**. In heterozygotes (β thalassemia trait), this is the only abnormality seen. Anemia is minimal. In more severe homozygous states, unbalanced α- and β-globin accumulation causes accumulation of highly insoluble unpaired α chains. They form toxic inclusion bodies that kill developing erythroblasts in the marrow. Few of the proerythroblasts beginning erythroid maturation survive. The surviving RBCs bear a burden of inclusion bodies that are detected in the spleen, shortening the RBC life span and producing severe hemolytic anemia. The resulting

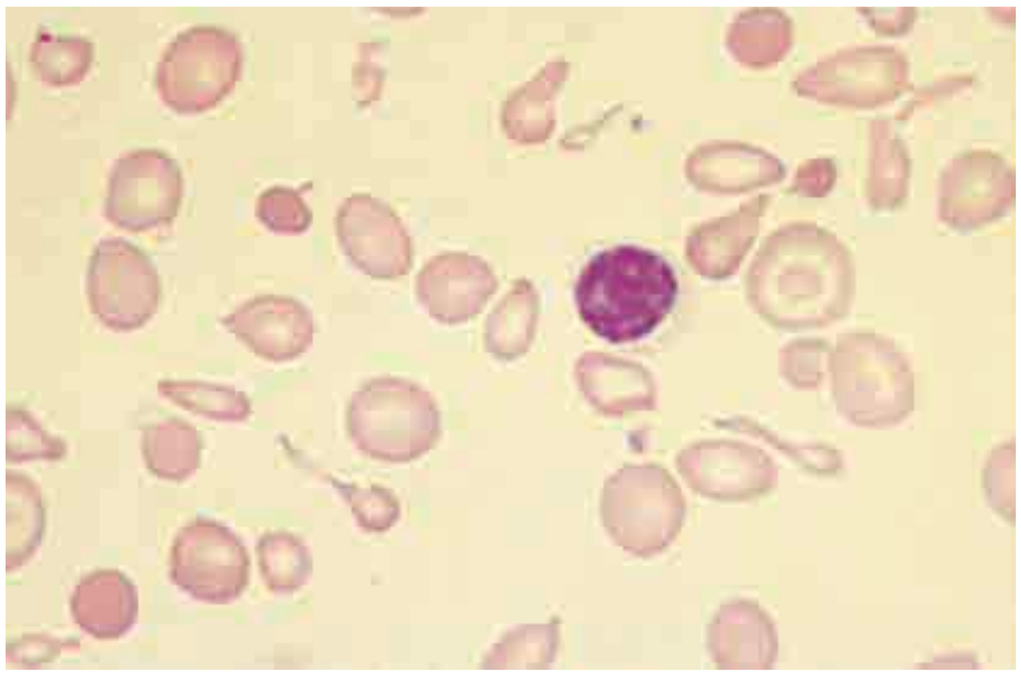


FIGURE 8-5
β Thalassemia intermedia. Microcytic and hypochromic red blood cells are seen that resemble the red blood cells of severe iron-deficiency anemia. Many elliptical and teardrop-shaped red blood cells are noted.

profound anemia stimulates erythropoietin release and compensatory erythroid hyperplasia, but the marrow response is sabotaged by the ineffective erythropoiesis. Anemia persists. Erythroid hyperplasia can become exuberant and produce masses of extramedullary erythropoietic tissue in the liver and spleen.

Massive bone marrow expansion deranges growth and development. Children develop characteristic "chipmunk" facies due to maxillary marrow hyperplasia and frontal bossing. Thinning and pathologic fracture of long bones and vertebrae may occur due to cortical invasion by erythroid elements and profound growth retardation. Hemolytic anemia causes hepatosplenomegaly, leg ulcers, gallstones, and high-output congestive heart failure. The conscription of caloric resources to support erythropoiesis leads to inanition, susceptibility to infection, endocrine dysfunction, and in the most severe cases, death during the first decade of life. Chronic transfusions with RBCs improve oxygen delivery, suppress the excessive ineffective erythropoiesis, and prolong life, but the inevitable side effects, notably iron overload, often prove fatal by age 30 years.

Severity is highly variable. Known modulating factors are those that ameliorate the burden of unpaired α-globin inclusions. Alleles associated with milder synthetic defects and coinheritance of α thalassemia trait reduce clinical severity by reducing accumulation of excess α globin. HbF persists to various degrees in β thalassemias. γ-Globin gene chains can substitute for β chains, generating more hemoglobin and reducing the burden of α-globin inclusions. The terms β thalassemia major and β thalassemia intermedia are used to reflect the clinical heterogeneity. Patients with β thalassemia major require intensive transfusion support to survive. Patients with β thalassemia intermedia have a

somewhat milder phenotype and can survive without transfusion. The terms β thalassemia minor and β thalassemia trait describe asymptomatic heterozygotes for β thalassemia.

THALASSEMIA SYNDROMES

The four classic α thalassemias, most common in Asians, are α thalassemia-2 trait, in which one of the four α-globin loci is deleted; α thalassemia-1 trait, with two deleted loci; HbH disease, with three loci deleted; and hydrops fetalis with Hb Barts, with all four loci deleted **(Table 8-4)**. Nondeletion forms of α thalassemia also exist.

α Thalassemia-2 trait is an asymptomatic, silent carrier state. α Thalassemia-1 trait resembles β thalassemia minor. Offspring doubly heterozygous for α thalassemia-2 and α thalassemia-1 exhibit a more severe phenotype called HbH disease. Heterozygosity for a deletion that removes both genes from the same chromosome (cis deletion) is common in Asians and in those from the Mediterranean region, as is homozygosity for α thalassemia-2 (trans deletion). Both produce asymptomatic hypochromia and microcytosis.

In HbH disease, HbA production is only 25–30% normal. Fetuses accumulate some unpaired γ chains (Hb Barts; γ-chain tetramers). In adults, unpaired β chains accumulate and are soluble enough to form β_4 tetramers called HbH. HbH forms few inclusions in erythroblasts and precipitates in circulating RBC. Patients with HbH disease have thalassemia intermedia characterized by moderately severe hemolytic anemia but milder ineffective erythropoiesis. Survival into midadult life without transfusions is common.

The homozygous state for the α thalassemia-1 cis deletion (hydrops fetalis) causes total absence of α-globin synthesis. No physiologically useful hemoglobin is produced beyond the embryonic stage. Excess γ globin forms tetramers called Hb Barts (γ_4), which has a very high oxygen affinity. It delivers almost no O_2 to fetal tissues, causing tissue asphyxia, edema (hydrops fetalis), congestive heart failure, and death in utero. α Thalassemia-2 trait is common (15–20%) among people of African descent. The cis α thalassemia-1 deletion is almost never seen, however. Thus, α thalassemia-2 and the trans form of α thalassemia-1 are very common, but HbH disease and hydrops fetalis are rare.

It has been known for some time that some patients with myelodysplasia or erythroleukemia produce RBC clones containing HbH. This phenomenon is due to mutations in the ATRX pathway that affect the LCR of the α-globin gene cluster.

DIAGNOSIS AND MANAGEMENT OF THALASSEMIAS

The diagnosis of β-thalassemia major is readily made during childhood on the basis of severe anemia accompanied by the characteristic signs of massive ineffective erythropoiesis: hepatosplenomegaly, profound microcytosis, a characteristic blood smear (Fig. 8-5), and elevated levels of HbF, HbA_2, or both. Many patients require chronic hypertransfusion therapy designed to maintain a hematocrit of at least 27–30% so that erythropoiesis is suppressed. Splenectomy is required if the annual transfusion requirement (volume of RBCs per kilogram of body weight per year) increases by >50%. Folic acid supplements may be useful. Vaccination with

TABLE 8-4

THE α THALASSEMIAS

CONDITION	HEMOGLOBIN A, %	HEMOGLOBIN H (β^4), %	HEMOGLOBIN LEVEL, g/L (g/dL)	MCV, fL
Normal	97	0	150 (15)	90
Silent thalassemia: −α/αα	98–100	0	150 (15)	90
Thalassemia trait: −α/−α homozygous α-thal-2[a] or −−/αα heterozygous α-thal-1[a]	85–95	Rare red blood cell inclusions	120–130 (12–13)	70–80
Hemoglobin H disease: −−/−α heterozygous α-thal-1/α-thal-2	70–95	5–30	60–100 (6–10)	60–70
Hydrops fetalis: −−/−− homozygous α-thal-1	0	5–10[b]	Fatal in utero or at birth	

[a]When both α alleles on one chromosome are deleted, the locus is called α-thal-1; when only a single α allele on one chromosome is deleted, the locus is called α-thal-2.
[b]90–95% of the hemoglobin is hemoglobin Barts (tetramers of γ chains).

Pneumovax in anticipation of eventual splenectomy is advised, as is close monitoring for infection, leg ulcers, and biliary tract disease. Many patients develop endocrine deficiencies as a result of iron overload. Early endocrine evaluation is required for glucose intolerance, thyroid dysfunction, and delayed onset of puberty or secondary sexual characteristics.

Patients with β thalassemia intermedia exhibit similar stigmata but can survive without chronic hypertransfusion. Management is particularly challenging because a number of factors can aggravate the anemia, including infection, onset of puberty, and development of splenomegaly and hypersplenism. Some patients may eventually benefit from splenectomy. T e expanded erythron can cause absorption of excessive dietary iron and hemosiderosis, even without transfusion. Some patients eventually become transfusion dependent.

β T alassemia minor (i.e., thalassemia trait) usually presents as profound microcytosis and hypochromia with target cells, but only minimal or mild anemia. T e mean corpuscular volume is rarely >75 fL; the hematocrit is rarely <30–33%. Hemoglobin analysis classically reveals an elevated HbA_2 (3.5–7.5%), but some forms are associated with normal HbA_2 and/or elevated HbF. Genetic counseling and patient education are essential. Patients with β thalassemia trait should be warned that their blood picture resembles iron deficiency and can be misdiagnosed. T ey should eschew empirical use of iron, yet iron deficiency requiring replacement therapy can develop during pregnancy or from chronic bleeding.

Persons with α thalassemia trait may exhibit mild hypochromia and microcytosis usually without anemia. HbA_2 and HbF levels are normal. Affected individuals usually require only genetic counseling. HbH disease resembles β thalassemia intermedia, with the added complication that the HbH molecule behaves like moderately unstable hemoglobin. Patients with HbH disease should undergo splenectomy if excessive anemia or a transfusion requirement develops. Oxidative drugs should be avoided. Iron overload leading to death can occur in more severely affected patients.

PREVENTION

Antenatal diagnosis of thalassemia syndromes is now widely available. DNA diagnosis is based on polymerase chain reaction (PCR) amplification of fetal DNA, obtained by amniocentesis or chorionic villus biopsy followed by hybridization to allele-specific oligonucleotide probes or direct DNA sequencing.

THALASSEMIC STRUCTURAL VARIANTS

T alassemic structural variants are characterized by both defective synthesis and abnormal structure.

HEMOGLOBIN LEPORE

Hb Lepore [$\alpha_2(\delta\beta)_2$] arises by an unequal crossover and recombination event that fuses the proximal end of the δ-gene with the distal end of the closely linked β-gene. It is common in the Mediterranean basin. T e resulting chromosome contains only the fused δβ gene. T e Lepore (δβ) globin is synthesized poorly because the fused gene is under the control of the weak δ-globin promoter. Hb Lepore alleles have a phenotype like β thalassemia, except for the added presence of 2–20% Hb Lepore. Compound heterozygotes for Hb Lepore and a classic β thalassemia allele may also have severe thalassemia.

HEMOGLOBIN E

HbE (i.e., $\alpha_2\beta_2^{26Glu\rightarrow Lys}$) is extremely common in Cambodia, T ailand, and Vietnam. T e gene has become far more prevalent in the United States as a result of immigration of Asian persons, especially in California, where HbE is the most common variant detected. HbE is mildly unstable but not enough to affect RBC life span significantly. Heterozygotes resemble individuals with a mild β-thalassemia trait. Homozygotes have somewhat more marked abnormalities but are asymptomatic. Compound heterozygotes for HbE and a β thalassemia gene can have β thalassemia intermedia or β thalassemia major, depending on the severity of the coinherited thalassemic gene.

T e β^E allele contains a single base change in codon 26 that causes the amino acid substitution. T is mutation also activates a cryptic RNA splice site, generating a structurally abnormal globin mRNA that cannot be translated, from about 50% of the initial pre-mRNA molecules. T e remaining 40–50% are normally spliced and generate functional mRNA that is translated into β^E-globin because the mature mRNA carries the base change that alters codon 26.

Genetic counseling of the persons at risk for HbE should focus especially on the interaction of HbE with β thalassemia, because HbE homozygosity is a condition associated with mildly asymptomatic microcytosis, hypochromia, and hemoglobin levels rarely <100 g/L (<10 g/dL).

HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN

HPFH is characterized by continued synthesis of high levels of HbF in adult life. No deleterious effects are apparent, even when all of the hemoglobin produced is HbF. T ese rare patients demonstrate convincingly that prevention or reversal of the fetal to adult hemoglobin switch would provide effective therapy for sickle cell anemia and β thalassemia.

ACQUIRED HEMOGLOBINOPATHIES

The two most important acquired hemoglobinopathies are carbon monoxide poisoning and methemoglobinemia (see above). Carbon monoxide has a higher affinity for hemoglobin than does oxygen; it can replace oxygen and diminish O_2 delivery. Chronic elevation of carboxyhemoglobin levels to 10 or 15%, as occurs in smokers, can lead to secondary polycythemia. Carboxyhemoglobin is cherry red in color and masks the development of cyanosis usually associated with poor O_2 delivery to tissues.

Abnormalities of hemoglobin biosynthesis have also been described in blood dyscrasias. In some patients with myelodysplasia, erythroleukemia, or myeloproliferative disorders, elevated HbF or a mild form of HbH disease may also be seen. The abnormalities are not severe enough to alter the course of the underlying disease.

TREATMENT Transfusional Hemosiderosis

Chronic blood transfusion can lead to bloodborne infection, alloimmunization, febrile reactions, and lethal iron overload **(Chap. 12)**. A unit of packed RBCs contains 250–300 mg iron (1 mg/mL). The iron assimilated by a single transfusion of 2 units of packed RBCs is thus equal to a 1- to 2-year oral intake of iron. Iron accumulates in chronically transfused patients because no mechanisms exist for increasing iron excretion: an expanded erythron causes especially rapid development of iron overload because accelerated erythropoiesis promotes excessive absorption of dietary iron. Vitamin C should not be supplemented because it generates free radicals in iron excess states.

Patients who receive >100 units of packed RBCs usually develop hemosiderosis. The ferritin level rises, followed by early endocrine dysfunction (glucose intolerance and delayed puberty), cirrhosis, and cardiomyopathy. Liver biopsy shows both parenchymal and reticuloendothelial iron. The superconducting quantum-interference device (SQUID) is accurate at measuring hepatic iron but not widely available. Cardiac toxicity is often insidious. Early development of pericarditis is followed by dysrhythmia and pump failure. The onset of heart failure is ominous, often presaging death within a year.

The decision to start long-term transfusion support should also prompt one to institute therapy with iron-chelating agents. Deferoxamine (Desferal) is for parenteral use. Its iron-binding kinetics require chronic slow infusion via a metering pump. The constant presence of the drug improves the efficiency of chelation and protects tissues from occasional releases of the most toxic fraction of iron—low-molecular-weight iron—which may not be sequestered by protective proteins.

Deferoxamine is relatively nontoxic. Occasional cataracts, deafness, and local skin reactions, including urticaria, occur. Skin reactions can usually be managed with antihistamines. Negative iron balance can be achieved, even in the face of a high transfusion requirement, but this alone does not prevent long-term morbidity and mortality in chronically transfused patients. Irreversible end-organ deterioration develops at relatively modest levels of iron overload, even if symptoms do not appear for many years thereafter. To enjoy a significant survival advantage, chelation must begin before 5–8 years of age in β thalassemia major.

Deferasirox is an oral iron-chelating agent. Single daily doses of 20–30 mg/kg deferasirox produced reductions in liver iron concentration comparable to deferoxamine in long-term transfused adult and pediatric patients. Deferasirox produces some elevations in liver enzymes and slight but persistent increases in serum creatinine, without apparent clinical consequence. Other toxicities are similar to those of deferoxamine. Its toxicity profile is acceptable, although long-term effects are still being evaluated.

EXPERIMENTAL THERAPIES

BONE MARROW TRANSPLANTATION, GENE THERAPY, AND MANIPULATION OF HbF

Bone marrow transplantation provides stem cells able to express normal hemoglobin; it has been used in a large number of patients with β thalassemia and a smaller number of patients with sickle cell anemia. Early in the course of disease, before end-organ damage occurs, transplantation is curative in 80–90% of patients. In highly experienced centers, the treatment-related mortality is <10%. Because survival into adult life is possible with conventional therapy, the decision to transplant is best made in consultation with specialized centers.

Gene therapy of thalassemia and sickle cell disease has proved to be an elusive goal, but experimental advances are raising expectations.

Reestablishing high levels of fetal hemoglobin synthesis should ameliorate the symptoms of β-chain hemoglobinopathies. Cytotoxic agents such as hydroxyurea and cytarabine promote high levels of HbF synthesis, probably by stimulating proliferation of the primitive HbF-producing progenitor cell population (i.e., F cell progenitors). Unfortunately, this regimen has not yet been effective in β thalassemia. Butyrates stimulate HbF production, but only transiently. Pulsed or intermittent administration has been found to sustain HbF induction in the majority of patients with sickle cell disease. It is unclear whether butyrates will have similar activity in patients with β thalassemia.

APLASTIC AND HYPOPLASTIC CRISIS IN PATIENTS WITH HEMOGLOBINOPATHIES

Patients with hemolytic anemias sometimes exhibit an alarming decline in hematocrit during and immediately af er acute illnesses. Bone marrow suppression occurs in almost everyone during acute and chronic inflammatory illnesses. In patients with short RBC life spans, suppression can affect RBC counts more dramatically. T ese hypoplastic crises are usually transient and self-correcting before intervention is required.

Aplastic crisis refers to a profound cessation of erythroid activity in patients with chronic hemolytic anemias. It is associated with a rapidly falling hematocrit. Episodes are usually self-limited. Aplastic crises are caused by infection with a particular strain of parvovirus, B19A. Children infected with this virus usually develop permanent immunity. Aplastic crises do not of en recur and are rarely seen in adults. Management requires close monitoring of the hematocrit and reticulocyte count. If anemia becomes symptomatic, transfusion support is indicated. Most crises resolve spontaneously within 1–2 weeks.

CHAPTER 9

MEGALOBLASTIC ANEMIAS

A. Victor Hoffbrand

The megaloblastic anemias are a group of disorders characterized by the presence of distinctive morphologic appearances of the developing red cells in the bone marrow. The marrow is usually hypercellular and the anemia is based on ineffective erythropoiesis. The cause is usually a deficiency of either cobalamin (vitamin B_{12}) or folate, but megaloblastic anemia may occur because of genetic or acquired abnormalities that affect the metabolism of these vitamins or because of defects in DNA synthesis not related to cobalamin or folate **(Table 9-1)**. Cobalamin and folate absorption and metabolism are described next, followed by the biochemical basis, clinical and laboratory features, causes, and treatment of megaloblastic anemia.

COBALAMIN

Cobalamin (vitamin B_{12}) exists in a number of different chemical forms. All have a cobalt atom at the center of a corrin ring. In nature, the vitamin is mainly in the 2-deoxyadenosyl (ado) form, which is located in mitochondria. It is the cofactor for the enzyme methylmalonyl coenzyme A (CoA) mutase. The other major natural cobalamin is methylcobalamin, the form in human plasma and in cell cytoplasm. It is the cofactor for methionine synthase. There are also minor amounts of hydroxocobalamin to which methyl- and adocobalamin are converted rapidly by exposure to light.

DIETARY SOURCES AND REQUIREMENTS

Cobalamin is synthesized solely by microorganisms. Ruminants obtain cobalamin from the foregut, but the only source for humans is food of animal origin, e.g., meat, fish, and dairy products. Vegetables, fruits, and other foods of nonanimal origin are free from cobalamin unless they are contaminated by bacteria. A normal Western diet contains 5–30 μg of cobalamin daily. Adult daily losses (mainly in the urine and feces) are 1–3 μg (~0.1% of body stores), and because the body does not have the ability to degrade cobalamin, daily requirements are also about 1–3 μg. Body stores are of the order of 2–3 mg, sufficient for 3–4 years if supplies are completely cut off.

ABSORPTION

Two mechanisms exist for cobalamin absorption. One is passive, occurring equally through buccal, duodenal, and ileal mucosa; it is rapid but extremely inefficient, with <1% of an oral dose being absorbed by this process. The normal physiologic mechanism is active; it occurs through the ileum and is efficient for small (a few micrograms) oral doses of cobalamin, and it is mediated by gastric intrinsic factor (IF). Dietary cobalamin is released from protein complexes by enzymes in the stomach, duodenum, and jejunum; it combines rapidly with a salivary glycoprotein that belongs to the family of cobalamin-binding proteins known as

TABLE 9-1

CAUSES OF MEGALOBLASTIC ANEMIA
Cobalamin deficiency or abnormalities of cobalamin metabolism (see Tables 9-3, 9-4)
Folate deficiency or abnormalities of folate metabolism (see Table 9-5)
Therapy with antifolate drugs (e.g., methotrexate)
Independent of either cobalamin or folate deficiency and refractory to cobalamin and folate therapy:
Some cases of acute myeloid leukemia, myelodysplasia
Therapy with drugs interfering with synthesis of DNA (e.g., cytosine arabinoside, hydroxyurea, 6-mercaptopurine, azidothymidine [AZT])
Orotic aciduria (responds to uridine)
Thiamine-responsive

haptocorrins (HCs). In the intestine, the haptocorrin is digested by pancreatic trypsin and the cobalamin is transferred to IF.

IF (gene at chromosome 11q13) is produced in the gastric parietal cells of the fundus and body of the stomach, and its secretion parallels that of hydrochloric acid. Normally, there is a vast excess of IF. The IF-cobalamin complex passes to the ileum, where IF attaches to a specific receptor (cubilin) on the microvillus membrane of the enterocytes. Cubilin also is present in yolk sac and renal proximal tubular epithelium. Cubilin appears to traffic by means of amnionless (AMN), an endocytic receptor protein that directs sublocalization and endocytosis of cubilin with its ligand IF-cobalamin complex. The cobalamin-IF complex enters the ileal cell, where IF is destroyed. After a delay of about 6 h, the cobalamin appears in portal blood attached to transcobalamin (TC) II.

Between 0.5 and 5 μg of cobalamin enter the bile each day. This binds to IF, and a major portion of biliary cobalamin normally is reabsorbed together with cobalamin derived from sloughed intestinal cells. Because of the appreciable amount of cobalamin undergoing enterohepatic circulation, cobalamin deficiency develops more rapidly in individuals who malabsorb cobalamin than it does in vegans, in whom reabsorption of biliary cobalamin is intact.

TRANSPORT

Two main cobalamin transport proteins exist in human plasma; they both bind cobalamin—one molecule for one molecule. One HC, also known as TC I, is closely related to other cobalamin-binding HCs in milk, gastric juice, bile, saliva, and other fluids. The gene TCNL is at chromosome 11q11-q12.3. These HCs differ from each other only in the carbohydrate moiety of the molecule. TC I is derived primarily from the specific granules in neutrophils. Normally, it is about two-thirds saturated with cobalamin, which it binds tightly. TC I does not enhance cobalamin entry into tissues. Glycoprotein receptors on liver cells are involved in the removal of TC I from plasma, and TC I may play a role in the transport of cobalamin analogues (which it binds more effectively than IF) to the liver for excretion in bile.

The other major cobalamin transport protein in plasma is transcobalamin, also known as TC II. The gene is on chromosome 22q11-q13.1. As for IF and HC, there are nine exons. The three proteins are likely to have a common ancestral origin. TC II is synthesized by liver and by other tissues, including macrophages, ileum, and vascular endothelium. It normally carries only 20–60 ng of cobalamin per liter of plasma and readily gives up cobalamin to marrow, placenta, and other tissues, which it enters by receptor-mediated endocytosis involving the TC II receptor and megalin (encoded by the LRP-2 gene). The TC II cobalamin is internalized by endocytosis via clathrin-coated pits; the complex is degraded, but the receptor probably is recycled to the cell membrane as is the case for transferrin. Export of "free" cobalamin is via the ATP-binding cassette drug transporter alias multidrug resistance protein 1.

FOLATE

DIETARY FOLATE

Folic (pteroylglutamic) acid is a yellow, crystalline, water-soluble substance. It is the parent compound of a large family of natural folate compounds, which differ from it in three respects: (1) they are partly or completely reduced to di- or tetrahydrofolate (THF) derivatives, (2) they usually contain a single carbon unit **(Table 9-2)**, and (3) 70–90% of natural folates are folate-polyglutamates.

Most foods contain some folate. The highest concentrations are found in liver, yeast, spinach, other greens, and nuts (>100 μg/100 g). The total folate content of an average Western diet is ~250 μg daily, but the amount varies widely according to the type of food eaten and the method of cooking. Folate is easily destroyed by heating, particularly in large volumes of water. Total body folate in the adult is ~10 mg, with the liver containing the largest store. Daily adult requirements are ~100 μg, and so stores are sufficient for only 3–4 months in normal adults and severe folate deficiency may develop rapidly.

ABSORPTION

Folates are absorbed rapidly from the upper small intestine. The absorption of folate polyglutamates is less efficient than that of monoglutamates; on average, ~50% of food folate is absorbed. Polyglutamate forms are hydrolyzed to the monoglutamate derivatives either in the lumen of the intestine or within the mucosa. All dietary folates are converted to 5-methylTHF (5-MTHF) within the small intestinal mucosa before entering portal plasma. The monoglutamates are actively transported across the enterocyte by a proton-coupled folate transporter (PCFT, SCL46A1). This is situated at the apical brush border and is most active at pH 5.5, which is about the pH of the duodenal and jejunal surface. Genetic mutations of this protein underlie hereditary malabsorption of folate (see below). Pteroylglutamic acid at doses >400 μg is absorbed largely unchanged and converted to natural folates in the liver. Lower doses are converted to 5-MTHF during absorption through the intestine.

TABLE 9-2

BIOCHEMICAL REACTIONS OF FOLATE COENZYMES

REACTION	COENZYME FORM OF FOLATE INVOLVED	SINGLE CARBON UNIT TRANSFERRED	IMPORTANCE
Formate activation	THF	−CHO	Generation of 10-formyl-THF
Purine synthesis			
Formation of glycinamide ribonucleotide	5,10-Methylene-THF	−CHO	Formation of purines needed for DNA, RNA synthesis, but reactions probably not rate-limiting
Formylation of aminoimidazole carboxamide ribonucleotide (AICAR)	10-Formyl (CHO)THF		
Pyrimidine synthesis			
Methylation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP)	5,10-Methylene-THF	$-CH_3$	Rate limiting in DNA synthesis Oxidizes THF to DHF Some breakdown of folate at the C-9–N-10 bond
Amino acid interconversion			
Serine–glycine interconversion	THF	$=CH_2$	Entry of single carbon units into active pool
Homocysteine to methionine	5-Methyl(M)THF	$-CH_3$	Demethylation of 5-MTHF to THF; also requires cobalamin, flavine adenine dinucleotide, ATP, and adenosylmethionine
Forminoglutamic acid to glutamic acid in histidine catabolism	THF	−HN−CH=	

Abbreviations: DHF, dihydrofolate; THF, tetrahydrofolate.

About 60–90 μg of folate enters the bile each day and is excreted into the small intestine. Loss of this folate, together with the folate of sloughed intestinal cells, accelerates the speed with which folate deficiency develops in malabsorption conditions.

TRANSPORT

Folate is transported in plasma; about one-third is loosely bound to albumin, and two-thirds is unbound. In all body fluids (plasma, cerebrospinal fluid, milk, bile), folate is largely, if not entirely, 5-MTHF in the monoglutamate form. Three types of folate-binding protein are involved. A reduced folate transporter (RFC, SLC19A1) is the major route of delivery of plasma folate (5-MTHF) to cells. Two folate receptors, FR2 and FR3 embedded in the cell membrane by a glycosyl phosphatidylinositol anchor, transport folate into the cell via receptor-mediated endocytosis. The third protein, PCFT, transports folate at low pH from the vesicle to the cell cytoplasm. The reduced folate transporter also mediates uptake of methotrexate by cells.

BIOCHEMICAL FUNCTIONS

Folates (as the intracellular polyglutamate derivatives) act as coenzymes in the transfer of single-carbon units (**Fig. 9-1** and Table 9-2). Two of these reactions are involved in purine synthesis and one in pyrimidine synthesis necessary for DNA and RNA replication. Folate is also a coenzyme for methionine synthesis, in which methylcobalamin is also involved and in which THF is regenerated. THF is the acceptor of single carbon units newly entering the active pool via conversion of serine to glycine. Methionine, the other product of the methionine synthase reaction, is the precursor for S-adenosylmethionine (SAM), the universal methyl donor involved in >100 methyltransferase reactions (Fig. 9-1).

During thymidylate synthesis, 5,10-methylene-THF is oxidized to DHF (dihydrofolate). The enzyme DHF reductase converts this to THF. The drugs methotrexate, pyrimethamine, and (mainly in bacteria) trimethoprim inhibit DHF reductase and so prevent formation of active THF coenzymes from DHF. A small fraction of the folate coenzyme is not recycled during thymidylate synthesis but is degraded at the C9-N10 bond.

BIOCHEMICAL BASIS OF MEGALOBLASTIC ANEMIA

The common feature of all megaloblastic anemias is a defect in DNA synthesis that affects rapidly dividing cells in the bone marrow. All conditions that give rise

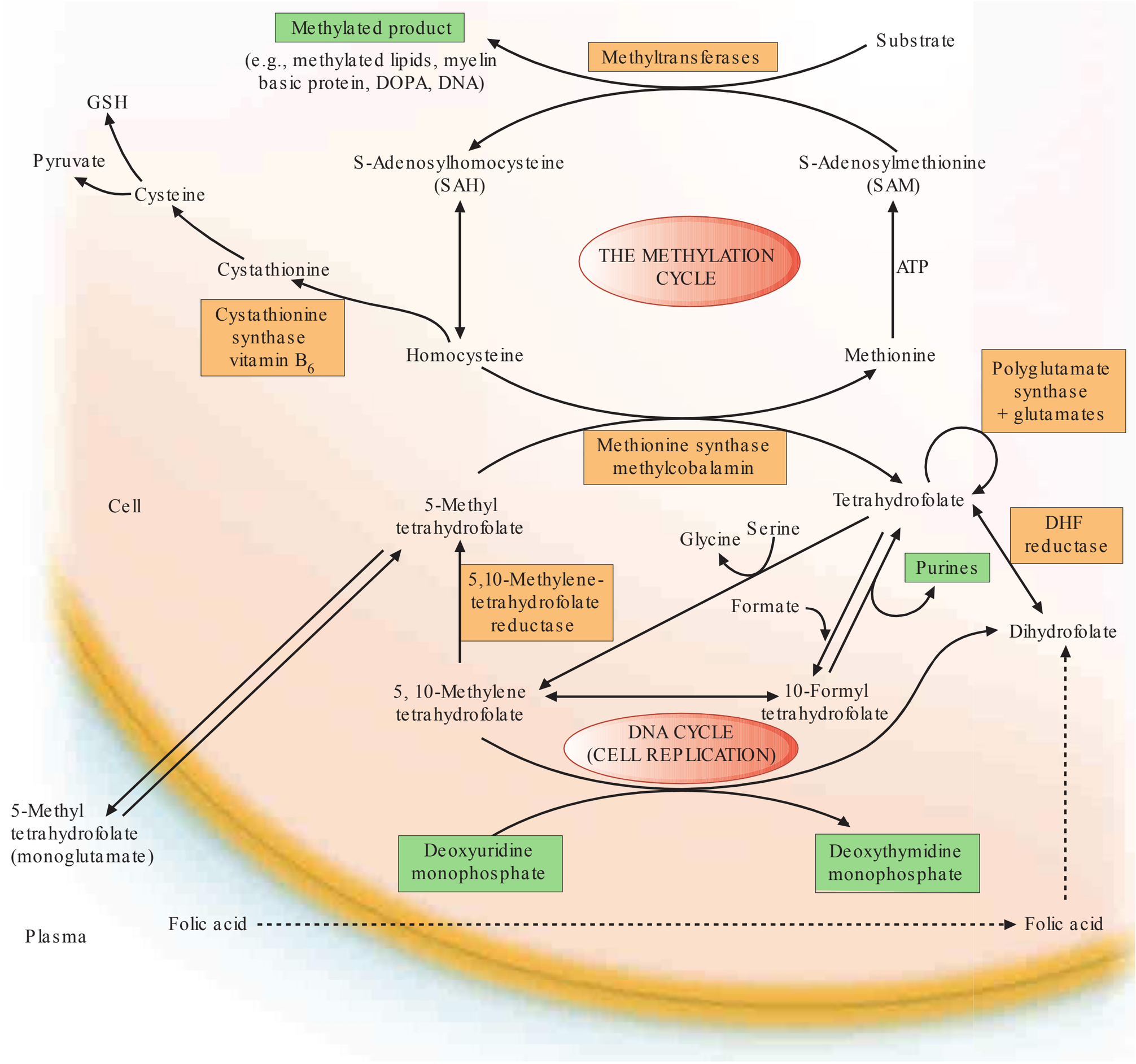


FIGURE 9-1

The role of folates in DNA synthesis and in formation of S-adenosylmethionine (SAM), which is involved in numerous methylation reactions. DHF, dihydrofolate; GSH, glutathione. (Reprinted from AV Hofbrand et al [eds]: Postgraduate Haematology,5th ed. Oxford, UK, Blackwell Publishing, 2005; with permission.)

to megaloblastic changes have in common a disparity in the rate of synthesis or availability of the four immediate precursors of DNA: the deoxyribonucleoside triphosphates (dNTPs)—dA(adenine)TP and dG(guanine)TP (purines), dT(thymine)TP and dC(cytosine)TP (pyrimidines). In deficiencies of either folate or cobalamin, there is failure to convert deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), the precursor of dTTP (Fig 9-1). T is is the case because folate is needed as the coenzyme 5,10-methylene-THF polyglutamate for conversion of dUMP to dTMP; the availability of 5,10-methylene-THF is reduced in either cobalamin or folate deficiency. An alternative theory for megaloblastic anemia in cobalamin or folate deficiency is misincorporation of uracil into DNA because of a buildup of deoxyuridine triphosphate (dUTP) at the DNA replication fork as a consequence of the block in conversion of dUMP to dTMP.

COBALAMIN-FOLATE RELATIONS

Folate is required for many reactions in mammalian tissues. Only two reactions in the body are known to require cobalamin. Methylmalonyl CoA isomerization requires adocobalamin, and the methylation of homocysteine to methionine requires both methylcobalamin and 5-MTHF (Fig. 9-1). T is reaction is the first step in the pathway by which 5-MTHF, which enters bone

marrow and other cells from plasma, is converted into all the intracellular folate coenzymes. T e coenzymes are all polyglutamated (the larger size aiding retention in the cell), but the enzyme folate polyglutamate synthase can use only THF, not MTHF, as substrate. In cobalamin deficiency, MTHF accumulates in plasma, and intracellular folate concentrations fall due to failure of formation of THF, the substrate on which folate polyglutamates are built. T is has been termed THF starvation, or the methylfolate trap.

T is theory explains the abnormalities of folate metabolism that occur in cobalamin deficiency (high serum folate, low cell folate, positive purine precursor aminoimidazole carboxamide ribonucleotide [AICAR] excretion; Table 9-2) and also why the anemia of cobalamin deficiency responds to folic acid in large doses.

CLINICAL FEATURES

Many symptomless patients are detected through the finding of a raised mean corpuscular volume (MCV) on a routine blood count. T e main clinical features in more severe cases are those of anemia. Anorexia is usually marked, and there may be weight loss, diarrhea, or constipation. Glossitis, angular cheilosis, a mild fever in more severely anemic patients, jaundice (unconjugated), and reversible melanin skin hyperpigmentation also may occur with a deficiency of either folate or cobalamin. T rombocytopenia sometimes leads to bruising, and this may be aggravated by vitamin C deficiency or alcohol in malnourished patients. T e anemia and low leukocyte count may predispose to infections, particularly of the respiratory and urinary tracts. Cobalamin deficiency has also been associated with impaired bactericidal function of phagocytes.

GENERAL TISSUE EFFECTS OF COBALAMIN AND FOLATE DEFICIENCIES

Epithelial surfaces

After the marrow, the next most frequently affected tissues are the epithelial cell surfaces of the mouth, stomach, and small intestine and the respiratory, urinary, and female genital tracts. T e cells show macrocytosis, with increased numbers of multinucleate and dying cells. T e deficiencies may cause cervical smear abnormalities.

Complications of pregnancy

T e gonads are also affected, and infertility is common in both men and women with either deficiency. Maternal folate deficiency has been implicated as a cause of prematurity, and both folate deficiency and cobalamin deficiency have been implicated in recurrent fetal loss and neural tube defects, as discussed below.

Neural tube defects

Folic acid supplements at the time of conception and in the first 12 weeks of pregnancy reduce by ~70% the incidence of neural tube defects (NTDs) (anencephaly, meningomyelocele, encephalocele, and spina bifida) in the fetus. Most of this protective effect can be achieved by taking folic acid, 0.4 mg daily, at the time of conception.

T e incidence of cleft palate and harelip also can be reduced by prophylactic folic acid. T ere is no clear simple relationship between maternal folate status and these fetal abnormalities, although overall the lower the maternal folate, the greater the risk to the fetus. NTDs also can be caused by antifolate and antiepileptic drugs.

An underlying maternal folate metabolic abnormality has also been postulated. One abnormality has been identified: reduced activity of the enzyme 5,10-methylene-THF reductase (MTHFR) (Fig. 9-1) caused by a common C677T polymorphism in the MTHFR gene. In one study, the prevalence of this polymorphism was found to be higher than in controls in the parents of NTD fetuses and in the fetuses themselves: homozygosity for the TT mutation was found in 13% of cases compared with 5% of control subjects. T e polymorphism codes for a thermolabile form of MTHFR. T e homozygous state results in a lower mean serum and red cell folate level compared with control subjects, as well as significantly higher serum homocysteine levels. Tests for mutations in other enzymes possibly associated with NTDs, e.g., methionine synthase and serine–glycine hydroxymethylase, have been negative. Serum vitamin B_{12} levels are also lower in the sera of mothers of NTD infants than in controls. In addition, maternal TC II receptor polymorphisms are associated with increased risk of NTD births. T ere are, however, no studies showing dietary fortification with vitamin B_{12} reduces the incidence of NTDs.

Cardiovascular disease

Children with severe homocystinuria (blood levels ≥100 μmol/L) due to deficiency of one of three enzymes, methionine synthase, MTHFR, or cystathionine synthase (Fig. 9-1), have vascular disease, e.g., ischemic heart disease, cerebrovascular disease, or pulmonary embolus, as teenagers or in young adulthood. Lesser degrees of raised serum homocysteine and low levels of serum folate and homozygous inherited mutations of MTHFR have been found to be associated with cerebrovascular, peripheral vascular, and coronary heart disease and with deep vein thrombosis. Prospective

randomized trials of lowering homocysteine levels with supplements of folic acid, vitamin B_{12}, and vitamin B_6 against placebo over a 5-year period in patients with vascular disease or diabetes have not, however, shown a reduction of first event fatal or nonfatal myocardial infarction, nor have these supplements reduced the risk of recurrent cardiovascular disease after an acute myocardial infarct. Meta-analysis showed an 18% reduction in strokes but no significant prevention of death from any cause. Venous thrombosis has been reported to be more frequent in vitamin B_{12}–deficient subjects than in controls. T is was ascribed to raised plasma homocysteine levels in vitamin B_{12} deficiency.

Malignancy

Prophylactic folic acid in pregnancy has been found in some but not all studies to reduce the subsequent incidence of acute lymphoblastic leukemia (ALL) in childhood. A significant negative association has also been found with the MTHFR C677T polymorphism and leukemias with mixed lineage leukemia (MLL) translocations, but a positive association with hyperdiploidy in infants with ALL or acute myeloid leukemia or with childhood ALL. A second polymorphism in the MTHFR gene, A1298C, is also strongly associated with hyperdiploid leukemia. T ere are various positive and negative associations between polymorphisms in folate-dependent enzymes and the incidence of adult ALL. T e C677T polymorphism is thought to lead to increased thymidine pools and "better quality" of DNA synthesis by shunting one-carbon groups toward thymidine and purine synthesis. T is may explain its reported association with a lower risk for colorectal cancer. Most but not all studies suggest that prophylactic folic acid also protects against colon adenomas. Other tumors that have been associated with folate polymorphisms or status include follicular lymphoma, breast cancer, and gastric cancer. A meta-analysis of 50,000 individuals given folic acid or placebo in cardiovascular or colon adenoma prevention trials found that folic acid supplementation did not substantially increase or decrease the incidence of site-specific cancer during the first 5 years of treatment. Because folic acid may "feed" tumors, it probably should be avoided in those with established tumors unless there is severe megaloblastic anemia due to folate deficiency.

Neurologic manifestations

Cobalamin deficiency may cause a bilateral peripheral neuropathy or degeneration (demyelination) of the posterior and pyramidal tracts of the spinal cord and, less frequently, optic atrophy or cerebral symptoms.

T e patient, more frequently male, presents with paresthesias, muscle weakness, or difficulty in walking and sometimes dementia, psychotic disturbances, or visual impairment. Long-term nutritional cobalamin deficiency in infancy leads to poor brain development and impaired intellectual development. Folate deficiency has been suggested to cause organic nervous disease, but this is uncertain, although methotrexate injected into the cerebrospinal f uid may cause brain or spinal cord damage.

An important clinical problem is the nonanemic patient with neurologic or psychiatric abnormalities and a low or borderline serum cobalamin level. In such patients, it is necessary to try to establish whether there is significant cobalamin deficiency, e.g., by careful examination of the blood film, tests for serum gastrin level and for antibodies to IF or parietal cells, along with serum methylmalonic acid (MMA) measurement if available. A trial of cobalamin therapy for at least 3 months will usually also be needed to determine whether the symptoms improve.

T e biochemical basis for cobalamin neuropathy remains obscure. Its occurrence in the absence of methylmalonic aciduria in TC II deficiency suggests that the neuropathy is related to the defect in homocysteine-methionine conversion. Accumulation of S-adenosylhomocysteine in the brain, resulting in inhibition of transmethylation reactions, has been suggested.

Psychiatric disturbance is common in both folate and cobalamin deficiencies. T is, like the neuropathy, has been attributed to a failure of the synthesis of SAM, which is needed in methylation of biogenic amines (e.g., dopamine) as well as that of proteins, phospholipids, and neurotransmitters in the brain (Fig. 9-1). Associations between lower serum folate or cobalamin levels and higher homocysteine levels and the development of decreased cognitive function and dementia in Alzheimer's disease have been reported. A meta-analysis of randomized, placebo-controlled trials of homocysteine-lowering B-vitamin supplementation of individuals with and without cognitive impairment, however, showed that supplementation with vitamin B_{12}, vitamin B_6, and folic acid alone or in combination did not improve cognitive function. It is unknown whether prolonged treatment with these B vitamins can reduce the risk of dementia in later life.

HEMATOLOGIC FINDINGS

PERIPHERAL BLOOD

Oval macrocytes, usually with considerable anisocytosis and poikilocytosis, are the main feature **(Fig. 9-2A)**. T e MCV is usually >100 fL unless a cause of microcytosis (e.g., iron deficiency or thalassemia trait) is present. Some of the neutrophils are hypersegmented (more than five nuclear lobes). T ere may be leukopenia due

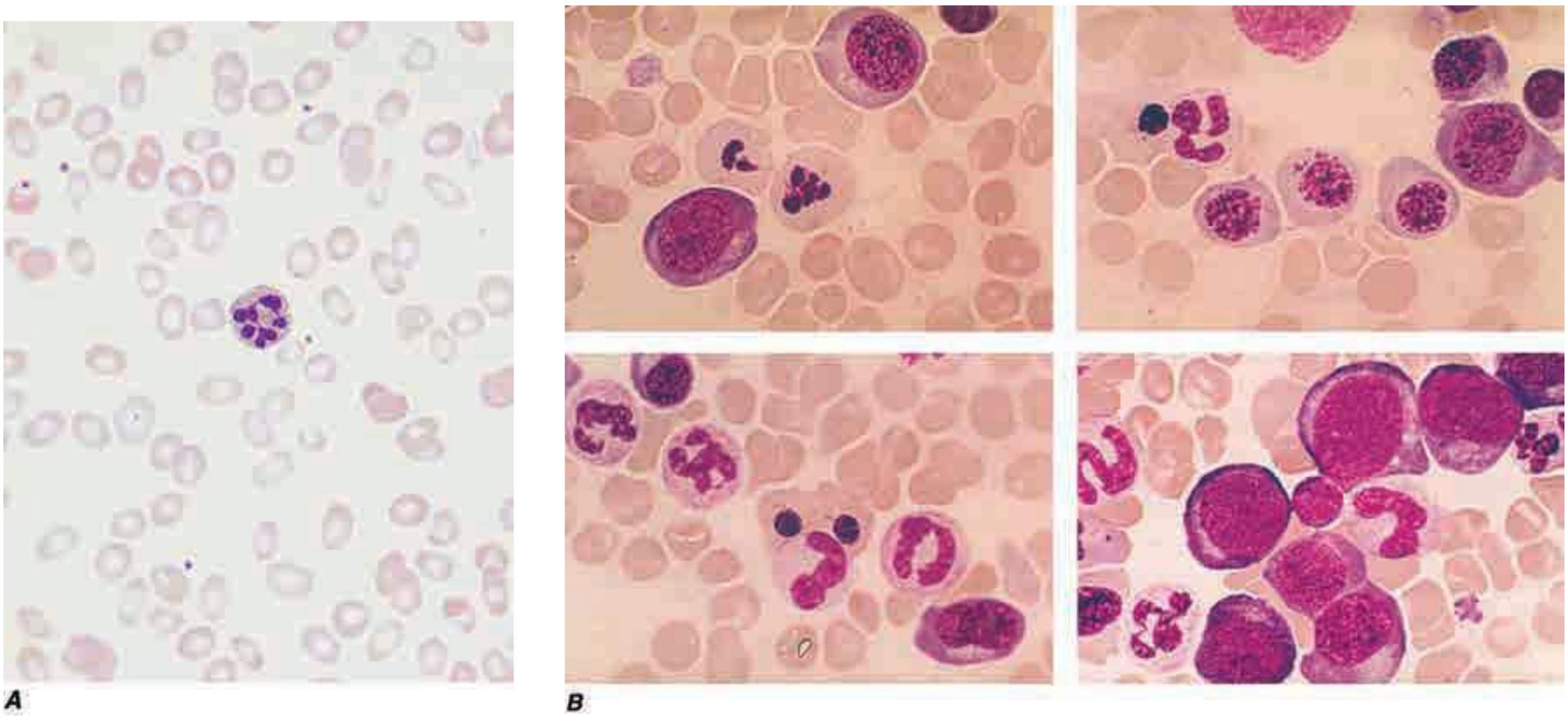


FIGURE 9-2

A. The peripheral blood in severe megaloblastic anemia. B. The bone marrow in severe megaloblastic anemia. (Reprinted from AV Hoffbrand et al [eds]: Postgraduate Haematology, 5th ed. Oxford, UK, Blackwell Publishing, 2005; with permission.)

to a reduction in granulocytes and lymphocytes, but this is usually >1.5 × 10^9/L; the platelet count may be moderately reduced, rarely to <40 × 10^9/L. The severity of all these changes parallels the degree of anemia. In a nonanemic patient, the presence of a few macrocytes and hypersegmented neutrophils in the peripheral blood may be the only indication of the underlying disorder.

BONE MARROW

In a severely anemic patient, the marrow is hypercellular with an accumulation of primitive cells due to selective death by apoptosis of more mature forms. The erythroblast nucleus maintains a primitive appearance despite maturation and hemoglobinization of the cytoplasm. The cells are larger than normoblasts, and an increased number of cells with eccentric lobulated nuclei or nuclear fragments may be present **(Fig. 9-2B)**. Giant and abnormally shaped metamyelocytes and enlarged hyperpolyploid megakaryocytes are characteristic. In severe cases, the accumulation of primitive cells may mimic acute myeloid leukemia, whereas in less anemic patients, the changes in the marrow may be difficult to recognize. The terms intermediate, mild, and early have been used. The term megaloblastoid does not mean mildly megaloblastic. It is used to describe cells with both immature-appearing nuclei and defective hemoglobinization and is usually seen in myelodysplasia.

CHROMOSOMES

Bone marrow cells, transformed lymphocytes, and other proliferating cells in the body show a variety of changes, including random breaks, reduced contraction, spreading of the centromere, and exaggeration of secondary chromosomal constrictions and overprominent satellites. Similar abnormalities may be produced by antimetabolite drugs (e.g., cytosine arabinoside, hydroxyurea, and methotrexate) that interfere with either DNA replication or folate metabolism and that also cause megaloblastic appearances.

INEFFECTIVE HEMATOPOIESIS

There is an accumulation of unconjugated bilirubin in plasma due to the death of nucleated red cells in the marrow (ineffective erythropoiesis). Other evidence for this includes raised urine urobilinogen, reduced haptoglobins and positive urine hemosiderin, and a raised serum lactate dehydrogenase. A weakly positive direct antiglobulin test due to complement can lead to a false diagnosis of autoimmune hemolytic anemia.

CAUSES OF COBALAMIN DEFICIENCY

Cobalamin deficiency is usually due to malabsorption. The only other cause is inadequate dietary intake.

INADEQUATE DIETARY INTAKE

Adults

Dietary cobalamin deficiency arises in vegans who omit meat, fish, eggs, cheese, and other animal products from their diet. The largest group in the world consists

of Hindus, and it is likely that many millions of Indians are at risk of deficiency of cobalamin on a nutritional basis. Subnormal serum cobalamin levels are found in up to 50% of randomly selected, young, adult Indian vegans, but the deficiency usually does not progress to megaloblastic anemia since the diet of most vegans is not totally lacking in cobalamin and the enterohepatic circulation of cobalamin is intact. Dietary cobalamin deficiency may also arise rarely in nonvegetarian individuals who exist on grossly inadequate diets because of poverty or psychiatric disturbance.

Infants

Cobalamin deficiency has been described in infants born to severely cobalamin-deficient mothers. These infants develop megaloblastic anemia at about 3–6 months of age, presumably because they are born with low stores of cobalamin and because they are fed breast milk with low cobalamin content. The babies have also shown growth retardation, impaired psychomotor development, and other neurologic sequelae.

GASTRIC CAUSES OF COBALAMIN MALABSORPTION

See **Tables 9-3** and **9-4**.

Pernicious anemia

Pernicious anemia (PA) may be defined as a severe lack of IF due to gastric atrophy. It is a common disease in north Europeans but occurs in all countries and ethnic groups. The overall incidence is about 120 per 100,000 population in the United Kingdom (UK). The ratio of incidence in men and women among whites is ~1:1.6, and the peak age of onset is 60 years, with only 10% of patients being <40 years of age. However, in some ethnic groups, notably black individuals and Latin Americans, the age at onset of PA is generally lower. The disease occurs more commonly than by chance in close relatives and in persons with other organ-specific autoimmune diseases, e.g., thyroid diseases, vitiligo, hypoparathyroidism, and Addison's disease. It is also associated with hypogammaglobulinemia, with premature graying or blue eyes, and persons of blood group A. An association with human leukocyte antigen (HLA) 3 has been reported in some but not all series and, in those with endocrine disease, with HLA-B8, -B12, and -BW15. Life expectancy is normal in women once regular treatment has begun. Men have a slightly subnormal life expectancy as a result of a higher incidence of carcinoma of the stomach than in control subjects. Gastric output of hydrochloric acid, pepsin, and IF is severely reduced. The serum gastrin level is raised, and serum pepsinogen I levels are low.

TABLE 9-3

CAUSES OF COBALAMIN DEFICIENCY SUFFICIENTLY SEVERE TO CAUSE MEGALOBLASTIC ANEMIA	
Nutritional	Vegans
Malabsorption	Pernicious anemia
Gastric causes	Congenital absence of intrinsic factor or functional abnormality Total or partial gastrectomy
Intestinal causes	Intestinal stagnant loop syndrome: jejunal diverticulosis, ileocolic fistula, anatomic blind loop, intestinal stricture, etc. Ileal resection and Crohn's disease Selective malabsorption with proteinuria Tropical sprue Transcobalamin II deficiency Fish tapeworm

TABLE 9-4

MALABSORPTION OF COBALAMIN MAY OCCUR IN THE FOLLOWING CONDITIONS BUT IS NOT USUALLY SUFFICIENTLY SEVERE AND PROLONGED TO CAUSE MEGALOBLASTIC ANEMIA
Gastric causes
Simple atrophic gastritis (food cobalamin malabsorption)
Zollinger-Ellison syndrome
Gastric bypass surgery
Use of proton pump inhibitors
Intestinal causes
Gluten-induced enteropathy
Severe pancreatitis
HIV infection
Radiotherapy
Graft-versus-host disease
Deficiencies of cobalamin, folate, protein, ?riboflavin, ?nicotinic acid
Therapy with colchicine, para-aminosalicylate, neomycin, slow-release potassium chloride, anticonvulsant drugs, metformin, phenformin, cytotoxic drugs
Alcohol

Gastric biopsy

A single endoscopic examination is recommended if PA is diagnosed. Gastric biopsy usually shows atrophy of all layers of the body and fundus, with loss of glandular elements, an absence of parietal and chief cells and replacement by mucous cells, a mixed inflammatory cell infiltrate, and perhaps intestinal metaplasia. The infiltrate of plasma cells and lymphocytes contains an excess of CD4 cells. These are directed against gastric H/K-ATPase. The antral mucosa is usually well preserved. Helicobacter pylori infection occurs infrequently in PA, but it has been suggested that H. pylori gastritis

occurs at an early phase of atrophic gastritis and presents in younger patients as iron-deficiency anemia but in older patients as PA. H. pylori is suggested to stimulate an autoimmune process directed against parietal cells, with the H. pylori infection then being gradually replaced, in some individuals, by an autoimmune process.

Serum antibodies

Two types of IF immunoglobulin G antibody may be found in the sera of patients with PA. One, the "blocking," or type I, antibody, prevents the combination of IF and cobalamin, whereas the "binding," or type II, antibody prevents attachment of IF to ileal mucosa. Type I occurs in the sera of ~55% of patients, and type II in 35%. IF antibodies cross the placenta and may cause temporary IF deficiency in a newborn infant. Patients with PA also show cell-mediated immunity to IF. Type I antibody has been detected rarely in the sera of patients without PA but with thyrotoxicosis, myxedema, Hashimoto's disease, or diabetes mellitus and in relatives of PA patients. IF antibodies also have been detected in gastric juice in ~80% of PA patients. T ese gastric antibodies may reduce absorption of dietary cobalamin by combining with small amounts of remaining IF.

Parietal cell antibody is present in the sera of almost 90% of adult patients with PA but is frequently present in other subjects. T us, it occurs in as many as 16% of randomly selected female subjects age >60 years. T e parietal cell antibody is directed against the α and β subunits of the gastric proton pump (H^+,K^+-ATPase).

JUVENILE PERNICIOUS ANEMIA

T is usually occurs in older children and resembles PA of adults. Gastric atrophy, achlorhydria, and serum IF antibodies are all present, although parietal cell antibodies are usually absent. About one-half of these patients show an associated endocrinopathy such as autoimmune thyroiditis, Addison's disease, or hypoparathyroidism; in some, mucocutaneous candidiasis occurs.

CONGENITAL INTRINSIC FACTOR DEFICIENCY OR FUNCTIONAL ABNORMALITY

An affected child usually presents with megaloblastic anemia in the first to third year of life; a few have presented as late as the second decade. T e child usually has no demonstrable IF but has a normal gastric mucosa and normal secretion of acid. T e inheritance is autosomal recessive. Parietal cell and IF antibodies are absent. Variants have been described in which the child is born with IF that can be detected immunologically but is unstable or functionally inactive, unable to bind cobalamin or to facilitate its uptake by ileal receptors.

GASTRECTOMY

After total gastrectomy, cobalamin deficiency is inevitable, and prophylactic cobalamin therapy should be commenced immediately after the operation. After partial gastrectomy, 10–15% of patients also develop this deficiency. T e exact incidence and time of onset are most inf uenced by the size of the resection and the preexisting size of cobalamin body stores.

FOOD COBALAMIN MALABSORPTION

Failure of release of cobalamin from binding proteins in food is believed to be responsible for this condition, which is more common in the elderly. It is associated with low serum cobalamin levels, with or without raised serum levels of MMA and homocysteine. Typically, these patients have normal cobalamin absorption, as measured with crystalline cobalamin, but show malabsorption when a modified test using food-bound cobalamin is used. T e frequency of progression to severe cobalamin deficiency and the reasons for this progression are not clear.

INTESTINAL CAUSES OF COBALAMIN MALABSORPTION

Intestinal stagnant loop syndrome

Malabsorption of cobalamin occurs in a variety of intestinal lesions in which there is colonization of the upper small intestine by fecal organisms. T is may occur in patients with jejunal diverticulosis, enteroanastomosis, or an intestinal stricture or fistula or with an anatomic blind loop due to Crohn's disease, tuberculosis, or an operative procedure.

Ileal resection

Removal of ≥1.2 m of terminal ileum causes malabsorption of cobalamin. In some patients after ileal resection, particularly if the ileocecal valve is incompetent, colonic bacteria may contribute further to the onset of cobalamin deficiency.

Selective malabsorption of cobalamin with proteinuria (Imerslund's syndrome; Imerslund-Gräsbeck syndrome; congenital cobalamin malabsorption; autosomal recessive megaloblastic anemia; MGA1)

T is autosomally recessive disease is the most common cause of megaloblastic anemia due to cobalamin deficiency in infancy in Western countries. More than 200 cases have been reported, with familial clusters in Finland, Norway, the Middle East, and North Africa. T e patients secrete normal amounts of IF and gastric

acid but are unable to absorb cobalamin. In Finland, impaired synthesis, processing, or ligand binding of cubilin due to inherited mutations is found. In Norway, mutation of the gene for AMN has been reported. Other tests of intestinal absorption are normal. Over 90% of these patients show nonspecific proteinuria, but renal function is otherwise normal and renal biopsy has not shown any consistent renal defect. A few have shown aminoaciduria and congenital renal abnormalities, such as duplication of the renal pelvis.

Tropical sprue

Nearly all patients with acute and subacute tropical sprue show malabsorption of cobalamin; this may persist as the principal abnormality in the chronic form of the disease, when the patient may present with megaloblastic anemia or neuropathy due to cobalamin deficiency. Absorption of cobalamin usually improves after antibiotic therapy and, in the early stages, folic acid therapy.

Fish tapeworm infestation

The fish tapeworm (Diphyllobothrium latum) lives in the small intestine of humans and accumulates cobalamin from food, rendering the cobalamin unavailable for absorption. Individuals acquire the worm by eating raw or partly cooked fish. Infestation is common around the lakes of Scandinavia, Germany, Japan, North America, and Russia. Megaloblastic anemia or cobalamin neuropathy occurs only in those with a heavy infestation.

Gluten-induced enteropathy

Malabsorption of cobalamin occurs in ~30% of untreated patients (presumably those in whom the disease extends to the ileum). Cobalamin deficiency is not severe in these patients and is corrected with a gluten-free diet.

Severe chronic pancreatitis

In this condition, lack of trypsin is thought to cause dietary cobalamin attached to gastric non-IF (R) binder to be unavailable for absorption. It also has been proposed that in pancreatitis, the concentration of calcium ions in the ileum falls below the level needed to maintain normal cobalamin absorption.

HIV infection

Serum cobalamin levels tend to fall in patients with HIV infection and are subnormal in 10–35% of those with AIDS. Malabsorption of cobalamin not corrected by IF has been shown in some, but not all, patients with subnormal serum cobalamin levels. Cobalamin deficiency sufficiently severe to cause megaloblastic anemia or neuropathy is rare.

Zollinger-ellison syndrome

Malabsorption of cobalamin has been reported in the Zollinger-Ellison syndrome. It is thought that there is a failure to release cobalamin from R-binding protein due to inactivation of pancreatic trypsin by high acidity, as well as interference with IF binding of cobalamin.

Radiotherapy

Both total-body irradiation and local radiotherapy to the ileum (e.g., as a complication of radiotherapy for carcinoma of the cervix) may cause malabsorption of cobalamin.

Graft-versus-host disease

T is commonly affects the small intestine. Malabsorption of cobalamin due to abnormal gut fora, as well as damage to ileal mucosa, is common.

Drugs

T e drugs that have been reported to cause malabsorption of cobalamin are listed in 34-4. However, megaloblastic anemia due to these drugs is rare.

ABNORMALITIES OF COBALAMIN METABOLISM

Congenital transcobalamin II deficiency or abnormality

Infants with TC II deficiency usually present with megaloblastic anemia within a few weeks of birth. Serum cobalamin and folate levels are normal, but the anemia responds to massive (e.g., 1 mg three times weekly) injections of cobalamin. Some cases show neurologic complications. T e protein may be present but functionally inert. Genetic abnormalities found include mutations of an intra-exonic cryptic splice site, extensive deletion, single nucleotide deletion, nonsense mutation, and an RNA editing defect. Malabsorption of cobalamin occurs in all cases, and serum immunoglobulins are usually reduced. Failure to institute adequate cobalamin therapy or treatment with folic acid may lead to neurologic damage.

Congenital methylmalonic acidemia and aciduria

Infants with this abnormality are ill from birth with vomiting, failure to thrive, severe metabolic acidosis, ketosis, and mental retardation. Anemia, if present, is normocytic and normoblastic. T e condition may be due to a functional defect in either mitochondrial methylmalonyl CoA mutase or its cofactor adocobalamin. Mutations in the methylmalonyl CoA mutase are

not responsive, or only poorly responsive, to treatment with cobalamin. A proportion of infants with failure of adocobalamin synthesis respond to cobalamin in large doses. Some children have combined methylmalonic aciduria and homocystinuria due to defective formation of both cobalamin coenzymes. T is usually presents in the first year of life with feeding difficulties, developmental delay, microcephaly, seizures, hypotonia, and megaloblastic anemia.

Acquired abnormality of cobalamin metabolism: nitrous oxide inhalation

Nitrous oxide (N_2O) irreversibly oxidizes methylcobalamin to an inactive precursor; this inactivates methionine synthase. Megaloblastic anemia has occurred in patients undergoing prolonged N_2O anesthesia (e.g., in intensive care units). A neuropathy resembling cobalamin neuropathy has been described in dentists and anesthetists who are exposed repeatedly to N_2O. Methylmalonic aciduria does not occur as adocobalamin is not inactivated by N_2O.

CAUSES OF FOLATE DEFICIENCY

(Table 9-5)

NUTRITIONAL

Dietary folate deficiency is common. Indeed, in most patients with folate deficiency a nutritional element is present. Certain individuals are particularly prone to have diets containing inadequate amounts of folate (Table 9-5). In the United States and other countries where fortification of the diet with folic acid has been adopted, the prevalence of folate deficiency has dropped dramatically and is now almost restricted to high-risk groups with increased folate needs. Nutritional folate deficiency occurs in kwashiorkor and scurvy and in infants with repeated infections or those who are fed solely on goats' milk, which has a low folate content.

MALABSORPTION

Malabsorption of dietary folate occurs in tropical sprue and in gluten-induced enteropathy. In the rare congenital recessive syndrome of selective malabsorption of folate due to mutation of the proton-coupled folate transporter (PCFT), there is an associated defect of folate transport into the cerebrospinal fuid, and these patients show megaloblastic anemia, which responds to physiologic doses of folic acid given parenterally but not orally. T ey also show mental retardation, convulsions, and other central nervous system abnormalities. Minor degrees of malabsorption may also occur after jejunal resection or partial gastrectomy, in Crohn's disease, and in systemic infections, but in these conditions, if severe deficiency occurs, it is usually largely due to poor nutrition. Malabsorption of folate has been described in patients receiving sulfasalazine (Salazopyrin), cholestyramine, and triamterene.

TABLE 9-5

CAUSES OF FOLATE DEFICIENCY

- Dietary[a]
  - Particularly in: old age, infancy, poverty, alcoholism, chronic invalids, and the psychiatrically disturbed; may be associated with scurvy or kwashiorkor
- Malabsorption
  - Major causes of deficiency
    - Tropical sprue, gluten-induced enteropathy in children and adults, and in association with dermatitis herpetiformis, specific malabsorption of folate, intestinal megaloblastosis caused by severe cobalamin or folate deficiency
  - Minor causes of deficiency
    - Extensive jejunal resection, Crohn's disease, partial gastrectomy, congestive heart failure, Whipple's disease, scleroderma, amyloid, diabetic enteropathy, systemic bacterial infection, lymphoma, sulfasalazine (Salazopyrin)
- Excess utilization or loss
  - Physiologic
    - Pregnancy and lactation, prematurity
  - Pathologic
    - Hematologic diseases: chronic hemolytic anemias, sickle cell anemia, thalassemia major, myelofibrosis
    - Malignant diseases: carcinoma, lymphoma, leukemia, myeloma
    - Inf ammatory diseases: tuberculosis, Crohn's disease, psoriasis, exfoliative dermatitis, malaria
    - Metabolic disease: homocystinuria
    - Excess urinary loss: congestive heart failure, active liver disease
    - Hemodialysis, peritoneal dialysis
- Antifolate drugs[b]
  - Anticonvulsant drugs (phenytoin, primidone, barbiturates), sulfasalazine
  - Nitrofurantoin, tetracycline, antituberculosis (less well documented)
- Mixed causes
  - Liver diseases, alcoholism, intensive care units

[a]In severely folate-deficient patients with causes other than those listed under Dietary, poor dietary intake is often present.
[b]Drugs inhibiting dihydrofolate reductase are discussed in the text.

EXCESS UTILIZATION OR LOSS

Pregnancy

Folate requirements are increased by 200–300 μg to ~400 μg daily in a normal pregnancy, partly because of transfer of the vitamin to the fetus but mainly because of increased folate catabolism due to cleavage of folate coenzymes in rapidly proliferating tissues. Megaloblastic

anemia due to this deficiency is prevented by prophylactic folic acid therapy. It occurred in 0.5% of pregnancies in the UK and other Western countries before prophylaxis with folic acid, but the incidence is much higher in countries where the general nutritional status is poor.

Prematurity

A newborn infant, whether full term or premature, has higher serum and red cell folate concentrations than does an adult. However, a newborn infant's demand for folate has been estimated to be up to 10 times that of adults on a weight basis, and the neonatal folate level falls rapidly to the lowest values at about 6 weeks of age. The falls are steepest and are liable to reach subnormal levels in premature babies, a number of whom develop megaloblastic anemia responsive to folic acid at about 4–6 weeks of age. This occurs particularly in the smallest babies (<1500 g birth weight) and those who have feeding difficulties or infections or have undergone multiple exchange transfusions. In these babies, prophylactic folic acid should be given.

Hematologic disorders

Folate deficiency frequently occurs in chronic hemolytic anemia, particularly in sickle cell disease, autoimmune hemolytic anemia, and congenital spherocytosis. In these and other conditions of increased cell turnover (e.g., myelofibrosis, malignancies), folate deficiency arises because it is not completely reutilized after performing coenzyme functions.

Inflammatory conditions

Chronic inflammatory diseases such as tuberculosis, rheumatoid arthritis, Crohn's disease, psoriasis, exfoliative dermatitis, bacterial endocarditis, and chronic bacterial infections cause deficiency by reducing the appetite and increasing the demand for folate. Systemic infections also may cause malabsorption of folate. Severe deficiency is virtually confined to the patients with the most active disease and the poorest diet.

Homocystinuria

This is a rare metabolic defect in the conversion of homocysteine to cystathionine. Folate deficiency occurring in most of these patients may be due to excessive utilization because of compensatory increased conversion of homocysteine to methionine.

Long-term dialysis

Because folate is only loosely bound to plasma proteins, it is easily removed from plasma by dialysis. In patients with anorexia, vomiting, infections, and hemolysis, folate stores are particularly likely to become depleted. Routine folate prophylaxis is now given.

Congestive heart failure, liver disease

Excess urinary folate losses of >100 μg per day may occur in some of these patients. The explanation appears to be release of folate from damaged liver cells.

ANTIFOLATE DRUGS

A large number of epileptics who are receiving long-term therapy with phenytoin or primidone, with or without barbiturates, develop low serum and red cell folate levels. The exact mechanism is unclear. Alcohol may also be a folate antagonist, as patients who are drinking spirits may develop megaloblastic anemia that will respond to normal quantities of dietary folate or to physiologic doses of folic acid only if alcohol is withdrawn. Macrocytosis of red cells is associated with chronic alcohol intake even when folate levels are normal. Inadequate folate intake is the major factor in the development of deficiency in spirit-drinking alcoholics. Beer is relatively folate-rich in some countries, depending on the technique used for brewing.

The drugs that inhibit DHF reductase include methotrexate, pyrimethamine, and trimethoprim. Methotrexate has the most powerful action against the human enzyme, whereas trimethoprim is most active against the bacterial enzyme and is likely to cause megaloblastic anemia only when used in conjunction with sulfamethoxazole in patients with preexisting folate or cobalamin deficiency. The activity of pyrimethamine is intermediate. The antidote to these drugs is folinic acid (5-formyl-THF).

CONGENITAL ABNORMALITIES OF FOLATE METABOLISM

Some infants with congenital defects of folate enzymes (e.g., cyclohydrolase or methionine synthase) have had megaloblastic anemia.

DIAGNOSIS OF COBALAMIN AND FOLATE DEFICIENCIES

The diagnosis of cobalamin or folate deficiency has traditionally depended on the recognition of the relevant abnormalities in the peripheral blood and analysis of the blood levels of the vitamins.

COBALAMIN DEFICIENCY

Serum cobalamin

This is measured by an automated enzyme-linked immunosorbent assay (ELISA) or competitive-binding

luminescence assay (CBLA). Normal serum levels range from 118–148 pmol/L (160–200 ng/L) to ~738 pmol/L (1000 ng/L). In patients with megaloblastic anemia due to cobalamin deficiency, the level is usually <74 pmol/L (100 ng/L). In general, the more severe the deficiency, the lower is the serum cobalamin level. In patients with spinal cord damage due to the deficiency, levels are very low even in the absence of anemia. Values between 74 and 148 pmol/L (100 and 200 ng/L) are regarded as borderline. They may occur, for instance, in pregnancy, in patients with megaloblastic anemia due to folate deficiency. They may also be due to heterozygous, homozygous, or compound heterozygous mutations of the gene TCN1 that codes for haptocorrin (transcobalamin I). There is no clinical or hematologic abnormality. The serum cobalamin level is sufficiently robust, cost-effective, and most convenient to rule out cobalamin deficiency in the vast majority of patients suspected of having this problem. However, problems have arisen with commercial CBLA assays involving intrinsic factor in PA patients with intrinsic antibodies in serum. These antibodies may cause false normal serum vitamin B_{12} levels in up to 50% of cases tested. Where clinical indications of PA are strong, a normal serum vitamin B_{12} does not rule out the diagnosis. Serum MMA levels will be elevated in PA (see below).

Serum methylmalonate and homocysteine

In patients with cobalamin deficiency sufficient to cause anemia or neuropathy, the serum MMA level is raised. Sensitive methods for measuring MMA and homocysteine in serum have been introduced and recommended for the early diagnosis of cobalamin deficiency, even in the absence of hematologic abnormalities or subnormal levels of serum cobalamin. Serum MMA levels fluctuate, however, in patients with renal failure. Mildly elevated serum MMA and/or homocysteine levels occur in up to 30% of apparently healthy volunteers, with serum cobalamin levels up to 258 pmol/L (350 ng/L) and normal serum folate levels; 15% of elderly subjects, even with cobalamin levels >258 pmol/L (>350 ng/L), have this pattern of raised metabolite levels. These findings bring into question the exact cutoff points for normal MMA and homocysteine levels. It is also unclear at present whether these mildly raised metabolite levels have clinical consequences.

Serum homocysteine is raised in both early cobalamin and folate deficiency but may be raised in other conditions, e.g., chronic renal disease, alcoholism, smoking, pyridoxine deficiency, hypothyroidism, and therapy with steroids, cyclosporine, and other drugs. Levels are also higher in serum than in plasma, in men than in premenopausal women, in women taking hormone replacement therapy or in oral contraceptive users, and in elderly persons and patients with several inborn errors of metabolism affecting enzymes in transsulfuration pathways of homocysteine metabolism. Thus, homocysteine levels must be carefully interpreted for diagnosis of cobalamin or folate deficiency.

Tests for the cause of cobalamin deficiency

Only vegans, strict vegetarians, or people living on a totally inadequate diet will become vitamin B_{12} deficient because of inadequate intake. Studies of cobalamin absorption once were widely used, but difficulty in obtaining radioactive cobalamin and ensuring that IF preparations are free of viruses has made these tests obsolete. Tests to diagnose PA include serum gastrin, which is raised; serum pepsinogen I, which is low in PA (90–92%) but also in other conditions; and gastric endoscopy. Tests for IF and parietal cell antibodies are also used, as well as tests for individual intestinal diseases.

FOLATE DEFICIENCY

Serum folate

This is also measured by an ELISA technique. In most laboratories, the normal range is from 11 nmol/L (2 μg/L) to ~82 nmol/L (15 μg/L). The serum folate level is low in all folate-deficient patients. It also reflects recent diet. Because of this, serum folate may be low before there is hematologic or biochemical evidence of deficiency. Serum folate rises in severe cobalamin deficiency because of the block in conversion of MTHF to THF inside cells; raised levels have also been reported in the intestinal stagnant loop syndrome due to absorption of bacterially synthesized folate.

Red cell folate

The red cell folate assay is a valuable test of body folate stores. It is less affected than the serum assay by recent diet and traces of hemolysis. In normal adults, concentrations range from 880–3520 μmol/L (160–640 μg/L) of packed red cells. Subnormal levels occur in patients with megaloblastic anemia due to folate deficiency but also in nearly two-thirds of patients with severe cobalamin deficiency. False-normal results may occur if a folate-deficient patient has received a recent blood transfusion or if a patient has a raised reticulocyte count. Serum homocysteine assay is discussed earlier.

Tests for the cause of folate deficiency

The diet history is important. Tests for transglutaminase antibodies are performed to confirm or exclude celiac disease. If positive, duodenal biopsy is needed. An underlying disease causing increased folate breakdown should also be excluded.

TREATMENT Cobalamin and Folate Deficiency

It is usually possible to establish which of the two deficiencies, folate or cobalamin, is the cause of the anemia and to treat only with the appropriate vitamin. In patients who enter the hospital severely ill, however, it may be necessary to treat with both vitamins in large doses once blood samples have been taken for cobalamin and folate assays and a bone marrow biopsy has been performed (if deemed necessary). Transfusion is usually unnecessary and inadvisable. If it is essential, packed red cells should be given slowly, one or two units only, with the usual treatment for heart failure if present. Potassium supplements have been recommended to obviate the danger of the hypokalemia but are not necessary. Occasionally, an excessive rise in platelets occurs after 1–2 weeks of therapy. Antiplatelet therapy, e.g., aspirin, should be considered if the platelet count rises to >800 × 10^9/L.

COBALAMIN DEFICIENCY It is usually necessary to treat patients who have developed cobalamin deficiency with lifelong regular cobalamin injections. In the UK, the form used is hydroxocobalamin; in the United States, cyanocobalamin. In a few instances, the underlying cause of cobalamin deficiency can be permanently corrected, e.g., fish tapeworm, tropical sprue, or an intestinal stagnant loop that is amenable to surgery. T e indications for starting cobalamin therapy are a well-documented megaloblastic anemia or other hematologic abnormalities and neuropathy due to the deficiency. Patients with borderline serum cobalamin levels but no hematologic or other abnormality may be followed to make sure that the cobalamin deficiency does not progress (see below). If malabsorption of cobalamin or rises in serum MMA levels have been demonstrated, however, these patients also should be given regular maintenance cobalamin therapy. Cobalamin should be given routinely to all patients who have had a total gastrectomy or ileal resection. Patients who have undergone gastric reduction for control of obesity or who are receiving long-term treatment with proton pump inhibitors should be screened and, if necessary, given cobalamin replacement.

Replenishment of body stores should be complete with six 1000-μg IM injections of hydroxocobalamin given at 3- to 7-day intervals. More frequent doses are usually used in patients with cobalamin neuropathy, but there is no evidence that they produce a better response. Allergic reactions are rare and may require desensitization or antihistamine or glucocorticoid cover. For maintenance therapy, 1000 μg hydroxocobalamin IM once every 3 months is satisfactory. Because of the poorer retention of cyanocobalamin, protocols generally use higher and more frequent doses, e.g., 1000 μg IM, monthly, for maintenance treatment.

Because a small fraction of cobalamin can be absorbed passively through mucous membranes even when there is complete failure of physiologic IF-dependent absorption, large daily oral doses (1000–2000 μg) of cyanocobalamin have been used in PA for replacement and maintenance of normal cobalamin status in, e.g., food malabsorption of cobalamin. Sublingual therapy has also been proposed for those in whom injections are difficult because of a bleeding tendency and who may not tolerate oral therapy. If oral therapy is used, it is important to monitor compliance, particularly with elderly, forgetful patients. T is author prefers parenteral therapy for initial treatment, particularly in severe anemia or if a neuropathy is present, and for maintenance.

For treatment of patients with subnormal serum vitamin B12 (B12) levels with a normal MCV and no hypersegmentation of neutrophils, a negative IF antibody test in the absence of tests of B_{12} absorption is problematic. Some (perhaps 15%) cases may be due to TC I (HC) deficiency. Homocysteine and/or MMA measurements may help, but in the absence of these tests and with otherwise normal gastrointestinal function, repeat serum B_{12} assay after 6–12 months may help one decide whether to start cobalamin therapy.

Vitamin B_{12} injections are used in a wide variety of diseases, often neurologic, despite normal serum B_{12} and folate levels and a normal blood count and in the absence of randomized, double-blind, controlled trials. T ese conditions include multiple sclerosis and chronic fatigue syndrome/myalgic encephalomyelitis (ME). It seems probable that any benefit is due to the placebo effect of a usually painless, pink injection. In ME, oral B_{12} therapy, despite providing equally large amounts of B_{12}, has not been beneficial, supporting the view of the effect of the injections being placebo only.

FOLATE DEFICIENCY Oral doses of 5–15 mg folic acid daily are satisfactory, as sufficient folate is absorbed from these extremely large doses even in patients with severe malabsorption. T e length of time therapy must be continued depends on the underlying disease. It is customary to continue therapy for about 4 months, when all folate-deficient red cells will have been eliminated and replaced by new folate-replete populations.

Before large doses of folic acid are given, cobalamin deficiency must be excluded and, if present, corrected; otherwise cobalamin neuropathy may develop despite a response of the anemia of cobalamin deficiency to folate therapy. Studies in the United States, however, suggest that there is no increase in the proportion of individuals with low serum cobalamin levels and no anemia since food fortification with folic acid, but it is unknown if there has been a change in incidence of cobalamin neuropathy.

Long-term folic acid therapy is required when the underlying cause of the deficiency cannot be corrected and the deficiency is likely to recur, e.g., in chronic dialysis or hemolytic anemias. It may also be necessary in gluten-induced enteropathy that does not respond to a gluten-free diet. Where mild but chronic folate deficiency occurs, it is preferable to encourage improvement in the diet after correcting the deficiency with a short course of folic acid. In any patient receiving long-term folic acid therapy, it is important to measure the serum cobalamin level at regular (e.g., once-yearly) intervals to exclude the coincidental development of cobalamin deficiency.

Folinic Acid (5-Formyl-THF) This is a stable form of fully reduced folate. It is given orally or parenterally to overcome the toxic effects of methotrexate or other DHF reductase inhibitors, e.g., trimethoprim or cotrimoxazole.

PROPHYLACTIC FOLIC ACID Prophylactic folic acid is used in chronic dialysis patients and in parenteral feeds. Prophylactic folic acid has been used to reduce homocysteine levels to prevent cardiovascular disease and for cognitive function in the elderly, but there are no firm data to show any benefit.

Pregnancy In over 70 countries (but none in Europe), food is fortified with folic acid (in grain or flour) to reduce the risk of NTDs. Nevertheless, folic acid, 400 μg daily, should be given as a supplement before and throughout pregnancy to prevent megaloblastic anemia and reduce the incidence of NTDs, even in countries with fortification of the diet. The levels of fortification provide up to 400 μg daily on average in Chile, but in most countries, it is nearer to 200 μg, so periconceptual folic acid is still needed. Studies in early pregnancy show significant lack of compliance with the folic acid supplements, emphasizing the benefit of food fortification. Supplemental folic acid reduces the incidence of birth defects in babies born to diabetic mothers. In women who have had a previous fetus with an NTD, 5 mg daily is recommended when pregnancy is contemplated and throughout the subsequent pregnancy.

Infancy and Childhood The incidence of folate deficiency is so high in the smallest premature babies during the first 6 weeks of life that folic acid (e.g., 1 mg daily) should be given routinely to those weighing <1500 g at birth and to larger premature babies who require exchange transfusions or develop feeding difficulties, infections, or vomiting and diarrhea.

The World Health Organization currently recommends routine supplementation with iron and folic acid in children in countries where iron deficiency is common and child mortality, largely due to infectious diseases, is high. However, some studies suggest that in areas where malaria rates are high, this approach may increase the incidence of severe illness and death. Even where malaria is rare, there appears to be no survival benefit.

MEGALOBLASTIC ANEMIA NOT DUE TO COBALAMIN OR FOLATE DEFICIENCY OR ALTERED METABOLISM

This may occur with many antimetabolic drugs (e.g., hydroxyurea, cytosine arabinoside, 6-mercaptopurine) that inhibit DNA replication. Antiviral nucleoside analogues used in treatment of HIV infection may also cause macrocytosis and megaloblastic marrow changes. In the rare disease orotic aciduria, two consecutive enzymes in purine synthesis are defective. The condition responds to therapy with uridine, which bypasses the block. In thiamine-responsive megaloblastic anemia, there is a genetic defect in the high-affinity thiamine transport (SLC19A2) gene. This causes defective RNA ribose synthesis through impaired activity of transketolase, a thiamine-dependent enzyme in the pentose cycle. This leads to reduced nucleic acid production. It may be associated with diabetes mellitus and deafness and the presence of many ringed sideroblasts in the marrow. The explanation is unclear for megaloblastic changes in the marrow in some patients with acute myeloid leukemia and myelodysplasia.

CHAPTER 10

HEMOLYTIC ANEMIAS AND ANEMIA DUE TO ACUTE BLOOD LOSS

Lucio Luzzatto

DEFINITIONS

A finite life span is a distinct characteristic of red cells. Hence, a logical, time-honored classification of anemias is in three groups: (1) decreased production of red cells, (2) increased destruction of red cells, and (3) acute blood loss. Decreased production is covered in **Chaps. 7, 9, and 11**; increased destruction and acute blood loss are covered in this chapter.

All patients who are anemic as a result of either increased destruction of red cells or acute blood loss have one important element in common: the anemia results from overconsumption of red cells from the peripheral blood, whereas the supply of cells from the bone marrow is normal (indeed, it is usually increased). On the other hand, these two groups differ in that physical loss of red cells from the bloodstream or from the body itself, as in acute hemorrhage, is fundamentally different from destruction of red cells within the body, as in hemolytic anemias. T erefore, the clinical aspects and pathophysiology of anemia in these two groups of patients are quite different, and they will be considered separately.

HEMOLYTIC ANEMIAS

With respect to primary etiology, anemias due to increased destruction of red cells, which we know as hemolytic anemias (HAs), may be inherited or acquired; from a clinical point of view, they may be more acute or more chronic, and they may vary from mild to very severe; the site of hemolysis may be predominantly intravascular or extravascular. With respect to mechanisms, HAs may be due to intracorpuscular causes or to extracorpuscular causes **(Table 10-1)**. But before reviewing the individual types of HA, it is appropriate to consider what they have in common.

TABLE 10-1

CLASSIFICATION OF HEMOLYTIC ANEMIAS[a]

	INTRACORPUSCULAR DEFECTS	EXTRACORPUSCULAR FACTORS
Hereditary	Hemoglobinopathies Enzymopathies Membrane-cytoskeletal defects	Familial (atypical) hemolytic-uremic syndrome
Acquired	Paroxysmal nocturnal hemoglobinuria (PNH)	Mechanical destruction (microangiopathic) Toxic agents Drugs Infectious Autoimmune

[a]Hereditary causes correlate with intracorpuscular defects, because these defects are due to inherited mutations; the one exception is PNH, because the defect is due to an acquired somatic mutation. Similarly, acquired causes correlate with extracorpuscular factors, because mostly these factors are exogenous; the one exception is familial hemolytic-uremic syndrome (HUS; often referred to as atypical HUS), because here an inherited abnormality allows complement activation to be excessive, with bouts of production of membrane attack complex capable of destroying normal red cells.

GENERAL CLINICAL AND LABORATORY FEATURES

T e clinical presentation of a patient with anemia is greatly influenced in the first place by whether the onset is abrupt or gradual, and HAs are no exception. A patient with autoimmune HA or with favism may be a medical emergency, whereas a patient with mild hereditary spherocytosis or with cold agglutinin disease may be diagnosed after years. T is is due in large measure to the remarkable ability of the body to adapt to anemia when it is slowly progressing **(Chap. 2)**.

TABLE 10-2

FEATURES COMMON TO MOST PATIENTS WITH A HEMOLYTIC DISORDER	
General examination	Jaundice, pallor
Other physical findings	Spleen may be enlarged; bossing of skull in severe congenital cases
Hemoglobin level	From normal to severely reduced
MCV, MCH	Usually increased
Reticulocytes	Increased
Bilirubin	Increased (mostly unconjugated)
LDH	Increased (up to 10 time normal with intravascular hemolysis)
Haptoglobin	Reduced to absent (if hemolysis in part intravascular)

Abbreviations: LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume.

What differentiates HAs from other anemias is that the patient has signs and symptoms arising directly from hemolysis **(Table 10-2)**. At the clinical level, the main sign is jaundice; in addition, the patient may report discoloration of the urine. In many cases of HA, the spleen is enlarged, because it is a preferential site of hemolysis; and in some cases, the liver may be enlarged as well. In all severe congenital forms of HA, there may also be skeletal changes due to overactivity of the bone marrow (although they are never as severe as they are in thalassemia).

T e laboratory features of HA are related to hemolysis per se and the erythropoietic response of the bone marrow. Hemolysis regularly produces an increase in unconjugated bilirubin and aspartate aminotransferase (AST) in the serum; urobilinogen will be increased in both urine and stool. If hemolysis is mainly intravascular, the telltale sign is hemoglobinuria (often associated with hemosiderinuria); in the serum, there is hemoglobin, lactate dehydrogenase (LDH) is increased, and haptoglobin is reduced. In contrast, the bilirubin level may be normal or only mildly elevated. T e main sign of the erythropoietic response by the bone marrow is an increase in reticulocytes (a test all too often neglected in the initial workup of a patient with anemia). Usually the increase will be reflected in both the percentage of reticulocytes (the more commonly quoted figure) and the absolute reticulocyte count (the more definitive parameter). T e increased number of reticulocytes is associated with an increased mean corpuscular volume (MCV) in the blood count. On the blood smear, this is reflected in the presence of macrocytes; there is also polychromasia, and sometimes one sees nucleated red cells. In most cases, a bone marrow aspirate is not necessary in the diagnostic workup; if it is done, it will show erythroid hyperplasia. In practice, once an HA is suspected, specific tests will usually be required for a definitive diagnosis of a specific type of HA.

GENERAL PATHOPHYSIOLOGY

T e mature red cell is the product of a developmental pathway that brings the phenomenon of differentiation to an extreme. An orderly sequence of events produces synchronous changes, whereby the gradual accumulation of a huge amount of hemoglobin in the cytoplasm (to a final level of 340 g/L, i.e., about 5 mM) goes hand in hand with the gradual loss of cellular organelles and of biosynthetic abilities. In the end, the erythroid cell undergoes a process that has features of apoptosis, including nuclear pyknosis and actual loss of the nucleus. However, the final result is more altruistic than suicidal; the cytoplasmic body, instead of disintegrating, is now able to provide oxygen to all cells in the human organism for some remaining 120 days of the red cell life span.

As a result of this unique process of differentiation and maturation, intermediary metabolism is drastically curtailed in mature red cells **(Fig. 10-1)**; for instance, cytochrome-mediated oxidative phosphorylation has been lost with the loss of mitochondria (through a process of physiologic autophagy); therefore, there is no backup to anaerobic glycolysis, which in the red cell is the only provider of adenosine triphosphate (ATP). Also the capacity of making protein has been lost with the loss of ribosomes. T is places the cell's limited metabolic apparatus at risk, because if any protein component deteriorates, it cannot be replaced, as it would be in most other cells; and in fact the activity of most enzymes gradually decreases as red cells age. At the same time, during their long time in circulation, various red cell components inevitably accumulate damage; in senescent red cells, the membrane protein band 3 molecules (see below and Fig. 10-1), having bound hemichromes on their intracellular domains, tend to cluster. Now they bind anti–band 3 IgG antibodies (present in most people) and C3 complement fragments; thus they become opsonized and are eventually removed by phagocytosis in the reticuloendothelial system.

Another consequence of the relative simplicity of red cells is that they have a very limited range of ways to manifest distress under hardship; in essence, any sort of metabolic failure will eventually lead either to structural damage to the membrane or to failure of the cation pump. In either case, the life span of the red cell is reduced, which is the definition of a hemolytic disorder. If the rate of red cell destruction exceeds the capacity of the bone marrow to produce more red cells, the hemolytic disorder will manifest as HA.

T us, the essential pathophysiologic process common to all HAs is an increased red cell turnover; and in many HAs, this is due at least in part to an acceleration of the senescence process described above. T e gold standard for proving that the life span of red cells is reduced (compared to the normal value of about 120 days) is a red cell survival study, which can be carried

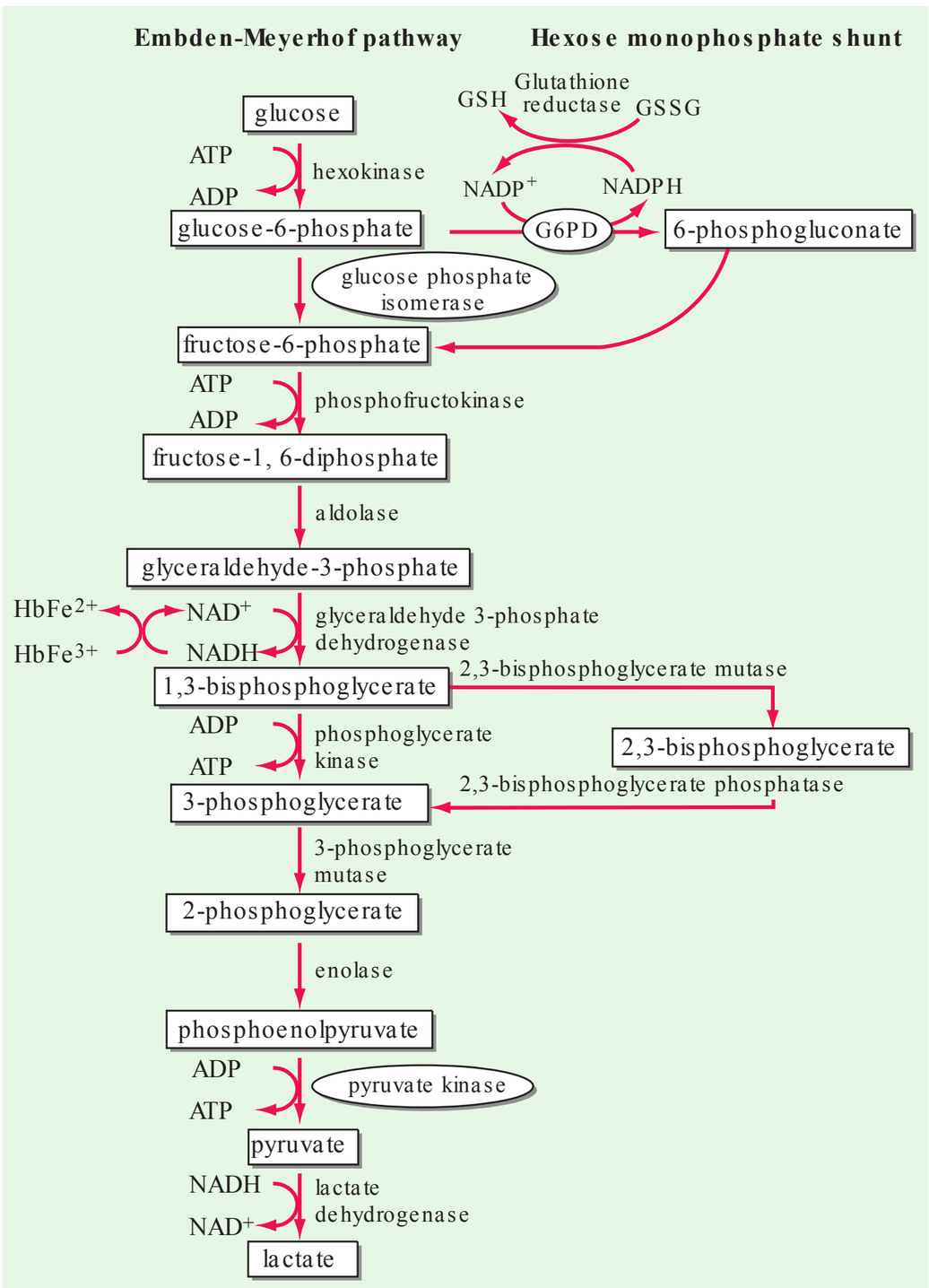


FIGURE 10-1
Red blood cell (RBC) metabolism. The Embden-Meyerhof pathway (glycolysis) generates ATP for energy and membrane maintenance. The generation of NADPH maintains hemoglobin in a reduced state. The hexose monophosphate shunt generates NADPH that is used to reduce glutathione, which protects the red cell against oxidant stress. Regulation of 2,3-bisphosphoglycerate levels is a critical determinant of oxygen affinity of hemoglobin. Enzyme deficiency states in order of prevalence: glucose 6-phosphate dehydrogenase (G6PD) > pyruvate kinase > glucose-6-phosphate isomerase > rare deficiencies of other enzymes in the pathway. The more common enzyme deficiencies are encircled.

out by labeling the red cells with ^{51}Cr and measuring residual radioactivity over several days or weeks: however, this classic test is now available in very few centers, and it is rarely necessary. If the hemolytic event is transient, it does not usually cause any long-term consequences, except for an increased requirement for erythropoietic factors, particularly folic acid. However, if hemolysis is recurrent or persistent, the increased bilirubin production favors the formation of gallstones. If a considerable proportion of hemolysis takes place in the spleen, as is often the case, splenomegaly may become increasingly a feature, and hypersplenism may develop, with consequent neutropenia and/or thrombocytopenia.

T e increased red cell turnover also has metabolic consequences. In normal subjects, the iron from effete red cells is very ef ciently recycled by the body; however, with chronic intravascular hemolysis, the persistent hemoglobinuria will cause considerable iron loss, needing replacement. With chronic extravascular hemolysis, the opposite problem, iron overload, is more common, especially if the patient needs frequent blood transfusions. Chronic iron overload will cause secondary hemochromatosis; this will cause damage particularly to the liver, eventually leading to cirrhosis, and to the heart muscle, eventually causing heart failure.

Compensated hemolysis versus hemolytic anemia

Red cell destruction is a potent stimulus for erythropoiesis, which is mediated by erythropoietin (EPO) produced by the kidney. T is mechanism is so effective that in many cases the increased output of red cells from the bone marrow can fully balance an increased destruction of red cells. In such cases, we say that hemolysis is compensated. T e pathophysiology of compensated hemolysis is similar to what we have just described, except there is no anemia. T is notion is important from the diagnostic point of view, because a patient with a hemolytic condition, even an inherited one, may present without anemia; and it is also important from the point of view of management, because compensated hemolysis may become "decompensated," i.e., anemia may suddenly appear, in certain circumstances, for instance in pregnancy, folate deficiency, or renal failure interfering with adequate EPO production. Another general feature of chronic HAs is seen when any intercurrent condition, such as an acute infection, depresses erythropoiesis. When this happens, in view of the increased rate of red cell turnover, the effect will be predictably much more marked than in a person who does not have hemolysis. T e most dramatic example is infection by parvovirus B19, which may cause a rather precipitous fall in hemoglobin—an occurrence sometimes referred to as aplastic crisis.

INHERITED HEMOLYTIC ANEMIAS

T ere are three essential components in the red cell: (1) hemoglobin, (2) the membrane-cytoskeleton complex, and (3) the metabolic machinery necessary to keep hemoglobin and the membrane-cytoskeleton complex in working order. Diseases caused by abnormalities of hemoglobin, or hemoglobinopathies, are covered in **Chap. 8**. Here we will deal with diseases of the other two components.

Hemolytic anemias due to abnormalities of the membrane-cytoskeleton complex

T e detailed architecture of the red cell membrane is complex, but its basic design is relatively simple **(Fig. 10-2)**.

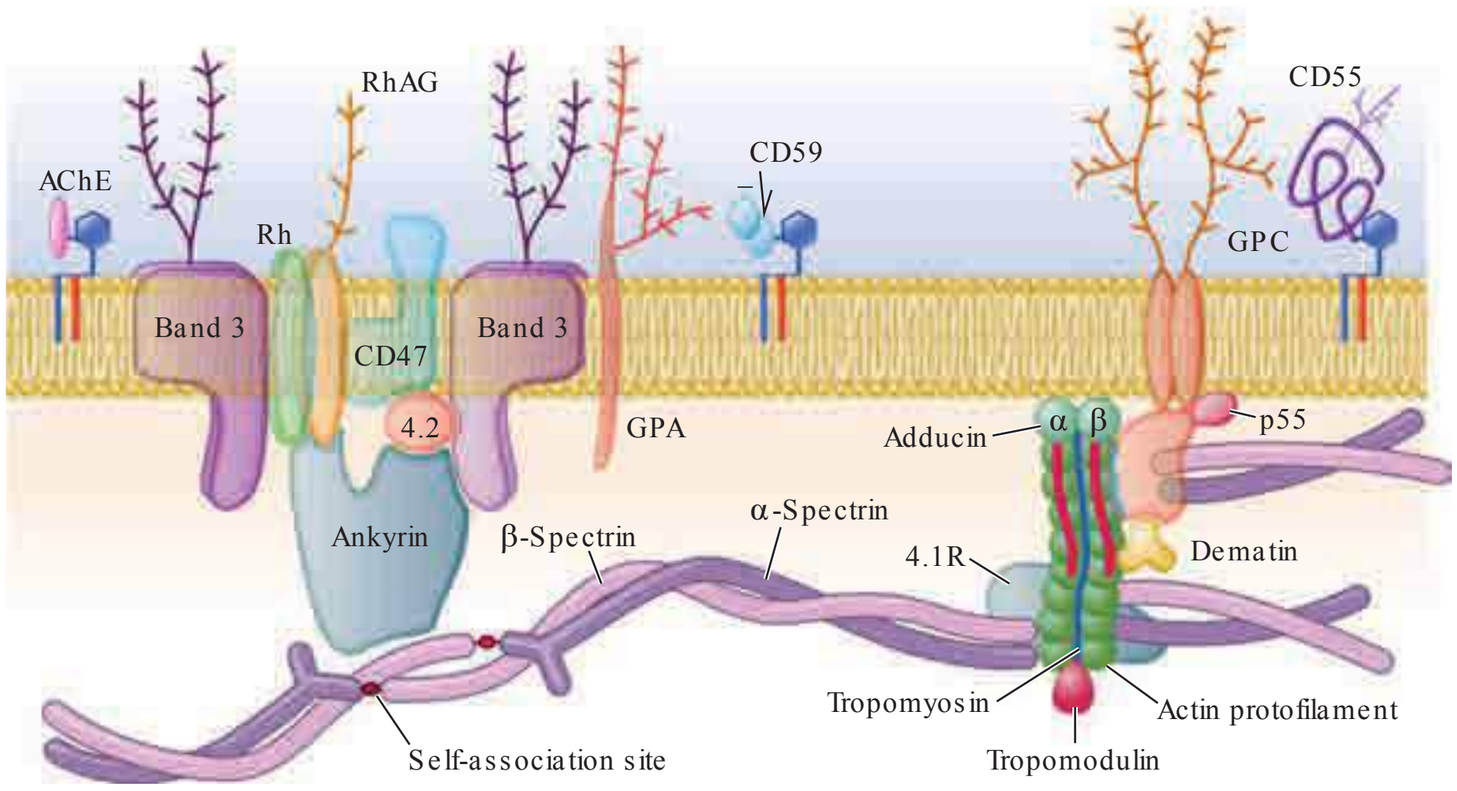


FIGURE 10-2
The red cell membrane. In this figure, one sees, within the lipid bilayer, several membrane proteins, of which band 3 (anion exchanger 1 [AE1]) is the most abundant; the α-β spectrin dimers that associate to form most of the cytoskeleton; and several proteins (e.g., ankyrin) that connect the membrane to the cytoskeleton. In addition, as examples of glycosylphosphatidylinositol (GPI)-linked proteins, one sees acetylcholinesterase (AChE) and the two complement-regulatory proteins CD59 and CD55. The (nonrealistic) shapes of the protein moieties of the GPI-linked proteins are meant to indicate that they can be very different from each other and that, unlike with the other membrane proteins shown, the entire polypeptide chain is extracellular. Branched lines symbolize carbohydrate moiety of proteins. The molecules are obviously not drawn to the same scale. Additional explanations can be found in the text. (From N Young et al: Clinical Hematology. Copyright Elsevier, 2006; with permission.)

T e lipid bilayer incorporates phospholipids and cholesterol, and it is spanned by a number of proteins that have their hydrophobic transmembrane domain(s) embedded in the membrane; most of these proteins also extend to both the outside (extracellular domains) and the inside of the cell (cytoplasmic domains). Other proteins are tethered to the membrane through a glycosylphosphatidylinositol (GPI) anchor; these have only an extracellular domain, and they include ion channels, receptors for complement components, and receptors for other ligands. T e most abundant red cell membrane proteins are glycophorins and the so-called band 3, an anion transporter. T e extracellular domains of many of these proteins are heavily glycosylated, and they carry antigenic determinants that correspond to blood groups. Underneath the membrane, and tangential to it, is a network of other proteins that make up the cytoskeleton. T e main cytoskeletal protein is spectrin, the basic unit of which is a dimer of α-spectrin and β-spectrin. T e membrane is physically linked to the cytoskeleton by a third set of proteins (including ankyrin and the so-called band 4.1 and band 4.2), which thus make these two structures intimately connected to each other.

T e membrane-cytoskeleton complex is so integrated that, not surprisingly, an abnormality of almost any of its components will be disturbing or disruptive, causing structural failure, which results ultimately in hemolysis. T ese abnormalities are almost invariably inherited mutations; thus, diseases of the membrane-cytoskeleton complex belong to the category of inherited HAs. Before the red cells lyse, they often exhibit more or less specific morphologic changes that alter the normal biconcave disk shape. T us, the majority of the diseases in this group have been known for over a century as hereditary spherocytosis and hereditary elliptocytosis. Over the past 20 years, their molecular basis has been elucidated; it has emerged that both conditions can arise from mutations in several genes with considerable overlap **(Fig. 10-3)**.

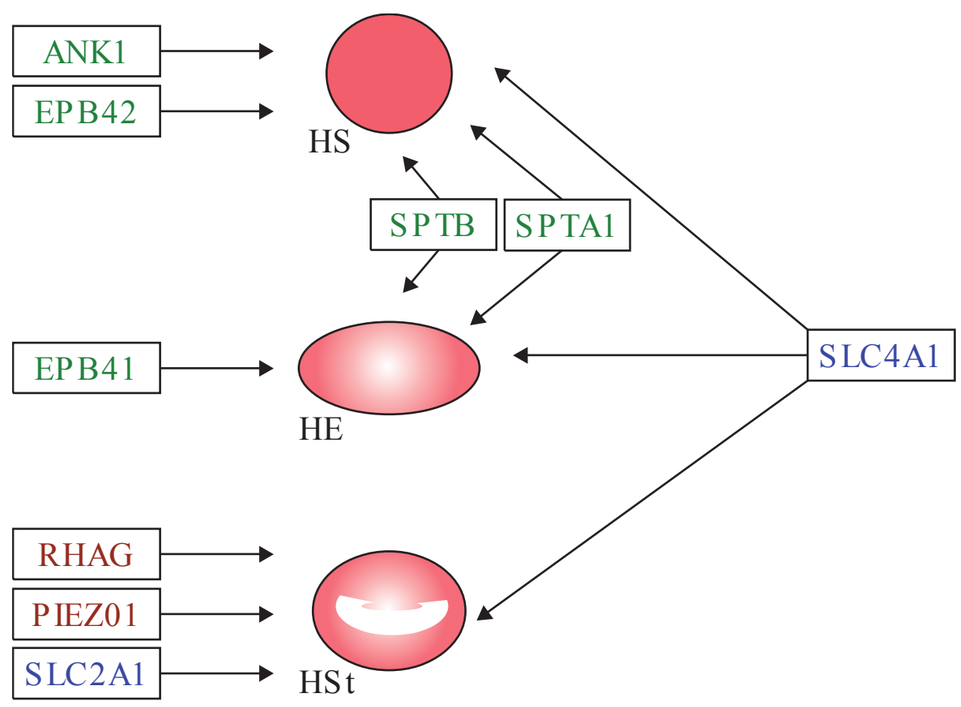


FIGURE 10-3
Hereditary spherocytosis (HS), hereditary elliptocytosis (HE), and hereditary stomatocytosis (HSt) are three morphologically distinct forms of congenital hemolytic anemia. It has emerged that each one can arise from mutation of one of several genes and that different mutations of the same gene can give one or another form. (See also Table 10-3.)

Hereditary spherocytosis (HS)

T is is a relatively common type of genetically determined HA, with an estimated frequency of at least 1 in 5000. Its identification is credited to Minkowksy and Chauffard, who, at the end of the nineteenth century, reported families who had the presence of numerous spherocytes in the peripheral blood **(Fig 10-4A)**. In vitro studies revealed that the red cells were abnormally susceptible to lysis in hypotonic media; indeed, the presence of osmotic fragility became the main diagnostic test for HS. Today we know that HS, thus defined, is genetically heterogeneous; i.e., it can arise from a variety of mutations in one of several genes **(Table 10-3)**. It has been also recognized that the inheritance of HS is not always autosomal dominant (with the patient being heterozygous); indeed, some of the most severe forms are instead autosomal recessive (with the patient being homozygous).

Clinical presentation and diagnosis

T e spectrum of clinical severity of HS is broad. Severe cases may present in infancy with severe anemia, whereas mild cases may present in young adults or even later in life. T e main clinical findings are jaundice, an enlarged spleen, and often gallstones; indeed, it may be the finding of gallstones in a young person that triggers diagnostic investigations.

T e variability in clinical manifestations that is observed among patients with HS is largely due to the different underlying molecular lesions (Table 10-3). Not only are mutations of several genes involved, but also individual mutations of the same gene can also give very different clinical manifestations. In milder cases, hemolysis is often compensated (see above), and this may cause variation in time even in the same patient, due to the fact that intercurrent conditions (e.g., pregnancy, infection) may cause decompensation. T e anemia is usually normocytic, with the characteristic morphology that gives the disease its name. An increased mean corpuscular hemoglobin concentration (MCHC) on an ordinary blood count report should raise the suspicion of HS, because HS is almost the only condition in which this abnormality occurs. It has been apparent for a long time that the spleen plays a special role in HS through a dual mechanism. On one hand, like in many other HAs, the spleen itself is a major site of destruction; on the other hand, transit through the splenic circulation makes the defective red cells more spherocytic and, therefore, accelerates their demise, even though that may take place elsewhere.

When there is a family history, it is usually easy to make a diagnosis based on features of HA and typical red cell morphology. However, there may be no family history for at least two reasons. First, the patient may have a de novo mutation, i.e., a mutation that has taken place in a germ cell of one of his parents or early after zygote formation. Second, the patient may have a

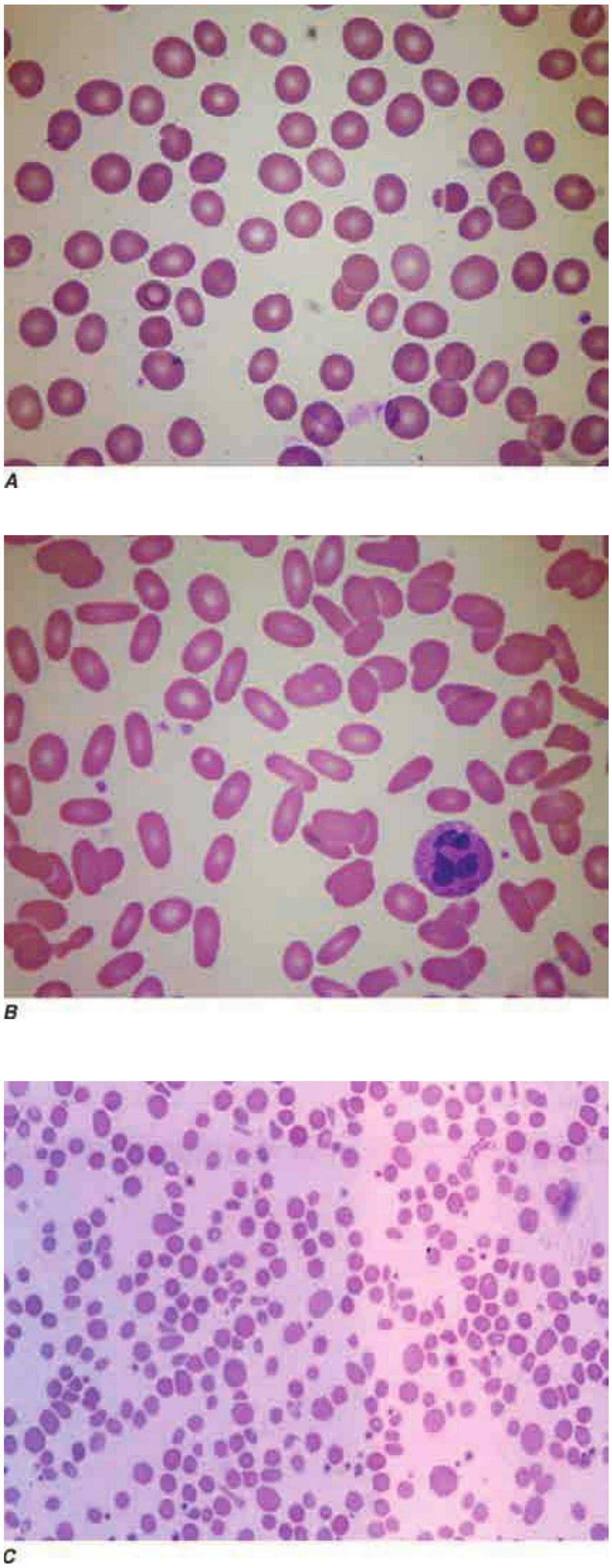


FIGURE 10-4
Peripheral blood smear from patients with membrane-cytoskeleton abnormalities. A. Hereditary spherocytosis. B. Hereditary elliptocytosis, heterozygote. C. Elliptocytosis, with both alleles of the α-spectrin gene mutated.

TABLE 10-3

INHERITED DISEASES OF THE RED CELL MEMBRANE-CYTOSKELETON COMPLEX

GENE	CHROMOSOMAL LOCATION	PROTEIN PRODUCED	DISEASE(S) WITH CERTAIN MUTATIONS (INHERITANCE)	COMMENTS
SPTA1	1q22-q23	α-Spectrin	HS (recessive) HE (dominant)	Rare Mutations of this gene account for about 65% of HE. More severe forms may be due to coexistence of an otherwise silent mutant allele.
SPTB	14q23-q24.1	β-Spectrin	HS (dominant) HE (dominant)	Rare Mutations of this gene account for about 30% of HE, including some severe forms.
ANK1	8p11.2	Ankyrin	HS (dominant)	May account for majority of HS.
SLC4A1	17q21	Band 3; also known as AE (anion exchanger) or AE1	HS (dominant) Southeast Asia ovalocytosis (dominant) Stomatocytosis	Mutations of this gene may account for about 25% of HS. Polymorphic mutation (deletion of 9 amino acids); clinically asymptomatic; protective against Plasmodium falciparum. Certain specific missense mutations shift protein function from anion exchanger to cation conductance.
EPB41	1p33-p34.2	Band 4.1	HE (dominant)	Mutations of this gene account for about 5% of HE, mostly with prominent morphology but no hemolysis in heterozygotes; severe hemolysis in homozygotes.
EPB42	15q15-q21	Band 4.2	HS (recessive)	Mutations of this gene account for about 3% of HS.
RHAG	6p21.1-p11	Rhesus antigen	Chronic nonspherocytic hemolytic anemia (recessive)	Very rare; associated with total loss of all Rh antigens. A specific mutation causes overhydrated stomatocytosis.
PIEZO1	16q23-q24	PIEZO1	Dehydrated hereditary stomatocytosis (dominant)	Also known as xerocytosis with pseudohyperkalemia. Patients may present with perinatal edema. PIEZO1 is a mechanosensitive cation channel.

Abbreviations: HE, hereditary elliptocytosis; HS, hereditary spherocytosis.

recessive form of HS (Table 10-3). In such cases, more extensive laboratory investigations are required, including osmotic fragility, the acid glycerol lysis test, the eosin-5′-maleimide (EMA)–binding test, and SDS-gel electrophoresis of membrane proteins; these tests are usually carried out in laboratories with special expertise in this area. Sometimes a definitive diagnosis can be obtained only by molecular studies demonstrating a mutation in one of the genes underlying HS (Table 10-3).

TREATMENT Hereditary Spherocytosis

We do not have a causal treatment for HS; i.e., no way has yet been found to correct the basic defect in the membrane-cytoskeleton structure. Given the special role of the spleen in HS (see above), it has long been thought that an almost obligatory therapeutic measure was splenectomy. Because this operation may have more than trivial consequences, today we have more articulate recommendations, based on disease severity (having found out, whenever possible, about the outcome of splenectomy in the patient's relatives with HS), as follows. In mild cases, avoid splenectomy. Delay splenectomy until puberty in moderate cases or until 4–6 years of age in severe cases. Antipneumococcal vaccination before splenectomy is imperative, whereas penicillin prophylaxis after splenectomy is controversial. Along with splenectomy, cholecystectomy should not be regarded as automatic; it should be carried out, usually by the laparoscopic approach, when clinically indicated.

Hereditary elliptocytosis (HE)

HE is at least as heterogeneous as HS, both from the genetic point of view (Table 10-3, Fig. 10-3) and from

the clinical point of view. Again, it is the shape of the red cells **(Fig. 10-4B)** that gives the name to the condition, but there is no direct correlation between the elliptocytic morphology and clinical severity. In fact, some mild or even asymptomatic cases may have nearly 100% elliptocytes, whereas in severe cases, all kinds of bizarre poikilocytes can predominate. Clinical features and recommended management are similar to those outlined above for HS. Although the spleen may not have the specific role it has in HS, in severe cases, splenectomy may be beneficial. T e prevalence of HE causing clinical disease is similar to that of HS. However, an in-frame deletion of nine amino acids in the SLC4A1 gene encoding band 3, causing the so-called Southeast Asia ovalocytosis, has a frequency of up to 7% in certain populations, presumably as a result of malaria selection; it is asymptomatic in heterozygotes and probably lethal in homozygotes.

Disorders of cation transport

T ese rare conditions with autosomal dominant inheritance are characterized by increased intracellular sodium in red cells, with concomitant loss of potassium; indeed, they are sometimes discovered through the incidental finding, in a blood test, of a high serum K^+ (pseudohyperkalemia). In patients from some families, the cation transport disturbance is associated with gain of water; as a result, the red cells are overhydrated (low MCHC), and on a blood smear, the normally round-shaped central pallor is replaced by a linear-shaped central pallor, which has earned this disorder the name stomatocytosis (Fig. 10-3). In patients from other families, instead, the red cells are dehydrated (high MCHC), and their consequent rigidity has earned this disorder the name xerocytosis. One would surmise that in these disorders the primary defect may be in a cation transporter; indeed, xerocytosis results from mutations in PIEZO1. In other patients with stomatocytosis, mutations are found in other genes also related to solute transport (Table 10-3), including SLC4A1 (encoding band 3), the Rhesus gene RHAG, and the glucose transporter gene SLC2A1 responsible for a special form called cryohydrocytosis. Hemolysis can vary from relatively mild to quite severe. From the practical point of view, it is important to know that in stomatocytosis, splenectomy is strongly contraindicated because it has been followed in a significant proportion of cases by severe thromboembolic complications.

Enzyme abnormalities

When there is an important defect in the membrane or in the cytoskeleton, hemolysis is a direct consequence of the fact that the very structure of the red cell is abnormal. Instead, when one of the enzymes is defective, the consequences will depend on the precise role of that enzyme in the metabolic machinery of the red cell, which, in first approximation, has two important functions: (1) to provide energy in the form of ATP and (2) to prevent oxidative damage to hemoglobin and to other proteins by providing suf cient reductive potential; the key molecule for this is NADPH.

Abnormalities of the glycolytic pathway

Because red cells, in the course of their differentiation, have sacrificed not only their nucleus and their ribosomes, but also their mitochondria, they rely exclusively on the anaerobic portion of the glycolytic pathway for producing energy in the form of ATP. Most of the ATP is required by the red cell for cation transport against a concentration gradient across the membrane. If this fails, due to a defect of any of the enzymes of the glycolytic pathway **(Table 10-4)**, the result will be hemolytic disease.

Pyruvate kinase def ciency

Abnormalities of the glycolytic pathway are all inherited and all rare. Among them, deficiency of pyruvate kinase (PK) is the least rare, with an estimated prevalence in most populations of the order of 1:10,000. However, very recently, a polymorphic PK mutation (E277K) was found in some African populations, with heterozygote frequencies of 1–7%, suggesting that this may be another malaria-related polymorphism. T e clinical picture of homozygous (or compound biallelic) PK deficiency is that of an HA that often presents in the newborn with neonatal jaundice; the jaundice persists, and it is usually associated with a very high reticulocytosis. T e anemia is of variable severity; sometimes it is so severe as to require regular blood transfusion treatment, whereas sometimes it is mild, bordering on a nearly compensated hemolytic disorder. As a result, the diagnosis may be delayed, and in some cases, it is made, for instance, in a young woman during her first pregnancy, when the anemia may get worse. T e delay in diagnosis may be also helped by the fact that the anemia is remarkably well tolerated, because the metabolic block at the last step in glycolysis causes an increase in bisphosphoglycerate (or DPG; Fig. 10-1), a major effector of the hemoglobin-oxygen dissociation curve; thus, the oxygen delivery to the tissues is enhanced, a remarkable compensatory feat.

TREATMENT Pyruvate Kinase Def ciency

T e management of PK deficiency is mainly supportive. In view of the marked increase in red cell turnover, oral folic acid supplements should be given constantly. Blood transfusion should be used as necessary, and iron chelation may have to be added if the blood transfusion requirement is high enough to cause iron overload. In these patients, who have more severe disease, splenectomy may be beneficial. T ere is a single case report of curative treatment of PK deficiency

TABLE 10-4

RED CELL ENZYME ABNORMALITIES CAUSING HEMOLYSIS

	ENZYME (ACRONYM)	CHROMOSOMAL LOCATION	PREVALENCE OF ENZYME DEFICIENCY (RANK)	CLINICAL MANIFESTATIONS EXTRA-RED CELL	COMMENTS
Glycolytic Pathway	Hexokinase (HK)	10q22	Very rare		Other isoenzymes known
	Glucose 6-phosphate isomerase (G6PI)	19q31.1	Rare (4)[a]	NM, CNS	
	Phosphofructokinase (PFK)	12q13	Very rare	Myopathy	
	Aldolase	16q22-24	Very rare		
	Triose phosphate isomerase (TPI)	12p13	Very rare	CNS (severe), NM	
	Glyceraldehyde 3-phosphate dehydrogenase (GAPD)	12p13.31-p13.1	Very rare	Myopathy	
	Diphosphoglycerate mutase (DPGM)	7q31-q34	Very rare		Erythrocytosis rather than hemolysis
	Phosphoglycerate kinase (PGK)	Xq13	Very rare	CNS, NM	May benefit from splenectomy
	Pyruvate kinase (PK)	1q21	Rare (2)[a]		May benefit from splenectomy
Redox	Glucose 6-phosphate dehydrogenase (G6PD)	Xq28	Common (1)[a]	Very rarely granulocytes	In almost all cases, only AHA from exogenous trigger
	Glutathione synthase	20q11.2	Very rare	CNS	
	γ-Glutamylcysteine synthase	6p12	Very rare	CNS	
	Cytochrome b5 reductase	22q13.31-qter	Rare	CNS	Methemoglobinemia rather than hemolysis
Nucleotide Metabolism	Adenylate kinase (AK)	9q34.1	Very rare	CNS	
	Pyrimidine 5′-nucleotidase (P5N)	3q11-q12	Rare (3)[a]		May benefit from splenectomy

[a]The numbers from (1) to (4) indicate the ranking order of these enzymopathies in terms of frequency.
Abbreviations: AHA, acquired hemolytic anemia; CNS, central nervous system; NM, neuromuscular.

by bone marrow transplantation from an HLA-identical PK-normal sibling. T is seems a viable option for severe cases when a sibling donor is available. Rescue of inherited PK deficiency through lentiviral-mediated human PK gene transfer has been successful in mice. Prenatal diagnosis has been carried out in a mother who had already had an affected child.

Other glycolytic enzyme abnormalities

All of these defects are rare to very rare (Table 10-4), and all cause hemolytic anemia with varying degrees of severity. It is not unusual for the presentation to be in the guise of severe neonatal jaundice, which may require exchange transfusion; if the anemia is less severe, it may present later in life, or it may even remain asymptomatic and be detected incidentally when a blood count is done for unrelated reasons. T e spleen is often enlarged. When other systemic manifestations occur, they can involve the central nervous system (sometimes entailing severe mental retardation, particularly in the case of triose phosphate isomerase deficiency), the neuromuscular system, or both. T is is not altogether surprising, if we consider that these are housekeeping genes. T e diagnosis of hemolytic anemia is usually not dif cult, thanks to the triad of normomacrocytic anemia, reticulocytosis, and hyperbilirubinemia. Enzymopathies should be considered in the differential diagnosis of any chronic Coombs-negative hemolytic anemia. Unlike with membrane disorders where the red cells show characteristic morphologic abnormalities, in most cases of glycolytic enzymopathies, these are conspicuous by their absence. A definitive diagnosis can be made only by demonstrating the deficiency of an individual enzyme by quantitative assays; these are carried out in only a few specialized laboratories. If a particular molecular abnormality is already known in the family, then one could test directly for that defect at the DNA level, thus bypassing the need for enzyme assays. Of course the time may be getting nearer when a patient will present with her or his exome already sequenced, and we will need to concentrate on which genes to look up within the file. T e

principles for the management of these conditions are similar as for PK deficiency. In one case of phosphoglycerate kinase deficiency, allogeneic bone marrow transplantation (BMT) effectively controlled the hematologic manifestations but did not reverse neurologic damage.

Abnormalities of redox metabolism

Glucose 6-phosphate dehydrogenase (G6PD) deficiency

G6PD is a housekeeping enzyme critical in the redox metabolism of all aerobic cells (Fig. 10-1). In red cells, its role is even more critical, because it is the only source of NADPH, which directly and via glutathione (GSH) defends these cells against oxidative stress (Fig. 10-5). G6PD deficiency is a prime example of an HA due to interaction between an intracorpuscular cause and an extracorpuscular cause, because in the majority of cases hemolysis is triggered by an exogenous agent. Although a decrease in G6PD activity is present in most tissues of G6PD-deficient subjects, in other cells, the decrease is much less marked than in red cells, and it does not seem to impact on clinical expression.

GENETIC CONSIDERATIONS

The G6PD gene is X-linked, and this has important implications. First, because males have only one G6PD gene (i.e., they are hemizygous for this gene), they must be either normal or G6PD deficient. By contrast, females, who have two G6PD genes, can be either normal or deficient (homozygous) or intermediate (heterozygous). As a result of the phenomenon of X chromosome inactivation, heterozygous females are genetic mosaics, with a highly variable ratio of G6PD-normal to G6PD-deficient cells and an equally variable degree of clinical expression; some heterozygotes can be just as affected as hemizygous males. The enzymatically active form of G6PD is either a dimer or a tetramer of a single protein subunit of 514 amino acids. G6PD-deficient subjects have been found invariably to have mutations in the coding region of the G6PD gene (Fig. 10-5). Almost all of the approximately 180 different mutations known are single missense point mutations, entailing single amino acid replacements in the G6PD protein. In most cases, these mutations cause G6PD deficiency by decreasing the in vivo stability of the protein; thus, the physiologic decrease in G6PD activity that takes place with red cell aging is greatly accelerated. In some cases, an amino acid replacement can also affect the catalytic function of the enzyme.

Among these mutations, those underlying chronic nonspherocytic hemolytic anemia (CNSHA; see below) are a discrete subset. The much more severe clinical phenotype can be ascribed in some cases to adverse qualitative changes (for instance, a decreased affinity for the substrate, glucose 6-phosphate) or simply to the fact that the enzyme deficit is more extreme, because of a more severe instability of the enzyme. For instance, a cluster of mutations map at or near the dimer interface, and clearly they compromise severely the formation of the dimer.

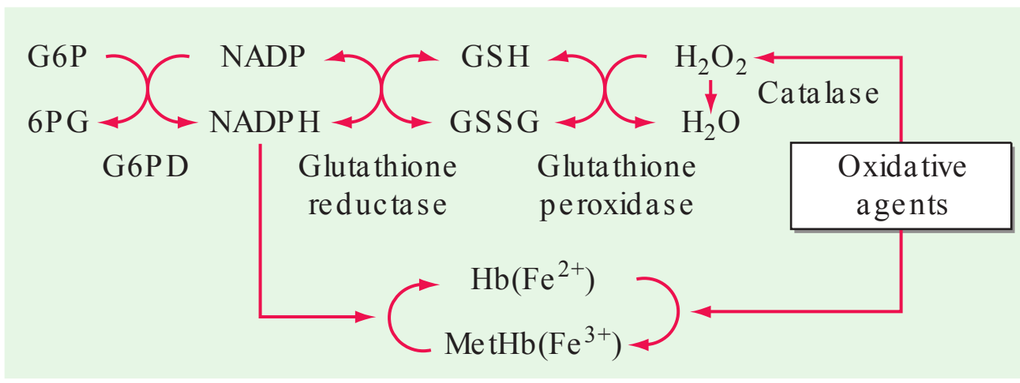


FIGURE 10-5

Diagram of redox metabolism in the red cell. 6PG, 6-phosphogluconate; G6P, glucose 6-phosphate; G6PD, glucose 6-phosphate dehydrogenase; GSH, reduced glutathione; GSSG, oxidized glutathione; Hb, hemoglobin; MetHb, methemoglobin; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate.

Epidemiology

G6PD deficiency is widely distributed in tropical and subtropical parts of the world (Africa, Southern Europe, the Middle East, Southeast Asia, and Oceania) (Fig. 10-6) and wherever people from those areas have migrated. A conservative estimate is that at least 400 million people have a G6PD deficiency gene. In several of these areas, the frequency of a G6PD deficiency gene may be as high as 20% or more. It would be quite extraordinary for a trait that causes significant pathology to spread widely and reach high frequencies in many populations without conferring some biologic advantage. Indeed, G6PD is one of the best-characterized examples of genetic polymorphisms in the human species. Clinical field studies and in vitro experiments strongly support the view that G6PD deficiency has been selected by Plasmodium falciparum malaria, by virtue of the fact that it confers a relative resistance against this highly lethal infection. Different G6PD variants underlie G6PD deficiency in different parts of the world. Some of the more widespread variants are G6PD Mediterranean on the shores of that sea, in the Middle East, and in India; G6PD A– in Africa and in Southern Europe; G6PD Vianchan and G6PD Mahidol in Southeast Asia; G6PD Canton in China; and G6PD Union worldwide. The heterogeneity of polymorphic G6PD variants is proof of their independent origin, and it supports the notion that they have been selected by a common environmental agent, in keeping with the concept of convergent evolution (Fig. 10-6).

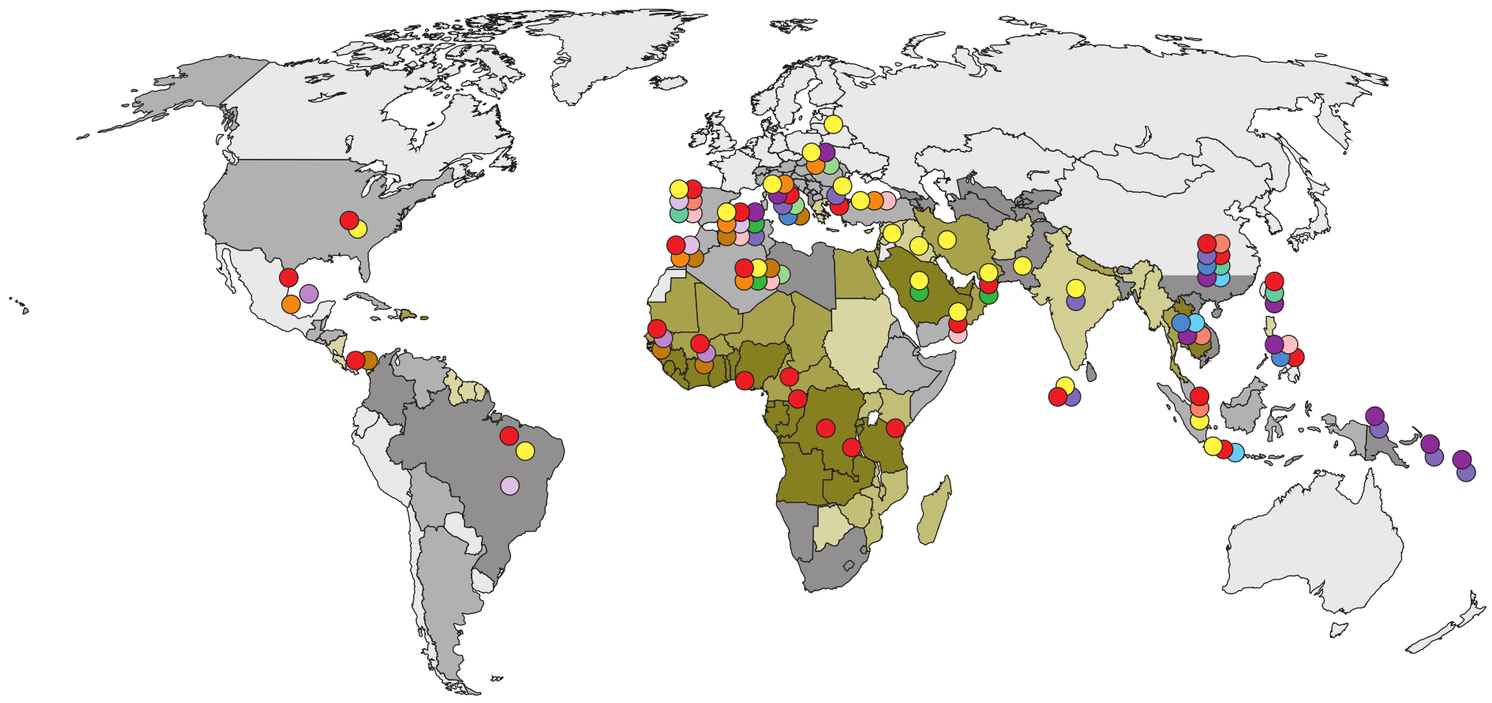


FIGURE 10-6

Epidemiology of glucose 6-phosphate dehydrogenase (G6PD) deficiency throughout the world. The different shadings indicate increasingly high levels of prevalence, up to about 20%; the different colored symbols indicate individual genetic variants of G6PD, each one having a different mutation. (From L Luzzatto et al, in C Scriver et al [eds]: The Metabolic & Molecular Bases of Inherited Disease, 8th ed. New York, McGraw-Hill, 2001.)

Clinical manifestations

The vast majority of people with G6PD deficiency remain clinically asymptomatic throughout their lifetime; however, all of them have an increased risk of developing neonatal jaundice (NNJ) and a risk of developing acute HA (AHA) when challenged by a number of oxidative agents. NNJ related to G6PD deficiency is very rarely present at birth; the peak incidence of clinical onset is between day 2 and day 3, and in most cases, the anemia is not severe. However, NNJ can be very severe in some G6PD-deficient babies, especially in association with prematurity, infection, and/or environmental factors (such as naphthalene-camphor balls, which are used in babies' bedding and clothing), and the risk of severe NNJ is also increased by the coexistence of a monoallelic or biallelic mutation in the uridyl transferase gene (UGT1A1; the same mutations are associated with Gilbert's syndrome). If inadequately managed, NNJ associated with G6PD deficiency can produce kernicterus and permanent neurologic damage.

AHA can develop as a result of three types of triggers: (1) fava beans, (2) infections, and (3) drugs **(Table 10-5)**. Typically, a hemolytic attack starts with malaise, weakness, and abdominal or lumbar pain. After an interval

TABLE 10-5

DRUGS THAT CARRY RISK OF CLINICAL HEMOLYSIS IN PERSONS WITH GLUCOSE 6-PHOSPHATE DEHYDROGENASE DEFICIENCY

	DEFINITE RISK	POSSIBLE RISK	DOUBTFUL RISK
Antimalarials	Primaquine Dapsone/chlorproguanil[a]	Chloroquine	Quinine
Sulphonamides/sulphones	Sulfamethoxazole Others Dapsone	Sulfasalazine Sulfadimidine	Sulfisoxazole Sulfadiazine
Antibacterial/antibiotics	Cotrimoxazole Nalidixic acid Nitrofurantoin Niridazole	Ciprofoxacin Norfoxacin	Chloramphenicol p-Aminosalicylic acid
Antipyretic/analgesics	Acetanilide Phenazopyridine	Acetylsalicylic acid high dose (>3 g/d)	Acetylsalicylic acid (<3 g/d) Acetaminophen Phenacetin
Other	Naphthalene Methylene blue Rasburicase	Vitamin K analogues Ascorbic acid (>1 g)	Doxorubicin Probenecid

[a]Marketed as Lapdap from 2003 to 2008.

of several hours to 2–3 days, the patient develops jaundice and often dark urine. T e onset can be extremely abrupt, especially with favism in children. T e anemia is moderate to extremely severe, usually normocytic and normochromic, and due partly to intravascular hemolysis; hence, it is associated with hemoglobinemia, hemoglobinuria, high LDH, and low or absent plasma haptoglobin. T e blood film shows anisocytosis, polychromasia, and spherocytes typical of hemolytic anemias. T e most typical feature of G6PD deficiency is the presence of bizarre poikilocytes, with red cells that appear to have unevenly distributed hemoglobin ("hemighosts") and red cells that appear to have had parts of them bitten away ("bite cells" or "blister cells") **(Fig. 10-7)**. A classical test, now rarely carried out, is supravital staining with methyl violet, which, if done promptly, reveals the presence of Heinz bodies (consisting of precipitates of denatured hemoglobin and hemichromes), which are regarded as a signature of oxidative damage to red cells (they are also seen with unstable hemoglobins). LDH is high, and so is the unconjugated bilirubin, indicating that there is also extravascular hemolysis. T e most serious threat from AHA in adults is the development of acute renal failure (this is exceedingly rare in children). Once the threat of acute anemia is over and in the absence of comorbidity, full recovery from AHA associated with G6PD deficiency is the rule.

Although it was primaquine (PQ) that led to the discovery of G6PD deficiency, this drug has not been very prominent subsequently, because it is not necessary for the treatment of life-threatening P. falciparum malaria. Today there is a revival of interest in PQ because it is the only effective agent for eliminating the gametocytes of P. falciparum (thus preventing further transmission) and eliminating the hypnozoites of Plasmodium vivax (thus preventing endogenous relapse). In countries aiming to eliminate malaria, there may be a call for mass administration of PQ; this ought to be associated with G6PD testing. At the other end of the historic spectrum, the latest addition to the list of potentially hemolytic drugs (Table 10-5) is rasburicase; again G6PD testing ought to be made mandatory before giving this drug because fatal cases have been reported in newborns with kidney injury and in adults with tumor lysis syndrome.

A very small minority of subjects with G6PD deficiency have chronic nonspherocytic hemolytic anemia (CNSHA) of variable severity. T e patient is nearly always a male, usually with a history of NNJ, who may present with anemia, unexplained jaundice, or gallstones later in life. T e spleen may be enlarged. T e severity of anemia ranges in different patients from borderline to transfusion dependent. T e anemia is usually normomacrocytic, with reticulocytosis. Bilirubin and LDH are increased. Although hemolysis is, by definition, chronic in these patients, they are also vulnerable to acute oxidative damage, and therefore the same agents that can cause AHA in people with the ordinary type of G6PD deficiency will cause severe exacerbations in people with CNSHA associated with G6PD deficiency. In some cases of CNSHA, the deficiency of G6PD is so severe in granulocytes that it becomes rate-limiting for their oxidative burst, with consequent increased susceptibility to some bacterial infections.

Laboratory diagnosis

T e suspicion of G6PD deficiency can be confirmed by semiquantitative methods often referred to as screening tests, which are suitable for population studies and can correctly classify male subjects, in the steady state, as G6PD normal or G6PD deficient. However, in clinical practice, a diagnostic test is usually needed when the patient has had a hemolytic attack; this implies that the oldest, most G6PD-deficient red cells have been selectively destroyed, and young red cells, having higher G6PD activity, are being released into the circulation. Under these conditions, only a quantitative test can give a definitive result. In males, this test will identify normal hemizygotes and G6PD-deficient hemizygotes; among females, some heterozygotes will be missed, but those who are at most risk of hemolysis will be identified. Of course, G6PD deficiency also can be diagnosed by DNA testing.

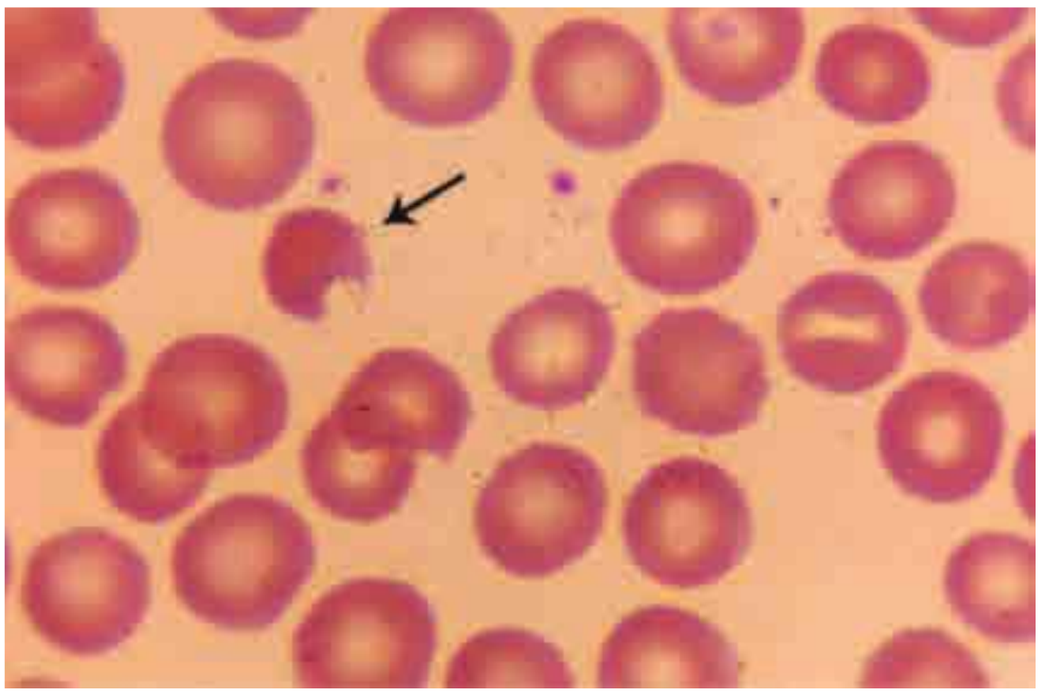


FIGURE 10-7
Peripheral blood smear from a glucose 6-phosphate dehydrogenase (G6PD)-deficient boy experiencing hemolysis. Note the red cells that are misshapen and called "bite" cells. (From MA Lichtman et al: Lichtman's Atlas of Hematology: http://www.accessmedicine.com. Copyright © The McGraw-Hill Companies, Inc. All rights reserved.)

TREATMENT G6PD Deficiency

T e AHA of G6PD deficiency is largely preventable by avoiding exposure to triggering factors of previously screened subjects. Of course, the practicability and cost-effectiveness of screening depend on the prevalence of G6PD deficiency in

each individual community. Favism is entirely preventable in G6PD-deficient subjects by not eating fava beans. Drug-induced hemolysis can be prevented by testing for G6PD deficiency before prescribing; in most cases, one can use alternative drugs. When AHA develops and once its cause is recognized, in most cases, no specific treatment is needed. However, if the anemia is severe, it may be a medical emergency, especially in children, requiring immediate action, including blood transfusion. T is has been the case with an antimalarial drug combination containing dapsone (called Lapdap, introduced in 2003) that has caused severe acute hemolytic episodes in children with malaria in several African countries; after a few years, the drug was taken off the market. If there is acute renal failure, hemodialysis may be necessary, but if there is no previous kidney disease, recovery is the rule. T e management of NNJ associated with G6PD deficiency is no different from that of NNJ due to other causes.

In cases with cnsha, if the anemia is not severe, regular folic acid supplements and regular hematologic surveillance will suf ce. It will be important to avoid exposure to potentially hemolytic drugs, and blood transfusion may be indicated when exacerbations occur, mostly in concomitance with intercurrent infection. In rare patients, regular blood transfusions may be required, in which case appropriate iron chelation should be instituted. Unlike in HS, there is no evidence of selective red cell destruction in the spleen; however, in practice, splenectomy has proven beneficial in severe cases.

Other abnormalities of the redox system

As mentioned above, GSH is a key player in the defense against oxidative stress. Inherited defects of GSH metabolism are exceedingly rare, but each one can give rise to chronic HA (Table 10-4). A rare, peculiar, usually self-limited severe HA of the first month of life, called infantile poikilocytosis, may be associated with deficiency of glutathione peroxidase (GSHPX) due not to an inherited abnormality, but to transient nutritional deficiency of selenium, an element essential for the activity of GSHPX.

Pyrimidine 5′-nucleotidase (P5N) def ciency

P5N is a key enzyme in the catabolism of nucleotides arising from the degradation of nucleic acids that takes place in the final stages of erythroid cell maturation. How exactly its deficiency causes HA is not well understood, but a highly distinctive feature of this condition is a morphologic abnormality of the red cells known as basophilic stippling. T e condition is rare, but it probably ranks third in frequency among red cell enzyme defects (after G6PD deficiency and PK deficiency). T e anemia is lifelong, of variable severity, and may benefit from splenectomy.

Familial (atypical) hemolytic-uremic syndrome

T e term familial (atypical) hemolytic-uremic syndrome is used to designate a group of rare disorders, mostly affecting children, characterized by microangiopathic HA with presence of fragmented erythrocytes in the peripheral blood smear, thrombocytopenia (usually mild), and acute renal failure. (T e word atypical is part of the phrase for historical reasons; it was hemolytic-uremic syndrome [HUS] caused by infection with Escherichia coli producing the Shiga toxin that was regarded as typical). T e genetic basis of atypical HUS (aHUS) has been elucidated. Studies of >100 families have revealed that those family members who developed HUS had mutations in any one of several genes encoding complement regulatory proteins: complement factor H (CFH), CD46 or membrane cofactor protein (MCP), complement factor I (CFI), complement component C3, complement factor B (CFB), and thrombomodulin. T us, whereas all other inherited HAs are due to intrinsic red cell abnormalities, this group is unique in that hemolysis results from an inherited defect external to red cells (Table 10-1). Because the regulation of the complement cascade has considerable redundancy, in the steady state, any of the above abnormalities can be tolerated. However, when an intercurrent infection or some other trigger activates complement through the alternative pathway, the deficiency of one of the complement regulators becomes critical. Endothelial cells get damaged, especially in the kidney; at the same time, and partly as a result of this, there will be brisk hemolysis (thus, the more common Shiga toxin–related HUS can be regarded as a phenocopy of aHUS). aHUS is a severe disease, with up to 15% mortality in the acute phase and up to 50% of cases progressing to end-stage renal disease. Not infrequently, aHUS undergoes spontaneous remission; but because its basis is an inherited abnormality, it is not surprising that, given renewed exposure to a trigger, the syndrome will tend to recur; when it does, the prognosis is always serious. T e standard treatment has been plasma exchange, which will supply the deficient complement regulator. T e anti-C5 complement inhibitor eculizumab (see below) was found to greatly ameliorate the microangiopathic picture, with improvement in platelet counts and in renal function, thus abrogating the need for plasma exchange. It remains to be seen for how long eculizumab treatment will have to be continued in individual patients and whether it will influence the controversial issue of kidney (and liver) transplantation.

ACQUIRED HEMOLYTIC ANEMIA

Mechanical destruction of red cells

Although red cells are characterized by the remarkable deformability that enables them to squeeze through

capillaries narrower than themselves for thousands of times in their lifetime, there are at least two situations in which they succumb to shear, if not to wear and tear; the result is intravascular hemolysis, resulting in hemoglobinuria **(Table 10-6)**. One situation is acute and self-inflicted, march hemoglobinuria. Why sometimes a marathon runner may develop this complication, whereas on another occasion, this does not happen, we do not know (perhaps her or his footwear needs attention). A similar syndrome may develop after prolonged barefoot ritual dancing or intense playing of bongo drums. T e other situation is chronic and iatrogenic (it has been called microangiopathic hemolytic anemia). It takes place in patients with prosthetic heart valves, especially when paraprosthetic regurgitation is present. If the hemolysis consequent on mechanical trauma to the red cells is mild, and if the supply of iron is adequate, the loss may be largely compensated; if more than mild anemia develops, reintervention to correct regurgitation may be required.

Infection

By far the most frequent infectious cause of HA, in endemic areas, is malaria. In other parts of the world, the most frequent direct cause is probably Shiga toxin–producing E. coli O157:H7, now recognized as the main etiologic agent of HUS, which is more common in children than in adults. Life-threatening intravascular hemolysis, due to a toxin with lecithinase activity, occurs with Clostridium perfringens sepsis, particularly following open wounds, septic abortion, or as a disastrous accident due to a contaminated blood unit. Rarely, and if at all in children, HA is seen with sepsis or endocarditis from a variety of organisms. In addition, bacterial and viral infections can cause HA by indirect mechanisms (see above section on G6PD deficiency and Table 10-6).

Immune hemolytic anemias

T ese can arise through at least two distinct mechanisms. (1) T ere is a true autoantibody directed against a red cell antigen, i.e., a molecule present on the surface of red cells. (2) When an antibody directed against a certain molecule (e.g., a drug) reacts with that molecule, red cells may get caught in the reaction, whereby they are damaged or destroyed. Because the antibodies involved differ in optimum reactivity temperatures, they are classified in the time-honored categories of "cold" and "warm" **(Table 10-7)**. Autoantibody-mediated HAs may be seen in isolation (when they are called idiopathic) or as part of a systemic autoimmune disorder such as systemic lupus erythematosus. Here we discuss the most distinctive clinical pictures.

TABLE 10-6

DISEASES AND CLINICAL SITUATIONS WITH PREDOMINANTLY INTRAVASCULAR HEMOLYSIS

	ONSET/TIME COURSE	MAIN MECHANISM	APPROPRIATE DIAGNOSTIC PROCEDURE	COMMENTS
Mismatched blood transfusion	Abrupt	Nearly always ABO incompatibility	Repeat cross-match	
Paroxysmal nocturnal hemoglobinuria (PNH)	Chronic with acute exacerbations	Complement (C)-mediated destruction of CD59(−) red cells	Flow cytometry to display a CD59(−) red cell population	Exacerbations due to C activation through any pathway
Paroxysmal cold hemoglobinuria (PCH)	Acute	Immune lysis of normal red cells	Test for Donath-Landsteiner antibody	Often triggered by viral infection
Septicemia	Very acute	Exotoxins produced by Clostridium perfringens	Blood cultures	Other organisms may be responsible
Microangiopathic	Acute or chronic	Red cell fragmentation	Red cell morphology on blood smear	Different causes ranging from endothelial damage to hemangioma to leaky prosthetic heart valve
March hemoglobinuria	Abrupt	Mechanical destruction	Targeted history taking	
Favism	Acute	Destruction of older fraction of G6PD-deficient red cells	G6PD assay	Triggered by ingestion of large dish of fava beans, but trigger can be infection or drug instead

Abbreviation: G6PD, glucose 6-phosphate dehydrogenase.

TABLE 10-7

CLASSIFICATION OF ACQUIRED IMMUNE HEMOLYTIC ANEMIAS

	TYPE OF ANTIBODY	
CLINICAL SETTING	COLD, MOSTLY IGM, OPTIMAL TEMPERATURE 4–30°C	WARM, MOSTLY IGG, OPTIMAL TEMPERATURE 37°C; OR MIXED
Primary	CAD	AIHA (idiopathic)
Secondary to viral infection	EBV CMV Other	HIV Viral vaccines
Secondary to other infection	Mycoplasma infection: paroxysmal cold hemoglobinuria	
Secondary to/ associated with other disease	CAD in: Waldenström's disease Lymphoma	AIHA in: SLE CLL Other malignancy Chronic inflammatory disorders (e.g., IBD) After allogeneic HSCT
Secondary to drugs: drug-induced immune hemolytic anemia	Small minority (e.g., with lenalidomide)	Majority: currently most common culprit drugs are cefotetan, ceftriaxone, piperacillin
	Drug-dependent: antibody destroys red cells only when drug present (e.g., rarely penicillin) Drug-independent: antibody can destroy red cells even when drug no longer present (e.g., methyldopa)	

Abbreviations: AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.

Autoimmune hemolytic anemia (AIHA)

Once a red cell is coated by an autoantibody (see [1] above), it will be destroyed by one or more mechanisms. In most cases, the Fc portion of the antibody will be recognized by the Fc receptor of macrophages, and this will trigger erythrophagocytosis. Thus, destruction of red cells will take place wherever macrophages are abundant, i.e., in the spleen, liver, or bone marrow; this is called extravascular hemolysis **(Fig. 10-8)**. Because of the special anatomy of the spleen, this organ is particularly efficient in trapping antibody-coated red cells, and often this is the predominant site of red cell destruction. In some cases, the nature of the antibody is such (usually an IgM antibody) that the antigen-antibody complex on the surface of red cells is able to activate complement (C); as a result, a large amount of membrane attack complex will form, and the red cells may be destroyed directly; this is known as intravascular hemolysis.

Clinical features

AIHA is a serious condition; without appropriate treatment, it may have a mortality of approximately 10%. The onset is often abrupt and can be dramatic. The hemoglobin level can drop, within days, to as low as 4 g/dL; the massive red cell removal will produce jaundice; and sometimes the spleen is enlarged. When this triad is present, the suspicion of AIHA must be high. When hemolysis is (in part) intravascular, the telltale sign will be hemoglobinuria, which the patient may report or about which we must enquire or test for. The diagnostic test for AIHA is the direct antiglobulin test developed in 1945 by R. R. A. Coombs and known since by this name. The beauty of this test is that it detects directly the pathogenetic mediator of the disease, i.e., the presence of antibody on the red cells themselves. When the test is positive, it clinches the diagnosis; when it is negative, the diagnosis is unlikely. However, the sensitivity of the Coombs test varies depending on the technique that is used, and in doubtful cases, a repeat in a specialized lab is advisable; the term Coombs-negative AIHA is a last resort. In some cases, the autoantibody has a defined identity; it may be specific for an antigen belonging to the Rhesus system (it is often anti-e). In many cases, it is regarded as "nonspecific" because it reacts with virtually all types of red cells.

When AIHA develops in a person who is already known to have, for instance, systemic lupus or chronic lymphocytic leukemia (Table 10-7), we call it a complication; conversely, when AIHA presents on its own, it may be a pointer to an underlying condition that we ought to seek out. In both cases, what brings about AIHA remains, as in other autoimmune disorders, obscure. In some cases, AIHA can be associated, on first presentation or subsequently, with autoimmune thrombocytopenia (Evans' syndrome).

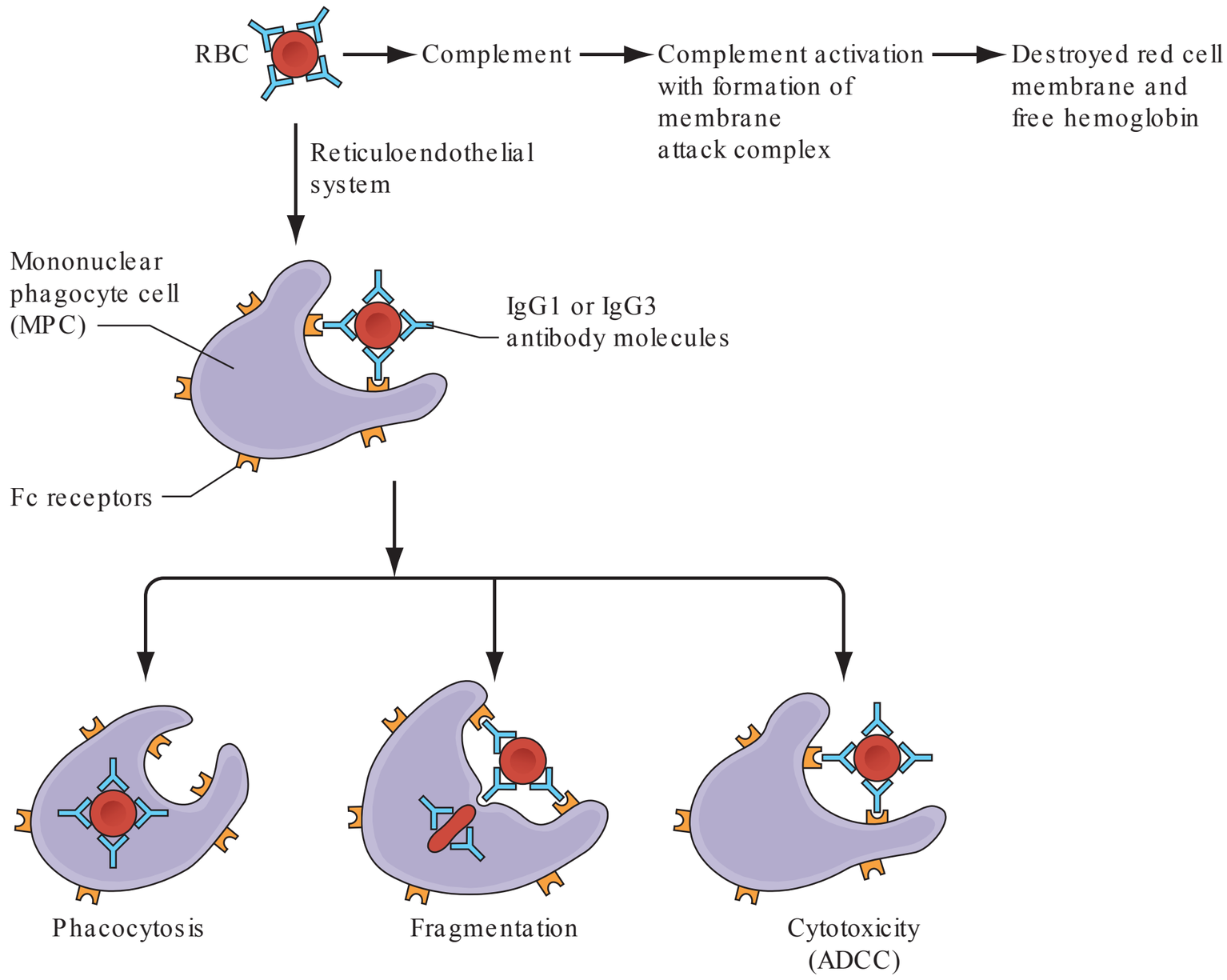


FIGURE 10-8
Mechanism of antibody-mediated immune destruction of red blood cells (RBCs). ADCC, antibody-dependent cell-mediated cytotoxicity. (From N Young et al: Clinical Hematology. Philadelphia, Elsevier, 2006; with permission.)

TREATMENT Autoimmune Hemolytic Anemia

Severe acute AIHA can be a medical emergency. The immediate treatment almost invariably includes transfusion of red cells. This may pose a special problem because, if the antibody involved is nonspecific, all of the blood units cross-matched will be incompatible. In these cases, it is often correct, paradoxically, to transfuse incompatible blood, with the rationale being that the transfused red cells will be destroyed no less but no more than the patient's own red cells, but in the meantime, the patient stays alive. A situation like this requires close liaison and understanding between the clinical unit treating the patient and the blood transfusion/serology lab. Whenever the anemia is not immediately life-threatening, blood transfusion should be withheld (because compatibility problems may increase with each unit of blood transfused), and medical treatment started immediately with prednisone (1 mg/kg per day), which will produce a remission promptly in at least one-half of patients. Rituximab (anti-CD20) was regarded as second-line treatment, but it is increasingly likely that a relatively low dose (100 mg/wk × 4) of rituximab together with prednisone will become a first-line standard. It is especially encouraging that this approach seems to reduce the rate of relapse, a common occurrence in AIHA. For patients who do relapse or are refractory to medical treatment, one may have to consider splenectomy, which, although it does not cure the disease, can produce significant benefit by removing a major site of hemolysis, thus improving the anemia and/or reducing the need for other therapies (e.g., the dose of prednisone). Since the introduction of rituximab, azathioprine, cyclophosphamide, cyclosporine, and intravenous immunoglobulin have become second- or third-line agents. In very rare severe refractory cases, either autologous or allogeneic hematopoietic stem cell transplantation may have to be considered.

Paroxysmal cold hemoglobinuria (PCH)

PCH is a rather rare form of AIHA occurring mostly in children, usually triggered by a viral infection, usually self-limited, and characterized by the involvement of the so-called Donath-Landsteiner antibody. In vitro, this antibody has unique serologic features; it has anti-P specificity and binds to red cells only at a low temperature (optimally at 4°C), but when the temperature is shifted to 37°C, lysis of red cells takes place in the presence of complement. Consequently, in vivo there is intravascular hemolysis, resulting in hemoglobinuria. Clinically the differential diagnosis must include other causes of hemoglobinuria (Table 10-6), but the presence of the Donath-Landsteiner antibody will prove PCH. Active supportive treatment, including blood transfusion, is needed to control the anemia; subsequently, recovery is the rule.

Cold agglutinin disease (CAD)

This designation is used for a form of chronic AIHA that usually affects the elderly and has special clinical and pathologic features. First, the term cold refers to the fact that the autoantibody involved reacts with red cells poorly or not at all at 37°C, whereas it reacts strongly at lower temperatures. As a result, hemolysis is more prominent the more the body is exposed to the cold. The antibody is usually IgM; usually it has an anti-I specificity (the I antigen is present on the red cells of almost everybody), and it may have a very high titer (1:100,000 or more has been observed). Second, the antibody is produced by an expanded clone of B lymphocytes, and sometimes its concentration in the plasma is high enough to show up as a spike in plasma protein electrophoresis, i.e., as a monoclonal gammopathy. Third, because the antibody is IgM, CAD is related to Waldenström's macroglobulinemia (WM) **(Chap. 18)**, although in most cases, the other clinical features of this disease are not present. Thus, CAD must be regarded as a form of WM (i.e., as a low-grade mature B cell lymphoma) that manifests at an earlier stage precisely because the unique biologic properties of the IgM that it produces give the clinical picture of chronic HA.

In mild forms of CAD, avoidance of exposure to cold may be all that is needed to enable the patient to have a reasonably comfortable quality of life; but in more severe forms, the management of CAD is not easy. Blood transfusion is not very effective because donor red cells are I positive and will be rapidly removed. Immunosuppressive/cytotoxic treatment with azathioprine or cyclophosphamide can reduce the antibody titer, but clinical efficacy is limited, and in view of the chronic nature of the disease, the side effects may prove unacceptable. Unlike in AIHA, prednisone and splenectomy are ineffective. Plasma exchange will remove antibody and is, therefore, in theory, a rational approach, but it is laborious and must be carried out at frequent intervals if it is to be beneficial. The management of CAD has changed significantly with the advent of rituximab; although its impact on CAD is not as great as on AIHA, up to 60% of patients respond, and remissions may be more durable with a rituximab-fludarabine combination. Given the long clinical course of CAD, it remains to be seen with what schedule or periodicity these agents will need to be administered.

Toxic agents and drugs

A number of chemicals with oxidative potential, whether medicinal or not, can cause hemolysis even in people who are not G6PD deficient (see above). Examples are hyperbaric oxygen (or 100% oxygen), nitrates, chlorates, methylene blue, dapsone, cisplatin, and numerous aromatic (cyclic) compounds. Other chemicals may be hemolytic through nonoxidative, largely unknown mechanisms; examples include arsine, stibine, copper, and lead. The HA caused by lead poisoning is characterized by basophilic stippling; it is in fact a phenocopy of that seen in P5N deficiency (see above), suggesting it is mediated at least in part by lead inhibiting this enzyme.

In these cases, hemolysis appears to be mediated by a direct chemical action on red cells. But drugs can cause hemolysis through at least two other mechanisms. (1) A drug can behave as a hapten and induce antibody production; in rare subjects, this happens, for instance, with penicillin. Upon a subsequent exposure, red cells are caught, as innocent bystanders, in the reaction between penicillin and antipenicillin antibodies. Hemolysis will subside as soon as penicillin administration is stopped. (2) A drug can trigger, perhaps through mimicry, the production of an antibody against a red cell antigen. The best known example is methyldopa, an antihypertensive agent no longer in use, which in a small fraction of patients stimulated the production of the Rhesus antibody anti-e. In patients who have this antigen, the anti-e is a true autoantibody, which then causes an autoimmune HA (see below). Usually this will gradually subside once methyldopa is discontinued.

Severe intravascular hemolysis can be caused by the venom of certain snakes (cobras and vipers), and HA can also follow spider bites.

Paroxysmal nocturnal hemoglobinuria (PNH)

PNH is an acquired chronic HA characterized by persistent intravascular hemolysis subject to recurrent exacerbations. In addition to hemolysis, there is often pancytopenia and a distinct tendency to venous thrombosis. This triad makes PNH a truly unique clinical condition; however, when not all of these three features are manifest on presentation, the diagnosis is often delayed, although it can always be made by appropriate laboratory investigations (see below).

PNH has about the same frequency in men and women and is encountered in all populations throughout the world, but it is a rare disease; its prevalence is estimated to be approximately 5 per million (it may be somewhat less rare in Southeast Asia and in the Far East). There is no evidence of inherited susceptibility. PNH has never been reported as a congenital disease, but it can present in small children or as late as in the seventies, although most patients are young adults.

Clinical features

The patient may seek medical attention because, one morning, she or he passed blood instead of urine **(Fig. 10-9)**. This is distressing or frightening event may be regarded as the classical presentation; however, more frequently, this symptom is not noticed or is suppressed. Indeed, the patient often presents simply as a problem in

FIGURE 10-9
Consecutive urine samples from a patient with paroxysmal nocturnal hemoglobinuria (PNH). The variation in the severity of hemoglobinuria within hours is probably unique to this condition.

the differential diagnosis of anemia, whether symptomatic or discovered incidentally. Sometimes, the anemia is associated from the outset with neutropenia, thrombocytopenia, or both, thus signaling an element of bone marrow failure (see below). Some patients may present with recurrent attacks of severe abdominal pain defying a specific diagnosis and eventually found to be related to thrombosis. When thrombosis affects the hepatic veins, it may produce acute hepatomegaly and ascites, i.e., a full-fledged Budd-Chiari syndrome, which, in the absence of liver disease, ought to raise the suspicion of PNH.

The natural history of PNH can extend over decades. Without treatment, the median survival is estimated to be about 8–10 years; in the past, the most common cause of death has been venous thrombosis, followed by infection secondary to severe neutropenia and hemorrhage secondary to severe thrombocytopenia. Rarely (estimated 1–2% of all cases), PNH may terminate in acute myeloid leukemia. On the other hand, full spontaneous recovery from PNH has been documented, albeit rarely.

Laboratory investigations and diagnosis

The most consistent blood finding is anemia, which may range from mild to moderate to very severe. The anemia is usually normomacrocytic, with unremarkable red cell morphology. If the MCV is high, it is usually largely accounted for by reticulocytosis, which may be quite marked (up to 20%, or up to 400,000/μL). The anemia may become microcytic if the patient is allowed to become iron deficient as a result of chronic urinary blood loss through hemoglobinuria. Unconjugated bilirubin is mildly or moderately elevated; LDH is typically markedly elevated (values in the thousands are common); and haptoglobin is usually undetectable. All of these findings make the diagnosis of hemolytic anemia compelling. Hemoglobinuria may be overt in a random urine sample; if it is not, it may be helpful to obtain serial urine samples, because hemoglobinuria can vary dramatically from day to day and even from hour to hour. The bone marrow is usually cellular, with marked to massive erythroid hyperplasia, often with mild to moderate dyserythropoietic features (not to be confused with myelodysplastic syndrome). At some stage of the disease, the marrow may become hypocellular or even frankly aplastic (see below).

The definitive diagnosis of PNH must be based on the demonstration that a substantial proportion of the patient's red cells have an increased susceptibility to complement (C), due to the deficiency on their surface of proteins (particularly CD59 and CD55) that normally protect the red cells from activated C. The sucrose hemolysis test is unreliable; in contrast, the acidified serum (Ham) test is highly reliable but is carried out only in a few labs. The gold standard today is flow cytometry, which can be carried out on granulocytes as well as on red cells. A bimodal distribution of cells, with a discrete population that is CD59 and CD55 negative, is diagnostic of PNH. In PNH patients, this population is at least 5% of the total red cells and at least 20% of the total granulocytes.

Pathophysiology

Hemolysis in PNH is mainly intravascular and is due to an intrinsic abnormality of the red cell, which makes it exquisitely sensitive to activated C, whether it is activated through the alternative pathway or through an antigen-antibody reaction. The former mechanism is mainly responsible for chronic hemolysis in PNH; the latter explains why the hemolysis can be dramatically exacerbated in the course of a viral or bacterial infection. Hypersusceptibility to C is due to deficiency of several protective membrane proteins **(Fig. 10-10)**, of which CD59 is the most important, because it hinders the insertion into the membrane of C9 polymers. The molecular basis for the deficiency of these proteins has been pinpointed not to a defect in any of the respective genes, but rather to the shortage of a unique glycolipid molecule, GPI (Fig. 10-2), which, through a peptide bond, anchors these proteins to the surface membrane of cells. The shortage of GPI is due in turn to a mutation in an X-linked gene, called PIG-A, required for an early step in GPI biosynthesis. In virtually each patient, the PIG-A mutation is different. This is not surprising, because these mutations are not inherited; rather, each one takes place de novo in a hemopoietic stem cell (i.e., they are somatic mutations). As a result, the patient's marrow is a mosaic of mutant and nonmutant cells, and the peripheral blood always contains both PNH cells and normal (non-PNH) cells. Thrombosis is one of the most immediately life-threatening complications of PNH and yet one of the least understood in its pathogenesis. It could be that deficiency of CD59 on the PNH platelet causes inappropriate platelet activation; however, other mechanisms are possible.

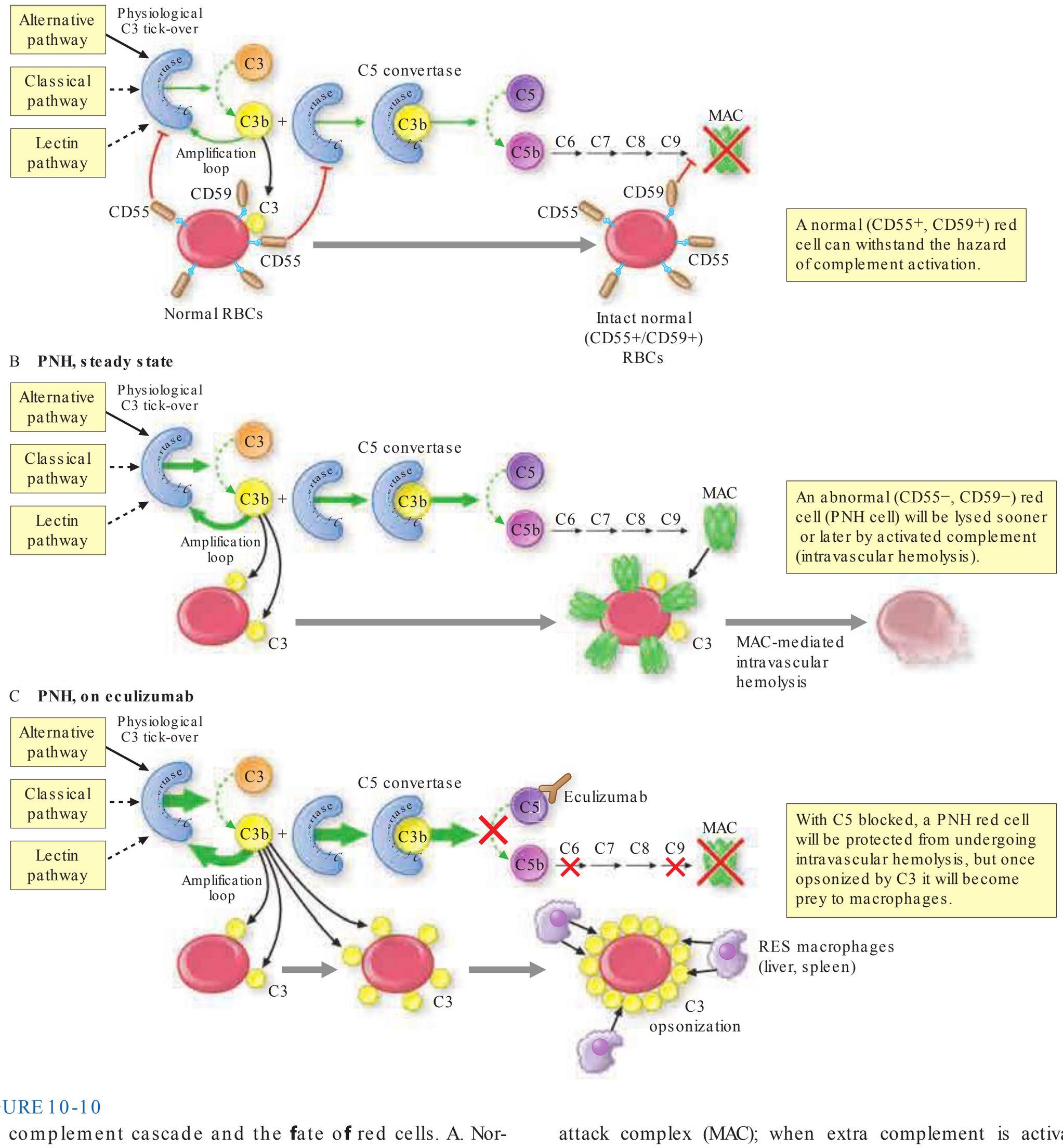


FIGURE 10-10

The complement cascade and the fate of red cells. A. Normal red cells are protected from complement activation and subsequent hemolysis by CD55 and CD59. These two proteins, being GPI-linked, are missing from the surface of PNH red cells as a result of a somatic mutation of the X-linked PIG-A gene that encodes a protein required for an early step of the GPI molecule biosynthesis. B. In the steady state, PNH erythrocytes suffer from spontaneous (tick-over) complement activation, with consequent intravascular hemolysis through formation of the membrane attack complex (MAC); when extra complement is activated through the classical pathway, an exacerbation of hemolysis will result. C. On eculizumab, PNH erythrocytes are protected from hemolysis from the inhibition of C5 cleavage; however, upstream complement activation may lead to C3 opsonization and possible extravascular hemolysis. GPI, glycosylphosphatidylinositol; PNH, paroxysmal nocturnal hemoglobinuria. (From L Luzzatto et al: Haematologica 95:523, 2010.)

Bone marrow failure (BMF) and relationship between PNH and aplastic anemia (AA)

It is not unusual that patients with firmly established PNH have a previous history of well-documented AA; indeed, BMF preceding overt PNH is probably the rule rather than the exception. On the other hand, sometimes a patient with PNH becomes less hemolytic and more pancytopenic and ultimately has the clinical picture of AA. Because AA is probably an organ-specific autoimmune disease, in which T cells cause damage to hematopoietic stem cells, the same may be true of PNH, with the specific proviso that the damage spares PNH stem cells. PIG-A mutations can be demonstrated in normal people, and there is evidence from mouse models that PNH stem cells do not expand when the rest of the bone marrow is normal. Thus, we can visualize PNH as always having two components: failure of normal hematopoiesis and massive expansion of a PNH clone. Findings supporting this notion include skewing of the T cell repertoire and the demonstration of GPI-reactive T cells in patients with PNH.

TREATMENT Paroxysmal Nocturnal Hemoglobinuria

Unlike other acquired hemolytic anemias, PNH may be a lifelong condition, and most patients receive supportive treatment only, including transfusion of filtered red cells[1] whenever necessary, which, for some patients, means quite frequently. Folic acid supplements (at least 3 mg/d) are mandatory; the serum iron should be checked periodically, and iron supplements should be administered as appropriate. Long-term glucocorticoids are not indicated because there is no evidence that they have any effect on chronic hemolysis; in fact, they are contraindicated because their side effects are considerable and potentially dangerous. A major advance in the management of PNH has been the development of a humanized monoclonal antibody, eculizumab, which binds to the complement component C5 near the site that, when cleaved, will trigger the distal part of the complement cascade leading to the formation of membrane attack complex (MAC). In an international, placebo-controlled, randomized trial of 87 patients (so far the only controlled therapeutic trial in PNH) who had been selected on grounds of having severe hemolysis making them transfusion-dependent, eculizumab proved effective and was licensed in 2007. Eculizumab, by abrogating complement-dependent intravascular hemolysis, significantly improves the quality of life of PNH patients. One would expect that the need for blood transfusion would also be abrogated; indeed, this is the case in about one-half of patients, in many of whom there is also a rise in hemoglobin levels. In the remaining patients, however, the anemia remains sufficiently severe to require blood transfusion. One reason for this is that, once the distal complement pathway is blocked, red cells no longer destroyed by the MAC become opsonized by complement (C3) fragments and undergo extravascular hemolysis (Fig. 10-10). The extent to which this happens depends in part on a genetic polymorphism of the complement receptor CR1. Based on its half-life, eculizumab must be administered intravenously every 14 days. The only form of treatment that currently can provide a definitive cure for PNH is allogeneic BMT. When an HLA-identical sibling is available, BMT should be offered to any young patient with severe PNH; the availability of eculizumab has decreased significantly the proportion of patients receiving BMT.

For patients with the PNH-AA syndrome, immunosuppressive treatment with antithymocyte globulin and cyclosporine A may be indicated, especially in order to relieve severe thrombocytopenia and/or neutropenia in patients in whom these were the main problem(s); of course, this treatment will have little or no effect on hemolysis. Any patient who has had venous thrombosis or who has a genetically determined thrombophilic state in addition to PNH should be on regular anticoagulant prophylaxis. With thrombotic complications that do not resolve otherwise, thrombolytic treatment with tissue plasminogen activator may be indicated.

ANEMIA DUE TO ACUTE BLOOD LOSS

Blood loss causes anemia by two main mechanisms: (1) by the direct loss of red cells; and (2) if the loss of blood is protracted, it will gradually deplete iron stores, eventually resulting in iron deficiency. The latter type of anemia is covered in **Chap. 7**; here we are concerned with the former type, i.e., posthemorrhagic anemia, which follows acute blood loss. This can be external (e.g., after trauma or obstetric hemorrhage) or internal (e.g., from bleeding in the gastrointestinal tract, rupture of the spleen, rupture of an ectopic pregnancy, subarachnoid hemorrhage). In any of these cases, after the sudden loss of a large amount of blood, there are three clinical/pathophysiologic stages. (1) At first, the dominant feature is hypovolemia, which poses a threat particularly to organs that normally have a high blood supply, like the brain and the kidneys; therefore, loss of consciousness and acute renal failure are major threats. It is important to note that at this stage an ordinary blood count will not show anemia, because the hemoglobin concentration is not affected. (2) Next, as an emergency response, baroreceptors and stretch receptors will cause release of vasopressin and other peptides, and the body will shift fluid from the extravascular to the intravascular compartment, producing hemodilution; thus, the hypovolemia gradually converts to anemia. The degree of anemia

[1]Now that filters with excellent retention of white cells are routinely used, the traditional washing of red cells, aiming to avoid white cell reactions triggering hemolysis, is no longer necessary and is wasteful.

will reflect the amount of blood lost. If after 3 days the hemoglobin is, for example, 7 g/dL, it means that about half of the entire blood has been lost. (3) Provided bleeding does not continue, the bone marrow response will gradually ameliorate the anemia.

T e diagnosis of acute posthemorrhagic anemia (APHA) is usually straightforward, although sometimes internal bleeding episodes (e.g., after a traumatic injury), even when large, may not be immediately obvious. Whenever an abrupt fall in hemoglobin has taken place, whatever history is given by the patient, APHA should be suspected. Supplementary history may have to be obtained by asking the appropriate questions, and appropriate investigations (e.g., a sonogram or an endoscopy) may have to be carried out.

TREATMENT Anemia Due to Acute Blood Loss

With respect to treatment, a two-pronged approach is imperative. (1) In many cases, the blood lost needs to be replaced promptly. Unlike with many chronic anemias, when finding and correcting the cause of the anemia is the first priority and blood transfusion may not be even necessary because the body is adapted to the anemia, with acute blood loss the reverse is true; because the body is not adapted to the anemia, blood transfusion takes priority. (1) While the emergency is being confronted, it is imperative to stop the hemorrhage and to eliminate its source.

A special type of APHA is blood loss during and immediately after surgery, which can be substantial (e.g., up to 2 L in the case of a radical prostatectomy). Of course with elective surgical procedures, the patient's own stored blood may be available (through preoperative autologous blood donation), and in any case, blood loss ought to have been carefully monitored/measured. T e fact that this blood loss is iatrogenic dictates that ever more effort should be invested in optimizing its management.

A Holy Grail of emergency medicine for a long time has been the idea of a blood substitute that would be universally available, suitable for all recipients, easy to store and to transport, safe, and as effective as blood itself. Two main paths have been pursued: (1) fluorocarbon synthetic chemicals that bind oxygen reversibly, and (2) artificially modified hemoglobins, known as hemoglobin-based oxygen carriers (HBOCs). Although there are numerous anecdotal reports of the use of both approaches in humans, and although HBOCs have reached the stage of phase 2–3 clinical trials, no "blood substitute" has yet become standard treatment.

CHAPTER 11

BONE MARROW FAILURE SYNDROMES INCLUDING APLASTIC ANEMIA AND MYELODYSPLASIA

Neal S. Young

The hypoproliferative anemias are normochromic, normocytic, or macrocytic and are characterized by a low reticulocyte count. Hypoproliferative anemia is also a prominent feature of hematologic diseases that are described as bone marrow failure states; these include aplastic anemia, myelodysplastic syndrome (MDS), pure red cell aplasia (PRCA), and myelophthisis. Anemia in these disorders is often not a solitary or even the major hematologic finding. More frequent in bone marrow failure is pancytopenia: anemia, leukopenia, and thrombocytopenia. Low blood counts in the marrow failure diseases result from deficient hematopoiesis, as distinguished from blood count depression due to peripheral destruction of red cells (hemolytic anemias), platelets (idiopathic thrombocytopenic purpura [ITP] or due to splenomegaly), and granulocytes (as in the immune leukopenias). Marrow damage and dysfunction also may be secondary to infection, inflammation, or cancer.

Hematopoietic failure syndromes are classified by dominant morphologic features of the bone marrow **(Table 11-1)**. Although practical distinction among these syndromes usually is clear, some processes are so closely related that the diagnosis may be complex. Patients may seem to suffer from two or three related diseases simultaneously, or one diagnosis may appear to evolve into another. Many of these syndromes share an immune-mediated mechanism of marrow destruction and some element of genomic instability resulting in a higher rate of malignant transformation.

It is important that the internist and general practitioner recognize the marrow failure syndromes, as their prognosis may be poor if the patient is untreated; effective therapies are often available but sufficiently complicated in their choice and delivery so as to warrant the care of a hematologist or oncologist.

APLASTIC ANEMIA

DEFINITION

Aplastic anemia is pancytopenia with bone marrow hypocellularity. Acquired aplastic anemia is distinguished from iatrogenic aplasia, marrow hypocellularity

TABLE 11-1

DIFFERENTIAL DIAGNOSIS OF PANCYTOPENIA

Pancytopenia with Hypocellular Bone Marrow	
Acquired aplastic anemia	
Constitutional aplastic anemia (Fanconi anemia, dyskeratosis congenita)	
Some myelodysplasia	
Rare aleukemic leukemia	
Some acute lymphoid leukemia	
Some lymphomas of bone marrow	
Pancytopenia with Cellular Bone Marrow	
Primary bone marrow diseases	Secondary to systemic diseases
Myelodysplasia	Systemic lupus erythematosus
Paroxysmal nocturnal hemoglobinuria	Hypersplenism
Myelofibrosis	B_{12}, folate deficiency
Some aleukemic leukemia	Overwhelming infection
Myelophthisis	Alcohol
Bone marrow lymphoma	Brucellosis
Hairy cell leukemia	Sarcoidosis
	Tuberculosis
	Leishmaniasis
Hypocellular Bone Marrow ± Cytopenia	
Q fever	
Legionnaires' disease	
Anorexia nervosa, starvation	
Mycobacterium	

after intensive cytotoxic chemotherapy for cancer. Aplastic anemia can also be constitutional: the genetic diseases Fanconi anemia and dyskeratosis congenita, although frequently associated with typical physical anomalies and the development of pancytopenia early in life, can also present as marrow failure in normal-appearing adults. Acquired aplastic anemia is often stereotypical in its manifestations, with the abrupt onset of low blood counts in a previously well young adult; seronegative hepatitis or a course of an incriminated medical drug may precede the onset. The diagnosis in these instances is uncomplicated. Sometimes blood count depression is moderate or incomplete, resulting in anemia, leukopenia, and thrombocytopenia in some combination. Aplastic anemia is related to both paroxysmal nocturnal hemoglobinuria (PNH; **Chap. 33**) and to MDS, and in some cases, a clear distinction among these disorders may not be possible.

EPIDEMIOLOGY

The incidence of acquired aplastic anemia in Europe and Israel is two cases per million persons annually. In Thailand and China, rates of five to seven per million have been established. In general, men and women are affected with equal frequency, but the age distribution is biphasic, with the major peak in the teens and twenties and a second rise in older adults.

ETIOLOGY

The origins of aplastic anemia have been inferred from several recurring clinical associations **(Table 11-2)**; unfortunately, these relationships are not reliable in an individual patient and may not be etiologic. In addition, although most cases of aplastic anemia are idiopathic, little other than history separates these cases from those with a presumed etiology such as a drug exposure.

Radiation

Marrow aplasia is a major acute sequela of radiation. Radiation damages DNA; tissues dependent on active mitosis are particularly susceptible. Nuclear accidents involve not only power plant workers but also employees of hospitals, laboratories, and industry (food sterilization, metal radiography, etc.), as well as innocents exposed to stolen, misplaced, or misused sources. Whereas the radiation dose can be approximated from the rate and degree of decline in blood counts, dosimetry by reconstruction of the exposure can help to estimate the patient's prognosis and also to protect medical personnel from contact with radioactive tissue and excreta. MDS and leukemia, but probably not aplastic anemia, are late effects of radiation.

TABLE 11-2

CLASSIFICATION OF APLASTIC ANEMIA AND SINGLE CYTOPENIAS

ACQUIRED	INHERITED
Aplastic Anemia	
Secondary	Fanconi anemia
Radiation	Dyskeratosis congenita
Drugs and chemicals	Shwachman-Diamond syndrome
Regular effects	Reticular dysgenesis
Idiosyncratic reactions	Amegakaryocytic thrombocytopenia
Viruses	Familial aplastic anemias
Epstein-Barr virus (infectious mononucleosis)	Preleukemia (monosomy 7, etc.)
Hepatitis (non-A, non-B, non-C hepatitis)	Nonhematologic syndrome (Down, Dubowitz, Seckel)
Parvovirus B19 (transient aplastic crisis, PRCA)	
HIV-1 (AIDS)	
Immune diseases	
Eosinophilic fasciitis	
Hyperimmunoglobulinemia	
Large granular lymphocytosis (LGL)	
Thymoma/thymic carcinoma	
Graft-versus-host disease in immunodeficiency	
Paroxysmal nocturnal hemoglobinuria (PNH)	
Pregnancy	
Idiopathic	
Cytopenias	
PRCA (see Table 11-4)	Congenital PRCA (Diamond-Blackfan anemia)
Neutropenia/agranulocytosis	
Idiopathic	Kostmann syndrome
Drugs, toxins	Shwachman-Diamond syndrome
LGL	Reticular dysgenesis
Pure white cell aplasia (+/– thymoma)	
Thrombocytopenia	
Drugs, toxins	Amegakaryocytic thrombocytopenia
Idiopathic amegakaryocytic	Thrombocytopenia with absent radii

Abbreviation: PRCA, pure red cell aplasia.

Chemicals

Benzene is a notorious cause of bone marrow failure: epidemiologic, clinical, and laboratory data link benzene to aplastic anemia, acute leukemia, and blood and marrow abnormalities. For leukemia, incidence is correlated with cumulative exposure, but susceptibility must also be important, because only a minority of even

heavily exposed workers develop myelotoxicity. The employment history is important, especially in industries where benzene is used for a secondary purpose, usually as a solvent. Benzene-related blood diseases have declined with regulation of industrial exposure. Although benzene is no longer generally available as a household solvent, exposure to its metabolites occurs in the normal diet and in the environment. The association between marrow failure and other chemicals is much less well substantiated.

Drugs

(Table 11-3) Many chemotherapeutic drugs have marrow suppression as a major toxicity; effects are dose dependent and will occur in all recipients. In contrast, idiosyncratic reactions to a large and diverse group of drugs may lead to aplastic anemia without a clear dose-response relationship. These associations rest largely on accumulated case reports until a large international study in Europe in the 1980s quantitated drug relationships, especially for nonsteroidal analgesics, sulfonamides, thyrostatic drugs, some psychotropics, penicillamine, allopurinol, and gold. Association does not equal causation: a drug may have been used to treat the first symptoms of bone marrow failure (antibiotics for fever or the preceding viral illness) or provoked the first symptom of a preexisting disease (petechiae by nonsteroidal anti-inflammatory agents administered to the thrombocytopenic patient). In the context of total drug use, idiosyncratic reactions, although individually devastating, are rare events. Risk estimates are usually lower when determined in population-based studies. Furthermore, the low absolute risk is also made more obvious: even a 10- or 20-fold increase in risk translates, in a rare disease, to just a handful of drug-induced aplastic anemia cases among hundreds of thousands of exposed persons.

TABLE 11-3

SOME DRUGS AND CHEMICALS ASSOCIATED WITH APLASTIC ANEMIA

- Agents that regularly produce marrow depression as major toxicity in commonly used doses or normal exposures:
  - Cytotoxic drugs used in cancer chemotherapy: alkylating agents, antimetabolites, antimitotics, some antibiotics
- Agents that frequently but not inevitably produce marrow aplasia:
  - Benzene
- Agents associated with aplastic anemia but with a relatively low probability:
  - Chloramphenicol
  - Insecticides
  - Antiprotozoals: quinacrine and chloroquine, mepacrine
  - Nonsteroidal anti-inflammatory drugs (including phenylbutazone, indomethacin, ibuprofen, sulindac, aspirin)
  - Anticonvulsants (hydantoins, carbamazepine, phenacemide, felbamate)
  - Heavy metals (gold, arsenic, bismuth, mercury)
  - Sulfonamides: some antibiotics, antithyroid drugs (methimazole, methylthiouracil, propylthiouracil), antidiabetes drugs (tolbutamide, chlorpropamide), carbonic anhydrase inhibitors (acetazolamide and methazolamide)
  - Antihistamines (cimetidine, chlorpheniramine)
  - d-Penicillamine
  - Estrogens (in pregnancy and in high doses in animals)
- Agents whose association with aplastic anemia is more tenuous:
  - Other antibiotics (streptomycin, tetracycline, methicillin, mebendazole, trimethoprim/sulfamethoxazole, flucytosine)
  - Sedatives and tranquilizers (chlorpromazine, prochlorperazine, piperacetazine, chlordiazepoxide, meprobamate, methyprylon)
  - Allopurinol
  - Methyldopa
  - Quinidine
  - Lithium
  - Guanidine
  - Potassium perchlorate
  - Thiocyanate
  - Carbimazole

Note: Terms set in italics show the most consistent association with aplastic anemia.

Infections

Hepatitis is the most common preceding infection, and posthepatitis marrow failure accounts for approximately 5% of etiologies in most series. Patients are usually young men who have recovered from a bout of liver inflammation 1 to 2 months earlier; the subsequent pancytopenia is very severe. The hepatitis is seronegative (non-A, non-B, non-C) and possibly due to an as yet undiscovered infectious agent. Fulminant liver failure in childhood also follows seronegative hepatitis, and marrow failure occurs at a high rate in these patients. Aplastic anemia can rarely follow infectious mononucleosis. Parvovirus B19, the cause of transient aplastic crisis in hemolytic anemias and of some PRCAs (see below), does not usually cause generalized bone marrow failure. Mild blood count depression is frequent in the course of many viral and bacterial infections but resolves with the infection.

Immunologic diseases

Aplasia is a major consequence and the inevitable cause of death in transfusion-associated graft-versus-host disease (GVHD) that can occur after infusion of nonirradiated blood products to an immunodeficient recipient. Aplastic anemia is strongly associated with the rare collagen vascular syndrome eosinophilic fasciitis that is characterized by painful induration of subcutaneous tissues. Thymoma and hypoimmunoglobulinemia are occasional associations with aplastic anemia. Pancytopenia with marrow hypoplasia can also occur in systemic lupus erythematosus (SLE).

Pregnancy

Aplastic anemia very rarely may occur and recur during pregnancy and resolve with delivery or with spontaneous or induced abortion.

Paroxysmal nocturnal hemoglobinuria

An acquired mutation in the PIG-A gene in a hematopoietic stem cell is required for the development of PNH, but PIG-A mutations probably occur commonly in normal individuals. If the PIG-A mutant stem cell proliferates, the result is a clone of progeny deficient in glycosylphosphatidylinositol-linked cell surface membrane proteins **(Chap. 33)**. Small clones of deficient cells can be detected by sensitive flow cytometry tests in one-half or more of patients with aplastic anemia at the time of presentation. Functional studies of bone marrow from PNH patients, even those with mainly hemolytic manifestations, show evidence of defective hematopoiesis. Patients with an initial clinical diagnosis of PNH, especially younger individuals, may later develop frank marrow aplasia and pancytopenia; patients with an initial diagnosis of aplastic anemia may suffer from hemolytic PNH years after recovery of blood counts.

Constitutional disorders

Fanconi anemia, an autosomal recessive disorder, manifests as congenital developmental anomalies, progressive pancytopenia, and an increased risk of malignancy. Chromosomes in Fanconi anemia are peculiarly susceptible to DNA cross-linking agents, the basis for a diagnostic assay. Patients with Fanconi anemia typically have short stature, café au lait spots, and anomalies involving the thumb, radius, and genitourinary tract. At least 16 different genetic defects (all but one with an identified gene) have been defined; the most common, type A Fanconi anemia, is due to a mutation in FANCA. Most of the Fanconi anemia gene products form a protein complex that activates FANCD2 by monoubiquitination to play a role in the cellular response to DNA damage and especially interstrand cross-linking.

Dyskeratosis congenita is characterized by the triad of mucous membrane leukoplasia, dystrophic nails, reticular hyperpigmentation, and with the development of aplastic anemia in childhood. Dyskeratosis is due to mutations in genes of the telomere repair complex, which acts to maintain telomere length in replicating cells: the X-linked variety is due to mutations in the DKC1 (dyskerin) gene; the more unusual autosomal dominant type is due to mutation in TERC, which encodes an RNA template, and TERT, which encodes the catalytic reverse transcriptase, telomerase. Mutations in TNF2, a component of the shelterin complex, proteins that bind the telomere DNA, also occur.

In Shwachman-Diamond syndrome, presentation is early in life with neutropenia with pancreatic insufficiency and malabsorption; most patients have compound heterozygous mutations in SBDS that may affect both ribosomal biogenesis (as in Diamond-Blackfan anemia; see below) and marrow stroma function.

While these constitutional syndromes can on occasion present in adults, genetic mutations are also risk factors for bone marrow failure. In the recently recognized telomeropathies, mutations in TERT and TERC have subtle effects on hematopoietic function. Typical presentations include not only severe but also moderate aplastic anemia, which can be chronic and not progressive, and isolated macrocytic anemia or thrombocytopenia. Physical anomalies are usually not found in the patient, although early hair graying is a clue to the diagnosis. A careful family history may disclose pulmonary fibrosis and hepatic cirrhosis. Specific involvement of the bone marrow, liver, and lung is highly variable, as is penetrance of clinical phenotype, both within families and among kindreds. Variable penetrance means that TERT and TERC mutations represent risk factors for marrow failure, as family members with the same mutations may have normal or only slight hematologic abnormalities but more subtle evidence of (compensated) hematopoietic insuf ciency.

PATHOPHYSIOLOGY

Bone marrow failure results from severe damage to the hematopoietic cell compartment. In aplastic anemia, replacement of the bone marrow by fat is apparent in the morphology of the biopsy specimen **(Fig. 11-1)** and magnetic resonance imaging (MRI) of the spine. Cells bearing the CD34 antigen, a marker of early hematopoietic cells, are greatly diminished, and in functional studies, committed and primitive progenitor cells are virtually absent; in vitro assays have suggested that the stem cell pool is reduced to ≤1% of normal in severe disease at the time of presentation.

An intrinsic stem cell defect exists for the constitutional aplastic anemias: cells from patients with Fanconi anemia exhibit chromosome damage and death on exposure to certain chemical agents. Telomeres are short in some patients with aplastic anemia, due to heterozygous mutations in genes of the telomere repair complex. Telomeres may also shorten physiologically in acquired marrow failure due to replicative demands on a limited stem cell pool.

Drug injury

Extrinsic damage to the marrow follows massive physical or chemical insults such as high doses of radiation and toxic chemicals. For the more common idiosyncratic reaction to modest doses of medical

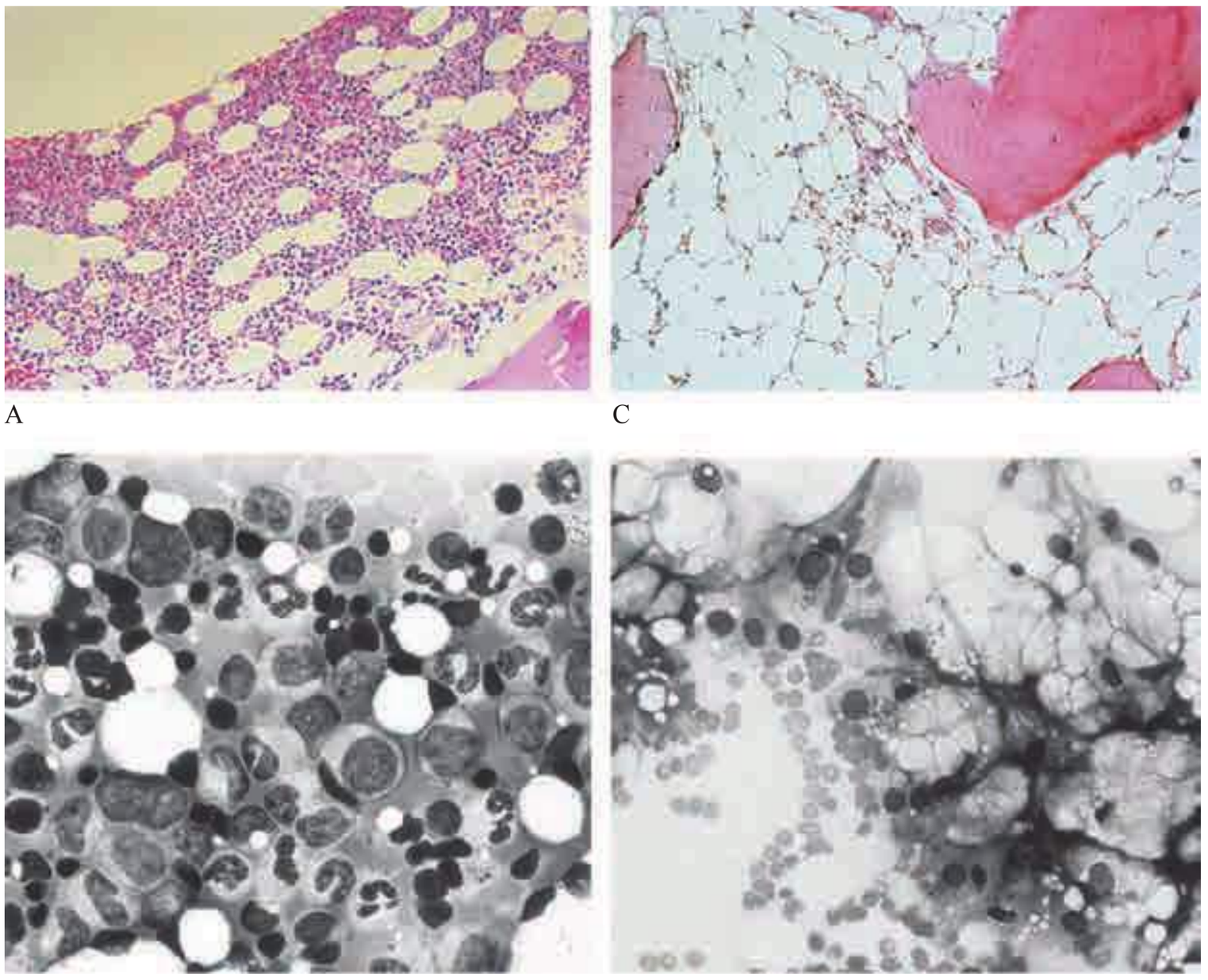


FIGURE 11-1
Normal and aplastic bone marrow. A. Normal bone marrow biopsy. B. Normal bone marrow aspirate smear. The marrow is normally 30–70% cellular, and there is a heterogeneous mix of myeloid, erythroid, and lymphoid cells. C. Aplastic anemia biopsy. D. Marrow smear in aplastic anemia. The marrow shows replacement of hematopoietic tissue by fat and only residual stromal and lymphoid cells.

drugs, altered drug metabolism has been invoked as a likely mechanism. The metabolic pathways of many drugs and chemicals, especially if they are polar and have limited water solubility, involve enzymatic degradation to highly reactive electrophilic compounds; these intermediates are toxic because of their propensity to bind to cellular macromolecules. For example, derivative hydroquinones and quinolones are responsible for benzene-induced tissue injury. Excessive generation of toxic intermediates or failure to detoxify the intermediates may be genetically determined and apparent only on specific drug challenge; the complexity and specificity of the pathways imply multiple susceptibility loci and would provide an explanation for the rarity of idiosyncratic drug reactions.

Immune-mediated injury

The recovery of marrow function in some patients prepared for bone marrow transplantation with antilymphocyte globulin first suggested that aplastic anemia might be immune mediated. Consistent with this hypothesis was the frequent failure of simple bone marrow transplantation from a syngeneic twin, without conditioning cytotoxic chemotherapy, which also argued both against simple stem cell absence as the cause and for the presence of a host factor producing marrow failure. Laboratory data support an important role for the immune system in aplastic anemia. Blood and bone marrow cells of patients can suppress normal hematopoietic progenitor cell growth, and removal of T cells from aplastic anemia bone marrow improves colony formation in vitro. Increased numbers of activated cytotoxic T cell clones are observed in aplastic anemia patients and usually decline with successful immunosuppressive therapy; type 1 cytokines are implicated; and interferon γ (IFN-γ) induces Fas expression on CD34 cells, leading to apoptotic cell death. The early immune system events in aplastic anemia are not well understood, but an oligoclonal, T cell response implies antigenic stimulus. The rarity of aplastic anemia despite common exposures (medicines, seronegative hepatitis) suggests that genetically determined features of the immune response can convert a normal physiologic response into a sustained abnormal autoimmune process, including polymorphisms in histocompatibility antigens, cytokine genes, and genes that regulate T cell polarization and effector function.

CLINICAL FEATURES

History

Aplastic anemia can appear abruptly or insidiously. Bleeding is the most common early symptom; a complaint of days to weeks of easy bruising, oozing from the gums, nose bleeds, heavy menstrual flow, and sometimes petechiae will have been noticed. With thrombocytopenia, massive hemorrhage is unusual, but small amounts of bleeding in the central nervous system can result in catastrophic intracranial or retinal hemorrhage. Symptoms of anemia are also frequent, including lassitude, weakness, shortness of breath, and a pounding sensation in the ears. Infection is an unusual first symptom in aplastic anemia (unlike in agranulocytosis, where pharyngitis, anorectal infection, or frank sepsis occurs early). A striking feature of aplastic anemia is the restriction of symptoms to the hematologic system, and patients often feel and look remarkably well despite drastically reduced blood counts. Systemic complaints and weight loss should point to other etiologies of pancytopenia. Prior drug use, chemical exposure, and preceding viral illnesses must often be elicited with repeated questioning. A family history of hematologic diseases or blood abnormalities, of pulmonary or liver fibrosis, or of early hair graying points to a telomeropathy.

Physical examination

Petechiae and ecchymoses are typical, and retinal hemorrhages may be present. Pelvic and rectal examinations can often be deferred but, when performed, should be undertaken with great gentleness to avoid trauma; these will often show bleeding from the cervical os and blood in the stool. Pallor of the skin and mucous membranes is common except in the most acute cases or those already transfused. Infection on presentation is unusual but may occur if the patient has been symptomatic for a few weeks. Lymphadenopathy and splenomegaly are highly atypical of aplastic anemia. Café au lait spots and short stature suggest Fanconi anemia; peculiar nails and leukoplakia suggest dyskeratosis congenita; early graying (and use of hair dyes to mask it!) suggests a telomerase defect.

LABORATORY STUDIES

Blood

T e smear shows large erythrocytes and a paucity of platelets and granulocytes. Mean corpuscular volume (MCV) is commonly increased. Reticulocytes are absent or few, and lymphocyte numbers may be normal or reduced. T e presence of immature myeloid forms suggests leukemia or MDS; nucleated red blood cells (RBCs) suggest marrow fibrosis or tumor invasion; abnormal platelets suggest either peripheral destruction or MDS.

Bone marrow

T e bone marrow is usually readily aspirated but dilute on smear, and the fatty biopsy specimen may be grossly pale on withdrawal; a "dry tap" instead suggests fibrosis or myelophthisis. In severe aplasia, the smear of the aspirated specimen shows only red cells, residual lymphocytes, and stromal cells; the biopsy (which should be >1 cm in length) is superior for determination of cellularity and shows mainly fat under the microscope, with hematopoietic cells occupying <25% of the marrow space; in the most serious cases, the biopsy is virtually all fat. T e correlation between marrow cellularity and disease severity is imperfect, in part because marrow cellularity declines physiologically with aging. Additionally, some patients with moderate disease by blood counts will have empty iliac crest biopsies, whereas "hot spots" of hematopoiesis may be seen in severe cases. If an iliac crest specimen is inadequate, cells may also be obtained by aspiration from the sternum. Residual hematopoietic cells should have normal morphology, except for mildly megaloblastic erythropoiesis; megakaryocytes are invariably greatly reduced and usually absent. Granulomas may indicate an infectious etiology of the marrow failure.

Ancillary studies

Chromosome breakage studies of peripheral blood using diepoxybutane or mitomycin C should be performed on children and younger adults to exclude Fanconi anemia. Very short telomere length (available commercially) strongly suggests the presence of a telomerase or shelterin mutation, which can be pursued by family studies and nucleotide sequencing. Chromosome studies of bone marrow cells are often revealing in MDS and should be negative in typical aplastic anemia. Flow cytometry offers a sensitive diagnostic test for PNH. Serologic studies may show evidence of viral infection, such as Epstein-Barr virus and HIV. Posthepatitis aplastic anemia is seronegative. T e spleen size should be determined by computed tomography (CT) scanning or ultrasound if the physical examination of the abdomen is unsatisfactory. Occasionally MRI may be helpful to assess the fat content of vertebrae in order to distinguish aplasia from MDS.

DIAGNOSIS

T e diagnosis of aplastic anemia is usually straightforward, based on the combination of pancytopenia with a fatty bone marrow. Aplastic anemia is a disease of the young and should be a leading diagnosis in the

pancytopenic adolescent or young adult. When pancytopenia is secondary, the primary diagnosis is usually obvious from either history or physical examination: the massive spleen of alcoholic cirrhosis, the history of metastatic cancer or SLE, or miliary tuberculosis on chest radiograph **(Table 11-1)**.

Diagnostic problems can occur with atypical presentations and among related hematologic diseases. Although pancytopenia is most common, some patients with bone marrow hypocellularity have depression of only one or two of three blood lines, with later progression to pancytopenia. The bone marrow in constitutional aplastic anemia is morphologically indistinguishable from the aspirate in acquired disease. The diagnosis can be suggested by family history, abnormal blood counts since childhood, or the presence of associated physical anomalies. Aplastic anemia may be difficult to distinguish from the hypocellular variety of MDS: MDS is favored by finding morphologic abnormalities, particularly of megakaryocytes and myeloid precursor cells, and typical cytogenetic abnormalities (see below).

PROGNOSIS

The natural history of severe aplastic anemia is rapid deterioration and death. Historically, provision first of RBC and later of platelet transfusions and effective antibiotics were of some benefit, but few patients show spontaneous recovery. The major prognostic determinant is the blood count. Severe disease has been defined by the presence of two of three parameters: absolute neutrophil count <500/μL, platelet count <20,000/μL, and corrected reticulocyte count <1% (or absolute reticulocyte count <60,000/μL). In the era of effective immunosuppressive therapies, absolute numbers of reticulocytes (>25,000/μL) and lymphocytes (>1000/μL) may be better predictors of response to treatment and long-term outcome.

TREATMENT Aplastic Anemia

Severe acquired aplastic anemia can be cured by replacement of the absent hematopoietic cells (and the immune system) by stem cell transplant, or it can be ameliorated by suppression of the immune system to allow recovery of the patient's residual bone marrow function. Glucocorticoids are not of value as primary therapy. Suspect exposures to drugs or chemicals should be discontinued; however, spontaneous recovery of severe blood count depression is rare, and a waiting period before beginning treatment may not be advisable unless the blood counts are only modestly depressed.

HEMATOPOIETIC STEM CELL TRANSPLANTATION This is the best therapy for the younger patient with a fully histocompatible sibling donor **(Chap. 31)**. Human leukocyte antigen (HLA) typing should be ordered as soon as the diagnosis of aplastic anemia is established in a child or younger adult. In transplant candidates, transfusion of blood from family members should be avoided so as to prevent sensitization to histocompatibility antigens, but limited numbers of blood products probably do not greatly affect outcome. For allogeneic transplant from fully matched siblings, long-term survival rates for children are approximately 90%. Transplant morbidity and mortality are increased among adults, due to the higher risk of chronic GVHD and serious infections.

Most patients do not have a suitable sibling donor. Occasionally, a full phenotypic match can be found within the family and serve as well. Far more available are other alternative donors, either unrelated but histocompatible volunteers or closely but not perfectly matched family members. High-resolution matching at HLA and more effective conditioning regimens and GVHD prophylaxis have led to improved survival rates in patients who proceed to alternative donor transplant, in some series approximating results with conventional sibling donors. Patients will be at risk for late complications, especially a higher rate of cancer, if radiation is used as a component of conditioning.

IMMUNOSUPPRESSION The standard regimen of antithymocyte globulin (ATG) in combination with cyclosporine induces hematologic recovery (independence from transfusion and a leukocyte count adequate to prevent infection) in 60–70% of patients. Children do especially well, whereas older adult patients often suffer complications due to the presence of comorbidities. An early robust hematologic response correlates with long-term survival. Improvement in granulocyte number is generally apparent within 2 months of treatment. Most recovered patients continue to have some degree of blood count depression, the MCV remains elevated, and bone marrow cellularity returns toward normal very slowly if at all. Relapse (recurrent pancytopenia) is frequent, often occurring as cyclosporine is discontinued; most, but not all, patients respond to reinstitution of immunosuppression, but some responders become dependent on continued cyclosporine administration. Development of MDS, with typical marrow morphologic or cytogenetic abnormalities, occurs in approximately 15% of treated patients, usually but not invariably associated with a return of pancytopenia, and some patients develop leukemia. A laboratory diagnosis of PNH can generally be made at the time of presentation of aplastic anemia by flow cytometry; recovered patients may have frank hemolysis if the PNH clone expands. Bone marrow examinations should be performed if there is an unfavorable change in blood counts.

Horse ATG is administered as intravenous infusions over 4 days. ATG binds to peripheral blood cells; therefore, platelet and granulocyte numbers may decrease further during active treatment. Serum sickness, a flulike illness with a characteristic cutaneous eruption and arthralgia, often develops approximately 10 days after initiating treatment.

Methylprednisolone is administered with ATG to ameliorate the immune consequences of heterologous protein infusion. Excessive or extended glucocorticoid therapy is associated with avascular joint necrosis. Cyclosporine is administered orally at an initial high dose, with subsequent adjustment according to blood levels obtained every 2 weeks; rough levels should be between 150 and 200 ng/mL. T e most important side effects are nephrotoxicity, hypertension, seizures, and opportunistic infections, especially Pneumocystis jiroveci (prophylactic treatment with monthly inhaled pentamidine is recommended).

Most patients with aplastic anemia lack a suitable marrow donor, and immunosuppression is the treatment of choice. Overall survival is equivalent with transplantation and immunosuppression. However, successful transplant cures marrow failure, whereas patients who recover adequate blood counts after immunosuppression remain at risk of relapse and malignant evolution. Because of excellent results in children and younger adults, allogeneic transplant should be performed if a suitable sibling donor is available. Increasing age and the severity of neutropenia are the most important factors weighing in the decision between transplant and immunosuppression in adults who have a matched family donor: older patients do better with ATG and cyclosporine, whereas transplant is preferred if granulocytopenia is profound.

Outcomes following both transplant and immunosuppression have improved with time. High doses of cyclophosphamide, without stem cell rescue, have been reported to produce durable hematologic recovery, without relapse or evolution to MDS, but this treatment can produce sustained severe fatal neutropenia, and response is often delayed.

OTHER THERAPIES T e effectiveness of androgens has not been verified in controlled trials, but occasional patients will respond or even demonstrate blood count dependence on continued therapy. Sex hormones upregulate telomerase gene activity in vitro, which is possibly also their mechanism of action in improving marrow function. For patients with moderate disease, especially if a telomere defect is present, or those with severe pancytopenia in whom immunosuppression has failed, a 3- to 4-month trial is appropriate.

Hematopoietic growth factors (HGFs) such as erythropoietin and granulocyte colony-stimulating factor (G-CSF) are not definitive therapy for severe aplastic anemia, and even their roles as adjuncts to immunosuppression are not clear. In research protocols, thrombopoietin mimetics have shown surprising activity in patients with refractory aplastic anemia, with patterns of blood count recovery suggesting that they act as stem cell stimulants.

SUPPORTIVE CARE Meticulous medical attention is required so that the patient may survive to benefit from definitive therapy or, having failed treatment, to maintain a reasonable existence in the face of pancytopenia. First and most important, infection in the presence of severe neutropenia must be aggressively treated by prompt institution of parenteral, broad-spectrum antibiotics, usually ceftazidime or a combination of an aminoglycoside, cephalosporin, and semisynthetic penicillin. T erapy is empirical and must not await results of culture, although specific foci of infection such as oropharyngeal or anorectal abscesses, pneumonia, sinusitis, and typhlitis (necrotizing colitis) should be sought on physical examination and with radiographic studies. When indwelling plastic catheters become contaminated, vancomycin should be added. Persistent or recrudescent fever implies fungal disease: Candida and Aspergillus are common, especially after several courses of antibacterial antibiotics. A major reason for the improved prognosis in aplastic anemia has been the development of better antifungal drugs and the timely institution of such therapy when infection is suspected. Granulocyte transfusions using G-CSF–mobilized peripheral blood may be effective in the treatment of overwhelming or refractory infections. Hand washing, the single best method of preventing the spread of infection, remains a neglected practice. Nonabsorbed antibiotics for gut decontamination are poorly tolerated and not of proven value. Total reverse isolation does not reduce mortality from infections.

Both platelet and erythrocyte numbers can be maintained by transfusion. Alloimmunization historically limited the usefulness of platelet transfusions and is now minimized by several strategies, including use of single donors to reduce exposure and physical or chemical methods to diminish leukocytes in the product; HLA-matched platelets are often effective in patients refractory to random donor products. Inhibitors of fibrinolysis such as aminocaproic acid have not been shown to relieve mucosal oozing; the use of low-dose glucocorticoids to induce “vascular stability” is unproven and not recommended. Whether platelet transfusions are better used prophylactically or only as needed remains unclear. Any rational regimen of prophylaxis requires transfusions once or twice weekly to maintain the platelet count >10,000/μL (oozing from the gut increases precipitously at counts <5000/μL). Menstruation should be suppressed either by oral estrogens or nasal follicle-stimulating hormone/luteinizing hormone (FSH/LH) antagonists. Aspirin and other nonsteroidal anti-inflammatory agents inhibit platelet function and must be avoided.

RBCs should be transfused to maintain a normal level of activity, usually at a hemoglobin value of 70 g/L (90 g/L if there is underlying cardiac or pulmonary disease); a regimen of 2 units every 2 weeks will replace normal losses in a patient without a functioning bone marrow. In chronic anemia, the iron chelators, deferoxamine and deferasirox, should be added at approximately the fiftieth transfusion to avoid secondary hemochromatosis.

PURE RED CELL APLASIA

Other, more restricted forms of marrow failure occur, in which only a single circulating cell type is affected and the marrow shows corresponding absence or decreased

numbers of specific precursor cells: are generative anemia as in PRCA (see below), thrombocytopenia with amegakaryocytosis **(Chap. 20)**, and neutropenia without marrow myeloid cells in agranulocytosis **(Chap. 5)**. In general, and in contrast to aplastic anemia and MDS, the unaffected lineages appear quantitatively and qualitatively normal. Agranulocytosis, the most frequent of these syndromes, is usually a complication of medical drug use (with agents similar to those related to aplastic anemia), either by a mechanism of direct chemical toxicity or by immune destruction. Agranulocytosis has an incidence similar to aplastic anemia but is especially frequent among older adults and in women. T e syndrome should resolve with discontinuation of exposure, but significant mortality is attached to neutropenia in the older and often previously unwell patient. Both pure white cell aplasia (agranulocytosis without incriminating drug exposure) and amegakaryocytic thrombocytopenia are exceedingly rare and, like PRCA, appear to be due to destructive antibodies or lymphocytes and can respond to immunosuppressive therapies. In all of the single-lineage failure syndromes, progression to pancytopenia or leukemia is unusual.

DEFINITION AND DIFFERENTIAL DIAGNOSIS

PRCA is characterized by anemia, reticulocytopenia, and absent or rare erythroid precursor cells in the bone marrow. T e classification of PRCA is shown in **Table 11-4**. In adults, PRCA is acquired. An identical syndrome can occur constitutionally: Diamond-Blackfan anemia, or congenital PRCA, is diagnosed at birth or in early childhood and often responds to glucocorticoid treatment; mutations in ribosome protein genes are etiologic. Temporary red cell failure occurs in transient aplastic crisis of hemolytic anemias due to acute parvovirus infection and in transient erythroblastopenia of childhood, which occurs in normal children.

TABLE 11-4

CLASSIFICATION OF PURE RED CELL APLASIA

- Self-limited
  - Transient erythroblastopenia of childhood
  - Transient aplastic crisis of hemolysis (acute B19 parvovirus infection)
- Fetal red blood cell aplasia
  - Nonimmune hydrops fetalis (in utero B19 parvovirus infection)
- Hereditary pure red cell aplasia
  - Congenital pure red cell aplasia (Diamond-Blackfan anemia)
- Acquired pure red cell aplasia
  - Cancer
    - Thymoma
    - Lymphoid malignancies (and more rarely other hematologic diseases)
    - Paraneoplastic to solid tumors
- Connective tissue disorders with immunologic abnormalities
  - Systemic lupus erythematosus, juvenile rheumatoid arthritis, rheumatoid arthritis
  - Multiple endocrine gland insuf ciency
- Viruses
  - Persistent B19 parvovirus, hepatitis, adult T cell leukemia virus, Epstein-Barr virus
- Pregnancy
- Drugs
  - Especially phenytoin, azathioprine, chloramphenicol, procainamide, isoniazid
- Antibodies to erythropoietin
- Idiopathic

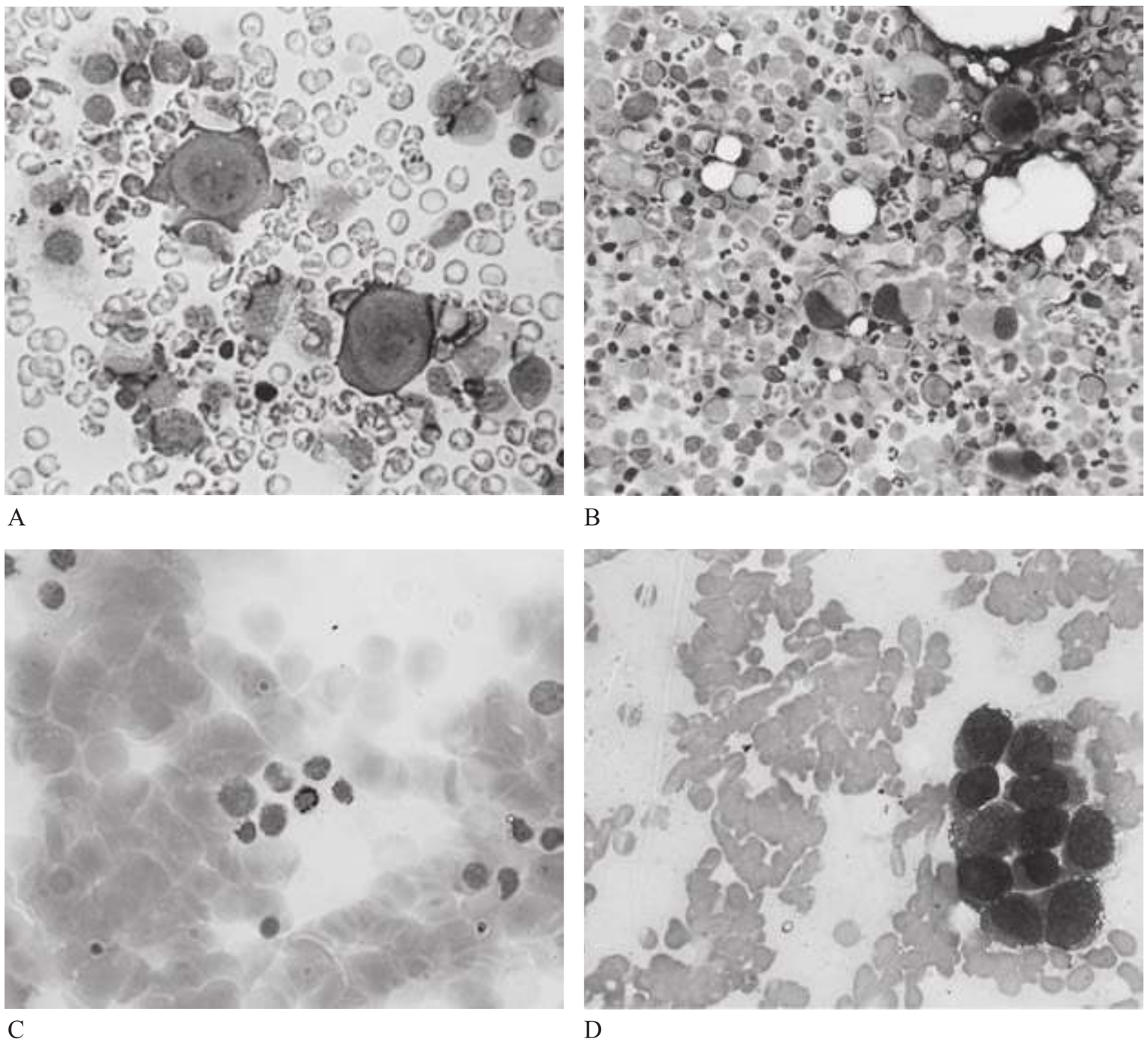
CLINICAL ASSOCIATIONS AND ETIOLOGY

PRCA has important associations with immune system diseases. A small minority of cases occur with a thymoma. More frequently, red cell aplasia can be the major manifestation of large granular lymphocytosis or complicate chronic lymphocytic leukemia. Some patients may be hypogammaglobulinemic. Infrequently (compared to agranulocytosis), PRCA can be due to an idiosyncratic drug reaction. Subcutaneous administration of erythropoietin (EPO) has provoked PRCA mediated by neutralizing antibodies.

Like aplastic anemia, PRCA results from diverse mechanisms. Antibodies to RBC precursors are frequently present in the blood, but T cell inhibition is probably the more common immune mechanism. Cytotoxic lymphocyte activity restricted by histocompatibility locus or specific for human T cell leukemia/lymphoma virus I–infected cells and natural killer cell activity inhibitory of erythropoiesis have been demonstrated in particularly well-studied individual cases.

PERSISTENT PARVOVIRUS B19 INFECTION

Chronic parvovirus infection is an important, treatable cause of PRCA. T is common virus causes a benign exanthem of childhood (fifth disease) and a polyarthralgia/arthritis syndrome in adults. In patients with underlying hemolysis (or any condition that increases demand for RBC production), parvovirus infection can cause a transient aplastic crisis and an abrupt but temporary worsening of the anemia due to failed erythropoiesis. In normal individuals, acute infection is resolved by production of neutralizing antibodies to the virus, but in the setting of congenital, acquired, or iatrogenic immunodeficiency, persistent viral infection may occur. T e bone marrow shows red cell aplasia and the presence of giant pronormoblasts **(Fig. 11-2)**, which is the cytopathic sign of B19 parvovirus infection. Viral tropism for human erythroid progenitor cells is due to its use of erythrocyte P antigen as a cellular



A B C D

FIGURE 11-2
Pathognomonic cells in marrow failure syndromes. A. Giant pronormoblast, the cytopathic effect of B19 parvovirus infection of the erythroid progenitor cell. B. Uninuclear megakaryocyte and microblastic erythroid precursors typical of the 5q–myelodysplasia syndrome. C. Ringed sideroblast showing perinuclear iron granules. D. Tumor cells present on a touch preparation made from the marrow biopsy of a patient with metastatic carcinoma.

receptor for entry. Direct cytotoxicity of virus causes anemia if demands on erythrocyte production are high; in normal individuals, the temporary cessation of red cell production is not clinically apparent, and skin and joint symptoms are mediated by immune complex deposition.

TREATMENT Pure Red Cell Aplasia

History, physical examination, and routine laboratory studies may disclose an underlying disease or a drug exposure. Thymoma should be sought by radiographic procedures. Tumor excision is indicated, but anemia does not necessarily improve with surgery. The diagnosis of parvovirus infection requires detection of viral DNA sequences in the blood (IgG and IgM antibodies are commonly absent). The presence of erythroid colonies has been considered predictive of response to immunosuppressive therapy in idiopathic PRCA.

Red cell aplasia is compatible with long-term survival with supportive care alone: a combination of erythrocyte transfusions and iron chelation. For persistent B19 parvovirus infection, almost all patients respond to intravenous immunoglobulin therapy (e.g., 0.4 g/kg daily for 5 days), although relapse and retreatment may be expected, especially in patients with AIDS. The majority of patients with idiopathic PRCA respond favorably to immunosuppression. Most first receive a course of glucocorticoids. Also effective are cyclosporine, ATG, azathioprine, and cyclophosphamide.

MYELODYSPLASIA

DEFINITION

The myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic disorders broadly characterized by both (1) cytopenias due to bone marrow failure and (2) a high risk of development of acute myeloid leukemia (AML). Anemia, often with thrombocytopenia and neutropenia, occurs with dysmorphic (abnormal appearing) and usually cellular bone marrow, which is evidence of ineffective blood cell production. In patients with "low-risk" MDS, marrow failure

dominates the clinical course. In other patients, myeloblasts are present at diagnosis, chromosomes are abnormal, and the "high risk" is due to leukemic progression. MDS may be fatal due to the complications of pancytopenia or the incurability of leukemia, but a large proportion of patients will die of concurrent disease, the comorbidities typical in an elderly population. A clinically useful nosology of these often confusing entities was first developed by the French-American-British Cooperative Group in 1983. Five entities were defined: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML). T e World Health Organization (WHO) classification (2002) recognized that the distinction between RAEB-t and AML is arbitrary and grouped them together as acute leukemia and that CMML behaves as a myeloproliferative disease; the WHO classification also separated refractory anemias with dysmorphic change restricted to erythroid lineage from those with multilineage changes. In a 2008 revision, specific categories for unilineage dysplasias were added **(Table 11-5)**.

TABLE 11-5

WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF MYELODYSPLASTIC SYNDROMES/NEOPLASMS

NAME	WHO ESTIMATED PROPORTION OF PATIENTS WITH MDS	PERIPHERAL BLOOD: KEY FEATURES	BONE MARROW: KEY FEATURES
Refractory cytopenias with unilineage dysplasia (RCUD):			
Refractory anemia (RA)	10–20%	Anemia <1% of blasts	Unilineage erythroid dysplasia (in ≥10% of cells) <5% blasts
Refractory neutropenia (RN)	<1%	Neutropenia <1% blasts	Unilineage granulocytic dysplasia <5% blasts
Refractory thrombocytopenia (RT)	<1%	Thrombocytopenia <1% blasts	Unilineage megakaryocytic dysplasia <5% blasts
Refractory anemia with ringed sideroblasts (RARS)	3–11%	Anemia No blasts	Unilineage erythroid dysplasia ≥15% of erythroid precursors are ringed sideroblasts <5% blasts
Refractory cytopenias with multilineage dysplasia (RCMD)	30%	Cytopenia(s) <1% blasts No Auer rods	Multilineage dysplasia ± ringed sideroblasts <5% blasts No Auer rods
Refractory anemia with excess blasts, type 1 (RAEB-1)	40%	Cytopenia(s) <5% blasts No Auer rods	Unilineage or multilineage dysplasia
Refractory anemia with excess blasts, type 2 (RAEB-2)		Cytopenia(s) 5–19% blasts ± Auer rods	Unilineage or multilineage dysplasia 10–19% blasts ± Auer rods
MDS associated with isolated del(5q) [del(5q)]	Uncommon	Anemia Normal or high platelet count <1% blasts	Isolated 5q31 chromosome deletion Anemia; hypolobated megakaryocytes <5% blasts
Childhood MDS, including refractory cytopenia of childhood (provisional) (RCC)	<1%	Pancytopenia	<5% marrow blasts for RCC Marrow usually hypocellular
MDS, unclassifiable (MDS-U)	?	Cytopenia ≤1% blasts	Does not fit other categories Dysplasia <5% blasts If no dysplasia, MDS-associated karyotype

Note: If peripheral blood blasts are 2–4%, the diagnosis is RAEB-1 even if marrow blasts are <5%. If Auer rods are present, the WHO considers the diagnosis RAEB-2 if the blast proportion is <20% (even if <10%), or acute myeloid leukemia (AML) if at least 20% blasts. For all subtypes, peripheral blood monocytes are $<1 \times 10^9$/L. Bicytopenia may be observed in RCUD subtypes, but pancytopenia with unilineage marrow dysplasia should be classified as MDS-U. Therapy-related MDS (t-MDS), whether due to alkylating agents or topoisomerase II inhibitors (t-MDS/t-AML) is now included in the WHO classification of myeloid neoplasms. The listing in this table excludes MDS/myeloproliferative neoplasm overlap categories, such as chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, and the provisional entity RARS with thrombocytosis.
Abbreviation: MDS, myelodysplastic syndrome.

T e diagnosis of MDS may be a challenge, because sometimes subtle clinical and pathologic features must be distinguished and precise diagnostic categorization requires a hematopathologist knowledgeable in the latest classification scheme. Nonetheless, it is important that the internist and primary care physician be sufficiently familiar with MDS to expedite referral to a hematologist, both because many new therapies are now available to improve hematopoietic function and the judicious use of supportive care can improve the patient's quality of life.

EPIDEMIOLOGY

Idiopathic MDS is a disease of the elderly; the mean age at onset is older than 70 years. T ere is a slight male preponderance. MDS is a relatively common form of bone marrow failure, with reported incidence rates of 35 to >100 per million persons in the general population and 120 to >500 per million in the older adult. MDS is rare in children, but monocytic leukemia can be seen. Secondary or therapy-related MDS is not age related. Rates of MDS have increased over time, due to better recognition of the syndrome by physicians and an aging population.

ETIOLOGY AND PATHOPHYSIOLOGY

MDS is associated with environmental exposures such as radiation and benzene; other risk factors have been reported inconsistently. Secondary MDS occurs as a late toxicity of cancer treatment, usually a combination of radiation and the radiomimetic alkylating agents such as busulfan, nitrosourea, or procarbazine (with a latent period of 5–7 years) or the DNA topoisomerase inhibitors (2-year latency). Acquired aplastic anemia, Fanconi anemia, and other constitutional marrow failure diseases can evolve into MDS. However, the typical MDS patient does not have a suggestive environmental exposure history or a preceding hematologic disease. MDS is a disease of aging, suggesting random cumulative intrinsic and environmental damage to marrow cells.

MDS is a clonal hematopoietic stem cell disorder characterized by disordered cell proliferation and impaired differentiation, resulting in cytopenias and risk of progression to leukemia. Both chromosomal and genetic instability have been implicated, and both are likely aging-related. Cytogenetic abnormalities are found in approximately one-half of patients, and some of the same specific lesions are also seen in frank leukemia; aneuploidy (chromosome loss or gain) is more frequent than translocations. More sensitive assays, such as comparative genomic hybridization and single nucleotide polymorphism arrays, reveal chromosomal abnormalities in a large proportion of patients with normal conventional cytogenetics. Accelerated telomere attrition may destabilize the genome in marrow failure and predispose to acquisition of chromosomal lesions. Cytogenetic abnormalities are not random (loss of all or part of 5, 7, and 20, trisomy of 8) and may be related to etiology (11q23 following topoisomerase II inhibitors). T e type and number of cytogenetic abnormalities strongly correlate with the probability of leukemic transformation and survival.

Genomics has illuminated the role of point mutations in the pathophysiology of MDS. Recurrent somatic mutations, acquired in the abnormal marrow cells and absent in the germline, have been identified in almost 100 genes. Many of the same genes are also mutated in AML without MDS, whereas others are distinctive in subtypes of MDS. A prominent example of the latter is the discovery of mutations in genes of the RNA splicing machinery, especially SF3B1, which strongly associate with sideroblastic anemia. Some mutations correlate with prognosis: spliceosome defects with favorable outcome, and mutations in EZH2, TP53, RUNX1, and ASXL1 with poor outcome. Mutations and cytogenetic abnormalities are not independent: TP53 mutations associate with complex cytogenetic abnormalities and TET2 mutations with normal cytogenetics. Correlation and exclusion in the pattern of mutations indicate a functional genomic architecture. Analysis of deep sequencing results in patients whose MDS evolved to AML has shown evidence of clonal succession, with founder clones acquiring further mutations that allow clonal dominance. Furthermore, the prevalence of abnormal cells by morphology underestimates bone marrow involvement by MDS clones, as cells normal in appearance are apparently derived from the abnormal clones. Both presenting and evolving hematologic manifestations result from the accumulation of multiple genetic lesions: loss of tumor-suppressor genes, activating oncogene mutations, epigenetic pathways that affect mRNA processing and methylation status, or other harmful alterations. Pathophysiology has been linked to mutations and chromosome abnormalities in some specific MDS syndromes. T e 5q– deletion leads to heterozygous loss of a ribosomal protein gene that is also mutant in Diamond-Blackfan anemia, and both are characterized by deficient erythropoiesis. An immune pathophysiology may underlie trisomy 8 MDS, in which patients often experience improved blood counts after immunosuppressive therapy; there is T cell activity directed to hematopoietic progenitors, which the cytogenetically aberrant clone resists. However, in general for MDS, the role of the immune system and its cells and cytokines; the role of the hematopoietic stem cell niche, the microenvironment, and cell-cell interactions; the fate of normal cells in the Darwinian competitive environment of the dysplastic marrow; and how mutant cells produce marrow failure in MDS are not well understood.

CLINICAL FEATURES

Anemia dominates the early course. Most symptomatic patients complain of the gradual onset of fatigue and weakness, dyspnea, and pallor, but at least one-half the patients are asymptomatic, and their MDS is discovered only incidentally on routine blood counts. Previous chemotherapy or radiation exposure is an important historic fact. Fever and weight loss should point to a myeloproliferative rather than myelodysplastic process. MDS in childhood is rare and, when diagnosed, increases the likelihood of an underlying genetic disease. Children with Down syndrome are susceptible to MDS, and a family history may indicate a hereditary form of sideroblastic anemia, Fanconi anemia, or a telomeropathy. Inherited GATA2 mutations, as in the MonoMAC syndrome (with increased susceptibility to viral, mycobacteria, and fungal infections, as well as deficient numbers of monocytes, natural killer cells, and B lymphocytes), also cause MDS in young patients.

The physical examination is remarkable for signs of anemia; approximately 20% of patients have splenomegaly. Some unusual skin lesions, including Sweet syndrome (febrile neutrophilic dermatosis), occur with MDS. Accompanying autoimmune syndromes are not infrequent. In the younger patient, stereotypical anomalies point to a constitutional syndrome (short stature, abnormal thumbs in Fanconi anemia; early graying in the telomeropathies; cutaneous warts in GATA2 deficiency).

LABORATORY STUDIES

Blood

Anemia is present in most cases, either alone or as part of bi- or pancytopenia; isolated neutropenia or thrombocytopenia is more unusual. Macrocytosis is common, and the smear may be dimorphic with a distinctive population of large red blood cells. Platelets are also large and lack granules. In functional studies, they may show marked abnormalities, and patients may have bleeding symptoms despite seemingly adequate numbers. Neutrophils are hypogranulated; have hyposegmented, ringed, or abnormally segmented nuclei; contain Döhle bodies; and may be functionally deficient. Circulating myeloblasts usually correlate with marrow blast numbers, and their quantity is important for classification and prognosis. The total white blood cell count (WBC) is usually normal or low, except in chronic myelomonocytic leukemia. As in aplastic anemia, MDS can be associated with a clonal population of PNH cells. Genetic testing is commercially available for constitutional syndromes.

Bone marrow

The bone marrow is usually normal or hypercellular, but in about 20% of cases, it is sufficiently hypocellular to be confused with aplasia. No single characteristic feature of marrow morphology distinguishes MDS, but the following are commonly observed: dyserythropoietic changes (especially nuclear abnormalities) and ringed sideroblasts in the erythroid lineage; hypogranulation and hyposegmentation in granulocytic precursors, with an increase in myeloblasts; and megakaryocytes showing reduced numbers of or disorganized nuclei. Megaloblastic nuclei associated with defective hemoglobinization in the erythroid lineage are common. Prognosis strongly correlates with the proportion of marrow blasts. Cytogenetic analysis and fluorescent in situ hybridization can identify chromosomal abnormalities.

DIFFERENTIAL DIAGNOSIS

Deficiencies of vitamin B_{12} or folate should be excluded by appropriate blood tests; vitamin B_6 deficiency can be assessed by a therapeutic trial of pyridoxine if the bone marrow shows ringed sideroblasts. Marrow dysplasia can be observed in acute viral infections, drug reactions, or chemical toxicity but should be transient. More difficult are the distinctions between hypocellular MDS and aplasia or between refractory anemia with excess blasts and early acute leukemia. The WHO considers the presence of 20% blasts in the marrow as the criterion that separates AML from MDS. In young patients, underlying, predisposing genetic diseases should be considered (see above).

PROGNOSIS

The median survival varies greatly from years for patients with 5q– or sideroblastic anemia to a few months in refractory anemia with excess blasts or severe pancytopenia associated with monosomy 7; an International Prognostic Scoring System (IPSS; **Table 11-6**) assists in making predictions. Even "low-risk" MDS has significant morbidity and mortality. Most patients die as a result of complications of pancytopenia and not due to leukemic transformation; perhaps one-third will succumb to other diseases unrelated to their MDS. Precipitous worsening of pancytopenia, acquisition of new chromosomal abnormalities on serial cytogenetic determination, increase in the number of blasts, and marrow fibrosis are all poor prognostic indicators. The outlook in therapy-related MDS, regardless of type, is extremely poor, and most patients will progress within a few months to refractory AML.

TREATMENT Myelodysplasia

Historically, the therapy of MDS has been unsatisfactory, but new drugs recently have been approved for this disease. Several regimens appear to not only improve blood counts

TABLE 11-6

INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)

	SCORE VALUE				
PROGNOSTIC VARIABLE	0	0.5	1	1.5	2
Bone marrow blasts (%)	<5%	5–10%		11–20%	21–30%
Karyotype[a]	Good	Intermediate	Poor		
Cytopenia[b] (lineages affected)	0 or 1	2 or 3			
Risk Group Scores	Score				
Low	0				
Intermediate-1	0.5–1				
Intermediate-2	1.5–2				
High	≥2.5				

[a]Good, normal, –Y, del(5q), del (20q); poor, complex (≥3 abnormalities) or chromosome 7 abnormalities; intermediate, all other abnormalities.
[b]Cytopenias defined as hemoglobin <100 g/L, platelet count <100,000/μL, and absolute neutrophil count <1500/μL

but to delay onset of leukemia and to improve survival. The choice of therapy for an individual patient, administration of treatment, and management of toxicities are complicated and require hematologic expertise.

Only hematopoietic stem cell transplantation offers cure of MDS. The current survival rate in selected patient cohorts is ~50% at 3 years and is improving. Results using unrelated matched donors are now similar to those obtained using siblings, and patients in their 50s and 60s have been successfully transplanted. Nevertheless, treatment-related mortality and morbidity increase with recipient age. Complicating the decision to undertake transplant is that the high-risk patient, for whom the procedure is most obviously indicated, has a high probability of a poor outcome from transplant-related mortality or disease relapse, whereas the low-risk patient, who is more likely to tolerate transplant, also may do well for years with less aggressive therapies.

MDS has been regarded as particularly refractory to cytotoxic chemotherapy regimens, and as in AML in the older adult, drug toxicity is frequent and often fatal, and remissions if achieved are brief. Low doses of cytotoxic drugs have been administered for their "differentiation" potential, and from this experience, drug therapies have emerged based on pyrimidine analogues. These new drugs are classified as epigenetic modulators, believed to act through a demethylating mechanism to alter gene regulation and allow differentiation to mature blood cells from the abnormal MDS stem cell (although global methylation status has not correlated with clinical efficacy). Azacitidine and decitabine are two epigenetic modifiers frequently used in bone marrow failure clinics. Azacitidine improves blood counts and survival in MDS, compared to best supportive care. Azacitidine is usually administered subcutaneously, daily for 7 days, at 4-week intervals, for at least four cycles before assessing for response. Overall, generally improved blood counts with a decrease in transfusion requirements occurred in ~50% of patients in published trials. Response is dependent on continued drug administration, and most patients eventually will no longer respond and experience recurrent cytopenias or progression to AML. Decitabine is closely related to azacitidine and more potent; 30–50% of patients show responses in blood counts, with a duration of response of almost a year. Decitabine is usually administered by continuous intravenous infusion in regimens of varying doses and durations of 3 to 10 days in repeating cycles. The major toxicity of azacitidine and decitabine is myelosuppression, leading to worsened blood counts. Other symptoms associated with cancer chemotherapy frequently occur. Demethylating agents are frequently used in the high-risk patient who is not a candidate for stem cell transplant. In the lower risk patient, they are also effective, but alternative therapies should be considered.

Lenalidomide, a thalidomide derivative with a more favorable toxicity profile, is particularly effective in reversing anemia in MDS patients with 5q– syndrome; not only do a high proportion of these patients become transfusion independent with normal or near-normal hemoglobin levels, but their cytogenetics also become normal. The drug has many biologic activities, and it is unclear which is critical for clinical efficacy. Lenalidomide is administered orally. Most patients will improve within 3 months of initiating therapy. Toxicities include myelosuppression (worsening thrombocytopenia and neutropenia, necessitating blood count monitoring) and an increased risk of deep vein thrombosis and pulmonary embolism.

Immunosuppression, as used in aplastic anemia, also may produce sustained independence from transfusion and improve survival. ATG, cyclosporine, and the anti-CD52 monoclonal antibody alemtuzumab are especially effective in younger MDS patients (<60 years old) with more favorable IPSS scores and who bear the histocompatibility antigen HLA-DR15.

HGFs can improve blood counts but, as in most other marrow failure states, have been most beneficial to patients with the least severe pancytopenia. EPO alone or in combination

with G-CSF can improve hemoglobin levels, but mainly in those with low serum EPO levels who have no or only a modest need for transfusions. Survival does not appear to be improved by G-CSF treatment alone but may be enhanced by erythropoietin and amelioration of anemia. G-CSF treatment alone failed to improve survival in a controlled trial.

T e same principles of supportive care described for aplastic anemia apply to MDS. Despite improvements in drug therapy, many patients will be anemic for years. RBC transfusion support should be accompanied by iron chelation to prevent secondary hemochromatosis.

MYELOPHTHISIC ANEMIAS

Fibrosis of the bone marrow **(see Fig. 10-2)**, usually accompanied by a characteristic blood smear picture called leukoerythroblastosis, can occur as a primary hematologic disease, called myelof brosis or myeloid metaplasia **(Chap. 13)**, and as a secondary process, called myelophthisis. Myelophthisis, or secondary myelofibrosis, is reactive. Fibrosis can be a response to invading tumor cells, usually an epithelial cancer of breast, lung, or prostate origin or neuroblastoma. Marrow fibrosis may occur with infection of mycobacteria (both Mycobacterium tuberculosis and Mycobacterium avium), fungi, or HIV and in sarcoidosis. Intracellular lipid deposition in Gaucher's disease and obliteration of the marrow space related to absence of osteoclast remodeling in congenital osteopetrosis also can produce fibrosis. Secondary myelofibrosis is a late consequence of radiation therapy or treatment with radiomimetic drugs. Usually the infectious or malignant underlying processes are obvious. Marrow fibrosis can also be a feature of a variety of hematologic syndromes, especially chronic myeloid leukemia, multiple myeloma, lymphomas, myeloma, and hairy cell leukemia.

T e pathophysiology has three distinct features: proliferation of fibroblasts in the marrow space (myelofibrosis); the extension of hematopoiesis into the long bones and into extramedullary sites, usually the spleen, liver, and lymph nodes (myeloid metaplasia); and ineffective erythropoiesis. T e etiology of the fibrosis is unknown but most likely involves dysregulated production of growth factors: platelet-derived growth factor and transforming growth factor β have been implicated. Abnormal regulation of other hematopoietins would lead to localization of blood-producing cells in nonhematopoietic tissues and uncoupling of the usually balanced processes of stem cell proliferation and differentiation. Myelofibrosis is remarkable for pancytopenia despite very large numbers of circulating hematopoietic progenitor cells.

Anemia is dominant in secondary myelofibrosis, usually normocytic and normochromic. T e diagnosis is suggested by the characteristic leukoerythroblastic smear **(see Fig. 10-1)**. Erythrocyte morphology is highly abnormal, with circulating nucleated RBCs, teardrops, and shape distortions. WBC numbers are often elevated, sometimes mimicking a leukemoid reaction, with circulating myelocytes, promyelocytes, and myeloblasts. Platelets may be abundant and are often of giant size. Inability to aspirate the bone marrow, the characteristic "dry tap," can allow a presumptive diagnosis in the appropriate setting before the biopsy is decalcified.

T e course of secondary myelofibrosis is determined by its etiology, usually a metastatic tumor or an advanced hematologic malignancy. Treatable causes must be excluded, especially tuberculosis and fungus. Transfusion support can relieve symptoms.

CHAPTER 12

TRANSFUSION BIOLOGY AND THERAPY

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BLOOD GROUP ANTIGENS AND ANTIBODIES

The study of red blood cell (RBC) antigens and antibodies forms the foundation of transfusion medicine. Serologic studies initially characterized these antigens, but now the molecular composition and structure of many are known. Antigens, either carbohydrate or protein, are assigned to a blood group system based on the structure and similarity of the determinant epitopes. Other cellular blood elements and plasma proteins are also antigenic and can result in alloimmunization, the production of antibodies directed against the blood group antigens of another individual. These antibodies are called alloantibodies.

Antibodies directed against RBC antigens may result from "natural" exposure, particularly to carbohydrates that mimic some blood group antigens. Those antibodies that occur via natural stimuli are usually produced by a T cell–independent response (thus, generating no memory) and are IgM isotype. Autoantibodies (antibodies against autologous blood group antigens) arise spontaneously or as the result of infectious sequelae (e.g., from Mycoplasma pneumoniae) and are also often IgM. These antibodies are often clinically insignificant due to their low affinity for antigen at body temperature. However, IgM antibodies can activate the complement cascade and result in hemolysis. Antibodies that result from allogeneic exposure, such as transfusion or pregnancy, are usually IgG. IgG antibodies commonly bind to antigen at warmer temperatures and may hemolyze RBCs. Unlike IgM antibodies, IgG antibodies can cross the placenta and bind fetal erythrocytes bearing the corresponding antigen, resulting in hemolytic disease of the newborn, or hydrops *fe*talis.

Alloimmunization to leukocytes, platelets, and plasma proteins may also result in transfusion complications such as fevers and urticaria but generally does not cause hemolysis. Assay for these other alloantibodies is not routinely performed; however, they may be detected using special assays.

ABO ANTIGENS AND ANTIBODIES

The first blood group antigen system, recognized in 1900, was ABO, the most important in transfusion medicine. The major blood groups of this system are A, B, AB, and O. O type RBCs lack A or B antigens. These antigens are carbohydrates attached to a precursor backbone, may be found on the cellular membrane either as glycosphingolipids or glycoproteins, and are secreted into plasma and body fluids as glycoproteins. H substance is the immediate precursor on which the A and B antigens are added. This H substance is formed by the addition of fucose to the glycolipid or glycoprotein backbone. The subsequent addition of N-acetylgalactosamine creates the A antigen, whereas the addition of galactose produces the B antigen.

The genes that determine the A and B phenotypes are found on chromosome 9p and are expressed in a Mendelian codominant manner. The gene products are glycosyl transferases, which confer the enzymatic capability of attaching the specific antigenic carbohydrate. Individuals who lack the "A" and "B" transferases are phenotypically type "O," whereas those who inherit both transferases are type "AB." Rare individuals lack the H gene, which codes for fucose transferase, and cannot form H substance. These individuals are homozygous for the silent h allele (hh) and have Bombay phenotype (O_h).

The ABO blood group system is important because essentially all individuals produce antibodies to the ABH carbohydrate antigen that they lack. The naturally occurring anti-A and anti-B antibodies are termed isoagglutinins. Thus, type A individuals produce anti-B, whereas type B individuals make anti-A. Neither isoagglutinin is found in type AB individuals, whereas type O individuals produce both anti-A and anti-B. Thus,

persons with type AB are "universal recipients" because they do not have antibodies against any ABO phenotype, whereas persons with type O blood can donate to essentially all recipients because their cells are not recognized by any ABO isoagglutinins. The rare individuals with Bombay phenotype produce antibodies to H substance (which is present on all red cells except those of hh phenotype) as well as to both A and B antigens and are therefore compatible only with other hh donors.

In most people, A and B antigens are secreted by the cells and are present in the circulation. Nonsecretors are susceptible to a variety of infections (e.g., Candida albicans, Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus in*fl*uenzae) because many organisms may bind to polysaccharides on cells. Soluble blood group antigens may block this binding.

RH SYSTEM

The Rh system is the second most important blood group system in pretransfusion testing. The Rh antigens are found on a 30- to 32-kDa RBC membrane protein that has no defined function. Although >40 different antigens in the Rh system have been described, five determinants account for the vast majority of phenotypes. The presence of the D antigen confers Rh "positivity," whereas persons who lack the D antigen are Rh negative. Two allelic antigen pairs, E/e and C/c, are also found on the Rh protein. The three Rh genes, E/e, D, and C/c, are arranged in tandem on chromosome 1 and inherited as a haplotype, i.e., cDE or Cde. Two haplotypes can result in the phenotypic expression of two to five Rh antigens.

The D antigen is a potent alloantigen. About 15% of individuals lack this antigen. Exposure of these Rh-negative people to even small amounts of Rh-positive cells, by either transfusion or pregnancy, can result in the production of anti-D alloantibody.

OTHER BLOOD GROUP SYSTEMS AND ALLOANTIBODIES

More than 100 blood group systems are recognized, composed of more than 500 antigens. The presence or absence of certain antigens has been associated with various diseases and anomalies; antigens also act as receptors for infectious agents. Alloantibodies of importance in routine clinical practice are listed in **Table 12-1**.

Antibodies to Lewis system carbohydrate antigens are the most common cause of incompatibility during pretransfusion screening. The Lewis gene product is a fucosyl transferase and maps to chromosome 19. The antigen is not an integral membrane structure but is adsorbed to the RBC membrane from the plasma. Antibodies to Lewis antigens are usually IgM and cannot cross the placenta. Lewis antigens may be adsorbed onto tumor cells and may be targets of therapy.

I system antigens are also oligosaccharides related to H, A, B, and Le. I and i are not allelic pairs but are carbohydrate antigens that differ only in the extent of branching. The i antigen is an unbranched chain that is converted by the I gene product, a glycosyltransferase, into a branched chain. The branching process affects all the ABH antigens, which become progressively more branched in the first 2 years of life. Some patients with cold agglutinin disease or lymphomas can produce anti-I autoantibodies that cause RBC destruction. Occasional patients with mononucleosis or Mycoplasma pneumonia may develop cold agglutinins of either anti-I or anti-i specificity. Most adults lack i expression; thus, finding a donor for patients with anti-i is not difficult. Even though most adults express I antigen, binding is generally low at body temperature. Thus, administration of warm blood prevents isoagglutination.

The P system is another group of carbohydrate antigens controlled by specific glycosyltransferases. Its clinical significance is in rare cases of syphilis and viral infection that lead to paroxysmal cold hemoglobinuria. In these cases, an unusual autoantibody to P is

TABLE 12-1

RBC BLOOD GROUP SYSTEMS AND ALLOANTIGENS

BLOOD GROUP SYSTEM	ANTIGEN	ALLOANTIBODY	CLINICAL SIGNIFICANCE
Rh (D, C/c, E/e)	RBC protein	IgG	HTR, HDN
Lewis (Le^a, Le^b)	Oligosaccharide	IgM/IgG	Rare HTR
Kell (K/k)	RBC protein	IgG	HTR, HDN
Duffy (Fy^a/Fy^b)	RBC protein	IgG	HTR, HDN
Kidd (Jk^a/Jk^b)	RBC protein	IgG	HTR (often delayed), HDN (mild)
I/i	Carbohydrate	IgM	None
MNSsU	RBC protein	IgM/IgG	Anti-M rare HDN, anti-S, -s, and -U HDN, HTR

Abbreviations: HDN, hemolytic disease of the newborn; HTR, hemolytic transfusion reaction; RBC, red blood cell.

produced that binds to RBCs in the cold and fixes complement upon warming. Antibodies with these biphasic properties are called Donath-Landsteiner antibodies. The P antigen is the cellular receptor of parvovirus B19 and also may be a receptor for Escherichia coli binding to urothelial cells.

The MNSsU system is regulated by genes on chromosome 4. M and N are determinants on glycophorin A, an RBC membrane protein, and S and s are determinants on glycophorin B. Anti-S and anti-s IgG antibodies may develop after pregnancy or transfusion and lead to hemolysis. Anti-U antibodies are rare but problematic; virtually every donor is incompatible because nearly all persons express U.

The Kell protein is very large (720 amino acids), and its secondary structure contains many different antigenic epitopes. The immunogenicity of Kell is third behind the ABO and Rh systems. The absence of the Kell precursor protein (controlled by a gene on X) is associated with acanthocytosis, shortened RBC survival, and a progressive form of muscular dystrophy that includes cardiac defects. This rare condition is called the McLeod phenotype. The K_x gene is linked to the 91-kDa component of the NADPH-oxidase on the X chromosome, deletion or mutation of which accounts for about 60% of cases of chronic granulomatous disease.

The Duffy antigens are codominant alleles, Fy^a and Fy^b, that also serve as receptors for Plasmodium vivax. More than 70% of persons in malaria-endemic areas lack these antigens, probably from selective influences of the infection on the population. For unknown reasons, the lack of the Duffy antigen receptor for cytokines (DARC) is associated with mild neutropenia.

The Kidd antigens, Jk^a and Jk^b, may elicit antibodies transiently. A delayed hemolytic transfusion reaction that occurs with blood tested as compatible is often related to delayed appearance of anti-Jk^a.

PRETRANSFUSION TESTING

Pretransfusion testing of a potential recipient consists of the "type and screen." The "forward type" determines the ABO and Rh phenotype of the recipient's RBC by using antisera directed against the A, B, and D antigens. The "reverse type" detects isoagglutinins in the patient's serum and should correlate with the ABO phenotype, or forward type.

The alloantibody screen identifies antibodies directed against other RBC antigens. The alloantibody screen is performed by mixing patient serum with type O RBCs that contain the major antigens of most blood group systems and whose extended phenotype is known. The specificity of the alloantibody is identified by correlating the presence or absence of antigen with the results of the agglutination.

Cross-matching is ordered when there is a high probability that the patient will require a packed RBC (PRBC) transfusion. Blood selected for cross-matching must be ABO compatible and lack antigens for which the patient has alloantibodies. Nonreactive cross-matching confirms the absence of any major incompatibility and reserves that unit for the patient.

In the case of Rh-negative patients, every attempt must be made to provide Rh-negative blood components to prevent alloimmunization to the D antigen. In an emergency, Rh-positive blood can be safely transfused to an Rh-negative patient who lacks anti-D; however, the recipient is likely to become alloimmunized and produce anti-D. Rh-negative women of childbearing age who are transfused with products containing Rh-positive RBCs should receive passive immunization with anti-D (RhoGam or WinRho) to reduce or prevent sensitization.

BLOOD COMPONENTS

Blood products intended for transfusion are routinely collected as whole blood (450 mL) in various anticoagulants. Most donated blood is processed into components: PRBCs, platelets, and fresh-frozen plasma (FFP) or cryoprecipitate **(Table 12-2)**. Whole blood is first separated into PRBCs and platelet-rich plasma by slow centrifugation. The platelet-rich plasma is then centrifuged at high speed to yield one unit of random donor (RD) platelets and one unit of FFP. Cryoprecipitate is produced by thawing FFP to precipitate the plasma proteins and then separated by centrifugation.

Apheresis technology is used for the collection of multiple units of platelets from a single donor. These single-donor apheresis platelets (SDAP) contain the equivalent of at least six units of RD platelets and have fewer contaminating leukocytes than pooled RD platelets.

Plasma may also be collected by apheresis. Plasma derivatives such as albumin, intravenous immunoglobulin, antithrombin, and coagulation factor concentrates are prepared from pooled plasma from many donors and are treated to eliminate infectious agents.

WHOLE BLOOD

Whole blood provides both oxygen-carrying capacity and volume expansion. It is the ideal component for patients who have sustained acute hemorrhage of ≥25% total blood volume loss. Whole blood is stored at 4°C to maintain erythrocyte viability, but platelet dysfunction and degradation of some coagulation factors occurs. In addition, 2,3-bisphosphoglycerate levels fall over time, leading to an increase in the oxygen affinity of the hemoglobin and a decreased capacity to deliver oxygen to the tissues, a problem with all red cell storage. Fresh

TABLE 12-2

CHARACTERISTICS OF SELECTED BLOOD COMPONENTS

COMPONENT	VOLUME, mL	CONTENT	CLINICAL RESPONSE
PRBC	180–200	RBCs with variable leukocyte content and small amount of plasma	Increase hemoglobin 10 g/L and hematocrit 3%
Platelets	50–70	5.5×10^{10}/RD unit	Increase platelet count 5000–10,000/μL
	200–400	$\geq 3 \times 10^{11}$/SDAP product	CCI $\geq 10 \times 10^9$/L within 1 h and $\geq 7.5 \times 10^9$/L within 24 h posttransfusion
FFP	200–250	Plasma proteins—coagulation factors, proteins C and S, antithrombin	Increases coagulation factors about 2%
Cryoprecipitate	10–15	Cold-insoluble plasma proteins, fibrinogen, factor VIII, VWF	Topical fibrin glue, also 80 IU factor VIII

Abbreviations: CCI, corrected count increment; FFP, fresh-frozen plasma; PRBC, packed red blood cells; RBC, red blood cell; RD, random donor; SDAP, single-donor apheresis platelets; VWF, von Willebrand factor.

whole blood avoids these problems, but it is typically used only in emergency settings (i.e., military). Whole blood is not readily available, because it is routinely processed into components.

PACKED RED BLOOD CELLS

This product increases oxygen-carrying capacity in the anemic patient. Adequate oxygenation can be maintained with a hemoglobin content of 70 g/L in the normovolemic patient without cardiac disease; however, comorbid factors may necessitate transfusion at a higher threshold. The decision to transfuse should be guided by the clinical situation and not by an arbitrary laboratory value. In the critical care setting, liberal use of transfusions to maintain near-normal levels of hemoglobin has not proven advantageous. In most patients requiring transfusion, levels of hemoglobin of 100 g/L are sufficient to keep oxygen supply from being critically low.

PRBCs may be modified to prevent certain adverse reactions. The majority of cellular blood products are now leukocyte reduced, and universal prestorage leukocyte reduction has been recommended. Prestorage filtration appears superior to bedside filtration as smaller amounts of cytokines are generated in the stored product. These PRBC units contain $<5 \times 10^6$ donor white blood cells (WBCs), and their use lowers the incidence of posttransfusion fever, cytomegalovirus (CMV) infections, and alloimmunization. Other theoretical benefits include less immunosuppression in the recipient and lower risk of infections. Plasma, which may cause allergic reactions, can be removed from cellular blood components by washing.

PLATELETS

Thrombocytopenia is a risk factor for hemorrhage, and platelet transfusion reduces the incidence of bleeding. The threshold for prophylactic platelet transfusion is 10,000/μL. In patients without fever or infections, a threshold of 5000/μL may be sufficient to prevent spontaneous hemorrhage. For invasive procedures, the usual target level is 50,000/μL platelets.

Platelets are given either as pools prepared from RDs or as SDAPs from a single donor. In an unsensitized patient without increased platelet consumption (splenomegaly, fever, disseminated intravascular coagulation [DIC]), two units of transfused RD per square-meter body surface area (BSA) is anticipated to increase the platelet count by approximately 10,000/μL. Patients who have received multiple transfusions may be alloimmunized to many HLA- and platelet-specific antigens and have little or no increase in their posttransfusion platelet counts. Patients who may require multiple transfusions are best served by receiving SDAP and leukocyte-reduced components to lower the risk of alloimmunization.

Refractoriness to platelet transfusion may be evaluated using the corrected count increment (CCI):

$$\text{CCI} = \frac{\text{posttransfusion count}(/\mu\text{L}) - \text{pretransfusion count}(/\mu\text{L})}{\text{number of platelets transfused} \times 10^{-11}} \times \text{BSA}(\text{m}^2)$$

where BSA is body surface area measured in square meters. The platelet count performed 1 h after the transfusion is acceptable if the CCI is 10×10^9/mL, and after 18–24 h an increment of 7.5×10^9/mL is expected. Patients who have suboptimal responses are likely to have received multiple transfusions and have antibodies directed against class I HLA antigens. Refractoriness can be investigated by detecting anti-HLA antibodies in the recipient's serum. Patients who are sensitized will often react with 100% of the lymphocytes used for the HLA-antibody screen, and HLA-matched SDAPs should be considered for patients who require transfusion. Although ABO-identical HLA-matched SDAPs provide the best chance for increasing the platelet

count, locating these products is difficult. Platelet crossmatching is available in some centers. Additional clinical causes for a low platelet CCI include fever, bleeding, splenomegaly, DIC, or medications in the recipient.

FRESH-FROZEN PLASMA

FFP contains stable coagulation factors and plasma proteins: fibrinogen, antithrombin, albumin, and proteins C and S. Indications for FFP include correction of coagulopathies, including the rapid reversal of warfarin; supplying deficient plasma proteins; and treatment of thrombotic thrombocytopenic purpura. FFP should not be routinely used to expand blood volume. FFP is an acellular component and does not transmit intracellular infections, e.g., CMV. Patients who are IgA-deficient and require plasma support should receive FFP from IgA-deficient donors to prevent anaphylaxis (see below).

CRYOPRECIPITATE

Cryoprecipitate is a source of fibrinogen, factor VIII, and von Willebrand factor (VWF). It is ideal for supplying fibrinogen to the volume-sensitive patient. When factor VIII concentrates are not available, cryoprecipitate may be used because each unit contains approximately 80 units of factor VIII. Cryoprecipitate may also supply VWF to patients with dysfunctional (type II) or absent (type III) von Willebrand's disease.

PLASMA DERIVATIVES

Plasma from thousands of donors may be pooled to derive specific protein concentrates, including albumin, intravenous immunoglobulin, antithrombin, and coagulation factors. In addition, donors who have high-titer antibodies to specific agents or antigens provide hyperimmune globulins, such as anti-D (RhoGam, WinRho), and antisera to hepatitis B virus (HBV), varicella-zoster virus, CMV, and other infectious agents.

ADVERSE REACTIONS TO BLOOD TRANSFUSION

Adverse reactions to transfused blood components occur despite multiple tests, inspections, and checks. Fortunately, the most common reactions are not life threatening, although serious reactions can present with mild symptoms and signs. Some reactions can be reduced or prevented by modified (filtered, washed, or irradiated) blood components. When an adverse reaction is suspected, the transfusion should be stopped and reported to the blood bank for investigation.

Transfusion reactions may result from immune and nonimmune mechanisms. Immune-mediated reactions are often due to preformed donor or recipient antibody; however, cellular elements may also cause adverse effects. Nonimmune causes of reactions are due to the chemical and physical properties of the stored blood component and its additives.

Transfusion-transmitted viral infections are increasingly rare due to improved screening and testing. As the risk of viral infection is reduced, the relative risk of other reactions increases, such as hemolytic transfusion reactions and sepsis from bacterially contaminated components. Pretransfusion quality assurance improvements further increase the safety of transfusion therapy. Infections, like any adverse transfusion reaction, must be brought to the attention of the blood bank for appropriate studies **(Table 12-3)**.

IMMUNE-MEDIATED REACTIONS

Acute hemolytic transfusion reactions

Immune-mediated hemolysis occurs when the recipient has preformed antibodies that lyse donor erythrocytes. The ABO isoagglutinins are responsible for the majority of these reactions. However, alloantibodies directed against other RBC antigens, i.e., Rh, Kell, and Duffy, are responsible for more fatal hemolytic transfusion reactions.

TABLE 12-3

RISKS OF TRANSFUSION COMPLICATIONS

	FREQUENCY, EPISODES: UNIT
Reactions	
Febrile (FNHTR)	• 1–4:100
Allergic	• 1–4:100
Delayed hemolytic	• 1:1000
TRALI	• 1:5000
Acute hemolytic	• 1:12,000
Fatal hemolytic	• 1:100,000
Anaphylactic	• 1:150,000
Infections[a]	
Hepatitis B	• 1:220,000
Hepatitis C	• 1:1,800,000
HIV-1, -2	• 1:2,300,000
HTLV-1 and -2	• 1:2,993,000
Malaria	• 1:4,000,000
Other Complications	
RBC allosensitization	• 1:100
HLA allosensitization	• 1:10
Graft-versus-host disease	• Rare

[a]Infectious agents rarely associated with transfusion, theoretically possible, or of unknown risk include West Nile virus, hepatitis A virus, parvovirus B19, Babesia microti and Babesia duncani (babesiosis), Borrelia burgdorferi (Lyme disease), Anaplasma phagocytophilum (human granulocytic ehrlichiosis), Trypanosoma cruzi (Chagas' disease), Treponema pallidum, and human herpesvirus-8.

Abbreviations: FNHTR, febrile nonhemolytic transfusion reaction; HTLV, human T lymphotropic virus; RBC, red blood cell; TRALI, transfusion-related acute lung injury.

Acute hemolytic reactions may present with hypotension, tachypnea, tachycardia, fever, chills, hemoglobinemia, hemoglobinuria, chest and/or flank pain, and discomfort at the infusion site. Monitoring the patient's vital signs before and during the transfusion is important to identify reactions promptly. When acute hemolysis is suspected, the transfusion must be stopped immediately, intravenous access maintained, and the reaction reported to the blood bank. A correctly labeled posttransfusion blood sample and any untransfused blood should be sent to the blood bank for analysis. T e laboratory evaluation for hemolysis includes the measurement of serum haptoglobin, lactate dehydrogenase (LDH), and indirect bilirubin levels.

T e immune complexes that result in RBC lysis can cause renal dysfunction and failure. Diuresis should be induced with intravenous fluids and furosemide or mannitol. Tissue factor released from the lysed erythrocytes may initiate DIC. Coagulation studies including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and platelet count should be monitored in patients with hemolytic reactions.

Errors at the patient's bedside, such as mislabeling the sample or transfusing the wrong patient, are responsible for the majority of these reactions. T e blood bank investigation of these reactions includes examination of the pre- and posttransfusion samples for hemolysis and repeat typing of the patient samples; direct antiglobulin test (DAT), sometimes called the direct Coombs test, of the posttransfusion sample; repeating the cross-matching of the blood component; and checking all clerical records for errors. DAT detects the presence of antibody or complement bound to RBCs in vivo **(Fig. 12-1)**.

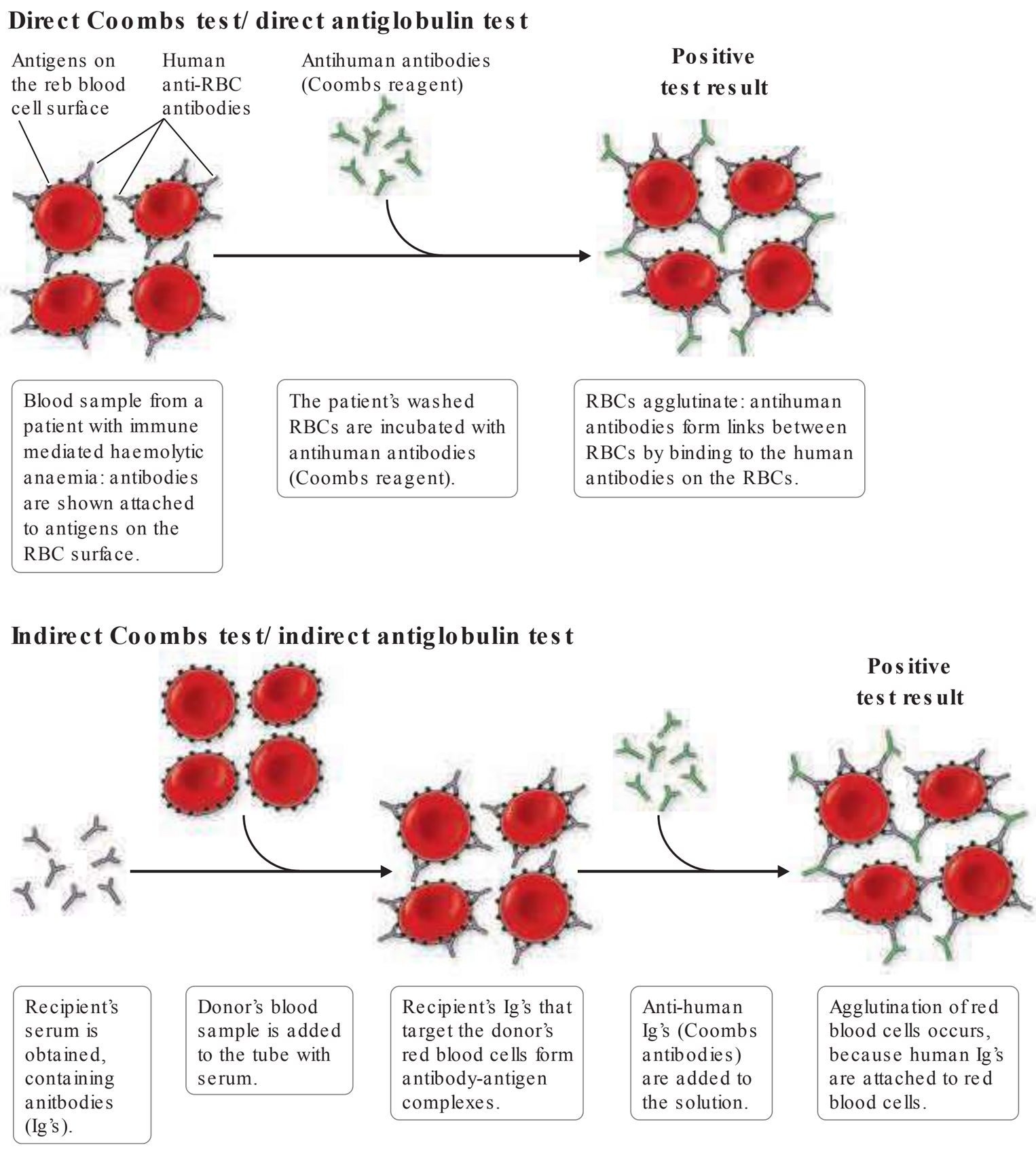

FIGURE 12-1
Direct and indirect Coombs test. The direct Coombs (antiglobulin) test detects the presence of antibodies (or complement) on the surface of erythrocytes. The indirect Coombs (antiglobulin) test detects antibodies in the serum that may bind to donor erythrocytes. RBC, red blood cell. (Adapted from http://upload.wikimedia.org/wikipedia/commons/1/1c/coombs_test_schematic.png.)

Delayed hemolytic and serologic transfusion reactions

Delayed hemolytic transfusion reactions (DHTRs) are not completely preventable. T ese reactions occur in patients previously sensitized to RBC alloantigens who have a negative alloantibody screen due to low antibody levels. When the patient is transfused with antigen-positive blood, an anamnestic response results in the early production of alloantibody that binds donor RBCs. T e alloantibody is detectable 1–2 weeks following the transfusion, and the posttransfusion DAT may become positive due to circulating donor RBCs coated with antibody or complement. T e transfused, alloantibody-coated erythrocytes are cleared by the reticuloendothelial system. T ese reactions are detected most commonly in the blood bank when a subsequent patient sample reveals a positive alloantibody screen or a new alloantibody in a recently transfused recipient.

No specific therapy is usually required, although additional RBC transfusions may be necessary. Delayed serologic transfusion reactions are similar to DHTR, because the DAT is positive and alloantibody is detected; however, RBC clearance is not increased.

Febrile nonhemolytic transfusion reaction

T e most frequent reaction associated with the transfusion of cellular blood components is a febrile nonhemolytic transfusion reaction (FNHTR). T ese reactions are characterized by chills and rigors and a ≥1°C rise in temperature. FNHTR is diagnosed when other causes of fever in the transfused patient are ruled out. Antibodies directed against donor leukocyte and HLA antigens may mediate these reactions; thus, multiply transfused patients and multiparous women are felt to be at increased risk. Although anti-HLA antibodies may be demonstrated in the recipient's serum, investigation is not routinely done because of the mild nature of most FNHTR. T e use of leukocyte-reduced blood products may prevent or delay sensitization to leukocyte antigens and thereby reduce the incidence of these febrile episodes. Cytokines released from cells within stored blood components may mediate FNHTR; thus, leukoreduction before storage may prevent these reactions.

Allergic reactions

Urticarial reactions are related to plasma proteins found in transfused components. Mild reactions may be treated symptomatically by temporarily stopping the transfusion and administering antihistamines (diphenhydramine, 50 mg orally or intramuscularly). T e transfusion may be completed after the signs and/or symptoms resolve. Patients with a history of allergic transfusion reaction should be premedicated with an antihistamine. Cellular components can be washed to remove residual plasma for the extremely sensitized patient.

Anaphylactic reaction

T is severe reaction presents after transfusion of only a few milliliters of the blood component. Symptoms and signs include difficulty breathing, coughing, nausea and vomiting, hypotension, bronchospasm, loss of consciousness, respiratory arrest, and shock. Treatment includes stopping the transfusion, maintaining vascular access, and administering epinephrine (0.5–1 mL of 1:1000 dilution subcutaneously). Glucocorticoids may be required in severe cases.

Patients who are IgA-deficient, <1% of the population, may be sensitized to this Ig class and are at risk for anaphylactic reactions associated with plasma transfusion. Individuals with severe IgA deficiency should therefore receive only IgA-deficient plasma and washed cellular blood components. Patients who have anaphylactic or repeated allergic reactions to blood components should be tested for IgA deficiency.

Graft-versus-host disease

Graft-versus-host disease (GVHD) is a frequent complication of allogeneic stem cell transplantation, in which lymphocytes from the donor attack and cannot be eliminated by an immunodeficient host. Transfusion-related GVHD is mediated by donor T lymphocytes that recognize host HLA antigens as foreign and mount an immune response, which is manifested clinically by the development of fever, a characteristic cutaneous eruption, diarrhea, and liver function abnormalities. GVHD can also occur when blood components that contain viable T lymphocytes are transfused to immunodeficient recipients or to immunocompetent recipients who share HLA antigens with the donor (e.g., a family donor). In addition to the aforementioned clinical features of GVHD, transfusion-associated GVHD (TA-GVHD) is characterized by marrow aplasia and pancytopenia. TA-GVHD is highly resistant to treatment with immunosuppressive therapies, including glucocorticoids, cyclosporine, antithymocyte globulin, and ablative therapy followed by allogeneic bone marrow transplantation. Clinical manifestations appear at 8–10 days, and death occurs at 3–4 weeks after transfusion.

TA-GVHD can be prevented by irradiation of cellular components (minimum of 2500 cGy) before transfusion to patients at risk. Patients at risk for TA-GVHD include fetuses receiving intrauterine transfusions, selected immunocompetent (e.g., lymphoma patients) or immunocompromised recipients, recipients of donor units known to be from a blood relative, and recipients who have undergone marrow transplantation. Directed

donations by family members should be discouraged (they are not less likely to transmit infection); lacking other options, the blood products from family members should always be irradiated.

Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is the most common cause of transfusion related fatalities. The recipient develops symptoms of hypoxia (Pao_2/FIo_2 <300 mmHg) and signs of noncardiogenic pulmonary edema, including bilateral interstitial infiltrates on chest x-ray, either during or within 6 h of transfusion. Treatment is supportive, and patients usually recover without sequelae. TRALI usually results from the transfusion of donor plasma that contains high-titer anti-HLA class II antibodies that bind recipient leukocytes. The leukocytes aggregate in the pulmonary vasculature and release mediators that increase capillary permeability. Testing the donor's plasma for anti-HLA antibodies can support this diagnosis. The implicated donors are frequently multiparous women. The transfusion of plasma from male and nulliparous women donors reduces the risk of TRALI. Recipient factors that are associated with increased risk of TRALI include smoking, chronic alcohol use, shock, liver surgery (transplantation), mechanical ventilation with >30 cmH_2O pressure support and positive fluid balance.

Posttransfusion purpura

This reaction presents as thrombocytopenia 7–10 days after platelet transfusion and occurs predominantly in women. Platelet-specific antibodies are found in the recipient's serum, and the most frequently recognized antigen is HPA-1a found on the platelet glycoprotein IIIa receptor. The delayed thrombocytopenia is due to the production of antibodies that react to both donor and recipient platelets. Additional platelet transfusions can worsen the thrombocytopenia and should be avoided. Treatment with intravenous immunoglobulin may neutralize the effector antibodies, or plasmapheresis can be used to remove the antibodies.

Alloimmunization

A recipient may become alloimmunized to a number of antigens on cellular blood elements and plasma proteins. Alloantibodies to RBC antigens are detected during pretransfusion testing, and their presence may delay finding antigen-negative cross-match-compatible products for transfusion. Women of childbearing age who are sensitized to certain RBC antigens (i.e., D, c, E, Kell, or Duffy) are at risk for bearing a fetus with hemolytic disease of the newborn. Matching for D antigen is the only pretransfusion selection test to prevent RBC alloimmunization.

Alloimmunization to antigens on leukocytes and platelets can result in refractoriness to platelet transfusions. Once alloimmunization has developed, HLA-compatible platelets from donors who share similar antigens with the recipient may be difficult to find. Hence, prudent transfusion practice is directed at preventing sensitization through the use of leukocyte-reduced cellular components, as well as limiting antigenic exposure by the judicious use of transfusions and use of SDAPs.

NONIMMUNOLOGIC REACTIONS

Fluid Overload

Blood components are excellent volume expanders, and transfusion may quickly lead to transfusion-associated circulatory overload (TACO). Dyspnea with PaO_2 <90% on room air, bilateral infiltrates on chest x-ray, and systolic hypertension are found with TACO. Brain natriuretic peptide (BNP) is often elevated (>1.5) compared with pretransfusion levels. Monitoring the rate and volume of the transfusion and using a diuretic can minimize this problem.

Hypothermia

Refrigerated (4°C) or frozen (−18°C or below) blood components can result in hypothermia when rapidly infused. Cardiac dysrhythmias can result from exposing the sinoatrial node to cold fluid. Use of an in-line warmer will prevent this complication.

Electrolyte toxicity

RBC leakage during storage increases the concentration of potassium in the unit. Neonates and patients in renal failure are at risk for hyperkalemia. Preventive measures, such as using fresh or washed RBCs, are warranted for neonatal transfusions because this complication can be fatal.

Citrate, commonly used to anticoagulate blood components, chelates calcium and thereby inhibits the coagulation cascade. Hypocalcemia, manifested by circumoral numbness and/or tingling sensation of the fingers and toes, may result from multiple rapid transfusions. Because citrate is quickly metabolized to bicarbonate, calcium infusion is seldom required in this setting. If calcium or any other intravenous infusion is necessary, it must be given through a separate line.

Iron overload

Each unit of RBCs contains 200–250 mg of iron. Symptoms and signs of iron overload affecting endocrine, hepatic, and cardiac function are common after 100 units of RBCs have been transfused (total-body iron

load of 20 g). Preventing this complication by using alternative therapies (e.g., erythropoietin) and judicious transfusion is preferable and cost effective. Chelating agents, such as deferoxamine and deferasirox, are available, but the response is often suboptimal.

Hypotensive reactions

Transient hypotension may be noted among transfused patients who take angiotensin-converting enzyme (ACE) inhibitors. Because blood products contain bradykinin that is normally degraded by ACE, patients on ACE inhibitors may have increased bradykinin levels that cause hypotension in the recipient. The blood pressure typically returns to normal without intervention.

Immunomodulation

Transfusion of allogeneic blood is immunosuppressive. Multiply transfused renal transplant recipients are less likely to reject the graft, and transfusion may result in poorer outcomes in cancer patients and increase the risk of infections. Transfusion-related immunomodulation is thought to be mediated by transfused leukocytes. Leukocyte-depleted cellular products may cause less immunosuppression, although controlled data are unlikely to be obtained as the blood supply becomes universally leukocyte depleted.

INFECTIOUS COMPLICATIONS

The blood supply is initially screened by selecting healthy donors without high-risk lifestyles, medical conditions, or exposure to transmissible pathogens, such as intravenous drug use or visiting malaria endemic areas. Multiple tests performed on donated blood to detect the presence of infectious agents using nucleic acid amplification testing (NAAT) or evidence of prior infections by testing for antibodies to pathogens and sterility of platelet products further reduce the risk of transfusion-acquired infections.

Viral infections

Hepatitis C virus (HCV)

Blood donations are tested for antibodies to HCV and HCV RNA. The risk of acquiring HCV through transfusion is now calculated to be approximately 1 in 2,000,000 units. Infection with HCV may be asymptomatic or lead to chronic active hepatitis, cirrhosis, and liver failure.

Human immunodeficiency virus type 1 (HIV-1)

Donated blood is tested for antibodies to HIV-1, HIV-1 p24 antigen, and HIV RNA using NAAT. Approximately a dozen seronegative donors have been shown to harbor HIV RNA. The risk of HIV-1 infection per transfusion episode is 1 in 2,000,000. Antibodies to HIV-2 are also measured in donated blood. No cases of HIV-2 infection have been reported in the United States since 1992.

Hepatitis B virus (HBV)

Donated blood is screened for HBV using assays for hepatitis B surface antigen (HbsAg). NAAT testing is not practical because of slow viral replication and lower levels of viremia. The risk of transfusion-associated HBV infection is several times greater than for HCV. Vaccination of individuals who require long-term transfusion therapy can prevent this complication.

Other hepatitis viruses

Hepatitis A virus is rarely transmitted by transfusion; infection is typically asymptomatic and does not lead to chronic disease. Other transfusion-transmitted viruses—TT virus, SEN virus, and GB virus C—do not cause chronic hepatitis or other disease states. Routine testing does not appear to be warranted.

West nile virus (WNV)

Transfusion-transmitted WNV infections were documented in 2002. This is RNA virus can be detected using NAAT; routine screening began in 2003. WNV infections range in severity from asymptomatic to fatal, with the older population at greater risk.

Cytomegalovirus

This is ubiquitous virus infects ≥50% of the general population and is transmitted by the infected "passenger" WBCs found in transfused PRBCs or platelet components. Cellular components that are leukocyte-reduced have a decreased risk of transmitting CMV, regardless of the serologic status of the donor. Groups at risk for CMV infections include immunosuppressed patients, CMV-seronegative transplant recipients, and neonates; these patients should receive leukocyte-depleted components or CMV seronegative products.

Human T lymphotropic virus (HTLV) type 1

Assays to detect HTLV-1 and -2 are used to screen all donated blood. HTLV-1 is associated with adult T cell leukemia/lymphoma and tropical spastic paraparesis in a small percentage of infected persons. The risk of HTLV-1 infection via transfusion is 1 in 641,000 transfusion episodes. HTLV-2 is not clearly associated with any disease.

Parvovirus B19

Blood components and pooled plasma products can transmit this virus, the etiologic agent of erythema infectiosum, or fifth disease, in children. Parvovirus B19 shows tropism for erythroid precursors and inhibits both erythrocyte production and maturation. Pure red cell aplasia, presenting either as acute aplastic

crisis or chronic anemia with shortened RBC survival, may occur in individuals with an underlying hematologic disease, such as sickle cell disease or thalassemia **(Chap. 11)**. T e fetus of a seronegative woman is at risk for developing hydrops from this virus.

Bacterial contamination

T e relative risk of transfusion-transmitted bacterial infection has increased as the absolute risk of viral infections has dramatically decreased.

Most bacteria do not grow well at cold temperatures; thus, PRBCs and FFP are not common sources of bacterial contamination. However, some gram-negative bacteria can grow at 1–6°C. Yersinia, Pseudomonas, Serratia, Acinetobacter, and Escherichia species have all been implicated in infections related to PRBC transfusion. Platelet concentrates, which are stored at room temperature, are more likely to contain skin contaminants such as gram-positive organisms, including coagulase-negative staphylococci. It is estimated that 1 in 1000–2000 platelet components is contaminated with bacteria. T e risk of death due to transfusion-associated sepsis has been calculated at 1 in 17,000 for single-unit platelets derived from whole blood donation and 1 in 61,000 for apheresis product. Since 2004, blood banks have instituted methods to detect contaminated platelet components.

Recipients of transfusion contaminated with bacteria may develop fever and chills, which can progress to septic shock and DIC. T ese reactions may occur abruptly, within minutes of initiating the transfusion, or after several hours. T e onset of symptoms and signs is often sudden and fulminant, which distinguishes bacterial contamination from an FNHTR. T e reactions, particularly those related to gram-negative contaminants, are the result of infused endotoxins formed within the contaminated stored component.

When these reactions are suspected, the transfusion must be stopped immediately. T erapy is directed at reversing any signs of shock, and broad-spectrum antibiotics should be given. T e blood bank should be notified to identify any clerical or serologic error. T e blood component bag should be sent for culture and Gram stain.

Other Infectious Agents

Various parasites, including those causing malaria, babesiosis, and Chagas' disease, can be transmitted by blood transfusion. Geographic migration and travel of donors shift the incidence of these rare infections. Other agents implicated in transfusion transmission include dengue, chikungunya virus, variant Creutzfeldt-Jakob disease, A. phagocytophilum, and yellow fever vaccine virus, and the list will grow. Tests for some pathogens are available, such as T. cruzi, but not universally required, whereas others are being developed (B. microti). T ese infections should be considered in the transfused patient in the appropriate clinical setting.

ALTERNATIVES TO TRANSFUSION

Alternatives to allogeneic blood transfusions that avoid homologous donor exposures with attendant immunologic and infectious risks remain attractive. Autologous blood is the best option when transfusion is anticipated. However, the cost-benefit ratio of autologous transfusion remains high. No transfusion is a zero-risk event; clerical errors and bacterial contamination remain potential complications even with autologous transfusions. Additional methods of autologous transfusion in the surgical patient include preoperative hemodilution, recovery of shed blood from sterile surgical sites, and postoperative drainage collection. Directed or designated donation from friends and family of the potential recipient has not been safer than volunteer donor component transfusions. Such directed donations may in fact place the recipient at higher risk for complications such as GVHD and alloimmunization.

Granulocyte and granulocyte-macrophage colony-stimulating factors are clinically useful to hasten leukocyte recovery in patients with leukopenia related to high-dose chemotherapy. Erythropoietin stimulates erythrocyte production in patients with anemia of chronic renal failure and other conditions, thus avoiding or reducing the need for transfusion. T is hormone can also stimulate erythropoiesis in the autologous donor to enable additional donation.

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SECTION IV

MYELOPROLIFERATIVE DISORDERS

CHAPTER 13

POLYCYTHEMIA VERA AND OTHER MYELOPROLIFERATIVE NEOPLASMS

Jerry L. Spivak

The World Health Organization (WHO) classification of the chronic myeloproliferative neoplasms (MPNs) includes eight disorders, some of which are rare or poorly characterized **(Table 13-1)** but all of which share an origin in a multipotent hematopoietic progenitor cell; overproduction of one or more of the formed elements of the blood without significant dysplasia; and a predilection to extramedullary hematopoiesis, myelofibrosis, and transformation at varying rates to acute leukemia. Within this broad classification, however, significant phenotypic heterogeneity exists. Some diseases such as chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), and chronic eosinophilic leukemia (CEL) express primarily a myeloid phenotype, whereas in other diseases, such as polycythemia vera (PV), primary myelofibrosis (PMF), and essential thrombocytosis (ET), erythroid or megakaryocytic hyperplasia predominates. The latter three disorders, in contrast to the former three, also appear capable of transforming into each other.

Such phenotypic heterogeneity has a genetic basis; CML is the consequence of the balanced translocation between chromosomes 9 and 22 [t(9;22)(q34;11)]; CNL has been associated with a t(15;19) translocation; and CEL occurs with a deletion or balanced translocations involving the PDGFRα gene. By contrast, to a greater or lesser extent, PV, PMF, and ET are characterized by a mutation, V617F, that causes constitutive activation of JAK2, a tyrosine kinase essential for the function of the erythropoietin and thrombopoietin receptors but not the granulocyte colony-stimulating factor receptor. This important distinction is also reflected in the natural histories of CML, CNL, and CEL, which are usually measured in years, and their high rate of leukemic transformation. By contrast, the natural history of PV, PMF, and ET is usually measured in decades, and transformation to acute leukemia is uncommon in PV and ET in the absence of exposure to mutagenic drugs. This chapter, therefore, will focus only on PV, PMF, and ET, because their clinical and genetic overlap is substantial even though their clinical courses are distinctly different.

The other chronic myeloproliferative neoplasms will be discussed in Chaps. 15 and 17.

TABLE 13-1

WORLD HEALTH ORGANIZATION CLASSIFICATION OF CHRONIC MYELOPROLIFERATIVE NEOPLASMS
Chronic myeloid leukemia, bcr-abl–positive
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia, not otherwise specified
Polycythemia vera
Primary myelofibrosis
Essential thrombocytosis
Mastocytosis
Myeloproliferative neoplasms, unclassifiable

POLYCYTHEMIA VERA

PV is a clonal disorder involving a multipotent hematopoietic progenitor cell in which phenotypically normal red cells, granulocytes, and platelets accumulate in the absence of a recognizable physiologic stimulus. The most common of the chronic MPNs, PV occurs in 2.5 per 100,000 persons, sparing no adult age group and increasing with age to rates over 10/100,000. Familial transmission is infrequent, and women predominate among sporadic cases.

ETIOLOGY

The etiology of PV is unknown. Although nonrandom chromosome abnormalities such as deletion 20q and trisomy 8 and 9 have been documented in

up to 30% of untreated PV patients, unlike CML, no consistent cytogenetic abnormality has been associated with the disorder. However, a mutation in the autoinhibitory pseudokinase domain of the tyrosine kinase JAK2—that replaces valine with phenylalanine (V617F), causing constitutive kinase activation—appears to have a central role in the pathogenesis of PV.

JAK2 is a member of an evolutionarily well-conserved, nonreceptor tyrosine kinase family and serves as the cognate tyrosine kinase for the erythropoietin and thrombopoietin receptors. It also functions as an obligate chaperone for these receptors in the Golgi apparatus and is responsible for their cell-surface expression. The conformational change induced in the erythropoietin and thrombopoietin receptors following binding to their respective cognate ligands, erythropoietin or thrombopoietin, leads to JAK2 autophosphorylation, receptor phosphorylation, and phosphorylation of proteins involved in cell proliferation, differentiation, and resistance to apoptosis. Transgenic animals lacking JAK2 die as embryos from severe anemia. Constitutive activation of JAK2, on the other hand, explains the erythropoietin hypersensitivity, erythropoietin-independent erythroid colony formation, rapid terminal differentiation, increase in Bcl-X_L expression, and apoptosis resistance in the absence of erythropoietin that characterize the in vitro behavior of PV erythroid progenitor cells.

Importantly, the JAK2 gene is located on the short arm of chromosome 9, and loss of heterozygosity on chromosome 9p due to mitotic recombination is the most common cytogenetic abnormality in PV. The segment of 9p involved contains the JAK2 locus, and loss of heterozygosity in this region leads to homozygosity for JAK2 V617F. More than 95% of PV patients express this mutation, as do approximately 50% of PMF and ET patients. Homozygosity for the mutation occurs in approximately 30% of PV patients and 60% of PMF patients but is rare in ET. Over time, a portion of PV JAK2 V617F heterozygotes become homozygotes due to mitotic recombination, but usually not after 10 years of the disease. Most PV patients who do not express JAK2 V617F express a mutation in exon 12 of the kinase and are not clinically different from those who do, nor do JAK2 V617F heterozygotes differ clinically from homozygotes. Interestingly, the predisposition to acquire mutations in JAK2 appears to be associated with a specific JAK2 gene haplotype, GGCC. JAK2 V617F is the basis for many of the phenotypic and biochemical characteristics of PV such as elevation of the leukocyte alkaline phosphatase (LAP) score; however, it cannot solely account for the entire PV phenotype and is probably not the initiating lesion in the three MPNs. First, PV patients with the same phenotype and documented clonal disease lack any mutation of JAK2. Second, ET and PMF patients have the same mutation but different clinical phenotypes. Third, familial PV can occur without the mutation, even when other members of the same family express it. Fourth, not all the cells of the malignant clone express JAK2 V617F. Fifth, JAK2 V617F has been observed in patients with long-standing idiopathic erythrocytosis. Sixth, in some patients, JAK2 V617F appears to be acquired after another mutation. Finally, in some JAK2 V617F–positive PV or ET patients, acute leukemia can occur in a JAK2 V617F–negative progenitor cell. However, although JAK2 V617F alone may not be sufficient to cause PV, it appears essential for the transformation of ET to PV, although not for its transformation to PMF.

CLINICAL FEATURES

Although isolated thrombocytosis, leukocytosis, or splenomegaly may be the initial presenting manifestation of PV, most often the disorder is first recognized by the incidental discovery of a high hemoglobin or hematocrit. With the exception of aquagenic pruritus, no symptoms distinguish PV from other causes of erythrocytosis.

Uncontrolled erythrocytosis causes hyperviscosity, leading to neurologic symptoms such as vertigo, tinnitus, headache, visual disturbances, and transient ischemic attacks (TIAs). Systolic hypertension is also a feature of the red cell mass elevation. In some patients, venous or arterial thrombosis may be the presenting manifestation of PV. Any vessel can be affected; but cerebral, cardiac, or mesenteric vessels are most commonly involved. Intraabdominal venous thrombosis is particularly common in young women and may be catastrophic if a sudden and complete obstruction of the hepatic vein occurs. Indeed, PV should be suspected in any patient who develops hepatic vein thrombosis. Digital ischemia, easy bruising, epistaxis, acid-peptic disease, or gastrointestinal hemorrhage may occur due to vascular stasis or thrombocytosis. Erythema, burning, and pain in the extremities, a symptom complex known as erythromelalgia, are other complications of the thrombocytosis of PV due to increased platelet stickiness. Given the large turnover of hematopoietic cells, hyperuricemia with secondary gout, uric acid stones, and symptoms due to hypermetabolism can also complicate the disorder.

DIAGNOSIS

When PV presents with erythrocytosis in combination with leukocytosis, thrombocytosis, or splenomegaly or a combination of these, the diagnosis is apparent. However, when patients present with an elevated hemoglobin or hematocrit alone, the diagnostic evaluation is more complex because of the many diagnostic

TABLE 13-2

CAUSES OF ERYTHROCYTOSIS	
Relative Erythrocytosis	
Hemoconcentration secondary to dehydration, diuretics, ethanol abuse, androgens, or tobacco abuse	
Absolute Erythrocytosis	
Hypoxia	Tumors
Carbon monoxide intoxication	Hypernephroma
High-oxygen-affinity hemoglobin	Hepatoma
High altitude	Cerebellar hemangioblastoma
Pulmonary disease	Uterine myoma
Right to left cardiac or vascular shunts	Adrenal tumors
Sleep apnea syndrome	Meningioma
Hepatopulmonary syndrome	Pheochromocytoma
Renal Disease	Drugs
Renal artery stenosis	Androgens
Focal sclerosing or membranous glomerulonephritis	Recombinant erythropoietin
Postrenal transplantation	Familial (with normal hemoglobin function)
Renal cysts	Erythropoietin receptor mutation
Bartter's syndrome	VHL mutations (Chuvash polycythemia)
	2,3-BPG mutation
	Polycythemia vera

Abbreviations: 2,3-BPG, 2,3-bisphosphoglycerate; VHL, von Hippel-Lindau.

possibilities **(Table 13-2)**. Furthermore, unless the hemoglobin level is ≥20 g/dL (hematocrit ≥60%), it is not possible to distinguish true erythrocytosis from disorders causing plasma volume contraction. This is because uniquely in PV, in contrast to other causes of true erythrocytosis, there is expansion of the plasma volume, which can mask the elevated red cell mass; thus, red cell mass and plasma volume determinations are necessary to establish the presence of an absolute erythrocytosis and to distinguish this from relative erythrocytosis due to a reduction in plasma volume alone (also known as stress or spurious erythrocytosis or Gaisböck's syndrome). Figure 2-18 illustrates a diagnostic algorithm for the evaluation of suspected erythrocytosis. Assay for JAK2 mutations in the presence of a normal arterial oxygen saturation provides an alternative diagnostic approach to erythrocytosis when red cell mass and plasma volume determinations are not available; a normal serum erythropoietin level does not exclude the presence of PV, but an elevated erythropoietin level is more consistent with a secondary cause for the erythrocytosis.

Other laboratory studies that may aid in diagnosis include the red cell count, mean corpuscular volume, and red cell distribution width (RDW), particularly when the hematocrit or hemoglobin levels are less than 60% or 20 g/dL, respectively. Only three situations cause microcytic erythrocytosis: β thalassemia trait, hypoxic erythrocytosis, and PV. With β thalassemia trait, the RDW is normal, whereas with hypoxic erythrocytosis and PV, the RDW may be elevated due to associated iron deficiency. Today, however, the assay for JAK2 V617F has superseded other tests for establishing the diagnosis of PV. Of course, in patients with associated acid-peptic disease, occult gastrointestinal bleeding may lead to a presentation with hypochromic, microcytic anemia, masking the presence of PV.

A bone marrow aspirate and biopsy provide no specific diagnostic information because these may be normal or indistinguishable from ET or PMF. Similarly, no specific cytogenetic abnormality is associated with the disease, and the absence of a cytogenetic marker does not exclude the diagnosis.

COMPLICATIONS

Many of the clinical complications of PV relate directly to the increase in blood viscosity associated with red cell mass elevation and indirectly to the increased turnover of red cells, leukocytes, and platelets with the attendant increase in uric acid and cytokine production. The latter appears to be responsible for constitutional symptoms. Peptic ulcer disease can also be due to Helicobacter pylori infection, the incidence of which is increased in PV, while the pruritus associated with this disorder may be a consequence of mast cell activation by JAK2 V617F. A sudden increase in spleen size can be associated with painful splenic infarction. Myelofibrosis appears to be part of the natural history of the disease but is a reactive, reversible process that does not itself impede hematopoiesis and by itself has no prognostic significance. In approximately 15% of patients, however, myelofibrosis is accompanied by significant extramedullary hematopoiesis, hepatosplenomegaly, and transfusion-dependent anemia, which are manifestations of stem cell failure. The organomegaly can cause significant mechanical discomfort, portal hypertension, and progressive cachexia. Although the incidence of acute nonlymphocytic leukemia is increased in PV, the incidence of acute leukemia in patients not exposed to chemotherapy or radiation therapy is low. Interestingly, chemotherapy, including hydroxyurea, has been associated with acute leukemia in JAK2 V617F–negative stem cells in some PV patients. Erythromelalgia is a curious syndrome of unknown etiology associated with thrombocytosis, primarily involving the lower extremities and usually manifested by erythema, warmth, and pain of the affected appendage and occasionally digital infarction. It occurs with a variable frequency and is usually responsive to salicylates. Some of the central nervous system symptoms observed in patients with PV, such as ocular migraine, appear to represent a variant of erythromelalgia.

Left uncontrolled, erythrocytosis can lead to thrombosis involving vital organs such as the liver, heart, brain, or lungs. Patients with massive splenomegaly are particularly prone to thrombotic events because the associated increase in plasma volume masks the true extent of the red cell mass elevation measured by the hematocrit or hemoglobin level. A "normal" hematocrit or hemoglobin level in a PV patient with massive splenomegaly should be considered indicative of an elevated red cell mass until proven otherwise.

TREATMENT Polycythemia Vera

PV is generally an indolent disorder, the clinical course of which is measured in decades, and its management should reflect its tempo. T rombosis due to erythrocytosis is the most significant complication and often the presenting manifestation, and maintenance of the hemoglobin level at ≤140 g/L (14 g/dL; hematocrit <45%) in men and ≤120 g/L (12 g/dL; hematocrit <42%) in women is mandatory to avoid thrombotic complications. Phlebotomy serves initially to reduce hyperviscosity by bringing the red cell mass into the normal range while further expanding the plasma volume. Periodic phlebotomies thereafter serve to maintain the red cell mass within the normal range and to induce a state of iron deficiency that prevents an accelerated reexpansion of the red cell mass. In most PV patients, once an iron-deficient state is achieved, phlebotomy is usually only required at 3-month intervals. Neither phlebotomy nor iron deficiency increases the platelet count relative to the effect of the disease itself, and thrombocytosis is not correlated with thrombosis in PV, in contrast to the strong correlation between erythrocytosis and thrombosis in this disease. T e use of salicylates as a tonic against thrombosis in PV patients is not only potentially harmful if the red cell mass is not controlled by phlebotomy, but is also an unproven remedy. Anticoagulants are only indicated when a thrombosis has occurred and can be difficult to monitor if the red cell mass is substantially elevated owing to the artifactual imbalance between the test tube anticoagulant and plasma that occurs when blood from these patients is assayed for prothrombin or partial thromboplastin activity. Asymptomatic hyperuricemia (<10 mg/dL) requires no therapy, but allopurinol should be administered to avoid further elevation of the uric acid when chemotherapy is used to reduce splenomegaly or leukocytosis or to treat pruritus. Generalized pruritus intractable to antihistamines or antidepressants such as doxepin can be a major problem in PV; interferon α (IFN-α), psoralens with ultraviolet light in the A range (PUVA) therapy, and hydroxyurea are other methods of palliation. Asymptomatic thrombocytosis requires no therapy unless the platelet count is sufficiently high to cause bleeding due an acquired form of von Willebrand's disease in which there is adsorption and proteolysis of high-molecular-weight von Willebrand factor (VWF) multimers by the expanded platelet mass. Symptomatic splenomegaly can be treated with pegylated IFN-α. Pegylated IFN-α can also produce complete hematologic and molecular remissions in PV, and its role in this disorder is currently under investigation. Anagrelide, a phosphodiesterase inhibitor, can reduce the platelet count and, if tolerated, is preferable to hydroxyurea because it lacks marrow toxicity and is protective against venous thrombosis. A reduction in platelet number may be necessary for the treatment of erythromelalgia or ocular migraine if salicylates are not effective or if the platelet count is sufficiently high to increase the risk of hemorrhage but only to the degree that symptoms are alleviated. Alkylating agents and radioactive sodium phosphate (^{32}P) are leukemogenic in PV, and their use should be avoided. If a cytotoxic agent must be used, hydroxyurea is preferred, but this drug does not prevent either thrombosis or myelofibrosis in PV, is itself leukemogenic, and should be used for as short a time as possible. Previously, PV patients with massive splenomegaly unresponsive to reduction by chemotherapy or interferon required splenectomy. However, with the introduction of the nonspecific JAK2 inhibitor ruxolitinib, it has been possible in the majority of patients with PV complicated by myelofibrosis and myeloid metaplasia to reduce spleen size while at the same time alleviating constitutional symptoms to due to cytokine release. T is drug is currently undergoing clinical trials in PV patients intolerant of hydroxyurea. In some patients with end-stage disease, pulmonary hypertension may develop due to fibrosis or extramedullary hematopoiesis. A role for allogeneic bone marrow transplantation in PV has not been defined.

Most patients with PV can live long lives without functional impairment when their red cell mass is effectively managed with phlebotomy alone. Chemotherapy is never indicated to control the red cell mass unless venous access is inadequate.

PRIMARY MYELOFIBROSIS

Chronic PMF (other designations include idiopathic myelof brosis, agnogenic myeloid metaplasia, or myelof - brosis with myeloid metaplasia) is a clonal disorder of a multipotent hematopoietic progenitor cell of unknown etiology characterized by marrow fibrosis, extramedullary hematopoiesis, and splenomegaly. PMF is the least common chronic MPN, and establishing this diagnosis in the absence of a specific clonal marker is difficult because myelofibrosis and splenomegaly are also features of both PV and CML. Furthermore, myelofibrosis and splenomegaly also occur in a variety of benign and malignant disorders **(Table 13-3)**, many of which are amenable to specific therapies not effective in PMF. In contrast to the other chronic MPNs and so-called acute or malignant myelofibrosis, which can occur at any age, PMF primarily af icts men in their sixth decade or later.

TABLE 13-3

DISORDERS CAUSING MYELOFIBROSIS	
MALIGNANT	NONMALIGNANT
Acute leukemia (lymphocytic, myelogenous, megakaryocytic)	HIV infection
Chronic myeloid leukemia	Hyperparathyroidism
Hairy cell leukemia	Renal osteodystrophy
Hodgkin's disease	Systemic lupus erythematosus
Primary myelofibrosis	Tuberculosis
Lymphoma	Vitamin D deficiency
Multiple myeloma	Thorium dioxide exposure
Myelodysplasia	Gray platelet syndrome
Metastatic carcinoma	
Polycythemia vera	
Systemic mastocytosis	

ETIOLOGY

The etiology of PMF is unknown. Nonrandom chromosome abnormalities such as 9p, 20q−, 13q−, trisomy 8 or 9, or partial trisomy 1q are common, but no cytogenetic abnormality specific to the disease has been identified. JAK2 V617F is present in approximately 50% of PMF patients, and mutations in the thrombopoietin receptor Mpl occur in about 5%. Most of the rest have mutations in the calreticulin gene (CALR) that alter the carboxy-terminal portion of the gene product. The degree of myelofibrosis and the extent of extramedullary hematopoiesis are also not related. Fibrosis in this disorder is associated with overproduction of transforming growth factor β and tissue inhibitors of metalloproteinases, whereas osteosclerosis is associated with overproduction of osteoprotegerin, an osteoclast inhibitor. Marrow angiogenesis occurs due to increased production of vascular endothelial growth factor. Importantly, fibroblasts in PMF are polyclonal and not part of the neoplastic clone.

CLINICAL FEATURES

No signs or symptoms are specific for PMF. Many patients are asymptomatic at presentation, and the disease is usually detected by the discovery of splenic enlargement and/or abnormal blood counts during a routine examination. However, in contrast to its companion MPN, night sweats, fatigue, and weight loss are common presenting complaints. A blood smear will show the characteristic features of extramedullary hematopoiesis: teardrop-shaped red cells, nucleated red cells, myelocytes, and promyelocytes; myeloblasts may also be present **(Fig. 13-1)**. Anemia, usually mild initially, is the rule, whereas the leukocyte and platelet counts are either normal or increased, but either can be depressed. Mild hepatomegaly may accompany the splenomegaly but is unusual in the absence of splenic enlargement; isolated lymphadenopathy should suggest another diagnosis. Both serum lactate dehydrogenase and alkaline phosphatase levels can be elevated. The LAP score can be low, normal, or high. Marrow is usually inaspirable due to the myelofibrosis **(Fig. 13-2)**, and bone x-rays may reveal osteosclerosis. Exuberant extramedullary hematopoiesis can cause ascites; portal, pulmonary, or intracranial hypertension; intestinal or ureteral obstruction; pericardial tamponade; spinal cord compression; or skin nodules. Splenic enlargement can be sufficiently rapid to cause splenic infarction with fever and pleuritic chest pain. Hyperuricemia and secondary gout may ensue.

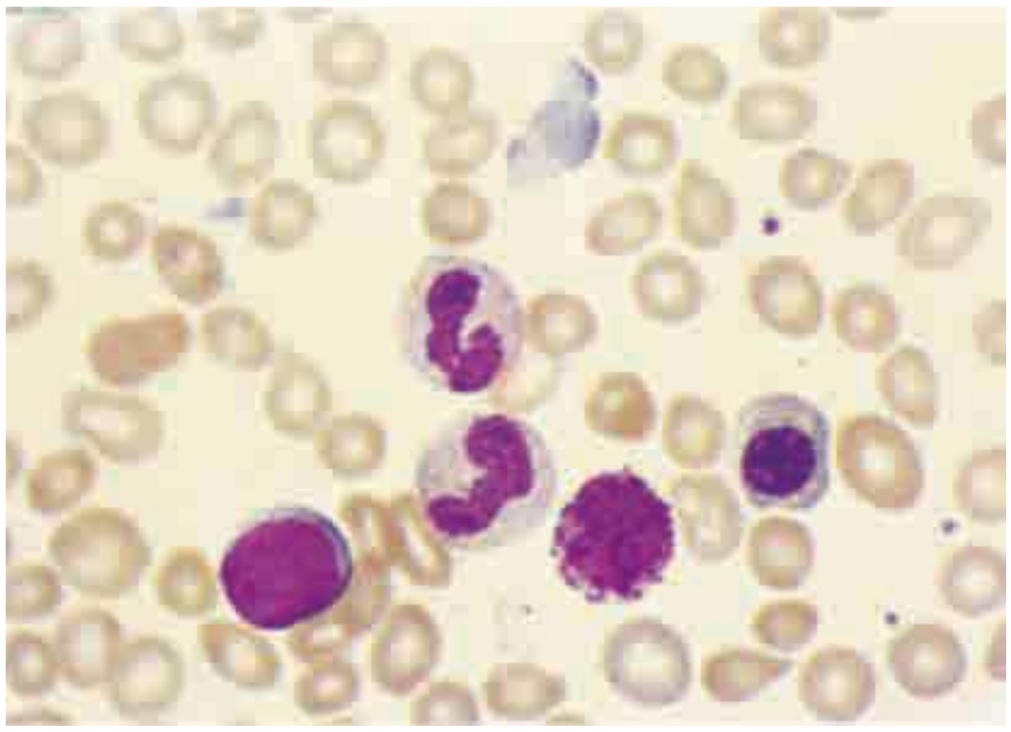

FIGURE 13-1
Teardrop-shaped red blood cells indicative of membrane damage from passage through the spleen, a nucleated red blood cell, and immature myeloid cells indicative of extramedullary hematopoiesis are noted. This peripheral blood smear is related to any cause of extramedullary hematopoiesis.

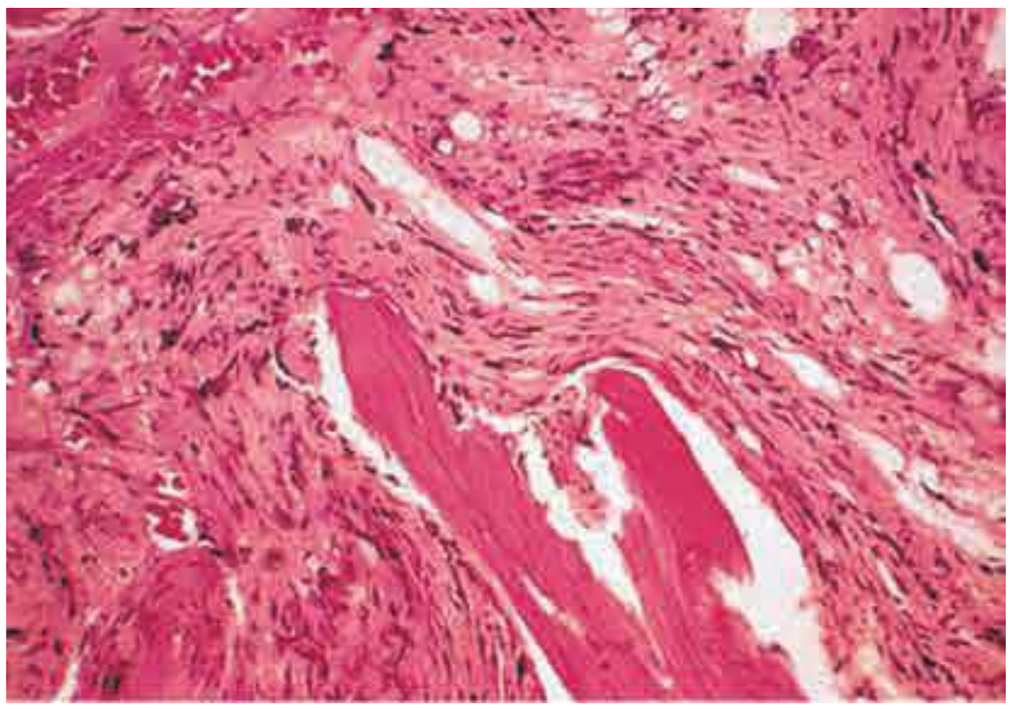

FIGURE 13-2
This marrow section shows the marrow cavity replaced by fibrous tissue composed of reticulin fibers and collagen. When this fibrosis is due to a primary hematologic process, it is called myelofibrosis. When the fibrosis is secondary to a tumor or a granulomatous process, it is called myelophthisis.

DIAGNOSIS

While the clinical picture described above is characteristic of PMF, all of the clinical features described can also be observed in PV or CML. Massive splenomegaly commonly masks erythrocytosis in PV, and reports of intraabdominal thrombosis in PMF most likely represent instances of unrecognized PV. In some patients with PMF, erythrocytosis has developed during the course of the disease. Furthermore, because many other disorders have features that overlap with PMF but respond to distinctly different therapies, the diagnosis of PMF is one of exclusion, which requires that the disorders listed in Table 13-3 be ruled out.

The presence of teardrop-shaped red cells, nucleated red cells, myelocytes, and promyelocytes establishes the presence of extramedullary hematopoiesis, while the presence of leukocytosis, thrombocytosis with large and bizarre platelets, and circulating myelocytes suggests the presence of an MPN as opposed to a secondary form of myelofibrosis (Table 13-3). Marrow is usually inaspirable due to increased marrow reticulin, but marrow biopsy will reveal a hypercellular marrow with trilineage hyperplasia and, in particular, increased numbers of megakaryocytes in clusters and with large, dysplastic nuclei. However, there are no characteristic bone marrow morphologic abnormalities that distinguish PMF from the other chronic MPNs. Splenomegaly due to extramedullary hematopoiesis may be sufficiently massive to cause portal hypertension and variceal formation. In some patients, exuberant extramedullary hematopoiesis can dominate the clinical picture. An intriguing feature of PMF is the occurrence of autoimmune abnormalities such as immune complexes, antinuclear antibodies, rheumatoid factor, or a positive Coombs' test. Whether these represent a host reaction to the disorder or are involved in its pathogenesis is unknown. Cytogenetic analysis of blood is useful both to exclude CML and for prognostic purposes, because complex karyotype abnormalities portend a poor prognosis in PMF. For unknown reasons, the number of circulating CD34+ cells is markedly increased in PMF (>15,000/μL) compared to the other chronic MPNs, unless they too develop myeloid metaplasia.

Importantly, approximately 50% of PMF patients, like patients with its companion myeloproliferative disorders PV and ET, express the JAK2 V617F mutation, often as homozygotes. Such patients are usually older and have higher hematocrits than the patients who are JAK2 V617F–negative, whereas PMF patients expressing an MPL mutation tend to be more anemic and have lower leukocyte counts. Somatic mutations in exon 9 of the calreticulin gene (CALR) have been found in a majority of patients with PMF and ET who lack mutations in either JAK2 or MPL, and their clinical course appears to be more indolent than patients expressing either a JAK2 or an MPL mutation.

TABLE 13-4

THREE CURRENT SCORING SYSTEMS FOR ESTIMATING PROGNOSIS IN PMF PATIENTS

RISK FACTOR	IPSS (2009)[a]	DIPSS (2010)[b]	DIPSS PLUS (2011)[c]
Anemia (<10 g/dL)	X	X	X
Leukocytosis (>25,000/μL)	X	X	X
Peripheral blood blasts (≥1%)	X	X	X
Constitutional symptoms	X	X	X
Age (>65 years)	X	X	X
Unfavorable karyotype			X
Platelet count (<100,000/μL)			X
Transfusion dependence			X

[a]Blood 113:2895, 2009.
[b]Blood 115:1703, 2010.
[c]J Clin Oncol 29:392, 2011.
Note: The Dynamic International Prognostic Scoring System (DIPSS) was developed to determine if the International Prognostic Scoring System (IPSS) risk factors identified as important for survival at the time of primary myelofibrosis (PMF) diagnosis could also be used for risk stratification following their acquisition during the course of the disease. One point is assigned to each risk factor for IPSS scoring. For DIPSS, the same is true, but age >65 years, anemia, blood blasts, and constitutional symptoms are assigned 2 points each. The DIPSS Plus scoring system represents recognition that the addition of unfavorable karyotype, thrombocytopenia, and transfusion dependence improved the DIPSS risk stratification system for which additional points are assigned (Table 13-5). More recent studies suggest that mutational analysis of the ASXL1, EZH2, SRSF2, and IDH1/2 genes further improves risk stratification for survival and leukemic transformation (Leukemia 27:1861, 2013).

COMPLICATIONS

Survival in PMF varies according to specific risk factors at diagnosis **(Tables 13-4 and 13-5)** but is shorter in most patients than in PV or ET patients. The natural history of PMF is one of increasing marrow failure with transfusion-dependent anemia and increasing organomegaly due to extramedullary hematopoiesis. As with CML, PMF can evolve from a chronic phase to an accelerated phase with constitutional symptoms and increasing marrow failure.

TABLE 13-5

IPSS AND DIPSS RISK STRATIFICATION SYSTEMS

	NUMBER OF RISK FACTORS		
RISK CATEGORIES[a]	IPSS	DIPSS	DIPSS PLUS
Low	0	0	0
Intermediate-1	1	1–2	1
Intermediate-2	2	3–4	2–3
High	≥3	>4	4–6

[a]The corresponding survival curves for each risk category can be found in the references cited in the footnotes of Table 13-4.
Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System.

About 10% of patients spontaneously transform to an aggressive form of acute leukemia for which therapy is usually ineffective. Additional important prognostic factors for disease acceleration during the course of PMF include the presence of complex cytogenetic abnormalities, thrombocytopenia, and transfusion-dependent anemia. Most recently, mutations in the ASXL1, EZH2, SRSF2, and IDH1/2 genes have been identified as risk factors for early death or transformation to acute leukemia and may prove to be more useful for PMF risk assessment than any clinical scoring system.

TREATMENT Primary Myelofibrosis

No specific therapy exists for PMF. The causes for anemia are multifarious and include ineffective erythropoiesis uncompensated by splenic extramedullary hematopoiesis, hemodilution due to splenomegaly, splenic sequestration, blood loss secondary to thrombocytopenia or portal hypertension, folic acid deficiency, systemic inflammation, and autoimmune hemolysis. Neither recombinant erythropoietin nor androgens such as danazol have proven to be consistently effective as therapy for anemia. Erythropoietin may worsen splenomegaly and will be ineffective if the serum erythropoietin level is >125 mU/L. Given the inflammatory milieu that characterizes PMF, corticosteroids can ameliorate anemia as well as constitutional symptoms such as fever, chills, night sweats, anorexia, and weight loss, and low-dose thalidomide together with prednisone has proved effective as well. Thrombocytopenia can be due to impaired marrow function, splenic sequestration, or autoimmune destruction and may also respond to low-dose thalidomide together with prednisone. Splenomegaly is by far the most distressing and intractable problem for PMF patients, causing abdominal pain, portal hypertension, easy satiety, and cachexia, whereas surgical removal of a massive spleen is associated with significant postoperative complications including mesenteric venous thrombosis, hemorrhage, rebound leukocytosis and thrombocytosis, and hepatic extramedullary hematopoiesis with no amelioration of either anemia or thrombocytopenia when present. For unexplained reasons, splenectomy also increases the risk of blastic transformation. Splenic irradiation is, at best, temporarily palliative and associated with a significant risk of neutropenia, infection, and subsequent operative hemorrhage if splenectomy is attempted. Allopurinol can control significant hyperuricemia, and bone pain can be alleviated by local irradiation. The role of IFN-α is still undefined; its side effects are more pronounced in the older individuals, and it may exacerbate the bone marrow failure. The JAK2 inhibitor, ruxolitinib, has proved effective in reducing splenomegaly and alleviating constitutional symptoms in a majority of advanced PMF patients while also prolonging survival, although it does not significantly influence the JAK2 V617F allele burden. Although anemia and thrombocytopenia are its major side effects, these are dose-dependent, and with time, anemia stabilizes and thrombocytopenia may improve. Allogeneic bone marrow transplantation is the only curative treatment for PMF and should be considered in younger patients; nonmyeloablative conditioning regimens may permit hematopoietic cell transplantation to be extended to older individuals, but this approach is currently under investigation.

ESSENTIAL THROMBOCYTOSIS

Essential thrombocytosis (other designations include essential thrombocythemia, idiopathic thrombocytosis, primary thrombocytosis, and hemorrhagic thrombocythemia) is a clonal disorder of unknown etiology involving a multipotent hematopoietic progenitor cell manifested clinically by overproduction of platelets without a definable cause. ET is an uncommon disorder, with an incidence of 1–2/100,000 and a distinct female predominance. No clonal marker is available to consistently distinguish ET from the more common nonclonal, reactive forms of thrombocytosis **(Table 13-6)**, making its diagnosis difficult. Once considered a disease of the elderly and responsible for significant morbidity due to hemorrhage or thrombosis, with the widespread use of electronic cell counters, it is now clear that ET can occur at any age in adults and often without symptoms or disturbances of hemostasis. There is an unexplained female predominance in contrast to PMF or the reactive forms of thrombocytosis where no sex difference exists. Because no specific clonal marker is available, clinical criteria have been proposed to distinguish ET from the other chronic MPNs, which may also present with thrombocytosis but have differing prognoses and therapies (Table 13-6). These criteria do not establish clonality; therefore, they are truly

TABLE 13-6

CAUSES OF THROMBOCYTOSIS	
Tissue inflammation: collagen vascular disease, inflammatory bowel disease	Hemorrhage
Malignancy	Iron-deficiency anemia
Infection	Surgery
Myeloproliferative disorders: polycythemia vera, primary myelofibrosis, essential thrombocytosis, chronic myelogenous leukemia	Rebound: Correction of vitamin B_{12} or folate deficiency, post-ethanol abuse
Myelodysplastic disorders: 5q– syndrome, idiopathic refractory sideroblastic anemia	Hemolysis
Postsplenectomy or hyposplenism	Familial: Thrombopoietin overproduction, MPL mutations

useful only in identifying disorders such as CML, PV, or myelodysplasia, which can masquerade as ET, as opposed to actually establishing the presence of ET. Furthermore, as with "idiopathic" erythrocytosis, nonclonal benign forms of thrombocytosis exist (such as hereditary overproduction of thrombopoietin) that are not widely recognized because we currently lack adequate diagnostic tools. Approximately 50% of ET patients carry the JAK2 V617F mutation, but its absence does not exclude the disorder.

ETIOLOGY

Megakaryocytopoiesis and platelet production depend on thrombopoietin and its receptor Mpl. As in the case of early erythroid and myeloid progenitor cells, early megakaryocytic progenitors require the presence of interleukin 3 (IL-3) and stem cell factor for optimal proliferation in addition to thrombopoietin. T eir subsequent development is also enhanced by the chemokine stromal cell-derived factor 1 (SDF-1). However, megakaryocyte maturation requires thrombopoietin.

Megakaryocytes are unique among hematopoietic progenitor cells because reduplication of their genome is endomitotic rather than mitotic. In the absence of thrombopoietin, endomitotic megakaryocytic reduplication and, by extension, the cytoplasmic development necessary for platelet production are impaired. Like erythropoietin, thrombopoietin is produced in both the liver and the kidneys, and an inverse correlation exists between the platelet count and plasma thrombopoietic activity. Unlike erythropoietin, thrombopoietin is only constitutively produced, and the plasma thrombopoietin level is controlled by the size of its progenitor cell pool. Also, in contrast to erythropoietin, but like its myeloid counterparts, granulocyte and granulocyte-macrophage colony-stimulating factors, thrombopoietin not only enhances the proliferation of its target cells but also enhances the reactivity of their end-stage product, the platelet. In addition to its role in thrombopoiesis, thrombopoietin also enhances the survival of multipotent hematopoietic stem cells and their bone marrow residence.

T e clonal nature of ET was established by analysis of glucose-6-phosphate dehydrogenase isoenzyme expression in patients hemizygous for this gene, by analysis of X-linked DNA polymorphisms in informative female patients, and by the expression in patients of nonrandom, though variable, cytogenetic abnormalities. Although thrombocytosis is its principal manifestation, like the other chronic MPNs, a multipotent hematopoietic progenitor cell is involved in ET. Furthermore, a number of families have been described in which ET was inherited, in one instance as an autosomal dominant trait. In addition to ET, PMF and PV have also been observed in some kindreds. Like PMF, most patients who do not have JAK2 mutations have CALR mutations.

CLINICAL FEATURES

Clinically, ET is most often identified incidentally when a platelet count is obtained during the course of a routine medical evaluation. Occasionally, review of previous blood counts will reveal that an elevated platelet count was present but overlooked for many years. No symptoms or signs are specific for ET, but these patients can have hemorrhagic and thrombotic tendencies expressed as easy bruising for the former and microvascular occlusive events for the latter such as erythromelalgia, ocular migraine, or a TIA. Physical examination is generally unremarkable except occasionally for mild splenomegaly. Splenomegaly is indicative of another MPN, in particular PV, PMF, or CML.

Anemia is unusual, but a mild neutrophilic leukocytosis is not. T e blood smear is most remarkable for the number of platelets present, some of which may be very large. T e large mass of circulating platelets may prevent the accurate measurement of serum potassium due to release of platelet potassium upon blood clotting. T is type of hyperkalemia is a laboratory artifact and not associated with electrocardiographic abnormalities. Similarly, arterial oxygen measurements can be inaccurate unless thrombocythemic blood is collected on ice. T e prothrombin and partial thromboplastin times are normal, whereas abnormalities of platelet function such as a prolonged bleeding time and impaired platelet aggregation can be present. However, despite much study, no platelet function abnormality is characteristic of ET, and no platelet function test predicts the risk of clinically significant bleeding or thrombosis.

T e elevated platelet count may hinder marrow aspiration, but marrow biopsy usually reveals megakaryocyte hypertrophy and hyperplasia, as well as an overall increase in marrow cellularity. If marrow reticulin is increased, another diagnosis should be considered. T e absence of stainable iron demands an explanation because iron deficiency alone can cause thrombocytosis, and absent marrow iron in the presence of marrow hypercellularity is a feature of PV.

Nonrandom cytogenetic abnormalities occur in ET but are uncommon, and no specific or consistent abnormality is notable, even those involving chromosomes 3 and 1, where the genes for thrombopoietin and its receptor Mpl, respectively, are located.

DIAGNOSIS

T rombocytosis is encountered in a broad variety of clinical disorders (Table 13-6), in many of which production of cytokines is increased. T e absolute level of the platelet count is not a useful diagnostic aid for distinguishing between benign and clonal causes of thrombocytosis. About 50% of ET patients express the JAK2

V617F mutation. When JAK2 V617F is absent, cytogenetic evaluation is mandatory to determine if the thrombocytosis is due to CML or a myelodysplastic disorder such as the 5q− syndrome. Because the bcr-abl translocation can be present in the absence of the Ph chromosome, and because bcr-abl reverse transcriptase polymerase chain reaction is associated with false-positive results, fluorescence in situ hybridization (FISH) analysis for bcr-abl is the preferred assay in patients with thrombocytosis in whom a cytogenetic study for the Ph chromosome is negative. CALR mutations are present in most patients who do not have JAK2 mutations, but diagnostic tools to detect these mutations are not yet widespread. Anemia and ringed sideroblasts are not features of ET, but they are features of idiopathic refractory sideroblastic anemia, and in some of these patients, the thrombocytosis occurs in association with JAK2 V617F expression. Splenomegaly should suggest the presence of another MPN, and in this setting, a red cell mass determination should be performed because splenomegaly can mask the presence of erythrocytosis. Importantly, what appears to be ET can evolve into PV or PMF after a period of many years, revealing the true nature of the underlying MPN. T ere is sufficient overlap of the JAK2 V617F neutrophil allele burden between ET and PV that this cannot be used as a distinguishing diagnostic feature; only a red cell mass and plasma volume determination can distinguish PV from ET, and importantly in this regard, 64% of JAK2 V617F–positive ET patients actually were found to have PV when red cell mass and plasma volume determinations were performed.

COMPLICATIONS

Perhaps no other condition in clinical medicine has caused otherwise astute physicians to intervene inappropriately more often than thrombocytosis, particularly if the platelet count is >1 × 10^6/μL. It is commonly believed that a high platelet count causes intravascular stasis and thrombosis; however, no controlled clinical study has ever established this association, and in patients younger than age 60 years, the incidence of thrombosis was not greater in patients with thrombocytosis than in age-matched controls, and tobacco use appears to be the most important risk factor for thrombosis in ET patients.

To the contrary, very high platelet counts are associated primarily with hemorrhage due to acquired von Willebrand's disease. T is is not meant to imply that an elevated platelet count cannot cause symptoms in an ET patient, but rather that the focus should be on the patient, not the platelet count. For example, some of the most dramatic neurologic problems in ET are migraine-related and respond only to lowering of the platelet count, whereas other symptoms such as erythromelalgia respond simply to platelet cyclooxygenase-1 inhibitors such as aspirin or ibuprofen, without a reduction in platelet number. Still others may represent an interaction between an atherosclerotic vascular system and a high platelet count, and others may have no relationship to the platelet count whatsoever. Recognition that PV can present with thrombocytosis alone as well as the discovery of previously unrecognized causes of hypercoagulability **(Chap. 22)** make the older literature on the complications of thrombocytosis unreliable.

ET can also evolve into PMF, but whether this is a feature of ET or represents PMF presenting initially with isolated thrombocytosis is unknown.

TREATMENT Essential Thrombocytosis

Survival of patients with ET is not different than for the general population. An elevated platelet count in an asymptomatic patient without cardiovascular risk factors requires no therapy. Indeed, before any therapy is initiated in a patient with thrombocytosis, the cause of symptoms must be clearly identified as due to the elevated platelet count. When the platelet count rises above 1 × 10^6/μL, a substantial quantity of high-molecular-weight von Willebrand multimers are removed from the circulation and destroyed by the enlarged platelet mass, resulting in an acquired form of von Willebrand's disease. T is can be identified by a reduction in ristocetin cofactor activity. In this situation, aspirin could promote hemorrhage. Bleeding in this situation usually responds to ε-aminocaproic acid, which can be given prophylactically before and after elective surgery. Plateletpheresis is at best a temporary and inefficient remedy that is rarely required. Importantly, ET patients treated with ^{32}P or alkylating agents are at risk of developing acute leukemia without any proof of benefit; combining either therapy with hydroxyurea increases this risk. If platelet reduction is deemed necessary on the basis of symptoms refractory to salicylates alone, pegylated IFN-α, the quinazoline derivative, anagrelide, or hydroxyurea can be used to reduce the platelet count, but none of these is uniformly effective or without significant side effects. Hydroxyurea and aspirin are more effective than anagrelide and aspirin for prevention of TIAs, but not more effective for the prevention of other types of arterial thrombosis and are actually less effective for venous thrombosis. T e effectiveness of hydroxyurea in preventing TIAs is because it is an NO donor. Normalizing the platelet count also does not prevent either arterial or venous thrombosis. T e risk of gastrointestinal bleeding is also higher when aspirin is combined with anagrelide.

As more clinical experience is acquired, ET appears more benign than previously thought. Evolution to acute leukemia is more likely to be a consequence of therapy than of the disease itself. In managing patients with thrombocytosis, the physician's first obligation is to do no harm.

SECTION V

HEMATOLOGIC MALIGNANCIES

CHAPTER 14

ACUTE MYELOID LEUKEMIA

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INCIDENCE

Acute myeloid leukemia (AML) is a neoplastic disease characterized by infiltration of the blood, bone marrow, and other tissues by proliferative, clonal undifferentiated cells of the hematopoietic system. These leukemias comprise a spectrum of malignancies that, untreated, range from rapidly fatal to slowly growing. In 2013, the estimated number of new AML cases in the United States was 14,590. The incidence of AML is ~3.5 per 100,000 people per year, and the age-adjusted incidence is higher in men than in women (4.5 vs 3.1). AML incidence increases with age; it is 1.7 in individuals age <65 years and 15.9 in those age >65 years. The median age at diagnosis is 67 years.

ETIOLOGY

Heredity, radiation, chemical and other occupational exposures, and drugs have been implicated in the development of AML. No direct evidence suggests a viral etiology.

Heredity

Certain syndromes with somatic cell chromosome aneuploidy, such as trisomy 21 noted in Down syndrome, are associated with an increased incidence of AML. Inherited diseases with defective DNA repair, e.g., Fanconi anemia, Bloom syndrome, and ataxia-telangiectasia, are also associated with AML. Congenital neutropenia (Kostmann syndrome) is a disease with mutations in the genes encoding the granulocyte colony-stimulating factor (G-CSF) receptor and, often, neutrophil elastase that may evolve into AML. Germline mutations of CCAAT/enhancer-binding protein α (CEBPA), runt-related transcription factor 1 (RUNX1), and tumor protein p53 (TP53) have also been associated with a higher predisposition to AML in some series.

Radiation

High-dose radiation, like that experienced by survivors of the atomic bombs in Japan or nuclear reactor accidents, increases the risk of myeloid leukemias that peaks 5–7 years after exposure. Therapeutic radiation alone seems to add little risk of AML but can increase the risk in people also exposed to alkylating agents.

Chemical and other exposures

Exposure to benzene, a solvent used in the chemical, plastic, rubber, and pharmaceutical industries, is associated with an increased incidence of AML. Smoking and exposure to petroleum products, paint, embalming fluids, ethylene oxide, herbicides, and pesticides have also been associated with an increased risk of AML.

Drugs

Anticancer drugs are the leading cause of therapy-associated AML. Alkylating agent–associated leukemias occur on average 4–6 years after exposure, and affected individuals have aberrations in chromosomes 5 and 7. Topoisomerase II inhibitor–associated leukemias occur 1–3 years after exposure, and affected individuals often have aberrations involving chromosome 11q23. Newer agents for treatment of other hematopoietic malignancies and solid tumors are also under scrutiny for increased risk of AML. Chloramphenicol, phenylbutazone, and, less commonly, chloroquine and methoxypsoralen can result in bone marrow failure that may evolve into AML.

CLASSIFICATION

The current categorization of AML uses the World Health Organization (WHO) classification **(Table 14-1)**, which includes different biologically distinct groups based on clinical features and cytogenetic and molecular

TABLE 14-1

WORLD HEALTH ORGANIZATION CLASSIFICATION OF ACUTE MYELOID LEUKEMIA (AML) AND RELATED NEOPLASMS[a]

- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22); RUNX1-RUNX1T1[b]
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11[b]
  - Acute promyelocytic leukemia with t(15;17)(q22;q12); PML-RARA[b]
  - AML with t(9;11)(p22;q23); MLLT3-MLL
  - AML with t(6;9)(p23;q34); DEK-NUP214
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
  - AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
  - Provisional entity: AML with mutated NPM1
  - Provisional entity: AML with mutated CEBPA
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, not otherwise specified
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic and monocytic leukemia
  - Acute erythroid leukemia
  - Acute megakaryoblastic leukemia
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
  - Transient abnormal myelopoiesis
  - Myeloid leukemia associated with Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

[a]From SH Swerdlow et al (eds): World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, IARC Press, 2008.
[b]Diagnosis is AML regardless of blast count.

abnormalities in addition to morphology. In contrast to the previously used French-American-British (FAB) schema, the WHO classification places limited reliance on cytochemistry. A major difference between the WHO and the FAB systems is the blast cutoff for a diagnosis of AML as opposed to myelodysplastic syndrome (MDS); it is 20% in the WHO classification and 30% in the FAB. However, within the WHO classification, specific chromosomal rearrangements, i.e., t(8;21)(q22;q22), inv(16)(p13.1q22), t(16;16)(p13.1;q22), and t(15;17)(q22;q12), define AML even with <20% blasts.

Immunophenotype and relevance to the WHO classification

The immunophenotype of human leukemia cells can be studied by multiparameter flow cytometry after the cells are labeled with monoclonal antibodies to cell-surface antigens. This can be important for separating AML from acute lymphoblastic leukemia (ALL) and identifying some subtypes of AML. For example, AML with minimal differentiation that is characterized by immature morphology and no lineage-specific cytochemical reactions may be diagnosed by flow-cytometric demonstration of the myeloid-specific antigens cluster designation (CD) 13 and/or 117. Similarly, acute megakaryoblastic leukemia can often be diagnosed only by expression of the platelet-specific antigens CD41 and/or CD61. Although flow cytometry is useful, widely used, and in some cases essential for the diagnosis of AML, it is supportive only in establishing the different subtypes of AML through the WHO classification.

Clinical features and relevance to the WHO classification

The WHO classification also considers clinical features in subdividing AML. For example, it identifies therapy-related AML as a separate entity that develops following prior therapy (e.g., alkylating agents, topoisomerase II inhibitors, ionizing radiation). It also identifies AML with myelodysplasia-related changes based in part on medical history of an antecedent MDS or myelodysplastic/myeloproliferative neoplasm. The clinical features likely contribute to the prognosis of AML and have therefore been included in the classification.

Genetic findings and relevance to the WHO classification

The WHO classification uses clinical, morphologic, and cytogenetic and/or molecular criteria to identify subtypes of AML and forces the clinician to take the appropriate steps to correctly identify the entity and thus tailor treatment(s) accordingly. The WHO classification is indeed the first AML classification that incorporates genetic (chromosomal and molecular) information. In this classification, subtypes of AML are recognized based on the presence or absence of specific recurrent genetic abnormalities. For example, the diagnosis of acute promyelocytic leukemia (APL) is based on the presence of either the t(15;17)(q22;q12) cytogenetic rearrangement or the PML-RARA fusion product of the translocation. A similar approach is taken with regard to core binding factor (CBF) AML that is now designated based on the presence of t(8;21)(q22;q22), inv(16)(p13.1q22), or t(16;16)(p13.1;q22) or the respective fusion products RUNX1-RUNX1T1 and CBFB-MYH11.

The WHO classification incorporates cytogenetics in the AML classification by recognizing a category of AML with recurrent genetic abnormalities and a category of AML with myelodysplasia-related changes (Table 14-1). The latter category is diagnosed not only by morphologic changes, but also in part by selected

myelodysplasia-related cytogenetic abnormalities (e.g., complex karyotypes and unbalanced and balanced changes involving, among others, chromosomes 5, 7, and 11). Only one cytogenetic abnormality has been invariably associated with specific morphologic features: t(15;17)(q22;q12) with APL. Other chromosomal abnormalities have been associated primarily with one morphologic/immunophenotypic group, including inv(16)(p13.1q22) with AML with abnormal bone marrow eosinophils; t(8;21)(q22;q22) with slender Auer rods, expression of CD19, and increased normal eosinophils; and t(9;11)(p22;q23), and other translocations involving 11q23, with monocytic features. Recurring chromosomal abnormalities in AML may also be associated with specific clinical characteristics. More commonly associated with younger age are t(8;21) and t(15;17), and with older age, del(5q) and del(7q). Myeloid sarcomas (see below) are associated with t(8;21), and disseminated intravascular coagulation (DIC) is associated with t(15;17).

T e WHO classification also incorporates molecular abnormalities by recognizing fusion genes that are products of recurrent cytogenetic aberrations or have been found mutated and may be involved in leukemogenesis. For instance, t(15;17) results in the fusion gene PML-RARA that encodes a chimeric protein, promyelocytic leukemia (Pml)–retinoic acid receptor α (Rarα), which is formed by the fusion of the retinoic acid receptor α (RARA) gene from chromosome 17 and the promyelocytic leukemia (PML) gene from chromosome 15. T e RARA gene encodes a member of the nuclear hormone receptor family of transcription factors. After binding retinoic acid, RARA can promote expression of a variety of genes. T e 15;17 translocation juxtaposes PML with RARA in a head-to-tail configuration that is under the transcriptional control of PML. T ree different breakpoints in the PML gene lead to various fusion protein isoforms. T e Pml-Rarα fusion protein tends to suppress gene transcription and blocks differentiation of the cells. Pharmacologic doses of the Rarα ligand, all-trans-retinoic acid (tretinoin), relieve the block and promote hematopoietic cell differentiation (see below). Similar examples of molecular subtypes of the disease included in the category of AML with recurrent genetic abnormalities are those characterized by the leukemogenic fusion genes RUNX1-RUNX1T1, CBFB-MYH11, MLLT3-MLL, and DEK-NUP214, resulting, respectively, from t(8;21), inv(16) or t(16;16), t(9;11), and t(6;9)(p23;q34).

Two new provisional entities defined by the presence of gene mutations, rather than microscopic chromosomal abnormalities, have been added to the category of AML with recurrent genetic abnormalities: AML with mutated nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1) and AML with mutated CEBPA. AML with fms-related tyrosine kinase 3 (FLT3) mutations is not considered a distinct entity, although determining the presence of such mutations is recommended by WHO in patients with cytogenetically normal AML (CN-AML) because the relatively frequent FLT3-internal tandem duplication (ITD) carries a negative prognostic significance and therefore is clinically relevant. FLT3 encodes a tyrosine kinase receptor important in the development of myeloid and lymphoid lineages. Activating mutations of FLT3 are present in ~30% of adult AML patients due to ITDs in the juxtamembrane domain or point mutations of the activating loop of the kinase (called tyrosine kinase domain mutations). Aberrant activation of the FLT3-encoded protein provides increased proliferation and antiapoptotic signals to the myeloid progenitor cell. FLT3-ITD, the more common of the FLT3 mutations, occurs preferentially in patients with CN-AML. T e importance of identifying FLT3-ITD at diagnosis relates to the fact that not only is it a useful prognosticator but it also may predict response to specific treatment such as the tyrosine kinase inhibitors that are in clinical investigation.

PROGNOSTIC FACTORS

Several factors have been demonstrated to predict outcome of AML patients treated with chemotherapy, and they can be used for risk stratification and treatment guidance.

Chromosome findings at diagnosis are currently the most important independent prognostic factors. Several studies have categorized patients as having favorable, intermediate, or poor cytogenetic risk based on the presence of structural and/or numerical aberrations. Patients with t(15;17) have a very good prognosis (~85% cured), and those with t(8;21) and inv(16) have a good prognosis (~55% cured), whereas those with no cytogenetic abnormality have an intermediate outcome risk (~40% cured). Patients with a complex karyotype, t(6;9), inv(3), or –7 have a very poor prognosis. Another cytogenetic subgroup, the monosomal karyotype, has been suggested to adversely impact the outcome of AML patients other than those with t(15;17), t(8;21), or inv(16) or t(16;16). T e monosomal karyotype subgroup is defined by the presence of at least two autosomal monosomies (loss of chromosomes other than Y or X) or a single autosomal monosomy with additional structural abnormalities.

For patients lacking prognostic cytogenetic abnormalities, such as those with CN-AML, outcome prediction uses mutated or aberrantly expressed genes. NPM1 mutations without concurrent presence of FLT3-ITD, and CEBPA mutations, especially if concurrently present in two different alleles, have been shown to predict favorable outcome, whereas FLT3-ITD predicts poor outcome. Given the proven prognostic importance of NPM1 and CEBPA mutations and FLT3-ITD,

molecular assessment of these genes at diagnosis has been incorporated in AML management guidelines by the National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN). The same markers have also been incorporated in the definitions of the genetic groups of the ELN standardized reporting system, which are based on both cytogenetic and molecular abnormalities and used for comparing clinical features and treatment response among subsets of patients reported in different studies **(Table 14-2)**. More recently, the prognostic impact of the genetic groups recognized by the ELN reporting system has been demonstrated. Thus, these genetic groups may also be used for risk stratification and treatment guidance.

In addition to NPM1 and CEBPA mutations and FLT3-ITD, other molecular aberrations **(Table 14-3)** may in the future be routinely used for prognostication in AML and incorporated in the WHO classification and the ELN reporting system. Among these prognostic mutated genes are those encoding receptor tyrosine kinases (e.g., v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog [KIT]), transcription factors (i.e., RUNX1 and Wilms tumor 1 [WT1]), and epigenetic modifiers (i.e., additional sex combs like transcriptional regulator 1 [ASXL1], DNA (cytosine-5-)-methyltransferase 3 alpha [DNMT3A], isocitrate dehydrogenase 1 (NADP+), soluble [IDH1] and isocitrate dehydrogenase 2 (NADP+), mitochondrial [IDH2], lysine (K)-specific methyltransferase 2A [KMT2A, also known as MLL], and tet methylcytosine dioxygenase 2 [TET2]). Although KIT mutations are almost exclusively present in CBF AML and impact adversely the outcome, the remaining markers have been reported primarily in CN-AML. These gene mutations have been shown to be associated with outcome in multivariable analyses independently from other prognostic factors. However, for some of them, the prognostic impact (e.g., TET2 mutations) or the type (adverse vs favorable) of prognostic impact (e.g., IDH1, IDH2) has been found in the majority, but not in all, of the reported studies.

An independent prognostic impact remains to be determined for mutated genes that are either associated primarily with unfavorable cytogenetic aberrations (e.g., TP53) or are found with a relatively lower

TABLE 14-2

EUROPEAN LEUKEMIANET RECOMMENDED STANDARDIZED REPORTING FOR CORRELATION OF CYTOGENETIC AND MOLECULAR GENETIC DATA IN AML WITH CLINICAL DATA[a]

GENETIC GROUP	SUBSETS
Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD (normal karyotype) Mutated CEBPA (normal karyotype)
Intermediate-I	Mutated NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 without FLT3-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); MLLT3-MLL Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9)(p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged –5 or del(5q); –7; abn(17p); complex karyotype (≥3 abnormalities)

[a]H Döhner et al: Blood 115:453, 2010.
Abbreviation: ITD, internal tandem duplication.

TABLE 14-3

MOLECULAR PROGNOSTIC MARKERS IN AML

GENE SYMBOL	GENE LOCATION	PROGNOSTIC IMPACT
Genes Included in the WHO Classification and ELN Reporting System		
NPM1 mutations	5q35.1	Favorable
CEBPA mutations	19q13.1	Favorable
FLT3-ITD	13q12	Adverse
Genes Encoding Receptor Tyrosine Kinases		
KIT mutation	4q12	Adverse
FLT3-TKD	13q12	Adverse
Genes Encoding Transcription Factors		
RUNX1 mutations	21q22.12	Adverse
WT1 mutations	11p13	Adverse
Genes Encoding Epigenetic Modifers		
ASXL1 mutations	20q11.21	Adverse
DNMT3A mutations	2p23.3	Adverse
IDH mutations (IDH1 and IDH2)	2q34 &15q26.1	Adverse
MLL-PTD	11q23	Adverse
TET2 mutations	4q24	Adverse
Deregulated Genes		
BAALC overexpression	8q22.3	Adverse
ERG overexpression	21q22.3	Adverse
MN1 overexpression	22q12.1	Adverse
EVI1 overexpression	3q26.2	Adverse
Deregulated MicroRNAs		
miR-155 overexpression	21q21.3	Adverse
miR-3151 overexpression	8q22.3	Adverse
miR-181a overexpression	1q32.1 and 9q33.3	Favorable

Abbreviations: AML, acute myeloid leukemia; ELN, European LeukemiaNet; ITD, internal tandem duplication; PTD, partial tandem duplication; TKD, tyrosine kinase domain; WHO, World Health Organization.

frequency in AML patients like those encoding epigenetic modifiers (e.g., enhancer of zeste 2 polycomb repressive complex 2 subunit [EZH2]), phosphatases (e.g., protein tyrosine phosphatase, non-receptor type 11 (PTPN11]), putative transcription factors (e.g., PHD finger protein 6 [PHF6]), splicing factors (e.g., U2 small nuclear RNA auxiliary factor 1 [U2AF1]), and proteins involved in chromosome segregation and genome stability (e.g., structural maintenance of chromosomes 1A [SMC1A] or structural maintenance of chromosomes 3 [SMC3]). Finally, other mutated genes are recognized as predictors of treatment response to distinct therapies rather than prognosticators; for example, neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) and Kirsten rat sarcoma viral oncogene homolog (KRAS) predict a better response to high-dose cytarabine in CBF AML.

In addition to gene mutations, deregulation of the expression levels of coding genes and of short noncoding RNAs (microRNAs) have been reported to provide prognostic information (Table 14-3). Overexpression of genes such as brain and acute leukemia, cytoplasmic (BAALC), v-ets avian erythroblastosis virus E26 oncogene homologue (avian) (ERG), meningioma (disrupted in balanced translocation) 1 (MN1), and MDS1 and EVI1 complex locus (MECOM, also known as EVI1) have been found to be predictive for poor outcome, especially in CN-AML. Similarly, deregulated expression levels of microRNAs, naturally occurring noncoding RNAs that have been shown to regulate the expression of proteins involved in hematopoietic differentiation and survival pathways by degradation or translation inhibition of target coding RNAs, have been associated with prognosis in AML. Overexpression of miR-155 and miR-3151 has been found to affect outcome adversely in CN-AML, whereas overexpression of miR-181a predicts a favorable outcome both in CN-AML and cytogenetically abnormal AML.

Because prognostic molecular markers in AML are not mutually exclusive and often occur concurrently (>80% patients have at least two or more prognostic gene mutations), the likelihood that distinct marker combinations may be more informative than single markers is being recognized.

Epigenetic changes (e.g., DNA methylation) and microRNAs are often involved in deregulation of genes involved in hematopoiesis, contribute to leukemogenesis, and are often associated with the previously discussed prognostic gene mutations. T ese changes not only have been shown to provide biologic insights into leukemogenic mechanisms, but also independent prognostic information. Indeed, it is anticipated that with the enormous progress made in DNA and RNA sequencing technology, additional genetic and epigenetic aberrations will soon be discovered and will contribute to classification and reporting systems and outcome risk determination in AML patients.

In addition to cytogenetics and/or molecular aberrations, several other factors are associated with outcome in AML. Age at diagnosis is one of the most important risk factors. Advancing age is associated with a poorer prognosis not only because of its influence on the ability to survive induction therapy due to coexisting comorbidities, but also because with each successive decade of age, a greater proportion of patients have an intrinsically more resistant disease. A prolonged symptomatic interval with cytopenias preceding diagnosis or a history of antecedent hematologic disorders including myeloproliferative neoplasms is often found in older patients and is a clinical feature associated with a lower complete remission (CR) rate and shorter survival time. T e CR rate is lower in patients who have had anemia, leukopenia, and/or thrombocytopenia for >3 months before the diagnosis of AML when compared to those without such a history. Responsiveness to chemotherapy declines as the duration of the antecedent disorder(s) increases. AML developing after treatment with cytotoxic agents for other malignancies is usually difficult to treat successfully. Finally, it is likely that AML in older patients is also associated with poor outcome because of the presence of distinct biologic features that may increase the aggressiveness of the disease and reduce the likelihood of treatment response. T e leukemic cells in older patients more commonly express the multidrug resistance 1 (MDR1) ef ux pump that conveys resistance to natural product–derived agents such as the anthracyclines that are frequently incorporated into the initial treatment. In addition, older patients less frequently harbor favorable cytogenetic abnormalities [i.e., t(8;21), inv(16), and t(16;16)] and more frequently harbor adverse cytogenetic (e.g., complex and monosomal karyotypes) and/or molecular (e.g., ASXL1, IDH2, RUNX1, TET2) abnormalities.

Other factors independently associated with worse outcome are a low performance status that influences ability to survive induction therapy and thus respond to treatment and a high presenting leukocyte count that in some series is an adverse prognostic factor for attaining a CR. Among patients with hyperleukocytosis (>100,000/μL), early central nervous system bleeding and pulmonary leukostasis contribute to poor outcome with initial therapy.

Achievement of CR is associated with better outcome and longer survival. CR is defined after examination of both blood and bone marrow. T e blood neutrophil count must be ≥1000/μL and the platelet count ≥100,000/μL. Hemoglobin concentration is not considered in determining CR. Circulating blasts should be absent. Although rare blasts may be detected in the blood during marrow regeneration, they should

disappear on successive studies. The bone marrow should contain <5% blasts, and Auer rods should be absent. Extramedullary leukemia should not be present. Patients who achieve CR after one induction cycle have longer CR durations than those requiring multiple cycles.

CLINICAL PRESENTATION

Symptoms

Patients with AML most often present with nonspecific symptoms that begin gradually or abruptly and are the consequence of anemia, leukocytosis, leukopenia or leukocyte dysfunction, or thrombocytopenia. Nearly half have had symptoms for ≤3 months before the leukemia was diagnosed.

Half of patients mention fatigue as the first symptom, but most complain of fatigue or weakness at the time of diagnosis. Anorexia and weight loss are common. Fever with or without an identifiable infection is the initial symptom in approximately 10% of patients. Signs of abnormal hemostasis (bleeding, easy bruising) are noted first in 5% of patients. On occasion, bone pain, lymphadenopathy, nonspecific cough, headache, or diaphoresis is the presenting symptom.

Rarely patients may present with symptoms from a myeloid sarcoma that is a tumor mass consisting of myeloid blasts occurring at anatomic sites other than bone marrow. Sites involved are most commonly the skin, lymph node, gastrointestinal tract, soft tissue, and testis. This is rare presentation, often characterized by chromosome aberrations [e.g., monosomy 7, trisomy 8, MLL rearrangement, inv(16), trisomy 4, t(8;21)], may precede or coincide with AML.

Physical findings

Fever, splenomegaly, hepatomegaly, lymphadenopathy, sternal tenderness, and evidence of infection and hemorrhage are often found at diagnosis. Significant gastrointestinal bleeding, intrapulmonary hemorrhage, or intracranial hemorrhage occurs most often in APL. Bleeding associated with coagulopathy may also occur in monocytic AML and with extreme degrees of leukocytosis or thrombocytopenia in other morphologic subtypes. Retinal hemorrhages are detected in 15% of patients. Infiltration of the gingivae, skin, soft tissues, or meninges with leukemic blasts at diagnosis is characteristic of the monocytic subtypes and those with 11q23 chromosomal abnormalities.

Hematologic findings

Anemia is usually present at diagnosis and can be severe. The degree varies considerably, irrespective of other hematologic findings, splenomegaly, or duration of symptoms. The anemia is usually normocytic normochromic. Decreased erythropoiesis often results in a reduced reticulocyte count, and red blood cell (RBC) survival is decreased by accelerated destruction. Active blood loss also contributes to the anemia.

The median presenting leukocyte count is about 15,000/μL. Between 25 and 40% of patients have counts <5000/μL, and 20% have counts >100,000/μL. Fewer than 5% have no detectable leukemic cells in the blood. The morphology of the malignant cell varies in different subsets. In AML, the cytoplasm often contains primary (nonspecific) granules, and the nucleus shows fine, lacy chromatin with one or more nucleoli characteristic of immature cells. Abnormal rod-shaped granules called Auer rods are not uniformly present, but when they are, myeloid lineage is virtually certain **(Fig. 14-1)**. Poor neutrophil function may be noted functionally by impaired phagocytosis and migration and morphologically by abnormal lobulation and deficient granulation.

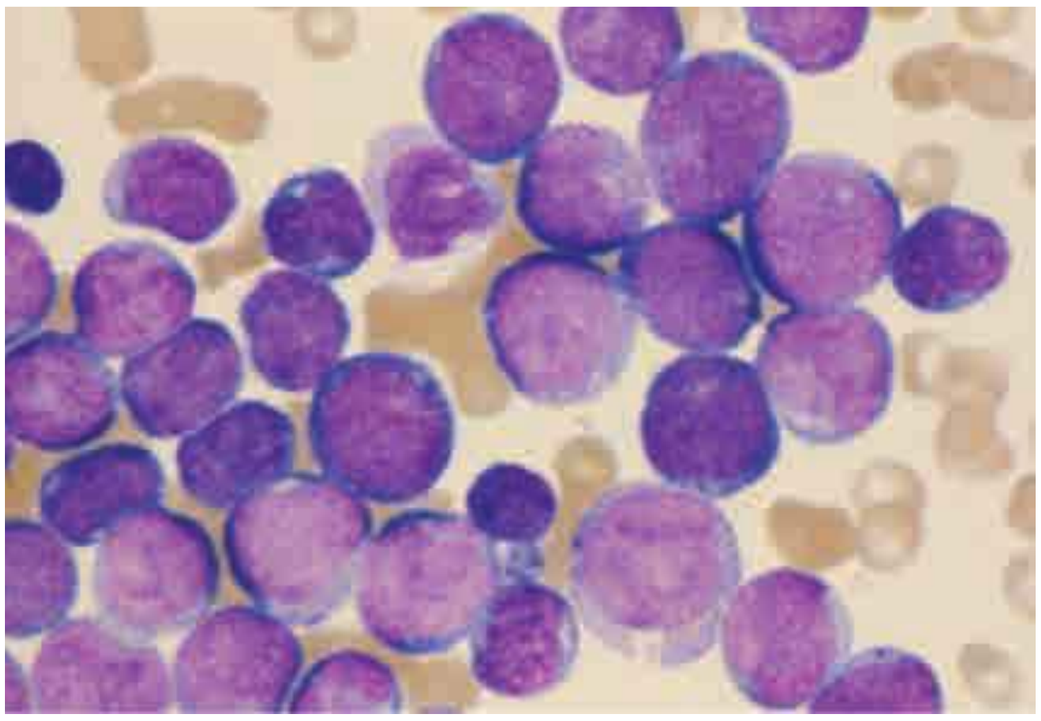
Platelet counts <100,000/μL are found at diagnosis in ~75% of patients, and about 25% have counts <25,000/μL. Both morphologic and functional platelet abnormalities can be observed, including large and bizarre shapes with abnormal granulation and inability of platelets to aggregate or adhere normally to one another.

Pretreatment evaluation

Once the diagnosis of AML is suspected, a rapid evaluation and initiation of appropriate therapy should follow. In addition to clarifying the subtype of leukemia, initial studies should evaluate the overall functional integrity of the major organ systems, including the cardiovascular, pulmonary, hepatic, and renal systems **(Table 14-4)**. Factors that have prognostic significance, either for achieving CR or for predicting the duration of CR, should also be assessed before initiating treatment, including cytogenetics and molecular markers (see above). Leukemic cells should be obtained from all patients and cryopreserved for future use as new tests and therapeutics become available. All patients should be evaluated for infection.

Most patients are anemic and thrombocytopenic at presentation. Replacement of the appropriate blood components, if necessary, should begin promptly. Because qualitative platelet dysfunction or the presence of an infection may increase the likelihood of bleeding, evidence of hemorrhage justifies the immediate use of platelet transfusion, even if the platelet count is only moderately decreased.

About 50% of patients have a mild to moderate elevation of serum uric acid at presentation. Only 10% have marked elevations, but renal precipitation of uric acid and the nephropathy that may result is a serious



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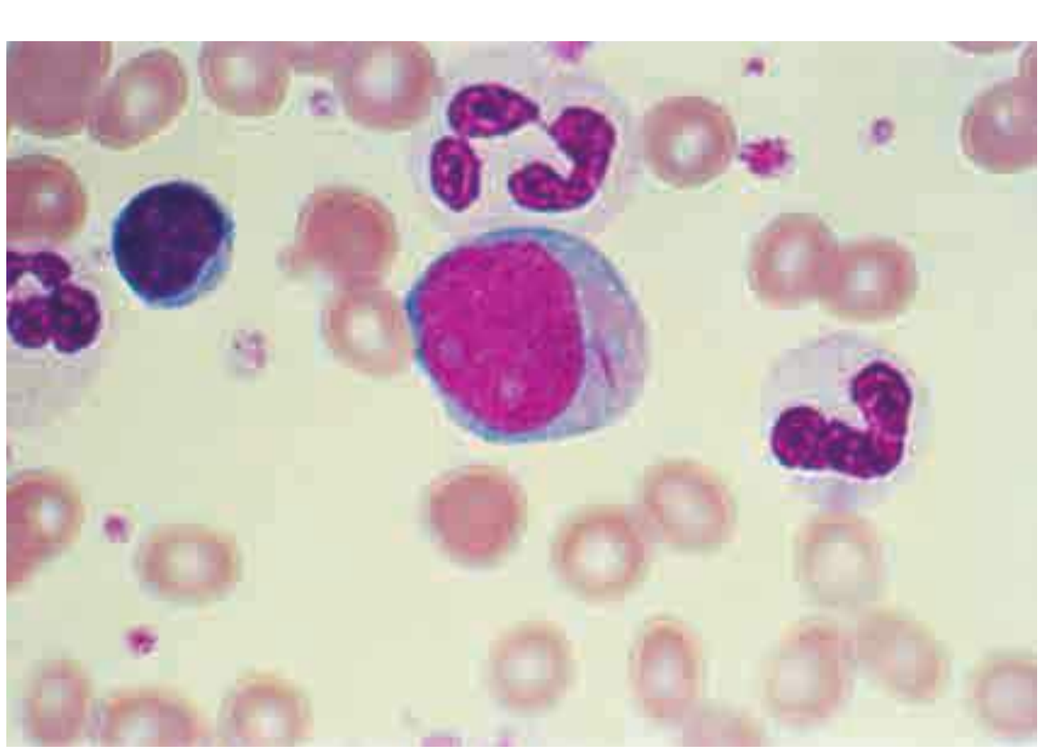

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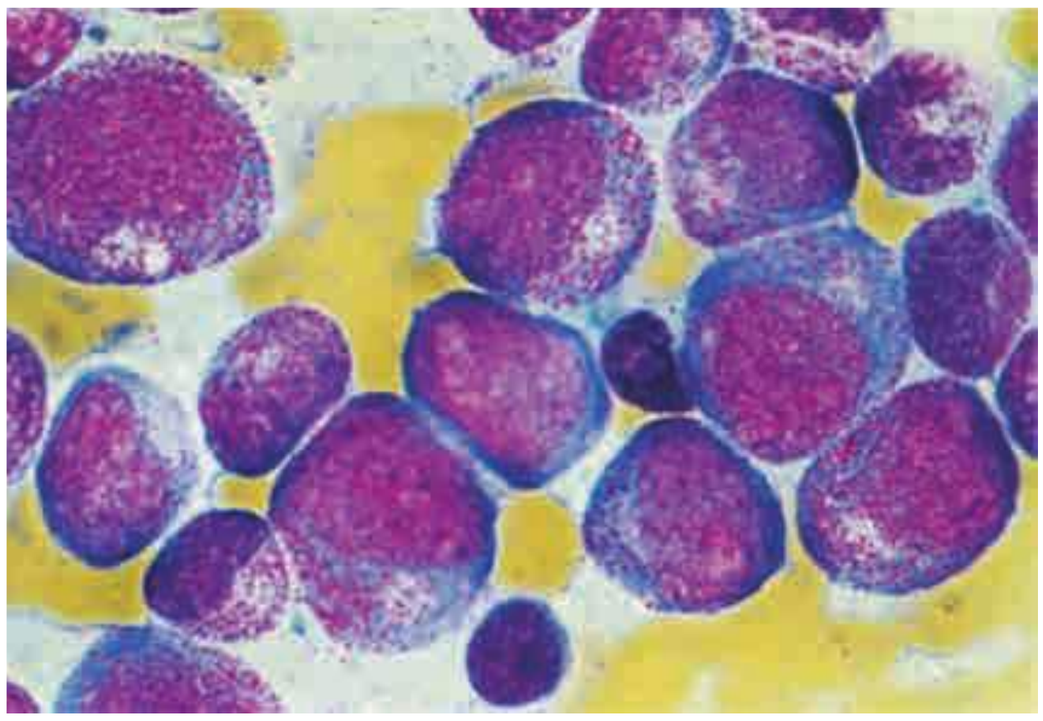

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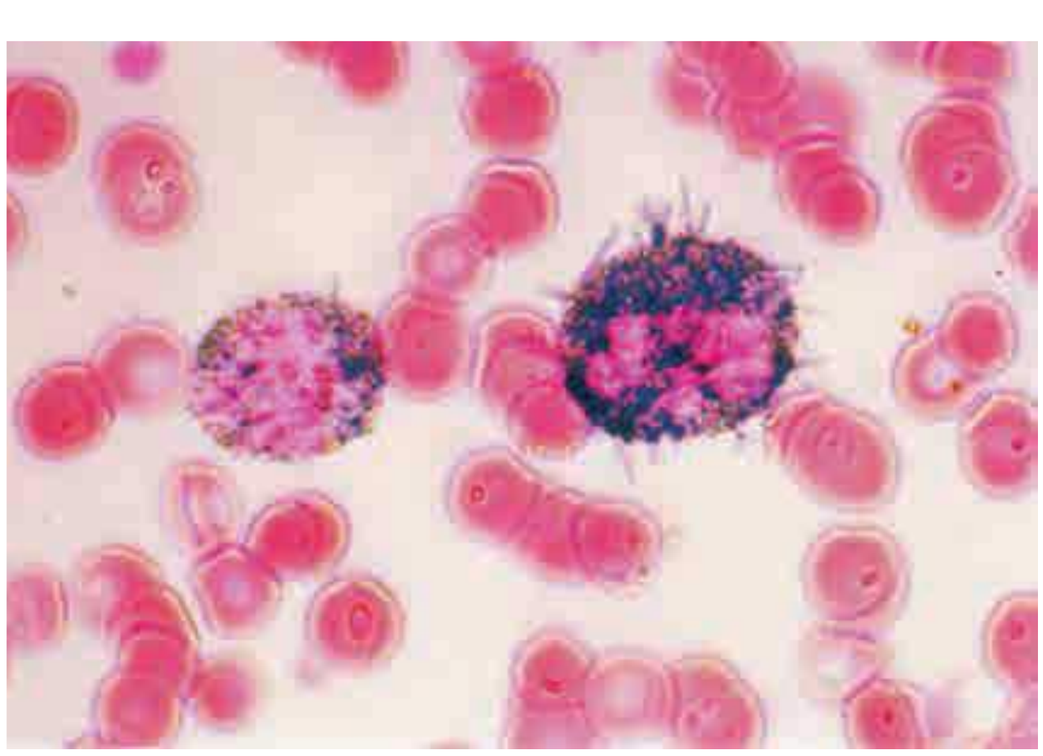

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FIGURE 14-1
Morphology of acute myeloid leukemia (AML) cells. A. Uniform population of primitive myeloblasts with immature chromatin, nucleoli in some cells, and primary cytoplasmic granules. B. Leukemic myeloblast containing an Auer rod. C. Promyelocytic leukemia cells with prominent cytoplasmic primary granules. D. Peroxidase stain shows dark blue color characteristic of peroxidase in granules in AML.

but uncommon complication. The initiation of chemotherapy may aggravate hyperuricemia, and patients are usually started immediately on allopurinol and hydration at diagnosis. Rasburicase (recombinant uric oxidase) is also useful for treating uric acid nephropathy and often can normalize the serum uric acid level within hours with a single dose of treatment. The presence of high concentrations of lysozyme, a marker for monocytic differentiation, may be etiologic in renal tubular dysfunction, which could worsen other renal problems that arise during the initial phases of therapy.

TREATMENT Acute Myeloid Leukemia

Treatment of the newly diagnosed patient with AML is usually divided into two phases, induction and postremission management **(Fig. 14-2)**. The initial goal is to induce CR. Once CR is obtained, further therapy must be used to prolong survival and achieve cure. The initial induction treatment and subsequent postremission therapy are often chosen based on the patient's age. Intensifying therapy with traditional chemotherapy agents such as cytarabine and anthracyclines in younger patients (<60 years) appears to increase the cure rate of AML. In older patients, the benefit of intensive therapy is controversial; novel approaches for selecting patients predicted to be responsive to treatment and new therapies are being pursued.

INDUCTION CHEMOTHERAPY The most commonly used CR induction regimens (for patients other than those with APL) consist of combination chemotherapy with cytarabine and an anthracycline (e.g., daunorubicin, idarubicin, mitoxantrone). Cytarabine is a cell cycle S-phase–specific antimetabolite that becomes phosphorylated intracellularly to an active triphosphate form that interferes with DNA synthesis. Anthracyclines are DNA intercalators. Their primary mode of action is

TABLE 14-4

INITIAL DIAGNOSTIC EVALUATION AND MANAGEMENT OF ADULT PATIENTS WITH AML
History
Increasing fatigue or decreased exercise tolerance (anemia) Excess bleeding or bleeding from unusual sites (DIC, thrombocytopenia) Fevers or recurrent infections (neutropenia) Headache, vision changes, nonfocal neurologic abnormalities (CNS leukemia or bleed) Early satiety (splenomegaly) Family history of AML (Fanconi, Bloom, or Kostmann syndromes or ataxia-telangiectasia) History of cancer (exposure to alkylating agents, radiation, topoisomerase II inhibitors) Occupational exposures (radiation, benzene, petroleum products, paint, smoking, pesticides)
Physical Examination
Performance status (prognostic factor) Ecchymosis and oozing from IV sites (DIC, possible acute promyelocytic leukemia) Fever and tachycardia (signs of infection) Papilledema, retinal infiltrates, cranial nerve abnormalities (CNS leukemia) Poor dentition, dental abscesses Gum hypertrophy (leukemic infiltration, most common in monocytic leukemia) Skin infiltration or nodules (leukemia infiltration, most common in monocytic leukemia) Lymphadenopathy, splenomegaly, hepatomegaly Back pain, lower extremity weakness [spinal granulocytic sarcoma, most likely in t(8;21) patients]
Laboratory and Radiologic Studies
CBC with manual differential cell count Chemistry tests (electrolytes, creatinine, BUN, calcium, phosphorus, uric acid, hepatic enzymes, bilirubin, LDH, amylase, lipase) Clotting studies (prothrombin time, partial thromboplastin time, fibrinogen, d-dimer) Viral serologies (CMV, HSV-1, varicella-zoster) RBC type and screen HLA typing for potential allogeneic HSCT Bone marrow aspirate and biopsy (morphology, cytogenetics, flow cytometry, molecular studies for NPM1 and CEBPA mutations and FLT3-ITD) Cryopreservation of viable leukemia cells Myocardial function (echocardiogram or MUGA scan) PA and lateral chest radiograph Placement of central venous access device
Interventions for Specific Patients
Dental evaluation (for those with poor dentition) Lumbar puncture (for those with symptoms of CNS involvement) Screening spine MRI (for patients with back pain, lower extremity weakness, paresthesias) Social work referral for patient and family psychosocial support
Counseling for All Patients
Provide patients with information regarding their disease, financial counseling, and support group contacts

Abbreviations: AML, acute myeloid leukemia; BUN, blood urea nitrogen; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; DIC, disseminated intravascular coagulation; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; IV, intravenous; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PA, posteroanterior; RBC, red blood (cell) count.

thought to be inhibition of topoisomerase II, leading to DNA breaks.

In younger adults (age <60 years), cytarabine is used either at standard dose (100–200 mg/m^2) administered as a continuous intravenous infusion for 7 days or higher dose (2 g/m^2) administered intravenously every 12 h for 6 days. With standard-dose cytarabine, anthracycline therapy generally consists of daunorubicin (60–90 mg/m^2) or idarubicin (12 mg/m^2) intravenously on days 1, 2, and 3 (the 7 and 3 regimen). Other agents can be added (i.e., cladribine) when 60 mg/m^2 of daunorubicin is used.

High-dose cytarabine-based regimens have also been shown to induce high CR rates. When given in high doses, higher intracellular levels of cytarabine may be achieved, thereby saturating the cytarabine-inactivating enzymes and increasing the intracellular levels of 1-β-d-arabinofuranylcytosine-triphosphate, the active metabolite incorporated into DNA. Thus, higher doses of cytarabine may increase the inhibition of DNA synthesis and thereby overcome resistance to standard-dose cytarabine. With high-dose cytarabine, daunorubicin 60 mg/m^2 or idarubicin 12 mg/m^2 is generally used.

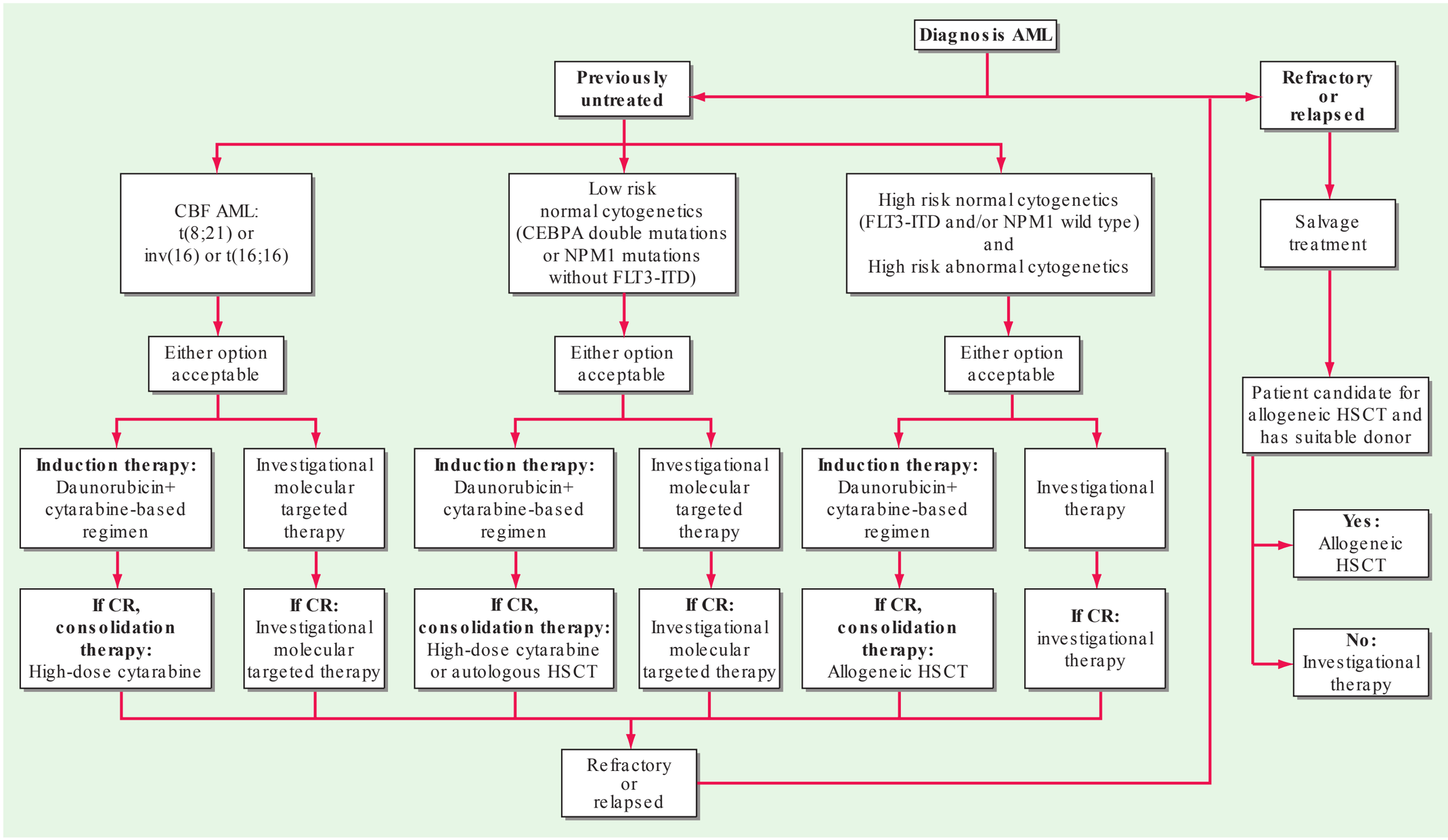


FIGURE 14-2

Flow chart for the therapy of newly diagnosed acute myeloid leukemia (AML). For all forms of AML except acute promyelocytic leukemia (APL), standard therapy includes a regimen based on a 7-day continuous infusion of cytarabine (100–200 mg/m^2 per day) and a 3-day course of daunorubicin (60–90 mg/m^2 per day) with or without additional drugs. Idarubicin (12–13 mg/m^2 per day) could be used in place of daunorubicin (not shown). Patients who achieve complete remission (CR) undergo postremission consolidation therapy, including sequential courses of high-dose cytarabine, autologous hematopoietic stem cell transplantation (HSCT), allogeneic HSCT, or novel therapies, based on their predicted risk of relapse (i.e., risk-stratified therapy). Patients with APL (see text for treatment) usually receive tretinoin and arsenic trioxide–based regimens with or without anthracycline-based chemotherapy and possibly maintenance with tretinoin. CBF, core binding factor; ITD, internal tandem duplication.

The hematologic toxicity of high-dose cytarabine-based induction regimens has typically been greater than that associated with 7 and 3 regimens. Toxicity with high-dose cytarabine also includes pulmonary toxicity and significant and occasionally irreversible cerebellar toxicity. All patients treated with high-dose cytarabine must be closely monitored for cerebellar toxicity. Full cerebellar testing should be performed before each dose, and further high-dose cytarabine should be withheld if evidence of cerebellar toxicity develops. This toxicity occurs more commonly in patients with renal impairment and in those older than age 60 years. The increased toxicity observed with high-dose cytarabine has limited the use of this therapy in older AML patients.

Incorporation of novel and molecular targeting agents into these regimens is currently under investigation. For patients with FLT3-ITD AML, trials with tyrosine kinase inhibitors are ongoing. Patients with CBF AML may benefit from the combination of gemtuzumab ozogamicin, a monoclonal CD33 antibody linked to the cytotoxic agent calicheamicin, with induction and consolidation chemotherapies. This agent, initially approved for older patients with relapsed disease, has been withdrawn from the U.S. market at the request of the U.S. Food and Drug Administration due to concerns about the product's toxicity, including myelosuppression, infusion toxicity, and venoocclusive disease and the clinical benefit of the initially recommended higher doses. However, the aforementioned recent results are encouraging and support the reintroduction of this agent into the therapeutic armamentarium for AML.

In older patients (age ≥60 years), the outcome is generally poor likely due to a higher induction treatment–related mortality rate and frequency of resistant disease, especially in patients with prior hematologic disorders (MDS or myeloproliferative syndromes) or who have received chemotherapy treatment for another malignancy or harbor cytogenetic and genetic abnormalities that adversely impact on clinical outcome. These patients should be considered for clinical trials. Alternatively, older patients can be also treated with the 7 and 3 regimen with standard-dose cytarabine and idarubicin (12 mg/m^2), daunorubicin (45–90 mg/m^2), or mitoxantrone

(12 mg/m^2). For patients older than 65 years, higher dose daunorubicin (90 mg/m^2) has not shown benefit due to the increased toxicity and is not recommended. T e combination of gemtuzumab ozogamicin with chemotherapy reduces the risk of relapse for patients age 50–70 years with previously untreated AML. Finally, older patients may be considered for single-agent therapies with clofarabine or hypomethylating agents (i.e., 5-azacitidine or decitabine). T e latter are often used for patients unfit for more intensive therapies.

After one cycle of the 7 and 3 chemotherapy induction regimen, if persistence of leukemia is documented, the patient is usually re-treated with the same agents (cytarabine and the anthracycline) for 5 and 2 days, respectively. Our recommendation, however, is to consider changing therapy in this setting.

POSTREMISSION THERAPY Induction of a durable first CR is critical to long-term disease-free survival in AML. However, without further therapy, virtually all patients experience relapse. T us, postremission therapy is designed to eradicate residual leukemic cells to prevent relapse and prolong survival. T e type of postremission therapy in AML is often based on age and cytogenetic and molecular risk.

For younger patients, most studies include intensive chemotherapy and allogeneic or autologous hematopoietic stem cell transplantation (HSCT). In the postremission setting, high-dose cytarabine for three to four cycles is more effective than standard-dose cytarabine. T e Cancer and Leukemia Group B (CALGB), for example, compared the duration of CR in patients randomly assigned after remission to four cycles of high (3 g/m^2, every 12 h on days 1, 3, and 5), intermediate (400 mg/m^2 for 5 days by continuous infusion), or standard (100 mg/m^2 per day for 5 days by continuous infusion) doses of cytarabine. A dose-response effect for cytarabine in patients with AML who were age ≤60 years was demonstrated. High-dose cytarabine significantly prolonged CR and increased the fraction cured in patients with favorable [t(8;21) and inv(16)] and normal cytogenetics, but it had no significant effect on patients with other abnormal karyotypes. As discussed, high-dose cytarabine has increased toxicity in older patients. T erefore, in this age group, for patients without CBF AML, exploration of attenuated chemotherapy regimens has been pursued. However, because the outcome of older patients is poor, allogeneic HSCT, when feasible, should be strongly considered. Postremission therapy is also a setting for introduction of new agents **(Table 14-5)**.

Autologous HSCT preceded by one to two cycles of high-dose cytarabine is also an option for intensive consolidation therapy. Autologous HSCT has been generally applied to AML patients in the context of a clinical trial or when the risk of repetitive intensive chemotherapy represents a higher risk than the autologous HSCT (e.g., in patients with severe platelet alloimmunization) or when other factors including patient age, comorbid conditions, and fertility are considered.

Allogeneic HSCT is used in patients age <70–75 years with a human leukocyte antigen (HLA)-compatible donor who have high-risk cytogenetics. Selected high-risk patients are also considered for alternative donor transplants (e.g., mismatched unrelated, haploidentical related, and unrelated umbilical cord donors). In patients with CN-AML and high-risk molecular features such as FLT3-ITD, allogeneic HSCT is best applied in the context of clinical trials because the impact of aggressive therapy on outcome is unknown. For older patients, exploration of reduced-intensity allogeneic HSCT has been pursued.

Trials comparing intensive chemotherapy and autologous and allogeneic HSCT have shown improved duration of remission with allogeneic HSCT compared to autologous HSCT or chemotherapy alone. However, overall survival is generally not different; the improved disease control with allogeneic HSCT is erased by the increase in fatal toxicity. In fact, relapse following allogeneic HSCT occurs in only a small fraction of patients, but treatment-related toxicity is relatively high; complications include venoocclusive disease, graft-versus-host disease (GVHD), and infections. Autologous HSCT can be administered in young and older patients and

TABLE 14-5

SELECTED AGENTS UNDER STUDY FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA

CLASS OF DRUGS	EXAMPLES OF AGENTS IN CLASS
Inhibitors of Mutant Proteins	
Tyrosine kinase inhibitors	Dasatinib, midostaurin, quizartinib, sorafenib
IDH2 mutation inhibitor	AG-221
Epigenetic Targeting Compounds	
Demethylating agents	S110 (decitabine dinucleotide), oral azacitidine
Histone deacetylase inhibitors	Suberoylanilide hydroxamic acid (SAHA), MS275, LBH589
Inhibitors of Cell Proliferation	
Cell cycle inhibitors	Flavopiridol, CYC202 (R-roscovitine), SNS-032
Farnesyl transferase inhibitors	R115777, SCH66336
Aurora inhibitors	AZD1152, MLN-8237, AT9283
Inhibitors of Protein Synthesis and Degradation	
Aminopeptide inhibitors	Tosedostat
HSP-90 antagonists	17-Allylaminogeldanamycin (17-AAG), DMAG, or derivatives
Nedd8 activating enzyme (NAE) inhibitors	MLN4924
Cytotoxic Compounds	
Nucleoside analogues	Clofarabine, troxacitabine, elacytarabine, sapacitabine
Compounds with Immuno-Mediated Mechanisms	
Antibodies	CSL362 (anti-CD123), anti-CD33 (SGN33), anti-KIR
Immunomodulatory	Lenalidomide, interleukin 2, histamine dihydrochloride

uses the same preparative regimens. Patients subsequently receive their own stem cells collected while in remission. T e toxicity is relatively low with autologous HSCT (5% mortality rate), but the relapse rate is higher than with allogeneic HSCT, due to the absence of the graft-versus-leukemia (GVL) effect seen with allogeneic HSCT and possible contamination of the autologous stem cells with residual tumor cells.

Prognostic factors may ultimately help to select the appropriate postremission therapy in patients in first CR. Our approach includes allogeneic HSCT in first CR for patients without favorable cytogenetics or genotype (e.g., patients who do not have CEBPA biallelic mutations or NPM1 mutations without FLT3-ITD) and/or with other poor risk factors (e.g., an antecedent hematologic disorder or failure to attain remission with a single induction course). If a suitable HLA donor does not exist, investigational therapeutic approaches are considered. Indeed, postremission therapy is also a setting for introduction of new agents (Table 14-5). Because FLT3-ITD can be targeted with emerging novel inhibitors, patients with this molecular abnormality should be considered for clinical trials with these agents whenever possible.

Patients with the favorable CBF AML [i.e., t(8;21), inv(16), or t(16;16)] are treated with repetitive doses of high-dose cytarabine, which offers a high frequency of cure without the morbidity of transplant. Among AML patients with t(8;21) and inv(16), those with KIT mutations, who have a worse prognosis, may be considered for novel investigational studies, including tyrosine kinase inhibitors. T e inclusion of gemtuzumab ozogamicin in induction and consolidation chemotherapy-based treatment has been reported to be beneficial in this subset of patients.

For patients in morphologic CR, immunophenotyping to detect minute populations of blasts or sensitive molecular assays (e.g., reverse transcriptase polymerase chain reaction [RT-PCR]) to detect AML-associated molecular abnormalities (e.g., NPM1 mutation, the CBF AML RUNX1/RUNX1T1 and CBFB/MYH11 transcripts, the APL PML/RARA transcript), and the less sensitive metaphase cytogenetics or interphase cytogenetics by fluorescence in situ hybridization (FISH) to detect AML-associated cytogenetic aberrations, can be performed to assess whether clinically meaningful minimal residual disease (MRD) is present at sequential time points during or after treatment. Detection of MRD may be a reliable discriminator between patients who will continue in CR and those who are destined to experience disease recurrence and therefore require early therapeutic intervention before clinical relapse occurs. Although assessment of MRD in bone marrow and/or blood during CR is routinely used in the clinic to anticipate clinical relapse and initiate timely salvage treatment for APL patients, for other cytogenetic and molecular subtypes of AML, this is an area of current investigation.

SUPPORTIVE CARE Measures geared to supporting patients through several weeks of neutropenia and thrombocytopenia are critical to the success of AML therapy. Patients with AML should be treated in centers expert in providing supportive measures. Multilumen right atrial catheters should be inserted as soon as patients with newly diagnosed AML have been stabilized. T ey should be used thereafter for administration of intravenous medications and transfusions, as well as for blood drawing.

Adequate and prompt blood bank support is critical to therapy of AML. Platelet transfusions should be given as needed to maintain a platelet count ≥10,000/μL. T e platelet count should be kept at higher levels in febrile patients and during episodes of active bleeding or DIC. Patients with poor posttransfusion platelet count increments may benefit from administration of platelets from HLA-matched donors. RBC transfusions should be administered to keep the hemoglobin level >80 g/L (8 g/dL) in the absence of active bleeding, DIC, or congestive heart failure, which require higher hemoglobin levels. Blood products leukodepleted by filtration should be used to avert or delay alloimmunization as well as febrile reactions. Blood products should also be irradiated to prevent transfusion-associated GVHD. Cytomegalovirus (CMV)-negative blood products should be used for CMV-seronegative patients who are potential candidates for allogeneic HSCT. Leukodepleted products are also effective for these patients if CMV-negative products are not available.

Neutropenia (neutrophils <500/μL or <1000/μL and predicted to decline to <500/μL over the next 48 h) can be part of the initial presentation and/or a side effect of the chemotherapy treatment in AML patients. T us, infectious complications remain the major cause of morbidity and death during induction and postremission chemotherapy for AML. Antibacterial (i.e., quinolones) and antifungal (i.e., posaconazole) prophylaxis in the absence of fever is likely to be beneficial. For patients who are herpes simplex virus or varicella-zoster seropositive, antiviral prophylaxis should be initiated (e.g., acyclovir, valacyclovir).

Fever develops in most patients with AML, but infections are documented in only half of febrile patients. Early initiation of empirical broad-spectrum antibacterial and antifungal antibiotics has significantly reduced the number of patients dying of infectious complications **(Chap. 30)**. An antibiotic regimen adequate to treat gram-negative organisms should be instituted at the onset of fever in a neutropenic patient after clinical evaluation, including a detailed physical examination with inspection of the indwelling catheter exit site and a perirectal examination, as well as procurement of cultures and radiographs aimed at documenting the source of fever. Specific antibiotic regimens should be based on antibiotic sensitivity data obtained from the institution at which the patient is being treated. Acceptable regimens for empiric antibiotic therapy include monotherapy with imipenem-cilastatin, meropenem, piperacillin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime or ceftazidime). T e combination of an aminoglycoside with an antipseudomonal penicillin (e.g., piperacillin) or an aminoglycoside in combination with an extended-spectrum antipseudomonal cephalosporin should be considered in complicated or

resistant cases. Aminoglycosides should be avoided if possible in patients with renal insufficiency. Empirical vancomycin should be added in neutropenic patients with catheter-related infections, blood cultures positive for gram-positive bacteria before final identification and susceptibility testing, hypotension or shock, or known colonization with penicillin/cephalosporin-resistant pneumococci or methicillin-resistant Staphylococcus aureus. In special situations where decreased susceptibility to vancomycin, vancomycin-resistant organisms, or vancomycin toxicity is documented, other options including linezolid, daptomycin, and quinupristin/dalfopristin need to be considered.

Caspofungin (or a similar echinocandin), voriconazole, or liposomal amphotericin B should be considered for antifungal treatment if fever persists for 4–7 days following initiation of empiric antibiotic therapy. Amphotericin B has long been used for antifungal therapy. Although liposomal formulations have improved the toxicity profile of this agent, its use has been limited to situations with high risk of or documented mold infections. Caspofungin has been approved for empiric antifungal treatment. Voriconazole has also been shown to be equivalent in efficacy and less toxic than amphotericin B. Antibacterial and antifungal antibiotics should be continued until patients are no longer neutropenic, regardless of whether a specific source has been found for the fever.

Recombinant hematopoietic growth factors have been incorporated into clinical trials in AML. T ese trials have been designed to lower the infection rate after chemotherapy. Both G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) have reduced the median time to neutrophil recovery. T is accelerated rate of neutrophil recovery, however, has not generally translated into significant reductions in infection rates or shortened hospitalizations. In most randomized studies, both G-CSF and GM-CSF have failed to improve the CR rate, disease-free survival, or overall survival. Although receptors for both G-CSF and GM-CSF are present on AML blasts, therapeutic efficacy is neither enhanced nor inhibited by these agents. T e use of growth factors as supportive care for AML patients is controversial. We favor their use in elderly patients with complicated courses, those receiving intensive postremission regimens, patients with uncontrolled infections, or those participating in clinical trials.

TREATMENT FOR REFRACTORY OR RELAPSED AML With the 7 and 3 regimen, 65–75% of younger and 50–60% of older patients with primary AML achieve CR. Two-thirds achieve CR after a single course of therapy, and one-third require two courses. Of patients who do not achieve CR, approximately 50% have a drug-resistant leukemia, and 50% do not achieve CR because of fatal complications of bone marrow aplasia or impaired recovery of normal stem cells. Patients with refractory disease after induction should be considered for salvage treatments, preferentially on clinical trials, before receiving allogeneic HSCT usually administered in patients who achieve a disease-free status. Because these patients are usually not cured even if they achieve second CR with salvage chemotherapy, allogeneic HSCT is a necessary therapeutic step.

In patients who relapse after achieving CR, the length of first CR is predictive of response to salvage chemotherapy treatment; patients with longer first CR (>12 months) generally relapse with drug-sensitive disease and have a higher chance of attaining a CR, even with the same chemotherapeutic agents used for first remission induction. Whether initial CR was achieved with one or two courses of chemotherapy and the type of postremission therapy may also predict achievement of second CR. Similar to patients with refractory disease, patients with relapsed disease are rarely cured by the salvage chemotherapy treatments. T erefore, patients who eventually achieve a second CR and are eligible for allogeneic HSCT should be transplanted.

Because achievement of a second CR with routine salvage therapies is relatively uncommon, especially in patients who relapse rapidly after achievement of first CR (<12 months), these patients and those lacking HLA-compatible donors or who are not candidates for allogeneic HSCT should be considered for innovative approaches on clinical trials (Table 14-5). T e discovery of novel gene mutations and mechanisms of leukemogenesis that might represent actionable therapeutic targets has prompted the development of new targeting agents. In addition to kinase inhibitors for FLT3- and KIT-mutated AML, other compounds targeting the aberrant activity of mutant proteins (e.g., IDH2 inhibitors) or biologic mechanisms deregulating epigenetics (e.g., histone deacetylase and DNA methyltransferase inhibitors), cell proliferation (e.g., farnesyl transferase inhibitors), protein synthesis (e.g., aminopeptide inhibitors) and folding (e.g., heat shock protein inhibitors), and ubiquitination, or with novel cytotoxic mechanisms (e.g., clofarabine, sapacitabine), are being tested in clinical trials. Furthermore, approaches with antibodies targeting commonly expressed leukemia blasts (e.g., CD33) or leukemia initiating cells (e.g., CD123) and immunomodulatory agents (e.g., lenalidomide) are also under investigation. Once these compounds have demonstrated safety and activity as single agents, investigation of combinations with other molecular targeting compounds and/or chemotherapy should be pursued.

TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA APL is a highly curable subtype of AML, and approximately 85% of these patients achieve long-term survival with current approaches. APL has long been shown to be responsive to cytarabine and daunorubicin, but previously patients treated with these drugs alone frequently died from DIC induced by the release of granule components by the chemotherapy-treated leukemia cells. However, the prognosis of APL patients has changed dramatically from adverse to favorable with the introduction of tretinoin, an oral drug that induces the differentiation of leukemic cells bearing the t(15;17), where disruption of the RARA gene encoding a retinoid acid receptor occurs. Tretinoin decreases the frequency of DIC but produces another complication called the APL differentiation

syndrome. Occurring within the first 3 weeks of treatment, it is characterized by fever, fluid retention, dyspnea, chest pain, pulmonary infiltrates, pleural and pericardial effusions, and hypoxemia. T e syndrome is related to adhesion of differentiated neoplastic cells to the pulmonary vasculature endothelium. Glucocorticoids, chemotherapy, and/or supportive measures can be effective for management of the APL differentiation syndrome. Temporary discontinuation of tretinoin is necessary in cases of severe APL differentiation syndrome (i.e., patients developing renal failure or requiring admission to the intensive care unit due to respiratory distress). T e mortality rate of this syndrome is about 10%.

Tretinoin (45 mg/m^2 per day orally until remission is documented) plus concurrent anthracycline-based (i.e., idarubicin or daunorubicin) chemotherapy appears to be among the most effective treatment for APL, leading to CR rates of 90–95%. T e role of cytarabine in APL induction and consolidation is controversial. T e addition of cytarabine, although not demonstrated to increase the CR rate, seemingly decreases the risk for relapse. Following achievement of CR, patients should receive at least two cycles of anthracycline-based chemotherapy.

Arsenic trioxide has significant antileukemic activity and is being explored as part of initial treatment in clinical trials of APL. In a randomized trial, arsenic trioxide improved outcome if used after achievement of CR and before consolidation therapy with anthracycline-based chemotherapy. Patients receiving arsenic trioxide are at risk of APL differentiation syndrome, especially when it is administered during induction or salvage treatment after disease relapse. In addition, arsenic trioxide may prolong the QT interval, increasing the risk of cardiac arrhythmias.

Given the progress made in APL resulting in high cure rates, in recent years the goal has been to identify patients with low risk of relapse (i.e., those presenting with a leukocyte count ≤10,000/μL) where attempts are being made to decrease the amount of therapy administered and to identify patients at greatest risk of relapse (i.e., those presenting with a leukocyte count ≥10,000/μL) where new approaches can be developed to increase cure. A study compared the gold standard (tretinoin plus chemotherapy) in newly diagnosed non-high-risk APL with a chemotherapy-free combination of tretinoin and arsenic trioxide. An equivalent outcome was demonstrated between the two arms, and the chemotherapy-free regimen will likely become a new standard for non-high-risk APL patients.

Combinations of tretinoin, arsenic trioxide, and/or chemotherapy and/or gemtuzumab ozogamicin have shown favorable responses in high-risk APL patients at diagnosis.

Assessment of residual disease by RT-PCR amplification of the t(15;17) chimeric gene product PML-RARA following the final cycle of chemotherapy is an important step in the management of APL patients. Disappearance of the signal is associated with long-term disease-free survival; its persistence documented by two consecutive tests performed 2 weeks apart invariably predicts relapse. Sequential monitoring of RT-PCR for PML-RARA is now considered standard for postremission monitoring of APL, especially in high-risk patients.

T e benefit from maintenance therapy with tretinoin has been documented in some studies and not in others. T us, the use of tretinoin depends on which regimen has been used for induction and consolidation treatment and the risk category of the patients, with those with high-risk disease seemingly benefiting the most from maintenance therapy.

Patients in molecular, cytogenetic, or clinical relapse should be salvaged with arsenic trioxide with or without tretinoin; it produces meaningful responses in up to 85% of patients and can be followed by autologous or, less frequently, especially if RT-PCR positive for PML-RARA, allogeneic HSCT.

CHAPTER 15

CHRONIC MYELOID LEUKEMIA

Hagop Kantarjian ■ Jorge Cortes

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder. The disease is driven by the BCR-ABL1 chimeric gene product, a constitutively active tyrosine kinase, resulting from a reciprocal balanced translocation between the long arms of chromosomes 9 and 22, t(9;22) (q34;q11.2), cytogenetically detected as the Philadelphia chromosome (Ph) **(Fig. 15-1)**. Untreated, the course of CML may be biphasic or triphasic, with an early indolent or chronic phase, followed often by an accelerated phase and a terminal blastic phase. Before the era of selective BCR-ABL1 tyrosine kinase inhibitors (TKIs), the median survival in CML was 3–7 years, and the 10-year survival rate was 30% or less. Introduced into CML therapy in 2000, TKIs have revolutionized the treatment, natural history, and prognosis of CML. Today, the estimated 10-year survival rate with imatinib mesylate, the first BCR-ABL1 TKI approved, is 85%. Allogeneic stem cell transplantation (SCT), a curative but risky treatment approach, is now offered as second- or third-line therapy after failure of TKIs.

INCIDENCE AND EPIDEMIOLOGY

CML accounts for 15% of all cases of leukemia. There is a slight male preponderance (male:female ratio 1.6:1). The median age at diagnosis is 55–65 years. It is uncommon in children; only 3% of patients with CML are younger than 20 years. CML incidence increases slowly with age, with a steeper increase after the age of 40–50 years. The annual incidence of CML is 1.5 cases per 100,000 individuals. In the United States, this translates into 4500–5000 new cases per year. The incidence of CML has not changed over several decades. By extrapolation, the worldwide annual incidence of CML is about 100,000 cases. With a median survival of 6 years before 2000, the disease prevalence in the United States was 20,000–30,000 cases. With TKI therapy, the annual mortality has been reduced from 10–20% to about 2%. Therefore, the prevalence of CML in the United States is expected to continue to increase (about 80,000 in 2013) and reach a plateau of approximately 180,000 cases around 2030. The worldwide prevalence will depend on the treatment penetration of TKIs and their effect on reduction of worldwide annual mortality. Ideally, with full TKI treatment penetration, the worldwide prevalence should plateau at 35 times the incidence, or around 3 million patients.

ETIOLOGY

There are no familial associations in CML. The risk of developing CML is not increased in monozygotic twins or in relatives of patients. No etiologic agents are incriminated, and no associations exist with exposures to benzene or other toxins, fertilizers, insecticides, or viruses. CML is not a frequent secondary leukemia following therapy of other cancers with alkylating agents and/or radiation. Exposure to ionizing radiation (e.g., nuclear accidents, radiation treatment for ankylosing spondylitis or cervical cancer) has increased the risk of CML, which peaks at 5–10 years after exposure and is dose-related. The median time to development of CML among atomic bomb survivors was 6.3 years. Following the Chernobyl accident, the incidence of CML did not increase, suggesting that only large doses of radiation can cause CML. Because of adequate protection, the risk of CML is not increased in individuals working in the nuclear industry or among radiologists in recent times.

PATHOPHYSIOLOGY

The t(9;22) (q34;q11.2) is present in more than 90% of classical CML cases. It results from a balanced reciprocal translocation between the long arms of chromosomes 9 and 22. It is present in hematopoietic cells (myeloid, erythroid, megakaryocytes, and monocytes;

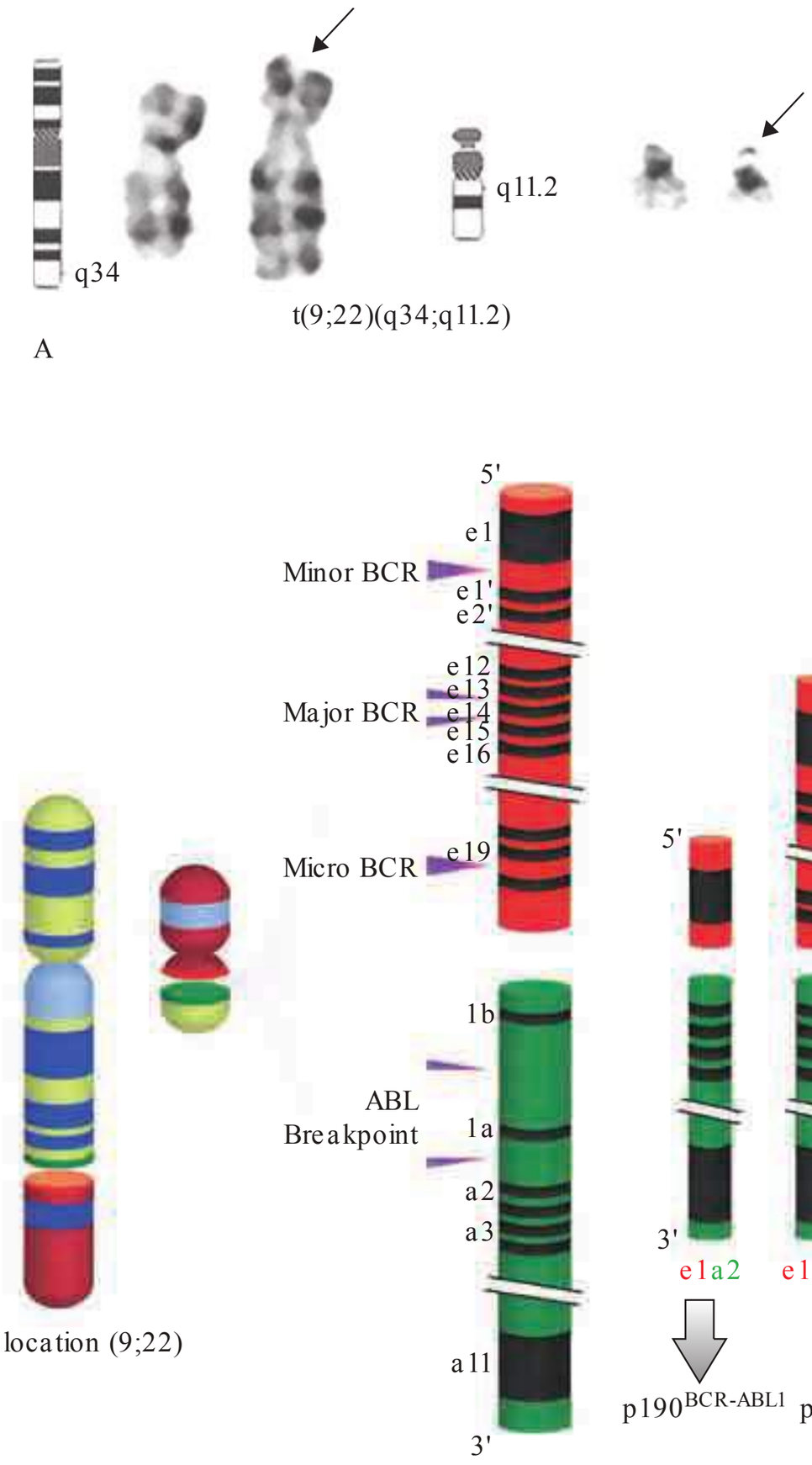


FIGURE 15-1

A. The Philadelphia (Ph) chromosome cytogenetic abnormality. B. Breakpoints in the long arms of chromosome 9 (ABL locus) and chromosome 22 (BCR regions) result in three different BCR-ABL oncoprotein messages, $p210^{BCR\text{-}ABL1}$ (most common message in chronic myeloid leukemia [CML]), $p190^{BCR\text{-}ABL1}$ (present in two-thirds of patients with Ph-positive acute lymphocytic leukemia; rare in CML), and $p230^{BCR\text{-}ABL1}$ (rare in CML and associated with an indolent course). (© 2013 The University of Texas MD Anderson Cancer Center.)

less often mature B lymphocytes; rarely mature T lymphocytes, but not stromal cells), but not in other cells in the human body. As a result of the translocation, DNA sequences from the cellular oncogene ABL1 are translocated next to the major breakpoint cluster region (BCR) gene on chromosome 22, generating a hybrid oncogene, BCR-ABL1. T is fusion gene codes for a novel oncoprotein of molecular weight 210 kDa, referred to as $p210^{BCR\text{-}ABL1}$ (Fig. 15-1B). T is BCR-ABL1 oncoprotein exhibits constitutive kinase activity that leads to excessive proliferation and reduced apoptosis of CML cells, endowing them with a growth advantage over their normal counterparts. Over time, normal hematopoiesis is suppressed, but normal stem cells can persist and may reemerge following effective therapy, for example with TKIs. In Ph-positive acute lymphocytic leukemia (ALL) and in rare cases of CML, the breakpoint in BCR is more centromeric, in a region called the minor BCR region (mBCR). As a result, a shorter sequence of BCR is fused to ABL1, with a consequent smaller BCR-ABL1 oncoprotein, $p190^{BCR\text{-}ABL1}$. When occurring in Ph-positive CML, this translocation may predict for a worse outcome. A third rare breakpoint in BCR occurs telomeric to the major BCR region and is called micro-BCR (μ-BCR). It juxtaposes a larger fragment of the BCR gene to ABL1 and produces a larger $p230^{BCR\text{-}ABL1}$ oncoprotein, which is associated with a more indolent CML course.

T e constitutive activation of BCR-ABL1 results in autophosphorylation and activation of multiple downstream pathways that modify gene transcription, apoptosis, skeletal organization, and degradation of inhibitory proteins. T ese transduction pathways may involve RAS, mitogen-activated protein (MAP) kinases, signal transducers and activators of transcription (STAT), phosphatidylinositol-3-kinase (PI3k), MYC, and others. T ese interactions are mostly mediated through tyrosine phosphorylation and require binding of BCR-ABL1 to adapter proteins such as GRB-2, CRK, CRK-like (CRK-L) protein, and Src homology containing proteins (SHC). BCR-ABL1 TKIs bind to the BCR-ABL1 kinase domain (KD), preventing the activation of transformation pathways and inhibiting downstream signaling. As a result, proliferation of CML cells is inhibited and apoptosis induced, leading to the reemergence of normal hematopoiesis. A plethora of signaling pathways have been implicated in BCR-ABL1-mediated cellular transformation. T e emerging picture is a complex and redundant transformation network. An additional layer of complexity is related to differences in signal transduction between CML differentiated cells and early progenitors. Beta-catenin, Wnt1, Foxo3a, transforming growth factor β, interleukin-6, PP2A, SIRT1, and others have been implicated in CML stem cell survival.

Experimental models have established the causal relationship between the Ph-related BCR-ABL1 molecular events and the development of CML. In animal models, expression of BCR-ABL1 in normal hematopoietic cells produced CML-like disorders or lymphoid leukemia, demonstrating the leukemogenic potential of BCR-ABL1 as a single oncogenic abnormality.

T e cause of the BCR-ABL1 molecular rearrangement is unknown. Molecular techniques that detect BCR-ABL1 at a level of 1 in 10^8 identify this molecular abnormality in the blood of up to 25% of normal adults and 5% of infants, but 0% of cord blood samples. T is suggests that BCR-ABL1 is not sufficient to cause overt CML in the overwhelming majority of individuals in whom it occurs. Because CML develops in only 1.5 of 100,000 individuals annually, it is evident that additional molecular events or poor immune recognition of the rearranged cells are needed to cause overt CML.

CML is defined by the presence of BCR-ABL1 abnormality in a patient with a myeloproliferative neoplasm. In some patients with a typical morphologic picture of CML, the Ph abnormality is not detectable by standard cytogenetic analysis, but fuorescence in situ hybridization (FISH) and molecular studies (polymerase chain reaction [PCR]) detect BCR-ABL1. T ese patients have a course similar to Ph-positive CML and respond to TKI therapy. Many of the remaining patients have atypical morphologic or clinical features and belong to other diagnostic groups, such as atypical CML or chronic myelomonocytic leukemia. T ese individuals do not respond to TKI therapy and have a poor prognosis with a median survival of about 2–3 years. Detection of mutations in the granulocyte colony-stimulating factor receptor (CSF3R) in chronic neutrophilic leukemia and in some cases of atypical CML and of mutations in SETBP1 in atypical CML confirmed that they are distinct entities.

T e mechanisms associated with the transition of CML from a chronic to accelerated-blastic phase are poorly understood. T ey are often associated with characteristic chromosomal abnormalities such as a double Ph, trisomy 8, isochromosome 17 or deletion of 17p (loss of TP53), 20q–, and others. Molecular events associated with transformation include mutations in TP53, retinoblastoma 1 (RB1), myeloid transcriptions factors like Runx1, and cell cycle regulators like p16. A plethora of other mutations or functional abnormalities have been implicated in blastic transformation, but no unifying theme has emerged other than that BCR-ABL1 itself induces genetic instability that leads to the acquisition of additional mutations and eventually to blastic transformation. In this frame of thinking, one critical effect of TKIs is their ability to stabilize the CML genome, leading to a much reduced transformation rate. In particular, the previously observed sudden blastic transformations (i.e., abrupt transformation to blastic phase in a patient who had been in cytogenetic response) have become uncommon, occurring rarely in younger patients in the first 1–2 years of TKI therapy (usually sudden lymphoid blastic transformations). Sudden transformations beyond the third year of TKI therapy are rare in patients who continue on TKI therapy. Moreover, initial experience suggests that the course of CML has become significantly more indolent, even without cytogenetic responses, in patients on TKI-based therapy compared to previous experience with hydroxyurea/busulfan.

Among patients developing resistance to TKIs, several resistance mechanisms have been observed. T e most clinically relevant one is the development of different ABL1 kinase domain mutations that prevent the binding of TKIs to the catalytic site (ATP binding site) of the kinase. More than 100 BCR-ABL1 mutations have now been described, many of which confer relative or absolute resistance to imatinib. T is has resulted in the development of second-generation TKIs (i.e., dasatinib, nilotinib, bosutinib) and of a third-generation TKI (ponatinib) with selective efficacy against T315I, a mutation of the gatekeeper residue of the kinase that causes resistance to all other TKIs.

CLINICAL PRESENTATION

T e presenting signs and symptoms in CML depend on the availability of and access to health care procedures, including physical exams and screening tests.

In the United States, because of the easy access to health care screening and physical exams, 50–60% of patients are diagnosed on routine blood tests and have minimal symptoms at presentation, such as fatigue. In geographic locations where access to health care is more limited, patients often present with high CML burden including splenomegaly, anemia, and related symptoms (abdominal pain, weight loss, fatigue), as well as a higher frequency of high-risk CML. Presenting findings in patients diagnosed in the United States are shown in **Table 15-1**.

Symptoms

Most patients with CML (90%) present in the indolent or chronic phase. Depending on the timing of diagnosis, patients are often asymptomatic (if the diagnosis is discovered during health care screening tests). Common symptoms, when present, are manifestations of anemia and splenomegaly. T ese may include fatigue, malaise, weight loss (if high leukemia burden), or early satiety and left upper quadrant pain or masses (from splenomegaly). Less common presenting findings include thrombotic or vasoocclusive events (from severe leukocytosis or thrombocytosis). T ese include priapism, cardiovascular complications, myocardial infarction, venous thrombosis, visual disturbances, dyspnea and pulmonary insufficiency, drowsiness, loss of coordination, confusion, or cerebrovascular accidents. Bleeding diatheses findings include retinal hemorrhages, gastrointestinal bleeding, and others. Patients who present with, or progress to, the accelerated or blastic phases have additional symptoms including unexplained fever, significant weight loss, severe fatigue, bone and joint aches, bleeding and thrombotic events, and infections.

TABLE 15-1

PRESENTING SIGNS AND SYMPTOMS OF NEWLY DIAGNOSED PHILADELPHIA CHROMOSOME–POSITIVE CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE

PARAMETER	PERCENTAGE
Age ≥60 years (median)	18 (46)
Female gender	35–45
Splenomegaly	30
Hepatomegaly	5
Lymphadenopathy	5
Other extramedullary disease	2
Hemoglobin <10 g/dL	10–15
Platelets	
>450 × 10^9 cells/L	30–35
<100 × 10^9 cells/L	3–5
White blood cells ≥50 × 10^9 cells/L	35–40
Marrow	
≥5% blasts	5
≥5% basophils	10–15
Peripheral blood	
≥3% blasts	8–10
≥7% basophils	10
Cytogenetic clonal evolution other than the Philadelphia chromosome	4–5
Sokal risk	
Low	60–65
Intermediate	25–30
High	10

Physical f ndings

Splenomegaly is the most common physical finding, occurring in 20–70% of patients depending on health care screening frequency. Other less common findings include hepatomegaly (10–20%), lymphadenopathy (5–10%), and extramedullary disease (skin or subcutaneous lesions). T e latter indicates CML transformation if a biopsy confirms the presence of sheets of blasts. Other physical findings are manifestations of complications of high tumor burden described earlier (e.g., cardiovascular, cerebrovascular, bleeding). High basophil counts may be associated with histamine overproduction causing pruritus, diarrhea, f ushing, and even gastrointestinal ulcers.

Hematologic and marrow f ndings

In untreated CML, leukocytosis ranging from 10–500 × 10^9/L is common. T e peripheral blood differential shows left-shifted hematopoiesis with predominance of neutrophils and the presence of bands, myelocytes, metamyelocytes, promyelocytes, and blasts (usually ≤5%). Basophils and/or eosinophils are frequently increased. T rombocytosis is common, but thrombocytopenia is rare and, when present, suggests a worse prognosis, disease acceleration, or an unrelated etiology. Anemia is present in one-third of patients. Cyclic oscillations of counts are noted in 25% of patients without treatment. Biochemical abnormalities include a low leukocyte alkaline phosphatase score and high levels of vitamin B_{12}, uric acid, lactic dehydrogenase, and lysozyme. T e presence of unexplained and sustained leukocytosis, with or without splenomegaly, should lead to a marrow examination and cytogenetic analysis.

T e bone marrow is hypercellular with marked myeloid hyperplasia and a high myeloid-to-erythroid

ratio of 15–20:1. Marrow blasts are 5% or less; when higher, they carry a worse prognosis or represent acceleration (if they are ≥15%). Increased reticulin fibrosis (by Snook's silver stain) is common, with 30–40% of patients demonstrating grade 3–4 reticulin fibrosis. T is was considered adverse in the pre-TKI era. With TKI therapy, reticulin fibrosis resolves in most patients and is not an indicator of poor prognosis. Collagen fibrosis (Wright-Giemsa stain) is rare at diagnosis. Disease progression with a "spent phase" of myelofibrosis (myelophthisis, or burnt-out marrow) was common with busulfan therapy (20–30%) but is rare with TKI therapy.

Cytogenetic and molecular findings

T e diagnosis of CML is straightforward and depends on documenting t(9;22)(q34;q11.2), which is found in 90% of cases. T is is known as the Philadelphia-chromosome abnormality (discovered in Philadelphia) and was initially identified as a shortened chromosome, later identified to be chromosome 22 (22q–) (Fig. 15-1). Some patients may have complex translocations (variant Ph) involving three or more translocations that include chromosomes 9 and 22 and one or more other chromosomes. Others may have a "masked Ph," involving translocations between chromosome 9 and a chromosome other than 22. T e prognosis of these patients and their response to TKI therapy are similar to those in patients with Ph. About 5–10% of patients may have additional chromosomal abnormalities in the Ph-positive cells. T ese usually involve trisomy 8, a double Ph, isochromosome 17 or 17p deletion, 20q–, or others. T is is referred to as clonal evolution and was historically a sign of adverse prognosis, particularly when trisomy 8, double Ph, or chromosome 17 abnormalities were noted.

Techniques such as FISH and PCR are now used to aid in the diagnosis of CML. T ey are more sensitive approaches to estimate the CML burden in patients on TKI therapy. T ey can be done on peripheral samples, and thus are less painful and more convenient. Patients with CML at diagnosis should have a FISH analysis to quantify the percentage of Ph-positive cells, if FISH is used to replace marrow cytogenetic analysis in monitoring response to therapy. FISH may not detect additional chromosomal abnormalities (clonal evolution); thus, a cytogenetic analysis is usually recommended at the time of diagnosis. T e BCR-ABL1 RNA message is usually one of two variants: e13a2 (formerly b2a2) and e14a2 (formerly b3a2). About 2–5% of patients may have other RNA fusion types (e.g., e1a2, e13a3, or e14a3). In these patients, the routine PCR primers may not amplify the BCR-ABL1 transcripts, thus leading to false-negative results. T erefore, molecular studies at diagnosis are important to document the type and presence of BCR-ABL1 transcripts to avoid erroneously "undetectable" BCR-ABL1 transcripts on follow-up studies, with the misconception of a complete molecular response.

Both FISH and PCR studies can be falsely positive at low levels or falsely negative because of technical issues. T erefore, a diagnosis of CML must always rely on a marrow analysis with routine cytogenetics. T e diagnostic bone marrow confirms the presence of the Ph chromosome, detects clonal evolution, i.e., chromosomal abnormalities in the Ph-positive cells (which may be prognostic), and also quantifies the percentage of marrow blasts and basophils. In 10% of patients, the percentage of marrow blasts and basophils can be significantly higher than in the peripheral blood, suggesting poorer prognosis or even disease transformation.

Monitoring patients on TKI therapy by cytogenetics, FISH, and molecular studies has become an important standard practice to assess response to therapy, emphasize compliance, evaluate possible treatment resistance, change TKI therapy, and order mutational analysis studies. It is thus important to recognize the comparability of these measures in monitoring response. A partial cytogenetic response is defined as the presence of 35% less Ph-positive metaphases by routine cytogenetic analysis. T is is roughly equivalent to BCR-ABL1 transcripts by the International Scale (IS) of 10% or less. A complete cytogenetic response refers to the absence of Ph-positive metaphases (0% Ph positivity). T is is approximately equivalent to BCR-ABL1 transcripts (IS) of 1% or less. A major molecular response refers to BCR-ABL1 transcripts (IS) ≤0.1%, or roughly a 3-log or greater reduction of CML burden from baseline. A complete molecular response usually refers to BCR-ABL1 transcripts (IS) <0.0032% (undetectable by current techniques), roughly equivalent to a more than 4.5-log reduction of CML burden from baseline.

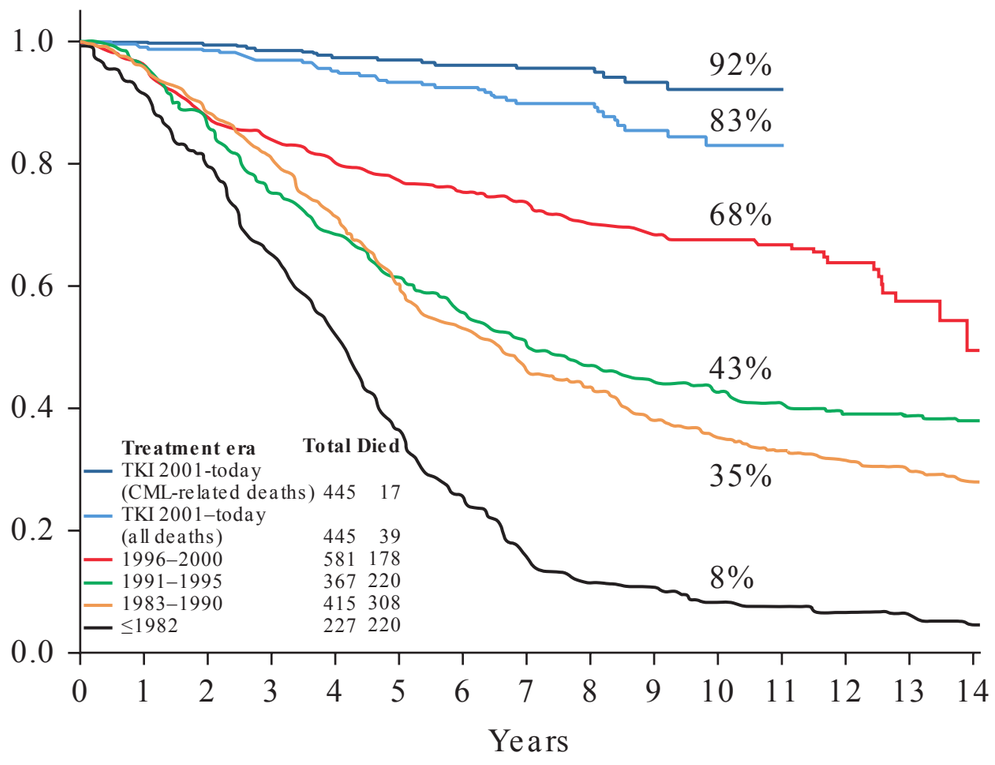
Findings in CML transformation

Progression of CML is usually associated with leukocytosis resistant to therapy, increasing anemia, fever and constitutional symptoms, and increased blasts and basophils in the peripheral blood or marrow. Criteria of accelerated-phase CML, historically associated with median survival of less than 1.5 years, include the presence of 15% or more peripheral blasts, 30% or more peripheral blasts plus promyelocytes, 20% or more peripheral basophils, cytogenetic clonal evolution (presence of chromosomal abnormalities in addition to Ph), and thrombocytopenia $<100 \times 10^9$/L (unrelated to therapy). About 5–10% of patients present with de novo accelerated phase or blastic phase. T e prognosis of de novo accelerated phase with TKI therapy has improved significantly, with an estimated 8-year survival rate of 75%. T e median survival of accelerated phase evolving from chronic phase has also improved from a historical

median survival of 18 months to an estimated 4-year survival rate of 70% on TKI therapy. T erefore, the criteria for accelerated-phase CML should be revisited because most have lost much of their prognostic significance. Blastic-phase CML is defined by the presence of 30% or more peripheral or marrow blasts or the presence of sheets of blasts in extramedullary disease (usually skin, soft tissues, or lytic bone lesions). Blastic-phase CML is commonly myeloid (60%) but can present uncommonly as erythroid, promyelocytic, monocytic, or megakaryocytic. Lymphoid blastic phase occurs in about 25% of patients. Lymphoblasts are terminal deoxynucleotide transferase positive and peroxidase negative (although occasionally with low positivity up to 3–5%) and express lymphoid markers (CD10, CD19, CD20, CD22). However, they also often express myeloid markers (50–80%), resulting in diagnostic confusion. T is is important because, unlike other morphologic blastic phases, lymphoid blastic-phase CML is quite responsive to anti-ALL-type chemotherapy (e.g., hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, and dexamethasone]) in combination with TKIs.

PROGNOSIS AND CML COURSE

Before the imatinib era, the annual mortality in CML was 10% in the first 2 years and 15–20% thereafter. T e median survival time in CML was 3–7 years (with hydroxyurea-busulfan and interferon α). Without a curative option of allogeneic SCT, the course of CML was inexorable toward transformation to, and death from, accelerated or blastic phases. T e disease stability was unpredictable, with some patients demonstrating sudden transformation to a blastic phase. With imatinib therapy, the annual mortality in CML has decreased to 2% in the first 12 years of observation. Half of the deaths are from factors other than CML, such as old age, accidents, suicides, other cancers, and other medical conditions (e.g., infections, surgical procedures). T e estimated 8- to 10-year survival rate is now 85%, or 93% if only CML-related deaths are considered (**Fig. 15-2**). T e course of CML has also become quite predictable. In the first 2 years of TKI therapy, rare sudden transformations are still noted (1–2%), usually lymphoid blastic transformations that respond to combinations of chemotherapy and TKIs followed by allogeneic SCT. T ese may be explained by the intrinsic mechanisms of sudden transformation already existing in the CML clones before the start of therapy that were not amenable to TKI inhibition, in particular imatinib. Second-generation TKIs (nilotinib, dasatinib) used as frontline therapy have reduced the incidence of transformation in the first 2–3 years from 6–8% with imatinib to 2–4% with nilotinib or dasatinib. Disease transformation to accelerated or blastic phase is rare on continued TKI therapy, estimated at <1% annually in years 4–8 of follow-up on the original imatinib trials. Patients usually develop resistance in the form of cytogenetic relapse, followed by hematologic relapse and subsequent transformation, rather than the previously feared sudden transformations without the warning signals of cytogenetic-hematologic relapse.



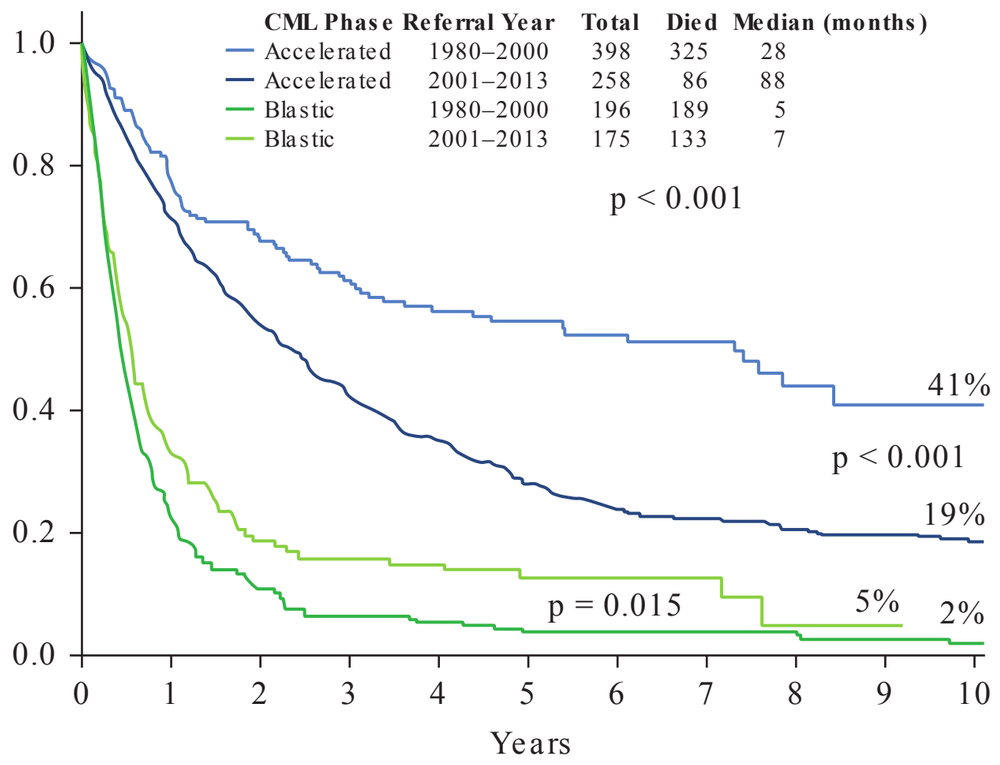


FIGURE 15-2

A. Survival in newly diagnosed chronic-phase chronic myeloid leukemia (CML) by era of therapy (M.D. Anderson Cancer Center experience from 1965 to present). Causes of non-CML deaths in 22 patients were other cancers (n = 7), postsurgical complications (n = 3), car accident (n = 2), suicide (n = 1), neurologic events (n = 3), cardiac (n = 3), pneumonia (n = 1), and unknown (n = 2).

B. Survival in patients with accelerated- and blastic-phase CML referred to M.D. Anderson Cancer Center by era of therapy, demonstrating the significant survival benefit in the tyrosine kinase inhibitor (TKI) era in accelerated-phase CML but the modest benefit in blastic-phase CML. Referred cases included de novo and post-chronic-phase transformations.

Before the imatinib era, several pretreatment prognostic factors predicted for worse outcome in CML and have been incorporated into prognostic models and staging systems. T ese have included older age, significant splenomegaly, anemia, thrombocytopenia or thrombocytosis, high percentages of blasts and basophils (and/or eosinophils), marrow fibrosis, deletions in the long arm of chromosome 9, clonal evolution, and others. Different risk models and staging systems, derived from multivariate analyses, were proposed to define different risk groups. As with the introduction of cisplatin into testicular cancer therapy, the introduction of TKIs into CML therapy has nullified or lessened the prognostic impact of most of these prognostic factors and the significance of the CML models (e.g., Sokal, Hasford, European Treatment and Outcome Study [EUTOS]). Treatment-related prognostic factors have emerged as the most important prognostic factors in the era of imatinib therapy. Achievement of complete cytogenetic response has become the major therapeutic endpoint and is the only endpoint associated with improvement in survival. Achievement of a major molecular response is associated with decreased risk of events (relapse) and CML progression, may predict for differences in event-free survival (depending on the definition of an event) and for small differences in transformation rates, but has not been associated with survival prolongation. Among patients in complete cytogenetic response, survival is similar independent of whether they achieve a major molecular response or not. T is may be due to the efficacy of salvage TKI therapies, which are and should be implemented at the first evidence of cytogenetic relapse. Achievement of complete molecular response (undetectable BCR-ABL1 transcripts), particularly when durable (>2 years), may offer the possibility of durable molecular response (molecular cure rather than functional cure) in the context of investigational trials and may allow temporary therapy interruption in women eager to have babies. T e lack of achievement of major or complete molecular responses should not be considered as "failure" of a particular TKI therapy and/or an indication to change the TKI or to consider allogeneic SCT.

Pretreatment prognostic factors and prognostic models have lost much of their clinical relevance to define prognosis and to select different therapies. However TKI-associated therapeutic responses have gained major clinical relevance and dictate appropriate and careful monitoring of patients to optimize their treatment.

TREATMENT Chronic Myeloid Leukemia

T e introduction of TKI therapy, first in the form of imatinib mesylate in 2001, has revolutionized the treatment and prognosis in CML. Before 2000, allogeneic SCT was frontline therapy, when available, because of its potentially curative capacity. Otherwise, patients were offered interferon α therapy (approved for the treatment of CML in 1986), which had modest benefits (improving survival from a median of 3–4 years with hydroxyurea-busulfan to a median of 6–7 years), but also significant side effects. Other alternatives included hydroxyurea, busulfan, and other nonspecific chemotherapies. With TKI therapy, the estimated 10-year survival in CML is 85%. Since 2001, six agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of CML. T ese include five oral BCR-ABL1-selective TKIs: imatinib (Gleevec), nilotinib (Tasigna), dasatinib (Sprycel), bosutinib (Bosulif), and ponatinib (Iclusig). Imatinib 400 mg orally daily, nilotinib 300 mg orally twice a day (on an empty stomach), and dasatinib 100 mg orally daily are approved for frontline therapy of CML. All three are also approved for salvage therapy (nilotinib 400 mg twice daily), in addition to bosutinib (500 mg daily) and ponatinib (45 mg daily). Imatinib, dasatinib (140 mg daily), bosutinib, and ponatinib are also approved for the treatment of CML transformation (accelerated and blastic phase), whereas nilotinib is only approved for chronic and accelerated phase. Dasatinib, nilotinib, and bosutinib are referred to as second-generation TKIs; ponatinib is referred to as a third-generation TKI. T e sixth approved agent is omacetaxine (Synribo), a protein synthesis inhibitor with presumed more selective inhibition of the synthesis of the BCR-ABL1 oncoprotein. It is approved for the treatment of chronic- and accelerated-phase CML after failure of two or more TKIs, at 1.25 mg/m^2 subcutaneously twice a day for 14 days for induction and for 7 days for consolidation-maintenance. Nilotinib is similar in structure to imatinib but 30 times more potent. Dasatinib and bosutinib are dual SRC-ABL1 TKIs (dasatinib is reported to be 300 times more potent and bosutinib 30–50 times more potent than imatinib). Ponatinib is effective against wild-type and mutant BCR-ABL1 clones. It is unique in being the only currently available BCR-ABL1 TKI that is active against T315I, a gatekeeper mutant resistant to the other four TKIs **(Table 15-2)**.

Imatinib, nilotinib, and dasatinib are all acceptable frontline therapies in CML. T e long-term results of imatinib are very favorable. T e 8-year follow-up results show a cumulative complete cytogenetic response rate (occurring at least once) of 83%, with 60–65% of patients being in complete cytogenetic response at 5-year follow-up. T e estimated 8-year event-free survival rate is 81%, and the overall survival rate is 85%. Among patients continuing on imatinib, the annual rate of transformation to accelerated-blastic phase in years 4–8 is <1%. In two randomized studies, one comparing nilotinib 300 mg twice daily or 400 mg twice daily with imatinib (ENEST-nd) and the other comparing dasatinib 100 mg daily with imatinib (DASISION), the second-generation TKIs were associated with better outcomes in early surrogate endpoints, including higher rates of complete cytogenetic responses (85–87% vs 77–82%), major molecular responses (65–76% vs 46–63%), and undetectable BCR-ABL1 transcripts (IS) (32–37% vs 15–30%), and lower rates

TABLE 15-2

MEDICAL THERAPEUTIC OPTIONS IN CHRONIC MYELOID LEUKEMIA

AGENT (BRAND NAME)	APPROVED INDICATIONS	DOSE SCHEDULE	NOTABLE TOXICITIES
Imatinib mesylate (Gleevec)	All phases	400 mg daily	See text
Dasatinib (Sprycel)	All phases	First-line: 100 mg daily Salvage: 140 mg daily	Myelosuppression; pleural and pericardial effusions; pulmonary hypertension
Nilotinib (Tasigna)	All phases except blastic phase	First-line: 300 mg twice daily Salvage: 400 mg twice daily	Diabetes; vasoocclusive disease; pancreatitis
Bosutinib (Bosulif)	All phases except frontline	500 mg daily	Diarrhea
Ponatinib (Iclusig)	All phases except frontline	45 mg daily (may consider lower starting doses in the future, e.g., 30 mg daily)	Skin rashes, pancreatitis; vasoocclusive disease (10–20%)
Omacetaxine mepesuccinate (Synribo)	Failure ≥2 tyrosine kinase inhibitors	1.25 mg/m^2 subcutaneously twice daily for 14 days for induction; 7 days of maintenance every month	Myelosuppression

of transformation to accelerated-blastic phase (2–4% vs 6%). However, neither study showed a survival benefit with second-generation TKIs (median follow-up times of 4–5 years). T is may be because salvage therapy with other TKIs (following close observation and treatment change at progression) provides highly effective salvage therapy that rebalances the negative effect of the relapse.

Salvage therapy in chronic phase with dasatinib, nilotinib, bosutinib, or ponatinib is associated with complete cytogenetic response rates of 30–60% of patients, depending on the salvage status (cytogenetic vs hematologic relapse), prior response to other TKIs, and the mutations at the time of relapse. Complete cytogenetic responses are generally durable, particularly in the absence of clonal evolution and mutations. Ponatinib is the only TKI active in the setting of T315I mutation, with complete cytogenetic response rates of 50–70%. T e estimated 3- to 5-year survival rates with new TKIs as salvage are 70–80% (compared with <50% before their availability). For example, with dasatinib salvage after imatinib failure in chronic-phase CML, the major molecular response rates were 40–43%, the estimated 6-year survival rates were 74–83%, and progression-free survival rates were 40–51%. T us, TKIs in the salvage setting have already reduced the annual mortality from the historical rate of 10–15% to ≤5%.

T e goal of CML therapy is viewed differently in the context of research versus standard practice. In current practice, functional cure, defined as survival with CML similar to survival among normal individuals, is the current goal of therapy. CML is now considered an indolent disease, which, with appropriate TKI therapy, treatment compliance, careful monitoring, and early change to other TKIs as indicated, can be associated with close to normal survival. T erefore, in standard practice, achievement and maintenance of a complete cytogenetic response are the aims of therapy, because complete cytogenetic response is the only treatment-related factor associated with survival prolongation. Lack of achievement of a major molecular response (protects against events; associated with longer event-free survival) or of negative BCR-ABL1 transcripts (offers the potential of TKI interruption on investigational studies) should not be considered indications to change TKI therapy or to consider allogeneic SCT. A general practice rule is to continue the particular TKI chosen at the most tolerable dose schedule not associated with grade 3–4 side effects or with bothersome chronic side effects, for as long as possible, until either cytogenetic relapse or the persistence of unacceptable side effects. T ese two factors (i.e., cytogenetic relapse and intolerable side effects as judged by the patient and treating physician) are the indicators of "failure" of a particular TKI therapy. Because of the increasing prevalence of CML (cost of TKI therapy) and the emerging long-term low rates of significant organ toxicities, the ultimate goal of CML therapy in the research setting is to achieve eradication of the disease (molecular cure) that is prolonged and durable, with recovery of nonneoplastic, nonclonal hematopoiesis off TKI therapy. T e first step toward this aim is to obtain the highest rates of undetectable BCR-ABL1 transcripts lasting for at least 2 or more years.

Recommendations provided by the National Comprehensive Cancer Network (NCCN) and by the European LeukemiaNet (ELN) discuss optimal/expected, suboptimal/warning, and failure response scenarios at different time points of TKI treatment duration. Unfortunately, they may have been misinterpreted in current practice, because oncologists often report that their aim of treatment is the achievement of major molecular response and disease eradication. Significantly, a substantial proportion of oncologists consider a change of TKI therapy in a patient in complete cytogenetic

response if they note "loss of major molecular response" (increase of BCR-ABL1 transcripts ([IS] from <0.1% to >0.1%). T is perception may be the result of confusion regarding the NCCN and ELN guidelines, which have been updated often as a result of maturing data and have multiple treatment endpoint considerations. Although such endpoints have been suggested by these recommendations as possible criteria for failure, it is important to emphasize that no randomized study has yet shown that a change of TKI treatment in patients with complete cytogenetic response because of a loss of major molecular response, versus changing at the time of cytogenetic relapse, has been shown to improve survival. T is is likely because of the high efficacy of salvage TKI therapy at the time of cytogenetic relapse.

Side effects of TKIs are generally mild to moderate, although with long-term TKI therapy, they could affect the patient's quality of life. Serious side effects occur in less than 5–10% of patients. With imatinib therapy, common mild to moderate side effects include fuid retention, weight gain, nausea, diarrhea, skin rashes, periorbital edema, bone or muscle aches, fatigue, and others (rates of 10–20%). In general, second-generation TKIs are associated with lower rates of these bothersome adverse events. However, dasatinib is associated with higher rates of myelosuppression (20–30%), particularly thrombocytopenia, and with pleural (10–25%) or pericardial effusions (≤5%). Nilotinib is associated with higher rates of hyperglycemia (10–20%), pruritus and skin rashes, and headaches. Nilotinib is also associated with rare events of pancreatitis (<5%). Bosutinib is associated with higher rates of early and self-limited gastrointestinal complications like diarrhea (50–70%). Ponatinib is associated with higher rates of skin rashes (10–15%), pancreatitis (5%), elevations of amylase/lipase (10%), and vasospastic/vasoocclusive events (10–20%). Nilotinib and dasatinib may cause prolongation of the QTc interval; therefore, they should be evaluated cautiously in patients with prolonged QTc interval on electrocardiogram (>470–480 ms), and drugs given for other medical conditions should have relatively smaller or no effects on QTc. T ese side effects can often be dose-dependent and are generally reversible with treatment interruptions and dose reductions. Dose reductions can be individualized. However, the lowest estimated effective doses of TKIs (from different studies and treatment practices) are imatinib 300 mg daily; nilotinib 200 mg twice daily; dasatinib 20 mg daily; bosutinib 300 mg daily; and ponatinib 15 mg daily.

With long-term follow-up, rare but clinically relevant serious toxicities are emerging. Renal dysfunction and renal failure (creatinine elevations >2–3 mg/dL) are observed in 2–3% of patients and reverse with TKI discontinuation and empirical use of other TKIs. Pulmonary hypertension has been reported with dasatinib (<1–2%) and should be considered in a patient with shortness of breath and a normal chest x-ray (echocardiogram with emphasis on measurement of pulmonary artery pressure). T is may be reversible with dasatinib discontinuation and occasionally the use of sildenafil citrate. Systemic hypertension has been observed more often with ponatinib therapy, as well as other TKIs. Hyperglycemia and diabetes have been noted more frequently with nilotinib. Finally, mid- and small-vessel vasoocclusive and vasospastic events have been reported at low but significant rates with nilotinib and ponatinib and should be considered possibly TKI-related and represent indications to interrupt or reduce the dose of the TKI. T ese events include angina, coronary artery disease, myocardial infarction, peripheral arterial occlusive disease, transient ischemic attacks, cerebral vascular accidents, Raynaud's phenomenon, and accelerated atherosclerosis. Although these events are uncommon (<5%), they are clinically significant for the patient's long-term prognosis and occur at significantly higher rates than in the general population (5–20 times more often).

ALLOGENEIC STEM CELL TRANSPLANT Allogeneic SCT, a curative modality in CML, is associated with long-term survival rates of 40–60% when implemented in the chronic phase. It is associated with early (1-year) mortality rates of 5–30%. Although the 5- to 10-year survival rates were reported to be around 50–60% (and considered as cure rates), about 10–15% of patients die in the subsequent 1–2 decades from subtle long-term complications of the transplant (rather than from CML relapse). T ese are related to chronic graft-versus-host disease (GVHD), organ dysfunction, development of second cancers, and hazard ratios for mortality higher than in the normal population. Other significant morbidities include infertility, chronic immune-mediated complications, cataracts, hip necrosis, and other morbidities affecting quality of life. T e cure and early mortality rates in chronic-phase CML are also associated with several factors: patient age, duration of chronic phase, whether the donor is related or unrelated, degree of matching, preparative regimen, and others. In accelerated-phase CML, the cure rates with allogeneic SCT are 20–40%, depending on the definition of acceleration. Patients with clonal evolution as the only criterion have cure rates of up to 40–50%. Patients undergoing allogeneic SCT in second chronic phase have cure rates of 40–50%. T e cure rates with allogeneic SCT in blastic phase CML are ≤15%. Post–allogeneic SCT strategies are now implemented in the setting of molecular or cytogenetic relapse or in hematologic relapse/transformation. T ese include the use of TKIs for prevention or treatment of relapse, donor lymphocyte infusions, and second allogeneic SCTs, among others. TKIs appear to be highly successful at reinducing cytogenetic/molecular remissions in the setting of cytogenetic or molecular relapse after allogeneic SCT.

Choice and Timing of Allogeneic SCT Allogeneic SCT was considered first-line CML therapy before 2000. The maturing positive experience with TKIs has now relegated its use to after first-line TKI failures. An important question is the optimal timing and sequence of TKIs and allogeneic SCT (whether allogeneic SCT should be used as second- or third-line therapy). Among patients who present with or evolve to blastic phase, combinations of chemotherapy and TKIs should be used to induce remission, followed by allogeneic

SCT as soon as possible. The same applies to patients who evolve from chronic to accelerated phase. Patients with de novo accelerated-phase CML may do well with long-term TKI therapy (estimated 8-year survival rate 75%); the timing of allogeneic SCT depends on their optimal response to TKI (achievement of complete cytogenetic response). Among patients who relapse in chronic phase, the treatment sequence depends on several factors: (1) patient age and availability of appropriate donors; (2) risk of allogeneic SCT; (3) presence or absence of clonal evolution and mutations; (4) patient's prior history and comorbidities; and (5) patient and physician preferences **(Table 15-3)**. Patients with T315I mutations at relapse should be offered ponatinib and considered for allogeneic SCT (because of the short follow-up with ponatinib). Patients with mutations involving Y253H, E255K/V, and F359V/C/I respond better to dasatinib or bosutinib. Patients with mutations involving V299L, T315A, and F317L/F/I/C respond better to nilotinib. Comorbidities such as diabetes, hypertension, pulmonary hypertension, chronic lung disease, cardiac conditions, and pancreatitis may influence the choice for or against a particular TKI. Patients with clonal evolution, unfavorable mutations, or lack of major/complete cytogenetic response within 1 year of salvage TKI therapy have short remission durations and should consider allogeneic SCT as more urgent in the setting of salvage. Patients without clonal evolution or mutations at relapse and who achieve a complete cytogenetic response with TKI salvage, have long-lasting complete remissions and may delay the option of allogeneic SCT to third-line therapy. Finally, older patients (age 65–70 years or older) and those with high risk of mortality with allogeneic SCT may forgo this curative option for several years of disease control in chronic phase with or without cytogenetic response (Table 15-3). Historically, before the availability of TKIs, patients without cytogenetic response on interferon α or hydroxyurea had expected short median survival times (2–3 years) with expected rapid disease transformation. The maturing experience with TKIs suggests a different course, whereby patients may remain in chronic phase on TKI-based therapies (combinations including hydroxyurea, cytarabine, decitabine, and others), with or without cytogenetic response, for many years. Table 15-3 summarizes a general guidance to the choice of TKIs versus allogeneic SCT.

TABLE 15-3

GENERAL SUGGESTIONS REGARDING THE USE OF TYROSINE KINASE INHIBITORS (TKIS) AND ALLOGENEIC STEM CELL TRANSPLANTATION (SCT) IN CHRONIC MYELOID LEUKEMIA (CML)

CML PHASE	USE OF TKI	CONSIDERATION OF ALLOGENEIC SCT
Accelerated or blastic	Interim therapy to achieve minimal CML burden	As soon as possible (exception: de novo accelerated phase)
Imatinib failure in chronic phase; T315I mutation	Ponatinib to achieve minimal CML burden	Depends on longer term follow-up results of ponatinib efficacy
Imatinib failure in chronic phase; no clonal evolution, no mutations, good initial response	Second-line kinase inhibitors long-term	Third-line after second-line TKI failures
Imatinib failure in chronic phase; clonal evolution or mutations, or no cytogenetic response to second-line TKI	Interim therapy to achieve minimal CML burden	Second-line
Older patients (≥65–70 years) after imatinib failure in chronic phase	Salvage TKIs as longer-term therapy	May forgo allogeneic SCT in favor of good quality of life and survival in chronic phase

Note: Mutations involving Y253H, E255K/V, or F359V/C/I: prefer dasatinib or bosutinib. Mutations involving V299L, T315A, or F317L/F/I/C: prefer nilotinib.

MONITORING THERAPY IN CML Achievement of complete cytogenetic response by 12 months of imatinib therapy and its persistence later, the only consistent prognostic factor associated with survival, is now the main therapeutic endpoint in CML. Failure to achieve a complete cytogenetic response by 12 months or occurrence of later cytogenetic or hematologic relapse is considered as treatment failure and an indication to change therapy. Because salvage therapy with other TKIs reestablishes good outcome, it is important to ensure patient compliance to continued TKI therapy and change therapy at the first sign of cytogenetic relapse. Patients on frontline imatinib therapy should be closely monitored until documentation of complete cytogenetic response, at which time they can be monitored every 6 months with peripheral blood FISH and PCR studies (to check for concordance of results), or more frequently if there are concerns about changes in BCR-ABL1 transcripts (e.g., every 3 months). Monitoring by molecular studies only is reasonable in patients who are in major molecular response. Cytogenetic relapse on imatinib is an indication of treatment failure and need to change TKI therapy. Mutational analysis in this instance helps in the selection of the next TKI and identifies mutations in 30–50% of patients. Mutational studies in patients in complete cytogenetic response (in whom there may be concerns of increasing BCR-ABL1 transcripts) identify mutations in ≤5% and are therefore not indicated. Earlier response has been identified as a prognostic factor for long-term outcome, including achievement of partial cytogenetic response (BCR-ABL1 transcripts ≤10%) by 3–6 months of therapy. Failure to achieve such a response on imatinib therapy has been associated with significantly worse survival in some studies (particularly when

second-generation TKIs were not readily available as salvage therapy), but not in others (when they were).

The use of second-generation TKIs (nilotinib, dasatinib) as frontline therapy changed the monitoring approach slightly. Patients are expected to achieve complete cytogenetic response by 3–6 months of therapy. Failure to do so is associated with worse event-free survival, transformation rates, and survival. However, the 3- to 5-year estimated survival among such patients is still high, around 80–90%, which is better than what would be anticipated if such patients were offered allogeneic SCT at that time. Thus, this adverse response to therapy is considered a warning signal, but it is not known whether changing therapy to other TKIs at that time would improve longer term outcome.

TREATMENT OF ACCELERATED AND BLASTIC PHASES

Patients in accelerated or blastic phase may receive therapy with TKIs, preferably second- or third-generation TKIs (dasatinib, nilotinib, bosutinib, ponatinib), alone or in combination with chemotherapy, to reduce the CML burden, before undergoing allogeneic SCT. Response rates with single-agent TKIs range from 30 to 50% in accelerated phase and from 20 to 30% in blastic phase. Cytogenetic responses, particularly complete cytogenetic responses, are uncommon (10–30%) and transient in blastic phase. Studies of TKIs in combination with chemotherapy are ongoing; the general experience suggests that combined TKI-chemotherapy strategies increase the response rates and their durability and improve survival. In CML lymphoid blastic phase, the combination of anti-ALL chemotherapy with TKIs results in complete response rates of 60–70% and median survival times of 2–3 years (compared with historical response rates of 40–50% and median survival times of 12–18 months). This allows many patients to undergo allogeneic SCT in a state of minimal CML burden or secondary chronic phase, which are associated with higher cure rates. In CML nonlymphoid blastic phase, anti-AML chemotherapy combined with TKIs results in CR rates of 30–50% and median survival times of 9–12 months (compared with historical response rates of 20–30% and median survival times of 3–5 months). In accelerated phase, response to single TKIs is significant in conditions where "softer" accelerated phase criteria are considered (e.g., clonal evolution alone, thrombocytosis alone, significant splenomegaly or resistance to hydroxyurea, but without evidence of high blast and basophil percentages). In accelerated phase, combinations usually include TKIs with low-intensity chemotherapy such as low-dose cytarabine, low-dose idarubicin, decitabine, interferon α, hydroxyurea, or others.

OTHER TREATMENTS AND SPECIAL THERAPEUTIC CONSIDERATIONS

Interferon α Interferon α was a standard of care before 2000. Today, it is considered in combination with TKIs (an investigational approach), sometimes after CML failure on TKIs, occasionally in patients during pregnancy, or as part of investigational strategies with TKIs to eradicate residual molecular disease.

Chemotherapeutic Agents Hydroxyurea and busulfan were commonly used chemotherapeutic agents in the past. Hydroxyurea remains a safe and effective agent (at daily doses of 0.5–10 g) to reduce initial CML burden, as a temporary measure in between definitive therapies, or in combination with TKIs to sustain complete hematologic or cytogenetic responses. Busulfan is often used in allogeneic SCT preparative regimens. Because of its side effects (delayed myelosuppression, Addison-like disease, pulmonary and cardiac fibrosis, myelofibrosis), it is now only rarely used in the chronic management of CML. Low-dose cytarabine, decitabine, anthracyclines, 6-mercaptopurine, 6-thioguanine, thiotepa, anagrelide, and other agents are useful in different CML settings to control the disease burden.

Others Splenectomy is occasionally considered to alleviate symptoms of massive splenomegaly and/or hypersplenism. Splenic irradiation is rarely used, if at all, because of the postirradiation adhesions and complications. Leukapheresis is rarely used in patients presenting with extreme leukocytosis and leukostatic complications. Single doses of high-dose cytarabine or high doses of hydroxyurea, with tumor lysis management, may be as effective and less cumbersome.

Special Considerations Women with CML who become pregnant should discontinue TKI therapy immediately. Among 125 babies delivered to women with CML who discontinued TKI therapy as soon as the pregnancy was known, three babies were born with ocular, skeletal, and renal malformations, suggesting the uncommon teratogenicity of imatinib. There are no or little data with other TKIs. Control of CML during pregnancy can be managed with leukapheresis for severe symptomatic leukocytosis in the first trimester and with hydroxyurea subsequently until delivery. There are case reports of successful pregnancies and deliveries of normal babies with interferon α therapy and registry studies in essential thrombocytosis of its safety, but interferon α can be antiangiogenic and may increase the risk of spontaneous abortions.

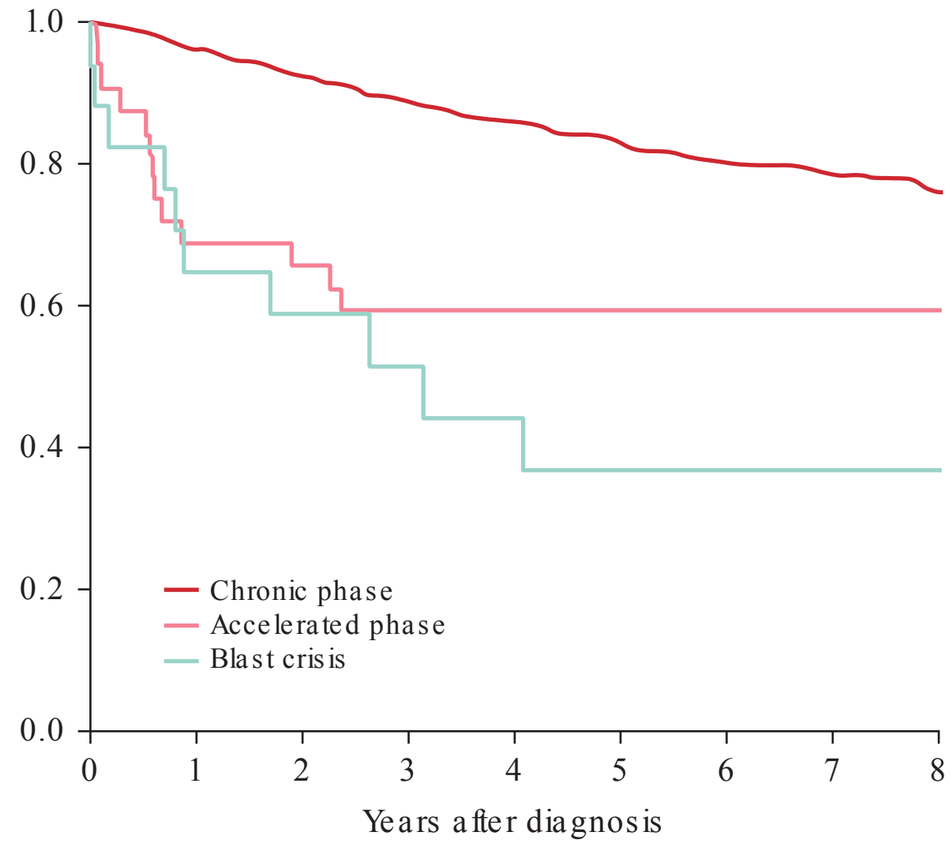
Patients on TKI therapy may develop chromosomal abnormalities in the Ph-negative cells. These may involve loss of chromosome Y, trisomy 8, 20q–, chromosome 5 or 7 abnormalities, and others. Most chromosomal abnormalities disappear spontaneously on follow-up and may be indicative of the genetic instability of the hematopoietic stem cells that predispose the patient to develop CML in the first place. Rarely, abnormalities involving chromosomes 5 or 7 may be truly clonal and evolve into myelodysplastic syndrome or acute myeloid leukemia. This is thought to be part of the natural course of patients in whom CML was suppressed and who live long enough to develop other hematologic malignancies.

GLOBAL ASPECTS OF CHRONIC MYELOID LEUKEMIA

Routine physical exams and blood tests in the United States and advanced countries result in early detection of CML in most patients. About 50–70% of patients with CML are diagnosed accidentally, and high-risk CML as defined by prognostic models (e.g., Sokal risk groups) is found in only 10–20% of patients. T is is not the same situation in emerging nations (e.g., India, China, African countries, the Middle East), where most patients are diagnosed following evaluation for symptoms and many present with high tumor burdens, such as massive splenomegaly, and advanced phases of CML (high-risk CML documented in 30–50%). T erefore, the prognosis of such patients on TKI therapy may be worse than the published experience.

T e high cost of TKI therapies (annual costs of $90,000–$140,000 in the United States; lower but variable in the rest of the world) makes the general affordability of such treatments difficult. Although TKI treatment penetration is high in nations where cost of therapy is not an issue (e.g., Sweden, European Union), it may be less so in other nations, even in advanced ones like the United States, where out-of-pocket expenses may be prohibitive to a subset of patients (perhaps 10–20%). Based on the sales of imatinib worldwide and charity free drug supplies, it is estimated that less than 30% of patients are treated with imatinib (or other TKIs) consistently. Although the estimated 10-year survival in CML is 85% in single-institution studies (e.g., M.D. Anderson Cancer Center), in national studies in countries with TKI affordability (Sweden) **(Figs. 15-2** and **15-3)** or in company-sponsored studies (where all patients have access to TKIs throughout their care), the estimated 10-year survival worldwide, even 12 years after the introduction of TKI therapies, is likely to be less than 50%. T e Surveillance, Epidemiology, and End Results (SEER) data from the United States report an estimated 5-year survival rate of 60% in the era of TKIs.

T e current high cost of TKI therapies poses two additional considerations. T e first are the treatment pathways and guidelines in nations where TKIs may not be affordable by patients or the health care system. In these conditions, there are trends of pathways advocating frontline allogeneic SCT (a one-time cost of $30,000–$50,000) despite the associated mortality and morbidities. T e second is the choice of frontline TKI therapy once imatinib becomes available in generic forms (hopefully at much lower annual prices, e.g., $2,000–$10,000). T is will depend on the maturing data in randomized studies of second-generation TKIs versus imatinib in relation to important long-term outcome endpoints, particularly survival, but also event-free survival and transformation-free survival.



No. at risk

CP	699	672	631	530	446	365	278	212	144
AP	32	22	21	18	14	10	5	4	2
BC	17	11	10	7	6	5	4	4	1

FIGURE 15-3

Survival in chronic (CP), accelerated (AP), and blastic crisis (BC) phases of chronic myeloid leukemia (CML) in the population-based Swedish national registry study. The accelerated- and blastic-phase cases are de novo presentations. The favorable outcome with de novo blastic phase may be due to use of 20% blasts or more to define blastic phase. (With permission from Dr. Martin Hoglund, Swedish CML Registry, 2013.)

CHAPTER 16

MALIGNANCIES OF LYMPHOID CELLS

Dan L. Longo

Malignancies of lymphoid cells range from the most indolent to the most aggressive human malignancies. T ese cancers arise from cells of the immune system at different stages of differentiation, resulting in a wide range of morphologic, immunologic, and clinical findings. Insights on the normal immune system have allowed a better understanding of these sometimes confusing disorders.

Some malignancies of lymphoid cells almost always present as leukemia (i.e., primary involvement of bone marrow and blood), while others almost always present as lymphomas (i.e., solid tumors of the immune system). However, other malignancies of lymphoid cells can present as either leukemia or lymphoma. In addition, the clinical pattern can change over the course of the illness. T is change is more often seen in a patient who seems to have a lymphoma and then develops the manifestations of leukemia over the course of the illness.

BIOLOGY OF LYMPHOID MALIGNANCIES: CONCEPTS OF THE WORLD HEALTH ORGANIZATION CLASSIFICATION OF LYMPHOID MALIGNANCIES

T e classification of lymphoid cancers evolved steadily throughout the twentieth century. T e distinction between leukemia and lymphoma was made early, and separate classification systems were developed for each. Leukemias were first divided into acute and chronic subtypes based on average survival. Chronic leukemias were easily subdivided into those of lymphoid or myeloid origin based on morphologic characteristics. However, a spectrum of diseases that were formerly all called chronic lymphoid leukemia has become apparent **(Table 16-1)**. T e acute leukemias were usually malignancies of blast cells with few identifying characteristics. When cytochemical stains became available, it was possible to divide these objectively into myeloid malignancies and acute leukemias of lymphoid cells. Acute leukemias of lymphoid cells have been subdivided based on morphologic characteristics by the French-American-British (FAB) group **(Table 16-2)**. Using this system, lymphoid malignancies of small uniform blasts (e.g., typical childhood acute lymphoblastic leukemia) were called L1, lymphoid malignancies with larger and more variable size cells were called L2, and lymphoid malignancies of uniform cells with basophilic and sometimes vacuolated cytoplasm were called L3 (e.g., typical Burkitt's lymphoma cells). Acute leukemias of lymphoid cells have also been subdivided based on immunologic (i.e., T cell vs B cell) and cytogenetic abnormalities (Table 16-2). Major cytogenetic subgroups include the t(9;22) (e.g., Philadelphia

TABLE 16-1

LYMPHOID DISORDERS THAT CAN PRESENT AS "CHRONIC LEUKEMIA" AND BE CONFUSED WITH TYPICAL B-CELL CHRONIC LYMPHOID LEUKEMIA

Follicular lymphoma	Prolymphocytic leukemia (Bcell or Tcell)
Splenic marginal zone lymphoma	Lymphoplasmacytic lymphoma
Nodal marginal zone lymphoma	Sézary's syndrome
Mantle cell lymphoma	Smoldering adult T-cell leukemia/lymphoma
Hairy cell leukemia	

TABLE 16-2

CLASSIFICATION OF ACUTE LYMPHOID LEUKEMIA (ALL)

IMMUNOLOGIC SUBTYPE	% OF CASES	FAB SUBTYPE	CYTOGENETIC ABNORMALITIES
Pre-B ALL	75	L1, L2	t(9;22), t(4;11), t(1;19)
T-cell ALL	20	L1, L2	14q11 or 7q34
B-cell ALL	5	L3	t(8;14), t(8;22), t(2;8)

Abbreviation: FAB, French-American-British classification.

chromosome–positive acute lymphoblastic leukemia) and the t(8;14) found in the L3 or Burkitt's leukemia.

Non-Hodgkin's lymphomas were separated from Hodgkin's lymphoma by recognition of the Sternberg-Reed cells early in the twentieth century. The histologic classification for non-Hodgkin's lymphomas has been one of the most contentious issues in oncology. Imperfect morphologic systems were supplanted by imperfect immunologic systems, and poor reproducibility of diagnosis has hampered progress. In 1999, the World Health Organization (WHO) classification of lymphoid malignancies was devised through a process of consensus development among international leaders in hematopathology and clinical oncology. The WHO classification takes into account morphologic, clinical, immunologic, and genetic information and attempts to divide non-Hodgkin's lymphomas and other lymphoid malignancies into clinical/pathologic entities that have clinical and therapeutic relevance. This system is presented in **Table 16-3**. This system is clinically relevant and has a higher degree of diagnostic accuracy than those used previously. The possibilities for subdividing lymphoid malignancies are extensive. However, Table 16-3 presents in bold those malignancies that occur in at least 1% of patients. Specific lymphoma subtypes will be dealt with in more detail below.

TABLE 16-3

WHO CLASSIFICATION OF LYMPHOID MALIGNANCIES

B CELL	T CELL	HODGKIN'S LYMPHOMA
Precursor B-cell neoplasm	Precursor T-cell neoplasm	Nodular lymphocyte-predominant Hodgkin's lymphoma
Precursor B lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia) includes subtypes with recurrent genetic abnormalities	Precursor T lymphoblastic lymphoma/leukemia (precursor T cell acute lymphoblastic leukemia)	
Mature (peripheral) B-cell neoplasms	Mature (peripheral) T-cell neoplasms	Classical Hodgkin's lymphoma
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma	T-cell prolymphocytic leukemia	Nodular sclerosis classical Hodgkin's lymphoma
B-cell prolymphocytic leukemia	T-cell granular lymphocytic leukemia	Lymphocyte-rich classical Hodgkin's lymphoma
Lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia)	Aggressive NK cell leukemia	Mixed-cellularity classical Hodgkin's lymphoma
Splenic marginal zone B-cell lymphoma (± villous lymphocytes)	Adult T-cell lymphoma/leukemia (HTLV-1+)	Lymphocyte-depletion classical Hodgkin's lymphoma
Hairy cell leukemia	Extranodal NK/T-cell lymphoma, nasal type	
Plasma cell myeloma/plasmacytoma	Enteropathy-type T-cell lymphoma	
Extranodal marginal zone B-cell lymphoma of MALT type	Hepatosplenic γδ T-cell lymphoma	
Mantle cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	
Follicular lymphoma	Mycosis fungoides/Sézary's syndrome	
Nodal marginal zone B-cell lymphoma (± monocytoid B cells)	Anaplastic large cell lymphoma, primary cutaneous type	
Diffuse large B-cell lymphoma (including subtypes)	Peripheral T-cell lymphoma, not otherwise specified (NOS)	
Burkitt's lymphoma/Burkitt's cell leukemia	Angioimmunoblastic T-cell lymphoma	
Primary mediastinal large B-cell lymphoma	Anaplastic large cell lymphoma, ALK+	
Plasmablastic lymphoma		
Primary effusion lymphoma		
Large B-cell lymphoma arising in HHV-8+ multicentric Castleman's disease		
Intravascular large B-cell lymphoma		
ALK+ large B-cell lymphoma		
Primary cutaneous γδ T-cell lymphoma		

Note: Malignancies in bold occur in at least 1% of patients.

Abbreviations: HHV, human herpesvirus; HTLV, human T-cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer; WHO, World Health Organization.

Source: Adapted from SH Swerdlow et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. World Health Organization, 2008.

Lymphomas occurring in fewer than 1%of patients with lymphoproliferative diseases are discussed in Chap. 17.

GENERAL ASPECTS OF LYMPHOID MALIGNANCIES

ETIOLOGY AND EPIDEMIOLOGY

T e relative frequency of the various lymphoid malignancies is shown in **Fig. 16-1**. Chronic lymphoid leukemia (CLL) is the most prevalent form of leukemia in Western countries. It occurs most frequently in older adults and is exceedingly rare in children. In 2014, 15,720 new cases were diagnosed in the United States, but because of the prolonged survival associated with this disorder, the total prevalence is many times higher. CLL is more common in men than in women and more common in whites than in blacks. T is is an uncommon malignancy in Asia. T e etiologic factors for typical CLL are unknown.

In contrast to CLL, acute lymphoid leukemias (ALLs) are predominantly cancers of children and young adults. T e L3 or Burkitt's leukemia occurring in children in developing countries seems to be associated with infection by the Epstein-Barr virus (EBV) in infancy. However, the explanation for the etiology of more common subtypes of ALL is much less certain. Childhood ALL occurs more often in higher socioeconomic subgroups. Children with trisomy 21 (Down's syndrome) have an increased risk for childhood ALL as well as acute myeloid leukemia (AML). Exposure to high-energy radiation in early childhood increases the risk of developing T-cell ALL.

T e etiology of ALL in adults is also uncertain. ALL is unusual in middle-aged adults but increases in incidence in the elderly. However, AML is still much more common in older patients. Environmental exposures, including certain industrial exposures, exposure to agricultural chemicals, and smoking, might increase the risk of developing ALL as an adult. ALL was diagnosed in 6020 persons and AML in 18,860 persons in the United States in 2014.

T e preponderance of evidence suggests that Hodgkin's lymphoma is of B-cell origin. T e incidence of Hodgkin's lymphoma appears fairly stable, with 9190 new cases diagnosed in 2014 in the United States. Hodgkin's lymphoma is more common in whites than in blacks and more common in males than in females. A bimodal distribution of age at diagnosis has been observed, with one peak incidence occurring in patients in their twenties and the other in those in their eighties. Some of the late age peak may be attributed

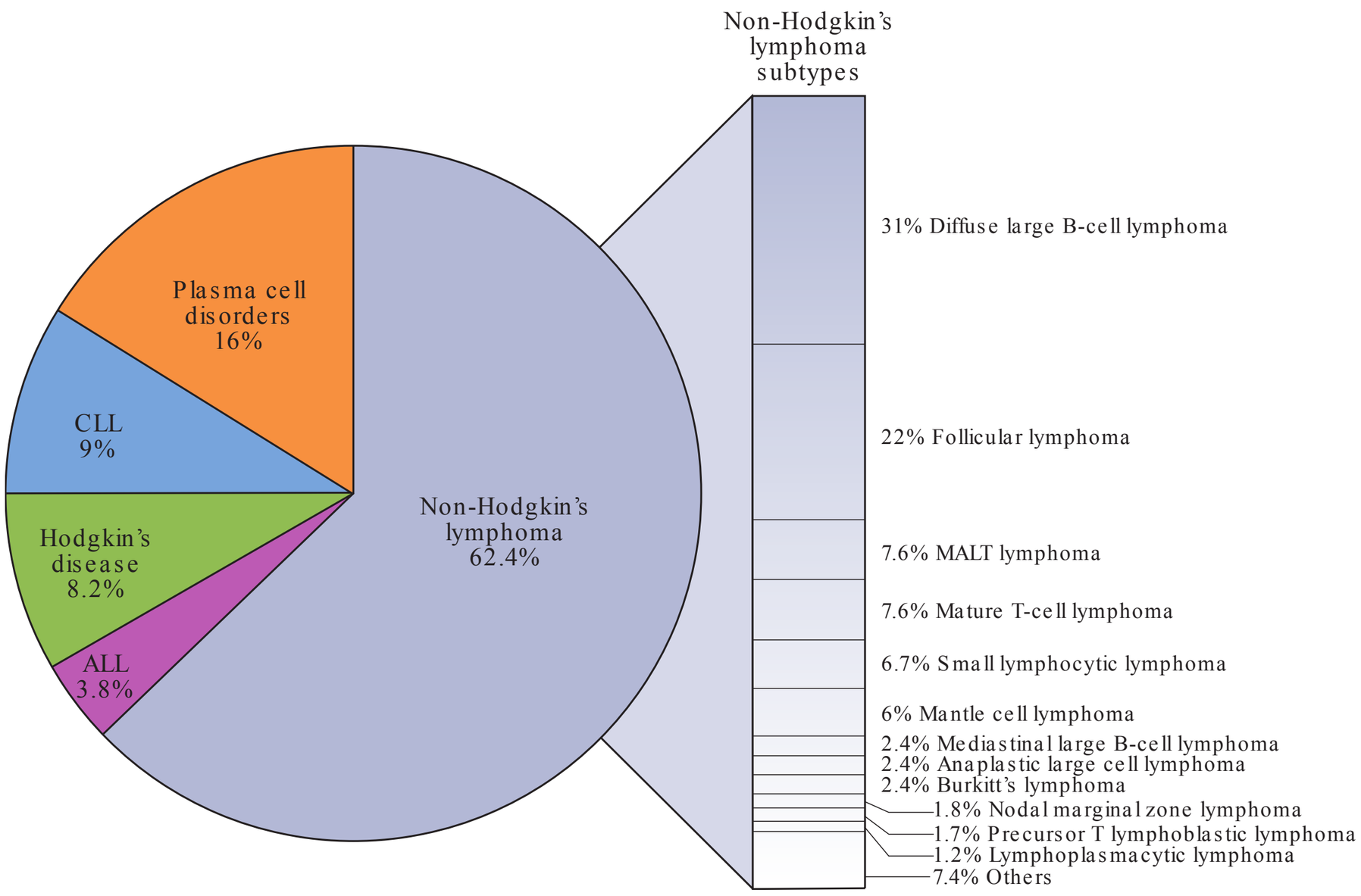


FIGURE 16-1
Relative frequency of lymphoid malignancies. ALL, acute lymphoid leukemia; CLL, chronic lymphoid leukemia; MALT, mucosa-associated lymphoid tissue.

to confusion among entities with similar appearance such as anaplastic large cell lymphoma and T-cell–rich B-cell lymphoma. Patients in the younger age groups diagnosed in the United States largely have the nodular sclerosing subtype of Hodgkin's lymphoma. Elderly patients, patients infected with HIV, and patients in T ird World countries more commonly have mixed-cellularity Hodgkin's lymphoma or lymphocyte-depleted Hodgkin's lymphoma. Infection by HIV is a risk factor for developing Hodgkin's lymphoma. In addition, an association between infection by EBV and Hodgkin's lymphoma has been suggested. A monoclonal or oligoclonal proliferation of EBV-infected cells in 20–40% of the patients with Hodgkin's lymphoma has led to proposals for this virus having an etiologic role in Hodgkin's lymphoma. However, the matter is not settled definitively.

For unknown reasons, non-Hodgkin's lymphomas increased in frequency in the United States at the rate of 4% per year and increased 2–8% per year globally between 1950 and the late 1990s. T e rate of increase in the past few years seems to be decreasing. About 70,800 new cases of non-Hodgkin's lymphoma were diagnosed in the United States in 2014 and nearly 360,000 cases worldwide. Non-Hodgkin's lymphomas are more frequent in the elderly and more frequent in men. Patients with both primary and secondary immunodeficiency states are predisposed to developing non-Hodgkin's lymphomas. T ese include patients with HIV infection; patients who have undergone organ transplantation; and patients with inherited immune deficiencies, the sicca syndrome, and rheumatoid arthritis.

T e incidence of non-Hodgkin's lymphomas and the patterns of expression of the various subtypes differ geographically. T-cell lymphomas are more common in Asia than in Western countries, while certain subtypes of B-cell lymphomas such as follicular lymphoma are more common in Western countries. A specific subtype of non-Hodgkin's lymphoma known as the angiocentric nasal T/natural killer (NK) cell lymphoma has a striking geographic occurrence, being most frequent in Southern Asia and parts of Latin America. Another subtype of non-Hodgkin's lymphoma associated with infection by human T-cell lymphotropic virus (HTLV) 1 is seen particularly in southern Japan and the Caribbean.

A number of environmental factors have been implicated in the occurrence of non-Hodgkin's lymphoma, including infectious agents, chemical exposures, and medical treatments. Several studies have demonstrated an association between exposure to agricultural chemicals and an increased incidence of non-Hodgkin's lymphoma. Patients treated for Hodgkin's lymphoma can develop non-Hodgkin's lymphoma; it is unclear whether this is a consequence of the Hodgkin's lymphoma or its treatment. However, a number of non-Hodgkin's lymphomas are associated with infectious agents **(Table 16-4)**. HTLV-1 infects T cells and leads directly to the development of adult T-cell lymphoma in a small percentage of infected patients. T e cumulative lifetime risk of developing lymphoma in an infected patient is 2.5%. T e virus is transmitted by infected lymphocytes ingested by nursing babies of infected mothers, bloodborne transmission, or sexually. T e median age of patients with adult T-cell lymphoma is ~56 years, emphasizing the long latency. HTLV-1 is also the cause of tropical spastic paraparesis—a neurologic disorder that occurs somewhat more frequently than lymphoma and with shorter latency and usually from transfusion-transmitted virus.

EBV is associated with the development of Burkitt's lymphoma in Central Africa and the occurrence of aggressive non-Hodgkin's lymphomas in immunosuppressed patients in Western countries. T e majority of primary central nervous system (CNS) lymphomas are associated with EBV. EBV infection is strongly associated with the occurrence of extranodal nasal T/NK cell lymphomas in Asia and South America. Infection with HIV predisposes to the development of aggressive, B-cell non-Hodgkin's lymphoma. T is may be through overexpression of interleukin 6 by infected macrophages. Infection of the stomach by the bacterium Helicobacter pylori induces the development of gastric MALT (mucosa-associated lymphoid tissue) lymphomas. T is association is supported by evidence that

TABLE 16-4

INFECTIOUS AGENTS ASSOCIATED WITH THE DEVELOPMENT OF LYMPHOID MALIGNANCIES

INFECTIOUS AGENT	LYMPHOID MALIGNANCY
Epstein-Barr virus	Burkitt's lymphoma Post–organ transplant lymphoma Primary CNS diffuse large B-cell lymphoma Hodgkin's lymphoma Extranodal NK/T-cell lymphoma, nasal type
HTLV-1	Adult T-cell leukemia/lymphoma
HIV	Diffuse large B-cell lymphoma Burkitt's lymphoma
Hepatitis C virus	Lymphoplasmacytic lymphoma
Helicobacter pylori	Gastric MALT lymphoma
Human herpesvirus 8	Primary effusion lymphoma Multicentric Castleman's disease

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

patients treated with antibiotics to eradicate H. pylori have regression of their MALT lymphoma. T e bacterium does not transform lymphocytes to produce the lymphoma; instead, a vigorous immune response is made to the bacterium, and the chronic antigenic stimulation leads to the neoplasia. MALT lymphomas of the skin may be related to Borrelia sp. infections, those of the eyes to Chlamydophila psittaci, and those of the small intestine to Campylobacter jejuni.

Chronic hepatitis C virus infection has been associated with the development of lymphoplasmacytic lymphoma. Human herpesvirus 8 is associated with primary effusion lymphoma in HIV-infected persons and multicentric Castleman's disease, a diffuse lymphadenopathy associated with systemic symptoms of fever, malaise, and weight loss.

In addition to infectious agents, a number of other diseases or exposures may predispose to developing lymphoma **(Table 16-5)**.

IMMUNOLOGY

All lymphoid cells are derived from a common hematopoietic progenitor that gives rise to lymphoid, myeloid, erythroid, monocyte, and megakaryocyte lineages. T rough the ordered and sequential activation of a series of transcription factors, the cell first becomes committed to the lymphoid lineage and then gives rise to B and T cells. About 75% of all lymphoid leukemias and 90% of all lymphomas are of B-cell origin. A cell becomes committed to B-cell development when it begins to rearrange its immunoglobulin genes. T e sequence of cellular changes, including changes in cell-surface phenotype, that characterizes normal B-cell development is shown in **Fig. 16-2**. A cell becomes committed to T-cell differentiation upon migration to the thymus and rearrangement of T-cell antigen receptor genes. T e sequence of the events that characterize T-cell development is depicted in **Fig. 16-3**.

Although lymphoid malignancies often retain the cell-surface phenotype of lymphoid cells at particular stages of differentiation, this information is of little consequence. T e so-called stage of differentiation of a malignant lymphoma does not predict its natural history. For example, the clinically most aggressive lymphoid leukemia is Burkitt's leukemia, which has the phenotype of a mature follicle center IgM-bearing B cell. Leukemias bearing the immunologic cell-surface phenotype of more primitive cells (e.g., pre-B ALL, CD10+) are less aggressive and more amenable to curative therapy than the "more mature" appearing Burkitt's leukemia cells. Furthermore, the apparent stage of differentiation of the malignant cell does not reflect the stage at which the genetic lesions that gave rise to the malignancy developed. For example, follicular lymphoma has the cell-surface phenotype of a follicle center cell, but its characteristic chromosomal translocation, the t(14;18), which involves juxtaposition of the antiapoptotic bcl-2 gene next to the immunoglobulin heavy chain gene (see below), had to develop early in ontogeny as an error in the process of immunoglobulin gene rearrangement. Why the subsequent steps that led to transformation became manifest in a cell of follicle center differentiation is not clear.

T e major value of cell-surface phenotyping is to aid in the differential diagnosis of lymphoid tumors that appear similar by light microscopy. For example, benign follicular hyperplasia may resemble follicular lymphoma; however, the demonstration that all the cells bear the same immunoglobulin light chain isotype strongly suggests the mass is a clonal proliferation rather than a polyclonal response to an exogenous stimulus.

Malignancies of lymphoid cells are associated with recurring genetic abnormalities. While specific genetic abnormalities have not been identified for all subtypes of lymphoid malignancies, it is presumed that they exist. Genetic abnormalities can be identified at a variety of levels including gross chromosomal changes (i.e., translocations, additions, or deletions); rearrangement of specific genes that may or may not be apparent from cytogenetic studies; and overexpression, underexpression, or mutation of specific oncogenes. Altered expression or mutation of specific proteins is particularly important. Many lymphomas contain balanced chromosomal translocations involving the antigen receptor genes; immunoglobulin genes on chromosomes 2, 14, and 22 in B cells; and T-cell antigen receptor genes on chromosomes 7 and 14 in T cells. T e rearrangement of chromosome segments

TABLE 16-5

DISEASES OR EXPOSURES ASSOCIATED WITH INCREASED RISK OF DEVELOPMENT OF MALIGNANT LYMPHOMA	
Inherited immunodeficiency disease	Autoimmune disease
Klinefelter's syndrome	Sjögren's syndrome
Chédiak-Higashi syndrome	Celiac sprue
Ataxia-telangiectasia syndrome	Rheumatoid arthritis and systemic lupus erythematosus
Wiskott-Aldrich syndrome	Chemical or drug exposures
Common variable immunodeficiency disease	Phenytoin
Acquired immunodeficiency diseases	Dioxin, phenoxy herbicides
Iatrogenic immunosuppression	Radiation
HIV-1 infection	Prior chemotherapy and radiation therapy
Acquired hypogammaglobulinemia	

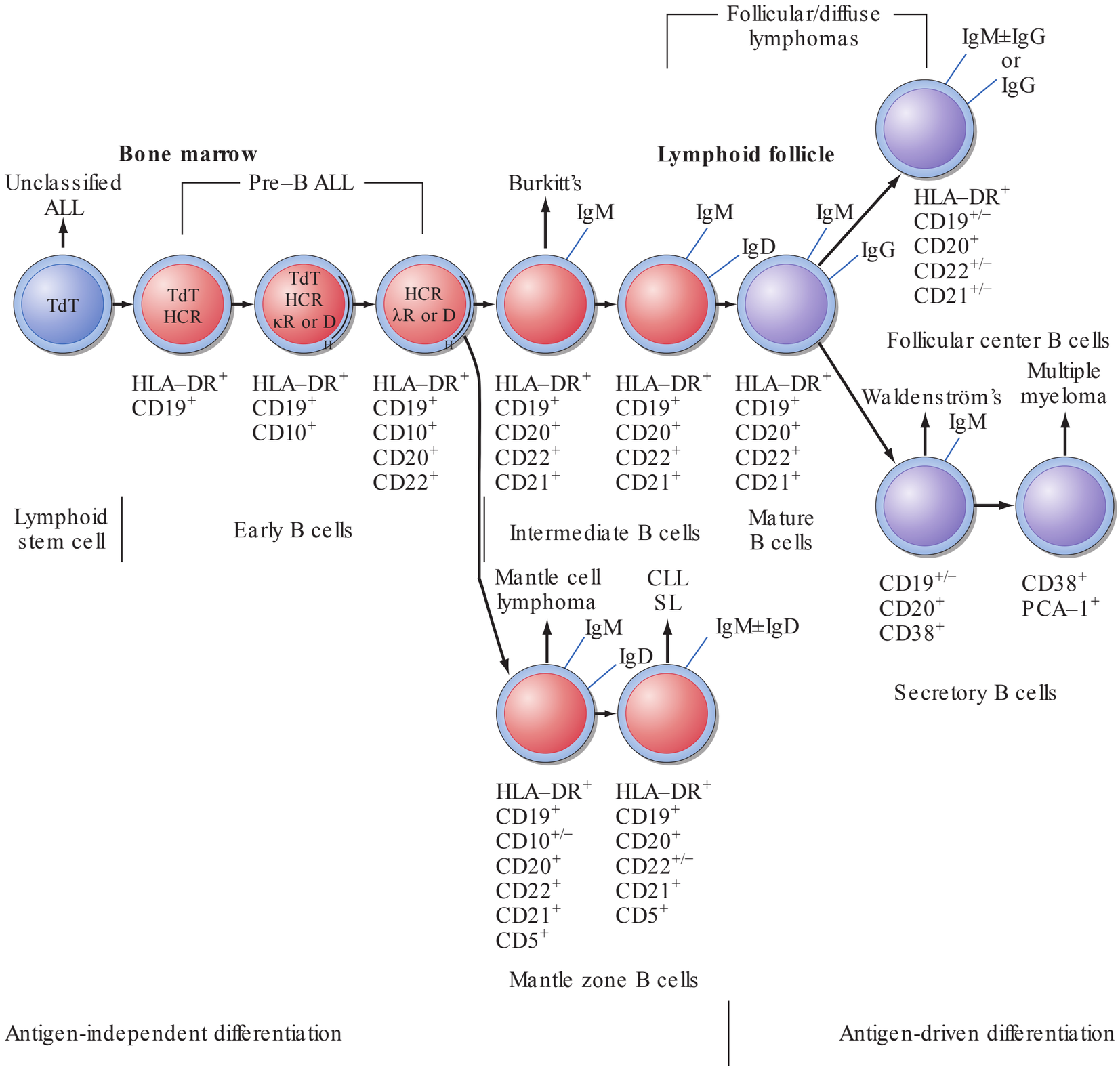


FIGURE 16-2

Pathway of normal B-cell differentiation and relationship to B-cell lymphomas. HLA-DR, CD10, CD19, CD20, CD21, CD22, CD5, and CD38 are cell markers used to distinguish stages of development. Terminal transferase (TdT) is a cellular enzyme. Immunoglobulin heavy chain gene rearrangement (HCR) and light chain gene rearrangement or deletion (κR or D, λR or D) occur early in B-cell development. The approximate normal stage of differentiation associated with particular lymphomas is shown. ALL, acute lymphoid leukemia; CLL, chronic lymphoid leukemia; SL, small lymphocytic lymphoma.

to generate mature antigen receptors must create a site of vulnerability to aberrant recombination. B cells are even more susceptible to acquiring mutations during their maturation in germinal centers; the generation of antibody of higher affinity requires the introduction of mutations into the variable region genes in the germinal centers. Other nonimmunoglobulin genes, e.g., bcl-6, may acquire mutations as well.

In the case of diffuse large B-cell lymphoma, the translocation t(14;18) occurs in ~30% of patients and leads to overexpression of the bcl-2 gene found on chromosome 18. Some other patients without the translocation also overexpress the BCL-2 protein. This protein is involved in suppressing apoptosis—i.e., the mechanism of cell death most often induced by cytotoxic chemotherapeutic agents. A higher relapse rate has been observed in patients whose tumors overexpress the BCL-2 protein, but not in those patients whose lymphoma cells show only the translocation. Thus, particular genetic mechanisms have clinical ramifications.

Table 16-6 presents the most common translocations and associated oncogenes for various subtypes of lymphoid malignancies. In some cases, such as the association of the t(14;18) in follicular lymphoma, the t(2;5) in anaplastic large T/null cell lymphoma, the t(8;14) in Burkitt's lymphoma, and the t(11;14) in mantle cell lymphoma, the great majority of tumors in patients with these diagnoses display these abnormalities. In other types of lymphoma where a minority of the patients have tumors expressing specific genetic abnormalities, the defects may have prognostic significance. No

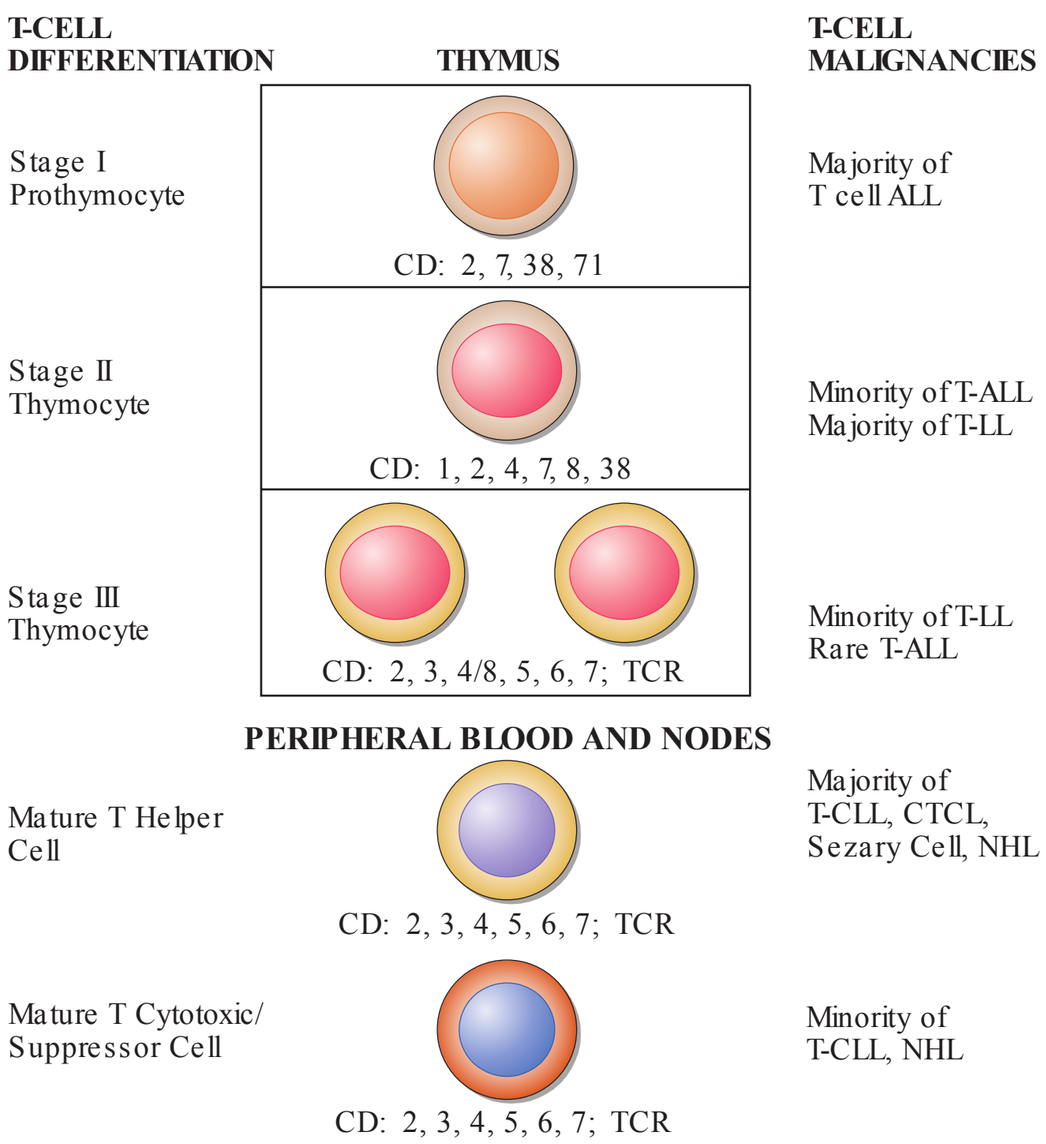


FIGURE 16-3

Pathway of normal T-cell differentiation and relationship to T-cell lymphomas. CD1, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD38, and CD71 are cell markers used to distinguish stages of development. T-cell antigen receptors (TCR) rearrange in the thymus, and mature T cells emigrate to nodes and peripheral blood. ALL, acute lymphoid leukemia; T-ALL, T-cell ALL; T-LL, T-cell lymphoblastic lymphoma; T-CLL, T-cell chronic lymphoid leukemia; CTCL, cutaneous T-cell lymphoma; NHL, non-Hodgkin's lymphoma.

TABLE 16-6

CYTOGENETIC TRANSLOCATION AND ASSOCIATED ONCOGENES OFTEN SEEN IN LYMPHOID MALIGNANCIES

DISEASE	CYTOGENETIC ABNORMALITY	ONCOGENE
CLL/small lymphocytic lymphoma	t(14;15)(q32;q13)	—
MALT lymphoma	t(11;18)(q21;q21)	API2/MALT, BCL-10
Precursor B-cell acute lymphoid leukemia	t(9;22)(q34;q11) or variant t(4;11)(q21;q23) t(12;21)	BCR/ABL AF4, MLLI TEL, AML1
Precursor acute lymphoid leukemia	t(9;22) t(1;19) t(17;19) t(5;14)	BCR, ABL E2A, PBX HLF, E2A HOX11L2, CTIP2
Mantle cell lymphoma	t(11;14)(q13;q32)	BCL-1, IgH
Follicular lymphoma	t(14;18)(q32;q21)	BCL-2, IgH
Diffuse large cell lymphoma	t(3;-)(q27;-)[a] t(17;-)(p13;-)	BCL-6 p53
Burkitt's lymphoma, Burkitt's leukemia	t(8;-)(q24;-)[a]	C-MYC
CD30+ anaplastic large cell lymphoma	t(2;5)(p23;q35)	ALK, NPM
Lymphoplasmacytoid lymphoma	t(9;14)(p13;q32)	PAX5, IgH

[a]Numerous sites of translocation may be involved with these genes.
Abbreviations: CLL, chronic lymphoid leukemia; IgH, immunoglobulin heavy chain; MALT, mucosa-associated lymphoid tissue.

specific genetic abnormalities have been identified in Hodgkin's lymphoma other than aneuploidy.

In typical B-cell CLL, trisomy 12 conveys a poorer prognosis. In ALL in both adults and children, genetic abnormalities have important prognostic significance. Patients whose tumor cells display the t(9;22) and translocations involving the MLL gene on chromosome 11q23 have a much poorer outlook than patients who do not have these translocations. Other genetic abnormalities that occur frequently in adults with ALL include the t(4;11) and the t(8;14). The t(4;11) is associated with younger age, female predominance, high white cell counts, and L1 morphology. The t(8;14) is associated with older age, male predominance, frequent CNS involvement, and L3 morphology. Both are associated with a poor prognosis. In childhood ALL, hyperdiploidy has been shown to have a favorable prognosis.

Gene profiling using array technology allows the simultaneous assessment of the expression of thousands of genes. This technology provides the possibility to identify new genes with pathologic importance in lymphomas, the identification of patterns of gene expression with diagnostic and/or prognostic significance, and the identification of new therapeutic targets. Recognition of patterns of gene expression is complicated and requires sophisticated mathematical techniques. Early successes using this technology in lymphoma include the identification of previously unrecognized subtypes of diffuse large B-cell lymphoma whose gene expression patterns resemble either those of follicular center B cells or activated peripheral blood B cells. Patients whose lymphomas have a germinal center B-cell pattern of gene expression have a considerably better prognosis than those whose lymphomas have a pattern resembling activated peripheral blood B cells. This improved prognosis is independent of other known prognostic factors. Similar information is being generated in follicular lymphoma and mantle cell lymphoma. The challenge remains to provide information from such techniques in a clinically useful time frame.

APPROACH TO THE PATIENT: Lymphoid Cell Malignancies

Regardless of the type of lymphoid malignancy, the initial evaluation of the patient should include performance of a careful history and physical examination. T ese will help confirm the diagnosis, identify those manifestations of the disease that might require prompt attention, and aid in the selection of further studies to optimally characterize the patient's status to allow the best choice of therapy. It is difficult to overemphasize the importance of a carefully done history and physical examination. T ey might provide observations that lead to reconsidering the diagnosis, provide hints at etiology, clarify the stage, and allow the physician to establish rapport with the patient that will make it possible to develop and carry out a therapeutic plan.

For patients with ALL, evaluation is usually completed after a complete blood count, chemistry studies reflecting major organ function, a bone marrow biopsy with genetic and immunologic studies, and a lumbar puncture. T e latter is necessary to rule out occult CNS involvement. At this point, most patients would be ready to begin therapy. In ALL, prognosis is dependent on the genetic characteristics of the tumor, the patient's age, the white cell count, and the patient's overall clinical status and major organ function.

In CLL, the patient evaluation should include a complete blood count, chemistry tests to measure major organ function, serum protein electrophoresis, and a bone marrow biopsy. However, some physicians believe that the diagnosis would not always require a bone marrow biopsy. Patients often have imaging studies of the chest and abdomen looking for pathologic lymphadenopathy. Patients with typical B-cell CLL can be subdivided into three major prognostic groups. T ose patients with only blood and bone marrow involvement by leukemia but no lymphadenopathy, organomegaly, or signs of bone marrow failure have the best prognosis. T ose with lymphadenopathy and organomegaly have an intermediate prognosis, and patients with bone marrow failure, defined as hemoglobin <100 g/L (10 g/dL) or platelet count <100,000/μL, have the worst prognosis. T e pathogenesis of the anemia or thrombocytopenia is important to discern. T e prognosis is adversely affected when either or both of these abnormalities are due to progressive marrow infiltration and loss of productive marrow. However, either or both may be due to autoimmune phenomena or to hypersplenism that can develop during the course of the disease. T ese destructive mechanisms are usually completely reversible (glucocorticoids for autoimmune disease; splenectomy for hypersplenism) and do not influence disease prognosis.

Two popular staging systems have been developed to reflect these prognostic groupings **(Table 16-7)**. Patients with typical B-cell CLL can have their course complicated by immunologic abnormalities, including autoimmune hemolytic anemia, autoimmune thrombocytopenia, and hypogammaglobulinemia. Patients with hypogammaglobulinemia benefit from regular (monthly) γ globulin administration. Because of expense, γ globulin is often withheld until the patient experiences a significant infection. T ese abnormalities do not have a clear prognostic significance and should not be used to assign a higher stage.

Two other features may be used to assess prognosis in B-cell CLL, but neither has yet been incorporated into a staging classification. At least two subsets of CLL have been identified based on the cytoplasmic expression of ZAP-70; expression of this protein, which is usually expressed in T cells, identifies a subgroup with poorer prognosis. A less powerful subsetting tool is CD38 expression. CD38+ tumors tend to have a poorer prognosis than CD38– tumors. A less easily measured feature, the presence of immunoglobulin variable region gene mutations, is also able to separate prognostic groups; patients with mutated immunoglobulin variable region genes respond better to treatment and have better survival than those with unmutated immunoglobulin variable region genes.

T e initial evaluation of a patient with Hodgkin's lymphoma or non-Hodgkin's lymphoma is similar. In both situations, the determination of an accurate anatomic stage is an important part of the evaluation. Staging is done using the Ann Arbor staging system originally developed for Hodgkin's lymphoma **(Table 16-8)**.

TABLE 16-7

STAGING OF TYPICAL B-CELL LYMPHOID LEUKEMIA

STAGE	CLINICAL FEATURES	MEDIAN SURVIVAL, YEARS
Rai System		
0: Low risk	Lymphocytosis only in blood and marrow	>10
I: Intermediate risk	Lymphocytosis + lymphadenopathy	7
II: Intermediate risk	Lymphocytosis + lymphadenopathy + splenomegaly ± hepatomegaly	
III: High risk	Lymphocytosis + anemia	1.5
IV: High risk	Lymphocytosis + thrombocytopenia	
Binet System		
A	Fewer than three areas of clinical lymphadenopathy; no anemia or thrombocytopenia	>10
B	Three or more involved node areas; no anemia or thrombocytopenia	7
C	Hemoglobin ≤10 g/dL and/or platelets <100,000/μL	2

TABLE 16-8

THE ANN ARBOR STAGING SYSTEM FOR HODGKIN'S LYMPHOMA

STAGE	DEFINITION
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as "E" More than one extranodal deposit at any location Any involvement of liver or bone marrow
A	No symptoms
B	Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

Evaluation of patients with Hodgkin's lymphoma will typically include a complete blood count; erythrocyte sedimentation rate; chemistry studies reflecting major organ function; computed tomography (CT) scans of the chest, abdomen, and pelvis; and a bone marrow biopsy. Neither a positron emission tomography (PET) scan nor a gallium scan is absolutely necessary for primary staging, but one performed at the completion of therapy allows evaluation of persisting radiographic abnormalities, particularly the mediastinum. Knowing that the PET scan or gallium scan is abnormal before treatment can help in this assessment. In most cases, these studies will allow assignment of anatomic stage and the development of a therapeutic plan.

In patients with non-Hodgkin's lymphoma, the same evaluation described for patients with Hodgkin's lymphoma is usually carried out. In addition, serum levels of lactate dehydrogenase (LDH) and β_2-microglobulin and serum protein electrophoresis are often included in the evaluation. Anatomic stage is assigned in the same manner as used for Hodgkin's lymphoma. However, the

TABLE 16-9

INTERNATIONAL PROGNOSTIC INDEX FOR NON-HODGKIN'S LYMPHOMA

Five clinical risk factors:
- Age ≥60 years
- Serum lactate dehydrogenase levels elevated
- Performance status ≥2 (ECOG) or ≤70 (Karnofsky)
- Ann Arbor stage III or IV
- >1 site of extranodal involvement

Patients are assigned a number for each risk factor they have
Patients are grouped differently based on the type of lymphoma

For diffuse large B-cell lymphoma:

0, 1 factor = low risk:	35% of cases; 5-year survival, 73%
2 factors = low-intermediate risk:	27% of cases; 5-year survival, 51%
3 factors = high-intermediate risk:	22% of cases; 5-year survival, 43%
4, 5 factors = high risk:	16% of cases; 5-year survival, 26%

For diffuse large B-cell lymphoma treated with R-CHOP:

0 factor = very good:	10% of cases; 5-year survival, 94%
1, 2 factors = good:	45% of cases; 5-year survival, 79%
3, 4, 5 factors = poor:	45% of cases; 5-year survival, 55%

Abbreviations: ECOG, Eastern Cooperative Oncology Group; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

prognosis of patients with non-Hodgkin's lymphoma is best assigned using the International Prognostic Index (IPI) **(Table 16-9)**. T is is a powerful predictor of outcome in all subtypes of non-Hodgkin's lymphoma. Patients are assigned an IPI score based on the presence or absence of five adverse prognostic factors and may have none or all five of these adverse prognostic factors. **Figure 16-4** shows the prognostic significance of this score in 1300

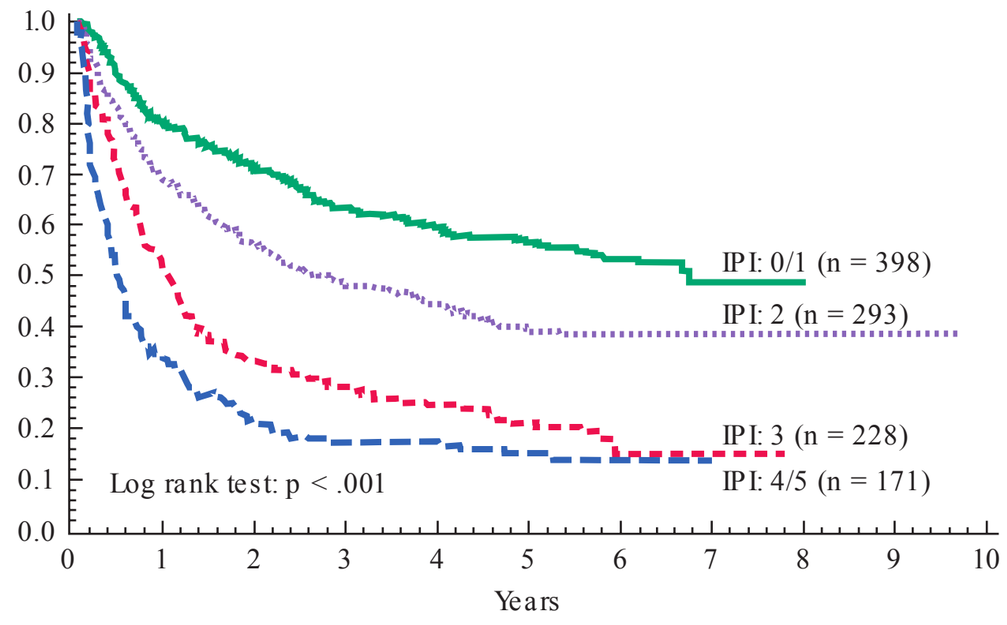


FIGURE 16-4

Relationship of International Prognostic Index (IPI) to survival. Kaplan-Meier survival curves for 1300 patients with various kinds of lymphoma stratified according to the IPI.

patients with all types of non-Hodgkin's lymphoma. With the addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), treatment outcomes have improved and the original IPI has lost some of its discrimination power. A revised IPI has been proposed that better predicts outcome of rituximab plus chemotherapy-based programs (Table 16-9). CT scans are routinely used in the evaluation of patients with all subtypes of non-Hodgkin's lymphoma, but PET and gallium scans are much more useful in aggressive subtypes such as diffuse large B-cell lymphoma than in more indolent subtypes such as follicular lymphoma or small lymphocytic lymphoma. Although the IPI does divide patients with follicular lymphoma into subsets with distinct prognoses, the distribution of such patients is skewed toward lower-risk categories. A follicular lymphoma–specific IPI (FLIPI) has been proposed that replaces performance status with hemoglobin level (<120 g/L [<12 g/dL]) and number of extranodal sites with number of nodal sites (more than four). Low risk (zero or one factor) was assigned to 36% of patients, intermediate risk (two factors) to 37%, and poor risk (more than two factors) to 27% of patients.

CLINICAL FEATURES, TREATMENT, AND PROGNOSIS OF SPECIFIC LYMPHOID MALIGNANCIES

PRECURSOR CELL B-CELL NEOPLASMS

Precursor B-cell lymphoblastic leukemia/lymphoma

The most common cancer in childhood is B-cell ALL. Although this disorder can also present as a lymphoma in either adults or children, presentation as lymphoma is rare.

The malignant cells in patients with precursor B-cell lymphoblastic leukemia are most commonly of pre–B cell origin. Patients typically present with signs of bone marrow failure such as pallor, fatigue, bleeding, fever, and infection related to peripheral blood cytopenias. Peripheral blood counts regularly show anemia and thrombocytopenia but might show leukopenia, a normal leukocyte count, or leukocytosis based largely on the number of circulating malignant cells **(Fig. 16-5)**. Extramedullary sites of disease are frequently involved in patients who present with leukemia, including lymphadenopathy, hepato- or splenomegaly, CNS disease, testicular enlargement, and/or cutaneous infiltration.

The diagnosis is usually made by bone marrow biopsy, which shows infiltration by malignant lymphoblasts. Demonstration of a pre–B cell immunophenotype (Fig. 16-2) and, often, characteristic cytogenetic abnormalities (Table 16-6) confirm the diagnosis. An adverse prognosis in patients with precursor B-cell ALL is predicted by a very high white cell count, the presence of symptomatic CNS disease, and unfavorable cytogenetic abnormalities. For example, t(9;22), frequently found in adults with B-cell ALL, has been associated with a very poor outlook. The bcr/abl kinase inhibitors have improved the prognosis.

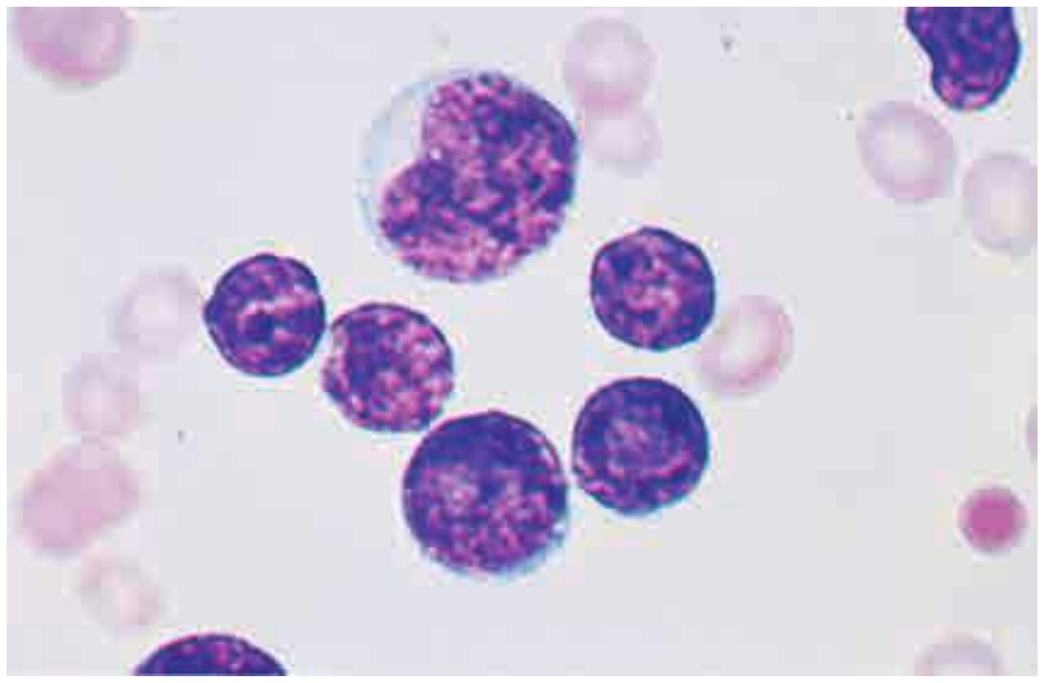


FIGURE 16-5
Acute lymphoblastic leukemia. The cells are heterogeneous in size and have round or convoluted nuclei, high nuclear/cytoplasmic ratio, and absence of cytoplasmic granules.

TREATMENT Precursor B-Cell Lymphoblastic Leukemia

The treatment of patients with precursor B-cell ALL involves remission induction with combination chemotherapy, a consolidation phase that includes administration of high-dose systemic therapy and treatment to eliminate disease in the CNS, and a period of continuing therapy to prevent relapse and effect cure. The overall cure rate in children is 90%, whereas ~50% of adults are long-term disease-free survivors. This is reflects the high proportion of adverse cytogenetic abnormalities seen in adults with precursor B-cell ALL.

Precursor B-cell lymphoblastic lymphoma is a rare presentation of precursor B-cell lymphoblastic malignancy. These patients often have a rapid transformation to leukemia and should be treated as though they had presented with leukemia. The few patients who present with the disease confined to lymph nodes have a high cure rate.

MATURE (PERIPHERAL) B-CELL NEOPLASMS

B-cell chronic lymphoid leukemia/small lymphocytic lymphoma

B-cell CLL/small lymphocytic lymphoma represents the most common lymphoid leukemia, and when presenting as a lymphoma, it accounts for ~7% of non-Hodgkin's lymphomas. Presentation can be as either leukemia or lymphoma. The major clinical characteristics of B-cell CLL/small lymphocytic lymphoma are presented in **Table 16-10**.

TABLE 16-10

CLINICAL CHARACTERISTICS OF PATIENTS WITH COMMON TYPES OF NON-HODGKIN'S LYMPHOMA (NHL)

DISEASE	MEDIAN AGE, YEARS	FREQUENCY IN CHILDREN	% MALE	STAGE I/II VS III/IV, %	B SYMPTOMS, %	BONE MARROW INVOLVEMENT, %	GASTROINTESTINAL TRACT INVOLVEMENT, %	% SURVIVING 5 YEARS
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma	65	Rare	53	9 vs 91	33	72	3	51
Mantle cell lymphoma	63	Rare	74	20 vs 80	28	64	9	27
Extranodal marginal zone B-cell lymphoma of MALT type	60	Rare	48	67 vs 33	19	14	50	74
Follicular lymphoma	59	Rare	42	33 vs 67	28	42	4	72
Diffuse large B-cell lymphoma	64	~25% of childhood NHL	55	54 vs 46	33	16	18	46
Burkitt's lymphoma	31	~30% of childhood NHL	89	62 vs 38	22	33	11	45
Precursor T-cell lymphoblastic lymphoma	28	~40% of childhood NHL	64	11 vs 89	21	50	4	26
Anaplastic large T/null-cell lymphoma	34	Common	69	51 vs 49	53	13	9	77
Peripheral T-cell NHL	61	~5% of childhood NHL	55	20 vs 80	50	36	15	25

Abbreviation: MALT, mucosa-associated lymphoid tissue.

The diagnosis of typical B-cell CLL is made when an increased number of circulating lymphocytes (i.e., $>4 \times 10^9$/L and usually $>10 \times 10^9$/L) is found **(Fig. 16-6)** that are monoclonal B cells expressing the CD5 antigen. Finding bone marrow infiltration by the same cells confirms the diagnosis. The peripheral blood smear in such patients typically shows many "smudge" or "basket" cells, nuclear remnants of cells damaged by the physical shear stress of making the blood smear. If cytogenetic studies are performed, trisomy 12 is found in 25–30% of patients. Abnormalities in chromosome 13 are also seen.

If the primary presentation is lymphadenopathy and a lymph node biopsy is performed, pathologists usually have little difficulty in making the diagnosis of small lymphocytic lymphoma based on morphologic findings and immunophenotype. However, even in these patients, 70–75% will be found to have bone marrow

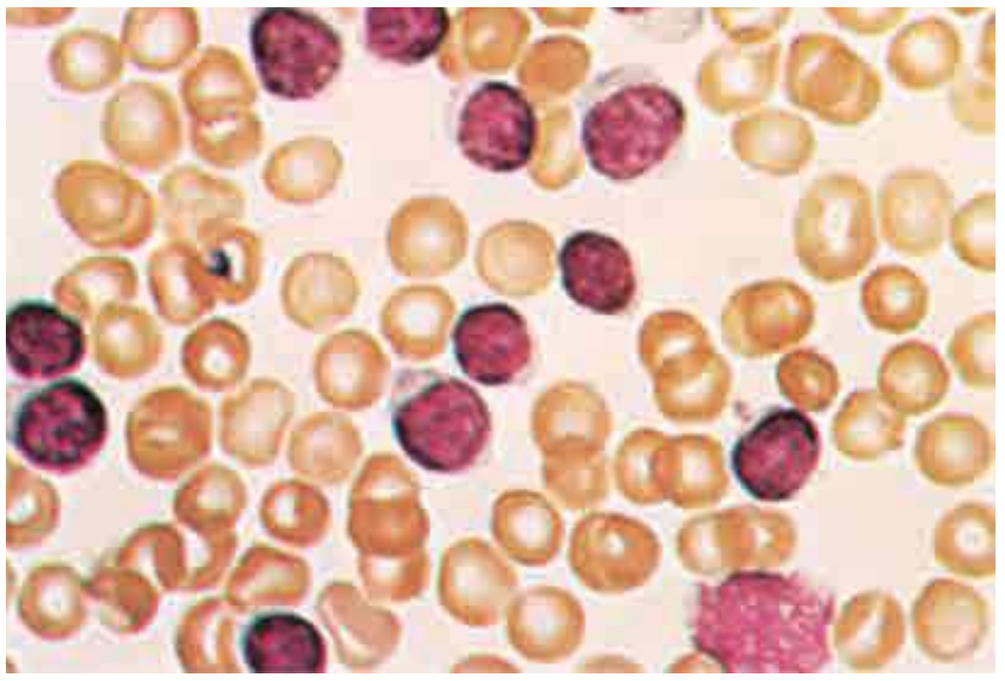


FIGURE 16-6

Chronic lymphocytic leukemia. The peripheral white blood cell count is high due to increased numbers of small, well-differentiated, normal-appearing lymphocytes. The leukemia lymphocytes are fragile, and substantial numbers of broken, smudged cells are usually also present on the blood smear.

involvement and circulating monoclonal B lymphocytes are often present.

The differential diagnosis of typical B-cell CLL is extensive (Table 16-1). Immunophenotyping will eliminate the T-cell disorders and can often help sort out other B-cell malignancies. For example, only mantle cell lymphoma and typical B-cell CLL are usually CD5 positive. Typical B-cell small lymphocytic lymphoma can be confused with other B-cell disorders, including lymphoplasmacytic lymphoma (i.e., the tissue manifestation of Waldenström's macroglobulinemia), nodal marginal zone B-cell lymphoma, and mantle cell lymphoma. In addition, some small lymphocytic lymphomas have areas of large cells that can lead to confusion with diffuse large B-cell lymphoma. An expert hematopathologist is vital for making this distinction.

Typical B-cell CLL is often found incidentally when a complete blood count is done for another reason. However, complaints that might lead to the diagnosis include fatigue, frequent infections, and new lymphadenopathy. The diagnosis of typical B-cell CLL should be considered in a patient presenting with an autoimmune hemolytic anemia or autoimmune thrombocytopenia. B-cell CLL has also been associated with red cell aplasia. When this disorder presents as lymphoma, the most common abnormality is asymptomatic lymphadenopathy, with or without splenomegaly. The staging systems predict prognosis in patients with typical B-cell CLL (Table 16-7). The evaluation of a new patient with typical B-cell CLL/small lymphocytic lymphoma will include many of the studies **(Table 16-11)** that are used in patients with other non-Hodgkin's lymphomas. In addition, particular attention needs to be given to detecting immune abnormalities such as autoimmune hemolytic anemia, autoimmune thrombocytopenia, hypogammaglobulinemia, and red cell aplasia. Molecular analysis of immunoglobulin gene sequences in CLL has demonstrated that about half the patients have tumors expressing mutated immunoglobulin genes and half have tumors expressing unmutated or germline immunoglobulin sequences. Patients with unmutated immunoglobulins tend to have a more aggressive clinical course and are less responsive to therapy. Unfortunately, immunoglobulin gene sequencing is not routinely available. CD38 expression is said to be low in the better-prognosis patients expressing mutated immunoglobulin and high in poorer-prognosis patients expressing unmutated immunoglobulin, but this test has not been confirmed as a reliable means of distinguishing the two groups. ZAP-70 expression correlates with the presence of unmutated immunoglobulin genes, but the assay is not yet standardized and widely available.

TABLE 16-11

STAGING EVALUATION FOR NON-HODGKIN'S LYMPHOMA

- Physical examination
- Documentation of B symptoms
- Laboratory evaluation
  - Complete blood counts
  - Liver function tests
  - Uric acid
  - Calcium
  - Serum protein electrophoresis
  - Serum β_2-microglobulin
- Chest radiograph
- CT scan of abdomen, pelvis, and usually chest
- Bone marrow biopsy
- Lumbar puncture in lymphoblastic, Burkitt's, and diffuse large B-cell lymphoma with positive marrow biopsy
- Gallium scan (SPECT) or PET scan in large cell lymphoma

Abbreviations: CT, computed tomography; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

TREATMENT B-Cell Chronic Lymphoid Leukemia/Small Lymphocytic Lymphoma

Patients whose presentation is typical B-cell CLL with no manifestations of the disease other than bone marrow involvement and lymphocytosis (i.e., Rai stage 0 and Binet stage A; Table 16-7) can be followed without specific therapy for their malignancy. These patients have a median survival >10 years, and some will never require therapy for this disorder. If the patient has an adequate number of circulating normal blood cells and is asymptomatic, many physicians would not initiate therapy for patients in the intermediate stage of the disease manifested by lymphadenopathy and/or hepatosplenomegaly. However, the median survival for these patients is ~7 years, and most will require treatment in the first few years of follow-up. Patients who present with bone marrow failure (i.e., Rai stage III or IV or Binet stage C) will require initial therapy in almost all cases. These patients have a serious disorder with a median survival of only 1.5 years. It must be remembered that immune manifestations of typical B-cell CLL should be managed independently of specific antileukemia therapy. For example, glucocorticoid therapy for autoimmune cytopenias and γ globulin replacement for patients with hypogammaglobulinemia should be used whether or not antileukemia therapy is given.

Patients who present primarily with lymphoma and have a low IPI score have a 5-year survival of ~75%, but those with a high IPI score have a 5-year survival of <40% and are more likely to require early therapy.

The most common treatments for patients with typical B-cell CLL/small lymphocytic lymphoma have been chlorambucil or fludarabine, alone or in combination. Chlorambucil can be administered orally with few immediate side effects,

while fludarabine is administered IV and is associated with significant immune suppression. However, fludarabine is by far the more active agent and is the only drug associated with a significant incidence of complete remission. T e combination of rituximab (375–500 mg/m^2 day 1), fludarabine (25 mg/m^2 days 2–4 on cycle 1 and days 1–3 in subsequent cycles), and cyclophosphamide (250 mg/m^2 with fludarabine) achieves complete responses in 69% of patients, and those responses are associated with molecular remissions in half of the cases. Half the patients experience grade III or IV neutropenia. For young patients presenting with leukemia requiring therapy, regimens containing fludarabine are the treatment of choice. Because fludarabine is an effective second-line agent in patients with tumors unresponsive to chlorambucil, the latter agent is often chosen in elderly patients who require therapy. Bendamustine, an alkylating agent structurally related to nitrogen mustard, is highly effective and is vying with fludarabine as the primary treatment of choice. Patients who present with lymphoma (rather than leukemia) are also highly responsive to bendamustine, and some patients will receive a combination chemotherapy regimen used in other lymphomas such as CVP (cyclophosphamide, vincristine, and prednisone) or CHOP plus rituximab. Alemtuzumab (anti-CD52) is an antibody with activity in the disease, but it kills both B and T cells and is associated with more immune compromise than rituximab. Young patients with this disease can be candidates for bone marrow transplantation. Allogeneic bone marrow transplantation can be curative but is associated with a significant treatment-related mortality rate. Mini-transplants using immunosuppressive rather than myeloablative doses of preparative drugs are being studied **(Chap. 31)**. T e use of autologous transplantation in patients with this disorder has been discouraging.

At least two newer anti-CD20 monoclonal antibodies have become available, ofatumumab and obinutuzumab. Both have activity in previously treated patients. Agents targeting signaling pathways, such as ibrutinib, an irreversible inhibitor of Bruton's tyrosine kinase, and idelalisib, an inhibitor of phosphoinositide-3-kinase delta, also have antitumor effects. T e ideal combination and sequence of these therapies have not been defined.

Extranodal marginal zone B-cell lymphoma of MALT type

Extranodal marginal zone B-cell lymphoma of MALT type (MALT lymphoma) makes up ~8% of non-Hodgkin's lymphomas. T is small cell lymphoma presents in extranodal sites. It was previously considered a small lymphocytic lymphoma or sometimes a pseudolymphoma. T e recognition that the gastric presentation of this lymphoma was associated with H. pylori infection was an important step in recognizing it as a separate entity. T e clinical characteristics of MALT lymphoma are presented in Table 16-10.

T e diagnosis of MALT lymphoma can be made accurately by an expert hematopathologist based on a characteristic pattern of infiltration of small lymphocytes that are monoclonal B cells and CD5 negative. In some cases, transformation to diffuse large B-cell lymphoma occurs, and both diagnoses may be made in the same biopsy. T e differential diagnosis includes benign lymphocytic infiltration of extranodal organs and other small cell B-cell lymphomas.

MALT lymphoma may occur in the stomach, orbit, intestine, lung, thyroid, salivary gland, skin, soft tissues, bladder, kidney, and CNS. It may present as a new mass, be found on routine imaging studies, or be associated with local symptoms such as upper abdominal discomfort in gastric lymphoma. Most MALT lymphomas are gastric in origin. At least two genetic forms of gastric MALT exist: one (accounting for ~50% of cases) characterized by t(11;18)(q21;q21) that juxtaposes the amino terminal of the API2 gene with the carboxy terminal of the MALT1 gene creating an API2/MALT1 fusion product, and the other characterized by multiple sites of genetic instability including trisomies of chromosomes 3, 7, 12, and 18. About 95% of gastric MALT lymphomas are associated with H. pylori infection, and those that are do not usually express t(11;18). The t(11;18) usually results in activation of nuclear factor-κB (NF-κB), which acts as a survival factor for the cells. Lymphomas with t(11;18) translocations are genetically stable and do not evolve to diffuse large B-cell lymphoma. By contrast, t(11;18)-negative MALT lymphomas often acquire BCL6 mutations and progress to aggressive histology lymphoma. MALT lymphomas are localized to the organ of origin in ~40% of cases and to the organ and regional lymph nodes in ~30% of patients. However, distant metastasis can occur—particularly with transformation to diffuse large B-cell lymphoma. Many patients who develop this lymphoma will have an autoimmune or inflammatory process such as Sjögren's syndrome (salivary gland MALT), Hashimoto's thyroiditis (thyroid MALT), Helicobacter gastritis (gastric MALT), C. psittaci conjunctivitis (ocular MALT), or Borrelia skin infections (cutaneous MALT).

Evaluation of patients with MALT lymphoma follows the pattern (Table 16-11) for staging a patient with non-Hodgkin's lymphoma. In particular, patients with gastric lymphoma need to have studies performed to document the presence or absence of H. pylori infection. Endoscopic studies including ultrasound can help define the extent of gastric involvement. Most patients with MALT lymphoma have a good prognosis, with a 5-year survival of ~75%. In patients with a low IPI score, the 5-year survival is ~90%, whereas it drops to ~40% in patients with a high IPI score.

TREATMENT Mucosa-Associated Lymphoid Tissue Lymphoma

MALT lymphoma is often localized. Patients with gastric MALT lymphomas who are infected with H. pylori can achieve remission in the 80% of cases with eradication of the infection. T ese remissions can be durable, but molecular evidence of persisting neoplasia is not infrequent. After H. pylori eradication, symptoms generally improve quickly, but molecular evidence of persistent disease may be present for 12–18 months. Additional therapy is not indicated unless progressive disease is documented. Patients with more extensive disease or progressive disease are most often treated with single-agent chemotherapy such as chlorambucil. Combination regimens that include rituximab are also highly effective. Coexistent diffuse large B-cell lymphoma must be treated with combination chemotherapy (see below). T e additional acquired mutations that mediate the histologic progression also convey Helicobacter independence to the growth.

Mantle cell lymphoma

Mantle cell lymphoma makes up ~6% of all non-Hodgkin's lymphomas. T is lymphoma was previously placed in a number of other subtypes. Its existence was confirmed by the recognition that these lymphomas have a characteristic chromosomal translocation, t(11;14), between the immunoglobulin heavy chain gene on chromosome 14 and the bcl-1 gene on chromosome 11, and regularly overexpress the BCL-1 protein, also known as cyclin D1. Table 16-10 shows the clinical characteristics of mantle cell lymphoma.

T e diagnosis of mantle cell lymphoma can be made accurately by an expert hematopathologist. As with all subtypes of lymphoma, an adequate biopsy is important. T e differential diagnosis of mantle cell lymphoma includes other small cell B-cell lymphomas. In particular, mantle cell lymphoma and small lymphocytic lymphoma share a characteristic expression of CD5. Mantle cell lymphoma usually has a slightly indented nucleus.

T e most common presentation of mantle cell lymphoma is with palpable lymphadenopathy, frequently accompanied by systemic symptoms. T e median age is 63 years, and men are affected four times as commonly as women. Approximately 70% of patients will be stage IV at the time of diagnosis, with frequent bone marrow and peripheral blood involvement. Of the extranodal organs that can be involved, gastrointestinal involvement is particularly important to recognize. Patients who present with lymphomatosis polyposis in the large intestine usually have mantle cell lymphoma. Table 16-11 outlines the evaluation of patients with mantle cell lymphoma. Patients who present with gastrointestinal tract involvement often have Waldeyer's ring involvement, and vice versa. T e 5-year survival for all patients with mantle cell lymphoma is ~25%, with only occasional patients who present with a high IPI score surviving 5 years and ~50% of patients with a low IPI score surviving 5 years.

TREATMENT Mantle Cell Lymphoma

Current therapies for mantle cell lymphoma are evolving. Patients with localized disease might be treated with combination chemotherapy followed by radiotherapy; however, these patients are exceedingly rare. For the usual presentation with disseminated disease, standard lymphoma treatments have been unsatisfactory, with the minority of patients achieving complete remission. Aggressive combination chemotherapy regimens followed by autologous or allogeneic bone marrow transplantation are frequently offered to younger patients. For the occasional elderly, asymptomatic patient, observation followed by single-agent chemotherapy might be the most practical approach. An intensive combination chemotherapy regimen originally used in the treatment of acute leukemia, HyperC-VAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, and methotrexate), in combination with rituximab, seems to be associated with better response rates, particularly in younger patients. Alternating two regimens, HyperC-VAD with rituximab added (R-HyperC-VAD) and rituximab plus high-dose methotrexate and cytarabine, can achieve complete responses in >80% of patients and an 8-year survival of 56%, comparable to regimens using high-dose therapy and autologous hematopoietic stem cell transplantation. Bendamustine plus rituximab has been found to induce complete responses in about 31% of patients, but the responses are generally not long lasting. Bortezomib and temsirolimus are single agents that induce transient partial responses in a minority of patients and are being added to primary combinations.

Follicular lymphoma

Follicular lymphomas make up 22% of non-Hodgkin's lymphomas worldwide and at least 30% of non-Hodgkin's lymphomas diagnosed in the United States. T is type of lymphoma can be diagnosed accurately on morphologic findings alone and has been the diagnosis in the majority of patients in therapeutic trials for "low-grade" lymphoma in the past. T e clinical characteristics of follicular lymphoma are presented in Table 16-10.

Evaluation of an adequate biopsy by an expert hematopathologist is suf cient to make a diagnosis of follicular lymphoma. T e tumor is composed of small cleaved and large cells in varying proportions organized in a follicular pattern of growth **(Fig. 16-7)**. Confirmation of B-cell immunophenotype and the existence of the t(14;18) and abnormal expression of BCL-2 protein are confirmatory. T e major differential diagnosis is

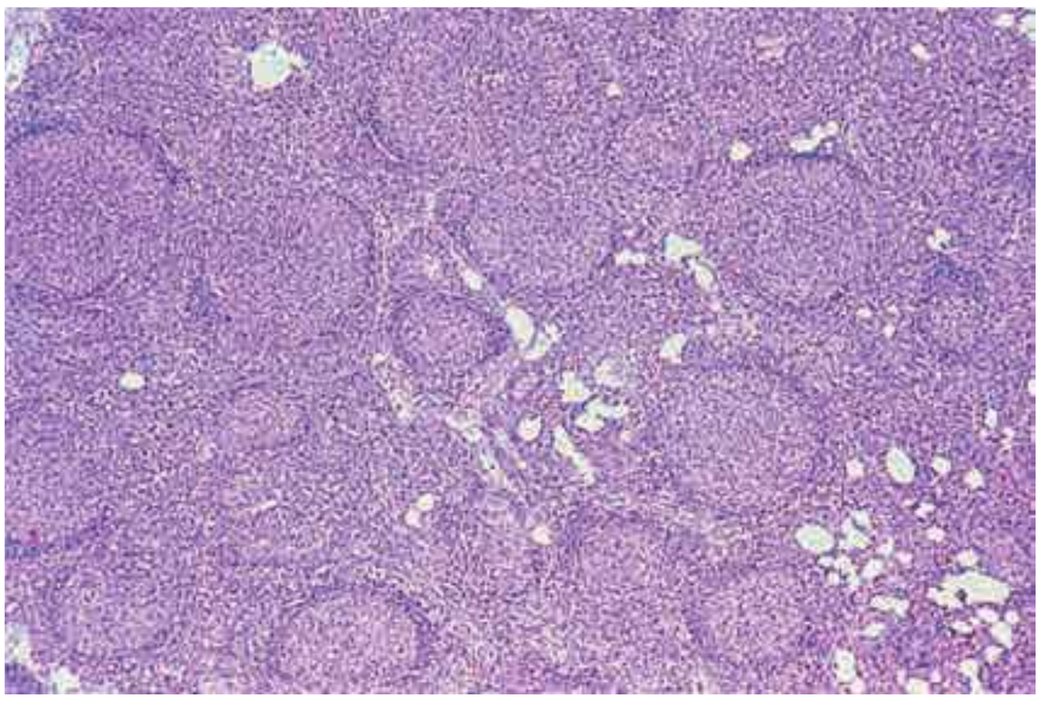


FIGURE 16-7
Follicular lymphoma. The normal nodal architecture is effaced by nodular expansions of tumor cells. Nodules vary in size and contain predominantly small lymphocytes with cleaved nuclei along with variable numbers of larger cells with vesicular chromatin and prominent nucleoli.

between lymphoma and reactive follicular hyperplasia. T e coexistence of diffuse large B-cell lymphoma must be considered. Patients with follicular lymphoma are often subclassified into those with predominantly small cells, those with a mixture of small and large cells, and those with predominantly large cells. Although this distinction cannot be made simply or very accurately, these subdivisions do have prognostic significance. Patients with follicular lymphoma with predominantly large cells have a higher proliferative fraction, progress more rapidly, and have a shorter overall survival with simple chemotherapy regimens.

T e most common presentation for follicular lymphoma is with new, painless lymphadenopathy. Multiple sites of lymphoid involvement are typical, and unusual sites such as epitrochlear nodes are sometimes seen. However, essentially any organ can be involved, and extranodal presentations do occur. Most patients do not have fevers, sweats, or weight loss, and an IPI score of 0 or 1 is found in ~50% of patients. Fewer than 10% of patients have a high (i.e., 4 or 5) IPI score. T e staging evaluation for patients with follicular lymphoma should include the studies shown in Table 16-11.

TREATMENT Follicular Lymphoma

Follicular lymphoma is one of the malignancies most responsive to chemotherapy and radiotherapy. In addition, tumors in as many as 25% of the patients undergo spontaneous regression—usually transient—without therapy. In an asymptomatic patient, no initial treatment and watchful waiting can be an appropriate management strategy and is particularly likely to be adopted for older patients with advanced-stage disease. For patients who do require treatment, single-agent chlorambucil or cyclophosphamide or combination chemotherapy with CVP or CHOP is most frequently used. With adequate treatment, 50–75% of patients will achieve a complete remission. Although most patients relapse (median response duration is ~2 years), at least 20% of complete responders will remain in remission for >10 years. For the rare patients (15%) with localized follicular lymphoma, involved-field radiotherapy produces long-term disease-free survival in the majority.

A number of therapies have been shown to be active in the treatment of patients with follicular lymphoma. T ese include cytotoxic agents such as fludarabine, biologic agents such as interferon α, monoclonal antibodies with or without radionuclides, and lymphoma vaccines. In patients treated with a doxorubicin-containing combination chemotherapy regimen, interferon α given to patients in complete remission seems to prolong survival, but interferon toxicities can affect quality of life. T e monoclonal antibody rituximab can cause objective responses in 35–50% of patients with relapsed follicular lymphoma, and radiolabeled antibodies appear to have response rates well in excess of 50%. T e addition of rituximab to CHOP and other effective combination chemotherapy programs achieves prolonged overall survival and a decreased risk of histologic progression. Complete remissions can be noted in 85% or more of patients treated with R-CHOP, and median remission durations can exceed 6 or 7 years. Maintenance intermittent rituximab therapy can prolong remissions even further, although it is not completely clear that overall survival is prolonged. Some trials with tumor vaccines have been encouraging. Both autologous and allogeneic hematopoietic stem cell transplantations yield high complete response rates in patients with relapsed follicular lymphoma, and long-term remissions can occur in 40% or more of patients.

Patients with follicular lymphoma with a predominance of large cells have a shorter survival when treated with single-agent chemotherapy but seem to benefit from receiving an anthracycline-containing combination chemotherapy regimen plus rituximab. When their disease is treated aggressively, the overall survival for such patients is no lower than for patients with other follicular lymphomas, and the failure-free survival is superior.

Patients with follicular lymphoma have a high rate of histologic transformation to diffuse large B-cell lymphoma (5–7% per year). T is is recognized ~40% of the time during the course of the illness by repeat biopsy and is present in almost all patients at autopsy. T is transformation is usually heralded by rapid growth of lymph nodes—often localized—and the development of systemic symptoms such as fevers, sweats, and weight loss. Although these patients have a poor prognosis, aggressive combination chemotherapy regimens can sometimes cause a complete remission in the diffuse large B-cell lymphoma, at times leaving the patient with persisting follicular lymphoma. With more frequent use of R-CHOP to treat follicular lymphoma at diagnosis, it

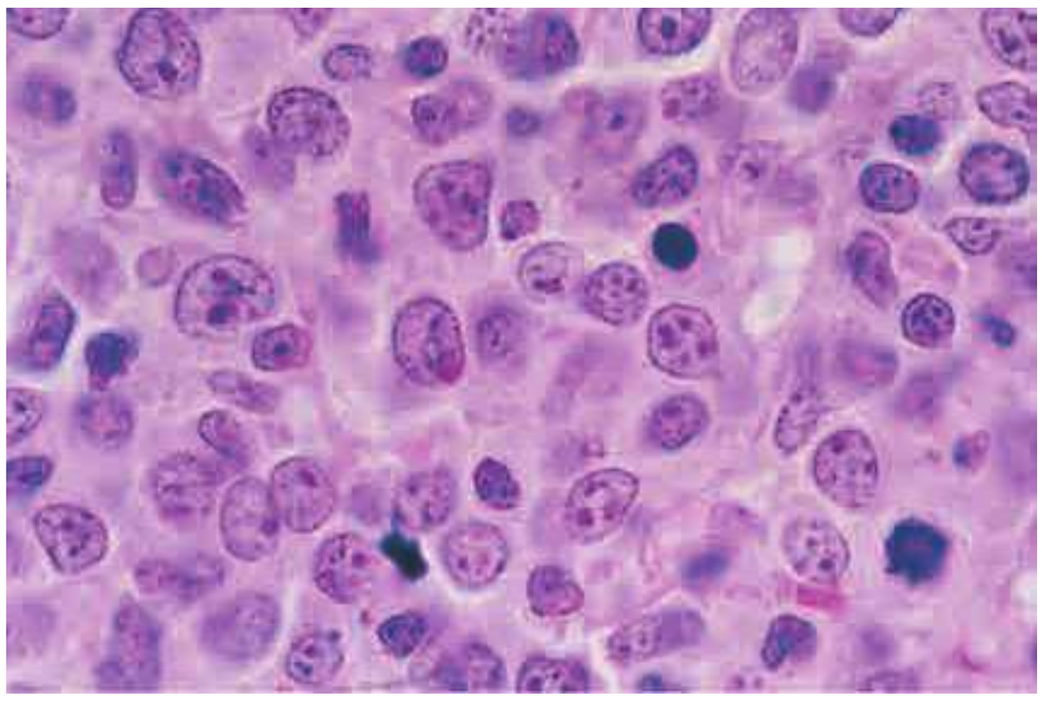


FIGURE 16-8
Diffuse large B-cell lymphoma. The neoplastic cells are heterogeneous but predominantly large cells with vesicular chromatin and prominent nucleoli.

appears that the rate of histologic progression is decreasing. R-CHOP or bendamustine plus rituximab with intermittent rituximab maintenance for 2 years are the most commonly used treatment approaches.

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma is the most common type of non-Hodgkin's lymphoma, representing approximately one-third of all cases. This lymphoma makes up the majority of cases in previous clinical trials of "aggressive" or "intermediate-grade" lymphoma. Table 16-10 shows the clinical characteristics of diffuse large B-cell lymphoma.

The diagnosis of diffuse large B-cell lymphoma can be made accurately by an expert hematopathologist **(Fig. 16-8)**. Cytogenetic and molecular genetic studies are not necessary for diagnosis, but some evidence has accumulated that patients whose tumors overexpress the BCL-2 protein might be more likely to relapse than others. A subset of patients have tumors with mutations in BCL6 and translocations involving MYC; these are called "double-hit" lymphomas and typically have more aggressive growth and are more poorly responsive to treatment than other diffuse large B-cell lymphomas. Patients with prominent mediastinal involvement are sometimes diagnosed as a separate subgroup having primary mediastinal diffuse large B-cell lymphoma. This latter group of patients has a younger median age (i.e., 37 years) and a female predominance (66%). Subtypes of diffuse large B-cell lymphoma, including those with an immunoblastic subtype and tumors with extensive fibrosis, are recognized by pathologists but do not appear to have important independent prognostic significance.

Diffuse large B-cell lymphoma can present as either primary lymph node disease or at extranodal sites. More than 50% of patients will have some site of extranodal involvement at diagnosis, with the most common sites being the gastrointestinal tract and bone marrow, each being involved in 15–20% of patients. Essentially any organ can be involved, making a diagnostic biopsy imperative. For example, diffuse large B-cell lymphoma of the pancreas has a much better prognosis than pancreatic carcinoma but would be missed without biopsy. Primary diffuse large B-cell lymphoma of the brain is being diagnosed with increasing frequency. Other unusual subtypes of diffuse large B-cell lymphoma such as pleural effusion lymphoma and intravascular lymphoma have been difficult to diagnose and associated with a very poor prognosis.

Table 16-11 shows the initial evaluation of patients with diffuse large B-cell lymphoma. After a careful staging evaluation, ~50% of patients will be found to have stage I or II disease, and ~50% will have widely disseminated lymphoma. Bone marrow biopsy shows involvement by lymphoma in ~15% of cases, with marrow involvement by small cells more frequent than by large cells.

TREATMENT Diffuse Large B-Cell Lymphoma

The initial treatment of all patients with diffuse large B-cell lymphoma should be with a combination chemotherapy regimen. The most popular regimen in the United States is CHOP plus rituximab, although a variety of other anthracycline-containing combination chemotherapy regimens appear to be equally efficacious. Patients with stage I or nonbulky stage II disease can be effectively treated with three to four cycles of combination chemotherapy with or without subsequent involved-field radiotherapy. The need for radiation therapy is unclear. Cure rates of 70–80% in stage II disease and 85–90% in stage I disease can be expected.

For patients with bulky stage II, stage III, or stage IV disease, six to eight cycles of CHOP plus rituximab are usually administered. A large randomized trial showed the superiority of CHOP combined with rituximab over CHOP alone in elderly patients. A frequent approach would be to administer four cycles of therapy and then reevaluate. If the patient has achieved a complete remission after four cycles, two more cycles of treatment might be given and then therapy discontinued. Using this approach, 70–80% of patients can be expected to achieve a complete remission, and 50–70% of complete responders will be cured. The chances for a favorable response to treatment are predicted by the IPI. In fact, the IPI was developed based on the outcome of patients with diffuse large B-cell lymphoma treated with CHOP-like regimens. For the 35% of patients with a low IPI score of 0–1, the 5-year survival is >70%, whereas for the 20% of patients

with a high IPI score of 4–5, the 5-year survival is ~20%. T e addition of rituximab to CHOP has improved each of those numbers by ~15%. A number of other factors, including molecular features of the tumor, levels of circulating cytokines and soluble receptors, and other surrogate markers, have been shown to influence prognosis. However, they have not been validated as rigorously as the IPI and have not been uniformly applied clinically.

Because a number of patients with diffuse large B-cell lymphoma are either initially refractory to therapy or relapse after apparently effective chemotherapy, 30–40% of patients will be candidates for salvage treatment at some point. Alternative combination chemotherapy regimens can induce complete remission in as many as 50% of these patients, but long-term disease-free survival is seen in ≤10%. Autologous bone marrow transplantation is superior to salvage chemotherapy at usual doses and leads to long-term disease-free survival in ~40% of patients whose lymphomas remain chemotherapy-sensitive after relapse.

Burkitt's lymphoma/leukemia

Burkitt's lymphoma/leukemia is a rare disease in adults in the United States, making up <1% of non-Hodgkin's lymphomas, but it makes up ~30% of childhood non-Hodgkin's lymphoma. Burkitt's leukemia, or L3 ALL, makes up a small proportion of childhood and adult acute leukemias. Table 16-10 shows the clinical features of Burkitt's lymphoma.

Burkitt's lymphoma can be diagnosed morphologically by an expert hematopathologist with a high degree of accuracy. T e cells are homogeneous in size and shape **(Fig. 16-9)**. Demonstration of a very high proliferative fraction and the presence of the t(8;14) or one of its variants, t(2;8) (c-myc and the λ light chain gene) or t(8;22) (c-myc and the κ light chain gene), can be confirmatory. Burkitt's cell leukemia is recognized by the typical monotonous mass of medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm with cytoplasmic vacuoles. Demonstration of surface expression of immunoglobulin and one of the above-noted cytogenetic abnormalities is confirmatory.

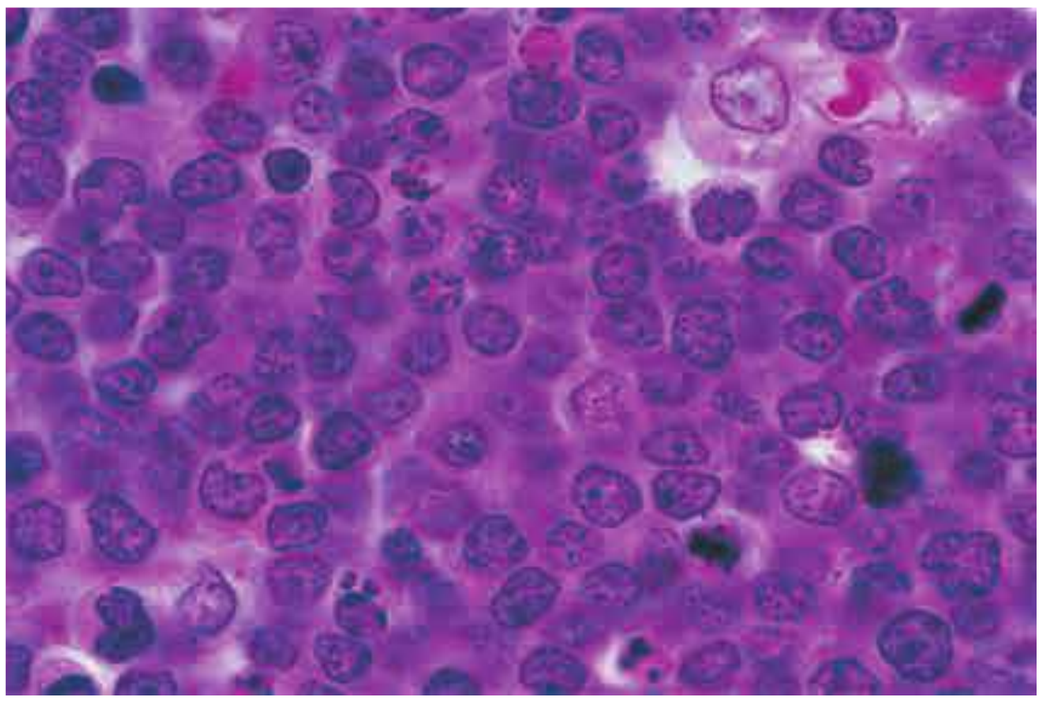


FIGURE 16-9
Burkitt's lymphoma. The neoplastic cells are homogeneous, medium-sized B cells with frequent mitotic figures, a morphologic correlate of high growth fraction. Reactive macrophages are scattered through the tumor, and their pale cytoplasm in a background of blue-staining tumor cells gives the tumor a so-called starry sky appearance.

T ree distinct clinical forms of Burkitt's lymphoma are recognized: endemic, sporadic, and immunodeficiency-associated. Endemic and sporadic Burkitt's lymphomas occur frequently in children in Africa, and the sporadic form occurs in Western countries. Immunodeficiency-associated Burkitt's lymphoma is seen in patients with HIV infection.

Pathologists sometimes have dif culty distinguishing between Burkitt's lymphoma and diffuse large B-cell lymphoma. In the past, a separate subgroup of non-Hodgkin's lymphoma intermediate between the two was recognized. When tested, this subgroup could not be diagnosed accurately. Distinction between the two major types of B-cell aggressive non-Hodgkin's lymphoma can sometimes be made based on the extremely high proliferative fraction seen in patients with Burkitt's lymphoma (i.e., essentially 100% of tumor cells are in cycle) caused by c-myc deregulation.

Most patients in the United States with Burkitt's lymphoma present with peripheral lymphadenopathy or an intraabdominal mass. T e disease is rapidly progressive and has a propensity to metastasize to the CNS. Initial evaluation should always include an examination of cerebrospinal fluid to rule out metastasis in addition to the other staging evaluations noted in Table 16-11. Once the diagnosis of Burkitt's lymphoma is suspected, a diagnosis must be made promptly, and staging evaluation must be accomplished expeditiously. T is is the most rapidly progressive human tumor, and any delay in initiating therapy can adversely affect the patient's prognosis.

TREATMENT Burkitt's Lymphoma

Treatment of Burkitt's lymphoma in both children and adults should begin within 48 h of diagnosis and involves the use of intensive combination chemotherapy regimens incorporating high doses of cyclophosphamide. Prophylactic therapy to the CNS is mandatory. Burkitt's lymphoma was one of the first cancers shown to be curable by chemotherapy. Today, cure can be expected in 70–80% of both children and young adults when effective therapy is administered precisely. Salvage therapy has been generally ineffective in patients in whom the initial treatment fails, emphasizing the importance of the initial treatment approach.

Other B-cell lymphoid malignancies

B-cell prolymphocytic leukemia involves blood and marrow infiltration by large lymphocytes with prominent nucleoli. Patients typically have a high white cell count, splenomegaly, and minimal lymphadenopathy. The chances for a complete response to therapy are poor.

Hairy cell leukemia is a rare disease that presents predominantly in older males. Typical presentation involves pancytopenia, although occasional patients will have a leukemic presentation. Splenomegaly is usual. The malignant cells appear to have "hairy" projections on light and electron microscopy and show a characteristic staining pattern with tartrate-resistant acid phosphatase. Bone marrow is typically not able to be aspirated, and biopsy shows a pattern of fibrosis with diffuse infiltration by the malignant cells. Patients with this disorder have monocytopenia and are prone to unusual infections, including infection by Mycobacterium avium intracellulare, and to vasculitic syndromes. Hairy cell leukemia is responsive to chemotherapy with interferon α, pentostatin, or cladribine, with the latter being the usually preferred treatment. Clinical complete remissions with cladribine occur in the majority of patients, and long-term disease-free survival is frequent. Many of these tumors have the V600E BRAF mutation and accordingly are responsive to BRAF inhibitors like vemurafenib.

Splenic marginal zone lymphoma involves infiltration of the splenic white pulp by small, monoclonal B cells. This is a rare disorder that can present as leukemia as well as lymphoma. Definitive diagnosis is often made at splenectomy, which is also an effective therapy. This is an extremely indolent disorder, but when chemotherapy is required, the most usual treatment has been chlorambucil.

Lymphoplasmacytic lymphoma is the tissue manifestation of Waldenström's macroglobulinemia **(Chap. 18)**. Many of these tumors harbor a specific mutation, L265P, in MYD88, a change that leads to NF-κB activation. This type of lymphoma has been associated with chronic hepatitis C virus infection, and an etiologic association has been proposed. Patients typically present with lymphadenopathy, splenomegaly, bone marrow involvement, and occasionally peripheral blood involvement. The tumor cells do not express CD5. Patients often have a monoclonal IgM protein, high levels of which can dominate the clinical picture with the symptoms of hyperviscosity. Treatment of lymphoplasmacytic lymphoma can be aimed primarily at reducing the abnormal protein, if present, but will usually also involve chemotherapy. Chlorambucil, fludarabine, and cladribine have been used. The median 5-year survival for patients with this disorder is ~60%.

Nodal marginal zone lymphoma, also known as monocytoid cell lymphoma, represents ~1% of non-Hodgkin's lymphomas. This lymphoma has a slight female predominance and presents with disseminated disease (i.e., stage III or IV) in 75% of patients. Approximately one-third of patients have bone marrow involvement, and a leukemic presentation occasionally occurs. The staging evaluation and therapy should use the same approach as used for patients with follicular lymphoma. Approximately 60% of the patients with nodal marginal zone lymphoma will survive 5 years after diagnosis.

Other more uncommon B-cell malignancies are discussed in Chap. 17.

PRECURSOR T-CELL MALIGNANCIES

Precursor T-cell lymphoblastic leukemia/lymphoma

Precursor T-cell malignancies can present either as ALL or as an aggressive lymphoma. These malignancies are more common in children and young adults, with males more frequently affected than females.

Precursor T-cell ALL can present with bone marrow failure, although the severity of anemia, neutropenia, and thrombocytopenia is often less than in precursor B-cell ALL. These patients sometimes have very high white cell counts, a mediastinal mass, lymphadenopathy, and hepatosplenomegaly. Precursor T-cell lymphoblastic lymphoma is most often found in young men presenting with a large mediastinal mass and pleural effusions. Both presentations have a propensity to metastasize to the CNS, and CNS involvement is often present at diagnosis.

TREATMENT Precursor T-Cell Lymphoblastic Leukemia/Lymphoma

Children with precursor T-cell ALL seem to benefit from very intensive remission induction and consolidation regimens. The majority of patients treated in this manner can be cured. Older children and young adults with precursor T-cell lymphoblastic lymphoma are also often treated with "leukemia-like" regimens. Patients who present with localized disease have an excellent prognosis. However, advanced age is an adverse prognostic factor. Adults with precursor T-cell lymphoblastic lymphoma who present with high LDH levels or bone marrow or CNS involvement are often offered bone marrow transplantation as part of their primary therapy.

MATURE (PERIPHERAL) T-CELL DISORDERS

Mycosis fungoides

Mycosis fungoides is also known as cutaneous T-cell lymphoma. This lymphoma is more often seen by dermatologists than internists. The median age of onset is in the mid-fifties, and the disease is more common in males and in blacks.

Mycosis fungoides is an indolent lymphoma with patients often having several years of eczematous or dermatitic skin lesions before the diagnosis is finally established. T e skin lesions progress from patch stage to plaque stage to cutaneous tumors. Early in the disease, biopsies are often dif cult to interpret, and the diagnosis may only become apparent by observing the patient over time. In advanced stages, the lymphoma can spread to lymph nodes and visceral organs. Patients with this lymphoma may develop generalized erythroderma and circulating tumor cells, called Sézary's syndrome.

Rare patients with localized early-stage mycosis fungoides can be cured with radiotherapy, often total-skin electron beam irradiation. More advanced disease has been treated with topical glucocorticoids, topical nitrogen mustard, phototherapy, psoralen with ultraviolet A (PUVA), extracorporeal photopheresis, retinoids (bexarotene), electron beam radiation, interferon, antibodies, fusion toxins, histone deacetylase inhibitors, and systemic cytotoxic therapy. Unfortunately, these treatments are palliative.

Adult T-cell lymphoma/leukemia

Adult T-cell lymphoma/leukemia is one manifestation of infection by the HTLV-1 retrovirus. Patients can be infected through transplacental transmission, mother's milk, blood transfusion, and by sexual transmission of the virus. Patients who acquire the virus from their mother through breast milk are most likely to develop lymphoma, but the risk is still only 2.5% and the latency averages 55 years. Nationwide testing for HTLV-1 antibodies and the aggressive implementation of public health measures could theoretically lead to the disappearance of adult T-cell lymphoma/leukemia. Tropical spastic paraparesis, another manifestation of HTLV-1 infection, occurs after a shorter latency (1–3 years) and is most common in individuals who acquire the virus during adulthood from transfusion or sex.

T e diagnosis of adult T-cell lymphoma/leukemia is made when an expert hematopathologist recognizes the typical morphologic picture, a T-cell immunophenotype (i.e., CD4 positive), and the presence in serum of antibodies to HTLV-1. Examination of the peripheral blood will usually reveal characteristic, pleomorphic abnormal CD4-positive cells with indented nuclei, which have been called "flower" cells **(Fig. 16-10)**.

A subset of patients have a smoldering clinical course and long survival, but most patients present with an aggressive disease manifested by lymphadenopathy, hepatosplenomegaly, skin infiltration, pulmonary infiltrates, hypercalcemia, lytic bone lesions, and elevated LDH levels. T e skin lesions can be papules, plaques, tumors, and ulcerations. Lung lesions can be either tumor or opportunistic infection in light of the underlying immunodeficiency in the disease. Bone marrow involvement is not usually extensive, and anemia and thrombocytopenia are not usually prominent. Although treatment with combination chemotherapy regimens can result in objective responses, true complete remissions are unusual, and the median survival of patients is ~7 months. A small phase II study reported a high response rate with interferon plus zidovudine and arsenic trioxide.

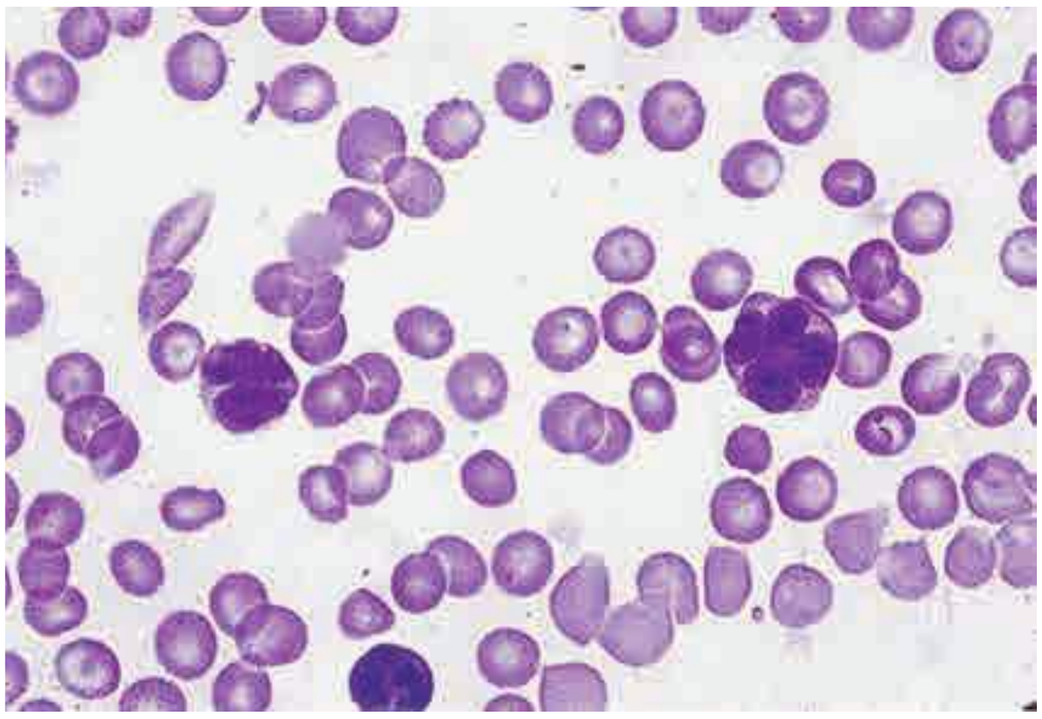


FIGURE 16-10
Adult T-cell leukemia/lymphoma. Peripheral blood smear showing leukemia cells with typical "flower-shaped" nucleus.

Anaplastic large T/null-cell lymphoma

Anaplastic large T/null-cell lymphoma was previously usually diagnosed as undifferentiated carcinoma or malignant histiocytosis. Discovery of the CD30 (Ki-1) antigen and the recognition that some patients with previously unclassified malignancies displayed this antigen led to the identification of a new type of lymphoma. Subsequently, discovery of the t(2;5) and the resultant frequent overexpression of the anaplastic lymphoma kinase (ALK) protein confirmed the existence of this entity. T is lymphoma accounts for ~2% of all non-Hodgkin's lymphomas. Table 16-10 shows the clinical characteristics of patients with anaplastic large T/null cell lymphoma.

T e diagnosis of anaplastic large T/null-cell lymphoma is made when an expert hematopathologist recognizes the typical morphologic picture and a T-cell or null-cell immunophenotype with CD30 positivity. Documentation of the t(2;5) and/or overexpression of ALK protein confirm the diagnosis. Some diffuse large B-cell lymphomas can also have an anaplastic appearance but have the same clinical course or response to therapy as other diffuse large B-cell lymphomas. A small percentage of anaplastic lymphomas are ALK negative.

Patients with anaplastic large T/null-cell lymphoma are typically young (median age, 33 years) and male (~70%). Some 50% of patients present in stage I/II, and

the remainder present with more extensive disease. Systemic symptoms and elevated LDH levels are seen in about one-half of patients. Bone marrow and the gastrointestinal tract are rarely involved, but skin involvement is frequent. Some patients with disease confined to the skin have a different and more indolent disorder that has been termed cutaneous anaplastic large T/null-cell lymphoma and might be related to lymphomatoid papulosis.

TREATMENT Anaplastic Large T/Null-Cell Lymphoma

Treatment regimens appropriate for other aggressive lymphomas, such as diffuse large B-cell lymphoma, should be used in patients with anaplastic large T/null-cell lymphoma, with the exception that the B-cell–specific antibody, rituximab, is omitted. Surprisingly, given the anaplastic appearance, this disorder has the best survival rate of any aggressive lymphoma. The 5-year survival is >75%. While traditional prognostic factors such as the IPI predict treatment outcome, overexpression of the ALK protein is an important prognostic factor, with patients overexpressing this protein having a superior treatment outcome. The ALK inhibitor crizotinib appears highly active as well. In addition, the CD30 immunotoxin, brentuximab vedotin, is active in the disease.

Peripheral T-cell lymphoma

The peripheral T-cell lymphomas make up a heterogeneous morphologic group of aggressive neoplasms that share a mature T-cell immunophenotype. They represent ~7% of all cases of non-Hodgkin's lymphoma. A number of distinct clinical syndromes are included in this group of disorders. Table 16-10 shows the clinical characteristics of patients with peripheral T-cell lymphoma.

The diagnosis of peripheral T-cell lymphoma, or any of its specific subtypes, requires an expert hematopathologist, an adequate biopsy, and immunophenotyping. Most peripheral T-cell lymphomas are CD4+, but a few will be CD8+, both CD4+ and CD8+, or have an NK cell immunophenotype. No characteristic genetic abnormalities have yet been identified, but translocations involving the T-cell antigen receptor genes on chromosomes 7 or 14 may be detected. The differential diagnosis of patients suspected of having peripheral T-cell lymphoma includes reactive T-cell infiltrative processes. In some cases, demonstration of a monoclonal T-cell population using T-cell receptor gene rearrangement studies will be required to make a diagnosis.

The initial evaluation of a patient with a peripheral T-cell lymphoma should include the studies in Table 16-11 for staging patients with non-Hodgkin's lymphoma. Unfortunately, patients with peripheral T-cell lymphoma usually present with adverse prognostic factors, with >80% of patients having an IPI score ≥2 and >30% having an IPI score ≥4. As this would predict, peripheral T-cell lymphomas are associated with a poor outcome, and only 25% of the patients survive 5 years after diagnosis. Treatment regimens are the same as those used for diffuse large B-cell lymphoma (omitting rituximab), but patients with peripheral T-cell lymphoma have a poorer response to treatment. Because of this poor treatment outcome, hematopoietic stem cell transplantation is often considered early in the care of young patients.

A number of specific clinical syndromes are seen in the peripheral T-cell lymphomas. Angioimmunoblastic T-cell lymphoma is one of the more common subtypes, making up ~20% of T-cell lymphomas. These patients typically present with generalized lymphadenopathy, fever, weight loss, skin rash, and polyclonal hypergammaglobulinemia. In some cases, it is difficult to separate patients with a reactive disorder from those with true lymphoma.

Extranodal T/NK-cell lymphoma of nasal type has also been called angiocentric lymphoma and was previously termed lethal midline granuloma. This disorder is more frequent in Asia and South America than in the United States and Europe. EBV is thought to play an etiologic role. Although most frequent in the upper airway, it can involve other organs. The course is aggressive, and patients frequently have the hemophagocytic syndrome. When marrow and blood involvement occur, distinction between this disease and leukemia might be difficult. Some patients will respond to aggressive combination chemotherapy regimens, but the overall outlook is poor.

Enteropathy-type intestinal T-cell lymphoma is a rare disorder that occurs in patients with untreated gluten-sensitive enteropathy. Patients are frequently wasted and sometimes present with intestinal perforation. The prognosis is poor. Hepatosplenic γδ T-cell lymphoma is a systemic illness that presents with sinusoidal infiltration of the liver, spleen, and bone marrow by malignant T cells. Tumor masses generally do not occur. The disease is associated with systemic symptoms and is often difficult to diagnose. Treatment outcome is poor. Subcutaneous panniculitis-like T-cell lymphoma is a rare disorder that is often confused with panniculitis. Patients present with multiple subcutaneous nodules, which progress and can ulcerate. Hemophagocytic syndrome is common. Response to therapy is poor. The development of the hemophagocytic syndrome (profound anemia, ingestion of erythrocytes by monocytes and macrophages, elevated ferritin levels) in the course of any peripheral T-cell lymphoma is generally associated with a fatal outcome.

HODGKIN'S LYMPHOMA

Classical hodgkin's lymphoma

Hodgkin's lymphoma occurs in 9000 patients in the United States each year, and the disease does not appear to be increasing in frequency. Most patients present with palpable lymphadenopathy that is nontender; in most patients, these lymph nodes are in the neck, supraclavicular area, and axilla. More than half the patients will have mediastinal adenopathy at diagnosis, and this is sometimes the initial manifestation. Subdiaphragmatic presentation of Hodgkin's lymphoma is unusual and more common in older males. One-third of patients present with fevers, night sweats, and/or weight loss—B symptoms in the Ann Arbor staging classification (Table 16-8). Occasionally, Hodgkin's lymphoma can present as a fever of unknown origin. T is is more common in older patients who are found to have mixed-cellularity Hodgkin's lymphoma in an abdominal site. Rarely, the fevers persist for days to weeks, followed by afebrile intervals and then recurrence of the fever. T is pattern is known as Pel-Ebstein fever. Hodgkin's lymphoma can occasionally present with unusual manifestations. T ese include severe and unexplained itching, cutaneous disorders such as erythema nodosum and ichthyosiform atrophy, paraneoplastic cerebellar degeneration and other distant effects on the CNS, nephrotic syndrome, immune hemolytic anemia and thrombocytopenia, hypercalcemia, and pain in lymph nodes on alcohol ingestion.

T e diagnosis of Hodgkin's lymphoma is established by review of an adequate biopsy specimen by an expert hematopathologist. In the United States, most patients have nodular sclerosing Hodgkin's lymphoma, with a minority of patients having mixed-cellularity Hodgkin's lymphoma. Lymphocyte-predominant and lymphocyte-depleted Hodgkin's lymphoma are rare. Mixed-cellularity Hodgkin's lymphoma or lymphocyte-depletion Hodgkin's lymphoma are seen more frequently in patients infected by HIV **(Fig. 16-11)**. Hodgkin's lymphoma is a tumor characterized by rare neoplastic cells of B-cell origin (immunoglobulin genes are rearranged but not expressed) in a tumor mass that is largely polyclonal inflammatory infiltrate, probably a reaction to cytokines produced by the tumor cells. T e differential diagnosis of a lymph node biopsy suspicious for Hodgkin's lymphoma includes inflammatory processes, mononucleosis, non-Hodgkin's lymphoma, phenytoin-induced adenopathy, and nonlymphomatous malignancies.

T e staging evaluation for a patient with Hodgkin's lymphoma would typically include a careful history and physical examination; complete blood count; erythrocyte sedimentation rate; serum chemistry studies including LDH; chest radiograph; CT scan of the chest, abdomen, and pelvis; and bone marrow biopsy. Many patients would also have a PET scan or a gallium scan. Although rarely used, a bipedal lymphangiogram can be helpful. PET and gallium scans are most useful to document remission. Staging laparotomies were once popular for most patients with Hodgkin's lymphoma but are now done rarely because of an increased reliance on systemic rather than local therapy.

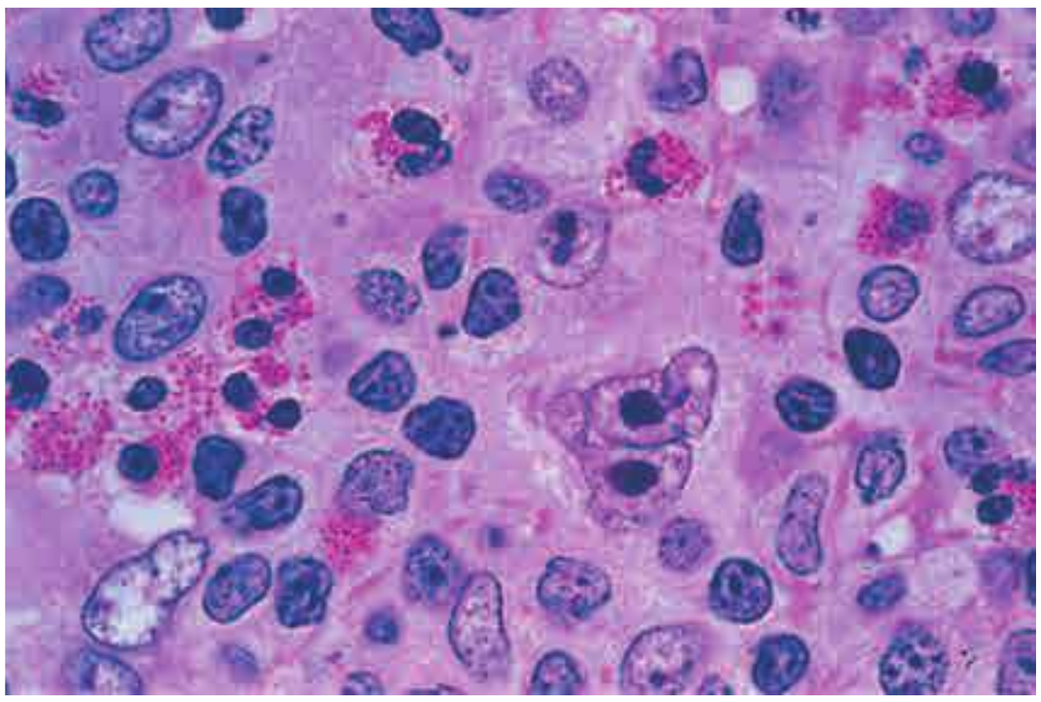


FIGURE 16-11
Mixed-cellularity Hodgkin's lymphoma. A Reed-Sternberg cell is present near the center of the field; a large cell with a bilobed nucleus and prominent nucleoli giving an "owl's eyes" appearance. The majority of the cells are normal lymphocytes, neutrophils, and eosinophils that form a pleomorphic cellular infiltrate.

TREATMENT Classical Hodgkin's Lymphoma

Patients with localized Hodgkin's lymphoma are cured >90% of the time. In patients with good prognostic factors, extended-field radiotherapy has a high cure rate. Increasingly, patients with all stages of Hodgkin's lymphoma are treated initially with chemotherapy. Patients with localized or good-prognosis disease receive a brief course of chemotherapy followed by radiotherapy to sites of node involvement. Patients with more extensive disease or those with B symptoms receive a complete course of chemotherapy. T e most popular chemotherapy regimen used in Hodgkin's lymphoma is a combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Today, most patients in the United States receive ABVD, but a weekly chemotherapy regimen administered for 12 weeks called Stanford V is becoming increasingly popular, but it includes radiation therapy, which has been associated with life-threatening late toxicities such as premature coronary artery disease and second solid tumors. In Europe, a high-dose regimen called BEACOPP incorporating alkylating agents has become popular and might have a better response rate in very-high-risk patients. Long-term disease-free survival in patients with advanced disease can be achieved in >75% of patients who

lack systemic symptoms and in 60–70% of patients with systemic symptoms.

Patients who relapse after primary therapy of Hodgkin's lymphoma can frequently still be cured. Patients who relapse after initial treatment with only radiotherapy have an excellent outcome when treated with chemotherapy. Patients who relapse after an effective chemotherapy regimen are usually not curable with subsequent chemotherapy administered at standard doses. However, patients with a long initial remission can be an exception to this rule. Autologous bone marrow transplantation can cure half of patients in whom effective chemotherapy regimens fail to induce durable remissions. T e immunotoxin, brentuximab vedotin, a CD30-directed chemotherapy that selectively targets cells expressing CD30, is active in the salvage setting and is being integrated into ABVD for initial treatment.

Because of the very high cure rate in patients with Hodgkin's lymphoma, long-term complications have become a major focus for clinical research. In fact, in some series of patients with early-stage disease, more patients died from late complications of therapy than from Hodgkin's lymphoma itself. T is is particularly true in patients with localized disease. T e most serious late side effects include second malignancies and cardiac injury. Patients are at risk for the development of acute leukemia in the first 10 years after treatment with combination chemotherapy regimens that contain alkylating agents plus radiation therapy. T e risk for development of acute leukemia appears to be greater after MOPP-like (mechlorethamine, vincristine, procarbazine, prednisone) regimens than with ABVD. T e risk of development of acute leukemia after treatment for Hodgkin's lymphoma is also related to the number of exposures to potentially leukemogenic agents (i.e., multiple treatments after relapse) and the age of the patient being treated, with those age >60 years at particularly high risk. T e development of carcinomas as a complication of treatment for Hodgkin's lymphoma has become a major problem. T ese tumors usually occur ≥10 years after treatment and are associated with use of radiotherapy. For this reason, young women treated with thoracic radiotherapy for Hodgkin's lymphoma should institute screening mammograms 5–10 years after treatment, and all patients who receive thoracic radiotherapy for Hodgkin's lymphoma should be discouraged from smoking. T oracic radiation also accelerates coronary artery disease, and patients should be encouraged to minimize risk factors for coronary artery disease such as smoking and elevated cholesterol levels. Cervical radiation therapy increases the risk of carotid atherosclerosis and stroke.

A number of other late side effects from the treatment of Hodgkin's lymphoma are well known. Patients who receive thoracic radiotherapy are at very high risk for the eventual development of hypothyroidism and should be observed for this complication; intermittent measurement of thyrotropin should be made to identify the condition before it becomes symptomatic. Lhermitte's syndrome occurs in ~15% of patients who receive thoracic radiotherapy. T is syndrome is manifested by an "electric shock" sensation into the lower extremities on flexion of the neck. Infertility is a concern for all patients undergoing treatment for Hodgkin's lymphoma. In both women and men, the risk of permanent infertility is age-related, with younger patients more likely to recover fertility. In addition, treatment with ABVD increases the chances to retain fertility.

Nodular lymphocyte-predominant Hodgkin's lymphoma

Nodular lymphocyte-predominant Hodgkin's lymphoma is now recognized as an entity distinct from classical Hodgkin's lymphoma. Previous classification systems recognized that biopsies from a subset of patients diagnosed as having Hodgkin's lymphoma contained a predominance of small lymphocytes and rare Reed-Sternberg cells (Fig. 16-11). A subset of these patients have tumors with nodular growth pattern and a clinical course that varied from that of patients with classical Hodgkin's lymphoma. T is is an unusual clinical entity and represents <5% of cases of Hodgkin's lymphoma.

Nodular lymphocyte-predominant Hodgkin's lymphoma has a number of characteristics that suggest its relationship to non-Hodgkin's lymphoma. T ese include a clonal proliferation of B cells and a distinctive immunophenotype; tumor cells express J chain and display CD45 and epithelial membrane antigen (EMA) and do not express two markers normally found on Reed-Sternberg cells, CD30 and CD15. T is lymphoma tends to have a chronic, relapsing course and sometimes transforms to diffuse large B-cell lymphoma.

T e treatment of patients with nodular lymphocyte-predominant Hodgkin's lymphoma is controversial. Some clinicians favor no treatment and merely close follow-up. In the United States, most physicians will treat localized disease with radiotherapy and disseminated disease with regimens used for patients with classical Hodgkin's lymphoma. Regardless of the therapy used, most series report a long-term survival of >80%.

LYMPHOMA-LIKE DISORDERS

T e most common condition that pathologists and clinicians might confuse with lymphoma is reactive, atypical lymphoid hyperplasia. Patients might have localized or disseminated lymphadenopathy and might have the systemic symptoms characteristic of lymphoma. Underlying causes include a drug reaction to phenytoin or carbamazepine. Immune disorders such as rheumatoid arthritis and lupus erythematosus, viral infections such as cytomegalovirus and EBV, and bacterial infections

such as cat-scratch disease may cause adenopathy **(Chap. 4)**. In the absence of a definitive diagnosis after initial biopsy, continued follow-up, further testing, and repeated biopsies, if necessary, constitute the appropriate approach, rather than instituting therapy.

Specific conditions that can be confused with lymphoma include Castleman's disease, which can present with localized or disseminated lymphadenopathy; some patients have systemic symptoms. T e disseminated form is often accompanied by anemia and polyclonal hypergammaglobulinemia, and the condition has been associated with overproduction of interleukin 6 (IL-6), in some cases produced by human herpesvirus 8 infection. Patients with localized disease can be treated effectively with local therapy, whereas the initial treatment for patients with disseminated disease is usually with systemic glucocorticoids. IL-6-directed therapy (tocilizumab) has produced short-term responses. Rituximab appears to produce longer remissions than tocilizumab.

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) usually presents with bulky lymphadenopathy in children or young adults. T e disease is usually nonprogressive and self-limited, but patients can manifest autoimmune hemolytic anemia.

Lymphomatoid papulosis is a cutaneous lymphoproliferative disorder that is often confused with anaplastic large cell lymphoma involving the skin. T e cells of lymphomatoid papulosis are similar to those seen in lymphoma and stain for CD30, and T-cell receptor gene rearrangements are sometimes seen. However, the condition is characterized by waxing and waning skin lesions that usually heal, leaving small scars. In the absence of effective communication between the clinician and the pathologist regarding the clinical course in the patient, this disease will be misdiagnosed. Since the clinical picture is usually benign, misdiagnosis is a serious mistake.

Acknowledgment

James Armitage was a coauthor of this chapter in prior editions, and substantial material from those editions has been included here.

CHAPTER 17

LESS COMMON HEMATOLOGIC MALIGNANCIES

Ayalew Tefferi ■ Dan L. Longo

The most common lymphoid malignancies are discussed in **Chap. 16**, myeloid leukemias in **Chaps. 14 and 15**, myelodysplastic syndromes in **Chap. 11**, and myeloproliferative syndromes in **Chap. 13**. This chapter will focus on the more unusual forms of hematologic malignancy. The diseases discussed here are listed in **Table 17-1**. Each of these entities accounts for less than 1% of hematologic neoplasms.

LYMPHOID MALIGNANCIES

Precursor B-cell and precursor T-cell neoplasms are discussed in **Chap. 16**. All the lymphoid tumors discussed here are mature B cell or T cell, natural killer (NK) cell neoplasms.

MATURE B-CELL NEOPLASMS

B-cell prolymphocytic leukemia (B-PLL)

This is a malignancy of medium-sized (about twice the size of a normal small lymphocyte), round lymphocytes with a prominent nucleolus and light blue cytoplasm on Wright's stain. It dominantly affects the blood, bone marrow, and spleen and usually does not cause adenopathy. The median age of affected patients is 70 years, and men are more often affected than women (male-to-female ratio is 1.6). This entity is distinct from chronic lymphoid leukemia (CLL) and does not develop as a consequence of that disease.

Clinical presentation is generally from symptoms of splenomegaly or incidental detection of an elevated white blood cell (WBC) count. The clinical course can be rapid. The cells express surface IgM (with or without IgD) and typical B-cell markers (CD19, CD20, CD22). CD23 is absent, and about one-third of cases express CD5. The CD5 expression along with the presence of the t(11;14) translocation in 20% of cases leads to confusion in distinguishing B-PLL from the leukemic form of mantle cell lymphoma. No reliable criteria for the distinction have emerged. About half of patients have mutation or loss of p53, and deletions have been noted in 11q23 and 13q14. Nucleoside analogues like fludarabine and cladribine and combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) have produced responses. CHOP plus rituximab may be more effective than CHOP alone, but the disease is sufficiently rare that large series have not been reported. Splenectomy can produce palliation of symptoms but appears to have little or no impact on the course of the disease.

Splenic marginal zone lymphoma (SMZL)

This tumor of mainly small lymphocytes originates in the marginal zone of the spleen white pulp, grows to efface the germinal centers and mantle, and invades the red pulp. Splenic hilar nodes, bone marrow, and peripheral blood may be involved. The circulating tumor cells have short surface villi and are called villous lymphocytes. **Table 17-2** shows differences in tumor cells of a number of neoplasms of small lymphocytes that aid in the differential diagnosis. SMZL cells express surface immunoglobulin and CD20, but are negative for CD5, CD10, CD43, and CD103. Lack of CD5 distinguishes SMZL from CLL, and lack of CD103 separates SMZL from hairy cell leukemia.

The median age of patients with SMZL is mid-fifties, and men and women are equally represented. Patients present with incidental or symptomatic splenomegaly or incidental detection of lymphocytosis in the peripheral blood with villous lymphocytes. Autoimmune anemia or thrombocytopenia may be present. The immunoglobulin produced by these cells contains somatic mutations that reflect transit through a germinal center, and ongoing mutations suggest that the mutation machinery has remained active. About

TABLE 17-1

UNUSUAL LYMPHOID AND MYELOID MALIGNANCIES
Lymphoid
Mature B-cell neoplasms
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Nodal marginal zone B-cell lymphoma
Mediastinal large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary effusion lymphoma
Lymphomatoid granulomatosis
Mature T-cell and natural killer (NK) cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Aggressive NK cell leukemia
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Blastic NK cell lymphoma
Primary cutaneous CD30+ T-cell lymphoma
Angioimmunoblastic T-cell lymphoma
Myeloid
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia/hypereosinophilic syndrome
Histiocytic and Dendritic Cell Neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Mast Cells
Mastocytosis
Cutaneous mastocytosis
Systemic mastocytosis
Mast cell sarcoma
Extracutaneous mastocytoma

40% of patients have either deletions or translocations involving 7q21, the site of the FLNC gene (filamin Cγ, involved in cross-linking actin filaments in the cytoplasm). NOTCH2 mutations are seen in 25% of patients. Chromosome 8p deletions may also be noted. The genetic lesions typically found in extranodal marginal zone lymphomas [e.g., trisomy 3 and t(11;18)] are uncommon in SMZL.

The clinical course of disease is generally indolent with median survivals exceeding 10 years. Patients with elevated lactate dehydrogenase (LDH) levels, anemia, and hypoalbuminemia generally have a poorer prognosis. Long remissions can be seen after splenectomy. Rituximab is also active. A small fraction of patients undergo histologic progression to diffuse large B-cell lymphoma with a concomitant change to a more aggressive natural history. Experience with combination chemotherapy in SMZL is limited.

Hairy cell leukemia

Hairy cell leukemia is a tumor of small lymphocytes with oval nuclei, abundant cytoplasm, and distinctive membrane projections (hairy cells). Patients have splenomegaly and diffuse bone marrow involvement. While some circulating cells are noted, the clinical picture is dominated by symptoms from the enlarged spleen and pancytopenia. The mechanism of the pancytopenia is not completely clear and may be mediated by both inhibitory cytokines and marrow replacement. The marrow has an increased level of reticulin fibers; indeed, hairy cell leukemia is a common cause of inability to aspirate bone marrow or so-called "dry tap" **(Table 17-3)**. Monocytopenia is profound and may explain a predisposition to atypical mycobacterial infection that is observed clinically. The tumor cells have strong expression of CD22, CD25, and CD103; soluble CD25 level in serum is an excellent tumor marker for disease activity. The cells also express tartrate-resistant acid phosphatase. The immunoglobulin genes are rearranged and mutated, indicating the influence of a

TABLE 17-2

IMMUNOPHENOTYPE OF TUMORS OF SMALL LYMPHOCYTES							
	CD5	CD20	CD43	CD10	CD103	SIG	CYCLIND1
Follicular lymphoma	neg	pos	pos	pos	neg	pos	neg
Chronic lymphoid leukemia	pos	pos	pos	neg	neg	pos	neg
B-cell prolymphocytic leukemia	pos	pos	pos	neg	neg	pos	pos
Mantle cell lymphoma	pos	pos	pos	neg	neg	pos	pos
Splenic marginal zone lymphoma	neg	pos	neg	neg	neg	pos	neg
Hairy cell leukemia	neg	pos	?	neg	pos	pos	neg

Abbreviations: neg, negative; pos, positive.

TABLE 17-3

DIFFERENTIAL DIAGNOSIS OF "DRY TAP"—INABILITY TO ASPIRATE BONE MARROW

Dry taps occur in about 4% of attempts and are associated with:

Metastatic carcinoma infiltration	17%
Chronic myeloid leukemia	15%
Myelofibrosis	14%
Hairy cell leukemia	10%
Acute leukemia	10%
Lymphomas, Hodgkin's disease	9%
Normal marrow	Rare

germinal center. No specific cytogenetic abnormality has been found, but most cases contain the activating BRAF mutation V600E.

The median age of affected patients is mid-fifties, and the male-to-female ratio is 5:1. Treatment options are numerous. Splenectomy is often associated with prolonged remission. Nucleosides including cladribine and deoxycoformycin are highly active but are also associated with further immunosuppression and can increase the risk of certain opportunistic infections. However, after brief courses of these agents, patients usually obtain very durable remissions during which immune function spontaneously recovers. Interferon α is also an effective therapy but is not as effective as nucleosides. Chemotherapy-refractory patients have responded to vemurafenib, a BRAF inhibitor.

Nodal marginal zone B-cell lymphoma

This rare node-based disease bears an uncertain relationship with extranodal marginal zone lymphomas, which are often mucosa-associated and are called mucosa-associated lymphoid tissue (MALT) lymphomas, and SMZLs. Patients may have localized or generalized adenopathy. The neoplastic cell is a marginal zone B cell with monocytoid features and has been called monocytoid B-cell lymphoma in the past. Up to one-third of the patients may have extranodal involvement, and involvement of the lymph nodes can be secondary to the spread of a mucosal primary lesion. In authentic nodal primaries, the cytogenetic abnormalities associated with MALT lymphomas [trisomy 3 and t(11;18)] are very rare. The clinical course is indolent. Patients often respond to combination chemotherapy, although remissions have not been durable. Few patients have received CHOP plus rituximab, which is likely to be an effective approach to management.

Mediastinal (thymic) large B-cell lymphoma

This entity was originally considered a subset of diffuse large B-cell lymphoma; however, additional study has identified it as a distinct entity with its own characteristic clinical, genetic, and immunophenotypic features. This is a disease that can be bulky in size but usually remains confined to the mediastinum. It can be locally aggressive, including progressing to produce a superior vena cava obstruction syndrome or pericardial effusion. About one-third of patients develop pleural effusions, and 5–10% can disseminate widely to kidney, adrenal, liver, skin, and even brain. The disease affects women more often than men (male-to-female ratio is 1:2–3), and the median age is 35–40 years.

The tumor is composed of sheets of large cells with abundant cytoplasm accompanied by variable, but often abundant, fibrosis. It is distinguished from nodular sclerosing Hodgkin's disease by the paucity of normal lymphoid cells and the absence of lacunar variants of Reed-Sternberg cells. However, more than one-third of the genes that are expressed to a greater extent in primary mediastinal large B-cell lymphoma than in usual diffuse large B-cell lymphoma are also overexpressed in Hodgkin's disease, suggesting a possible pathogenetic relationship between the two entities that affect the same anatomic site. Tumor cells may overexpress MAL. The genome of tumor cells is characterized by frequent chromosomal gains and losses. The tumor cells in mediastinal large B-cell lymphoma express CD20, but surface immunoglobulin and HLA class I and class II molecules may be absent or incompletely expressed. Expression of lower levels of class II HLA identifies a subset with poorer prognosis. The cells are CD5 and CD10 negative but may show light staining with anti-CD30. The cells are CD45 positive, unlike cells of classical Hodgkin's disease.

Methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) and rituximab plus CHOP are effective treatments, achieving 5-year survival of 75–87%. Dose-adjusted therapy with prednisone, etoposide, vincristine, cyclophosphamide, and doxorubicin (EPOCH) plus rituximab has produced 5-year survival of 97%. A role for mediastinal radiation therapy has not been definitively demonstrated, but it is frequently used, especially in patients whose mediastinal area remains positron emission tomography–avid after four to six cycles of chemotherapy.

Intravascular large B-cell lymphoma

This is an extremely rare form of diffuse large B-cell lymphoma characterized by the presence of lymphoma in the lumen of small vessels, particularly capillaries. It is also known as malignant angioendotheliomatosis or angiotropic large cell lymphoma. It is sufficiently rare that no consistent picture has emerged to define a clinical syndrome or its epidemiologic and genetic features. It is thought to remain inside vessels because of a

defect in adhesion molecules and homing mechanisms, an idea supported by scant data suggesting absence of expression of β-1 integrin and ICAM-1. Patients commonly present with symptoms of small-vessel occlusion, skin lesions, or neurologic symptoms. The tumor cell clusters can promote thrombus formation. In general, the clinical course is aggressive and the disease is poorly responsive to therapy. Often a diagnosis is not made until very late in the course of the disease.

Primary effusion lymphoma

This entity is another variant of diffuse large B-cell lymphoma that presents with pleural effusions, usually without apparent tumor mass lesions. It is most common in the setting of immune deficiency disease, especially AIDS, and is caused by human herpes virus 8 (HHV-8)/Kaposi's sarcoma herpes virus (KSHV). It is also known as body cavity–based lymphoma. Some patients have been previously diagnosed with Kaposi's sarcoma. It can also occur in the absence of immunodeficiency in elderly men of Mediterranean heritage, similar to Kaposi's sarcoma but even less common.

The malignant effusions contain cells positive for HHV-8/KSHV, and many are also co-infected with Epstein-Barr virus. The cells are large with large nuclei and prominent nucleoli that can be confused with Reed-Sternberg cells. The cells express CD20 and CD79a (immunoglobulin-signaling molecule), although they often do not express immunoglobulin. Some cases aberrantly express T-cell markers such as CD3 or rearranged T-cell receptor genes. No characteristic genetic lesions have been reported, but gains in chromosome 12 and X material has been seen, similar to other HIV-associated lymphomas. The clinical course is generally characterized by rapid progression and death within 6 months.

Lymphomatoid granulomatosis

This is an angiocentric, angiodestructive lymphoproliferative disease comprised by neoplastic Epstein-Barr virus–infected monoclonal B cells accompanied and outnumbered by a polyclonal reactive T-cell infiltrate. The disease is graded based on histologic features such as cell number and atypia in the B cells. It is most often confused with extranodal NK–T cell lymphoma, nasal type, which can also be angiodestructive and is Epstein-Barr virus–related. The disease usually presents in adults (males > females) as a pulmonary infiltrate. Involvement is often entirely extranodal and can include kidney (32%), liver (29%), skin (25%), and brain (25%). The disease often but not always occurs in the setting of immune deficiency.

The disease can be remitting and relapsing in nature or can be rapidly progressive. The course is usually predicted by the histologic grade. The disease is highly responsive to combination chemotherapy and is curable in most cases. Some investigators have claimed that low-grade disease (grade I and II) can be treated with interferon α.

MATURE T-CELL AND NK CELL NEOPLASMS

T-cell prolymphocytic leukemia

This is an aggressive leukemia of medium-sized prolymphocytes involving the blood, marrow, nodes, liver, spleen, and skin. It accounts for 1–2% of all small lymphocytic leukemias. Most patients present with elevated WBC count (often >100,000/μL), hepatosplenomegaly, and adenopathy. Skin involvement occurs in 20%. The diagnosis is made from peripheral blood smear, which shows cells about 25% larger than those in small lymphocytes, with cytoplasmic blebs and nuclei that may be indented. The cells express T-cell markers like CD2, CD3, and CD7; two-thirds of patients have cells that are CD4+ and CD8–, and 25% have cells that are CD4+ and CD8+. T-cell receptor β chains are clonally rearranged. In 80% of patients, inversion of chromosome 14 occurs between q11 and q32. Ten percent have t(14;14) translocations that bring the T-cell receptor alpha/beta gene locus into juxtaposition with oncogenes TCL1 and TCL1b at 14q32.1. Chromosome 8 abnormalities are also common. Deletions in the ATM gene are also noted. Activating JAK3 mutations have also been reported.

The course of the disease is generally rapid, with median survival of about 12 months. Responses have been seen with the anti-CD52 antibody, nucleoside analogs, and CHOP chemotherapy. Small numbers of patients with T-cell prolymphocytic leukemia have also been treated with high-dose therapy and allogeneic bone marrow transplantation after remission has been achieved with conventional-dose therapy.

T-cell large granular lymphocytic leukemia

T-cell large granular lymphocytic leukemia (LGL leukemia) is characterized by increases in the number of LGLs in the peripheral blood (2000–20,000/μL) often accompanied by severe neutropenia, with or without concomitant anemia. Patients may have splenomegaly and frequently have evidence of systemic autoimmune disease, including rheumatoid arthritis, hypergammaglobulinemia, autoantibodies, and circulating immune complexes. Bone marrow involvement is mainly interstitial in pattern, with fewer than 50% lymphocytes on differential count. Usually the cells express CD3, T-cell receptors, and CD8; NK-like variants may be CD3–. The leukemic cells often express Fas and Fas ligand.

The course of the disease is generally indolent and dominated by the neutropenia. Paradoxically,

immunosuppressive therapy with cyclosporine, methotrexate, or cyclophosphamide plus glucocorticoids can produce an increase in granulocyte counts. Nucleosides have been used anecdotally. Occasionally the disease can accelerate to a more aggressive clinical course.

Aggressive NK cell leukemia

NK neoplasms are very rare, and they may follow a range of clinical courses from very indolent to highly aggressive. They are more common in Asians than whites, and the cells frequently harbor a clonal Epstein-Barr virus episome. The peripheral blood white count is usually not greatly elevated, but abnormal large lymphoid cells with granular cytoplasm are noted. The aggressive form is characterized by symptoms of fever and laboratory abnormalities of pancytopenia. Hepatosplenomegaly is common; node involvement is less common. Patients may have hemophagocytosis, coagulopathy, or multiorgan failure. Serum levels of Fas ligand are elevated.

The cells express CD2 and CD56 and do not have rearranged T-cell receptor genes. Deletions involving chromosome 6 are common. The disease can be rapidly progressive. Some forms of NK neoplasms are more indolent. They tend to be discovered incidentally with LGL lymphocytosis and do not manifest the fever and hepatosplenomegaly characteristic of the aggressive leukemia. The cells are also CD2 and CD56 positive, but they do not contain clonal forms of Epstein-Barr virus and are not accompanied by pancytopenia or autoimmune disease.

Extranodal NK/T-cell lymphoma, nasal type

Like lymphomatoid granulomatosis, extranodal NK/T-cell lymphoma tends to be an angiocentric and angiodestructive lesion, but the malignant cells are not B cells. In most cases, they are CD56+ Epstein-Barr virus–infected cells; occasionally they are CD56– Epstein-Barr virus–infected cytotoxic T cells. They are most commonly found in the nasal cavity. Historically, this illness was called lethal midline granuloma, polymorphic reticulosis, and angiocentric immunoproliferative lesion. This is form of lymphoma is prevalent in Asia, Mexico, and Central and South America; it affects males more commonly than females. When it spreads beyond the nasal cavity, it may affect soft tissue, the gastrointestinal tract, or the testis. In some cases, hemophagocytic syndrome may influence the clinical picture. Patients may have B symptoms. Many of the systemic manifestations of disease are related to the production of cytokines by the tumor cells and the cells responding to their signals. Deletions and inversions of chromosome 6 are common.

Many patients with extranodal NK/T-cell lymphoma, nasal type have excellent antitumor responses with combination chemotherapy regimens, particularly those with localized disease. Radiation therapy is often used after completion of chemotherapy. Four risk factors have been defined, including B symptoms, advanced stage, elevated LDH, and regional lymph node involvement. Patient survival is linked to the number of risk factors: 5-year survival is 81% for zero risk factors, 64% for one risk factor, 32% for two risk factors, and 7% for three or four risk factors. Combination regimens without anthracyclines have been touted as superior to CHOP, but data are sparse. High-dose therapy with stem cell transplantation has been used, but its role is unclear.

Enteropathy-type T-cell lymphoma

Enteropathy-type T-cell lymphoma is a rare complication of longstanding celiac disease. It most commonly occurs in the jejunum or the ileum. In adults, the lymphoma may be diagnosed at the same time as celiac disease, but the suspicion is that the celiac disease was a longstanding precursor to the development of lymphoma. The tumor usually presents as multiple ulcerating mucosal masses, but may also produce a dominant exophytic mass or multiple ulcerations. The tumor expresses CD3 and CD7 nearly always and may or may not express CD8. The normal-appearing lymphocytes in the adjacent mucosa often have a similar phenotype to the tumor. Most patients have the HLA genotype associated with celiac disease, HLA DQA1*0501 or DQB1*0201.

The prognosis of this form of lymphoma is typically (median survival is 7 months) poor, but some patients have a good response to CHOP chemotherapy. Patients who respond can develop bowel perforation from responding tumor. If the tumor responds to treatment, recurrence may develop elsewhere in the celiac disease–affected small bowel.

Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma is a malignancy derived from T cells expressing the gamma/delta T-cell antigen receptor that affects mainly the liver and fills the sinusoids with medium-size lymphoid cells. When the spleen is involved, dominantly the red pulp is infiltrated. It is a disease of young people, especially young people with an underlying immunodeficiency or with an autoimmune disease that demands immunosuppressive therapy. The use of thiopurine and infliximab is particularly common in the history of patients with this disease. The cells are CD3+ and usually CD4– and CD8–. The cells may contain isochromosome 7q, often together with trisomy 8. The lymphoma has an aggressive natural history. Combination chemotherapy may induce remissions, but most patients relapse. Median survival is about 2 years. The tumor does not appear to respond to reversal of immunosuppressive therapy.

Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma involves multiple subcutaneous collections of neoplastic T cells that are usually cytotoxic cells in phenotype (i.e., contain perforin and granzyme B and express CD3 and CD8). The rearranged T-cell receptor is usually alpha/beta-derived, but occasionally the gamma/delta receptors are involved, particularly in the setting of immunosuppression. The cells are negative for Epstein-Barr virus. Patients may have a hemophagocytic syndrome in addition to the skin infiltration; fever and hepatosplenomegaly may also be present. Nodes are generally not involved. Patients frequently respond to combination chemotherapy, including CHOP. When the disease is progressive, the hemophagocytic syndrome can be a component of a fulminant downhill course. Effective therapy can reverse the hemophagocytic syndrome.

Blastic NK cell lymphoma

The neoplastic cells express NK cell markers, especially CD56, and are CD3 negative. They are large blastic-appearing cells and may produce a leukemia picture, but the dominant site of involvement is the skin. Morphologically, the cells are similar to the neoplastic cells in acute lymphoid and myeloid leukemia. No characteristic chromosomal abnormalities have been described. The clinical course is rapid, and the disease is largely unresponsive to typical lymphoma treatments.

Primary cutaneous CD30+ T-cell lymphoma

This tumor involves the skin and is composed of cells that appear similar to the cells of anaplastic T-cell lymphoma. Among cutaneous T-cell tumors, about 25% are CD30+ anaplastic lymphomas. If dissemination to lymph nodes occurs, it is difficult to distinguish between the cutaneous and systemic forms of the disease. The tumor cells are often CD4+, and the cells contain granules that are positive for granzyme B and perforin in 70% of cases. The typical t(2;5) of anaplastic T-cell lymphoma is absent; indeed, its presence should prompt a closer look for systemic involvement and a switch to a diagnosis of anaplastic T-cell lymphoma. This form of lymphoma has sporadically been noted as a rare complication of silicone on saline breast implants. Cutaneous CD30+ T-cell lymphoma often responds to therapy. Radiation therapy can be effective, and surgery can also produce long-term disease control. Five-year survival exceeds 90%.

Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma is a systemic disease that accounts for about 15% of all T-cell lymphomas. Patients frequently have fever, advanced stage, diffuse adenopathy, hepatosplenomegaly, skin rash, polyclonal hypergammaglobulinemia, and a wide range of autoantibodies including cold agglutinins, rheumatoid factor, and circulating immune complexes. Patients may have edema, arthritis, pleural effusions, and ascites. The nodes contain a polymorphous infiltrate of neoplastic T cells and nonneoplastic inflammatory cells together with proliferation of high endothelial venules and follicular dendritic cells. The most common chromosomal abnormalities are trisomy 3, trisomy 5, and an extra X chromosome. Aggressive combination chemotherapy can induce regressions. The underlying immune defects make conventional lymphoma treatments more likely to produce infectious complications.

MYELOID MALIGNANCIES

The World Health Organization (WHO) system uses peripheral blood counts and smear analysis, bone marrow morphology, and cytogenetic and molecular genetic tests in order to classify myeloid malignancies into five major categories **(Table 17-4)**. In this chapter, we focus on chronic neutrophilic leukemia; atypical chronic myeloid leukemia, BCR-ABL1 negative; chronic myelomonocytic leukemia; juvenile myelomonocytic leukemia; chronic eosinophilic leukemia, not otherwise specified; mastocytosis; myeloproliferative neoplasm (MPN), unclassifiable (MPN-U); myelodysplastic syndrome (MDS)/MPN, unclassifiable (MDS/MPN-U); refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T); and myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1. This chapter also includes histiocytic and dendritic cell neoplasms, transient myeloproliferative disorders, and a broader discussion on primary eosinophilic disorders including hypereosinophilic syndrome (HES).

CHRONIC NEUTROPHILIC LEUKEMIA

Chronic neutrophilic leukemia (CNL) is characterized by mature neutrophilic leukocytosis with few or no circulating immature granulocytes. CNL is associated with activating mutations of the gene (CSF3R) encoding for the receptor for granulocyte colony-stimulating factor (G-CSF), also known as colony-stimulating factor 3 (CSF3). Patients with CNL might be asymptomatic at presentation but also display constitutional symptoms, splenomegaly, anemia, and thrombocytopenia. Median survival is approximately 2 years, and causes of death include leukemic transformation, progressive disease associated with severe cytopenias, and marked treatment-refractory leukocytosis. CNL is rare, with

TABLE 17-4

WORLD HEALTH ORGANIZATION CLASSIFICATION OF MYELOID MALIGNANCIES

1. Acute myeloid leukemia (AML) and related precursor neoplasms[a]
2. Myeloproliferative neoplasms (MPN)
   - 2.1. Chronic myelogenous leukemia, BCR-ABL1 positive (CML)
   - 2.2. BCR-ABL1-negative MPN
     - 2.2.1. Polycythemia vera
     - 2.2.2. Primary myelofibrosis
     - 2.2.3. Essential thrombocythemia
   - 2.3. Chronic neutrophilic leukemia
   - 2.4. Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)
   - 2.5. Mastocytosis
   - 2.6. Myeloproliferative neoplasm, unclassifiable (MPN-U)
3. Myelodysplastic syndromes (MDS)
   - 3.1. Refractory cytopenia[b] with unilineage dysplasia (RCUD)
     - 3.1.1. Refractory anemia (ring sideroblasts <15% of erythroid precursors)
     - 3.1.2. Refractory neutropenia
     - 3.1.3. Refractory thrombocytopenia
   - 3.2. Refractory anemia with ring sideroblasts (RARS; dysplasia limited to erythroid lineage and ring sideroblasts ≥15% of bone marrow erythroid precursors)
   - 3.3. Refractory cytopenia with multilineage dysplasia (RCMD; ring sideroblast count does not matter)
   - 3.4. Refractory anemia with excess blasts (RAEB)
     - 3.4.1. RAEB-1 (2–4% circulating or 5–9% marrow blasts)
     - 3.4.2. RAEB-2 (5–19% circulating or 10–19% marrow blasts or Auer rods present)
   - 3.5. MDS associated with isolated del(5q)
   - 3.6. MDS, unclassifiable (MDS-U)
4. MDS/MPN overlap
   - 4.1. Chronic myelomonocytic leukemia (CMML)
   - 4.2. Atypical chronic myeloid leukemia, BCR-ABL1 negative (aCML)
   - 4.3. Juvenile myelomonocytic leukemia (JMML)
   - 4.4. MDS/MPN, unclassifiable (MDS/MPN-U)
     - 4.4.1. Provisional entity: Refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T)
5. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1[c]
   - 5.1. Myeloid and lymphoid neoplasms with PDGFRA rearrangement
   - 5.2. Myeloid neoplasms with PDGFRB rearrangement
   - 5.3. Myeloid and lymphoid neoplasms with FGFR1 abnormalities

[a]AML-related precursor neoplasms include therapy-related MDS and myeloid sarcoma.

[b]Either monocytopenia or bicytopenia: hemoglobin level <10 g/dL, absolute neutrophil count <1.8 × 10^9/L, or platelet count <100 × 10^9/L. However, higher blood counts do not exclude the diagnosis in the presence of unequivocal histologic/cytogenetic evidence for MDS.

[c]Genetic rearrangements involving platelet-derived growth factor receptor α/β (PDGFRA/PDGFRB) or fibroblast growth factor receptor 1 (FGFR1).

less than 200 reported cases. Median age at diagnosis is approximately 67 years, and the disease is equally prevalent in both genders.

Pathogenesis

CSF3 is the main growth factor for granulocyte proliferation and differentiation. Accordingly, recombinant CSF3 is used for the treatment of severe neutropenia, including severe congenital neutropenia (SCN). Some patients with SCN acquire CSF3R mutations, and the frequency of such mutations is significantly higher (~80%) in patients who experience leukemic transformation. SCN-associated CSF3R mutations occur in the region of the gene coding for the cytoplasmic domain of CSF3R and result in truncation of the C-terminal-negative regulatory domain. A different class of CSF3R mutations is noted in ~90% of patients with CNL; these are mostly membrane proximal, with the most frequent being a C-to-T substitution at nucleotide 1853 (T618I). About 40% of the T618I-mutated cases also harbored SETBP1 mutations. CSF3R T618I induces a lethal myeloproliferative disorder in a mouse model and is associated with in vitro sensitivity to JAK inhibition.

Diagnosis

Diagnosis of CNL requires exclusion of the more common causes of neutrophilia including infections and inflammatory processes. In addition, one should be mindful of the association between some forms of metastatic cancer or plasma cell neoplasms with secondary neutrophilia. Neoplastic neutrophilia also occurs in other myeloid malignancies including atypical chronic myeloid leukemia and chronic myelomonocytic leukemia. Accordingly, the WHO diagnostic criteria for CNL are designed to exclude the possibilities of both secondary/reactive neutrophilia and leukocytosis associated with myeloid malignancies other than CNL **(Table 17-5)**: leukocytosis (≥25 × 10^9/L), >80% segmented/band neutrophils, <10% immature myeloid cells, <1% circulating blasts, and absence of dysgranulopoiesis or monocytosis. Bone marrow in CNL is hypercellular and displays increased number and percentage of neutrophils with a very high myeloid-to-erythroid ratio and minimal left shift, myeloid dysplasia, or reticulin fibrosis.

Treatment

Current treatment in CNL is largely palliative and suboptimal in its efficacy. Several drugs alone or in combination have been tried, and none have shown remarkable efficacy. As such, allogeneic stem cell transplantation (ASCT) is reasonable to consider in the presence of symptomatic disease, especially in younger

TABLE 17-5

WORLD HEALTH ORGANIZATION DIAGNOSTIC CRITERIA FOR CHRONIC NEUTROPHILIC LEUKEMIA (CNL); ATYPICAL CHRONIC MYELOID LEUKEMIA, BCR-ABL1 NEGATIVE (ACML); AND CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

VARIABLES	CNL	ACML	CMML
PB leukocyte count	≥25 × 10^9/L	≥13 × 10^9/L	
PB segmented neutrophils/bands	>80%		
PB immature granulocytes[a]	<10%	≥10%	
PB blast count	<1%		
PB monocyte count	<1 × 10^9/L	<1 × 10^9/L	>1 × 10^9/L
PB increased neutrophils or precursors with dysgranulopoiesis	No	Yes	
PB basophil percentage		<2%	
PB monocyte percentage		<10%	
Bone marrow	↑ Neutrophils, number and % <5% blasts Normal neutrophilic maturation Megakaryocytes normal or left shifted	↑ Granulocyte proliferation Granulocytic dysplasia ± erythroid/megakaryocyte dysplasia	Dysplasia in ≥1 myeloid lineages or Clonal cytogenetic/molecular abnormality
BCR-ABL1	No	No	No
PDGFRA, PDGFRB, or FGFR1 mutation	No	No	No
PB and BM blasts/promonocytes	<20%	<20%	<20%
Hepatosplenomegaly	±	±	±
Evidence for other MDS/MPN	No	No	No
Evidence for other MPN	No	No	No
Evidence for reactive leukocytosis[b] or monocytosis	No	No	No

[a] Immature granulocytes include myeloblasts, promyelocytes, myelocytes, and metamyelocytes.
[b] Causes of reactive neutrophilia include plasma cell neoplasms, solid tumor, infections, and inflammatory processes.
Abbreviations: BM, bone marrow; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; PB, peripheral blood.

patients. Otherwise, cytoreductive therapy with hydroxyurea is probably as good as any treatment, and a more intensive combination chemotherapy may not have additional value. However, response to hydroxyurea therapy is often transient, and some have successfully used interferon α as an alternative drug. Response to treatment with ruxolitinib (a JAK1 and JAK2 inhibitor) has been reported but has not been confirmed.

ATYPICAL CHRONIC MYELOID LEUKEMIA

Atypical chronic myeloid leukemia, BCR-ABL1 negative (aCML) is formally classified under the MDS/MPN category of myeloid malignancies and is characterized by left shifted granulocytosis and dysgranulopoiesis. The differential diagnosis of aCML includes chronic myeloid leukemia (CML), which is distinguished by the presence of BCR-ABL1; CNL, which is distinguished by the absence of dysgranulopoiesis and presence of CSF3R mutations; and chronic myelomonocytic leukemia, which is distinguished by the presence of monocytosis (absolute monocyte count >1 × 10^9/L). The WHO diagnostic criteria for aCML are listed in Table 17-5 and include granulocytosis (WBC ≥13 × 10^9/L), neutrophilia with dysgranulopoiesis, ≥10% immature granulocytes, <20% peripheral blood myeloblasts, <10% peripheral blood monocytes, <2% basophils, and absence of otherwise specific mutations such as BCR-ABL1. The bone marrow is hypercellular with granulocyte proliferation and dysplasia with or without erythroid or megakaryocytic dysplasia.

The molecular pathogenesis of aCML is incompletely understood; about one-fourth of the patients express SETBP1 mutations, which are, however, also found in several other myeloid malignancies, including CNL and chronic myelomonocytic leukemia. SETBP1 mutations in aCML were prognostically detrimental and mostly located between codons 858 and 871; similar mutations

are seen with Schinzel-Giedion syndrome (a congenital disease with severe developmental delay and various physical stigmata including midface retraction, large forehead, and macroglossia).

In a series of 55 patients with WHO-defined aCML, median age at diagnosis was 62 years with female preponderance (57%); splenomegaly was reported in 54% of the patients, red cell transfusion requirement in 65%, abnormal karyotype in 20% (20q– and trisomy 8 being the most frequent), and leukemic transformation in 40%. Median survival was 25 months. Outcome was worse in patients with marked leukocytosis, transfusion requirement, and increased immature cells in the peripheral blood. Conventional chemotherapy is largely ineffective in the treatment of aCML. However, a favorable experience with ASCT was reported in nine patients; after a median follow-up of 55 months, the majority of the patients remained in complete remission.

CHRONIC MYELOMONOCYTIC LEUKEMIA

Chronic myelomonocytic leukemia (CMML) is classified under the WHO category of MDS/MPN and is defined by an absolute monocyte count (AMC) of >1 × 10^9/L in the peripheral blood. Median age at diagnosis ranges between 65 and 75 years, and there is a 2:1 male predominance. Clinical presentation is variable and depends on whether the disease presents with MDS-like or MPN-like phenotype; the former is associated with cytopenias and the latter with splenomegaly and features of myeloproliferation such as fatigue, night sweats, weight loss, and cachexia. About 20% of patients with CMML experience serositis involving the joints (arthritis), pericardium (pericarditis and pericardial effusion), pleura (pleural effusion), or peritoneum (ascites).

Pathogenesis

Clonal cytogenetic abnormalities are seen in about one-third of patients with CMML and include trisomy 8 and abnormalities of chromosome 7. Almost all patients with CMML harbor somatic mutations involving epigenetic regulator genes (e.g., ASXL1, TET2), spliceosome pathway genes (e.g., SRSF2), DNA damage response genes (e.g., TP53), and tyrosine kinases/transcription factors (e.g., KRAS, NRAS, CBL, and RUNX1). However, none of these mutations are specific to CMML, and their precise pathogenetic contribution is unclear.

Diagnosis

Reactive monocytosis is uncommon but has been reported in association with certain infections and inflammatory conditions. Clonal (i.e., neoplastic) monocytosis defines CMML but is also seen with juvenile myelomonocytic leukemia and acute myeloid leukemia with monocytic differentiation. The WHO diagnostic criteria for CMML are listed in Table 17-5 and include persistent AMC >1 × 10^9/L, absence of BCR-ABL1, absence of the PDGFRA or PDGFRB mutations, <20% blasts and promonocytes in the peripheral blood and bone marrow, and dysplasia involving one or more myeloid lineages.

The bone marrow in CMML is hypercellular with granulocytic and monocytic proliferation. Dysplasia is often present and may involve one, two, or all myeloid lineages. On immunophenotyping, the abnormal cells often express myelomonocytic antigens such as CD13 and CD33, with variable expression of CD14, CD68, CD64, and CD163. Monocytic-derived cells are almost always positive for the cytochemical nonspecific esterases (e.g., butyrate esterase), whereas normal granulocytic precursors are positive for lysozyme and chloroacetate esterase. In CMML, it is common to have a hybrid cytochemical staining pattern with cells expressing both chloroacetate and butyrate esterases simultaneously (dual esterase staining).

Prognosis

A meta-analysis showed median survival of 1.5 years in CMML. Numerous prognostic systems have attempted to better define and stratify the natural history of CMML. One of these, the Mayo prognostic model, assigns one point each to the following four independent prognostic variables: AMC >10 × 10^9/L, presence of circulating immature cells, hemoglobin <10 g/dL, and platelet count <100,000/mL. This is model stratified patients into three risk groups: low (0 points), intermediate (1 point), and high (≥2 points), translating to median survival times of 32, 18, and 10 months, respectively.

A French study incorporated ASXL1 mutational status in 312 CMML patients. In a multivariable model, independent predictors of poor survival were WBC >15 × 10^9/L (3 points), ASXL1 mutations (2 points), age >65 years (2 points), platelet count <100,000/mL (2 points), and hemoglobin <10 g/dL in females and <11 g/dL in males (2 points). This is model stratified patients into three groups: low (0–4 points), intermediate (5–7 points), and high risk (8–12 points), with median survival times of not reached, 38.5 months, and 14.4 months, respectively.

Treatment

Current treatment consists of hydroxyurea and supportive care, including red cell transfusions and use of erythropoiesis-stimulating agents (ESAs). The value of hydroxyurea was reinforced by a randomized trial against oral etoposide. No other single or combination

chemotherapy has been shown to be superior to hydroxyurea. ASCT is a viable treatment option for transplant-eligible patients with poor prognostic features. Given the MDS/MPN overlap phenotype and the presence of MDS-like genetic/methylation abnormalities in CMML, hypomethylating agents such as 5-azacitidine and decitabine have been used with limited efficacy.

JUVENILE MYELOMONOCYTIC LEUKEMIA

Juvenile myelomonocytic leukemia (JMML) is primarily a disease of early childhood and is included, along with CMML, in the MDS/MPN WHO category. Both CMML and JMML feature leukocytosis, monocytosis, and hepatosplenomegaly. Additional characteristic features in JMML include thrombocytopenia and elevated fetal hemoglobin. Myeloid progenitors in JMML display granulocyte-macrophage colony-stimulating factor (GM-CSF) hypersensitivity that has been attributed to dysregulated RAS/MAPK signaling. The latter is believed to result from mutually exclusive mutations involving RAS, PTPN11, and NF1. A third of patients with JMML that is not associated with Noonan's syndrome carry PTPN11 mutations, whereas the incidence of NF1 in patients without neurofibromatosis type 1 and RAS mutations is approximately 15% each. Drug therapy is relatively ineffective in JMML, and the treatment of choice is ASCT, which results in a 5-year survival of approximately 50%.

MDS/MPN-U

The WHO classifies patients with morphologic and laboratory features that resemble both MDS and MPN as MDS/MPN overlap. This category includes CMML, aCML, and JMML, which have been described above. In addition, MDS/MPN includes a fourth category referred to as MDS/MPN, unclassifiable (MDS/MPN-U). Diagnosis of MDS/MPN-U requires the presence of both MDS and MPN features that are not adequate to classify patients as CMML, aCML, or JMML. MDS/MPN includes the provisional category of RARS-T.

RARS-T is classified in the MDS/MPN category because it shares dysplastic features with RARS and myeloproliferative features with essential thrombocythemia (ET). In one study, 111 patients with RARS-T were compared with 33 patients with RARS. The frequency of SF3B1 mutations in RARS-T (87%) was similar to that in RARS (85%). JAK2 V617F mutation was detected in 49% of RARS-T patients (including 48% of those mutated for SF3B1) but none of those with RARS. In RARS-T, SF3B1 mutations were more frequent in females (95%) than in males (77%), and mean ring sideroblast counts were higher in SF3B1-mutated patients. Median overall survival was 6.9 years in SF3B1-mutated patients versus 3.3 years in unmutated patients. Six-year survival was 67% in JAK2-mutated patients versus 32% in unmutated patients. Multivariable analysis identified younger age and JAK2 and SF3B1 mutations as favorable factors.

In one series, 85 patients with non-RARS-T MDS/MPN, median age was 70 years, and 72% were males. Splenomegaly at presentation was present in 33%, thrombocytosis in 13%, leukocytosis in 18%, JAK2 mutations in 30%, and abnormal karyotype in 51%; the most frequent cytogenetic abnormality was trisomy 8. Median survival was 12.4 months and favorably affected by thrombocytosis. Treatment with hypomethylating agents, immunomodulators, or ASCT did not appear to favorably affect survival.

MYELOPROLIFERATIVE NEOPLASM, UNCLASSIFIABLE (MPN-U)

The category of MPN-U includes MPN-like neoplasms that cannot be clearly classified as one of the other seven subcategories of MPN (Table 17-4). Examples include patients presenting with unusual thrombosis or unexplained organomegaly with normal blood counts but found to carry MPN-characteristic mutations such as JAK2 and CALR or display bone marrow morphology that is consistent with MPN. It is possible that some cases of MPN-U represent earlier disease stages in polycythemia vera (PV) or ET that fail to meet the threshold hemoglobin levels (18.5 g/dL in men or 16.5 g/dL in women) or platelet counts (450×10^9/L) that are required by the WHO diagnostic criteria. Specific treatment interventions might not be necessary in asymptomatic patients with MPN-U, whereas patients with arterial thrombotic complications might require cytoreductive and aspirin therapy and those with venous thrombosis might require systemic anticoagulation.

TRANSIENT MYELOPROLIFERATIVE DISORDER (TMD)

TMD constitutes an often but not always transient phenomenon of abnormal megakaryoblast proliferation, which occurs in approximately 10% of infants with Down's syndrome. TMD is usually recognized at birth and either undergoes spontaneous regression (75% of cases) or progresses into acute megakaryoblastic leukemia (AMKL) (25% of cases). Almost all patients with TMD and TMD-derived AMKL display somatic GATA1 mutations. TMD-associated GATA1 mutations constitute exon 2 insertions, deletions, or missense mutations, affecting the N-terminal transactivation domain of GATA-1, and result in loss of full-length (50-kDa)

GATA-1 and its replacement with a shorter isoform (40-kDa) that retains friend of GATA-1 (FOG-1) binding. In contrast, inherited forms of exon 2 GATA1 mutations produce a phenotype with anemia, whereas exon 4 mutations that affect the N-terminal, FOG-1-interactive domain produce familial dyserythropoietic anemia with thrombocytopenia or X-linked macrothrombocytopenia.

EOSINOPHILIC DISORDERS

Eosinophilia refers to a peripheral blood absolute eosinophil count (AEC) that is above the upper normal limit of the reference range. The term hypereosinophilia is used when the AEC is >1500 × 10^9/L. Eosinophilia is operationally classified as secondary (nonneoplastic proliferation of eosinophils) and primary (proliferation of eosinophils that is either neoplastic or otherwise unexplained) **(Table 17-6)**. Secondary eosinophilia is by far the most frequent cause of eosinophilia and is often associated with infections, especially those related to tissue-invasive helminths; allergic/vasculitic diseases; drugs; and metastatic cancer. Primary eosinophilia is the focus of this chapter and is considered when a cause for secondary eosinophilia is not readily apparent.

TABLE 17-6

DIAGNOSIS OF CHRONIC EOSINOPHILIC LEUKEMIA AND HYPEREOSINOPHILIC SYNDROME

Required: Persistent eosinophilia ≥1500/μL in blood, increased marrow eosinophils, and myeloblasts <20% in blood or marrow.

1. Exclude all causes of reactive eosinophilia: allergy, parasites, infection, pulmonary disease (e.g., hypersensitivity pneumonitis, Loeffler's), and collagen vascular diseases
2. Exclude primary neoplasms associated with secondary eosinophilia: T-cell lymphomas, Hodgkin's disease, acute lymphoid leukemia, mastocytosis
3. Exclude other primary myeloid neoplasms that may involve eosinophils: chronic myeloid leukemia, acute myeloid leukemia with inv(16) or t(16;16)(p13;q22), other myeloproliferative syndromes, and myelodysplasia
4. Exclude T-cell reaction with increased interleukin 5 or other cytokine production

If these entities have been excluded and no evidence documents a clonal myeloid disorder, the diagnosis is hypereosinophilic syndrome.

If these entities have been excluded and the myeloid cells show a clonal chromosome abnormality or some other evidence of clonality and blast cells are present in the peripheral blood (>2%) or are increased in the marrow (but <20%), the diagnosis is chronic eosinophilic leukemia.

Primary eosinophilia

Primary eosinophilia is classified as clonal or idiopathic. Diagnosis of clonal eosinophilia requires morphologic, cytogenetic, or molecular evidence of a myeloid neoplasm. Idiopathic eosinophilia is considered when both secondary and clonal eosinophilias have been ruled out as a possibility. HES is a subcategory of idiopathic eosinophilia with persistent AEC of ≥1.5 × 10^9/L and associated with eosinophil-mediated organ damage **(Table 17-7)**. An HES-like disorder that is associated with clonal or phenotypically abnormal T cells is referred to as lymphocytic variant hypereosinophilia (Table 17-7).

Clonal eosinophilia

Examples of clonal eosinophilia include eosinophilia associated with acute myeloid leukemia (AML), MDS, CML, mastocytosis, and MDS/MPN overlap. Myeloid neoplasm-associated eosinophilia also includes the WHO MPN subcategory of chronic eosinophilic leukemia, not otherwise specified (CEL-NOS) and the WHO myeloid malignancy subcategory referred to as myeloid/lymphoid neoplasms with eosinophilia and mutations involving platelet-derived growth factor receptor (PDGFR) α/β or fibroblast growth factor receptor 1 (FGFR1).

The diagnostic workup for clonal eosinophilia that is not associated with morphologically overt myeloid malignancy should start with peripheral blood mutation screening for FIP1L1-PDGFRA and PDGFRB mutations using fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction. This is crucial because such eosinophilia is easily treated with imatinib. If mutation screening is negative, a bone marrow examination with cytogenetic studies is indicated. In this regard, one must first pay attention to the presence or absence of 5q33, 4q12, or 8p11.2 translocations, which, if present, would suggest PDGFRB-, PDGFRA-, or FGFR1-rearranged clonal eosinophilia, respectively. The presence of 5q33 or 4q12 translocations predicts favorable response to treatment with imatinib mesylate, whereas 8p11.2 translocations are associated with aggressive myeloid malignancies that are refractory to current drug therapy.

CEL-NOS is considered in the presence of cytogenetic/morphologic evidence of a myeloid malignancy that is otherwise not classifiable. Specifically, CEL-NOS is distinguished from HES by the presence of either a cytogenetic abnormality or greater than 2% peripheral blood blasts or greater than 5% bone marrow blasts (Table 17-7). HES or idiopathic eosinophilia is considered in the absence of both morphologic and molecular evidence of clonal eosinophilia. However, before making a working diagnosis of HES, one has

TABLE 17-7 PRIMARY EOSINOPHILIA CLASSIFICATION

VARIABLES	PDGFRA-,PDGFRB-, OR FGFR1-MUTATED EOSINOPHILIA	CHRONIC EOSINOPHILIA, NOT OTHERWISE SPECIFIED	LYMPHOCYTIC VARIANT HYPEREOSINOPHILIA	HYPEREOSINOPHILIC SYNDROME
Absolute eosinophil count	>600 $\times 10^9$/L	>1500 $\times 10^9$/L	>1500 $\times 10^9$/L	>1500 $\times 10^9$/L
Peripheral blood blast >2%	Yes or no	Yes or no	No	No
Bone marrow blast >5%	Yes or no	Yes or No	No	No
Abnormal karyotype	Yes or no	Yes or no	No	No
PDGFRA, PDGFRB, or FGFR1 mutation	Yes	No	No	No
BCR-ABL1	No	No	No	No
Abnormal T lymphocyte phenotype or clonal T-cell clones	No	No	Yes	No
Eosinophil-mediated tissue damage	Yes or no	Yes or no	Yes or no	Yes

to exclude lymphocytic variant hypereosinophilia by excluding the presence of phenotypically abnormal T lymphocytes (by flow cytometry) and clonal T-cell gene rearrangements.

Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)

CEL-NOS is a subset of clonal eosinophilia that is neither molecularly defined nor classified as an alternative clinicopathologically assigned myeloid malignancy. We prefer to use the term strictly in patients with an HES phenotype who also display either a clonal cytogenetic/molecular abnormality or excess blasts in the bone marrow or peripheral blood. The WHO defines CEL-NOS in the presence of an AEC $\geq 1.5 \times 10^9$/L that is accompanied by either the presence of myeloblast excess (either >2% in the peripheral blood or 5–19% in the bone marrow) or evidence of myeloid clonality. Cytogenetic abnormalities in CEL, other than those that are associated with molecularly defined eosinophilic disorders, include trisomy 8 (the most frequent), t(10;11)(p14;q21), and t(7;12)(q11;p11). CEL-NOS does not respond to imatinib, and treatment strategies are often not different from those used in other similar MPNs and include ASCT for transplant-eligible patients with poor risk factors and participation in experimental treatment protocols otherwise.

PDGFR-mutated eosinophilia

Both platelet-derived growth factor receptors α (PDGFRA located on chromosome 4q12) and β (PDGFRB located on chromosome 5q31-q32) are involved in MPN-relevant activating mutations. Clinical phenotype in both instances includes prominent blood eosinophilia and excellent response to imatinib therapy. In regard to PDGFRA mutations, the most popular is FIP1L1-PDGFRA, a karyotypically occult del(4)(q12) that was described in 2003 as an imatinib-sensitive activating mutation. Functional studies have demonstrated transforming properties in cell lines and the induction of MPN in mice. Cloning of the FIP1L1-PDGFRA fusion gene identified a novel molecular mechanism for generating this constitutively active fusion tyrosine kinase, wherein a ~800-kb interstitial deletion within 4q12 fuses the 5′ portion of FIP1L1 to the 3′ portion of PDGFRA. FIP1L1-PDGFRA occurs in a very small subset of patients who present with the phenotypic features of either systemic mastocytosis or HES, but the presence of the mutation reliably predicts complete hematologic and molecular response to imatinib therapy.

The association between eosinophilic myeloid malignancies and PDGFRB rearrangement was first characterized and published in 1994 when fusion of the tyrosine kinase–encoding region of PDGFRB to the ets-like gene, ETV6 [ETV6-PDGFRB, t(5;12)(q33;p13)] was demonstrated. The fusion protein was transforming to cell lines and resulted in constitutive activation of PDGFRB signaling. Since then, several other PDGFRB fusion transcripts with similar disease phenotypes have been described, cell line transformation and myeloproliferative disease (MPD) induction in mice has been demonstrated, and imatinib therapy was proven effective when used.

FGFR1-mutated eosinophilia

The 8p11 myeloproliferative syndrome (EMS) (also known as human stem cell leukemic/lymphoma

syndrome) constitutes a clinical phenotype with features of both lymphoma and eosinophilic MPN and characterized by a fusion mutation that involves the gene for fibroblast growth factor receptor 1 (FGFR1), which is located on chromosome 8p11. In EMS, both myeloid and lymphoid lineage cells exhibit the 8p11 translocation, thus demonstrating the stem cell origin of the disease. The disease features several 8p11-linked chromosome translocations, and some of the corresponding fusion FGFR1 mutants have been shown to transform cell lines and induce EMS- or CML-like disease in mice depending on the specific FGFR1 partner gene (ZNF198 or BCR, respectively). Consistent with this laboratory observation, some patients with BCR-FGFR1 mutation manifest a more indolent CML-like disease. The mechanism of FGFR1 activation in EMS is similar to that seen with PDGFRB-associated MPD; the tyrosine kinase domain of FGFR1 is juxtaposed to a dimerization domain from the partner gene. EMS is aggressive and requires combination chemotherapy followed by ASCT.

Hypereosinophilic syndrome (HES)

Blood eosinophilia that is neither secondary nor clonal is operationally labeled as being idiopathic. HES is a subcategory of idiopathic eosinophilia with persistent increase of the AEC to $\geq 1.5 \times 10^9$/L and presence of eosinophil-mediated organ damage, including cardiomyopathy, gastroenteritis, cutaneous lesions, sinusitis, pneumonitis, neuritis, and vasculitis. In addition, some patients manifest thromboembolic complications, hepatosplenomegaly, and either cytopenia or cytosis.

Bone marrow histologic and cytogenetic/molecular studies should be examined before a working diagnosis of HES is made. Additional blood studies that are currently recommended during the evaluation of HES include serum tryptase (an increased level suggests systemic mastocytosis and warrants molecular studies to detect FIP1L1-PDGFRA), T-cell immunophenotyping, and T-cell receptor antigen gene rearrangement analysis (a positive test suggests an underlying clonal or phenotypically abnormal T-cell disorder). In addition, initial evaluation in HES should include echocardiogram and measurement of serum troponin levels to screen for myocardial involvement by the disease.

Initial evaluation of the patient with eosinophilia should include tests that facilitate assessment of target organ damage, including complete blood count, chest x-ray, echocardiogram, and serum troponin level. An increased level of serum cardiac troponin has been shown to correlate with the presence of cardiomyopathy in HES. Typical echocardiographic findings in HES include ventricular apical thrombus, posterior mitral leaflet or tricuspid valve abnormality, endocardial thickening, dilated left ventricle, and pericardial effusion.

Glucocorticoids are the cornerstone of therapy in HES. Treatment with oral prednisone is usually started at 1 mg/kg per day and continued for 1–2 weeks before the dose is tapered slowly over the ensuing 2–3 months. If symptoms recur at a prednisone dose level of >10 mg/d, either hydroxyurea or interferon α is used as steroid-sparing agent. In patients who do not respond to usual therapy as outlined above, mepolizumab or alemtuzumab might be considered. Mepolizumab targets interleukin 5 (IL-5), a well-recognized survival factor for eosinophils. Alemtuzumab targets the CD52 antigen, which has been shown to be expressed by eosinophils but not by neutrophils.

MASTOCYTOSIS

Mast cell disease (MCD) is defined as tissue infiltration by morphologically and immunophenotypically abnormal mast cells. MCD is classified into two broad categories: cutaneous mastocytosis and systemic mastocytosis (SM). MCD in adults is usually systemic, and the clinical course can be either indolent or aggressive, depending on the respective absence or presence of impaired organ function. Symptoms and signs of MCD include urticaria pigmentosa, mast cell mediator release symptoms (e.g., headache, flushing, lightheadedness, syncope, anaphylaxis, pruritus, urticaria, angioedema, nausea, diarrhea, abdominal cramps), and organ damage (lytic bone lesions, osteoporosis, hepatosplenomegaly, cytopenia). Aggressive SM can be associated with another myeloid malignancy, including MPN, MDS, or MDS/MPN overlap (e.g., CMML), or present as overt mast cell leukemia. In general, life expectancy is near normal in indolent SM but significantly shortened in aggressive SM.

Diagnosis of SM is based on bone marrow examination that shows clusters of morphologically abnormal, spindle-shaped mast cells that are best evaluated by the use of immunohistochemical stains that are specific to mast cells (tryptase, CD117). In addition, mast cell immunophenotyping reveals aberrant CD25 expression by neoplastic mast cells. Other laboratory findings in SM include increased levels of serum tryptase, histamine and urine histamine metabolites, and prostaglandins. SM is associated with KIT mutations, usually KIT D816V, in the majority of patients. Accordingly, mutation screening for KIT D816V is diagnostically useful. However, the ability to detect KIT D816V depends on assay sensitivity and mast cell content of the test sample.

Both indolent and aggressive SM patients might experience mast cell mediator release symptoms, which are usually managed by both H_1 and H_2 histamine receptor blockers as well as cromolyn sodium. In addition, patients with propensity to vasodilatory shock should wear a medical alert bracelet and carry an

Epi-Pen self-injector for self-administration of subcutaneous epinephrine. Urticaria pigmentosa shows variable response to both topical and systemic glucocorticoid therapy. Cytoreductive therapy is not recommended for indolent SM. In aggressive SM, either interferon α or cladribine is considered first-line therapy and benefits the majority of patients. In contrast, imatinib is ineffective in the treatment of PDGFR-unmutated SM.

DENDRITIC AND HISTIOCYTIC NEOPLASMS

Dendritic cell (DC) and histiocyte/macrophage neoplasms are extremely rare. DCs are antigen-presenting cells, whereas histiocyte/macrophages are antigen-processing cells. Bone marrow myeloid stem cells (CD34+) give rise to monocyte (CD14+, CD68+, CD11c+, CD1a–) and DC (CD14–, CD11c+/–, CD1a+/c) precursors. Monocyte precursors, in turn, give rise to macrophages (CD14+, CD68+, CD11c+, CD163+, lysozyme+) and interstitial DCs (CD68+, CD1a–). DC precursors give rise to Langerhans cell DCs (Birbeck granules, CD1a+, S100+, langerin+) and plasmacytoid DCs (CD68+, CD123+). Follicular DCs (CD21+, CD23+, CD35+) originate from mesenchymal stem cells. Dendritic and histiocytic neoplasms are operationally classified into macrophage/histiocyte-related and DC-related neoplasms. The former includes histiocytic sarcoma/malignant histiocytosis and the latter Langerhans cell histiocytosis, Langerhans cell sarcoma, interdigitating DC sarcoma, and follicular DC sarcoma.

Histiocytic sarcoma/malignant histiocytosis

Histiocytic sarcoma represents malignant proliferation of mature tissue histiocytes and is often localized. Median age at diagnosis is estimated at 46 years with slight male predilection. Some patients might have history of lymphoma, MDS, or germ cell tumors at time of disease presentation. The three typical disease sites are lymph nodes, skin, and the gastrointestinal system. Patients may or may not have systemic symptoms including fever and weight loss, and other symptoms include hepatosplenomegaly, lytic bone lesions, and pancytopenia. Immunophenotype includes presence of histiocytic markers (CD68, lysozyme, CD11c, CD14) and absence of myeloid or lymphoid markers. Prognosis is poor, and treatment is often ineffective. The term malignant histiocytosis refers to a disseminated disease and systemic symptoms. Lymphoma-like treatment induces complete remissions in some patients, and median survival is estimated at 2 years.

Langerhans cell histiocytosis

Langerhans cells (LCs) are specialized DCs that reside in mucocutaneous tissue and upon activation become specialized for antigen presentation to T cells. LC histiocytosis (LCH; also known as histiocytosis X) represents neoplastic proliferation of LCs (S-100+, CD1a+, and Birbeck granules on electron microscopy). LCH incidence is estimated at 5 per million, and the disease typically affects children with a male predilection. Presentation can be either unifocal (eosinophilic granuloma) or multifocal. The former usually affects bones and less frequently lymph nodes, skin, and lung, whereas the latter is more disseminated. Unifocal disease often affects older children and adults, whereas multisystem disease affects infants. LCH of the lung in adults is characterized by bilateral nodules. Prognosis depends on organs involved. Only 10% of patients progress from unifocal to multiorgan disease. LCH of the lung might improve upon cessation of smoking.

Langerhans cell sarcoma

Langerhans cell sarcoma (LCS) also represents neoplastic proliferation of LCs with overtly malignant morphology. The disease can present de novo or progress from antecedent LCH. There is a female predilection, and median age at diagnosis is estimated at 41 years. Immunophenotype is similar to that seen in LCH, and liver, spleen, lung, and bone are the usual sites of disease. Prognosis is poor, and treatment is generally ineffective.

Interdigitating dendritic cell sarcoma

Interdigitating DC sarcoma (IDCS), also known as reticulum cell sarcoma, represents neoplastic proliferation of interdigitating DCs. The disease is extremely rare and affects elderly adults with no sex predilection. Typical presentation is asymptomatic solitary lymphadenopathy. Immunophenotype includes S-100+ and negative for vimentin and CD1a. Prognosis ranges from benign local disease to widespread lethal disease.

Follicular dendritic cell neoplasm

Follicular DCs (FDCs) reside in B-cell follicles and present antigen to B cells. FDC neoplasms (FDCNs) are usually localized and often affect adults. FDCN might be associated with Castleman's disease in 10–20% of cases, and increased incidence in schizophrenia has been reported. Cervical lymph nodes are the most frequent site of involvement in FDCN, and other sites include maxillary, mediastinal, and retroperitoneal lymph nodes; oral cavity; gastrointestinal system; skin; and breast. Sites of metastasis include lung and liver. Immunophenotype includes CD21, CD35, and CD23. Clinical course is typically indolent, and treatment includes surgical excision followed by regional radiotherapy and sometimes systemic chemotherapy.

Hemophagocytic syndromes

Hemophagocytic syndrome (HPS) represents non-neoplastic proliferation and activation of macrophages that induce cytokine-mediated bone marrow suppression and features of intense phagocytosis in bone marrow and liver. HPS may result from genetic or acquired disorders of macrophages. T e former entail genetically determined inability to regulate macrophage proliferation and activation. Acquired HPS is often precipitated by viral infections, most notably Epstein-Barr virus. HPS might also accompany certain malignancies such as T-cell lymphoma. Clinical course is often fulminant and fatal.

CHAPTER 18

PLASMA CELL DISORDERS

Nikhil C. Munshi ■ Dan L. Longo ■ Kenneth C. Anderson

The plasma cell disorders are monoclonal neoplasms related to each other by virtue of their development from common progenitors in the B-lymphocyte lineage. Multiple myeloma, Waldenström's macroglobulinemia, primary amyloidosis **(Chap. 19)**, and the heavy chain diseases comprise this group and may be designated by a variety of synonyms such as monoclonal gammopathies, paraproteinemias, plasma cell dyscrasias, and dysproteinemias. Mature B lymphocytes destined to produce IgG bear surface immunoglobulin molecules of both M and G heavy chain isotypes with both isotypes having identical idiotypes (variable regions). Under normal circumstances, maturation to antibody-secreting plasma cells and their proliferation is stimulated by exposure to the antigen for which the surface immunoglobulin is specific; however, in the plasma cell disorders, the control over this process is lost. The clinical manifestations of all the plasma cell disorders relate to the expansion of the neoplastic cells, to the secretion of cell products (immunoglobulin molecules or subunits, lymphokines), and to some extent to the host's response to the tumor. **Normal development of B lymphocytes is depicted in Fig. 16-2.**

There are three categories of structural variation among immunoglobulin molecules that form antigenic determinants, and these are used to classify immunoglobulins. Isotypes are those determinants that distinguish among the main classes of antibodies of a given species and are the same in all normal individuals of that species. Therefore, isotypic determinants are, by definition, recognized by antibodies from a distinct species (heterologous sera) but not by antibodies from the same species (homologous sera). There are five heavy chain isotypes (M, G, A, D, E) and two light chain isotypes (κ, λ). Allotypes are distinct determinants that reflect regular small differences between individuals of the same species in the amino acid sequences of otherwise similar immunoglobulins. These differences are determined by allelic genes; by definition, they are detected by antibodies made in the same species. Idiotypes are the third category of antigenic determinants. They are unique to the molecules produced by a given clone of antibody-producing cells. Idiotypes are formed by the unique structure of the antigen-binding portion of the molecule.

Antibody molecules **(Fig. 18-1)** are composed of two heavy chains (~50,000 mol wt) and two light chains (~25,000 mol wt). Each chain has a constant portion (limited amino acid sequence variability) and a variable region (extensive sequence variability). The light and heavy chains are linked by disulfide bonds and are aligned so that their variable regions are adjacent to one another. This variable region forms the antigen recognition site of the antibody molecule; its unique structural features form idiotypes that are reliable markers for a particular clone of cells because each antibody is formed and secreted by a single clone. Because of the mechanics of the gene rearrangements necessary to specify the immunoglobulin variable regions (VDJ joining for the heavy chain, VJ joining for the light chain), a particular clone rearranges only one of the two chromosomes to produce an immunoglobulin molecule of only one light chain isotype and only one allotype (allelic exclusion) (Fig. 18-1). After exposure to antigen, the variable region may become associated with a new heavy chain isotype (class switch). Each clone of cells performs these sequential gene arrangements in a unique way. This is results in each clone producing a unique immunoglobulin molecule. In most plasma cells, light chains are synthesized in slight excess, secreted as free light chains, and cleared by the kidney, but <10 mg of such light chains is excreted per day.

Electrophoretic analysis permits separation of components of the serum proteins **(Fig. 18-2)**. The immunoglobulins move heterogeneously in an electric field and form a broad peak in the gamma region, which is usually increased in the sera of patients with plasma cell tumors. There is a sharp spike in this region called

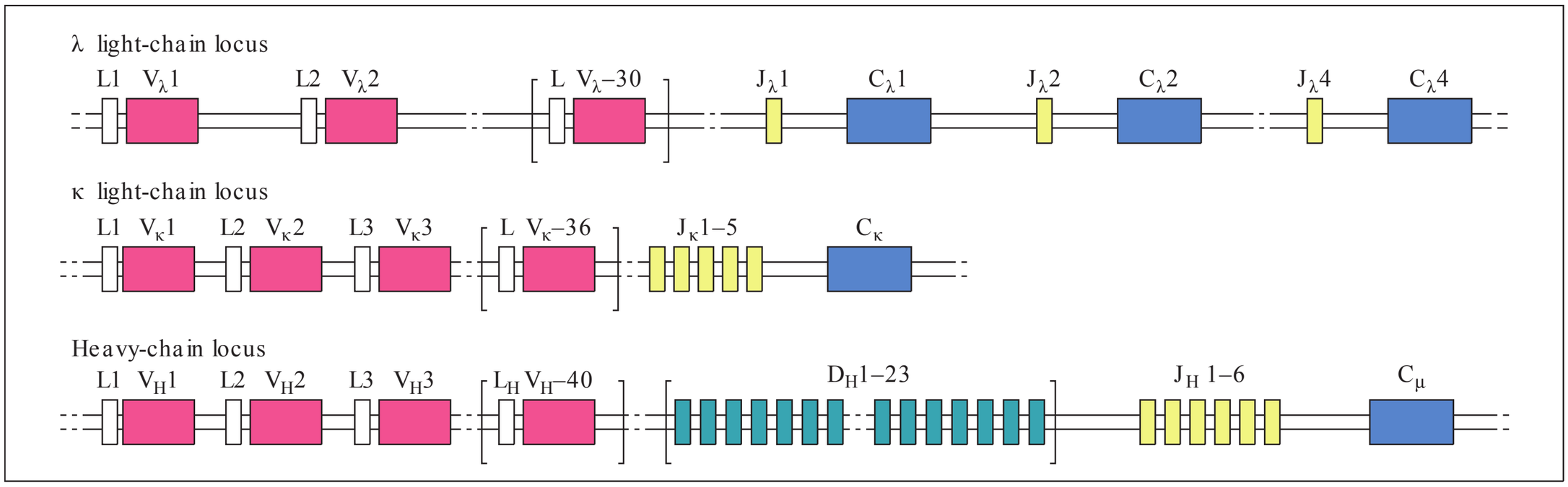


FIGURE 18-1

Immunoglobulin genetics and the relationship of gene segments to the antibody protein. The top portion of the figure is a schematic of the organization of the immunoglobulin genes, λ on chromosome 22, κ on chromosome 2, and the heavy chain locus on chromosome 14. The heavy chain locus is longer than 2 megabases, and some of the D region gene segments are only a few bases long, so the figure depicts the schematic relationship among the segments, not their actual size. The bottom portion of the figure outlines the steps in going from the noncontiguous germline gene segments to an intact antibody molecule. Two recombination events juxtapose the V-D-J (or V-J for light chains) segments. The rearranged gene is transcribed, and RNA splicing cuts out intervening sequences to produce an mRNA, which is then translated into an antibody light or heavy chain. The sites on the antibody that bind to antigen (the so called CDR3 regions) are encoded by D and J segments for heavy chains and the J segments for light chains. (From K Murphy: Janeway's Immunobiology, 8th ed. Garland Science, 2011.)

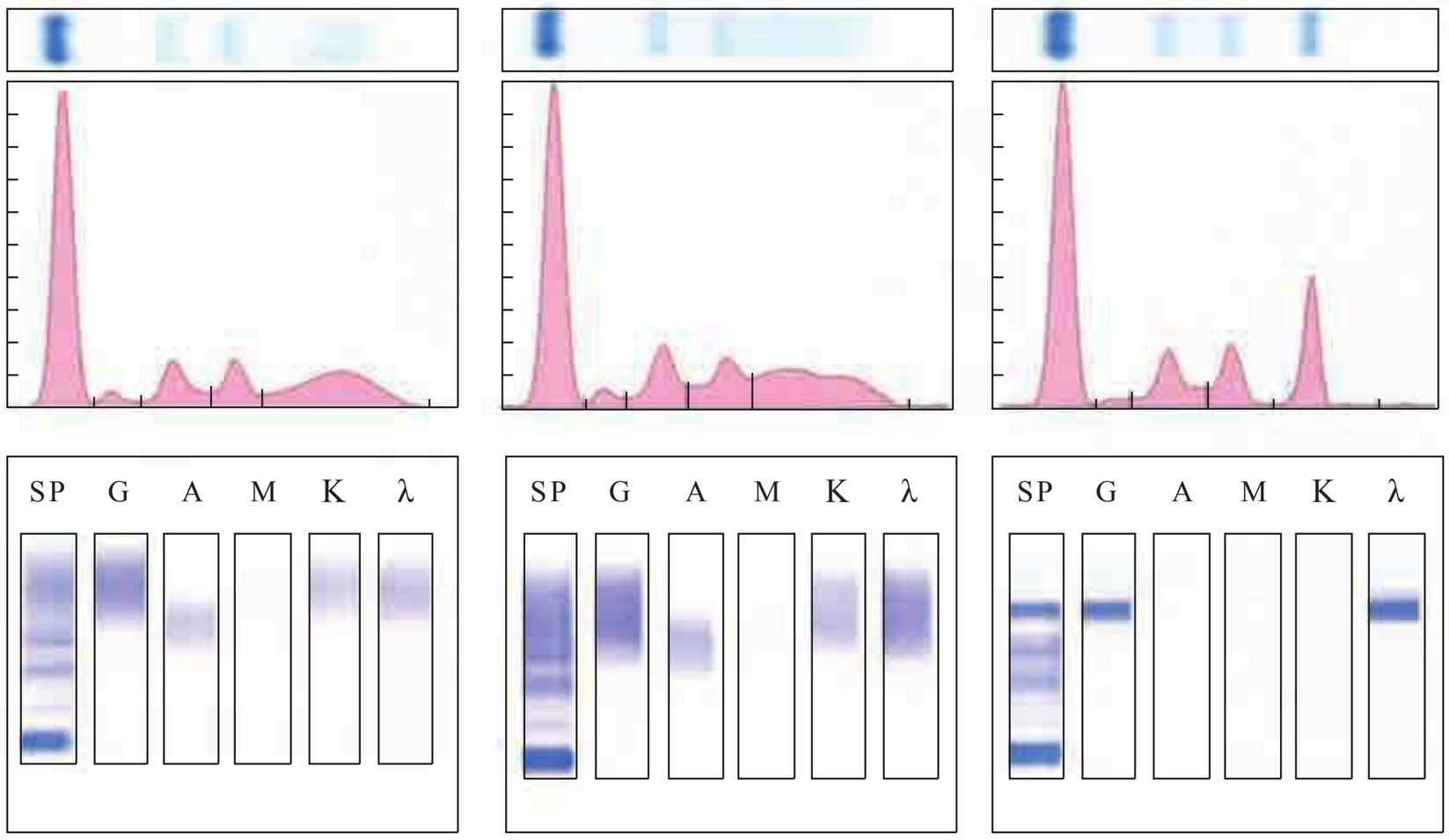


FIGURE 18-2
Representative patterns of serum electrophoresis and immunofixation. The upper panels represent agarose gel, middle panels are the densitometric tracing of the gel, and lower panels are immunofixation patterns. Panel on the left illustrates the normal pattern of serum protein on electrophoresis. Because there are many different immunoglobulins in the serum, their differing mobilities in an electric field produce a broad peak. In conditions associated with increases in polyclonal immunoglobulin, the broad peak is more prominent (middle panel). In monoclonal gammopathies, the predominance of a product of a single cell produces a "church spire" sharp peak, usually in the γ globulin region (right panel). The immunofixation (lower panel) identifies the type of immunoglobulin. For example, normal and polyclonal increase in immunoglobulins produce no distinct bands; however, the right panel shows distinct bands in IgG and lambda protein lanes, confirming the presence of IgG lambda monoclonal protein. (Courtesy of Dr. Neal I. Lindeman; with permission.)

an M component (M for monoclonal). Less commonly, the M component may appear in the β_2 or α_2 globulin region. The monoclonal antibody must be present at a concentration of at least 5 g/L (0.5 g/dL) to be accurately quantitated by this method. This corresponds to ~10^9 cells producing the antibody. Confirmation of the type of immunoglobulin and that it is truly monoclonal is determined by immunoelectrophoresis that reveals a single heavy and/or light chain type. Hence immunoelectrophoresis and electrophoresis provide qualitative and quantitative assessment of the M component, respectively. Once the presence of an M component has been confirmed, the amount of M component in the serum is a reliable measure of the tumor burden, making M component an excellent tumor marker to manage therapy, yet it is not specific enough to be used to screen asymptomatic patients. In addition to the plasma cell disorders, M components may be detected in other lymphoid neoplasms such as chronic lymphocytic leukemia and lymphomas of B- or T-cell origin; nonlymphoid neoplasms such as chronic myeloid leukemia, breast cancer, and colon cancer; a variety of nonneoplastic conditions such as cirrhosis, sarcoidosis, parasitic diseases, Gaucher's disease, and pyoderma gangrenosum; and a number of autoimmune conditions, including rheumatoid arthritis, myasthenia gravis, and cold agglutinin disease. Monoclonal proteins are also observed in immunosuppressed patients after organ transplant and, rarely, allogeneic transplant. At least two very rare skin diseases—lichen myxedematosus (also known as papular mucinosis) and necrobiotic xanthogranuloma—are associated with a monoclonal gammopathy. In papular mucinosis, highly cationic IgG is deposited in the dermis of patients. This organ specificity may reflect the specificity of the antibody for some antigenic component of the dermis. Necrobiotic xanthogranuloma is a histiocytic infiltration of the skin, usually of the face, that produces red or yellow nodules that can enlarge to plaques. Approximately 10% progress to myeloma. Five percent of patients with sensory motor neuropathy also have a monoclonal paraprotein.

The nature of the M component is variable in plasma cell disorders. It may be an intact antibody molecule of any heavy chain subclass, or it may be an altered antibody or fragment. Isolated light or heavy chains may

be produced. In some plasma cell tumors such as extramedullary or solitary bone plasmacytomas, less than one-third of patients will have an M component. In ~20% of myelomas, only light chains are produced and, in most cases, are secreted in the urine as Bence Jones proteins. The frequency of myelomas of a particular heavy chain class is roughly proportional to the serum concentration, and therefore, IgG myelomas are more common than IgA and IgD myelomas. In approximately 1% of patients with myeloma, biclonal or triclonal gammopathy is observed.

MULTIPLE MYELOMA

DEFINITION

Multiple myeloma represents a malignant proliferation of plasma cells derived from a single clone. The tumor, its products, and the host response to it result in a number of organ dysfunctions and symptoms, including bone pain or fracture, renal failure, susceptibility to infection, anemia, hypercalcemia, and occasionally clotting abnormalities, neurologic symptoms, and manifestations of hyperviscosity.

ETIOLOGY

The cause of myeloma is not known. Myeloma occurred with increased frequency in those exposed to the radiation of nuclear warheads in World War II after a 20-year latency. Myeloma has been seen more commonly than expected among farmers, wood workers, leather workers, and those exposed to petroleum products. A variety of chromosomal alterations have been found in patients with myeloma: hyperdiploidy, 13q14 deletions, translocations t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16), and 17p13 deletions. Evidence is strong that errors in switch recombination—the genetic mechanism to change antibody heavy chain isotype—participate in the transformation process. However, no common molecular pathogenetic pathway has yet emerged. Genome sequencing studies have failed to identify any recurrent mutation with frequency >20%; N-ras, K-ras, and B-raf mutations are most common and combined occur in over 40% of patients. There is also evidence of complex clusters of subclonal variants at diagnosis that acquire additional mutations over time, indicative of genomic evolution that may drive disease progression. The neoplastic event in myeloma may involve cells earlier in B-cell differentiation than the plasma cell. Interleukin (IL) 6 may play a role in driving myeloma cell proliferation. It remains difficult to distinguish benign from malignant plasma cells based on morphologic criteria in all but a few cases **(Fig. 18-3)**.

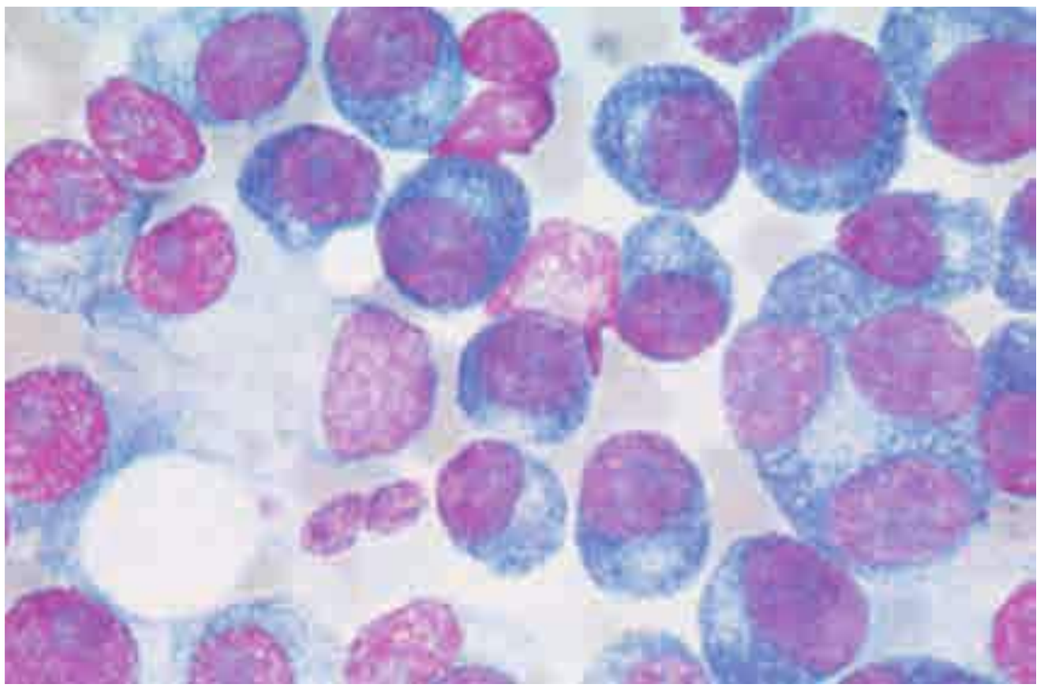


FIGURE 18-3
Multiple myeloma (marrow). The cells bear characteristic morphologic features of plasma cells, round or oval cells with an eccentric nucleus composed of coarsely clumped chromatin, a densely basophilic cytoplasm, and a perinuclear clear zone containing the Golgi apparatus. Binucleate and multinucleate malignant plasma cells can be seen.

INCIDENCE AND PREVALENCE

An estimated 24,050 new cases of myeloma were diagnosed in 2014, and 11,090 people died from the disease in the United States. Myeloma increases in incidence with age. The median age at diagnosis is 70 years; it is uncommon under age 40. Males are more commonly affected than females, and blacks have nearly twice the incidence of whites. Myeloma accounts for 1.3% of all malignancies in whites and 2% in blacks, and 13% of all hematologic cancers in whites and 33% in blacks.

GLOBAL CONSIDERATIONS

The incidence of myeloma is highest in African Americans and Pacific Islanders; intermediate in Europeans and North American whites; and lowest in people from developing countries including Asia. The higher incidence in more developed countries may result from the combination of a longer life expectancy and more frequent medical surveillance. Incidence of multiple myeloma in other ethnic groups including native Hawaiians, female Hispanics, American Indians from New Mexico, and Alaskan natives is higher relative to U.S. whites in the same geographic area. Chinese and Japanese populations have a lower incidence than whites. Immunoproliferative small-intestinal disease with alpha heavy chain disease is most prevalent in the Mediterranean area. Despite these differences in prevalence, the characteristics, response to therapy, and prognosis of myeloma are similar worldwide.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Multiple myeloma (MM) cells bind via cell-surface adhesion molecules to bone marrow stromal cells (BMSCs) and extracellular matrix (ECM), which triggers MM cell growth, survival, drug resistance, and migration in the bone marrow milieu **(Fig. 18-4)**. T ese effects are due both to direct MM cell–BMSC binding and to induction of various cytokines, including IL-6, insulin-like growth factor type I (IGF-I), vascular endothelial growth factor (VEGF), and stromal cell–derived growth factor (SDF)-1α. Growth, drug resistance, and migration are mediated via Ras/Raf/mitogen-activated protein kinase, PI3K/Akt, and protein kinase C signaling cascades, respectively.

Bone pain is the most common symptom in myeloma, affecting nearly 70% of patients. Unlike the pain of metastatic carcinoma, which often is worse at night, the pain of myeloma is precipitated by movement. Persistent localized pain in a patient with myeloma usually signifies a pathologic fracture. T e bone lesions of myeloma are caused by the proliferation of tumor cells, activation of osteoclasts that destroy bone, and suppression of osteoblasts that form new bone. T e increased osteoclast activity is mediated by osteoclast activating factors (OAFs) made by the myeloma cells (OAF activity can be mediated by several cytokines, including IL-1, lymphotoxin, VEGF, receptor activator of NF-κB [RANK] ligand, macrophage inhibitory factor [MIP]-1α, and tumor necrosis factor [TNF]). T e bone lesions are lytic in nature and are rarely associated with osteoblastic new bone formation due to their suppression by dickhoff-1 (DKK-1) produced by myeloma cells. T erefore, radioisotopic bone scanning is less useful in diagnosis than is plain radiography. T e bony lysis results in substantial mobilization of calcium from bone, and serious acute and chronic complications of hypercalcemia may dominate the clinical picture (see below). Localized bone lesions may expand to the point that mass lesions may be palpated, especially on the skull **(Fig. 18-5)**, clavicles, and sternum; and the collapse of vertebrae may lead to spinal cord compression. T e next most common clinical problem in patients with myeloma is susceptibility to bacterial infections. T e most common infections are pneumonias and pyelonephritis, and the most frequent pathogens are Streptococcus pneumoniae, Staphylococcus aureus, and Klebsiella pneumoniae in the lungs and Escherichia coli and other gram-negative organisms in the urinary tract. In ~25% of patients, recurrent

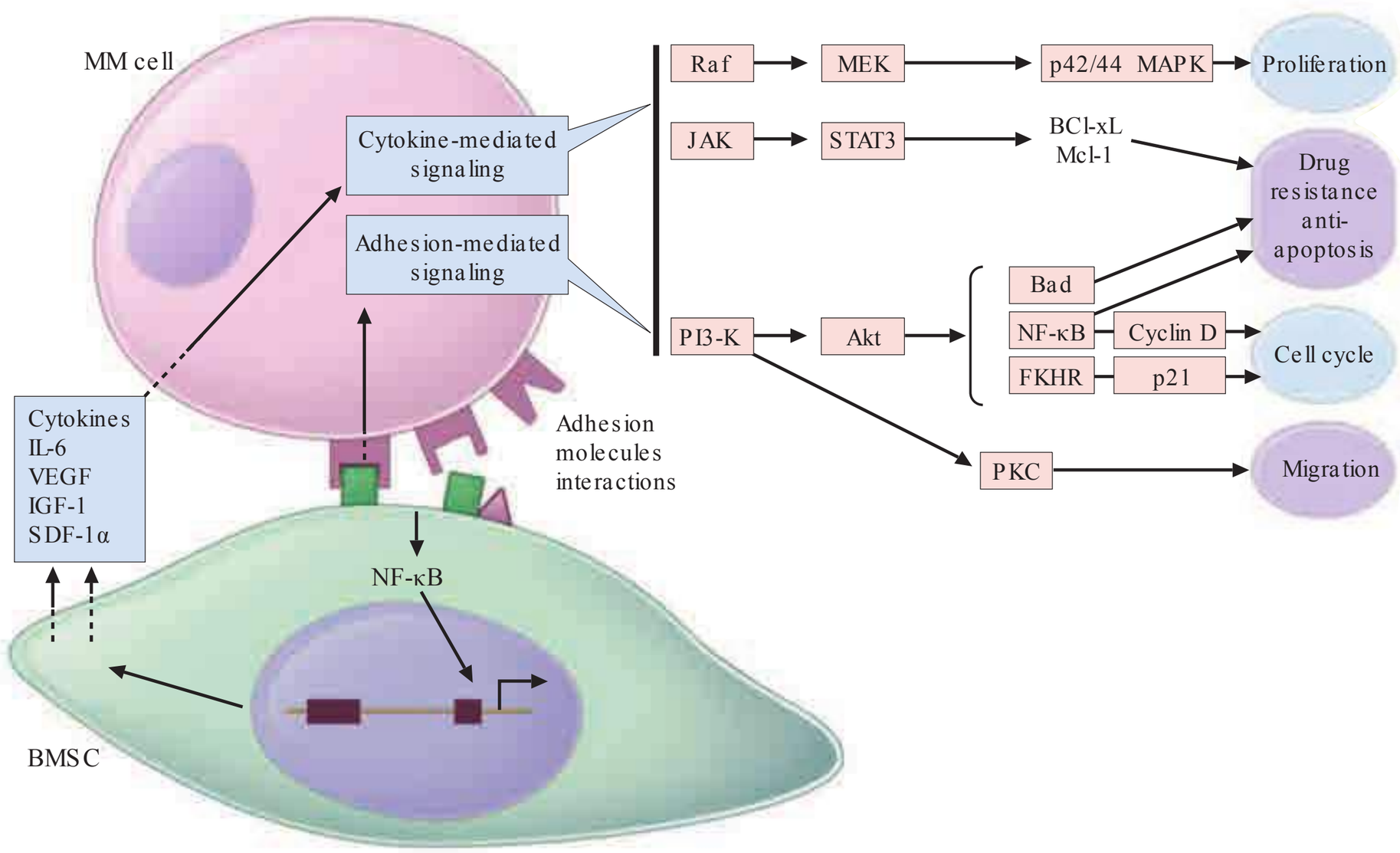


FIGURE 18-4

Pathogenesis o**f** multiple myeloma. Multiple myeloma (MM) cells interact with bone marrow stromal cells (BMSCs) and extracellular matrix proteins via adhesion molecules, triggering adhesion-mediated signaling as well as cytokine production. This triggers cytokine-mediated signaling that provides growth, survival, and antiapoptotic effects as well as development of drug resistance.

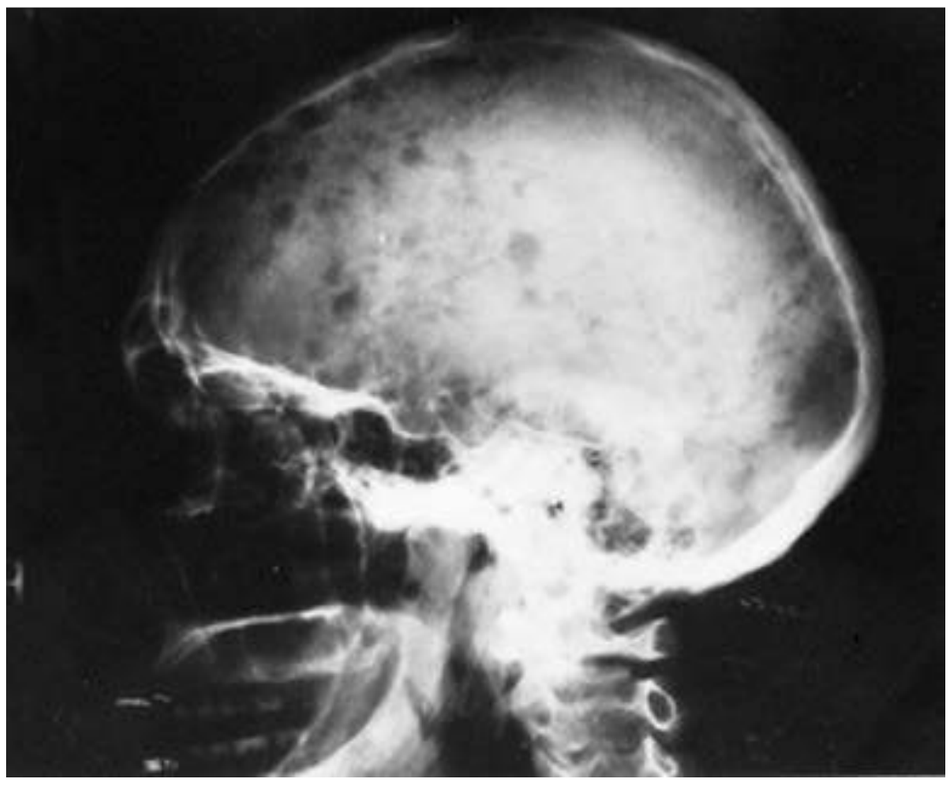


FIGURE 18-5
Bony lesions in multiple myeloma. The skull demonstrates the typical "punched out" lesions characteristic of multiple myeloma. The lesion represents a purely osteolytic lesion with little or no osteoblastic activity. (Courtesy of Dr. Geraldine Schechter; with permission.)

infections are the presenting features, and >75% of patients will have a serious infection at some time in their course. The susceptibility to infection has several contributing causes. First, patients with myeloma have diffuse hypogammaglobulinemia if the M component is excluded. The hypogammaglobulinemia is related to both decreased production and increased destruction of normal antibodies. Moreover, some patients generate a population of circulating regulatory cells in response to their myeloma that can suppress normal antibody synthesis. In the case of IgG myeloma, normal IgG antibodies are broken down more rapidly than normal because the catabolic rate for IgG antibodies varies directly with the serum concentration. The large M component results in fractional catabolic rates of 8–16% instead of the normal 2%. These patients have very poor antibody responses, especially to polysaccharide antigens such as those on bacterial cell walls. Most measures of T-cell function in myeloma are normal, but a subset of CD4+ cells may be decreased. Granulocyte lysozyme content is low, and granulocyte migration is not as rapid as normal in patients with myeloma, probably the result of a tumor product. There are also a variety of abnormalities in complement functions in myeloma patients. All these factors contribute to the immune deficiency of these patients. Some commonly used therapeutic agents, e.g., dexamethasone, suppress immune responses and increase susceptibility to bacterial and fungal infection, and bortezomib predisposes to herpesvirus reactivation.

Renal failure occurs in nearly 25% of myeloma patients, and some renal pathology is noted in more than 50%. Many factors contribute to this. Hypercalcemia is the most common cause of renal failure. Glomerular deposits of amyloid, hyperuricemia, recurrent infections, frequent use of nonsteroidal anti-inflammatory agents for pain control, use of iodinated contrast dye for imaging, bisphosphonate use, and occasional infiltration of the kidney by myeloma cells all may contribute to renal dysfunction. However, tubular damage associated with the excretion of light chains is almost always present. Normally, light chains are filtered, reabsorbed in the tubules, and catabolized. With the increase in the amount of light chains presented to the tubule, the tubular cells become overloaded with these proteins, and tubular damage results either directly from light chain toxic effects or indirectly from the release of intracellular lysosomal enzymes. The earliest manifestation of this tubular damage is the adult Fanconi's syndrome (a type 2 proximal renal tubular acidosis), with loss of glucose and amino acids, as well as defects in the ability of the kidney to acidify and concentrate the urine. The proteinuria is not accompanied by hypertension, and the protein is nearly all light chains. Generally, very little albumin is in the urine because glomerular function is usually normal. When the glomeruli are involved, nonselective proteinuria is also observed. Patients with myeloma also have a decreased anion gap [i.e., $Na^+ - (Cl^- + HCO_3^-)$] because the M component is cationic, resulting in retention of chloride. This is often accompanied by hyponatremia that is felt to be artificial (pseudohyponatremia) because each volume of serum has less water as a result of the increased protein. Renal dysfunction due to light chain deposition disease, light chain cast nephropathy, and amyloidosis is partially reversible with effective therapy. Myeloma patients are susceptible to developing acute renal failure if they become dehydrated.

Normocytic and normochromic anemia occurs in ~80% of myeloma patients. It is usually related to the replacement of normal marrow by expanding tumor cells, to the inhibition of hematopoiesis by factors made by the tumor, to reduced production of erythropoietin by the kidney, and to the effects of long-term therapy. In addition, mild hemolysis may contribute to the anemia. A larger than expected fraction of patients may have megaloblastic anemia due to either folate or vitamin B_{12} deficiency. Granulocytopenia and thrombocytopenia are rare except when therapy-induced. Clotting abnormalities may be seen due to the failure of antibody-coated platelets to function properly; the interaction of the M component with clotting factors I, II, V, VII, or VIII; antibody to clotting factors; or amyloid damage of endothelium. Deep venous thrombosis is also observed with use of thalidomide, lenalidomide, or pomalidomide in combination with dexamethasone. Raynaud's phenomenon and impaired circulation may

result if the M component forms cryoglobulins, and hyperviscosity syndromes may develop depending on the physical properties of the M component (most common with IgM, IgG3, and IgA paraproteins). Hyperviscosity is defined based on the relative viscosity of serum as compared with water. Normal relative serum viscosity is 1.8 (i.e., serum is normally almost twice as viscous as water). Symptoms of hyperviscosity occur at a level greater than 4 centipoise (cP), which is usually reached at paraprotein concentrations of ~40 g/L (4 g/dL) for IgM, 50 g/L (5 g/dL) for IgG3, and 70 g/L (7 g/dL) for IgA; however, depending on chemical and physical properties of the paraprotein molecule, it can occasionally be observed at lower levels.

Although neurologic symptoms occur in a minority of patients, they may have many causes. Hypercalcemia may produce lethargy, weakness, depression, and confusion. Hyperviscosity may lead to headache, fatigue, shortness of breath, exacerbation or precipitation of heart failure, visual disturbances, ataxia, vertigo, retinopathy, somnolence, and coma. Bony damage and collapse may lead to cord compression, radicular pain, and loss of bowel and bladder control. Infiltration of peripheral nerves by amyloid can be a cause of carpal tunnel syndrome and other sensorimotor mono- and polyneuropathies. Neuropathy associated with monoclonal gammopathy of undetermined significance (MGUS) and myeloma is more frequently sensory than motor neuropathy and is associated with IgM more than other isotypes. In >50% of patients with neuropathy, the IgM monoclonal protein is directed against myelin-associated globulin (MAG). Sensory neuropathy is also a side effect of thalidomide and bortezomib therapy.

Many of the clinical features of myeloma, e.g., cord compression, pathologic fractures, hyperviscosity, sepsis, and hypercalcemia, can present as medical emergencies. Despite the widespread distribution of plasma cells in the body, tumor expansion is dominantly within bone and bone marrow and, for reasons unknown, rarely causes enlargement of spleen, lymph nodes, or gut-associated lymphatic tissue.

DIAGNOSIS AND STAGING

T e diagnosis of myeloma requires marrow plasmacytosis (>10%), a serum and/or urine M component, and end organ damage detailed in Table 18-1. Bone marrow plasma cells are CD138 and either monoclonal kappa or lambda light chain positive. T e most important differential diagnosis in patients with myeloma involves their separation from individuals with MGUS or smoldering multiple myeloma (SMM). MGUS is vastly more common than myeloma, occurring in 1% of the population older than age 50 years and in up to 10% of individuals older than age 75 years. T e diagnostic criteria for MGUS, SMM, and myeloma are described in Table 18-1. Although ~1% of patients per year with MGUS go on to develop myeloma, all myeloma is preceded by MGUS. Non-IgG subtype, abnormal kappa/lambda free light chain ratio, and serum M protein >15 g/L (1.5 g/dL) are associated with higher incidence of progression of MGUS to myeloma. Absence of all three features predicts a 5% chance of progression, whereas higher risk MGUS with the presence of all three features predicts a 60% chance of progression over 20 years. T e features responsible for higher risk of progression from SMM to MM are bone marrow plasmacytosis >10%, abnormal kappa/lambda free light chain ratio, and serum M protein >30 g/L (3 g/dL). Patients with only one of these three features have a 25% chance of progression to MM in 5 years, whereas patients with high-risk SMM with all three features have a 76% chance of progression. T ere are two important variants of myeloma—solitary bone plasmacytoma and solitary extramedullary plasmacytoma. T ese lesions are associated with an M component in <30% of the cases, they may affect younger individuals, and both are associated with median survivals of ≥10 years. Solitary bone plasmacytoma is a single lytic bone lesion without marrow plasmacytosis. Extramedullary plasmacytomas usually involve the submucosal lymphoid tissue of the nasopharynx or paranasal sinuses without marrow plasmacytosis. Both tumors are highly responsive to local radiation therapy. If an M component is present, it should disappear after treatment. Solitary bone plasmacytomas may recur in other bony sites or evolve into myeloma. Extramedullary plasmacytomas rarely recur or progress.

T e clinical evaluation of patients with myeloma includes a careful physical examination searching for tender bones and masses. Chest and bone radiographs may reveal lytic lesions or diffuse osteopenia. Magnetic resonance imaging (MRI) offers a sensitive means to document extent of bone marrow infiltration and cord or root compression in patients with pain syndromes. A complete blood count with differential may reveal anemia. Erythrocyte sedimentation rate is elevated. Rare patients (~1%) may have plasma cell leukemia with >2000 plasma cells/μL. T is may be seen in disproportionate frequency in IgD (12%) and IgE (25%) myelomas. Serum calcium, urea nitrogen, creatinine, and uric acid levels may be elevated. Protein electrophoresis and measurement of serum immunoglobulins and free light chains are useful for detecting and characterizing M spikes, supplemented by immunoelectrophoresis, which is especially sensitive for identifying low concentrations of M components not detectable by protein electrophoresis. A 24-h urine specimen is necessary to quantitate Bence Jones protein excretion. Serum alkaline phosphatase is usually normal even with extensive

TABLE 18-1

DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA, MYELOMA VARIANTS, AND MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE
MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)
M protein in serum <30 g/L Bone marrow clonal plasma cells <10% No evidence of other B cell proliferative disorders No myeloma-related organ or tissue impairment (no end organ damage, including bone lesions)[a]
Smoldering Multiple Myeloma (Asymptomatic Myeloma)
M protein in serum ≥30 g/L and/or Bone marrow clonal plasma cells ≥10% No myeloma-related organ or tissue impairment (no end organ damage, including bone lesions)[a] or symptoms
Symptomatic Multiple Myeloma
M protein in serum and/or urine Bone marrow (clonal) plasma cells[b] or plasmacytoma Myeloma-related organ or tissue impairment (end organ damage, including bone lesions)
Nonsecretory Myeloma
No M protein in serum and/or urine with immunofixation Bone marrow clonal plasmacytosis ≥10% or plasmacytoma Myeloma-related organ or tissue impairment (end organ damage, including bone lesions)a
Solitary Plasmacytoma of Bone
No M protein in serum and/or urine[c] Single area of bone destruction due to clonal plasma cells Bone marrow not consistent with multiple myeloma Normal skeletal survey (and magnetic resonance imaging of spine and pelvis if done) No related organ or tissue impairment (no end organ damage other than solitary bone lesion)a
POEMS Syndrome
All of the following four criteria must be met: 1. Polyneuropathy 2. Monoclonal plasma cell proliferative disorder 3. Any one of the following: (a) sclerotic bone lesions; (b) Castleman's disease; (c) elevated levels of vascular endothelial growth factor (VEGF) 4. Any one of the following: (a) organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy); (b) extravascular volume overload (edema, pleural effusion, or ascites); (c) endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic); (d) skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, and white nails); (e) papilledema; (f) thrombocytosis/polycythemia[d]

[a]Myeloma-related organ or tissue impairment (end organ damage): calcium levels increased: serum calcium >0.25 mmol/L above the upper limit of normal or >2.75 mmol/L; renal insufficiency: creatinine >173 mmol/L; anemia: hemoglobin 2 g/dL below the lower limit of normal or hemoglobin <10 g/dL; bone lesions: lytic lesions or osteoporosis with compression fractures (magnetic resonance imaging or computed tomography may clarify); other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months).
[b]If flow cytometry is performed, most plasma cells (>90%) will show a "neoplastic" phenotype.
[c]A small M component may sometimes be present.
[d]These features should have no attributable other causes and have temporal relation with each other.
Abbreviation: POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes.

bone involvement because of the absence of osteoblastic activity. It is also important to quantitate serum β_2-microglobulin and albumin (see below).

The serum M component will be IgG in 53% of patients, IgA in 25%, and IgD in 1%; 20% of patients will have only light chains in serum and urine. Dipsticks for detecting proteinuria are not reliable at identifying light chains, and the heat test for detecting Bence Jones protein is falsely negative in ~50% of patients with light chain myeloma. Fewer than 1% of patients have no identifiable M component; these patients usually have light chain myeloma in which renal catabolism has made the light chains undetectable in the urine. In most of these patients, light chains can now be detected by serum free light chain assay. IgD myeloma may also present with light chain disease. About two-thirds of patients with serum M components also have urinary light chains. The light chain isotype may have an impact on survival. Patients secreting lambda light chains have a significantly shorter

overall survival than those secreting kappa light chains. Whether this is due to some genetically important determinant of cell proliferation or because lambda light chains are more likely to cause renal damage and form amyloid than are kappa light chains is unclear. The heavy chain isotype may have an impact on patient management as well. About half of patients with IgM paraproteins develop hyperviscosity compared with only 2–4% of patients with IgA and IgG M components. Among IgG myelomas, it is the IgG3 subclass that has the highest tendency to form both concentration- and temperature-dependent aggregates, leading to hyperviscosity and cold agglutination at lower serum concentrations.

PROGNOSIS

Serum β_2-microglobulin is the single most powerful predictor of survival and can substitute for staging. β_2-Microglobulin is a protein of 11,000 mol wt with homologies to the constant region of immunoglobulins that is the light chain of the class I major histocompatibility antigens (HLA-A, -B, -C) on the surface of every cell. Patients with β_2-microglobulin levels <0.004 g/L have a median survival of 43 months, and those with levels >0.004 g/L have a survival of only 12 months. Combination of serum β_2-microglobulin and albumin levels forms the basis for a three-stage International Staging System (ISS) **(Table 18-2)** that predicts survival. With the use of high-dose therapy and the newer agents, the Durie-Salmon staging system is unable to predict outcome and thus is no longer used. High labeling index, circulating plasma cells, performance status, and high levels of lactate dehydrogenase are also associated with poor prognosis.

Other factors that may influence prognosis are the presence of cytogenetic abnormalities and hypodiploidy by karyotype, fluorescent in situ hybridization (FISH)–identified chromosome 17p deletion, and translocations t(4;14), (14;16), and t(14;20). Chromosome 13q deletion, previously thought to predict poor outcome, is not a predictor following the use of newer agents. Microarray profiling and comparative genomic hybridization have formed the basis for RNA- and DNA-based prognostic staging systems, respectively. The ISS system, along with cytogenetic changes, is the most widely used method for assessing prognosis (Table 18-2).

TABLE 18-2

RISK STRATIFICATION IN MYELOMA

Chromosomal Abnormalities		
Method	Standard Risk (80%) (Expected Survival 6–7+ Years)	High Risk (20%) (Expected Survival 2–3 Years)
Karyotype	No chromosomal aberration	Any abnormality on conventional karyotype
FISH	t(11;14)	Del(17p)
	t(6:14)	t(4:14)
	Del(13)	t(14:16)
		t(14;20)
International Staging System		
	Stage	Median Survival, Months
β_2M <3.5, alb ≥3.5	I (28%)[a]	62
β_2M <3.5, alb <3.5 or β_2M = 3.5–5.5	II (39%)	44
β_2M >5.5	III (33%)	29
Other features suggesting high-risk disease: De novo plasma cell leukemia; Extramedullary disease; Elevated lactate dehydrogenate (LDH); High-risk gene expression profile		

[a]Percentage of patients presenting at each stage.
Abbreviations: β_2M, serum β_2-microglobulin in mg/L; alb, serum albumin in g/dL; FISH, fluorescent in situ hybridization.

TREATMENT Multiple Myeloma

No specific intervention is indicated for patients with MGUS. Follow-up once a year or less frequently is adequate except in higher risk MGUS, where serum protein electrophoresis, complete blood count, creatinine, and calcium should be repeated every 6 months. A patient with MGUS and severe polyneuropathy is considered for therapeutic intervention if a causal relationship can be assumed, especially in absence of any other potential causes for neuropathy. Therapy can include plasmapheresis and occasionally rituximab in patients with IgM MGUS or myeloma-like therapy in those with IgG or IgA disease. About 10% of patients with myeloma are asymptomatic (SMM) and will have an indolent course demonstrating only very slow progression of disease over many years. For these patients, no specific therapeutic intervention is indicated, although early intervention with lenalidomide and dexamethasone may prevent progression from high-risk SMM to active MM. At present, patients with SMM only require antitumor therapy when the disease becomes symptomatic with development of anemia, hypercalcemia, progressive lytic bone lesions, renal dysfunction, or recurrent infections. Patients with solitary bone plasmacytomas and extramedullary plasmacytomas may be expected to enjoy prolonged disease-free survival after local radiation therapy at a dose of around 40 Gy. There is a low incidence of occult marrow involvement in patients with solitary bone plasmacytoma. Such patients are usually identified because their serum M component falls slowly or disappears initially, only to return after a few months. These patients respond well to systemic therapy.

Patients with symptomatic and/or progressive myeloma require therapeutic intervention. In general, such therapy is of two sorts: (1) systemic therapy to control the progression of myeloma and (2) symptomatic supportive care to prevent serious morbidity from the complications of the disease. T erapy can significantly prolong survival and improve the quality of life for myeloma patients.

T e therapy of myeloma includes an initial induction regimen followed by consolidation and/or maintenance therapy and, on subsequent progression, management of relapsed disease. T e therapy is partly dictated by the patient's age and comorbidities, which may affect a patient's ability to undergo high-dose therapy and transplantation.

T alidomide (200 mg daily), when combined with dexamethasone, achieved responses in two-thirds of newly diagnosed MM patients. Subsequently, lenalidomide (25 mg/d on days 1–21 every 4 weeks), an immunomodulatory derivative of thalidomide, and bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks), a proteasome inhibitor, have each been combined with dexamethasone (40 mg once every week) and obtained high response rates (>80%) in newly diagnosed patients with MM. Importantly, their superior toxicity profile with improved ef cacy has made them the preferred agents for induction therapy. Efforts to improve the fraction of patients responding and the degree of response have involved adding agents to the treatment regimen. T e combination of lenalidomide, bortezomib, and dexamethasone achieves close to a 100% response rate and 30% complete response rate, making it one of the preferred induction regimens in transplant-eligible patients. Other similar three-drug combinations (bortezomib, thalidomide, and dexamethasone or bortezomib, cyclophosphamide, and dexamethasone) also achieve >90% response rate. Herpes zoster prophylaxis is indicated if bortezomib is used, and neuropathy attendant to bortezomib can be decreased both by its subcutaneous administration and administration on a weekly schedule. Lenalidomide use requires prophylaxis for deep vein thrombosis (DVT) with either aspirin or warfarin or low-molecular-weight heparin if patients are at a greater risk of DVT. In patients receiving lenalidomide, stem cells should be collected within 6 months, because the continued use of lenalidomide may compromise the ability to collect adequate numbers of stem cells. Initial therapy is continued until maximal cytoreduction. In patients who are transplant candidates, alkylating agents such as melphalan should be avoided because they damage stem cells, leading to decreased ability to collect stem cells for autologous transplant.

In patients who are not transplant candidates due to physiologic age >70 years, significant cardiopulmonary problems, or other comorbid illnesses, the same two- or three-drug combinations described above are considered standard of care as induction therapy. Previously, therapy consisting of intermittent pulses of melphalan, an alkylating agent, with prednisone (MP; melphalan, 0.25 mg/kg per day, and prednisone, 1 mg/kg per day for 4 days) every 4–6 weeks was used. However, a number of studies have combined novel agents with MP and reported superior response and survival outcomes. In patients >65 years old, combining thalidomide with MP (MPT) obtains higher response rates and overall survival compared with MP alone. Similarly, significantly improved response (71 vs 35%) and overall survival (3-year survival 72 vs 59%) were observed with the combination of bortezomib and MP compared with MP alone. Lenalidomide added to MP followed by lenalidomide maintenance also prolonged progression-free survival compared with MP alone. T ese combinations of novel agents with MP also achieve high complete response rates (MPT, ~15%; MP plus bortezomib, ~30%; MP plus lenalidomide, ~20%; and MP, ~2–4%). Although combinations of MP with newer agents are an alternative in these patients, most studies favor continuous therapy with non-MP-containing regimens (e.g., lenalidomide plus dexamethasone) due to longer term safety profile and ef cacy.

Improvement in the serum M component may lag behind the symptomatic improvement. T e fall in M component depends on the rate of tumor kill and the fractional catabolic rate of immunoglobulin, which in turn depends on the serum concentration (for IgG). Light chain excretion, with a functional half-life of ~6 h, may fall within the first week of treatment. Because urine light chain levels may relate to renal tubular function, they are not a reliable measure of tumor cell kill, especially in patients with renal dysfunction; however, improvements in serum free light chain measurement are often seen sooner. Although patients may not achieve complete remission, clinical responses may last for long periods of time.

High-dose therapy and consolidation/maintenance are standard practice in the majority of eligible patients. Randomized studies comparing standard-dose therapy to high-dose melphalan therapy (HDT) with hematopoietic stem cell support have shown that HDT can achieve high overall response rates, with up to 25–40% additional complete responses and prolonged progression-free and overall survival; however, few, if any, patients are cured. Although two successive HDTs (tandem transplantations) are more effective than single HDT, the benefit is only observed in the subset of patients who do not achieve a complete or very good partial response to the first transplantation, which is rare. Moreover, a randomized study failed to show any significant difference in overall survival between early transplantation after induction therapy versus delayed transplantation at relapse. T ese data allow an option to delay transplantation, especially with the availability of more agents and combinations. Allogeneic transplantations may also produce high response rates, but treatment-related mortality may be as high as 40%. Nonmyeloablative allogeneic transplantation can reduce toxicity but is recommended only under the auspices of a clinical trial to exploit an immune graft-versus-myeloma effect while avoiding attendant toxicity.

Maintenance therapy prolongs remissions following standard-dose regimens as well as HDT. Two phase 3 studies have demonstrated improved progression-free survival, and one study showed prolonged overall survival in patients

receiving lenalidomide compared to placebo as maintenance therapy after HDT. In nontransplant candidates, another phase 3 study showed prolonged progression-free survival with lenalidomide maintenance after MP plus lenalidomide induction therapy. Although there is concern regarding an increased incidence of second primary malignancies in patients receiving lenalidomide maintenance, its benefits far outweigh the risk of progressive disease and death from myeloma. In patients with high-risk cytogenetics, lenalidomide and bortezomib have been combined and show promise as maintenance therapy after transplantation.

Relapsed myeloma can be treated with a number of agents including lenalidomide and/or bortezomib. T ese agents in combination with dexamethasone can achieve a partial response rate of up to 60% and a 10–15% complete response rate in patients with relapsed disease. T e combination of bortezomib and liposomal doxorubicin is active in relapsed myeloma. T alidomide, if not used as initial therapy, can achieve responses in refractory cases. T e second-generation proteasome inhibitor carfilzomib and immunomodulatory agent pomalidomide have shown ef cacy in relapsed and refractory MM, even MM refractory to lenalidomide and bortezomib. High-dose melphalan and stem cell transplantation, if not used earlier, also have activity as salvage therapy in patients with refractory disease.

T e median overall survival of patients with myeloma is 7–8+ years, with subsets of younger patients surviving more than 10 years. T e major causes of death are progressive myeloma, renal failure, sepsis, or therapy-related myelodysplasia. Nearly a quarter of patients die of myocardial infarction, chronic lung disease, diabetes, or stroke—all intercurrent illnesses related more to the age of the patient group than to the tumor.

Supportive care directed at the anticipated complications of the disease may be as important as primary antitumor therapy. Hypercalcemia generally responds well to bisphosphonates, glucocorticoid therapy, hydration, and natriuresis, and rarely requires calcitonin as well. Bisphosphonates (e.g., pamidronate 90 mg or zoledronate 4 mg once a month) reduce osteoclastic bone resorption and preserve performance status and quality of life, decrease bone-related complications, and may also have antitumor effects. Osteonecrosis of the jaw and renal dysfunction can occur in a minority of patients receiving aminobisphosphonate therapy. Treatments aimed at strengthening the skeleton such as fluorides, calcium, and vitamin D, with or without androgens, have been suggested, but are not of proven ef cacy. Kyphoplasty or vertebroplasty should be considered in patients with painful collapsed vertebra. Iatrogenic worsening of renal function may be prevented by maintaining a high fluid intake to prevent dehydration and enhance excretion of light chains and calcium. In the event of acute renal failure, plasmapheresis is ~10 times more effective at clearing light chains than peritoneal dialysis; however, its role in reversing renal failure remains controversial. Importantly, reducing the protein load by effective antitumor therapy with agents such as bortezomib may result in improvement in renal function in over half of the patients. Use of lenalidomide in renal failure is possible but requires dose modification, because it is renally excreted. Urinary tract infections should be watched for and treated early. Plasmapheresis may be the treatment of choice for hyperviscosity syndromes. Although the pneumococcus is a dreaded pathogen in myeloma patients, pneumococcal polysaccharide vaccines may not elicit an antibody response. Prophylactic administration of intravenous γ globulin preparations is used in the setting of recurrent serious infections. Chronic oral antibiotic prophylaxis is not warranted. Patients developing neurologic symptoms in the lower extremities, severe localized back pain, or problems with bowel and bladder control may need emergency MRI and local radiation therapy and glucocorticoids if cord compression is identified. In patients in whom neurologic deficit is increasing or substantial, emergent surgical decompression may be necessary. Most bone lesions respond to analgesics and systemic therapy, but certain painful lesions may respond most promptly to localized radiation. T e anemia associated with myeloma may respond to erythropoietin along with hematinics (iron, folate, cobalamin). T e pathogenesis of the anemia should be established and specific therapy instituted, whenever possible.

WALDENSTRÖM'S MACROGLOBULINEMIA

In 1948, Waldenström described a malignancy of lymphoplasmacytoid cells that secreted IgM. In contrast to myeloma, the disease was associated with lymphadenopathy and hepatosplenomegaly, but the major clinical manifestation was hyperviscosity syndrome. T e disease resembles the related diseases chronic lymphocytic leukemia, myeloma, and lymphocytic lymphoma. It originates from a post–germinal center B cell that has undergone somatic mutations and antigenic selection in the lymphoid follicle and has the characteristics of an IgM-bearing memory B cell. Waldenström's macroglobulinemia (WM) and IgM myeloma follow a similar clinical course, but therapeutic options are different. T e diagnosis of IgM myeloma is usually reserved for patients with lytic bone lesions and predominant infiltration with CD138+ plasma cells in the bone marrow. Such patients are at greater risk of pathologic fractures than patients with WM.

A familial occurrence is common in WM, but its molecular bases are yet unclear. A distinct MYD88 L265P somatic mutation has been reported in over 90% of patients with WM and the majority of IgM MGUS. Presence of this mutation is now used as a diagnostic test to discriminate WM from marginal zone lymphomas (MZLs), IgM-secreting myeloma, and chronic lymphocytic leukemia (CLL) with plasmacytic

differentiation. T is mutation also explains the molecular pathogenesis of the disease, with involvement of Toll-like receptor (TLR) and interleukin 1 receptor (IL-1R) signaling leading to activation of IL-1R–associated kinase (IRAK) 4 and IRAK1 followed by nuclear factor-κB (NF-κB) activation. T e disease is similar to myeloma in being slightly more common in men and occurring with increased incidence with increasing age (median 64 years). T ere have been reports that the IgM in some patients with macroglobulinemia may have specificity for myelin-associated glycoprotein (MAG), a protein that has been associated with demyelinating disease of the peripheral nervous system and may be lost earlier and to a greater extent than the better known myelin basic protein in patients with multiple sclerosis. Sometimes patients with macroglobulinemia develop a peripheral neuropathy, and half of these patients are positive for anti-MAG antibody. T e neuropathy may precede the appearance of the neoplasm. T ere is speculation that the whole process begins with a viral infection that may elicit an antibody response that cross-reacts with a normal tissue component.

Like myeloma, the disease involves the bone marrow, but unlike myeloma, it does not cause bone lesions or hypercalcemia. Bone marrow shows >10% infiltration with lymphoplasmacytic cells (surface IgM+, CD19+, CD20+, and CD22+, rarely CD5+, but CD10− and CD23−) with an increase in number of mast cells. Like myeloma, an M component is present in the serum in excess of 30 g/L (3 g/dL), but unlike myeloma, the size of the IgM paraprotein results in little renal excretion, and only ~20% of patients excrete light chains. T erefore, renal disease is not common. T e light chain isotype is kappa in 80% of the cases. Patients present with weakness, fatigue, and recurrent infections similar to myeloma patients, but epistaxis, visual disturbances, and neurologic symptoms such as peripheral neuropathy, dizziness, headache, and transient paresis are much more common in macroglobulinemia. Physical examination reveals adenopathy and hepatosplenomegaly, and ophthalmoscopic examination may reveal vascular segmentation and dilation of the retinal veins characteristic of hyperviscosity states. Patients may have a normocytic, normochromic anemia, but rouleaux formation and a positive Coombs' test are much more common than in myeloma. Malignant lymphocytes are usually present in the peripheral blood. About 10% of macroglobulins are cryoglobulins. T ese are pure M components and are not the mixed cryoglobulins seen in rheumatoid arthritis and other autoimmune diseases. Mixed cryoglobulins are composed of IgM or IgA complexed with IgG, for which they are specific. In both cases, Raynaud's phenomenon and serious vascular symptoms precipitated by the cold may occur, but mixed cryoglobulins are not commonly associated with malignancy. Patients suspected of having a cryoglobulin based on history and physical examination should have their blood drawn into a warm syringe and delivered to the laboratory in a container of warm water to avoid errors in quantitating the cryoglobulin.

TREATMENT Waldenström's Macroglobulinemia

Control of serious hyperviscosity symptoms such as an altered state of consciousness or paresis can be achieved acutely by plasmapheresis because 80% of the IgM paraprotein is intravascular. T e median survival of affected individuals is ~50 months, similar to that of MM. However, many patients with WM have indolent disease that does not require therapy. Pretreatment parameters including older age, male sex, general symptoms, and cytopenias define a high-risk population. Treatment is usually not initiated unless the disease is symptomatic or increasing anemia, hyperviscosity, lymphadenopathy, or hepatosplenomegaly is present. Bortezomib and bendamustine are two agents with significant ef cacy in WM. Rituximab (anti-CD20) can produce responses, alone or combined with either of these two agents. Rituximab can produce IgM flare, so its use is initially withheld in patients with high IgM levels. Fludarabine (25 mg/m^2 per day for 5 days every 4 weeks) and cladribine (0.1 mg/kg per day for 7 days every 4 weeks) are also highly effective single agents. With identification of the MYD88 mutation, BTK and IRAK1/4 inhibitors are being evaluated and show significant responses. Although high-dose therapy plus autologous transplantation is an option, its use has declined due to the availability of other effective agents.

POEMS SYNDROME

T e features of this syndrome are polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS). Diagnostic criteria are described in Table 18-1. Patients usually have a severe, progressive sensorimotor polyneuropathy associated with sclerotic bone lesions from myeloma. Polyneuropathy occurs in ~1.4% of myelomas, but the POEMS syndrome is only a rare subset of that group. Unlike typical myeloma, hepatomegaly and lymphadenopathy occur in about two-thirds of patients, and splenomegaly is seen in one-third. T e lymphadenopathy frequently resembles Castleman's disease histologically, a condition that has been linked to IL-6 overproduction. T e endocrine manifestations include amenorrhea in women and impotence and gynecomastia in men. Hyperprolactinemia due to loss of normal inhibitory control by the hypothalamus may be associated with other central nervous system manifestations such as papilledema

and elevated cerebrospinal fluid pressure and protein. Type 2 diabetes mellitus occurs in about one-third of patients. Hypothyroidism and adrenal insuf ciency are occasionally noted. Skin changes are diverse: hyperpigmentation, hypertrichosis, skin thickening, and digital clubbing. Other manifestations include peripheral edema, ascites, pleural effusions, fever, and thrombocytosis. Not all the components of POEMS syndrome may be present initially.

T e pathogenesis of the disease is unclear, but high circulating levels of the proinflammatory cytokines IL-1, IL-6, VEGF, and TNF have been documented, and levels of the inhibitory cytokine transforming growth factor β are lower than expected. Treatment of the myeloma may result in an improvement in the other disease manifestations.

Patients are often treated similarly to those with myeloma. Plasmapheresis does not appear to be of benefit in POEMS syndrome. Patients presenting with isolated sclerotic lesions may have resolution of neuropathic symptoms after local therapy for plasmacytoma with radiotherapy. Similar to multiple myeloma, novel agents and high-dose therapy with autologous stem cell transplantation have been pursued in selected patients and have been associated with prolonged progression-free survival.

HEAVY CHAIN DISEASES

T e heavy chain diseases are rare lymphoplasmacytic malignancies. T eir clinical manifestations vary with the heavy chain isotype. Patients have absence of light chain and secrete a defective heavy chain that usually has an intact Fc fragment and a deletion in the Fd region. Gamma, alpha, and mu heavy chain diseases have been described, but no reports of delta or epsilon heavy chain diseases have appeared. Molecular biologic analysis of these tumors has revealed structural genetic defects that may account for the aberrant chain secreted.

GAMMA HEAVY CHAIN DISEASE (FRANKLIN'S DISEASE)

T is disease affects individuals of widely different age groups and countries of origin. It is characterized by lymphadenopathy, fever, anemia, malaise, hepatosplenomegaly, and weakness. It is frequently associated with autoimmune diseases, especially rheumatoid arthritis. Its most distinctive symptom is palatal edema, resulting from involvement of nodes in Waldeyer's ring, and this may progress to produce respiratory compromise. T e diagnosis depends on the demonstration of an anomalous serum M component (often <20 g/L [<2 g/dL]) that reacts with anti-IgG but not anti–light chain reagents. T e M component is typically present in both serum and urine. Most of the paraproteins have been of the γ_1 subclass, but other subclasses have been seen. T e patients may have thrombocytopenia, eosinophilia, and nondiagnostic bone marrow that may show increased numbers of lymphocytes or plasma cells that do not stain for light chain. Patients usually have a rapid downhill course and die of infection; however, some patients have survived 5 years with chemotherapy. T erapy is indicated when symptomatic and involves chemotherapeutic combinations used in low-grade lymphoma. Rituximab has also been reported to show ef cacy.

ALPHA HEAVY CHAIN DISEASE (SELIGMANN'S DISEASE)

T is is the most common of the heavy chain diseases. It is closely related to a malignancy known as Mediterranean lymphoma, a disease that affects young persons in parts of the world where intestinal parasites are common, such as the Mediterranean, Asia, and South America. T e disease is characterized by an infiltration of the lamina propria of the small intestine with lymphoplasmacytoid cells that secrete truncated alpha chains. Demonstrating alpha heavy chains is dif cult because the alpha chains tend to polymerize and appear as a smear instead of a sharp peak on electrophoretic profiles. Despite the polymerization, hyperviscosity is not a common problem in alpha heavy chain disease. Without J chain–facilitated dimerization, viscosity does not increase dramatically. Light chains are absent from serum and urine. T e patients present with chronic diarrhea, weight loss, and malabsorption and have extensive mesenteric and paraaortic adenopathy. Respiratory tract involvement occurs rarely. Patients may vary widely in their clinical course. Some may develop diffuse aggressive histologies of malignant lymphoma. Chemotherapy may produce long-term remissions. Rare patients appear to have responded to antibiotic therapy, raising the question of the etiologic role of antigenic stimulation, perhaps by some chronic intestinal infection. Chemotherapy plus antibiotics may be more effective than chemotherapy alone. Immunoproliferative small-intestinal disease (IPSID) is recognized as an infectious pathogen–associated human lymphoma that has association with Campylobacter jejuni. It involves mainly the proximal small intestine resulting in malabsorption, diarrhea, and abdominal pain. IPSID is associated with excessive plasma cell differentiation and produces truncated alpha heavy chain proteins lacking the light chains as well as the first constant domain. Early-stage IPSID responds to antibiotics (30–70% complete remission). Most untreated IPSID patients progress to lymphoplasmacytic and immunoblastic

lymphoma. Patients not responding to antibiotic therapy are considered for treatment with combination chemotherapy used to treat low-grade lymphoma.

MU HEAVY CHAIN DISEASE

T e secretion of isolated mu heavy chains into the serum appears to occur in a very rare subset of patients with CLL. T e only features that may distinguish patients with mu heavy chain disease are the presence of vacuoles in the malignant lymphocytes and the excretion of kappa light chains in the urine. T e diagnosis requires ultracentrifugation or gel filtration to confirm the nonreactivity of the paraprotein with the light chain reagents, because some intact macroglobulins fail to interact with these serums. T e tumor cells seem to have a defect in the assembly of light and heavy chains, because they appear to contain both in their cytoplasm. T ere is no evidence that such patients should be treated differently from other patients with CLL **(Chap. 16)**.

CHAPTER 19

AMYLOIDOSIS

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GENERAL PRINCIPLES

Amyloidosis is the term for a group of protein folding disorders characterized by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. A robust cellular machinery exists to chaperone proteins during the process of synthesis and secretion, to ensure that they achieve correct tertiary conformation and function, and to eliminate proteins that misfold. However, genetic mutation, incorrect processing, and other factors may favor misfolding, with consequent loss of normal protein function and intracellular or extracellular aggregation. Many diseases, ranging from cystic fibrosis to Alzheimer's disease, are now known to involve protein misfolding. In the amyloidoses, the aggregates are typically extracellular, and the misfolded protein subunits assume a common antiparallel, β-pleated sheet–rich structural conformation that leads to the formation of higher-order oligomers and then of fibrils with unique staining properties. The term amyloid was coined around 1854 by the pathologist Rudolf Virchow, who thought that these deposits resembled starch (Latin amylum) under the microscope.

Amyloid diseases, defined by the biochemical nature of the protein composing the fibril deposits, are classified according to whether they are systemic or localized, whether they are acquired or inherited, and their clinical patterns **(Table 19-1)**. The standard nomenclature is AX, where A indicates amyloidosis and X represents the protein present in the fibril. This chapter focuses primarily on the systemic forms. AL refers to amyloid composed of immunoglobulin light chains (LCs); this disorder, formerly termed primary systemic amyloidosis, arises from a clonal B cell or plasma cell disorder and can be associated with myeloma or lymphoma. AF refers to the familial amyloidoses, which are most commonly due to mutations in transthyretin (TTR), the transport protein for thyroid hormone and retinol-binding protein. AA amyloid is composed of the acute-phase reactant protein serum amyloid A (SAA) and occurs in the setting of chronic inflammatory or infectious diseases; for this reason, this type was formerly known as secondary amyloidosis. $A\beta_2M$ amyloid results from misfolded β_2-microglobulin, occurring in individuals with long-standing renal disease who have undergone dialysis, typically for years. Aβ, the most common form of localized amyloidosis, is found in the brain of patients with Alzheimer's disease after abnormal proteolytic processing and aggregation of polypeptides derived from the amyloid precursor protein.

Diagnosis and treatment of the amyloidoses rest upon the histopathologic identification of amyloid deposits and immunohistochemical, biochemical, or genetic determination of amyloid type **(Fig. 19-1)**. In the systemic amyloidoses, the clinically involved organs can be biopsied, but amyloid deposits may be found in any tissue of the body. Historically, blood vessels of the gingiva or rectal mucosa were often examined, but the most easily accessible tissue—positive in more than 80% of patients with systemic amyloidosis—is fat. After local anesthesia, fat is aspirated from the abdominal pannus with a 16-gauge needle. Fat globules expelled onto a glass slide can be stained, thus avoiding a surgical procedure. If this material is negative, more invasive biopsies of the kidney, heart, liver, or gastrointestinal tract can be considered in patients in whom amyloidosis is suspected. The regular β-sheet structure of amyloid deposits exhibits a unique "apple green" birefringence by polarized light microscopy when stained with Congo red dye; other regular protein structures (e.g., collagen) appear white under these conditions. The 10-nm-diameter fibrils can also be visualized by electron microscopy of paraformaldehyde-fixed tissue. Once amyloid is found, the protein type must be determined by immunohistochemistry, immunoelectron microscopy, or extraction and biochemical analysis employing mass spectrometry; gene sequencing is used to identify mutants causing AF amyloid. The patient's history, physical findings, and clinical presentation, including

TABLE 19-1

AMYLOID PRECURSOR PROTEINS AND THEIR CLINICAL SYNDROMES

DESIGNATION	PRECURSOR	CLINICAL SYNDROME	CLINICAL INVOLVEMENT
Systemic Amyloidoses			
AL	Immunoglobulin light chain	Primary or myeloma-associated[a]	Any
AH	Immunoglobulin heavy chain	Rare variant of primary or myeloma-associated	Any
AA	Serum amyloid A protein	Secondary; reactive[b]	Renal, other
Aβ2M	β2-Microglobulin	Hemodialysis-associated	Synovial tissue, bone
ATTR	Transthyretin	Familial (mutant) Age-related (wild type)	Cardiac, peripheral and autonomic nerves
AApoAI	Apolipoprotein AI	Familial	Hepatic, renal
AApoAII	Apolipoprotein AII	Familial	Renal
AGel	Gelsolin	Familial	Cornea, cranial nerves, skin, renal
AFib	Fibrinogen Aα	Familial	Renal
ALys	Lysozyme	Familial	Renal, hepatic
ALECT2	Leukocyte chemotactic factor 2	Undefined	Renal
Localized Amyloidoses			
Aβ	Amyloid β protein	Alzheimer's disease; Down syndrome	Central nervous system
ACys	Cystatin C	Cerebral amyloid angiopathy	Central nervous system, vascular
APrP	Prion protein	Spongiform encephalopathies	Central nervous system
AIAPP	Islet amyloid polypeptide (amylin)	Diabetes-associated	Pancreas
ACal	Calcitonin	Medullary carcinoma of the thyroid	Thyroid
AANF	Atrial natriuretic factor	Atrial fibrillation	Cardiac atria
APro	Prolactin	Endocrinopathy	Pituitary
ASgl	Semenogelin I	Age-related; incidental autopsy or biopsy finding	Seminal vesicles

[a]Localized AL deposits can occur in skin, conjunctiva, urinary bladder, and the tracheobronchial tree.
[b]Secondary to chronic inflammation or infection or to a hereditary periodic fever syndrome such as familial Mediterranean fever.

age and ethnic origin, organ system involvement, underlying diseases, and family history, may provide helpful clues as to the type of amyloid. However, there can be considerable overlap in clinical presentations, and accurate typing is essential to guide appropriate therapy.

The mechanisms of fibril formation and tissue toxicity remain controversial. The "amyloid hypothesis," as it is currently understood, proposes that precursor proteins undergo a process of reversible unfolding or misfolding; misfolded proteins form oligomeric aggregates, higher-order polymers, and then fibrils that deposit in tissues. Accumulating evidence suggests that the oligomeric intermediates may constitute the most toxic species. Oligomers are more capable than large fibrils of interacting with cells and inducing formation of reactive oxygen species and stress signaling. Ultimately, the fibrillar tissue deposits are likely to interfere with normal organ function. A more sophisticated understanding of the mechanisms leading to amyloid formation and cell and tissue dysfunction will continue to provide new targets for therapies.

The clinical syndromes of the amyloidoses are associated with relatively nonspecific alterations in routine laboratory tests. Blood counts are usually normal, although the erythrocyte sedimentation rate is frequently elevated. Patients with glomerular kidney involvement generally have proteinuria, often in the nephrotic range, leading to hypoalbuminemia that may be severe; patients with serum albumin levels below 2 g/dL generally have pedal edema or anasarca. Amyloid cardiomyopathy is characterized by concentric ventricular hypertrophy and diastolic dysfunction associated with elevation of brain natriuretic peptide or N-terminal pro–brain natriuretic peptide as well as troponin. These cardiac biomarkers can be used for disease staging, prognostication, and disease activity monitoring in patients with AL amyloidosis. Notably, renal insufficiency can falsely elevate levels of these biomarkers. Recently, biomarkers of cardiac remodeling—i.e., matrix metalloproteinases and tissue inhibitors of metalloproteinases—have been found to be altered in the serum of patients with amyloid cardiomyopathy. Electrocardiographic and echocardiographic features of amyloid cardiomyopathy are described below. Patients with liver involvement, even when advanced, usually develop cholestasis with an elevated alkaline

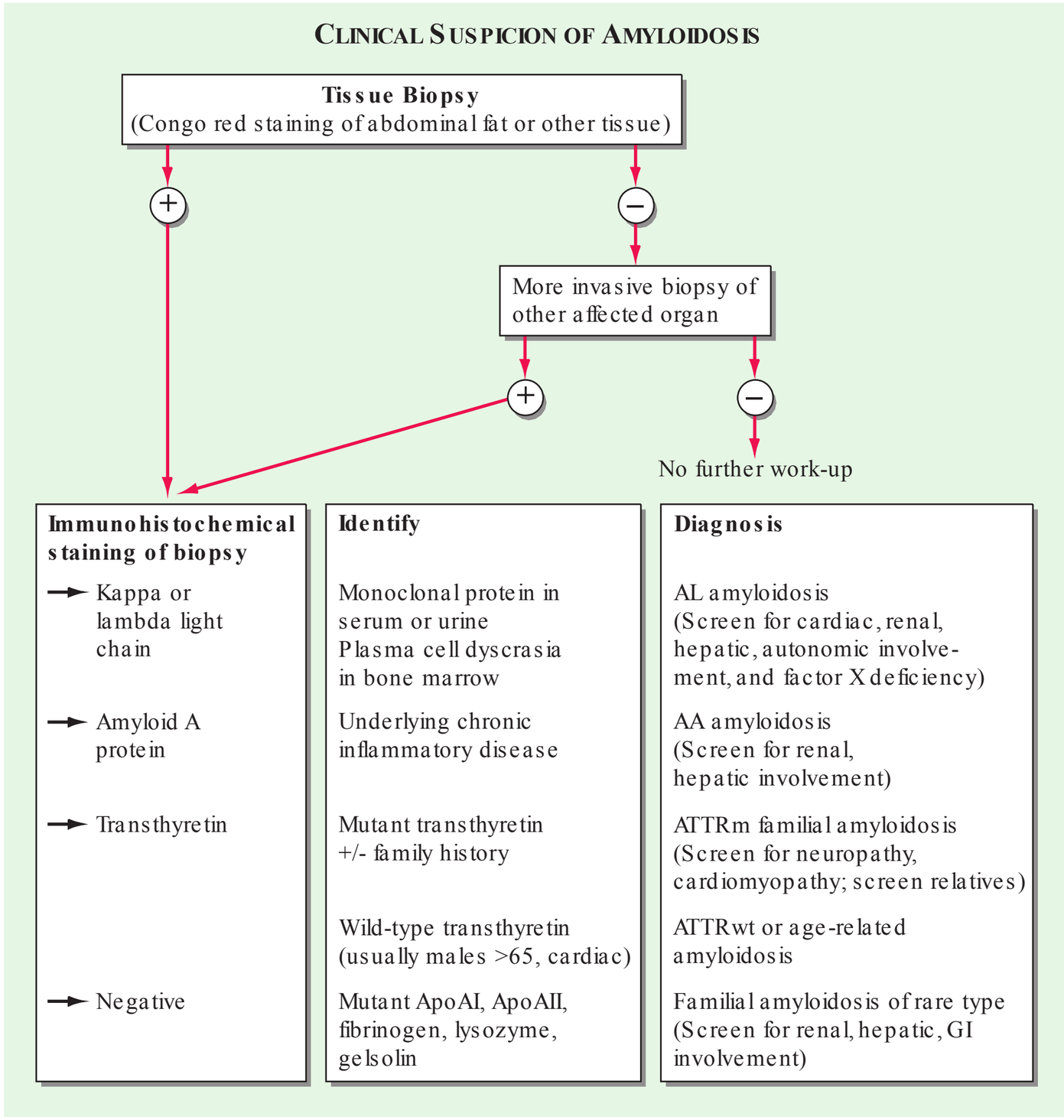

FIGURE 19-1
Algorithm for the diagnosis of amyloidosis and determination of type. Clinical suspicion: unexplained nephropathy, cardiomyopathy, neuropathy, enteropathy, arthropathy, and macroglossia. ApoAI, apolipoprotein AI; ApoAII, apolipoprotein AII; GI, gastrointestinal.

phosphatase concentration but minimal alteration of the aminotransferases and preservation of synthetic function. In AL amyloidosis, endocrine organs may be infiltrated with fibrils, and hypothyroidism, hypoadrenalism, or even hypopituitarism can occur. Although none of these findings is specific for amyloidosis, the presence of abnormalities in multiple organ systems should raise suspicion regarding this diagnosis.

AL AMYLOIDOSIS

Etiology and incidence

AL amyloidosis is most frequently caused by a clonal expansion of bone-marrow plasma cells that secrete a monoclonal immunoglobulin LC depositing as amyloid fibrils in tissues. Whether the clonal plasma cells produce an LC that misfolds and leads to AL amyloidosis or an LC that folds properly, allowing the cells to inexorably expand over time and develop into multiple myeloma **(Chap. 18),** may depend upon primary sequence or other genetic or epigenetic factors. AL amyloidosis can occur with multiple myeloma or other B lymphoproliferative diseases, including non-Hodgkin's lymphoma **(Chap. 16)** and Waldenström's macroglobulinemia **(Chap. 18).** AL amyloidosis is the most common type of systemic amyloidosis diagnosed in North America. Its incidence has been estimated at 4.5 cases/100,000 population; however, ascertainment continues to be inadequate, and the true incidence may be much higher. AL amyloidosis, like other plasma cell diseases, usually occurs after age 40 and is often rapidly progressive and fatal if untreated.

Pathology and clinical features

Amyloid deposits are usually widespread in AL amyloidosis and can be present in the interstitium of any organ outside the central nervous system. T e amyloid fibril deposits are composed of full-length 23-kDa monoclonal immunoglobulin LCs as well as fragments. Accessory molecules co-deposited with LC fibrils (as well as with other amyloid fibrils) include serum amyloid P component, other proteins,

glycosaminoglycans, and metal ions. Although all kappa and lambda LC subtypes have been identified in AL amyloid fibrils, lambda subtypes predominate. The lambda 6 subtype appears to have unique structural properties that predispose it to fibril formation, often in the kidney.

AL amyloidosis is often a rapidly progressive disease that presents as a pleiotropic set of clinical syndromes, recognition of which is key for initiation of the appropriate workup. Nonspecific symptoms of fatigue and weight loss are common; however, the diagnosis is rarely considered until symptoms referable to a specific organ develop. The kidneys are the most frequently involved organ and are affected in 70–80% of patients. Renal amyloidosis usually manifests as proteinuria, often in the nephrotic range and associated with hypoalbuminemia, secondary hypercholesterolemia and hypertriglyceridemia, and edema or anasarca. In some patients, interstitial rather than glomerular amyloid deposition can produce azotemia without proteinuria. The heart is the second most commonly affected organ (50–60% of patients), and cardiac involvement is the leading cause of death from AL amyloidosis. Early on, the electrocardiogram may show low voltage in the limb leads with a pseudo-infarct pattern. Echocardiographic features of disease include concentrically thickened ventricles and diastolic dysfunction with an abnormal strain pattern a "sparkly" appearance has been described but is often not seen with modern high-resolution echocardiographic techniques. Poor atrial contractility occurs even in sinus rhythm, and patients with cardiac amyloidosis are at risk for development of atrial thrombi and stroke. Cardiac MRI can show increased wall thickness, and characteristic enhancement of the subendocardium has been described following injection of gadolinium contrast. Nervous system symptoms include peripheral sensorimotor neuropathy and/or autonomic dysfunction manifesting as gastrointestinal motility disturbances (early satiety, diarrhea, constipation), impotence, orthostatic hypotension, and/or neurogenic bladder. Macroglossia **(Fig. 19-2A)**, a pathognomonic sign of AL amyloidosis, is seen in only ~10% of patients. Liver involvement causes cholestasis and hepatomegaly. The spleen is frequently involved, and there may be functional hyposplenism in the absence of significant splenomegaly. Many patients experience "easy bruising" due to amyloid deposits in capillaries or deficiency of clotting factor X, which can bind to amyloid fibrils; cutaneous ecchymoses appear, particularly around the eyes, producing the "raccoon-eye" sign **(Fig. 19-2B)**, another uncommon but pathognomonic finding. Other findings include nail dystrophy **(Fig. 19-2C)**, alopecia, and amyloid arthropathy with thickening of synovial membranes in the wrists and shoulders. The presence of a

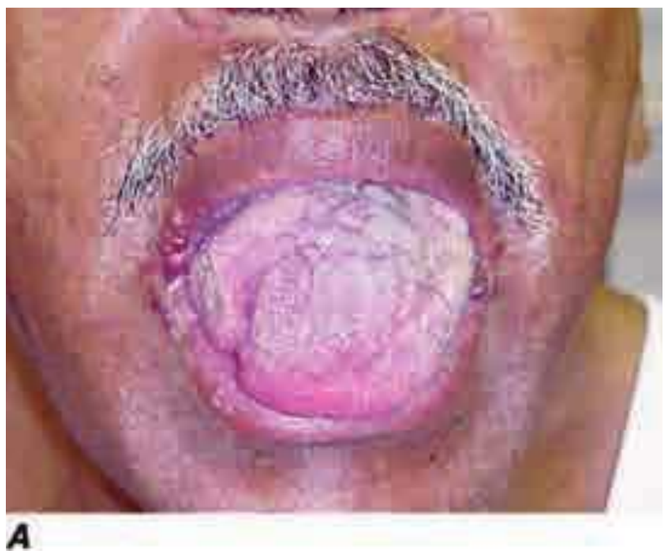

FIGURE 19-2
Clinical signs of AL amyloidosis. A. Macroglossia. B. Periorbital ecchymoses. C. Fingernail dystrophy.

multisystemic illness or general fatigue along with any of these clinical syndromes should prompt a workup for amyloidosis.

Diagnosis

Identification of an underlying clonal plasma cell or B lymphoproliferative process and a clonal LC are key to the diagnosis of AL amyloidosis. Serum protein electrophoresis and urine protein electrophoresis, although of value in multiple myeloma, are not useful screening tests if AL amyloidosis is suspected because the clonal LC or whole immunoglobulin often is not present in sufficient amounts to produce a monoclonal "M-spike" in the serum or LC (Bence Jones) protein in the urine. However, more than 90% of patients with AL amyloidosis have serum or urine monoclonal LC or whole immunoglobulin detectable by immunofixation electrophoresis of serum (SIFE) or urine (UIFE) **(Fig. 19-3A)** or by nephelometric measurement of "free" LCs (i.e.,

LCs circulating in monomeric form rather than in an immunoglobulin tetramer with heavy chain). Examining the ratio as well as the absolute amount of free LCs is essential, as renal insufficiency reduces LC clearance, elevating both isotypes. In addition, an increased percentage of plasma cells in the bone marrow—typically 5–30% of nucleated cells—is found in ~90% of patients. Kappa or lambda clonality should be demonstrated by flow cytometry, immunohistochemistry, or in situ hybridization for LC mRNA **(Fig. 19-3B)**.

A monoclonal serum protein by itself is not diagnostic of amyloidosis, since monoclonal gammopathy of uncertain significance is common in older patients **(Chap. 18)**. However, when monoclonal gammopathy of uncertain significance is found in patients with biopsy-proven amyloidosis, the AL type should be strongly suspected. Similarly, patients thought to have "smoldering myeloma" because of a modest elevation of bone-marrow plasma cells should be screened for AL amyloidosis if they have signs or symptoms of renal, cardiac, or neurologic disease. Accurate tissue amyloid typing is essential for appropriate treatment. Immunohistochemical staining of the amyloid deposits is useful if they bind one LC antibody in preference to the other; some AL deposits bind antibodies nonspecifically. Immunoelectron microscopy is more reliable, and mass

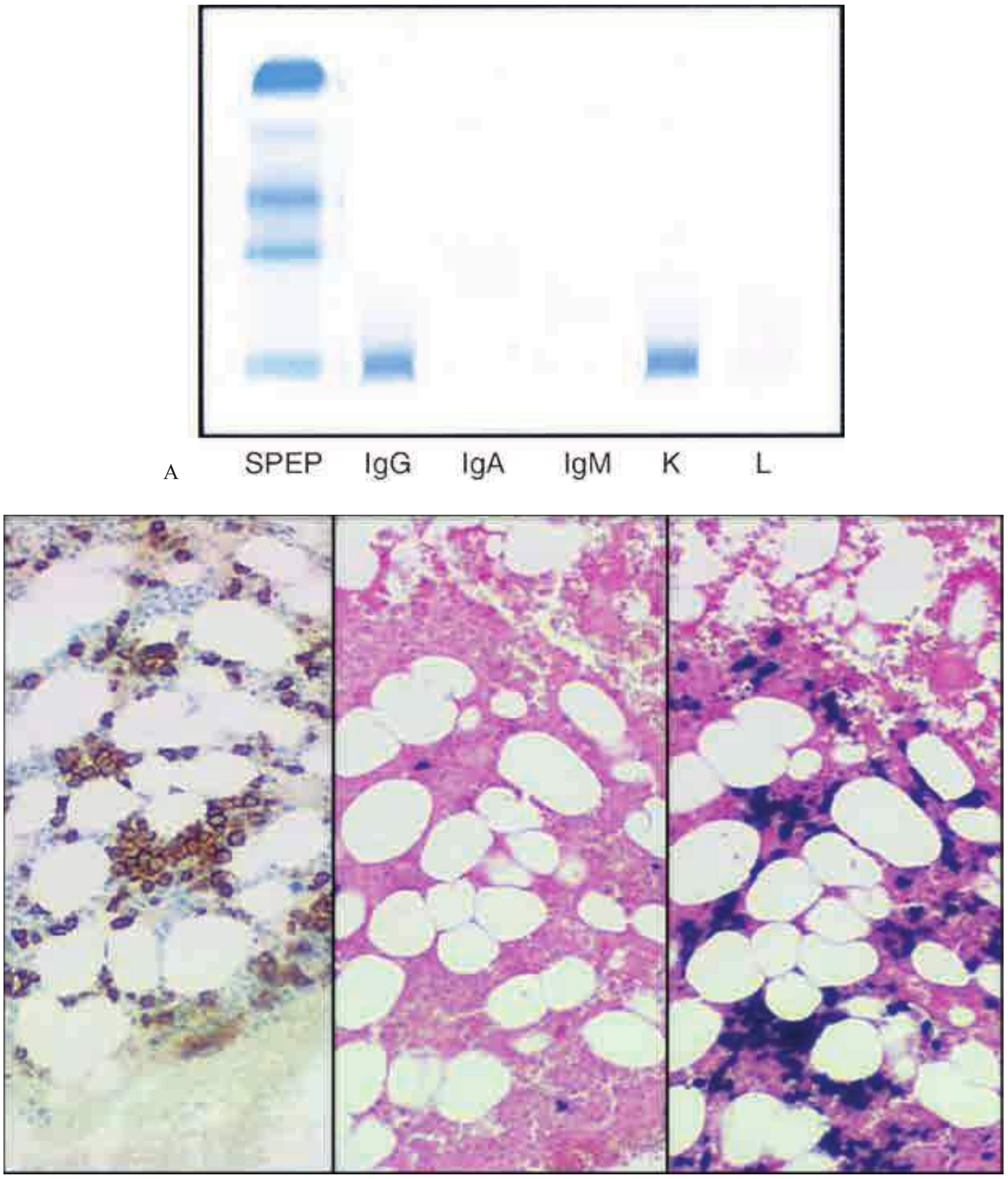

FIGURE 19-3
Laboratory features of AL amyloidosis. A. Serum immunofixation electrophoresis reveals an IgGκ monoclonal protein in this example; serum protein electrophoresis is often normal. B. Bone-marrow biopsy sections stained by immunohistochemistry with antibody to CD138 (syndecan, highly expressed on plasma cells) (left) or by in situ hybridization with fuorescein-tagged probes (Ventana Medical Systems) binding to κ mRNA (center) and λ mRNA (right) in plasma cells. (Photomicrograph courtesy of C. O'Hara; with permission.)

spectrometry–based microsequencing of small amounts of protein extracted from fibril deposits can also be undertaken. In ambiguous cases, other forms of amyloidosis should be thoroughly excluded with appropriate genetic and other testing.

TREATMENT AL Amyloidosis

Extensive multisystemic involvement typifies AL amyloidosis, and the median survival period without treatment is usually only ~1–2 years from the time of diagnosis. Current therapies target the clonal bone-marrow plasma cells, using approaches employed for multiple myeloma. Treatment with oral melphalan and prednisone can decrease the plasma cell burden but rarely leads to complete hematologic remission, meaningful organ responses, or improved survival and is no longer widely used. T e substitution of dexamethasone for prednisone produces a higher response rate and more durable remissions, although dexamethasone is not always well tolerated by patients with significant edema or cardiac disease. High-dose IV melphalan followed by autologous stem cell transplantation (HDM/SCT) produces complete hematologic responses in ~40% of treated patients, as determined by loss of clonal plasma cells in the bone marrow and disappearance of the monoclonal LC, as determined by SIFE/UIFE and free LC quantitation. Hematologic responses can be followed in the subsequent 6–12 months as improvements in organ function and quality of life. Hematologic responses appear to be more durable after HDM/SCT than in multiple myeloma, with remissions continuing in some patients beyond 15 years without additional treatment. Unfortunately, only about half of AL amyloidosis patients are suitable for aggressive treatment, and, even at specialized treatment centers, transplantation-related mortality rates are higher than those for other hematologic diseases because of impaired organ function. Amyloid cardiomyopathy, poor nutritional and performance status, and multiorgan disease contribute to excess morbidity and mortality. A bleeding diathesis resulting from adsorption of clotting factor X to amyloid fibrils also increases mortality rates; however, this syndrome occurs in only 5–10% of patients. A randomized multicenter trial conducted in France compared oral melphalan and dexamethasone with HDM/SCT and failed to show a benefit of dose-intensive treatment, although the transplantation-related mortality rate in this study was very high. It has become clear that careful selection of patients and expert peritransplantation management are essential in reducing transplantation-related mortality.

For patients with impaired cardiac function or arrhythmias due to amyloid involvement of the myocardium, the median survival period is only ~6 months without treatment. In these patients, cardiac transplantation can be performed and followed by HDM/SCT to eliminate the noxious clone and prevent amyloid deposition in the transplanted heart or other organs.

Novel anti–plasma cell agents have been investigated for treatment of plasma cell diseases. T e immunomodulators thalidomide, lenalidomide, and pomalidomide display activity; dosing may need to be adjusted compared to their usage for myeloma. T e proteasome inhibitor bortezomib has also been found to be ef ective in single-center and multicenter trials. Anti-fibril small molecules and humanized monoclonal antibodies are also being tested. Clinical trials are essential in improving therapy for this rare disease.

Supportive care is important for patients with any type of amyloidosis. For nephrotic syndrome, diuretics and supportive stockings can ameliorate edema; angiotensin-converting enzyme inhibitors should be used with caution and have not been shown to slow renal disease progression. Ef ective diuresis can be facilitated with albumin infusions to raise intravascular oncotic pressure. Congestive heart failure due to amyloid cardiomyopathy is best treated with diuretics; it is important to note that digitalis, calcium channel blockers, and beta blockers are relatively contraindicated as they can interact with amyloid fibrils and produce heart block and worsening heart failure. Amiodarone has been used for atrial and ventricular arrhythmias. Automatic implantable defibrillators have reduced ef ectiveness due to the thickened myocardium, but they may benefit some patients. Atrial ablation is an ef ective approach for atrial fibrillation. For conduction abnormalities, ventricular pacing may be indicated. Atrial contractile dysfunction is common in amyloid cardiomyopathy and is an indication for anticoagulation even in the absence of atrial fibrillation. Autonomic neuropathy can be treated with α agonists such as midodrine to support the blood pressure; gastrointestinal dysfunction may respond to motility or bulk agents. Nutritional supplementation, either oral or parenteral, is also important.

In localized AL disease, amyloid deposits can be produced by clonal plasma cells infiltrating local sites in the airways, bladder, skin, or lymph nodes (Table 19-1). T ese deposits may respond to surgical intervention or low-dose radiation therapy (typically only 20 Gy); systemic treatment generally is not appropriate. Patients should be referred to a center familiar with management of these rare manifestations of amyloidosis.

AA AMYLOIDOSIS

Etiology and incidence

AA amyloidosis can occur in association with almost any chronic inflammatory state (e.g., rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever, or other periodic fever syndromes) or chronic infections such as tuberculosis or subacute bacterial endocarditis. In the United States and Europe, AA amyloidosis has become less common, occurring in fewer than 2% of patients with these diseases, presumably because of advances in anti-inflammatory and antimicrobial therapies. It has also been described in association with Castleman's disease, and patients with AA amyloidosis should undergo CT scanning to look

for such tumors as well as serologic and microbiologic studies. AA amyloidosis can also be seen without any identifiable underlying disease. AA is the only type of systemic amyloidosis that occurs in children.

Pathology and clinical features

Organ involvement in AA amyloidosis usually begins in the kidneys. Hepatomegaly, splenomegaly, and autonomic neuropathy can also occur as the disease progresses; cardiomyopathy occurs, albeit rarely. The symptoms and signs of AA disease cannot be reliably distinguished from those of AL amyloidosis. AA amyloid fibrils are usually composed of an 8-kDa, 76-amino-acid N-terminal portion of the 12-kDa precursor protein SAA. This is acute-phase apoprotein is synthesized in the liver and transported by high-density lipoprotein (HDL3) in the plasma. Several years of an underlying inflammatory disease causing chronic elevation of SAA levels usually precede fibril formation, although infections can lead to AA deposition more rapidly.

TREATMENT AA Amyloidosis

Primary therapy for AA amyloidosis consists of treatment of the underlying inflammatory or infectious disease. Treatment that suppresses or eliminates the inflammation or infection also decreases the SAA concentration. For familial Mediterranean fever, colchicine at a dose of 1.2–1.8 mg/d is the standard treatment. However, colchicine has not been helpful for AA amyloidosis of other causes or for other amyloidoses. Tumor necrosis factor and interleukin 1 antagonists can be effective in syndromes related to cytokine elevation. For this disease, there is also a fibril-specific agent: eprodisate was designed to interfere with the interaction of AA amyloid protein with glycosaminoglycans and to prevent or disrupt fibril formation. The drug is well tolerated and delays progression of AA renal disease. Randomized phase III clinical trials with eprodisate are ongoing; the drug is not otherwise available.

ATTR AND AF AMYLOIDOSIS

The familial amyloidoses are autosomal dominant diseases in which, beginning in midlife, a variant (FINE) plasma protein forms amyloid deposits. These diseases are rare, with an estimated incidence of <1 case/100,000 population in the United States, although founder effects in isolated areas of Portugal, Sweden, and Japan have led to a much higher incidence. The most common form of AF amyloidosis is ATTRm in the updated nomenclature, caused by mutation of the abundant plasma protein transthyretin (TTR, also known as prealbumin). More than 100 TTR mutations are known, and most are associated with ATTR amyloidosis. One variant, V122I, has a carrier frequency that may be as high as 4% in the African-American population and is associated with late-onset cardiac amyloidosis. The actual incidence and penetrance of disease in the African-American population is the subject of ongoing research, but ATTR amyloidosis warrants consideration in the differential diagnosis of African-American patients who present with concentric cardiac hypertrophy and evidence of diastolic dysfunction, particularly in the absence of a history of hypertension. Other familial amyloidoses, caused by variant apolipoproteins AI or AII, gelsolin, fibrinogen Aα, or lysozyme, are reported in only a few families worldwide. New amyloidogenic serum proteins continue to be identified periodically, including recently the leukocyte chemotactic factor LECT2, a cause of renal amyloidosis in Hispanic and Pakistani populations. To date, no mutation in the coding sequence for the LECT2 gene has been identified, so the heritability of ALECT2 is uncertain.

TTR deposits composed of unmutated fibrils occur with aging, and ATTRwt is being diagnosed with increasing frequency in Caucasian men >65 years of age with amyloid cardiomyopathy. Formerly termed senile systemic amyloidosis, ATTRwt has been found at autopsy in 25% of hearts from patients older than age 80 years. Why a wild type protein becomes amyloidogenic, and why patients bearing mutant TTR genes do not express disease until adulthood, remains a mystery.

Clinical features and diagnosis

AF amyloidosis has a presentation that is variable but is usually consistent within kindreds affected by the same mutant protein. A family history makes AF disease more likely, but many patients present sporadically with new mutations. ATTR amyloidosis typically presents as a syndrome of familial amyloidotic polyneuropathy or familial amyloidotic cardiomyopathy. Peripheral neuropathy begins as a small-fiber lower-extremity sensory and motor neuropathy and progresses to the upper extremities. Autonomic neuropathy manifests as diarrhea with weight loss and orthostatic hypotension. Patients with TTR V30M, the most common mutation, have normal electrocardiograms but may develop conduction defects late in the disease. Patients with TTR T60A and several other mutations have myocardial thickening similar to that caused by AL amyloidosis, although heart failure is less common and long-term survival rates are usually better. Vitreous opacities caused by amyloid deposits are pathognomonic for ATTR amyloidosis.

Typical syndromes associated with other forms of AF disease include renal amyloidosis with mutant fibrinogen, lysozyme, or apolipoproteins; hepatic amyloidosis

with apolipoprotein AI; and amyloidosis of cranial nerves and cornea with gelsolin. Patients with AF amyloidosis can present with clinical syndromes that mimic those of patients with AL disease. Rarely, AF carriers can develop AL disease or AF patients may have monoclonal gammopathy without AL. T us, it is important to screen both for plasma cell disorders and for mutations in patients with amyloidosis. Variant TTRs can usually be detected by isoelectric focusing, but DNA sequencing is now standard for diagnosis of ATTR and other AF mutations.

TREATMENT ATTR Amyloidosis

Without intervention, the survival period after onset of ATTR disease is 5–15 years. Orthotopic liver transplantation replaces the major source of variant TTR production with a source of normal TTR. While liver transplantation can slow disease progression and improve chances of survival, it does not reverse sensorimotor neuropathy. Liver transplants are most successful in young patients with early peripheral neuropathy; older patients with familial amyloidotic cardiomyopathy or advanced polyneuropathy often experience end-organ disease progression despite successful liver transplantation. Progressive disease has been attributed to accumulation of wild-type TTR in fibrillar deposits initiated by the mutant.

T e rate-limiting step in ATTR amyloidosis is dissociation of the TTR tetramer into monomer followed by misfolding and aggregation. TTR tetramers can be stabilized by thyroxine binding or by small molecules such as the non-steroidal anti-inflammatory drug diflunisal or the rationally designed small-molecule therapeutic tafamidis. A placebo-controlled randomized trial of diflunisal demonstrated a reduction in the progression of polyneuropathy and maintenance of quality of life in patients with a wide variety of ATTR mutations who received the "repurposed" diflunisal. Tafamidis tested in a similar fashion in patients with the V30M ATTR mutation failed to meet its primary endpoints, but tafamidis was approved by the European Medicines Agency since most secondary endpoints favored the drug. T ese agents are now being investigated for ef ects on cardiomyopathy, and in ATTRwt. In vitro data and serendipitous observations in patients suggest that ATTRm disease can be ameliorated by "trans-suppression," in which a T119M TTR variant stabilizes tetramers that also contain amyloidogenic subunits. Interestingly, in a large population study in Denmark, 0.5% of participants were heterozygous for the T119M allele, and this small group had higher levels of TTR in their blood, a reduced incidence of cerebrovascular disease, and a 5- to 10-year survival advantage compared with participants lacking this allele.

Aβ$_2$M AMYLOIDOSIS

Aβ$_2$M amyloid is composed of β$_2$-microglobulin, the invariant chain of class I human leukocyte antigens, and produces rheumatologic manifestations in patients undergoing long-term hemodialysis. β$_2$-Microglobulin is excreted by the kidney, and levels become elevated in end-stage renal disease. T e molecular mass of β$_2$M is 11.8 kDa—above the cutof of some dialysis membranes. T e incidence of this disease appears to be declining with the use of newer membranes in high-flow dialysis techniques. Aβ$_2$M amyloidosis usually presents as carpal tunnel syndrome, persistent joint ef usions, spondyloarthropathy, or cystic bone lesions. Carpal tunnel syndrome is often the first symptom. In the past, persistent joint ef usions accompanied by mild discomfort were found in up to 50% of patients who had undergone dialysis for >12 years. Involvement is bilateral, and large joints (shoulders, knees, wrists, and hips) are most frequently af ected. T e synovial fluid is noninflammatory, and β$_2$M amyloid can be found if the sediment is stained with Congo red. Although less common, visceral β$_2$M amyloid deposits do occasionally occur in the gastrointestinal tract, heart, tendons, and subcutaneous tissues of the buttocks. T ere is no specific therapy for Aβ$_2$M amyloidosis, but cessation of dialysis after renal allografting may lead to symptomatic improvement.

SUMMARY

A diagnosis of amyloidosis should be considered in patients with unexplained nephropathy, cardiomyopathy (particularly with diastolic dysfunction), neuropathy (either peripheral or autonomic), enteropathy, or the pathognomonic soft tissue findings of macroglossia or periorbital ecchymoses. Pathologic identification of amyloid fibrils can be made with Congo red staining of aspirated abdominal fat or of an involved-organ biopsy specimen. Accurate typing by a combination of immunologic, biochemical, and genetic testing is essential in selecting appropriate therapy (Fig. 19-1). Systemic amyloidosis should not be considered an untreatable condition, as anti–plasma cell chemotherapy is highly ef ective in AL disease and targeted therapies are being developed for AA and ATTR disease. Tertiary referral centers can provide specialized diagnostic techniques and access to clinical trials for patients with these rare diseases.

Acknowledgment

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SECTION VI

DISORDERS OF HEMOSTASIS

CHAPTER 20

DISORDERS OF PLATELETS AND VESSEL WALL

Barbara A. Konkle

Hemostasis is a dynamic process in which the platelet and the blood vessel wall play key roles. Platelets become activated upon adhesion to von Willebrand factor (VWF) and collagen in the exposed subendothelium after injury. Platelet activation is also mediated through shear forces imposed by blood flow itself, particularly in areas where the vessel wall is diseased, and is also affected by the inflammatory state of the endothelium. T e activated platelet surface provides the major physiologic site for coagulation factor activation, which results in further platelet activation and fibrin formation. Genetic and acquired influences on the platelet and vessel wall, as well as on the coagulation and fibrinolytic systems, determine whether normal hemostasis or bleeding or clotting symptoms will result.

THE PLATELET

Platelets are released from the megakaryocyte, likely under the influence of flow in the capillary sinuses. T e normal blood platelet count is 150,000–450,000/μL. T e major regulator of platelet production is the hormone thrombopoietin (TPO), which is synthesized in the liver. Synthesis is increased with inflammation and specifically by interleukin 6. TPO binds to its receptor on platelets and megakaryocytes, by which it is removed from the circulation. T us a reduction in platelet and megakaryocyte mass increases the level of TPO, which then stimulates platelet production. Platelets circulate with an average life span of 7–10 days. Approximately one-third of the platelets reside in the spleen, and this number increases in proportion to splenic size, although the platelet count rarely decreases to <40,000/μL as the spleen enlarges. Platelets are physiologically very active, but are anucleate, and thus have limited capacity to synthesize new proteins.

Normal vascular endothelium contributes to preventing thrombosis by inhibiting platelet function **(Chap. 3)**. When vascular endothelium is injured, these inhibitory effects are overcome, and platelets adhere to the exposed intimal surface primarily through VWF, a large multimeric protein present in both plasma and in the extracellular matrix of the subendothelial vessel wall. Platelet adhesion results in the generation of intracellular signals that lead to activation of the platelet glycoprotein (Gp) IIb/IIIa ($\alpha_{IIb}\beta_3$) receptor and resultant platelet aggregation.

Activated platelets undergo release of their granule contents, which include nucleotides, adhesive proteins, growth factors, and procoagulants that serve to promote platelet aggregation and blood clot formation and influence the environment of the forming clot. During platelet aggregation, additional platelets are recruited to the site of injury, leading to the formation of an occlusive platelet thrombus. T e platelet plug is stabilized by the fibrin mesh that develops simultaneously as the product of the coagulation cascade.

THE VESSEL WALL

Endothelial cells line the surface of the entire circulatory tree, totaling 1–6 × 10^{13} cells, enough to cover a surface area equivalent to about six tennis courts. T e endothelium is physiologically active, controlling vascular permeability, flow of biologically active molecules and nutrients, blood cell interactions with the vessel wall, the inflammatory response, and angiogenesis.

T e endothelium normally presents an antithrombotic surface **(Chap. 3)** but rapidly becomes prothrombotic when stimulated, which promotes coagulation, inhibits fibrinolysis, and activates platelets. In many cases, endothelium-derived vasodilators are

also platelet inhibitors (e.g., nitric oxide) and, conversely, endothelium-derived vasoconstrictors (e.g., endothelin) can also be platelet activators. The net effect of vasodilation and inhibition of platelet function is to promote blood fluidity, whereas the net effect of vasoconstriction and platelet activation is to promote thrombosis. Thus, blood fluidity and hemostasis are regulated by the balance of antithrombotic/prothrombotic and vasodilatory/vasoconstrictor properties of endothelial cells.

DISORDERS OF PLATELETS

THROMBOCYTOPENIA

Thrombocytopenia results from one or more of three processes: (1) decreased bone marrow production; (2) sequestration, usually in an enlarged spleen; and/or (3) increased platelet destruction. Disorders of production may be either inherited or acquired. In evaluating a patient with thrombocytopenia, a key step is to review the peripheral blood smear and to first rule out "pseudothrombocytopenia," particularly in a patient without an apparent cause for the thrombocytopenia. Pseudothrombocytopenia **(Fig. 20-1B)** is an in vitro artifact resulting from platelet agglutination via antibodies (usually IgG, but also IgM and IgA) when the calcium content is decreased by blood collection in ethylenediamine tetraacetic (EDTA) (the anticoagulant present in tubes [purple top] used to collect blood for complete blood counts [CBCs]). If a low platelet count is obtained in EDTA-anticoagulated blood, a blood smear should be evaluated and a platelet count determined in blood collected into sodium citrate (blue top tube) or heparin (green top tube), or a smear of freshly obtained unanticoagulated blood, such as from a finger stick, can be examined.

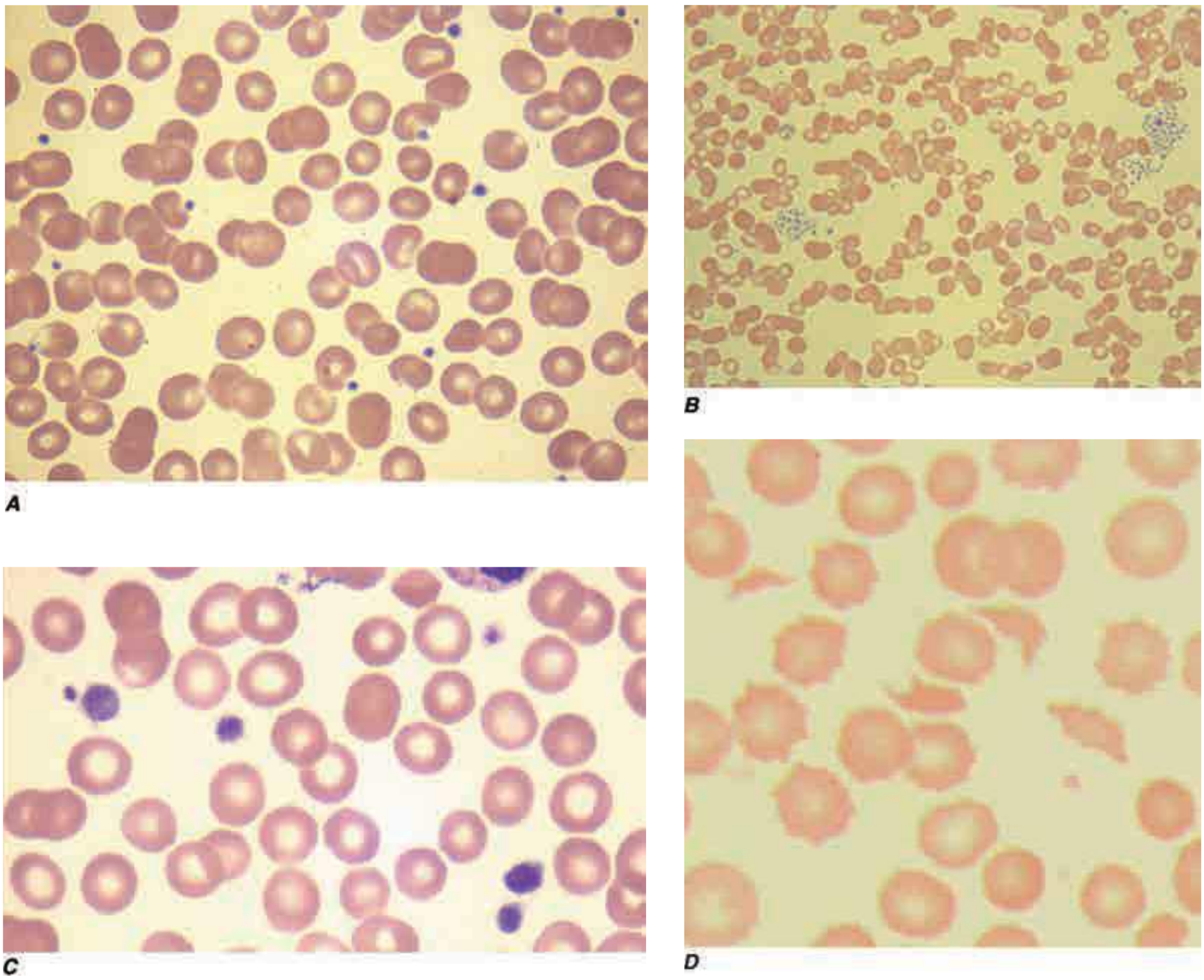

FIGURE 20-1
Photomicrographs of peripheral blood smears. A. Normal peripheral blood. B. Platelet clumping in pseudothrombocytopenia. C. Abnormal large platelet in autosomal dominant macrothrombocytopenia. D. Schistocytes and decreased platelets in microangiopathic hemolytic anemia.

APPROACH TO THE PATIENT: Thrombocytopenia

T e history and physical examination, results of the CBC, and review of the peripheral blood smear are all critical components in the initial evaluation of thrombocytopenic patients **(Fig. 20-2)**. T e overall health of the patient and whether he or she is receiving drug treatment will influence the differential diagnosis. A healthy young adult with thrombocytopenia will have a much more limited differential diagnosis than an ill hospitalized patient who is receiving multiple medications. Except in unusual inherited disorders, decreased platelet production usually results from bone marrow disorders that also affect red blood cell (RBC) and/or white blood cell (WBC) production. Because myelodysplasia can present with isolated thrombocytopenia, the bone marrow should be examined in patients presenting with isolated thrombocytopenia who are older than 60 years of age. While inherited thrombocytopenia is rare, any prior platelet counts should be retrieved and a family history regarding thrombocytopenia obtained. A careful history of drug ingestion should be obtained, including nonprescription and herbal remedies, because drugs are the most common cause of thrombocytopenia.

T e physical examination can document an enlarged spleen, evidence of chronic liver disease, and other underlying disorders. Mild to moderate splenomegaly may be dif cult to appreciate in many individuals due to body habitus and/or obesity but can be easily assessed by abdominal ultrasound. A platelet count of approximately 5000–10,000 is required to maintain vascular integrity in the microcirculation. When the count is markedly decreased, petechiae first appear in areas of increased venous pressure, the ankles and feet in an ambulatory patient. Petechiae are pinpoint, nonblanching hemorrhages and are usually a sign of a decreased platelet number and not platelet dysfunction. Wet purpura, blood blisters that form on the oral mucosa, are thought to denote an increased risk of life-threatening hemorrhage in the thrombocytopenic patient. Excessive bruising is seen in disorders of both platelet number and function.

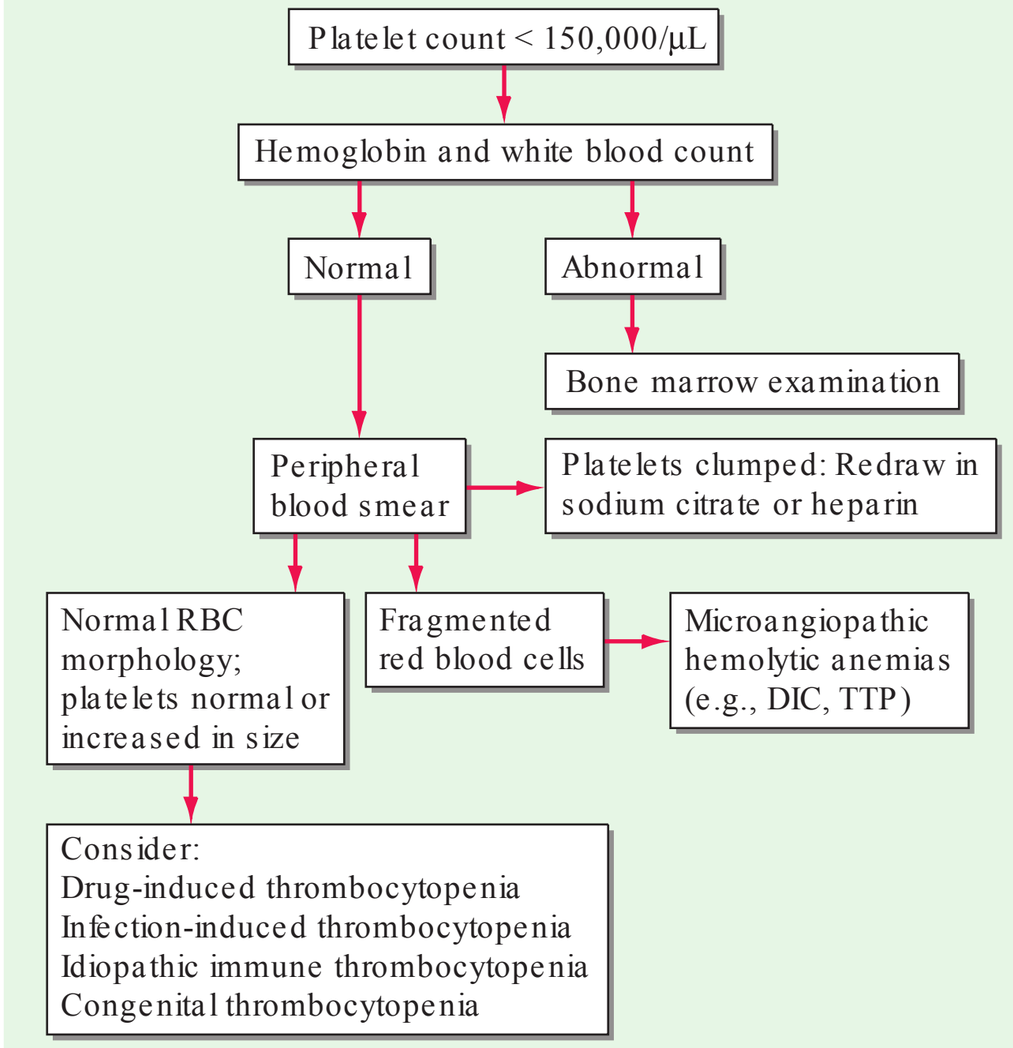

FIGURE 20-2
Algorithm for evaluating the thrombocytopenic patient. DIC, disseminated intravascular coagulation; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.

Infection-induced thrombocytopenia

Many viral and bacterial infections result in thrombocytopenia and are the most common noniatrogenic cause of thrombocytopenia. T is may or may not be associated with laboratory evidence of disseminated intravascular coagulation (DIC), which is most commonly seen in patients with systemic infections with gram-negative bacteria. Infections can affect both platelet production and platelet survival. In addition, immune mechanisms can be at work, as in infectious mononucleosis and early HIV infection. Late in HIV infection, pancytopenia and decreased and dysplastic platelet production are more common. Immune-mediated thrombocytopenia in children usually follows a viral infection and almost always resolves spontaneously. T is association of infection with immune thrombocytopenic purpura is less clear in adults.

Bone marrow examination is often requested for evaluation of occult infections. A study evaluating the role of bone marrow examination in fever of unknown origin in HIV-infected patients found that for 86% of patients, the same diagnosis was established by less invasive techniques, notably blood culture. In some instances, however, the diagnosis can be made earlier; thus, a bone marrow examination and culture are recommended when the diagnosis is needed urgently or when other, less invasive methods have been unsuccessful.

Drug-induced thrombocytopenia

Many drugs have been associated with thrombocytopenia. A predictable decrease in platelet count occurs after treatment with many chemotherapeutic drugs due to bone marrow suppression **(Chap. 29)**. Drugs that cause isolated thrombocytopenia and have been confirmed with positive laboratory testing are listed in **Table 20-1**, but all drugs should be suspect in a patient with thrombocytopenia without an apparent cause and should be stopped, or substituted, if possible. A helpful website, Platelets on the Internet (http://www.ouhsc.edu/platelets/ditp.html), lists drugs and supplements reported to have

TABLE 20-1

DRUGS REPORTED AS DEFINITELY OR PROBABLY CAUSING ISOLATED THROMBOCYTOPENIA[a]	
Abciximab	Mirtazapine
Acetaminophen	Naproxen
Amiodarone	Oxaliplatin
Amlodipine	Penicillin
Ampicillin	Phenytoin
Carbamazepine	Piperacillin
Ceftriaxone	Quinine
Cephamandole	Quinidine
Ciprofloxacin	Ranitidine
Diazepam	Rosiglitazone
Eptifibatide	Roxifiban
Furosemide	Sulfisoxazole
Gold	Suramin
Haloperidol	Tirofiban
Heparin	Tranilast
Ibuprofen	Trimethoprim/sulfamethoxazole
Lorazepam	Vancomycin

[a]Based on scoring requiring a compatible clinical picture and positive laboratory testing.
Source: Adapted from DM Arnold et al: J Thromb Hemost 11:169, 2013.

caused thrombocytopenia and the level of evidence supporting the association. Although not as well studied, herbal and over-the-counter preparations may also result in thrombocytopenia and should be discontinued in patients who are thrombocytopenic.

Classic drug-dependent antibodies are antibodies that react with specific platelet surface antigens and result in thrombocytopenia only when the drug is present. Many drugs are capable of inducing these antibodies, but for some reason, they are more common with quinine and sulfonamides. Drug-dependent antibody binding can be demonstrated by laboratory assays, showing antibody binding in the presence of, but not without, the drug present in the assay. The thrombocytopenia typically occurs after a period of initial exposure (median length 21 days), or upon reexposure, and usually resolves in 7–10 days after drug withdrawal. The thrombocytopenia caused by the platelet Gp IIb/IIIa inhibitory drugs, such as abciximab, differs in that it may occur within 24 h of initial exposure. This appears to be due to the presence of naturally occurring antibodies that cross-react with the drug bound to the platelet.

Heparin-induced thrombocytopenia

Drug-induced thrombocytopenia due to heparin differs from that seen with other drugs in two major ways. (1) The thrombocytopenia is not usually severe, with nadir counts rarely <20,000/μL. (2) Heparin-induced thrombocytopenia (HIT) is not associated with bleeding and, in fact, markedly increases the risk of thrombosis. HIT results from antibody formation to a complex of the platelet-specific protein platelet factor 4 (PF4) and heparin. The anti-heparin/PF4 antibody can activate platelets through the FcγRIIa receptor and also activate monocytes and endothelial cells. Many patients exposed to heparin develop antibodies to heparin/PF4, but do not appear to have adverse consequences. A fraction of those who develop antibodies will develop HIT, and a portion of those (up to 50%) will develop thrombosis (HITT).

HIT can occur after exposure to low-molecular-weight heparin (LMWH) as well as unfractionated heparin (UFH), although it is more common with the latter. Most patients develop HIT after exposure to heparin for 5–14 days **(Fig. 20-3)**. It occurs before 5 days in those who were exposed to heparin in the prior few weeks or months (<~100 days) and have circulating anti-heparin/PF4 antibodies. Rarely, thrombocytopenia and thrombosis begin several days after all heparin has been stopped (termed delayed-onset HIT). The "4T's" have been recommended to be used in a diagnostic algorithm for HIT: thrombocytopenia, timing of platelet count drop, thrombosis and other sequelae such as localized skin reactions, and other causes of thrombocytopenia not evident. Application of the 4T scoring system is very useful in excluding a diagnosis of HIT but will result in overdiagnosis of HIT in situations where thrombocytopenia and thrombosis due to other etiologies are common, such as in the intensive care unit. A scoring model based on broad expert opinion (the HIT Expert Probability [HEP] Score) has improved operating characteristics and may provide better utility as a scoring system.

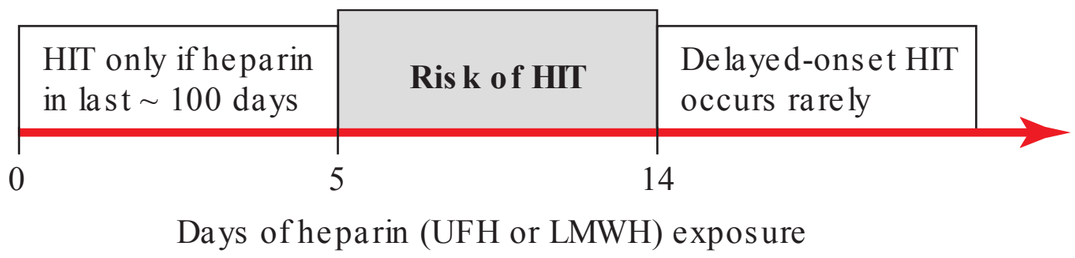

FIGURE 20-3
Time course of heparin-induced thrombocytopenia (HIT) development after heparin exposure. The timing of development after heparin exposure is a critical factor in determining the likelihood of HIT in a patient. HIT occurs early after heparin exposure in the presence of preexisting heparin/platelet factor 4 (PF4) antibodies, which disappear from circulation by ~100 days following a prior exposure. Rarely, HIT may occur later after heparin exposure (termed delayed-onset HIT). In this setting, heparin/PF4 antibody testing is usually markedly positive. HIT can occur after exposure to either unfractionated (UFH) or low-molecular-weight heparin (LMWH).

Laboratory testing for HIT

HIT (anti-heparin/PF4) antibodies can be detected using two types of assays. T e most widely available is an enzyme-linked immunoassay (ELISA) with PF4/polyanion complex as the antigen. Because many patients develop antibodies but do not develop clinical HIT, the test has a low specificity for the diagnosis of HIT. T is is especially true in patients who have undergone cardiopulmonary bypass surgery, where approximately 50% of patients develop these antibodies postoperatively. IgG-specific ELISAs increase specificity but may decrease sensitivity. T e other assay is a platelet activation assay, most commonly the serotonin release assay, which measures the ability of the patient's serum to activate platelets in the presence of heparin in a concentration-dependent manner. T is test has lower sensitivity but higher specificity than the ELISA. However, HIT remains a clinical diagnosis.

TREATMENT Heparin-Induced Thrombocytopenia

Early recognition is key in treatment of HIT, with prompt discontinuation of heparin and use of alternative anticoagulants if bleeding risk does not outweigh thrombotic risk. T rombosis is a common complication of HIT, even after heparin discontinuation, and can occur in both the venous and arterial systems. Patients with higher anti-heparin/PF4 antibody titers may have a higher risk of thrombosis. In patients diagnosed with HIT, imaging studies to evaluate the patient for thrombosis (at least lower extremity duplex Doppler imaging) are recommended. Patients requiring anticoagulation should be switched from heparin to an alternative anticoagulant. T e direct thrombin inhibitors (DTIs) argatroban and lepirudin are effective in HITT. T e DTI bivalirudin and the antithrombin-binding pentasaccharide fondaparinux are also effective but not yet approved by the U.S. Food and Drug Administration (FDA) for this indication. Danaparoid, a mixture of glycosaminoglycans with anti-Xa activity, has been used extensively for the treatment of HITT; it is no longer available in the United States but is in other countries. HIT antibodies cross-react with LMWH, and these preparations should not be used in the treatment of HIT.

Because of the high rate of thrombosis in patients with HIT, anticoagulation should be considered, even in the absence of thrombosis. In patients with thrombosis, patients can be transitioned to warfarin, with treatment usually for 3–6 months. In patients without thrombosis, the duration of anticoagulation needed is undefined. An increased risk of thrombosis is present for at least 1 month after diagnosis; however, most thromboses occur early, and whether thrombosis occurs later if the patient is initially anticoagulated is unknown. Options include continuing anticoagulation until a few days after platelet recovery or for 1 month. Introduction of warfarin alone in the setting of HIT or HITT may precipitate thrombosis, particularly venous gangrene, presumably due to clotting activation and severely reduced levels of proteins C and S. Warfarin therapy, if started, should be overlapped with a DTI or fondaparinux and started after resolution of the thrombocytopenia and lessening of the prothrombotic state.

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP; also termed idiopathic thrombocytopenic purpura) is an acquired disorder in which there is immune-mediated destruction of platelets and possibly inhibition of platelet release from the megakaryocyte. In children, it is usually an acute disease, most commonly following an infection, and with a self-limited course. In adults, it is a more chronic disease, although in some adults, spontaneous remission occurs, usually within months of diagnosis. ITP is termed secondary if it is associated with an underlying disorder; autoimmune disorders, particularly systemic lupus erythematosus (SLE), and infections, such as HIV and hepatitis C, are common causes. T e association of ITP with Helicobacter pylori infection is unclear.

ITP is characterized by mucocutaneous bleeding and a low, often very low, platelet count, with an otherwise normal peripheral blood cells and smear. Patients usually present either with ecchymoses and petechiae, or with thrombocytopenia incidentally found on a routine CBC. Mucocutaneous bleeding, such as oral mucosa, gastrointestinal, or heavy menstrual bleeding, may be present. Rarely, life-threatening, including central nervous system, bleeding can occur. Wet purpura (blood blisters in the mouth) and retinal hemorrhages may herald life-threatening bleeding.

Laboratory testing in ITP

Laboratory testing for antibodies (serologic testing) is usually not helpful due to the low sensitivity and specificity of the current tests. Bone marrow examination can be reserved for those who have other signs or laboratory abnormalities not explained by ITP or in patients who do not respond to initial therapy. T e peripheral blood smear may show large platelets, with otherwise normal morphology. Depending on the bleeding history, iron-deficiency anemia may be present.

Laboratory testing is performed to evaluate for secondary causes of ITP and should include testing for HIV infection and hepatitis C (and other infections if indicated). Serologic testing for SLE, serum protein electrophoresis, immunoglobulin levels to potentially detect hypogammaglobulinemia, selective testing for IgA deficiency or monoclonal gammopathies, and testing for H. pylori infection should be considered, depending on the clinical circumstance. If anemia is present, direct antiglobulin testing (Coombs' test) should be performed to rule out combined autoimmune hemolytic anemia with ITP (Evans' syndrome).

TREATMENT Immune Thrombocytopenic Purpura

T e treatment of ITP uses drugs that decrease reticuloendothelial uptake of the antibody-bound platelet, decrease antibody production, and/or increase platelet production. T e diagnosis of ITP does not necessarily mean that treatment must be instituted. Patients with platelet counts >30,000/μL appear not to have increased mortality related to the thrombocytopenia.

Initial treatment in patients without significant bleeding symptoms, severe thrombocytopenia (<5000/μL), or signs of impending bleeding (such as retinal hemorrhage or large oral mucosal hemorrhages) can be instituted as an outpatient using single agents. Traditionally, this has been prednisone at 1 mg/kg, although Rh_0(D) immune globulin therapy (WinRho SDF), at 50–75 μg/kg, is also being used in this setting. Rh_0(D) immune globulin must be used only in Rh-positive patients because the mechanism of action is production of limited hemolysis, with antibody-coated cells "saturating" the Fc receptors, inhibiting Fc receptor function. Monitoring patients for 8 h after infusion is now advised by the FDA because of the rare complication of severe intravascular hemolysis. Intravenous gamma globulin (IVIgG), which is pooled, primarily IgG antibodies, also blocks the Fc receptor system, but appears to work primarily through different mechanism(s). IVIgG has more ef cacy than anti-Rh_0(D) in postsplenectomized patients. IVIgG is dosed at 1–2 g/kg total, given over 1–5 days. Side effects are usually related to the volume of infusion and infrequently include aseptic meningitis and renal failure. All immunoglobulin preparations are derived from human plasma and undergo treatment for viral inactivation.

For patients with severe ITP and/or symptoms of bleeding, hospital admission and combined-modality therapy is given using high-dose glucocorticoids with IVIgG or anti-Rh_0(D) therapy and, as needed, additional immunosuppressive agents. Rituximab, an anti-CD20 (B cell) antibody, has shown ef - cacy in the treatment of refractory ITP, although long-lasting remission only occurs in approximately 30% of patients.

Splenectomy has been used for treatment of patients who relapse after glucocorticoids are tapered. Splenectomy remains an important treatment option; however, more patients than previously thought will go into a remission over time. Observation, if the platelet count is high enough, or intermittent treatment with anti-Rh_0(D) or IVIgG, or initiation of treatment with a TPO receptor agonist (see below) may be a reasonable approach to see if the ITP will resolve. Vaccination against encapsulated organisms (especially pneumococcus, but also meningococcus and Haemophilus infuenzae, depending on patient age and potential exposure) is recommended before splenectomy. Accessory spleen(s) are a very rare cause of relapse.

TPO receptor agonists are now available for the treatment of ITP. T is approach stems from the finding that many patients with ITP do not have increased TPO levels, as was previously hypothesized. TPO levels reflect megakaryocyte mass, which is usually normal in ITP. TPO levels are not increased in the setting of platelet destruction. Two agents, one administered subcutaneously (romiplostim) and another orally (eltrombopag), are effective in raising platelet counts in patients with ITP and are recommended for adults at risk of bleeding who relapse after splenectomy or who have been unresponsive to at least one other therapy, particularly in those who have a contraindication to splenectomy. However, with the recognition that ITP will resolve spontaneously in some adult patients, short-term treatment with a TPO agonist can be considered before splenectomy in patients who need therapy.

Inherited thrombocytopenia

T rombocytopenia is rarely inherited, either as an isolated finding or as part of a syndrome, and may be inherited in an autosomal dominant, autosomal recessive, or X-linked pattern. Many forms of autosomal dominant thrombocytopenia are now known to be associated with mutations in the nonmuscle myosin heavy chain MYH9 gene. Interestingly, these include the May-Hegglin anomaly, and Sebastian, Epstein's, and Fechtner syndromes, all of which have distinct distinguishing features. A common feature of these disorders is large platelets (Fig. 20-1C). Autosomal recessive disorders include congenital amegakaryocytic thrombocytopenia, thrombocytopenia with absent radii, and Bernard-Soulier syndrome. T e latter is primarily a functional platelet disorder due to absence of Gp Ib-IX-V, the VWF adhesion receptor. X-linked disorders include Wiskott-Aldrich syndrome and a dyshematopoietic syndrome resulting from a mutation in GATA-1, an important transcriptional regulator of hematopoiesis.

THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOLYTIC-UREMIC SYNDROME

T rombotic thrombocytopenic microangiopathies are a group of disorders characterized by thrombocytopenia, a microangiopathic hemolytic anemia evident by fragmented RBCs (Fig. 20-1D) and laboratory evidence of hemolysis, and microvascular thrombosis. T ey include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS), as well as syndromes complicating bone marrow transplantation, certain medications and infections, pregnancy, and vasculitis. In DIC, although thrombocytopenia and microangiopathy are seen, a coagulopathy predominates, with consumption of clotting factors and fibrinogen resulting in an elevated prothrombin time (PT) and often activated partial thromboplastin time (aPTT). T e PT and aPTT are characteristically normal in TTP or HUS.

TTP and HUS were previously considered overlap syndromes. However, in the past few years, the pathophysiology of inherited and idiopathic TTP has become better understood and clearly differs from HUS. TTP was first described in 1924 by Eli Moschcowitz and characterized by a pentad of findings that include microangiopathic hemolytic anemia, thrombocytopenia, renal failure, neurologic findings, and fever. T e full-blown syndrome is less commonly seen now, probably due to earlier diagnosis. T e introduction of treatment with plasma exchange markedly improved the prognosis in patients, with a decrease in mortality from 85–100% to 10–30%.

T e pathogenesis of inherited (Upshaw-Schulman syndrome) and idiopathic TTP is related to a deficiency of, or antibodies to, the metalloprotease ADAMTS13, which cleaves VWF. VWF is normally secreted as ultra-large multimers, which are then cleaved by ADAMTS13. T e persistence of ultra-large VWF molecules is thought to contribute to pathogenic platelet adhesion and aggregation **(Fig. 20-4)**. T is defect alone, however, is not suf cient to result in TTP because individuals with a congenital absence of ADAMTS13 develop TTP only episodically. Additional provocative factors have not been defined. T e level of ADAMTS13 activity, as well as antibodies, can now be detected by laboratory assays. Although assays with suf cient sensitivity and specificity to direct clinical management have yet to be clearly defined, ADAMTS13 activity levels of <10% are more clearly associated with idiopathic TTP.

Idiopathic TTP appears to be more common in women than in men. No geographic or racial distribution has been defined. TTP is more common in patients with HIV infection and in pregnant women. TTP in pregnancy is not clearly related to ADAMTS13. Medication-related microangiopathic hemolytic anemia may be secondary to antibody formation (ticlopidine and possibly clopidogrel) or direct endothelial toxicity (cyclosporine, mitomycin C, tacrolimus, quinine), although this is not always so clear, and fear of withholding treatment, as well as lack of other treatment alternatives, results in broad application of plasma exchange. However, withdrawal, or reduction in dose, of endothelial toxic agents usually decreases the microangiopathy.

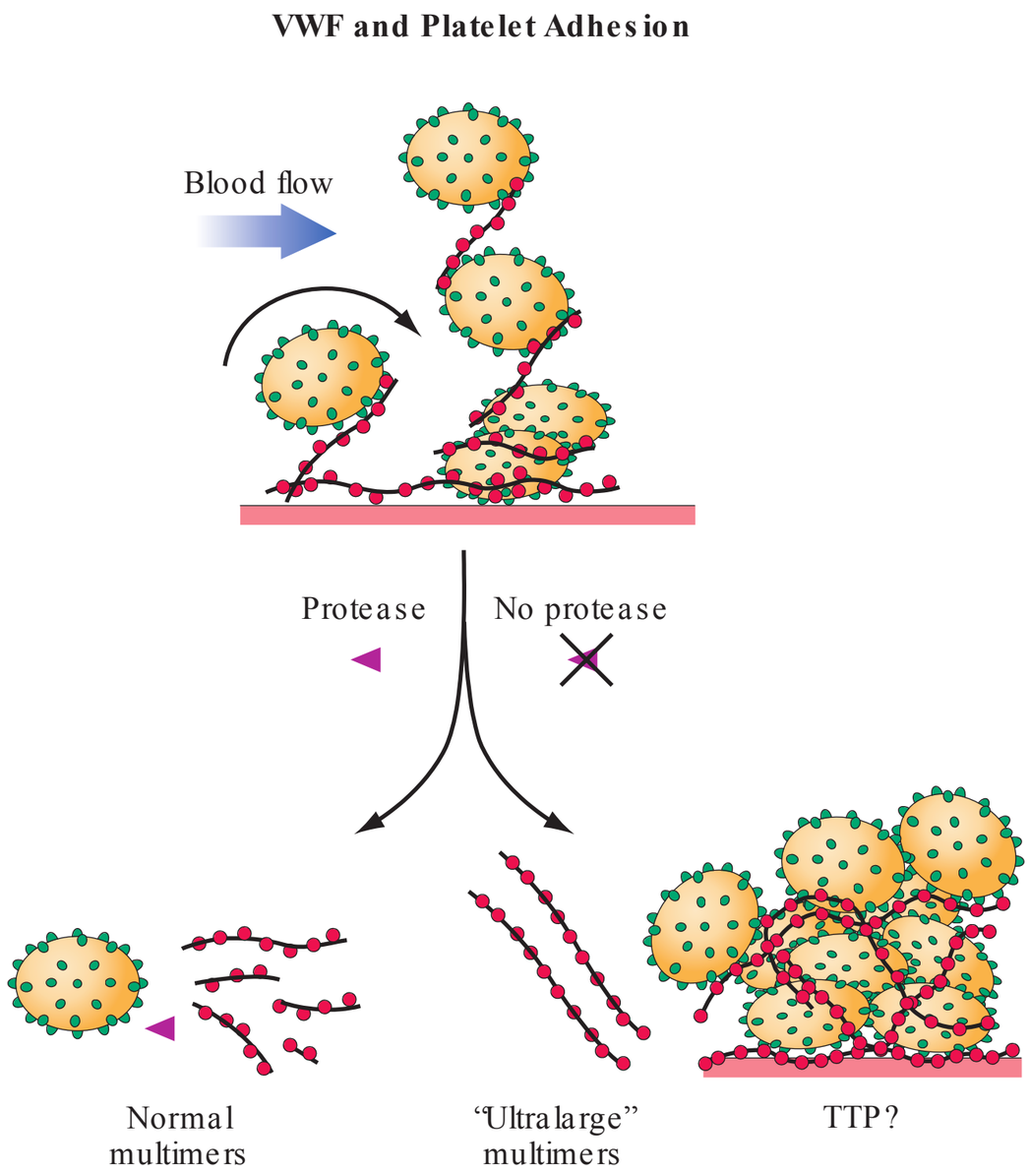

FIGURE 20-4
Pathogenesis of thrombotic thrombocytopenic purpura (TTP). Normally the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) produced by the endothelial cells are processed into smaller multimers by a plasma metalloproteinase called ADAMTS13. In TTP, the activity of the protease is inhibited, and the ultra-high-molecular-weight multimers of VWF initiate platelet aggregation and thrombosis.

TREATMENT Thrombotic Thrombocytopenic Purpura

TTP is a devastating disease if not diagnosed and treated promptly. In patients presenting with new thrombocytopenia, with or without evidence of renal insuf ciency and other elements of classic TTP, laboratory data should be obtained to rule out DIC and to evaluate for evidence of microangiopathic hemolytic anemia. Findings to support the TTP diagnosis include an increased lactate dehydrogenase and indirect bilirubin, decreased haptoglobin, and increased reticulocyte count, with a negative direct antiglobulin test. T e peripheral smear should be examined for evidence of schistocytes (Fig. 20-1D). Polychromasia is usually also present due to the increased number of young red blood cells, and nucleated RBCs are often present, which is thought to be due to infarction in the microcirculatory system of the bone marrow.

Plasma exchange remains the mainstay of treatment of TTP. ADAMTS13 antibody-mediated TTP (idiopathic TTP) appears to respond best to plasma exchange. Plasma exchange is continued until the platelet count is normal and signs of hemolysis are resolved for at least 2 days. Although never evaluated in clinical trials, the use of glucocorticoids seems a reasonable approach, but should only be used as an adjunct to plasma exchange. Additionally, other immunomodulatory therapies have been reported to be successful in refractory or relapsing TTP, including rituximab, vincristine, cyclophosphamide, and splenectomy. A significant relapse rate is noted; 25–45% of patients relapse within 30 days of initial "remission," and 12–40% of patients have late relapses. Relapses are more frequent in patients with severe ADAMTS13 deficiency at presentation.

Hemolytic-uremic syndrome

HUS is a syndrome characterized by acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. It is seen predominantly in children and in most cases is preceded by an episode of diarrhea, often hemorrhagic in nature. Escherichia coli O157:H7 is the most frequent, although not only, etiologic serotype. HUS not associated with diarrhea is more heterogeneous in presentation and course. Atypical HUS (aHUS) due to genetic defects that result in chronic complement activation has been defined, and screening for mutations in complement regulatory genes is available.

TREATMENT Hemolytic-Uremic Syndrome

Treatment of HUS is primarily supportive. In HUS associated with diarrhea, many (~40%) children require at least some period of support with dialysis; however, the overall mortality is <5%. In HUS not associated with diarrhea, the mortality is higher, approximately 26%. Plasma infusion or plasma exchange has not been shown to alter the overall course. ADAMTS13 levels are generally reported to be normal in HUS, although occasionally they have been reported to be decreased. In patients with atypical HUS, eculizumab therapy increases the platelet count and preserves renal function.

THROMBOCYTOSIS

T rombocytosis is almost always due to (1) iron deficiency; (2) inflammation, cancer, or infection (reactive thrombocytosis); or (3) an underlying myeloproliferative process (essential thrombocythemia or polycythemia vera) **(Chap. 13)** or, rarely, the 5q– myelodysplastic process **(Chap. 11)**. Patients presenting with an elevated platelet count should be evaluated for underlying inflammation or malignancy, and iron deficiency should be ruled out. T rombocytosis in response to acute or chronic inflammation has not been clearly associated with an increased thrombotic risk. In fact, patients with markedly elevated platelet counts (>1.5 million), usually seen in the setting of a myeloproliferative disorder, have an increased risk of bleeding. T is appears to be due, at least in part, to acquired von Willebrand disease (VWD) due to platelet-VWF binding and removal from the circulation.

QUALITATIVE DISORDERS OF PLATELET FUNCTION

Inherited disorders of platelet function

Inherited platelet function disorders are thought to be relatively rare, although the prevalence of mild disorders of platelet function is unclear, in part because our testing for such disorders is suboptimal. Rare qualitative disorders include the autosomal recessive disorders Glanzmann's thrombasthenia (absence of the platelet Gp IIb/IIIa receptor) and Bernard-Soulier syndrome (absence of the platelet Gp Ib-IX-V receptor). Both are inherited in an autosomal recessive fashion and present with bleeding symptoms in childhood.

Platelet storage pool disorder (SPD) is the classic autosomal dominant qualitative platelet disorder. T is results from abnormalities of platelet granule formation. It is also seen as a part of inherited disorders of granule formation, such as Hermansky-Pudlak syndrome. Bleeding symptoms in SPD are variable, but often are mild. T e most common inherited disorders of platelet function prevent normal secretion of granule content and are termed secretion defects. Few of these abnormalities have been dissected at the molecular level but they likely result from various mutations.

TREATMENT Inherited Disorders of Platelet Dysfunction

Bleeding symptoms or prevention of bleeding in patients with severe platelet dysfunction frequently requires platelet transfusion. Care is taken to limit the risk of alloimmunization by limiting exposure, using HLA-matched leuko-depleted platelet concentrates for transfusion. Platelet disorders associated with milder bleeding symptoms frequently respond to desmopressin (1-deamino-8-d-arginine vasopressin [DDAVP]). DDAVP increases plasma VWF and factor VIII levels; it may also have a direct effect on platelet function. Particularly for mucosal bleeding symptoms, antifibrinolytic therapy (ε-aminocaproic acid or tranexamic acid) is used alone or in conjunction with DDAVP or platelet therapy.

Acquired disorders of platelet function

Acquired platelet dysfunction is common, usually due to medications, either intentionally as with antiplatelet therapy or unintentionally as with high-dose penicillins. Acquired platelet dysfunction occurs in uremia. T is is likely multifactorial, but the resultant effect is defective adhesion and activation. T e platelet defect is improved most by dialysis but may also be improved by increasing the hematocrit to 27–32%, giving DDAVP (0.3 μg/kg), or use of conjugated estrogens. Platelet dysfunction also occurs with cardiopulmonary bypass due to the effect of the artificial circuit on platelets, and bleeding symptoms respond to platelet transfusion. Platelet dysfunction seen with underlying hematologic disorders can result from nonspecific interference by circulating paraproteins or intrinsic platelet defects in myeloproliferative and myelodysplastic syndromes.

VON WILLEBRAND DISEASE

VWD is the most common inherited bleeding disorder. Estimates from laboratory data suggest a prevalence of approximately 1%, but data based on symptomatic individuals suggest that it is closer to 0.1% of the population. VWF serves two roles: (1) as the major adhesion molecule that tethers the platelet to the exposed subendothelium; and (2) as the binding protein for factor VIII (FVIII), resulting in significant prolongation of the FVIII half-life in circulation. T e platelet-adhesive function of VWF is critically dependent on the presence of large VWF multimers, whereas FVIII binding is not. Most of the symptoms of VWD are "platelet-like" except in more severe VWD when the FVIII is low enough to produce symptoms similar to those found in FVIII deficiency (hemophilia A).

VWD has been classified into three major types, with four subtypes of type 2 **(Table 20-2; Fig. 20-5)**. By far the most common type of VWD is type 1 disease, with a parallel decrease in VWF protein, VWF function, and FVIII levels, accounting for at least 80% of cases. Patients have predominantly mucosal bleeding symptoms, although postoperative bleeding can also be seen. Bleeding symptoms are very uncommon in infancy and usually manifest later in childhood with excessive bruising and epistaxis. Because these symptoms occur commonly in childhood, the clinician should particularly note bruising at sites unlikely to be traumatized and/or prolonged epistaxis requiring medical attention. Menorrhagia is a common manifestation of VWD. Menstrual bleeding resulting in anemia should warrant an evaluation for VWD and, if negative, functional platelet disorders. Frequently, mild type 1 VWD first manifests with dental extractions, particularly wisdom tooth extraction, or tonsillectomy.

Not all patients with low VWF levels have bleeding symptoms. Whether patients bleed or not will depend on the overall hemostatic balance they have inherited, along with environmental influences and the type of

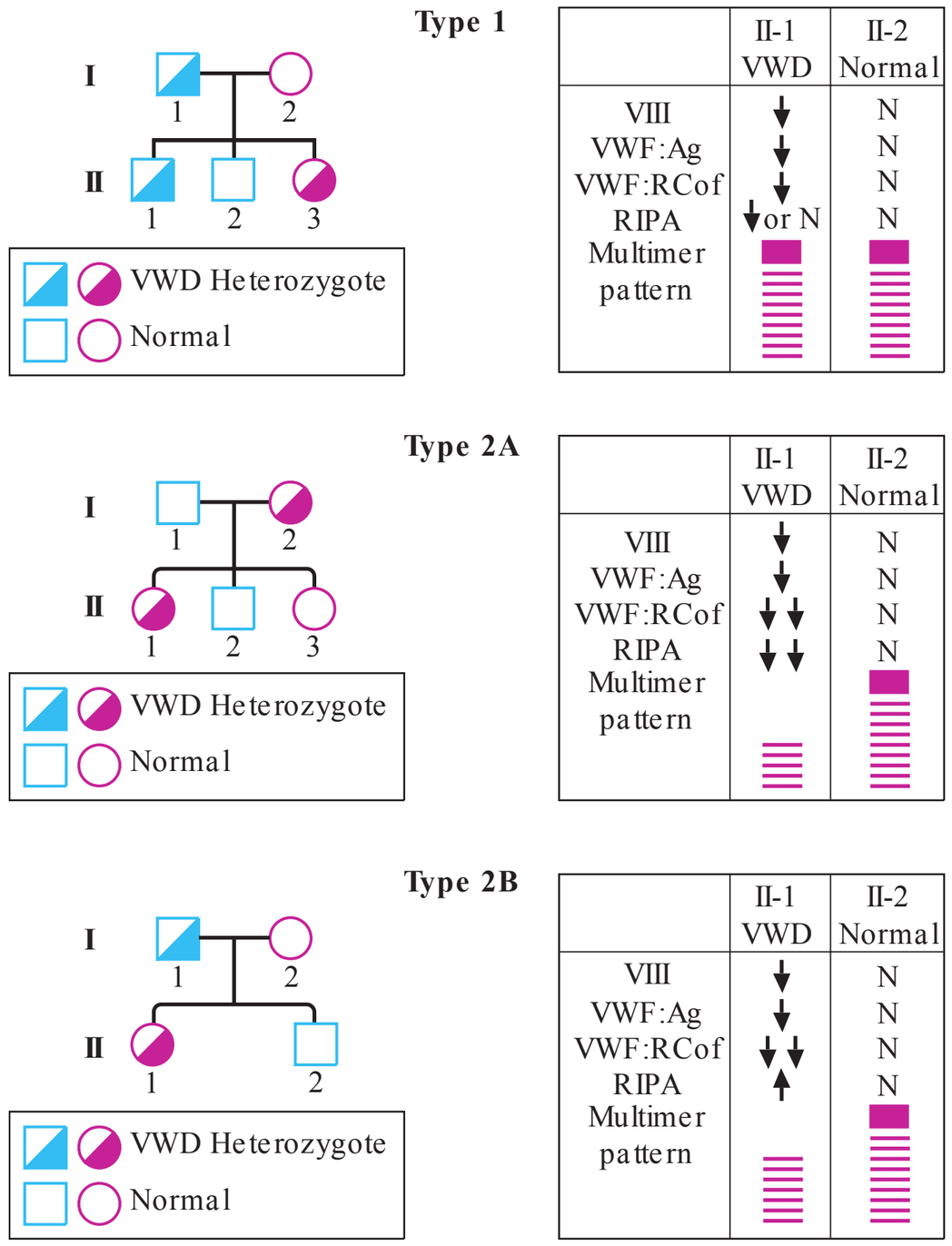

FIGURE 20-5
Pattern of inheritance and laboratory findings in von Willebrand disease (VWD). The assays of platelet function include a coagulation assay of factor VIII bound and carried by von Willebrand factor (VWF), abbreviated as VIII; immunoassay of total VWF protein (VWF:Ag); bioassay of the ability of patient plasma to support ristocetin-induced agglutination of normal platelets (VWF:RCoF); and ristocetin-induced aggregation of patient platelets, abbreviated RIPA. The multimer pattern illustrates the protein bands present when plasma is electrophoresed in a polyacrylamide gel. The II-1 and II-2 columns refer to the phenotypes of the second-generation of spring.

TABLE 20-2

LABORATORY DIAGNOSIS OF VON WILLEBRAND DISEASE (VWD)

TYPE	aPTT	VWF ANTIGEN	VWF ACTIVITY	FVIII ACTIVITY	MULTIMER
1	Nl or ↑	↓	↓	↓	Normal distribution, decreased in quantity
2A	Nl or ↑	↓	↓ ↓	↓	Loss of high- and intermediate-MW multimers
2B[a]	Nl or ↑	↓	↓ ↓	↓	Loss of high-MW multimers
2M	Nl or ↑	↓	↓ ↓	↓	Normal distribution, decreased in quantity
2N	↑↑	Nl or ↓[b]	Nl or ↓[b]	↓↓	Normal distribution
3	↑↑	↓↓	↓↓	↓↓	Absent

[a]Usually also decreased platelet count.
[b]For type 2N, in the homozygous state, FVIII is very low; in the heterozygous state, it is only seen in conjunction with type 1 VWD.
Abbreviations: aPTT, activated partial thromboplastin time; F, factor; MW, molecular weight; Nl, normal; VWF, von Willebrand factor.

hemostatic challenges they experience. Although the inheritance of VWD is autosomal, many factors modulate both VWF levels and bleeding symptoms. T ese have not all been defined, but include blood type, thyroid hormone status, race, stress, exercise, and hormonal (both endogenous and exogenous) influences. Patients with type O blood have VWF protein levels of approximately one-half that of patients with AB blood type; and, in fact, the normal range for patients with type O blood overlaps that which has been considered diagnostic for VWD. A mildly decreased VWF level should be viewed more as a risk factor for bleeding than as an actual disease.

Patients with type 2 VWD have functional defects; thus, the VWF antigen measurement is significantly higher than the test of function. For types 2A, 2B, and 2M VWD, platelet-binding and/or collagen binding VWF activity is decreased. In type 2A VWD, the impaired function is due either to increased susceptibility to cleavage by ADAMTS13, resulting in loss of intermediate- and high-molecular-weight multimers, or to decreased secretion of these multimers by the cell. Type 2B VWD results from gain-of-function mutations that result in increased spontaneous binding of VWF to platelets in circulation, with subsequent clearance of this complex by the reticuloendothelial system. T e resulting VWF in the patients' plasma lacks the highest molecular-weight multimers, and the platelet count is usually modestly reduced. Type 2M occurs as a consequence of a group of mutations that cause dysfunction but do not affect multimer structure.

Type 2N VWD is due to mutations in VWF that affect binding of FVIII. As FVIII is stabilized by binding to VWF, the FVIII in patients with type 2N VWD has a very short half-life, and the FVIII level is markedly decreased. T is is sometimes termed autosomal hemophilia. Type 3 VWD, or severe VWD, describes patients with virtually no VWF protein and FVIII levels <10%. Patients experience mucosal and joint bleeding, surgery-related bleeding, and other bleeding symptoms. Some patients with type 3 VWD, particularly those with large VWF gene deletions, are at risk of developing antibodies to infused VWF.

Acquired VWD is a rare disorder, most commonly seen in patients with underlying lymphoproliferative disorders, including monoclonal gammopathies of undetermined significance (MGUS), multiple myeloma, and Waldenström's macroglobulinemia. It is seen most commonly in the setting of MGUS and should be suspected in patients, particularly elderly patients, with a new onset of severe mucosal bleeding symptoms. Laboratory evidence of acquired VWD is found in some patients with aortic valvular disease. Heyde's syndrome (aortic stenosis with gastrointestinal bleeding) is attributed to the presence of angiodysplasia of the gastrointestinal tract in patients with aortic stenosis. T e shear stress on blood passing through the stenotic aortic valve appears to produce a change in VWF, making it susceptible to serum proteases. Consequently, large multimer forms are lost, leading to an acquired type 2 VWD, but return when the stenotic valve is replaced.

TREATMENT Von Willebrand Disease

T e mainstay of treatment for type 1 VWD is DDAVP (desmopressin), which results in release of VWF and FVIII from endothelial stores. DDAVP can be given intravenously or by a high-concentration intranasal spray (1.5 mg/mL). T e peak activity when given intravenously is approximately 30 min, whereas it is 2 h when given intranasally. T e usual dose is 0.3 μg/kg intravenously or two squirts (one in each nostril) for patients >50 kg (one squirt for those <50 kg). It is recommended that patients with VWD be tested with DDAVP to assess their response before using it. In patients who respond well (increase in laboratory values of two- to fourfold), it can be used for procedures with minor to moderate risk of bleeding. Depending on the procedure, additional doses may be needed; it is usually given every 12–24 h. Less frequent dosing may result in less tachyphylaxis, which occurs when synthesis cannot compensate for the released stores. T e major side effect of DDAVP is hyponatremia due to decreased free water clearance. T is occurs most commonly in the very young and the very old, but fluid restriction should be advised for all patients for the 24 h following each dose.

Some patients with types 2A and 2M VWD respond to DDAVP such that it can be used for minor procedures. For the other subtypes, for type 3 disease, and for major procedures requiring longer periods of normal hemostasis, VWF replacement can be given. Virally inactivated VWF-containing factor concentrates are safer than cryoprecipitate as the replacement product.

Antifibrinolytic therapy using either ε-aminocaproic acid or tranexamic acid is an important therapy, either alone or in an adjunctive capacity, particularly for the prevention or treatment of mucosal bleeding. T ese agents are particularly useful in prophylaxis for dental procedures, with DDAVP for dental extractions and tonsillectomy, menorrhagia, and prostate procedures. It is contraindicated in the setting of upper urinary tract bleeding, due to the risk of ureteral obstruction.

DISORDERS OF THE VESSEL WALL

T e vessel wall is an integral part of hemostasis, and separation of a fluid phase is artificial, particularly in disorders such as TTP or HIT that clearly involve the endothelium as well. Inflammation localized to the vessel wall, such as vasculitis, and inherited connective tissue disorders are abnormalities inherent to the vessel wall.

METABOLIC AND INFLAMMATORY DISORDERS

Acute febrile illnesses may result in vascular damage. T is can result from immune complexes containing viral antigens or the viruses themselves. Certain pathogens, such as the rickettsiae causing Rocky Mountain spotted fever, replicate in endothelial cells and damage them. Vascular purpura may occur in patients with polyclonal gammopathies but more commonly in those with monoclonal gammopathies, including Waldenström's macroglobulinemia, multiple myeloma, and cryoglobulinemia. Patients with mixed cryoglobulinemia develop a more extensive maculopapular rash due to immune complex–mediated damage to the vessel wall.

Patients with scurvy (vitamin C deficiency) develop painful episodes of perifollicular skin bleeding as well as more systemic bleeding symptoms. Vitamin C is needed to synthesize hydroxyproline, an essential constituent of collagen. Patients with Cushing's syndrome or on chronic glucocorticoid therapy develop skin bleeding and easy bruising due to atrophy of supporting connective tissue. A similar phenomenon is seen with aging, where following minor trauma, blood spreads superficially under the epidermis. T is has been termed senile purpura. It is most common on skin that has been previously damaged by sun exposure.

Henoch-Schönlein, or anaphylactoid, purpura is a distinct, self-limited type of vasculitis that occurs in children and young adults. Patients have an acute inflammatory reaction with IgA and complement components in capillaries, mesangial tissues, and small arterioles leading to increased vascular permeability and localized hemorrhage. T e syndrome is often preceded by an upper respiratory infection, commonly with streptococcal pharyngitis, or is triggered by drug or food allergies. Patients develop a purpuric rash on the extensor surfaces of the arms and legs, usually accompanied by polyarthralgias or arthritis, abdominal pain, and hematuria from focal glomerulonephritis. All coagulation tests are normal, but renal impairment may occur. Glucocorticoids can provide symptomatic relief but do not alter the course of the illness.

INHERITED DISORDERS OF THE VESSEL WALL

Patients with inherited disorders of the connective tissue matrix, such as Marfan's syndrome, Ehlers-Danlos syndrome, and pseudoxanthoma elasticum, frequently report easy bruising. Inherited vascular abnormalities can result in increased bleeding. T is is notably seen in hereditary hemorrhagic telangiectasia (HHT, or Osler-Weber-Rendu disease), a disorder where abnormal telangiectatic capillaries result in frequent bleeding episodes, primarily from the nose and gastrointestinal tract. Arteriovenous malformation (AVM) in the lung, brain, and liver may also occur in HHT. T e telangiectasia can often be visualized on the oral and nasal mucosa. Signs and symptoms develop over time. Epistaxis begins, on average, at the age of 12 and occurs in >95% of affected individuals by middle age. Two genes involved in the pathogenesis are eng (endoglin) on chromosome 9q33-34 (so-called HHT type 1), associated with pulmonary AVM in 40% of cases, and alk1 (activin-receptor-like kinase 1) on chromosome 12q13, associated with a much lower risk of pulmonary AVM.

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CHAPTER 21

COAGULATION DISORDERS

Valder R. Arruda ■ Katherine A. High

Deficiencies of coagulation factors have been recognized for centuries. Patients with genetic deficiencies of plasma coagulation factors exhibit life-long recurrent bleeding episodes into joints, muscles, and closed spaces, either spontaneously or following an injury. T e most common inherited factor deficiencies are the hemophilias, X-linked diseases caused by deficiency of factor (F) VIII (hemophilia A) or FIX (hemophilia B). Rare congenital bleeding disorders due to deficiencies of other factors, including FII (prothrombin), FV, FVII, FX, FXI, and FXIII, and fibrinogen are commonly inherited in an autosomal recessive manner **(Table 21-1)**. Advances in characterization of the molecular bases of clotting factor deficiencies have contributed to better understanding of the disease phenotypes and may eventually allow more targeted therapeutic approaches through the development of small molecules, recombinant proteins, or cell and gene-based therapies.

Commonly used tests of hemostasis provide the initial screening for clotting factor activity **(Fig. 21-1)**, and disease phenotype often correlates with the level of clotting activity. An isolated abnormal prothrombin time (PT) suggests FVII deficiency, whereas a prolonged activated partial thromboplastin time (aPTT) indicates most commonly hemophilia or FXI deficiency (Fig. 21-1). T e prolongation of both PT and aPTT suggests deficiency of FV, FX, FII, or fibrinogen abnormalities. T e addition of the missing factor at a range of doses to the subject's plasma will correct the abnormal clotting times; the result is expressed as a percentage of the activity observed in normal subjects.

Acquired deficiencies of plasma coagulation factors are more frequent than congenital disorders; the most common disorders include hemorrhagic diathesis of liver disease, disseminated intravascular coagulation (DIC), and vitamin K deficiency. In these disorders, blood coagulation is hampered by the deficiency of more than one clotting factor, and the bleeding episodes are the result of perturbation of both primary (e.g., platelet and vessel wall interactions) and secondary (coagulation) hemostasis.

T e development of antibodies to coagulation plasma proteins, clinically termed inhibitors, is a relatively rare disease that often affects hemophilia A or B and FXI-deficient patients on repetitive exposure to the missing protein to control bleeding episodes. Inhibitors also occur among subjects without genetic deficiency of clotting factors (e.g., in the postpartum setting as a manifestation of underlying autoimmune or neoplastic disease or idiopathically). Rare cases of inhibitors to thrombin or FV have been reported in patients receiving topical bovine thrombin preparation as a local hemostatic agent in complex surgeries. T e diagnosis of inhibitors is based on the same tests as those used to diagnose inherited plasma coagulation factor deficiencies. However, the addition of the missing protein to the plasma of a subject with an inhibitor does not correct the abnormal aPTT and/or PT tests (known as mixing tests). T is is the major laboratory difference between deficiencies and inhibitors. Additional tests are required to measure the specificity of the inhibitor and its titer.

T e treatment of these bleeding disorders often requires replacement of the deficient protein using recombinant or purified plasma-derived products or fresh-frozen plasma (FFP). T erefore, it is imperative to arrive at a proper diagnosis to optimize patient care without unnecessary exposure to suboptimal treatment and the risks of bloodborne disease.

HEMOPHILIA

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Hemophilia is an X-linked recessive hemorrhagic disease due to mutations in the F8 gene (hemophilia A or classic hemophilia) or F9 gene (hemophilia B).

TABLE 21-1

GENETIC AND LABORATORY CHARACTERISTICS OF INHERITED COAGULATION DISORDERS

CLOTTING FACTOR DEFICIENCY	INHERITANCE	PREVALENCE IN GENERAL POPULATION	LABORATORY ABNORMALITY[a]			MINIMUM HEMOSTATIC LEVELS	TREATMENT	PLASMA HALF-LIFE
			aPTT	PT	TT			
Fibrinogen	AR	1 in 1,000,000	+	+	+	100 mg/dL	Cryoprecipitate	2–4 d
Prothrombin	AR	1 in 2,000,000	+	+	−	20–30%	FFP/PCC	3–4 d
Factor V	AR	1 in 1,000,000	+/−	+/−	−	15–20%	FFP	36 h
Factor VII	AR	1 in 500,000	−	+	−	15–20%	FFP/PCC	4–6 h
Factor VIII	X-linked	1 in 5,000	+	−	−	30%	FVIII concentrates	8–12 h
Factor IX	X-linked	1 in 30,000	+	−	−	30%	FIX concentrates	18–24 h
Factor X	AR	1 in 1,000,000	+/−	+/−	−	15–20%	FFP/PCC	40–60 h
Factor XI	AR	1 in 1,000,000	+	−	−	15–20%	FFP	40–70 h
Factor XII	AR	ND	+	−	−	[b]	[b]	60 h
HK	AR	ND	+	−	−	[b]	[b]	150 h
Prekallikrein	AR	ND	+	−	−	[b]	[b]	35 h
Factor XIII	AR	1 in 2,000,000	−	−	+/−	2–5%	Cryoprecipitate/ FXIII concentrates	11–14 d

[a]Values within normal range (−) or prolonged (+).
[b]No risk for bleeding; treatment is not indicated.
Abbreviations: aPTT, activated partial thromboplastin time; AR, autosomal recessive; FFP, fresh-frozen plasma; HK, high-molecular-weight kininogen; ND, not determined; PCC, prothrombin complex concentrates; PT, prothrombin time; TT, thrombin time.

T e disease affects 1 in 10,000 males worldwide, in all ethnic groups; hemophilia A represents 80% of all cases. Male subjects are clinically affected; women, who carry a single mutated gene, are generally asymptomatic. Family history of the disease is absent in ~30% of cases, and in these cases, 80% of the mothers are carriers of the de novo mutated allele. More than 500 different mutations have been identified in the F8 or F9 genes of patients with hemophilia A or B, respectively. One of the most common hemophilia A mutations results from an inversion of the intron 22 sequence, and it is present in 40% of cases of severe hemophilia A. Advances in

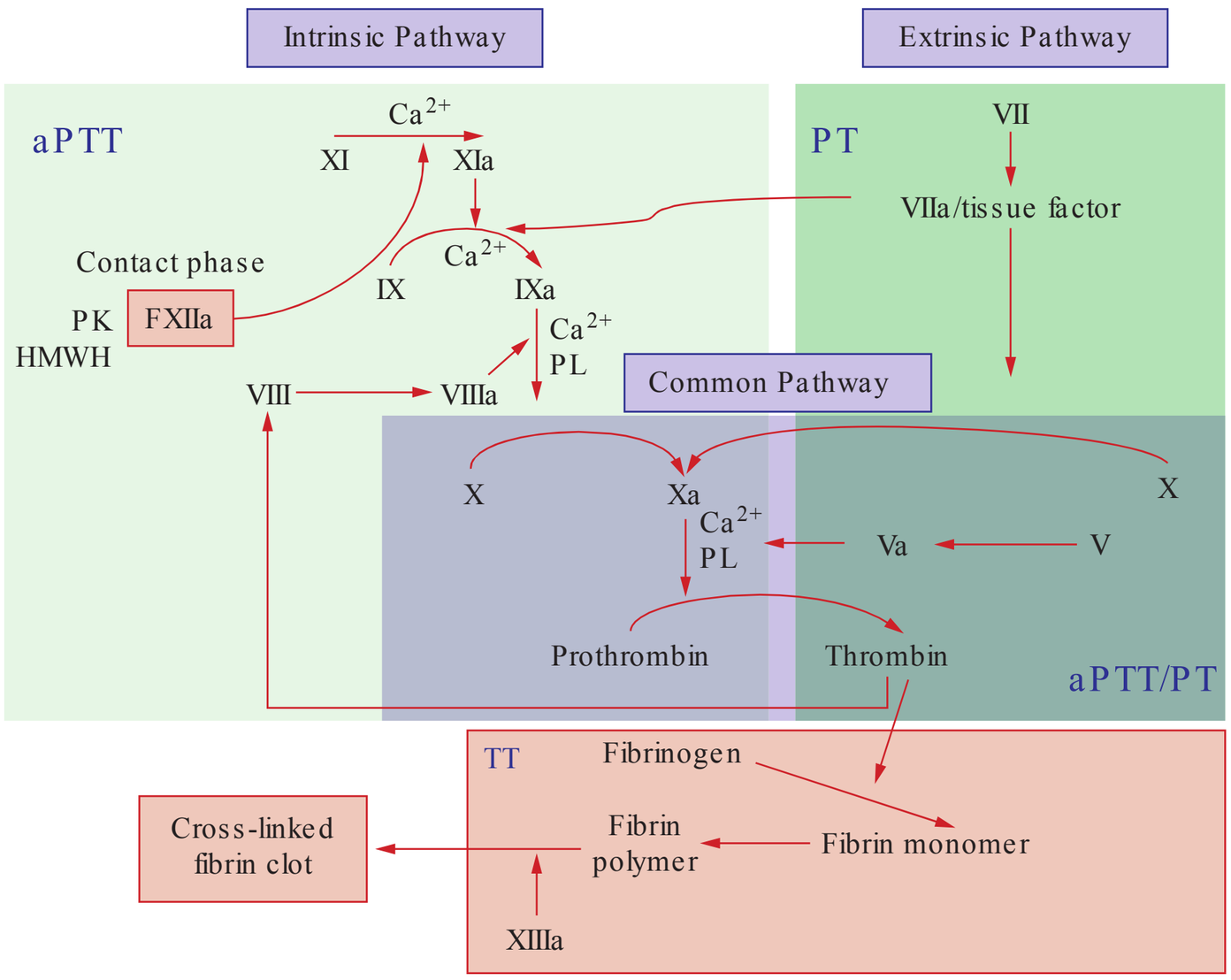

FIGURE 21-1
Coagulation cascade and laboratory assessment of clotting factor deficiency by activated partial prothrombin time (aPTT), prothrombin time (PT), thrombin time (TT), and phospholipid (PL).

molecular diagnosis now permit precise identification of mutations, allowing accurate diagnosis of women carriers of the hemophilia gene in affected families.

Clinically, hemophilia A and hemophilia B are indistinguishable. T e disease phenotype correlates with the residual activity of FVIII or FIX and can be classified as severe (<1%), moderate (1–5%), or mild (6–30%). In the severe and moderate forms, the disease is characterized by bleeding into the joints (hemarthrosis), soft tissues, and muscles after minor trauma or even spontaneously. Patients with mild disease experience infrequent bleeding that is usually secondary to trauma. Among those with residual FVIII or FIX activity >25% of normal, the disease is discovered only by bleeding after major trauma or during routine presurgery laboratory tests. Typically, the global tests of coagulation show only an isolated prolongation of the aPTT assay. Patients with hemophilia have normal bleeding times and platelet counts. T e diagnosis is made after specific determination of FVIII or FIX clotting activity.

Early in life, bleeding may present after circumcision or rarely as intracranial hemorrhages. T e disease is more evident when children begin to walk or crawl. In the severe form, the most common bleeding manifestations are the recurrent hemarthroses, which can affect every joint but mainly affect knees, elbows, ankles, shoulders, and hips. Acute hemarthroses are painful, and clinical signs are local swelling and erythema. To avoid pain, the patient may adopt a fixed position, which leads eventually to muscle contractures. Very young children unable to communicate verbally show irritability and a lack of movement of the affected joint. Chronic hemarthroses are debilitating, with synovial thickening and synovitis in response to the intraarticular blood. After a joint has been damaged, recurrent bleeding episodes result in the clinically recognized "target joint," which then establishes a vicious cycle of bleeding, resulting in progressive joint deformity that in critical cases requires surgery as the only therapeutic option. Hematomas into the muscle of distal parts of the limbs may lead to external compression of arteries, veins, or nerves that can evolve to a compartment syndrome.

Bleeding into the oropharyngeal spaces, central nervous system (CNS), or retroperitoneum is life threatening and requires immediate therapy. Retroperitoneal hemorrhages can accumulate large quantities of blood with formation of masses with calcification and inflammatory tissue reaction (pseudotumor syndrome) and also result in damage to the femoral nerve. Pseudotumors can also form in bones, especially long bones of the lower limbs. Hematuria is frequent among hemophilia patients, even in the absence of genitourinary pathology. It is often self-limited and may not require specific therapy.

TREATMENT Hemophilia

Without treatment, severe hemophilia has a limited life expectancy. Advances in the blood fractionation industry during World War II resulted in the realization that plasma could be used to treat hemophilia, but the volumes required to achieve even modest elevation of circulating factor levels limit the utility of plasma infusion as an approach to disease management. T e discovery in the 1960s that the cryoprecipitate fraction of plasma was enriched for FVIII, and the eventual purification of FVIII and FIX from plasma, led to the introduction of home infusion therapy with factor concentrates in the 1970s. T e availability of factor concentrates resulted in a dramatic improvement in life expectancy and in quality of life for people with severe hemophilia. However, the contamination of the blood supply with hepatitis viruses and, subsequently, HIV resulted in widespread transmission of these bloodborne infections within the hemophilia population; complications of HIV and of hepatitis C are now the leading causes of death among U.S. adults with severe hemophilia. T e introduction of viral inactivation steps in the preparation of plasma-derived products in the mid-1980s greatly reduced the risk of HIV and hepatitis, and the risks were further reduced by the successful production of recombinant FVIII and FIX proteins, both licensed in the 1990s. It is uncommon for hemophilic patients born after 1985 to have contracted either hepatitis or HIV, and for these individuals, life expectancy is approximately 65 years. In fact, since 1998, no evidence of new infections with viral hepatitis or HIV has been reported in patients using blood products. Factor replacement therapy for hemophilia can be provided either in response to a bleeding episode or as a prophylactic treatment. Primary prophylaxis is defined as a strategy for maintaining the missing clotting factor at levels ~1% or higher on a regular basis in order to prevent bleeds, especially the onset of hemarthroses. Hemophilic boys receiving regular infusions of FVIII (3 days/week) or FIX (2 days/week) can reach puberty without detectable joint abnormalities. Prophylaxis has become gradually more common in young patients. T e Centers for Disease Control and Prevention reported that 51% of children with severe hemophilia who are younger than age 6 years receive prophylaxis, increasing considerably from 33% in 1995. Although highly recommended, the high cost and dif culties in accessing peripheral veins in young patients and the potential infectious and thrombotic risks of long-term central vein catheters are important limiting factors for many young patients. Emerging data show that prophylaxis is also increasing among adults with severe hemophilia.

General considerations regarding the treatment of bleeds in hemophilia include the following: (1) Treatment should begin as soon as possible because symptoms often precede objective evidence of bleeding; because of the superior ef - cacy of early therapeutic intervention, classic symptoms of bleeding into the joint in a reliable patient, headaches, or automobile or other accidents require prompt replacement

and further laboratory investigation. (2) Drugs that hamper platelet function, such as aspirin or aspirin-containing drugs, should be avoided; to control pain, drugs such as ibuprofen or propoxyphene are preferred. FVIII and FIX are dosed in units. One unit is defined as amount of FVIII (100 ng/mL) or FIX (5 μg/mL) in 1 mL of normal plasma. One unit of FVIII per kilogram of body weight increases the plasma FVIII level by 2%. One can calculate the dose needed to increase FVIII levels to 100% in a 70-kg severe hemophilia patient (<1%) using the simple formula below. T us, 3500 units of FVIII will raise the circulating level to 100%.

$$\text{FVIII dose (IU)} = \text{Target FVIII Ievels} - \text{FVIII baseline levels} \times \text{body weight (kg)} \times 0.5 \text{ unit/kg}$$

T e doses for FIX replacement are different from those for FVIII, because FIX recovery after infusion is usually only 50% of the predicted value. T erefore, the formula for FIX replacement is as follows:

$$\text{FIX dose (IU)} = \text{Target FIX levels} - \text{FIX baseline levels} \times \text{body weight (kg)} \times 1 \text{ unit/kg}$$

T e FVIII half-life of 8–12 h requires injections twice a day to maintain therapeutic levels, whereas the FIX half-life is longer, ~24 h, so that once-a-day injection is suf cient. In specific situations such as after surgery, continuous infusion of factor may be desirable because of its safety in achieving sustained factor levels at a lower total cost.

Cryoprecipitate is enriched with FVIII protein (each bag contains ~80 IU of FVIII) and was commonly used for the treatment of hemophilia A decades ago; it is still in use in some developing countries, but because of the risk of blood-borne diseases, this product should be avoided in hemophilia patients when factor concentrates are available.

Mild bleeds such as uncomplicated hemarthroses or superficial hematomas require initial therapy with factor levels of 30–50%. Additional doses to maintain levels of 15–25% for 2 or 3 days are indicated for severe hemarthroses, especially when these episodes affect the "target joint." Large hematomas, or bleeds into deep muscles, require factor levels of 50% or even higher if the clinical symptoms do not improve, and factor replacement may be required for a period of 1 week or longer. T e control of serious bleeds including those that affect the oropharyngeal spaces, CNS, and the retroperitoneum require sustained protein levels of 50–100% for 7–10 days. Prophylactic replacement for surgery is aimed at achieving normal factor levels (100%) for a period of 7–10 days; replacement can then be tapered depending on the extent of the surgical wounds. Oral surgery is associated with extensive tissue damage that usually requires factor replacement for 1–3 days coupled with oral antifibrinolytic drugs.

NONTRANSFUSION THERAPY IN HEMOPHILIA

DDAVP (1-Amino-8-d-Arginine Vasopressin) DDAVP is a synthetic vasopressin analog that causes a transient rise in FVIII and von Willebrand factor (VWF), but not FIX, through a mechanism involving release from endothelial cells. Patients with moderate or mild hemophilia A should be tested to determine if they respond to DDAVP before a therapeutic application. DDAVP at doses of 0.3 μg/kg body weight, over a 20-min period, is expected to raise FVIII levels by two- to threefold over baseline, peaking between 30 and 60 min after infusion. DDAVP does not improve FVIII levels in severe hemophilia A patients, because there are no stores to release. Repeated dosing of DDAVP results in tachyphylaxis because the mechanism is an increase in release rather than de novo synthesis of FVIII and VWF. More than three consecutive doses become ineffective, and if further therapy is indicated, FVIII replacement is required to achieve hemostasis.

Antifibrinolytic Drugs Bleeding in the gums, gastrointestinal tract, and during oral surgery requires the use of oral antifibrinolytic drugs such as ε-amino caproic acid (EACA) or tranexamic acid to control local hemostasis. The duration of the treatment depending on the clinical indication is 1 week or longer. Tranexamic acid is given at doses of 25 mg/kg three to four times a day. EACA treatment requires a loading dose of 200 mg/kg (maximum of 10 g) followed by 100 mg/kg per dose (maximum 30 g/d) every 6 h. These drugs are not indicated to control hematuria because of the risk of formation of an occlusive clot in the lumen of genitourinary tract structures.

COMPLICATIONS

Inhibitor Formation T e formation of alloantibodies to FVIII or FIX is currently the major complication of hemophilia treatment. T e prevalence of inhibitors to FVIII is estimated to be between 5 and 10% of all cases and ~20% of severe hemophilia A patients. Inhibitors to FIX are detected in only 3–5% of all hemophilia B patients. T e high-risk group for inhibitor formation includes severe deficiency (>80% of all cases of inhibitors), familial history of inhibitor, African descent, mutations in the FVIII or FIX gene resulting in deletion of large coding regions, or gross gene rearrangements. Inhibitors usually appear early in life, at a median of 2 years of age, and after 10 cumulative days of exposure. However, intensive replacement therapy such as for major surgery, intracranial bleeding, or trauma increases the risk of inhibitor formation for patients of all ages and degree of clinical severity, which requires close laboratory monitoring in the following weeks.

T e clinical diagnosis of an inhibitor is suspected when patients do not respond to factor replacement at therapeutic doses. Inhibitors increase both morbidity and mortality in hemophilia. Because early detection of an inhibitor is critical to a successful correction of the bleeding or to eradication of the antibody, most hemophilia centers perform annual screening for inhibitors. T e laboratory test required to confirm the presence of an inhibitor is an aPTT with a mix (with normal plasma). In most hemophilia patients, a 1:1 mix with normal plasma completely corrects the aPTT.

In inhibitor patients, the aPTT on a 1:1 mix is abnormally prolonged, because the inhibitor neutralizes the FVIII clotting activity of the normal plasma. The Bethesda assay uses a similar principle and defines the specificity of the inhibitor and its titer. The results are expressed in Bethesda units (BU), in which 1 BU is the amount of antibody that neutralizes 50% of the FVIII or FIX present in normal plasma after 2 h of incubation at 37°C. Clinically, inhibitor patients are classified as low responders or high responders, which provides guidelines for optimal therapy. Therapy for inhibitor patients has two goals: the control of acute bleeding episodes and the eradication of the inhibitor. For the control of bleeding episodes, low responders, those with titer <5 BU, respond well to high doses of human or porcine FVIII (50–100 U/kg), with minimal or no increase in the inhibitor titers. However, high-responder patients, those with initial inhibitor titer >10 BU or an anamnestic response in the antibody titer to >10 BU even if low titer initially, do not respond to FVIII or FIX concentrates. The control of bleeding episodes in high-responder patients can be achieved by using concentrates enriched for prothrombin, FVII, FIX, FX (prothrombin complex concentrates [PCCs] or activated PCCs [aPCCs]), and more recently recombinant activated factor VII (FVIIa) known as "bypass agents" (Fig. 21-1). The rates of therapeutic success have been higher for FVIIa than for PCC or aPCC. For eradication of the inhibitory antibody, immunosuppression alone is not effective. The most effective strategy is the immune tolerance induction (ITI) based on daily infusion of missing protein until the inhibitor disappears, typically requiring periods longer than 1 year, with success rates of approximately 60%. The management of patients with severe hemophilia and inhibitors resistant to ITI is challenging. The use of anti-CD20 monoclonal antibody (rituximab) combined with ITI was thought to be effective. Although this therapy may reduce the inhibitor titers in some cases, sustained eradication is uncommon and may require two to three infusions weekly of clotting factor concentrates.

Novel Therapeutic Approaches in Development for Hemophilia Clinical studies using long-acting clotting factors with prolonged half-lives are in the late phase of clinical testing, and these new-generation products (for FVIII and FIX) may facilitate prophylaxis by requiring fewer injections to maintain circulating levels above 1%.

The use of recombinant interleukin 11 in patients with moderate or mild hemophilia A unresponsive to DDAVP has been tested in early-phase clinical trials and may be an alternate therapeutic strategy for clinical situations that require transient increases in FVIII levels.

Gene therapy trials for hemophilia B using adeno-associated viral vectors are ongoing, and initial data are promising.

INFECTIOUS DISEASES Hepatitis C virus (HCV) infection is the major cause of morbidity and the second leading cause of death in hemophilia patients exposed to older clotting factor concentrates. The vast majority of young patients treated with plasma-derived products from 1970 to 1985 became infected with HCV. It has been estimated that >80% of patients older than 20 years of age are HCV antibody positive as of 2006. The comorbidity of the underlying liver disease in hemophilia patients is clear when these individuals require invasive procedures; correction of both genetic and acquired (secondary to liver disease) deficiencies may be needed. Infection with HIV also swept the population of patients using plasma-derived concentrates two decades ago. Co-infection of HCV and HIV, present in almost 50% of hemophilia patients, is an aggravating factor for the evolution of liver disease. The response to HCV antiviral therapy in hemophilia is restricted to <30% of patients and even poorer among those with both HCV and HIV infection. End-stage liver disease requiring organ transplantation may be curative for both the liver disease and for hemophilia.

EMERGING CLINICAL PROBLEMS IN AGING HEMOPHILIA PATIENTS There has been continuous improvement of the management of hemophilia since the increase in the population of adults living beyond middle age in the developing world. The life expectancy of a patient with severe hemophilia is only ~10 years shorter than the general male population. In patients with mild or moderate hemophilia, life expectancy is approaching that of the male population without coagulopathy. Elderly hemophilia patients have different problems compared to the younger generation; they have more severe arthropathy and chronic pain, due to suboptimal treatment, and high rates of HCV and/or HIV infections.

Early data indicate that mortality from coronary artery disease is lower in hemophilia patients than the general male population. The underlying hypocoagulability probably provides a protective effect against thrombus formation, but it does not prevent atherogenesis. Similar to the general population, these patients are exposed to cardiovascular risk factors such as age, obesity, and smoking. Moreover, physical inactivity, hypertension, and chronic renal disease are commonly observed in hemophilia patients. In HIV patients on combined antiretroviral therapy, there may be a further increase in the risk of cardiovascular disease. Therefore, these patients should be carefully considered for preventive and therapeutic approaches to minimize the risk of cardiovascular disease.

Excessive replacement therapy should be avoided, and it is prudent to slowly infuse factor concentrates. Continuous infusion of clotting factor is preferable to bolus dosing in patients with cardiovascular risk factors undergoing invasive procedures. The management of an acute ischemic event and coronary revascularization should include the collaboration of hematologists and internists. The early assumption that hemophilia would protect against occlusive vascular disease may change in this aging population. Cancer is a common cause of mortality in aging hemophilia patients because they are at risk for HIV- and HCV-related malignancies. Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer and a common cause of death in HIV-negative

patients. The recommendations for cancer screening for the general population should be the same for age-matched hemophilia patients. Among those with high-risk HCV, a semiannual or annual ultrasound and α fetoprotein are recommended for HCC. Screening for urogenital neoplasm in the presence of hematuria or hematochezia may be delayed due to the underlying bleeding disease, thus preventing early intervention. Multidisciplinary interaction should facilitate the attempts to ensure optimal cancer prevention and treatment recommendations for those with hemophilia.

MANAGEMENT OF CARRIERS OF HEMOPHILIA Usually hemophilia carriers, with factor levels of ~50% of normal, have not been considered to be at risk for bleeding. However, a wide range of values (22–116%) have been reported due to random inactivation of the X chromosomes (lyonization). Therefore, it is important to measure the factor level of carriers to recognize those at risk of bleeding and to optimize preoperative and postoperative management. During pregnancy, both FVIII and FIX levels increase gradually until delivery. FVIII levels increase approximately two- to threefold compared to nonpregnant women, whereas an FIX increase is less pronounced. After delivery, there is a rapid fall in the pregnancy-induced rise of maternal clotting factor levels. This represents an imminent risk of bleeding that can be prevented by infusion of factor concentrate to levels of 50–70% for 3 days in the setting of vaginal delivery and up to 5 days for cesarean section. In mild cases, the use of DDAVP and/or antifibrinolytic drugs is recommended.

FACTOR XI DEFICIENCY

Factor XI is a zymogen of an active serine protease (FIXa) in the intrinsic pathway of blood coagulation that activates FIX (Fig. 21-1). There are two pathways for the formation of FXIa. In an aPTT-based assay, the protease is the result of activation by FXIIa in conjunction with high-molecular-weight kininogen and kallikrein. In vivo data suggest that thrombin is the physiologic activator of FXI. The generation of thrombin by the tissue factor/factor VIIa pathway activates FXI on the platelet surface that contributes to additional thrombin generation after the clot has formed and thus augments resistance to fibrinolysis through a thrombin-activated fibrinolytic inhibitor (TAFI).

Factor XI deficiency is a rare bleeding disorder that occurs in the general population at a frequency of one in a million. However, the disease is highly prevalent among Ashkenazi and Iraqi Jewish populations, reaching a frequency of 6% as heterozygotes and 0.1–0.3% as homozygotes. More than 65 mutations in the FXI gene have been reported, whereas fewer mutations (two to three) are found among affected Jewish populations.

Normal FXI clotting activity levels range from 70 to 150 U/dL. In heterozygous patients with moderate deficiency, FXI ranges from 20 to 70 U/dL, whereas in homozygous or double heterozygote patients, FXI levels are <1–20 U/dL. Patients with FXI levels <10% of normal have a high risk of bleeding, but the disease phenotype does not always correlate with residual FXI clotting activity. A family history is indicative of the risk of bleeding in the propositus. Clinically, the presence of mucocutaneous hemorrhages such as bruises, gum bleeding, epistaxis, hematuria, and menorrhagia are common, especially following trauma. This hemorrhagic phenotype suggests that tissues rich in fibrinolytic activity are more susceptible to FXI deficiency. Postoperative bleeding is common but not always present, even among patients with very low FXI levels.

FXI replacement is indicated in patients with severe disease required to undergo a surgical procedure. A negative history of bleeding complications following invasive procedures does not exclude the possibility of an increased risk for hemorrhage.

TREATMENT Factor XI Deficiency

The treatment of FXI deficiency is based on the infusion of FFP at doses of 15–20 mL/kg to maintain trough levels ranging from 10 to 20%. Because FXI has a half-life of 40–70 h, the replacement therapy can be given on alternate days. The use of antifibrinolytic drugs is beneficial to control bleeds, with the exception of hematuria or bleeds in the bladder. The development of an FXI inhibitor was observed in 10% of severely FXI-deficient patients who received replacement therapy. Patients with severe FXI deficiency who develop inhibitors usually do not bleed spontaneously. However, bleeding following a surgical procedure or trauma can be severe. In these patients, FFP and FXI concentrates should be avoided. The use of PCC/aPCC or recombinant activated FVII has been effective.

RARE BLEEDING DISORDERS

Collectively, the inherited disorders resulting from deficiencies of clotting factors other than FVIII, FIX, and FXI (Table 21-1) represent a group of rare bleeding diseases. The bleeding symptoms in these patients vary from asymptomatic (dysfibrinogenemia or FVII deficiency) to life-threatening (FX or FXIII deficiency). There is no pathognomonic clinical manifestation that suggests one specific disease, but overall, in contrast to hemophilia, hemarthrosis is a rare event and bleeding in the mucosal tract or after umbilical cord clamping is common. Individuals heterozygous for plasma coagulation deficiencies are often asymptomatic. The laboratory assessment for the specific deficient factor following screening with general coagulation tests (Table 21-1) will define the diagnosis.

Replacement therapy using FFP or prothrombin complex concentrates (containing prothrombin, FVII, FIX, and FX) provides adequate hemostasis in response to bleeds or as prophylactic treatment. T e use of PCC should be carefully monitored and avoided in patients with underlying liver disease, or those at high risk for thrombosis because of the risk of DIC.

FAMILIAL MULTIPLE COAGULATION DEFICIENCIES

T ere are several bleeding disorders characterized by the inherited deficiency of more than one plasma coagulation factor. To date, the genetic defects in two of these diseases have been characterized, and they provide new insights into the regulation of hemostasis by gene-encoding proteins outside blood coagulation.

Combined deficiency of FV and FVIII

Patients with combined FV and FVIII deficiency exhibit ~5% of residual clotting activity of each factor. Interestingly, the disease phenotype is a mild bleeding tendency, often following trauma. An underlying mutation has been identified in the endoplasmic reticulum/Golgi intermediate compartment (ERGIC-53) gene, a mannose-binding protein localized in the Golgi apparatus that functions as a chaperone for both FV and FVIII. In other families, mutations in the multiple coagulation factor deficiency 2 (MCFD2) gene have been defined; this gene encodes a protein that forms a Ca^{2+} dependent complex with ERGIC-53 and provides cofactor activity in the intracellular mobilization of both FV and FVIII.

Multiple deficiencies of vitamin K–dependent coagulation factors

Two enzymes involved in vitamin K metabolism have been associated with combined deficiency of all vitamin K–dependent proteins, including the procoagulant proteins prothrombin, VII, IX, and X and the anticoagulant proteins C and S. Vitamin K is a fat-soluble vitamin that is a cofactor for carboxylation of the gamma carbon of the glutamic acid residues in the vitamin K–dependent factors, a critical step for calcium and phospholipid binding of these proteins **(Fig. 21-2)**. T e enzymes γ-glutamylcarboxylase and epoxide reductase are critical for the metabolism and regeneration of vitamin K. Mutations in the genes encoding the γ-carboxylase (GGCX) or vitamin K epoxide reductase complex 1 (VKORC1) result in defective enzymes and thus in vitamin K–dependent factors with reduced activity, varying from 1 to 30% of normal. T e disease phenotype is characterized by mild to severe bleeding episodes present from birth. Some patients respond to high doses of vitamin K. For severe bleeding, replacement therapy with FFP or PCC may be necessary to achieve full hemostatic control.

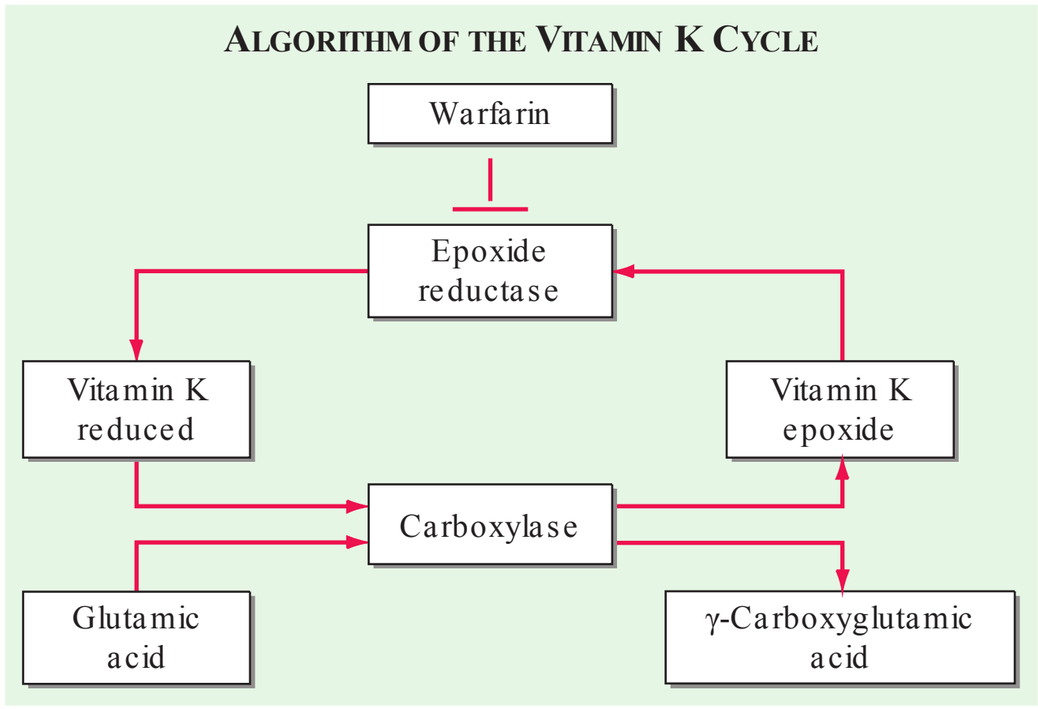

FIGURE 21-2
The vitamin K cycle. Vitamin K is a cofactor for the formation of γ-carboxyglutamic acid residues on coagulation proteins. Vitamin K–dependent γ-glutamylcarboxylase, the enzyme that catalyzes the vitamin K epoxide reductase, regenerates reduced vitamin K. Warfarin blocks the action of the reductase and competitively inhibits the effects of vitamin K.

DISSEMINATED INTRAVASCULAR COAGULATION

DIC is a clinicopathologic syndrome characterized by widespread intravascular fibrin formation in response to excessive blood protease activity that overcomes the natural anticoagulant mechanisms. T ere are several underlying pathologies associated with DIC **(Table 21-2)**.

T e most common causes are bacterial sepsis, malignant disorders such as solid tumors or acute promyelocytic leukemia, and obstetric causes. DIC is diagnosed in almost one-half of pregnant women with abruptio placentae or with amniotic fluid embolism. Trauma, particularly to the brain, can also result in DIC. T e exposure of blood to phospholipids from damaged tissue, hemolysis, and endothelial damage are all contributing factors to the development of DIC in this setting. Purpura fulminans is a severe form of DIC resulting from thrombosis of extensive areas of the skin; it affects predominantly young children following viral or bacterial infection, particularly those with inherited or acquired hypercoagulability due to deficiencies of the components of the protein C pathway. Neonates homozygous for protein C deficiency also present high risk for purpura fulminans with or without thrombosis of large vessels.

T e central mechanism of DIC is the uncontrolled generation of thrombin by exposure of the blood to pathologic levels of tissue factor **(Fig. 21-3)**.

TABLE 21-2

COMMON CLINICAL CAUSES OF DISSEMINATED INTRAVASCULAR COAGULATION

SEPSIS	IMMUNOLOGIC DISORDERS
• Bacterial: Staphylococci, streptococci, pneumococci, meningococci, gram-negative bacilli • Viral • Mycotic • Parasitic • Rickettsial	• Acute hemolytic transfusion reaction • Organ or tissue transplant rejection • Immunotherapy • Graft-versus-host disease
TRAUMA AND TISSUE INJURY	**DRUGS**
• Brain injury (gunshot) • Extensive burns • Fat embolism • Rhabdomyolysis	• Fibrinolytic agents • Aprotinin • Warfarin (especially in neonates with protein C deficiency) • Prothrombin complex concentrates • Recreational drugs (amphetamines)
VASCULAR DISORDERS	**ENVENOMATION**
• Giant hemangiomas (Kasabach-Merritt syndrome) • Large vessel aneurysms (e.g., aorta)	• Snake • Insects
OBSTETRICAL COMPLICATIONS	**LIVER DISEASE**
• Abruptio placentae • Amniotic fluid embolism • Dead fetus syndrome • Septic abortion	• Fulminant hepatic failure • Cirrhosis • Fatty liver of pregnancy
CANCER	**MISCELLANEOUS**
• Adenocarcinoma (prostate, pancreas, etc.) • Hematologic malignancies (acute promyelocytic leukemia)	• Shock • Respiratory distress syndrome • Massive transfusion

Simultaneous suppression of physiologic anticoagulant mechanisms and abnormal fibrinolysis further accelerate the process. Together, these abnormalities contribute to systemic fibrin deposition in small and midsize vessels. The duration and intensity of the fibrin deposition can compromise the blood supply of many organs, especially the lung, kidney, liver, and brain, with consequent organ failure. The sustained activation of coagulation results in consumption of clotting factors and platelets, which in turn leads to systemic bleeding. This is further aggravated by secondary hyperfibrinolysis. Studies in animals demonstrate that the fibrinolytic system is indeed suppressed at the time of maximal activation of coagulation. Interestingly, in patients with acute promyelocytic leukemia, a severe hyperfibrinolytic state often occurs in addition to the coagulation activation. The release of several proinflammatory cytokines such as interleukin 6 and tumor necrosis factor α plays a central role in mediating the coagulation defects in DIC and symptoms associated with systemic inflammatory response syndrome (SIRS).

Clinical manifestations of DIC are related to the magnitude of the imbalance of hemostasis, to the underlying disease, or to both. The most common findings are bleeding ranging from oozing from venipuncture sites, petechiae, and ecchymoses to severe hemorrhage from the gastrointestinal tract, lung, or into the CNS. In chronic DIC, the bleeding symptoms are discrete and restricted to skin or mucosal surfaces. The hypercoagulability of DIC manifests as the occlusion of vessels in the microcirculation and resulting organ failure. Thrombosis of large vessels and cerebral embolism can also occur. Hemodynamic complications and shock are common among patients with acute DIC. The mortality ranges from 30 to >80% depending on the underlying disease, the severity of the DIC, and the age of the patient.

The diagnosis of clinically significant DIC is based on the presence of clinical and/or laboratory abnormalities of coagulation or thrombocytopenia. The laboratory diagnosis of DIC should prompt a search for the underlying disease if it is not already apparent. There is no single test that establishes the diagnosis of DIC. The laboratory investigation should include coagulation tests (aPTT, PT, thrombin time [TT]) and markers of fibrin degradation products (FDPs), in addition to platelet and red cell count and analysis of the blood smear. These tests should be repeated over a period of 6–8 h because an initially mild abnormality can change dramatically in patients with severe DIC.

Common findings include the prolongation of PT and/or aPTT; platelet counts μ100,000/μL, or a rapid decline in platelet numbers; the presence of schistocytes (fragmented red cells) in the blood smear; and elevated levels of FDP. The most sensitive test for DIC is the FDP level. DIC is an unlikely diagnosis in the presence of normal levels of FDP. The d-dimer test is more specific for detection of fibrin—but not fibrinogen—degradation products and indicates that the cross-linked fibrin has been digested by plasmin. Because fibrinogen has a prolonged half-life, plasma levels diminish acutely only in severe cases of DIC. High-grade DIC is also associated with levels of antithrombin III or plasminogen activity <60% of normal.

Chronic DIC

Low-grade, compensated DIC can occur in clinical situations including giant hemangioma, metastatic carcinoma, or the dead fetus syndrome. Plasma levels of FDP or d-dimers are elevated. aPTT, PT, and fibrinogen

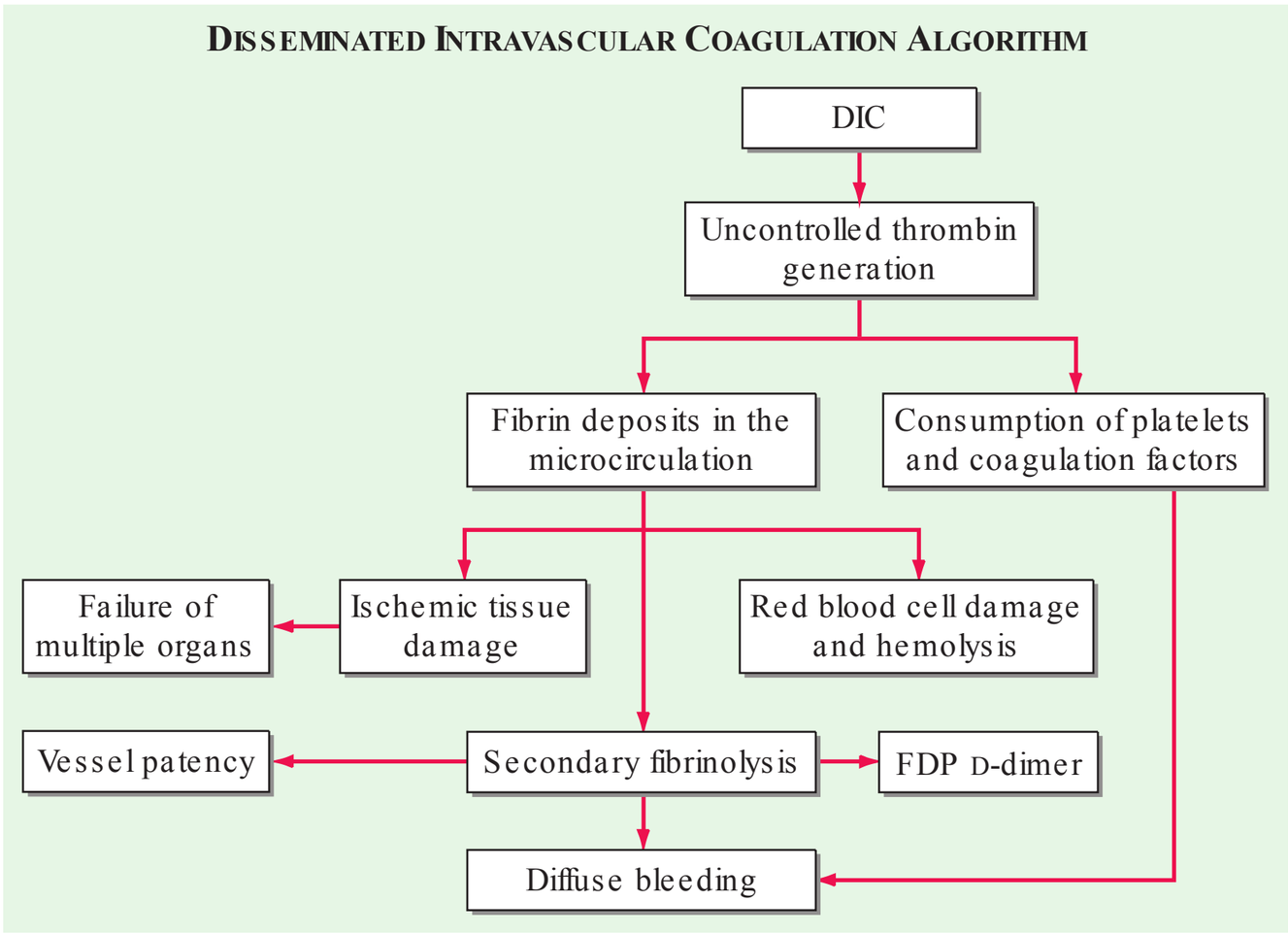

FIGURE 21-3
The pathophysiology of disseminated intravascular coagulation (DIC). Interactions between coagulation and fibrinolytic pathways result in bleeding and thrombosis in the microcirculation in patients with DIC. FDP, fibrin degradation product.

values are within the normal range or high. Mild thrombocytopenia or normal platelet counts are also common findings. Red cell fragmentation is often detected but at a lower degree than in acute DIC.

Differential diagnosis

The differential diagnosis between DIC and severe liver disease is challenging and requires serial measurements of the laboratory parameters of DIC. Patients with severe liver disease are at risk for bleeding and manifest laboratory features including thrombocytopenia (due to platelet sequestration, portal hypertension, or hypersplenism), decreased synthesis of coagulation factors and natural anticoagulants, and elevated levels of FDP due to reduced hepatic clearance. However, in contrast to DIC, these laboratory parameters in liver disease do not change rapidly. Other important differential findings include the presence of portal hypertension or other clinical or laboratory evidence of an underlying liver disease.

Microangiopathic disorders such as thrombotic thrombocytopenic purpura present an acute clinical onset of illness accompanied by thrombocytopenia, red cell fragmentation, and multiorgan failure. However, there is no consumption of clotting factors or hyperfibrinolysis.

Over the last few years, several clinical trials on immune therapies for neoplasias using monoclonal antibodies or gene-modified T cells targeting tumor-specific antigens showed unwanted inflammatory responses with increased cytokine release. These complications are sometimes associated with increased d-dimers and decreased fibrinogen levels, cytopenias, and liver dysfunction; thus, careful screening tests for DIC are indicated.

TREATMENT Disseminated Intravascular Coagulation

The morbidity and mortality associated with DIC are primarily related to the underlying disease rather than the complications of the DIC. The control or elimination of the underlying cause should therefore be the primary concern. Patients with severe DIC require control of hemodynamic parameters, respiratory support, and sometimes invasive surgical procedures. Attempts to treat DIC without accompanying treatment of the causative disease are likely to fail.

MANAGEMENT OF HEMORRHAGIC SYMPTOMS Administration of FFP and/or platelet concentrates is indicated for patients with active bleeding or at high risk of bleeding, such as in preparation for invasive procedures or after chemotherapy. The control of bleeding in DIC patients with marked thrombocytopenia (platelet counts <10,000–20,000/μL) and low levels of coagulation factors will require replacement therapy. The PT (>1.5 times the normal) provides a good indicator of the severity of the clotting factor consumption. Replacement with FFP is indicated (1 unit of FFP increases most coagulation factors by 30% in an adult without DIC). Low levels of fibrinogen (<100 mg/dL) or brisk hyperfibrinolysis will require infusion of cryoprecipitate (plasma fraction enriched for fibrinogen, FVIII, and VWF). The replacement of 10 U of cryoprecipitate for every 2–3 U of FFP is sufficient to correct the hemostasis. The transfusion scheme must be adjusted according to the patient's clinical and laboratory evolution. Platelet concentrates at a dose of 1–2 U/10 kg body weight are sufficient for most DIC patients with severe thrombocytopenia. Clotting factor concentrates are not recommended for control of bleeding in DIC because of the limited efficacy afforded by replacement of single factors (FVIII or FIX concentrates) and the high risk of products containing traces of aPCCs that further aggravate the disease.

REPLACEMENT OF COAGULATION OR FIBRINOLYSIS INHIBITORS Drugs to control coagulation such as heparin, antithrombin III (ATIII) concentrates, or antifibrinolytic drugs have all been tried in the treatment of DIC. Low doses of continuous-infusion heparin (5–10 U/kg per h) may be effective in patients with low-grade DIC associated with solid tumor, acute promyelocytic leukemia, or in a setting with recognized thrombosis. Heparin is also indicated for the treatment of purpura fulminans during the surgical resection of giant hemangiomas and during removal of a dead fetus. In acute DIC, the use of heparin is likely to aggravate bleeding. To date, the use of heparin in patients with severe DIC has no proven survival benefit. T e use of antifibrinolytic drugs, EACA, or tranexamic acid to prevent fibrin degradation by plasmin may reduce bleeding episodes in patients with DIC and confirmed hyperfibrinolysis. However, these drugs can increase the risk of thrombosis, and concomitant use of heparin is indicated. Patients with acute promyelocytic leukemia or those with chronic DIC associated with giant hemangiomas are among the few patients who may benefit from this therapy. T e use of protein C concentrates to treat purpura fulminans associated with acquired protein C deficiency or meningococcemia has been proven ef cacious. T e results from the replacement of ATIII in early-phase studies are promising but require further study.

Guidance for diagnosis and treatment of DIC had been proposed by the International Society of T rombosis and Haemostasis. T is initiative will permit more detailed clinical data on diagnosis and treatment of DIC. T e clinical utility of these scoring systems and therapeutic recommendations contained in these guidelines is not yet known.

Vitamin K deficiency

Vitamin K–dependent proteins are a heterogenous group, including clotting factor proteins and also proteins found in bone, lung, kidney, and placenta. Vitamin K mediates posttranslational modification of glutamate residues to γ-carboxylglutamate, a critical step for the activity of vitamin K–dependent proteins for calcium binding and proper assembly to phospholipid membranes (Fig. 21-2). Inherited deficiency of the functional activity of the enzymes involved in vitamin K metabolism, notably the GGCX or VKORC1 (see above), results in bleeding disorders. T e amount of vitamin K in the diet is often limiting for the carboxylation reaction; thus recycling of the vitamin K is essential to maintain normal levels of vitamin K–dependent proteins. In adults, low dietary intake alone is seldom reason for severe vitamin K deficiency but may become common in association with the use of broad-spectrum antibiotics. Disease or surgical interventions that affect the ability of the intestinal tract to absorb vitamin K, either through anatomic alterations or by changing the fat content of bile salts and pancreatic juices in the proximal small bowel, can result in significant reduction of vitamin K levels. Chronic liver diseases such as primary biliary cirrhosis also deplete vitamin K stores. Neonatal vitamin K deficiency and the resulting hemorrhagic disease of the newborn have been almost entirely eliminated by routine administration of vitamin K to all neonates. Prolongation of PT values is the most common and earliest finding in vitamin K–deficient patients due to reduction in prothrombin, FVII, FIX, and FX levels. FVII has the shortest half-life among these factors that can prolong the PT before changes in the aPTT. Parenteral administration of vitamin K at a total dose of 10 mg is suf - cient to restore normal levels of clotting factor within 8–10 h. In the presence of ongoing bleeding or a need for immediate correction before an invasive procedure, replacement with FFP or PCC is required. T e latter should be avoided in patients with severe underlying liver disorders due to high risk of thrombosis. T e reversal of excessive anticoagulant therapy with warfarin or warfarin-like drugs can be achieved by minimal doses of vitamin K (1 mg orally or by intravenous injection) for asymptomatic patients. T is strategy can diminish the risk of bleeding while maintaining therapeutic anticoagulation for an underlying prothrombotic state.

In patients with life-threatening bleeds, the use of recombinant factor VIIa in nonhemophilia patients on anticoagulant therapy has been shown to be effective at restoring hemostasis rapidly, allowing emergency surgical intervention. However, patients with underlying vascular disease, vascular trauma and other comorbidities are at risk for thromboembolic complications that affect both arterial and venous systems. T us, the use of factor VIIa in this setting is limited to administration of low doses given for only a limited number of injections. Close monitoring for vascular complications is highly indicated.

Coagulation disorders associated with liver failure

T e liver is central to hemostasis because it is the site of synthesis and clearance of most procoagulant and natural anticoagulant proteins and of essential components of the fibrinolytic system. Liver failure is associated with a high risk of bleeding due to deficient synthesis of procoagulant factors and enhanced fibrinolysis. T rombocytopenia is common in patients with liver disease, and may be due to congestive splenomegaly (hypersplenism) or immune-mediated shortened platelet lifespan (primary biliary cirrhosis). In addition, several anatomic abnormalities secondary to underlying liver disease further promote the occurrence of hemorrhage **(Table 21-3)**. Dysfibrinogenemia is a relatively common finding in patients with liver disease due to impaired fibrin polymerization. T e development of DIC concomitant to chronic liver disease is

TABLE 21-3

COAGULATION DISORDERS AND HEMOSTASIS IN LIVER DISEASE

BLEEDING
Portal hypertension
Esophageal varices
Thrombocytopenia
Splenomegaly
Chronic or acute DIC
Decreased synthesis of clotting factors
Hepatocyte failure
Vitamin K deficiency
Systemic fibrinolysis
DIC
Dysfibrinogenemia
THROMBOSIS
Decreased synthesis of coagulation inhibitors: protein C, protein S, antithrombin
Hepatocyte failure
Vitamin K deficiency (protein C, protein S)
Failure to clear activated coagulation proteins (DIC)
Dysfibrinogenemia
Iatrogenic: Transfusion of prothrombin complex concentrates
Antifibrinolytic agents: EACA, tranexamic acid

Abbreviations: DIC, disseminated intravascular coagulation; EACA, ε-aminocaproic acid.

not uncommon and may enhance the risk for bleeding. Laboratory evaluation is mandatory for an optimal therapeutic strategy, either to control ongoing bleeding or to prepare patients with liver disease for invasive procedures. Typically, these patients present with prolonged PT, aPTT, and TT depending on the degree of liver damage, thrombocytopenia, and normal or slight increase of FDP. Fibrinogen levels are diminished only in fulminant hepatitis, decompensated cirrhosis, or advanced liver disease, or in the presence of DIC. The presence of prolonged TT and normal fibrinogen and FDP levels suggest dysfibrinogenemia. FVIII levels are often normal or elevated in patients with liver failure, and decreased levels suggest superimposing DIC. Because FV is only synthesized in the hepatocyte and is not a vitamin K–dependent protein, reduced levels of FV may be an indicator of hepatocyte failure. Normal levels of FV and low levels of FVII suggest vitamin K deficiency. Vitamin K levels may be reduced in patients with liver failure due to compromised storage in hepatocellular disease, changes in bile acids, or cholestasis that can diminish the absorption of vitamin K. Replacement of vitamin K may be desirable (10 mg given by slow intravenous injection) to improve hemostasis.

Treatment with FFP is the most effective to correct hemostasis in patients with liver failure. Infusion of FFP (5–10 mL/kg; each bag contains ~200 mL) is sufficient to ensure 10–20% of normal levels of clotting factors but not correction of PT or aPTT. Even high doses of FFP (20 mL/kg) do not correct the clotting times in all patients. Monitoring for clinical symptoms and clotting times will determine if repeated doses are required 8–12 h after the first infusion. Platelet concentrates are indicated when platelet counts are <10,000–20,000/μL to control an ongoing bleed or immediately before an invasive procedure if counts are <50,000/μL. Cryoprecipitate is indicated only when fibrinogen levels are less than 100 mg/mL; dosing is six bags for a 70-kg patient daily. Prothrombin complex concentrate infusion in patients with liver failure should be avoided due to the high risk of thrombotic complications. The safety of the use of antifibrinolytic drugs to control bleeding in patients with liver failure is not yet well defined and should be avoided.

Liver disease and thromboembolism

The clinical bleeding phenotype of hemostasis in patients with stable liver disease is often mild or even asymptomatic. However, as the disease progresses, the hemostatic balance is less stable and more easily disturbed than in healthy individuals. Furthermore, the hemostatic balance is compromised by comorbid complications such as infections and renal failure **(Fig. 21-4)**. Based on the clinical bleeding complications in patients with cirrhosis and laboratory evidence of hypocoagulation such as a prolonged PT/aPTT, it has long been assumed that these patients are protected against thrombotic disease. Cumulative clinical experience, however, has demonstrated that these patients are at risk for thrombosis, especially those with advanced liver disease. Although hypercoagulability could explain the occurrence of venous thrombosis, according to Virchow's triad, hemodynamic changes and damaged vasculature may also be a contributing factor, and both processes may potentially also occur in patients with liver disease. Liver-related thrombosis, in particular, thrombosis of the portal and mesenteric veins, is common in patients with advanced cirrhosis. Hemodynamic changes, such as decreased portal flow, and evidence that inherited thrombophilia may enhance the risk for portal vein thrombosis in patients with cirrhosis suggest that hypercoagulability may play a role as well. Patients with liver disease develop deep vein thrombosis and pulmonary embolism at appreciable rates (ranging from 0.5 to 1.9%). The implication of these findings is relevant to the erroneous exclusion of thrombosis in patients with advanced liver disease, even in the presence of prolongation of routine clotting times, and caution should be advised on overcorrection of these laboratory abnormalities.

Acquired inhibitors of coagulation factors

An acquired inhibitor is an immune-mediated disease characterized by the presence of an autoantibody against

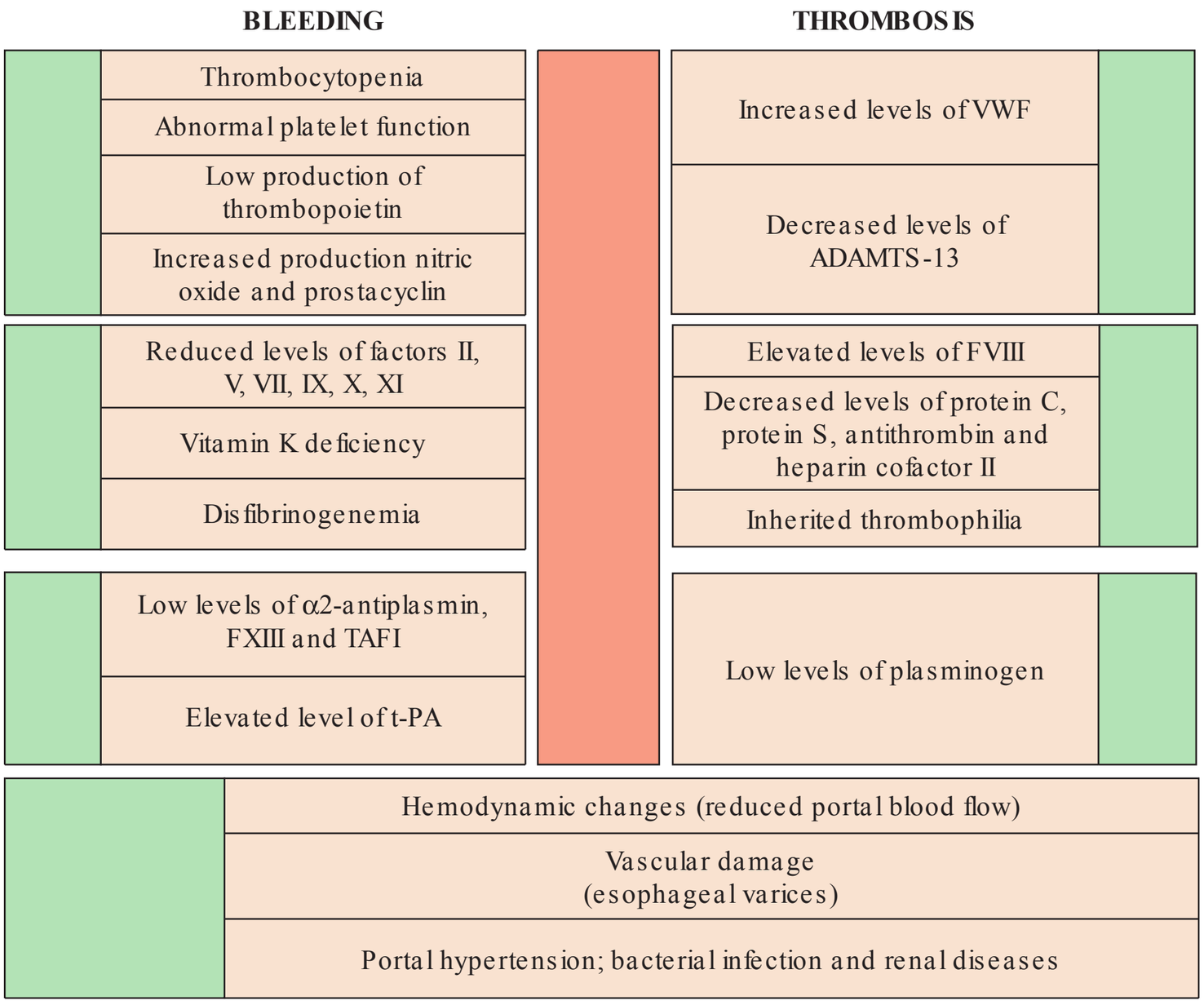

FIGURE 21-4
Balance of hemostasis in liver disease. TAFI, thrombin-activated fibrinolytic inhibitor; t-PA, tissue plasminogen activator; VWF, von Willebrand factor.

a specific clotting factor. FVIII is the most common target of antibody formation, and is sometimes referred to as acquired hemophilia A, but inhibitors to prothrombin, FV, FIX, FX, and FXI are also reported. Acquired inhibitor to FVIII occurs predominantly in older adults (median age of 60 years), but occasionally in pregnant or postpartum women with no previous history of bleeding. In 50% of patients with inhibitors, no underlying disease is identified at the time of diagnosis. In the remaining patients, the causes are autoimmune diseases, malignancies (lymphomas, prostate cancer), dermatologic diseases, and pregnancy. Bleeding episodes occur commonly in soft tissues, the gastrointestinal or urinary tracts, and skin. In contrast to hemophilia, hemarthrosis is rare in these patients. Retroperitoneal hemorrhages and other life-threatening bleeding may appear suddenly. The overall mortality in untreated patients ranges from 8 to 22%, and most deaths occur within the first few weeks after presentation. The diagnosis is based on the prolonged aPTT with normal PT and TT. The aPTT remains prolonged after mixture of the test plasma with equal amounts of pooled normal plasma for 2 h at 37°C. The Bethesda assay using FVIII-deficient plasma as performed for inhibitor detection in hemophilia will confirm the diagnosis. Major bleeding is treated with bypass products such as PCC/aPCC or recombinant FVIIa. In contrast to hemophilia, inhibitors in nonhemophilic patients are typically responsive to immune suppression, and therapy should be initiated early for most cases. The first choice includes steroid or a combination of steroid with cytotoxic therapy (e.g., cyclophosphamide), with complete eradication of the inhibitors in more than 70% of patients. High-dose intravenous γ-globulin and anti-CD20 monoclonal antibody have been reported to be effective in patients with autoantibodies to FVIII; however, there is no firm evidence that these alternatives are superior to the first line of immunosuppressive drugs. Notably, relapse of the inhibitor to FVIII is relatively common (up to 20%) within the first 6 months following withdrawal of immunosuppression. Thus, after eradication, patients should be followed up regularly for early therapeutic intervention when indicated or prior to invasive procedure.

Topical plasma-derived bovine and human thrombin are commonly used in the United States and worldwide. These effective hemostatic sealants are used during major surgery such as for cardiovascular, thoracic, neurologic, pelvic, and trauma indications, as well as in the setting of extensive burns. The development of antibody formation to the xenoantigen or its contaminant (bovine clotting protein) has the potential to show cross-reactivity with human clotting factors that may hamper their function and induce bleeding.

Clinical features of these antibodies include bleeding from a primary hemostatic defect or coagulopathy that sometimes can be life threatening. The clinical diagnosis of these acquired coagulopathies is often complicated by the fact that the bleeding episodes may be detectable during or immediately following major surgery and could be assumed to be due to the procedure itself.

Notably, the risk of this complication is further increased by repeated exposure to topical thrombin preparations. T us, a careful medical history of previous surgical interventions that may have occurred even decades earlier is critical to assessing risk.

T e laboratory abnormalities are reflected by combined prolongation of the aPTT and PT that often fails to improve by transfusion of FFP and vitamin K. T e abnormal laboratory tests cannot be corrected by mixing a test with equal parts of normal plasma that denotes the presence of inhibitory antibodies. T e diagnosis of a specific antibody is obtained by the determination of the residual activity of human FV or other suspected human clotting factor. T ere are no commercially available assays specific for bovine thrombin coagulopathy.

T ere are no established treatment guidelines. Platelet transfusions have been used as a source of FV replacement for patients with FV inhibitors. Frequent injections of FFP and vitamin K supplementation may function as co-adjuvant rather than an effective treatment of the coagulopathy itself. Experience with recombinant FVIIa as a bypass agent is limited, and outcomes have been generally poor. Specific treatments to eradicate the antibodies based on immunosuppression with steroids, intravenous immunoglobulin, or serial plasmapheresis have been sporadically reported. Patients should be advised to avoid any topical thrombin sealant in the future.

Novel plasma-derived and recombinant human thrombin preparations for topical hemostasis have been approved by the U.S. Food and Drug Administration. T ese preparations have demonstrated hemostatic ef - cacy with reduced immunogenicity compared to the first generation of bovine thrombin products.

T e presence of lupus anticoagulant can be associated with venous or arterial thrombotic disease. However, bleeding has also been reported in lupus anticoagulant; it is due to the presence of antibodies to prothrombin, which results in hypoprothrombinemia. Both disorders show a prolonged PTT that does not correct on mixing. To distinguish acquired inhibitors from lupus anticoagulant, note that the dilute Russell's viper venom test and the hexagonal-phase phospholipids test will be negative in patients with an acquired inhibitor and positive in patients with lupus anticoagulants. Moreover, lupus anticoagulant interferes with the clotting activity of many factors (FVIII, FIX, FXII, FXI), whereas acquired inhibitors are specific to a single factor.

CHAPTER 22

ARTERIAL AND VENOUS THROMBOSIS

Jane E. Freedman ■ Joseph Loscalzo

OVERVIEW OF THROMBOSIS

GENERAL OVERVIEW

T rombosis, the obstruction of blood flow due to the formation of clot, may result in tissue anoxia and damage, and it is a major cause of morbidity and mortality in a wide range of arterial and venous diseases and patient populations. In 2009 in the United States, an estimated 785,000 people had a new coronary thrombotic event, and about 470,000 had a recurrent ischemic episode. Each year, approximately 795,000 people have a new or recurrent stroke. It is estimated that 300,000–600,000 people each year have a pulmonary embolism or deep venous thrombotic event. In the nondiseased state, physiologic hemostasis reflects a delicate interplay between factors that promote and inhibit blood clotting, favoring the former. T is response is crucial as it prevents uncontrolled hemorrhage and exsanguination following injury. In specific settings, the same processes that regulate normal hemostasis can cause pathologic thrombosis, leading to arterial or venous occlusion. Importantly, many commonly used therapeutic interventions may also alter the thrombotic–hemostatic balance adversely.

Hemostasis and thrombosis primarily involve the interplay among three factors: the vessel wall, coagulation proteins, and platelets. Many prevalent acute vascular diseases are due to thrombus formation within a vessel, including myocardial infarction, thrombotic cerebrovascular events, and venous thrombosis. Although the end result is vessel occlusion and tissue ischemia, the pathophysiologic processes governing these pathologies have similarities as well as distinct differences. While many of the pathways regulating thrombus formation are similar to those that regulate hemostasis, the processes triggering thrombosis and, often, perpetuating the thrombus may be distinct and can vary in different clinical and genetic settings. In venous thrombosis, primary hypercoagulable states reflecting defects in the proteins governing coagulation and/or fibrinolysis or secondary hypercoagulable states involving abnormalities of blood vessels and blood flow or stasis lead to thrombosis. By contrast, arterial thrombosis is highly dependent on the state of the vessel wall, the platelet, and factors related to blood flow.

ARTERIAL THROMBOSIS

OVERVIEW OF ARTERIAL THROMBOSIS

In arterial thrombosis, the platelets and abnormalities of the vessel wall typically play a key role in vessel occlusion. Arterial thrombus forms via a series of sequential steps in which platelets adhere to the vessel wall, additional platelets are recruited, and thrombin is activated **(Fig. 22-1)**. T e regulation of platelet adhesion, activation, aggregation, and recruitment will be described in detail below. In addition, while the primary function of platelets is regulation of hemostasis, our understanding of their role in other processes, such as immunity, wound healing, and inflammation, continues to grow.

ARTERIAL THROMBOSIS AND VASCULAR DISEASE

Arterial thrombosis is a major cause of morbidity and mortality both in the United States and, increasingly, worldwide. Although the rates have declined in the United States, the overall burden remains high and accounts for approximately 33% of deaths. Overall, coronary heart disease is estimated to cause about 1 of every 5 deaths in the United States. In addition to the 785,000 Americans who will have a new coronary event, an additional 195,000 silent first myocardial infarctions are projected to occur annually. Although the rate of strokes has fallen by a third, each year, about 795,000 people experience a new or recurrent stroke, although not all are caused by thrombotic occlusion of

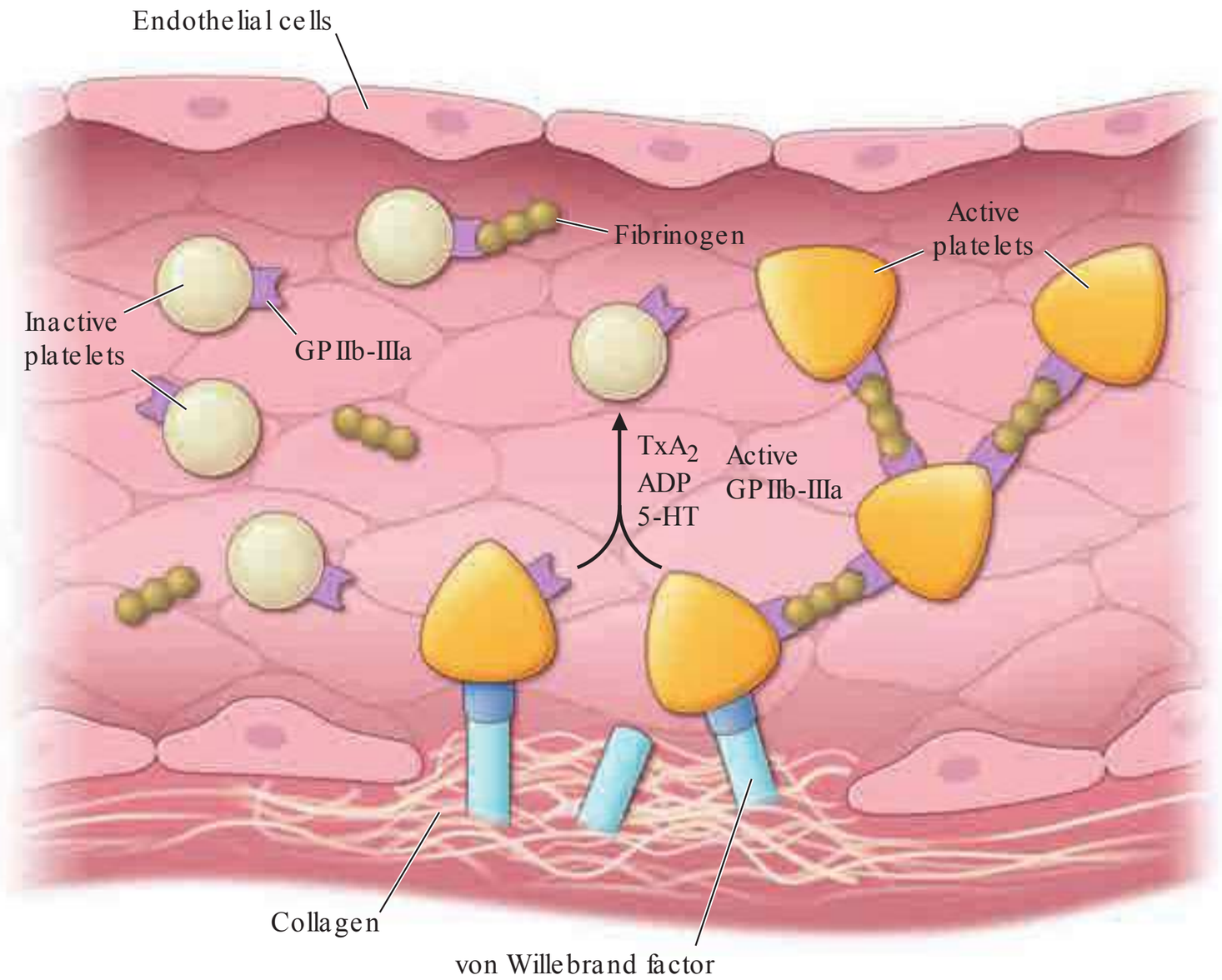

FIGURE 22-1
Platelet activation and thrombosis. Platelets circulate in an inactive form in the vasculature. Damage to the endothelium and/or external stimuli activates platelets that adhere to the exposed subendothelial von Willebrand factor and collagen. This adhesion leads to activation of the platelet, shape change, and the synthesis and release of thromboxane (TxA_2), serotonin (5-HT), and adenosine diphosphate (ADP). Platelet stimuli cause conformational change in the platelet integrin glycoprotein (GP) IIb/IIIa receptor, leading to the high-affinity binding of fibrinogen and the formation of a stable platelet thrombus.

the vessel. Approximately 610,000 strokes are first events and 185,000 are recurrent events; it is estimated that 1 of every 18 deaths in the United States is due to stroke.

THE PLATELET

Many processes in platelets have parallels with other cell types, such as the presence of specific receptors and signaling pathways; however, unlike most cells, platelets lack a nucleus and are unable to adapt to changing biologic settings by altered gene transcription. Platelets sustain limited protein synthetic capacity from megakaryocyte-derived and intracellularly transported microRNA (miRNA) and messenger RNA (mRNA). Most of the molecules needed to respond to various stimuli, however, are maintained in storage granules and membrane compartments.

Platelets are disc-shaped, very small, anucleate cells (1–5 μm in diameter) that circulate in the blood at concentrations of 200–400,000/μL, with an average lifespan of 7–10 days. Platelets are derived from megakaryocytes, polyploidal hematopoietic cells found in the bone marrow. The primary regulator of platelet formation is thrombopoietin (TPO). The precise mechanism by which megakaryocytes produce and release fully formed platelets is unclear, but the process likely involves formation of proplatelets, pseudopod-like structures generated by the evagination of the cytoplasm from which platelets bud. Platelet granules are synthesized in megakaryocytes before thrombopoiesis and contain an array of prothrombotic, proinflammatory, and antimicrobial mediators. The two major types of platelet granules, alpha and dense, are distinguished by their size, abundance, and content. Alpha-granules contain soluble coagulation proteins, adhesion molecules, growth factors, integrins, cytokines, and inflammatory modulators. Platelet dense-granules are smaller than alpha-granules and less abundant. Whereas alpha-granules contain proteins that may be more important in the inflammatory response, dense-granules contain high concentrations of small molecules, including adenosine diphosphate (ADP) and serotonin, that influence platelet aggregation.

Platelet adhesion

(See Fig. 22-1) The formation of a thrombus is initiated by the adherence of platelets to the damaged vessel wall. Damage exposes subendothelial components responsible

for triggering platelet reactivity, including collagen, von Willebrand factor, fibronectin, and other adhesive proteins, such as vitronectin and thrombospondin. The hemostatic response may vary, depending on the extent of damage, the specific proteins exposed, and flow conditions. Certain proteins are expressed on the platelet surface that subsequently regulate collagen-induced platelet adhesion, particularly under flow conditions, and include glycoprotein (GP) IV, GPVI, and the integrin $\alpha_2\beta_1$. The platelet GPIb-IX-V complex adhesive receptor is central both to platelet adhesion and to the initiation of platelet activation. Damage to the blood vessel wall exposes subendothelial von Willebrand factor and collagen to the circulating blood. The GPIb-IX-V complex binds to the exposed von Willebrand factor, causing platelets to adhere (Fig. 22-1). In addition, the engagement of the GPIb-IX-V complex with ligand induces signaling pathways that lead to platelet activation. von Willebrand factor–bound GPIb-IX-V promotes a calcium-dependent conformational change in the GPIIb/IIIa receptor, transforming it from an inactive low-affinity state to an active high-affinity receptor for fibrinogen.

Platelet activation

The activation of platelets is controlled by a variety of surface receptors that regulate various functions in the activation process. Platelet receptors control many distinct processes and are stimulated by a wide variety of agonists and adhesive proteins that result in variable degrees of activation. In general terms, the stimulation of platelet receptors triggers two specific processes: (1) activation of internal signaling pathways that lead to further platelet activation and granule release and (2) the capacity of the platelet to bind to other adhesive proteins/platelets. Both of these processes contribute to the formation of a thrombus. Stimulation of nonthrombotic receptors results in platelet adhesion or interaction with other vascular cells including endothelial cells, neutrophils, and mononuclear cells.

Many families and subfamilies of receptors are found on platelets that regulate a variety of platelet functions. These include the seven transmembrane receptor family, which is the main agonist-stimulated receptor family. Several seven transmembrane receptors are found on platelets, including the ADP receptors, prostaglandin receptors, lipid receptors, and chemokine receptors. Receptors for thrombin comprise the major seven transmembrane receptors found on platelets. Among this last group, the first identified was the protease activation receptor 1 (PAR1). The PAR class of receptors has a distinct mechanism of activation that involves specific cleavage of the N-terminus of thrombin, which, in turn, acts as a ligand for the receptor. Other PAR receptors are present on platelets, including PAR2 (not activated by thrombin) and PAR4. Adenosine receptors are responsible for transduction of ADP-induced signaling events, which are initiated by the binding of ADP to purinergic receptors on the platelet surface. There are several distinct ADP receptors, classified as $P2X_1$, $P2Y_1$, and $P2Y_{12}$. The activation of both the $P2Y_{12}$ and $P2Y_1$ receptors is essential for ADP-induced platelet aggregation. The thienopyridine derivatives, clopidogrel and prasugrel, are clinically used inhibitors of ADP-induced platelet aggregation.

Platelet aggregation

Activation of platelets results in a rapid series of signal transduction events, including tyrosine kinase, serine/threonine kinase, and lipid kinase activation. In unstimulated platelets, the major platelet integrin GPIIb/IIIa is maintained in an inactive conformation and functions as a low-affinity adhesion receptor for fibrinogen. This integrin is unique as it is only expressed on platelets. After stimulation, the interaction between fibrinogen and GPIIb/IIIa forms intercellular connections between platelets, leading to the formation of a platelet aggregate (Fig. 22-1). A calcium-sensitive conformational change in the extracellular domain of GPIIb/IIIa enables the high-affinity binding of soluble plasma fibrinogen as a result of a complex network of inside-out signaling events. The GPIIb/IIIa receptor serves as a bidirectional conduit with GPIIb/IIIa-mediated signaling (outside-in) occurring immediately after the binding of fibrinogen. This leads to additional intracellular signaling that further stabilizes the platelet aggregate and transforms platelet aggregation from a reversible to an irreversible process (inside-out).

THE ROLE OF PLATELETS AND THROMBOSIS IN INFLAMMATION

Inflammation plays an important role during the acute thrombotic phase of acute coronary syndromes. In the setting of acute upper respiratory infections, people are at higher risk of myocardial infarction and thrombotic stroke. Patients with acute coronary syndromes have not only increased interactions between platelets (homotypic aggregates), but also increased interactions between platelets and leukocytes (heterotypic aggregates) detectable in circulating blood. These latter aggregates form when platelets are activated and adhere to circulating leukocytes. Platelets bind via P-selectin (CD62P) expressed on the surface of activated platelets to the leukocyte receptor, P-selectin glycoprotein ligand 1 (PSGL-1). This is association leads to increased expression of CD11b/CD18 (Mac-1) on leukocytes, which itself supports interactions with platelets partially via bivalent fibrinogen linking this integrin with its platelet surface counterpart, GPIIb/IIIa. Platelet surface P-selectin also induces the expression of tissue factor on monocytes, which promotes fibrin formation.

In addition to platelet–monocyte aggregates, the immunomodulator, soluble CD40 ligand (CD40L or

CD154), also reflects a link between thrombosis and inflammation. The CD40 ligand is a trimeric transmembrane protein of the tumor necrosis factor family and, with its receptor CD40, is an important contributor to the inflammatory process leading both to thrombosis and atherosclerosis. While many immunologic and vascular cells have been found to express CD40 and/or CD40 ligand, in platelets, CD40 ligand is rapidly translocated to the surface after stimulation and is upregulated in the newly formed thrombus. The surface-expressed CD40 ligand is cleaved from the platelet to generate a soluble fragment (soluble CD40 ligand).

Links have also been established among platelets, infection, immunity, and inflammation. Bacterial and viral infections are associated with a transient increase in the risk of acute thrombotic events, such as acute myocardial infarction and stroke. In addition, platelets contribute significantly to the pathophysiology and high mortality rates of sepsis. The expression, functionality, and signaling pathways of toll-like receptors (TLRs) have been established in platelets. Stimulation of platelet TLR2, TLR3, and TLR4 directly and indirectly activates the platelet's thrombotic and inflammatory responses, and live bacteria induce a proinflammatory response in platelets in a TLR2-dependent manner, suggesting a mechanism by which specific bacteria and bacterial components can directly activate platelet-dependent thrombosis.

GENETICS OF ARTERIAL THROMBOSIS

Some studies have associated arterial thrombosis with genetic variants **(Table 22-1A)**; however, the associations have been weak and not confirmed in larger series. Platelet count and mean platelet volume have been studied by genome-wide association studies (GWAS), and this approach identified signals located to noncoding regions. Of 15 quantitative trait loci associated with mean platelet volume and platelet count, one located at 12q24 is also a risk locus for coronary artery disease.

In the area of genetic variability and platelet function, studies have primarily dealt with pharmacogenetics, the field of pharmacology dealing with the interindividual variability in drug response based on genetic determinants **(Table 22-2)**. This focus has been driven by the wide variability among individuals in terms of response to antithrombotic drugs and the lack of a common explanation for this variance. The best described is the issue of "aspirin resistance," although heterogeneity for other antithrombotics (e.g., clopidogrel) has also been extensively examined. Primarily, platelet-dependent genetic determinants have been defined at the level of (1) drug effect, (2) drug compliance, and (3) drug metabolism. Many candidate platelet genes have been studied for their interaction with antiplatelet and antithrombotic agents.

Many patients have an inadequate response to the inhibitory effects of aspirin. Heritable factors contribute

TABLE 22-1

HERITABLE CAUSES OF ARTERIAL AND VENOUS THROMBOSIS

A. Arterial Thrombosis
Platelet Receptors
β3 and α2 integrins
P_1 A2 polymorphism
Fc(gamma)RIIA
GPIVT13254C polymorphism
GPIb
Thrombin receptor PAR1-5061 → D
Redox Enzymes
Plasma glutathione peroxidase
H2 promoter haplotype
Endothelial nitric oxide synthase
−786T/C, −922A/G, −1468T/A
Paraoxonase
−107T allele, 192R allele
Homocysteine
Cystathionine β-synthase 833T → C
5,10-Methylene tetrahydrofolate reductase (MTHFR)
677C → T
B. Venous Thrombosis
Procoagulant Proteins
Fibrinogen
−455G/A, −854G/A
Prothrombin (20210G → A)
Protein C Anticoagulant Pathway
Factor V Leiden: 1691G → A (Arg506Gln)
Thrombomodulin 1481C → T (Ala455Val)
Fibrinolytic Proteins with Known Polymorphisms
Tissue plasminogen activator (tPA)
7351C/T, 20 099T/C in exon 6, 27 445T/A in intron 10
Plasminogen activator inhibitor (PAI-1)
4G/5G insertion/deletion polymorphism at position −675
Homocysteine
Cystathionine β-synthase 833T → C
5,10-MTHFR 677C → T

TABLE 22-2

GENETIC VARIATION AND PHARMACOGENETIC RESPONSES TO PLATELET INHIBITORS

POTENTIAL GENE ALTERED	TARGET THERAPEUTIC CLASS	SPECIFIC DRUG
P2Y1 and P2Y12 CYP2C19, CYP3A4, CYP3A5	ADP receptor inhibitors	Clopidogrel, prasugrel
COX1, COX2	Cyclooxygenase inhibitors	Aspirin
PlA1/A2	Receptor inhibitors	Abciximab, eptifbatide, tirofban
INTB3, GPIbA	Glycoprotein IIb-IIIa receptor inhibitors	

to the variability; however, ex vivo tests of residual platelet responsiveness after aspirin administration have not provided firm evidence for a pharmacogenetic interaction between aspirin and COX1 or other relevant platelet receptors. As such, currently, there is no clinical indication for genotyping to optimize aspirin's antiplatelet ef ciency. For the platelet P2Y12 receptor inhibitor clopidogrel, additional data suggest that genetics may affect the drug's responsiveness and utility. T e responsible genetic variant appears not to be the expected P2Y12 receptor but an enzyme responsible for drug metabolism. Clopidogrel is a prodrug, and liver metabolism by specific cytochrome P450 enzymes is required for activation. T e genes encoding the CYP-dependent oxidative steps are polymorphic, and carriers of specific alleles of the CYP2C19 and CYP3A4 loci have increased platelet aggregability. Increased platelet activity has also been specifically associated with the CYP2C19*2 allele, which causes loss of platelet function in select patients. Because these are common genetic variants, this observation has been shown to be clinically relevant in large studies. In summary, although the loss-of-function polymorphisms in CYP2C19 is the strongest individual variable affecting pharmacokinetics and antiplatelet response to clopidogrel, it only accounts for 5–12% of the variability in ADP-induced platelet aggregation on clopidogrel. In addition, genetic variables do not appear to significantly contribute to the clinical outcomes of patients treated with the P2Y12 receptor antagonists prasugrel or ticagrelor.

VENOUS THROMBOSIS

OVERVIEW OF VENOUS THROMBOSIS

Coagulation is the process by which thrombin is activated and soluble plasma fibrinogen is converted into insoluble fibrin. T ese steps account for both normal hemostasis and the pathophysiologic processes influencing the development of venous thrombosis. T e primary forms of venous thrombosis are deep vein thrombosis (DVT) in the extremities and the subsequent embolization to the lungs (pulmonary embolism), referred to together as venous thromboembolic disease. Venous thrombosis occurs due to heritable causes (Table 22-1B) and acquired causes **(Table 22-3)**.

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

More than 200,000 new cases of venous thromboembolism occur each year. Of these cases, up to 30% of patients die within 30 days and one-fifth suffer sudden death due to pulmonary embolism; 30% go on to develop recurrent venous thromboembolism within 10 years. Data from the Atherosclerosis Risk in Communities (ARIC) study reported a 9% 28-day fatality rate from DVT and a 15% fatality rate from pulmonary embolism. Pulmonary embolism in the setting of cancer has a 25% fatality rate. T e mean incidence of first DVT in the general population is 5 per 10,000 person-years; the incidence is similar in males and females when adjusting for factors related to reproduction and birth control and increases dramatically with age from 2 to 3 per 10,000 person-years at 30–49 years of age to 20 at 70–79 years of age.

TABLE 22-3

ACQUIRED CAUSES OF VENOUS THROMBOSIS

Surgery
Neurosurgery
Major abdominal surgery
Malignancy
Antiphospholipid syndrome
Other
Trauma
Pregnancy
Long-haul travel
Obesity
Oral contraceptives/hormone replacement
Myeloproliferative disorders
Polycythemia vera

OVERVIEW OF THE COAGULATION CASCADE AND ITS ROLE IN VENOUS THROMBOSIS

Coagulation is defined as the formation of fibrin by a series of linked enzymatic reactions in which each reaction product converts the subsequent inactive zymogen into an active serine protease **(Fig. 22-2)**. T is coordinated sequence is called the coagulation cascade and is a key mechanism for regulating hemostasis. Central to the function of the coagulation cascade is the principle of amplification: due to a series of linked enzymatic reactions, a small stimulus can lead to much greater quantities of fibrin, the end product that prevents hemorrhage at the site of vascular injury. In addition to the known risk factors relevant to hypercoagulopathy, stasis, and vascular dysfunction, newer areas of research have identified contributions from procoagulant microparticles, inflammatory cells, microvesicles, and fibrin structure.

T e coagulation cascade is primarily initiated by vascular injury exposing tissue factor to blood components (Fig. 22-2). Tissue factor may also be found in blood-borne cell-derived microparticles and, under pathophysiologic conditions, in leukocytes or platelets. Plasma factor VII (FVII) is the ligand for and is activated (FVIIa) by binding to tissue factor exposed at the site of vessel damage. T e binding of FVII/VIIa to tissue factor activates the downstream conversion of factor X (FX) to active FX (FXa). In an alternative reaction, the FVII/FVIIa–tissue

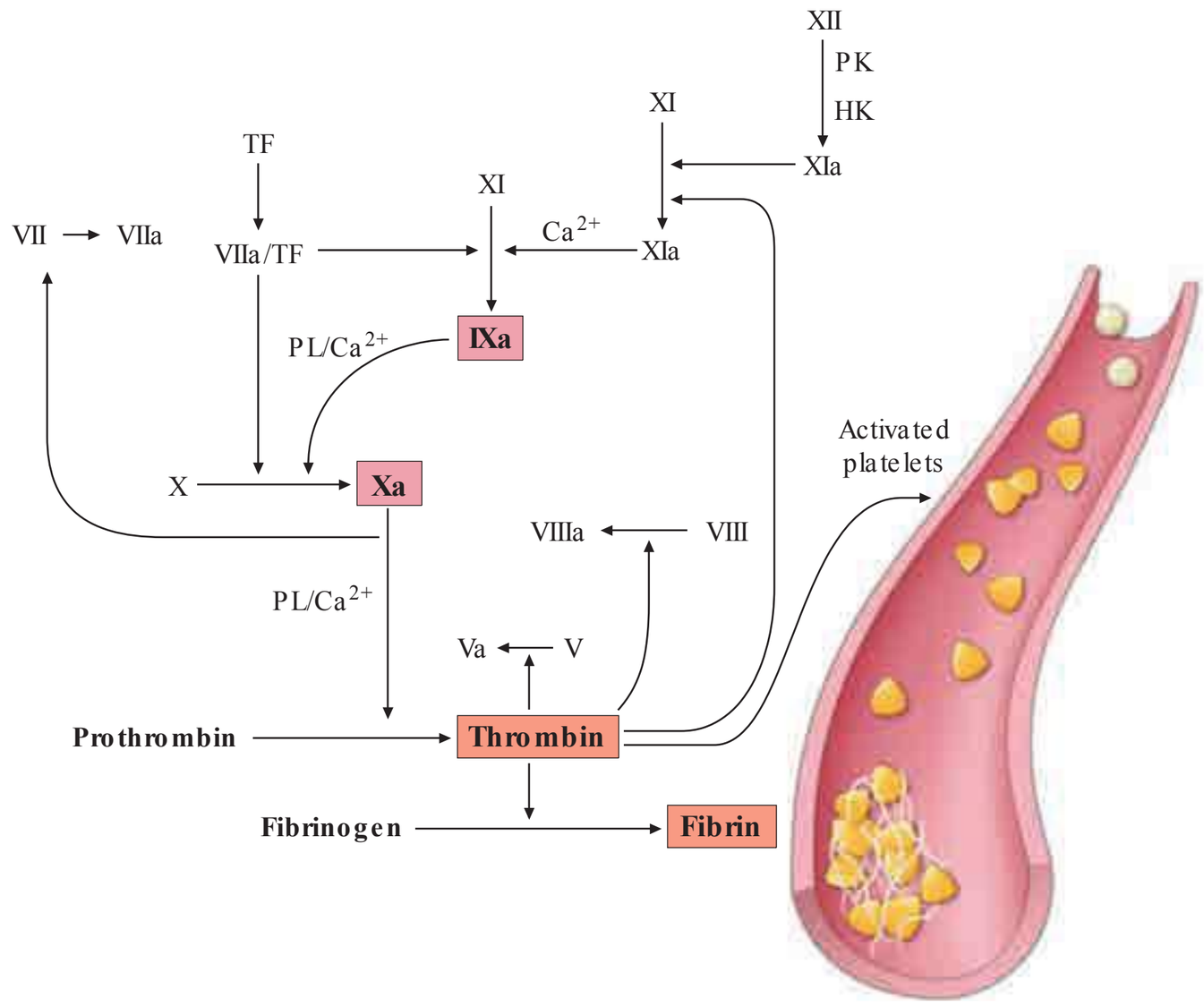

FIGURE 22-2
Summary of the coagulation pathways. Specifc coagulation factors ("a" indicates activated form) are responsible for the conversion of soluble plasma fbrinogen into insoluble fbrin. This process occurs via a series of linked reactions in which the enzymatically active product subsequently converts the downstream inactive protein into an active serine protease. In addition, the activation of thrombin leads to stimulation of platelets. HK, high-molecular-weight kininogen; PK, prekallikrein; TF, tissue factor.

factor complex initially converts FIX to FIXa, which then activates FX in conjunction with its cofactor factor VIII (FVIIIa). Factor Xa with its cofactor FVa converts prothrombin to thrombin, which then converts soluble plasma fibrinogen to insoluble fibrin, leading to clot or thrombus formation. T rombin also activates FXIII to FXIIIa, a transglutaminase that covalently cross-links and stabilizes the fibrin clot. Formation of thrombi is affected by mechanisms governing fibrin structure and stability including specific fibrinogen variants and how they alter fibrin formation, strength and structure.

Several antithrombotic factors also regulate coagulation; these include antithrombin, tissue factor pathway inhibitor (TFPI), heparin cofactor II, and protein C/protein S. Under normal conditions, these factors limit the production of thrombin to prevent the perpetuation of coagulation and thrombus formation. Typically, after the clot has caused occlusion at the damaged site and begins to expand toward adjacent uninjured vessel segments, the anticoagulant reactions governed by the normal endothelium become pivotal in limiting the extent of this hemostatically protective clot.

RISK FACTORS FOR VENOUS THROMBOSIS

T e risk factors for venous thrombosis are primarily related to hypercoagulability, which can be genetic (Table 22-1) or acquired, or due to immobilization and venous stasis. Independent predictors for recurrence include increasing age, obesity, malignant neoplasm, and acute extremity paresis. It is estimated that 5–8% of the U.S. population has a genetic risk factor known to predispose to venous thrombosis. Often, multiple risk factors are present in a single individual. Significant risk is incurred by major orthopedic, abdominal, or neurologic surgeries. Moderate risk is promoted by prolonged bedrest; certain types of cancer, pregnancy, hormone replacement therapy, or oral contraceptive use; and other sedentary conditions such as long-distance plane travel. It has been reported that the risk of developing a venous thromboembolic event doubles after air travel lasting 4 h, although the absolute risk remains low (1 in 6000). T e relative risk of venous thromboembolism among pregnant or postpartum women is 4.3, and the overall incidence (absolute risk) is 199.7 per 100,000 woman-years.

GENETICS OF VENOUS THROMBOSIS

(See Table 22-2) Less common causes of venous thrombosis are those due to genetic variants. T ese abnormalities include loss-of-function mutations of endogenous anticoagulants as well as gain-of-function mutations of procoagulant proteins. Heterozygous antithrombin deficiency and homozygosity of the factor V Leiden mutation significantly increase the risk of venous

thrombosis. While homozygous protein C or protein S deficiencies are rare and may lead to fatal purpura fulminans, heterozygous deficiencies are associated with a moderate risk of thrombosis. Activated protein C impairs coagulation by proteolytic degradation of FVa. Patients resistant to the activity of activated protein C may have a point mutation in the FV gene located on chromosome 1, a mutant denoted factor V Leiden. Mildly increased risk has been attributed to elevated levels of procoagulant factors, as well as low levels of tissue factor pathway inhibitor. Polymorphisms of methylene tetrahydrofolate reductase as well as hyperhomocysteinemia have been shown to be independent risk factors for venous thrombosis, as well as arterial vascular disease; however, many of the initial descriptions of genetic variants and their associations with thromboembolism are being questioned in larger, more current studies.

FIBRINOLYSIS AND THROMBOSIS

Specific abnormalities in the fibrinolytic system have been associated with enhanced thrombosis. Factors such as elevated levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor type 1 (PAI-1) have been associated with decreased fibrinolytic activity and an increased risk of arterial thrombotic disease. Specific genetic variants have been associated with decreased fibrinolytic activity, including the 4G/5G insertion/deletion polymorphism in the (plasminogen activator type 1) PAI-1 gene. Additionally, the 311-bp Alu insertion/deletion in tPA's intron 8 has been associated with enhanced thrombosis; however, genetic abnormalities have not been associated consistently with altered function or tPA levels, raising questions about the relevant pathophysiologic mechanism. T rombin-activatable fibrinolysis inhibitor (TAFI) is a carboxypeptidase that regulates fibrinolysis; elevated plasma TAFI levels have been associated with an increased risk of both DVT and cardiovascular disease.

T e metabolic syndrome also is accompanied by altered fibrinolytic activity. T is syndrome, which comprises abdominal fat (central obesity), altered glucose and insulin metabolism, dyslipidemia, and hypertension, has been associated with atherothrombosis. T e mechanism for enhanced thrombosis appears to be due both to altered platelet function and to a procoagulant and hypofibrinolytic state. One of the most frequently documented prothrombotic abnormalities reported in this syndrome is an increase in plasma levels of PAI-1.

In addition to contributing to platelet function, inflammation plays a role in both coagulation-dependent thrombus formation and thrombus resolution. Both polymorphonuclear neutrophils and monocytes/macrophages contribute to multiple overlapping thrombotic functions, including fibrinolysis, chemokine and cytokine production, and phagocytosis.

THE DISTINCTION BETWEEN ARTERIAL AND VENOUS THROMBOSIS

Although there is overlap, venous thrombosis and arterial thrombosis are initiated differently, and clot formation progresses by somewhat distinct pathways. In the setting of stasis or states of hypercoagulability, venous thrombosis is activated with the initiation of the coagulation cascade primarily due to exposure of tissue factor; this leads to the formation of thrombin and the subsequent conversion of fibrinogen to fibrin. In the artery, thrombin formation also occurs, but thrombosis is primarily promoted by the adhesion of platelets to an injured vessel and stimulated by exposed extracellular matrix (Figs. 22-1 and 22-2). T ere is wide variation in individual responses to vascular injury, an important determinant of which is the predisposition an individual has to arterial or venous thrombosis. T is concept has been supported indirectly in prothrombotic animal models in which there is poor correlation between the propensity to develop venous versus arterial thrombosis.

Despite considerable progress in understanding the role of hypercoagulable states in venous thromboembolic disease, the contribution of hypercoagulability to arterial vascular disease is much less well understood. Although specific thrombophilic conditions, such as factor V Leiden and the prothrombin G20210A mutation, are risk factors for DVT, pulmonary embolism, and other venous thromboembolic events, their contribution to arterial thrombosis is less well defined. In fact, to the contrary, many of these thrombophilic factors have not been found to be clinically important risk factors for arterial thrombotic events, such as acute coronary syndromes.

Clinically, although the pathophysiology is distinct, arterial and venous thrombosis do share common risk factors, including age, obesity, cigarette smoking, diabetes mellitus, arterial hypertension, hyperlipidemia, and metabolic syndrome. Select genetic variants, including those of the glutathione peroxidase gene, have also been associated with arterial and venous thrombo-occlusive disease. Importantly, arterial and venous thrombosis may both be triggered by pathophysiologic stimuli responsible for activating inflammatory and oxidative pathways.

T e diagnosis and management of DVT and pulmonary embolus are discussed in Chap. 23.

CHAPTER 23

DEEP VENOUS THROMBOSIS AND PULMONARY THROMBOEMBOLISM

Samuel Z. Goldhaber

EPIDEMIOLOGY

Venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE) and causes cardiovascular death and disability. In the United States, the Surgeon General estimates there are 100,000 to 180,000 deaths annually from PE and has declared that PE is the most common preventable cause of death among hospitalized patients. Survivors may succumb to the disabilities of chronic thromboembolic pulmonary hypertension or postthrombotic syndrome. Chronic thromboembolic pulmonary hypertension causes breathlessness, especially with exertion. Postthrombotic syndrome (also known as chronic venous insufficiency) damages the venous valves of the leg and causes ankle or calf swelling and leg aching, especially after prolonged standing. In its most severe form, postthrombotic syndrome causes skin ulceration **(Fig. 23-1)**.

PATHOPHYSIOLOGY

Inflammation and platelet activation

Virchow's triad of inflammation, hypercoagulability, and endothelial injury leads to recruitment of activated platelets, which release microparticles. These microparticles contain proinflammatory mediators that bind neutrophils, stimulating them to release their nuclear material and form web-like extracellular networks called neutrophil extracellular traps. These prothrombotic networks contain histones that stimulate platelet aggregation and promote platelet-dependent thrombin generation. Venous thrombi form and flourish in an environment of stasis, low oxygen tension, and upregulation of proinflammatory genes.

Prothrombotic states

The two most common autosomal dominant genetic mutations are factor V Leiden, which causes resistance to the endogenous anticoagulant, activated protein C (which inactivates clotting factors V and VIII), and the prothrombin gene mutation, which increases the

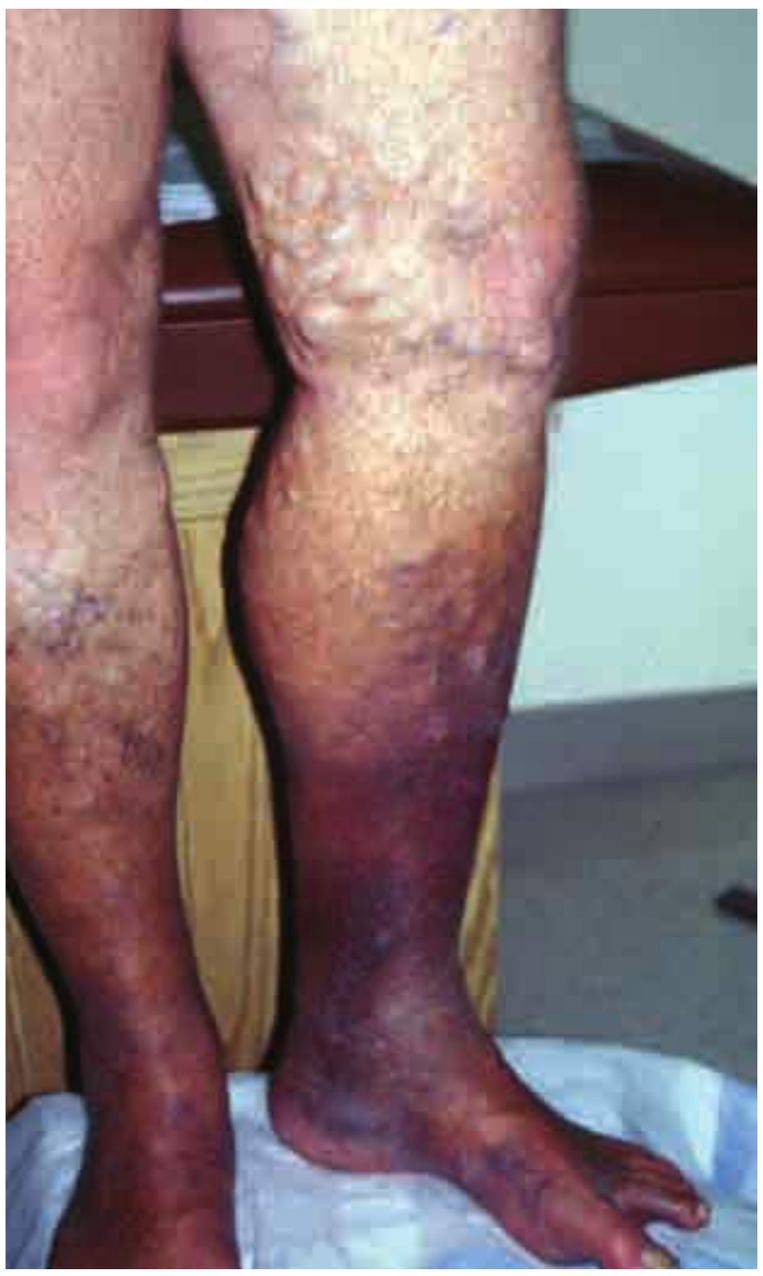

FIGURE 23-1
Skin ulceration in the lateral malleolus from postthrombotic syndrome of the leg.

plasma prothrombin concentration **(Chaps. 3 and 22)**. Antithrombin, protein C, and protein S are naturally occurring coagulation inhibitors. Deficiencies of these inhibitors are associated with VTE but are rare. Antiphospholipid antibody syndrome is the most common acquired cause of thrombophilia and is associated with venous or arterial thrombosis. Other common predisposing factors include cancer, obesity, cigarette smoking, systemic arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, blood transfusion, long-haul air travel, air pollution, oral contraceptives, pregnancy, postmenopausal hormone replacement, surgery, and trauma.

Embolization

When deep venous thrombi **(Fig. 23-2)** detach from their site of formation, they embolize to the vena cava, right atrium, and right ventricle, and lodge in the pulmonary arterial circulation, thereby causing acute PE. Paradoxically, these thrombi occasionally embolize to the arterial circulation through a patent foramen ovale or atrial septal defect. Many patients with PE have no evidence of DVT because the clot has already embolized to the lungs.

Physiology

The most common gas exchange abnormalities are arterial hypoxemia and an increased alveolar-arterial O_2 tension gradient, which represents the inefficiency of O_2 transfer across the lungs. Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries.

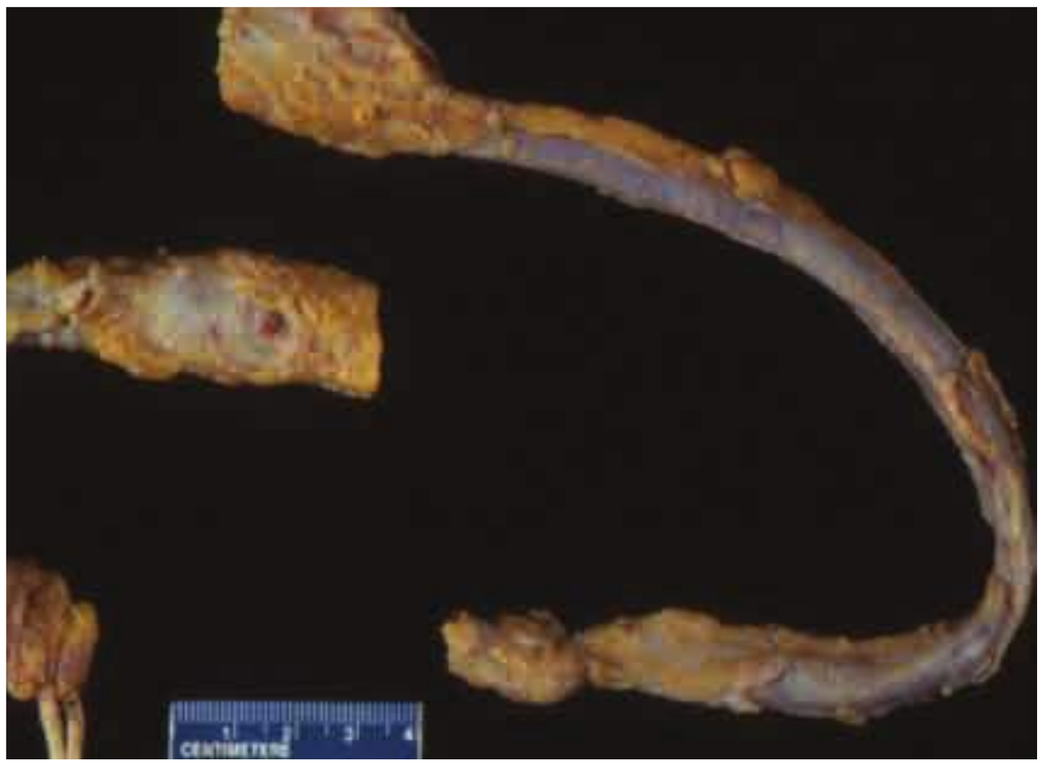

FIGURE 23-2
Deep venous thrombosis at autopsy.

Other pathophysiologic abnormalities include:

1. Increased pulmonary vascular resistance due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents such as serotonin. Release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for discordance between a small PE and a large alveolar-arterial O_2 gradient.
2. Impaired gas exchange due to increased alveolar dead space from vascular obstruction, hypoxemia from alveolar hypoventilation relative to perfusion in the nonobstructed lung, right-to-left shunting, or impaired carbon monoxide transfer due to loss of gas exchange surface.
3. Alveolar hyperventilation due to reflex stimulation of irritant receptors.
4. Increased airway resistance due to constriction of airways distal to the bronchi.
5. Decreased pulmonary compliance due to lung edema, lung hemorrhage, or loss of surfactant.

Pulmonary hypertension, right ventricular (RV) dysfunction, and RV microinfarction

Pulmonary artery obstruction causes a rise in pulmonary artery pressure and in pulmonary vascular resistance. When RV wall tension rises, RV dilation and dysfunction ensue, with release of the cardiac biomarker, brain natriuretic peptide. The interventricular septum bulges into and compresses an intrinsically normal left ventricle (LV). Diastolic LV dysfunction reduces LV distensibility and impairs LV filling. Increased RV wall tension also compresses the right coronary artery, limits myocardial oxygen supply, and precipitates right coronary artery ischemia and RV microinfarction, with release of cardiac biomarkers such as troponin. Underfilling of the LV may lead to a fall in LV cardiac output and systemic arterial pressure, with consequent circulatory collapse and death.

CLASSIFICATION OF PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

Pulmonary embolism

Massive PE accounts for 5–10% of cases, and is characterized by extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE. Patients with massive PE may present in cardiogenic shock and can die from multisystem organ failure. **Submassive PE** accounts for 20–25% of patients, and is characterized by RV dysfunction despite normal systemic arterial pressure. The combination of right heart failure and release of cardiac biomarkers indicates an increased likelihood of clinical deterioration. **Low-risk**

PE constitutes about 70–75% of cases. T ese patients have an excellent prognosis.

Deep venous thrombosis

Lower extremity DVT usually begins in the calf and propagates proximally to the popliteal vein, femoral vein, and iliac veins. Leg DVT is about 10 times more common than **upper extremity DVT,** which is often precipitated by placement of pacemakers, internal cardiac defibrillators, or indwelling central venous catheters. T e likelihood of upper extremity DVT increases as the catheter diameter and number of lumens increase. **Superf cial venous thrombosis** usually presents with erythema, tenderness, and a "palpable cord." Patients are at risk for extension of the thrombosis to the deep venous system.

DIAGNOSIS

Clinical evaluation

PE is known as "the Great Masquerader." Diagnosis is dif cult because symptoms and signs are nonspecific. T e most common symptom is unexplained breathlessness. When occult PE occurs concomitantly with overt congestive heart failure or pneumonia, clinical improvement often fails to occur despite standard medical treatment of the concomitant illness. T is scenario presents a clinical clue to the possible coexistence of PE.

With DVT, the most common symptom is a cramp or "charley horse" in the lower calf that persists and intensifies over several days. Point score criteria help estimate the clinical likelihood of DVT and PE **(Table 23-1)**. Patients with a low-to-moderate likelihood of DVT or PE should undergo initial diagnostic evaluation with d-dimer testing alone (see "Blood Tests") without obligatory imaging tests **(Fig. 23-3)**. However, patients with a high clinical likelihood of VTE should skip d-dimer testing and undergo imaging as the next step in the diagnostic algorithm.

Clinical pearls

Not all leg pain is due to DVT, and not all dyspnea is due to PE **(Table 23-2)**. Sudden, severe calf discomfort suggests a ruptured Baker's cyst. Fever and chills usually herald cellulitis rather than DVT. Physical findings, if present, may consist only of mild palpation discomfort in the lower calf. However, massive DVT often presents with marked thigh swelling, tenderness, and erythema. If the leg is diffusely edematous, DVT is unlikely. More probable is an acute exacerbation of venous insuf ciency due to postthrombotic syndrome. Upper extremity venous thrombosis may present with asymmetry in the supraclavicular fossa or in the circumference of the upper arms.

Pulmonary *in*farction usually indicates a small PE. T is condition is exquisitely painful because the thrombus lodges peripherally, near the innervation of pleural nerves. Nonthrombotic PE etiologies include fat embolism after pelvic or long bone fracture, tumor embolism, bone marrow, and air embolism. Cement embolism and bony fragment embolism can occur after total hip or knee replacement. Intravenous drug users may inject themselves with a wide array of substances that can embolize such as hair, talc, and cotton. Amniotic f ui*d* embolism occurs when fetal membranes leak or tear at the placental margin.

TABLE 23-1

CLINICAL DECISION RULES

Low Clinical Likelihood of DVT if Point Score Is Zero or Less; Moderate Likelihood if Score Is 1 to 2; High Likelihood if Score Is 3 or Greater

CLINICAL VARIABLE	DVT SCORE
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	–2

High Clinical Likelihood of PE if Point Score Exceeds 4

CLINICAL VARIABLE	PE SCORE
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

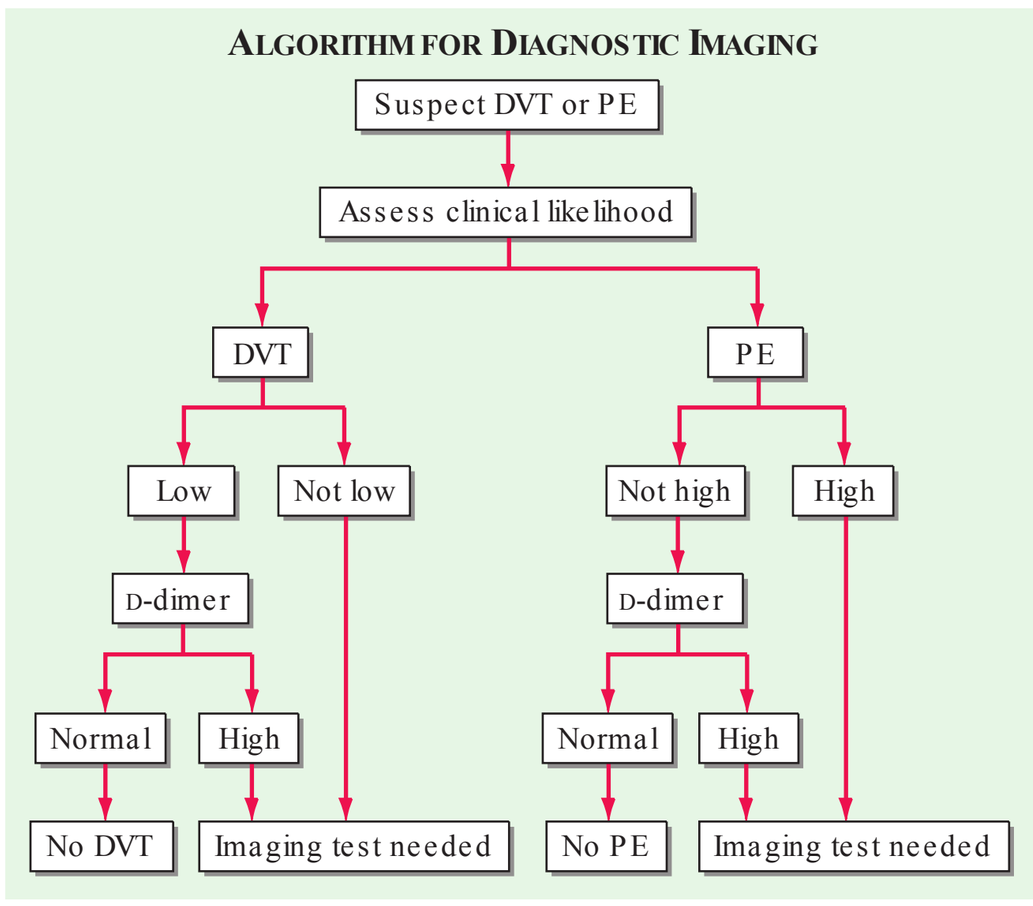

FIGURE 23-3
How to decide whether diagnostic imaging is needed. For assessment of clinical likelihood, see Table 23-1.

TABLE 23-2

DIFFERENTIAL DIAGNOSIS
DVT
Ruptured Baker's cyst
Cellulitis
Postphlebitic syndrome/venous insufficiency
PE
Pneumonia, asthma, chronic obstructive pulmonary disease
Congestive heart failure
Pericarditis
Pleurisy: "viral syndrome," costochondritis, musculoskeletal discomfort
Rib fracture, pneumothorax
Acute coronary syndrome
Anxiety

Nonimaging diagnostic modalities

Blood tests

The quantitative plasma d-*d*imer enzyme-linked immunosorbent assay (ELISA) rises in the presence of DVT or PE because of the breakdown of fibrin by plasmin. Elevation of d-dimer indicates endogenous although often clinically ineffective thrombolysis. The sensitivity of the d-dimer is >80% for DVT (including isolated calf DVT) and >95% for PE. The d-dimer is less sensitive for DVT than for PE because the DVT thrombus size is smaller. A normal d-dimer is a useful "rule out" test. However, the d-dimer assay is not specific. Levels increase in patients with myocardial infarction, pneumonia, sepsis, cancer, and the postoperative state and those in the second or third trimester of pregnancy. Therefore, d-dimer rarely has a useful role among hospitalized patients, because levels are frequently elevated due to systemic illness.

Elevated cardiac biomarkers

Serum troponin and plasma heart-type fatty acid–binding protein levels increase because of RV microinfarction. Myocardial stretch causes release of brain natriuretic peptide or NT-pro-brain natriuretic peptide.

Electrocardiogram

The most frequently cited abnormality, in addition to sinus tachycardia, is the S1Q3T3 sign: an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III. This finding is relatively specific but insensitive. RV strain and ischemia cause the most common abnormality, T-wave inversion in leads V_1 to V_4.

Noninvasive imaging modalities

Venous ultrasonography

Ultrasonography of the deep venous system relies on loss of vein compressibility as the primary criterion for DVT. When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure from the ultrasound transducer. This creates the illusion of a "wink." With acute DVT, the vein loses its compressibility because of passive distention by acute thrombus. The diagnosis of acute DVT is even more secure when thrombus is directly visualized. It appears homogeneous and has low echogenicity **(Fig. 23-4)**. The vein itself often appears mildly dilated, and collateral channels may be absent.

Venous flow dynamics can be examined with Doppler imaging. Normally, manual calf compression causes augmentation of the Doppler flow pattern. Loss of normal respiratory variation is caused by an obstructing DVT or by any obstructive process within the pelvis. For patients with a technically poor or nondiagnostic venous ultrasound, one should consider alternative imaging

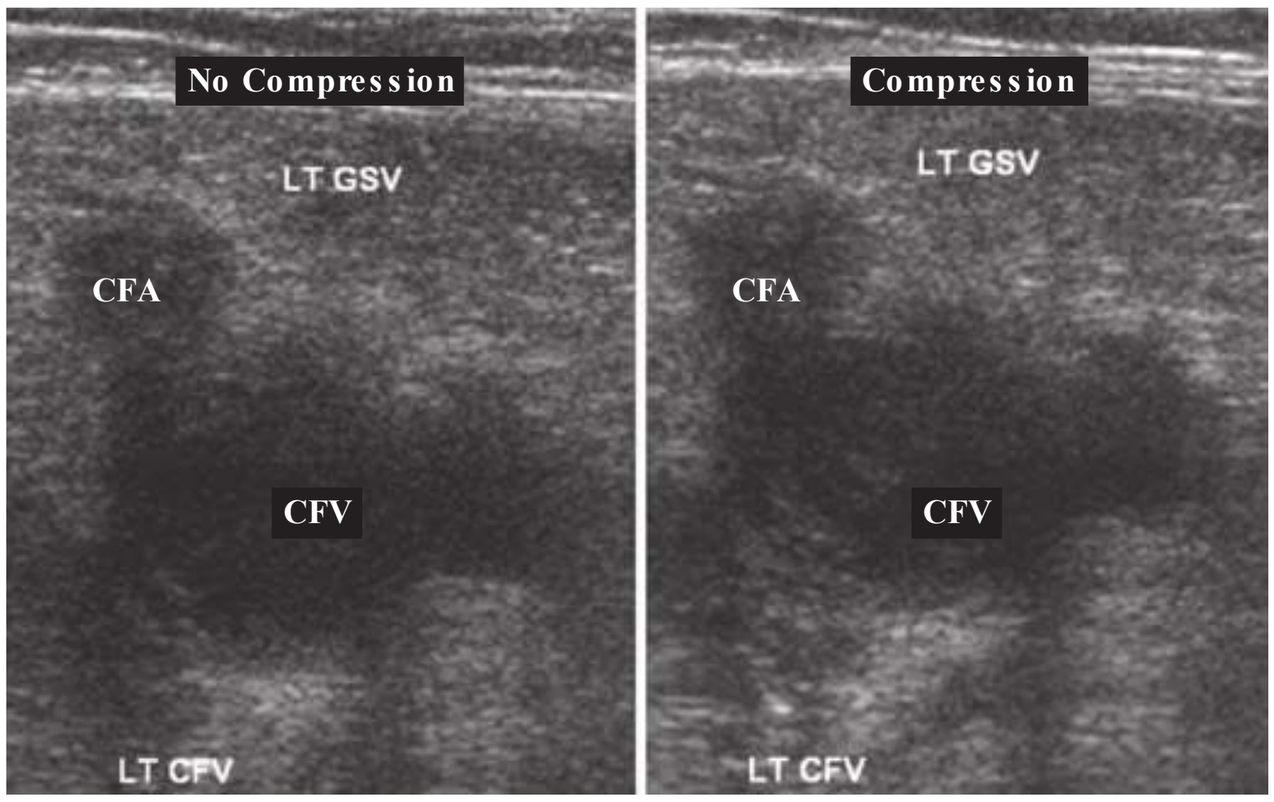

FIGURE 23-4

Venous ultrasound, with and without compression of the leg veins. CFA, common femoral artery; CFV, common femoral vein; GSV, great saphenous vein; LT, left.

modalities for DVT, such as computed tomography (CT) and magnetic resonance imaging.

Chest roentgenography

A normal or nearly normal chest x-ray often occurs in PE. Well-established abnormalities include focal oligemia (Westermark's sign), a peripheral wedged-shaped density above the diaphragm (Hampton's hump), and an enlarged right descending pulmonary artery (Palla's sign).

Chest CT

CT of the chest with intravenous contrast is the principal imaging test for the diagnosis of PE **(Fig. 23-5)**. Multidetector-row spiral CT acquires all chest images with ≤1 mm of resolution during a short breath hold. Sixth-order branches can be visualized with resolution superior to that of conventional invasive contrast pulmonary angiography. T e CT scan also provides an excellent four-chamber view of the heart. RV enlargement on chest CT indicates an increased likelihood of death within the next 30 days compared with PE patients who have normal RV size. When imaging is continued below the chest to the knee, pelvic and proximal leg DVT also can be diagnosed by CT scanning. In patients without PE, the lung parenchymal images may establish alternative diagnoses not apparent on chest x-ray that explain the presenting symptoms and signs such as pneumonia, emphysema, pulmonary fibrosis, pulmonary mass, and aortic pathology. Sometimes asymptomatic early-stage lung cancer is diagnosed incidentally.

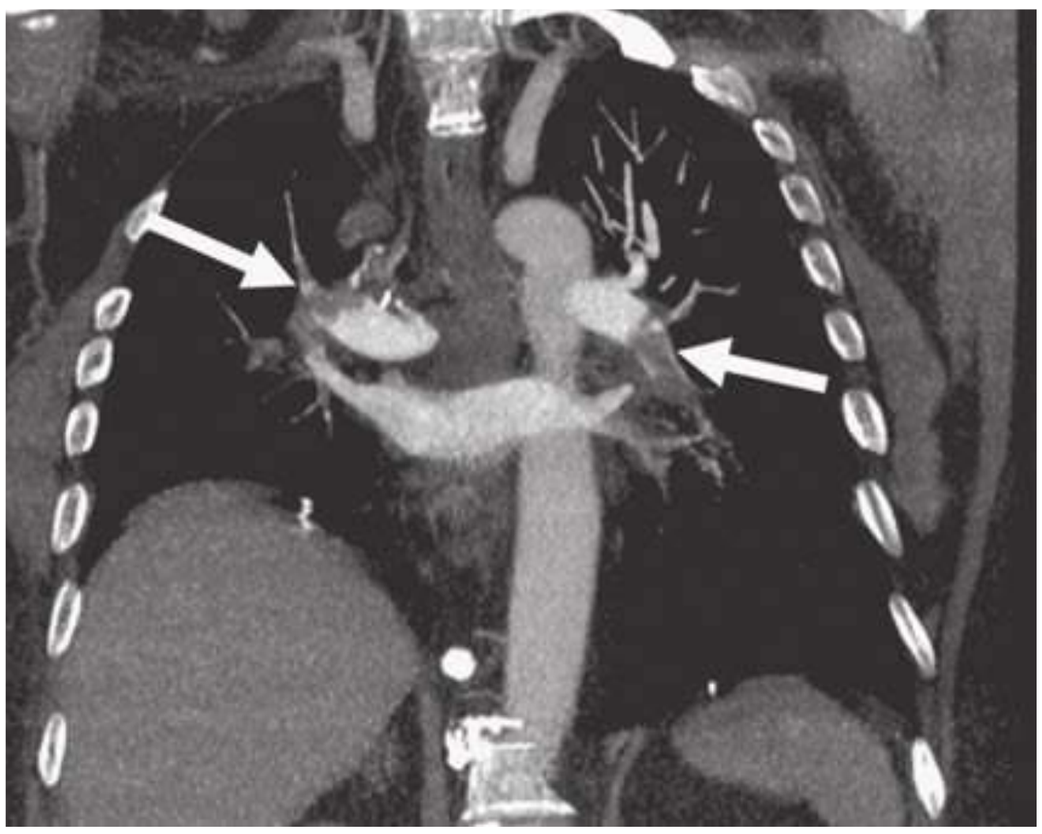

FIGURE 23-5
Large bilateral proximal PE on a coronal chest CT image in a 54-year-old man with lung cancer and brain metastases. He had developed sudden onset of chest heaviness and shortness of breath while at home. There are filling defects in the main and segmental pulmonary arteries bilaterally (white arrows). Only the left upper lobe segmental artery is free of thrombus.

Lung scanning

Lung scanning has become a second-line diagnostic test for PE, used mostly for patients who cannot tolerate intravenous contrast. Small particulate aggregates of albumin labeled with a gamma-emitting radionuclide are injected intravenously and are trapped in the pulmonary capillary bed. T e perfusion scan defect indicates absent or decreased blood flow, possibly due to PE. Ventilation scans, obtained with a radiolabeled inhaled gas such as xenon or krypton, improve the specificity of the perfusion scan. Abnormal ventilation scans indicate abnormal nonventilated lung, thereby providing possible explanations for perfusion defects other than acute PE, such as asthma and chronic obstructive pulmonary disease. A high-probability scan for PE is defined as two or more segmental perfusion defects in the presence of normal ventilation.

T e diagnosis of PE is very unlikely in patients with normal and nearly normal scans and is about 90% certain in patients with high-probability scans. Unfortunately, most patients have nondiagnostic scans, and fewer than one-half of patients with angiographically confirmed PE have a high probability scan. As many as 40% of patients with high clinical suspicion for PE but "low-probability" scans do, in fact, have PE at angiography.

Magnetic resonance (MR) (contrast-enhanced) imaging

When ultrasound is equivocal, MR venography with gadolinium contrast is an excellent imaging modality to diagnose DVT. MR pulmonary angiography may detect large proximal PE but is not reliable for smaller segmental and subsegmental PE.

Echocardiography

Echocardiography is not a reliable diagnostic imaging tool for acute PE because most patients with PE have normal echocardiograms. However, echocardiography is a very useful diagnostic tool for detecting conditions that may mimic PE, such as acute myocardial infarction, pericardial tamponade, and aortic dissection. Transthoracic echocardiography rarely images thrombus directly. T e best-known indirect sign of PE on transthoracic echocardiography is McConnell's sign: hypokinesis of the RV free wall with normal or hyperkinetic motion of the RV apex. One should consider transesophageal echocardiography when CT scanning facilities are not available or when a patient has renal failure or severe contrast allergy that precludes administration of contrast despite premedication with high-dose steroids. T is imaging modality can identify saddle, right main, or left main PE.

Invasive diagnostic modalities

Pulmonary angiography

Chest CT with contrast (see above) has virtually replaced invasive pulmonary angiography as a

diagnostic test. Invasive catheter-based diagnostic testing is reserved for patients with technically unsatisfactory chest CTs and for those in whom an interventional procedure such as catheter-directed thrombolysis is planned. A definitive diagnosis of PE depends on visualization of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion ("cut-off") of vessels, segmental oligemia or avascularity, a prolonged arterial phase with slow filling, and tortuous, tapering peripheral vessels.

Contrast phlebography

Venous ultrasonography has virtually replaced contrast phlebography as the diagnostic test for suspected DVT.

Integrated diagnostic approach

An integrated diagnostic approach (Fig. 23-3) streamlines the workup of suspected DVT and PE **(Fig. 23-6)**.

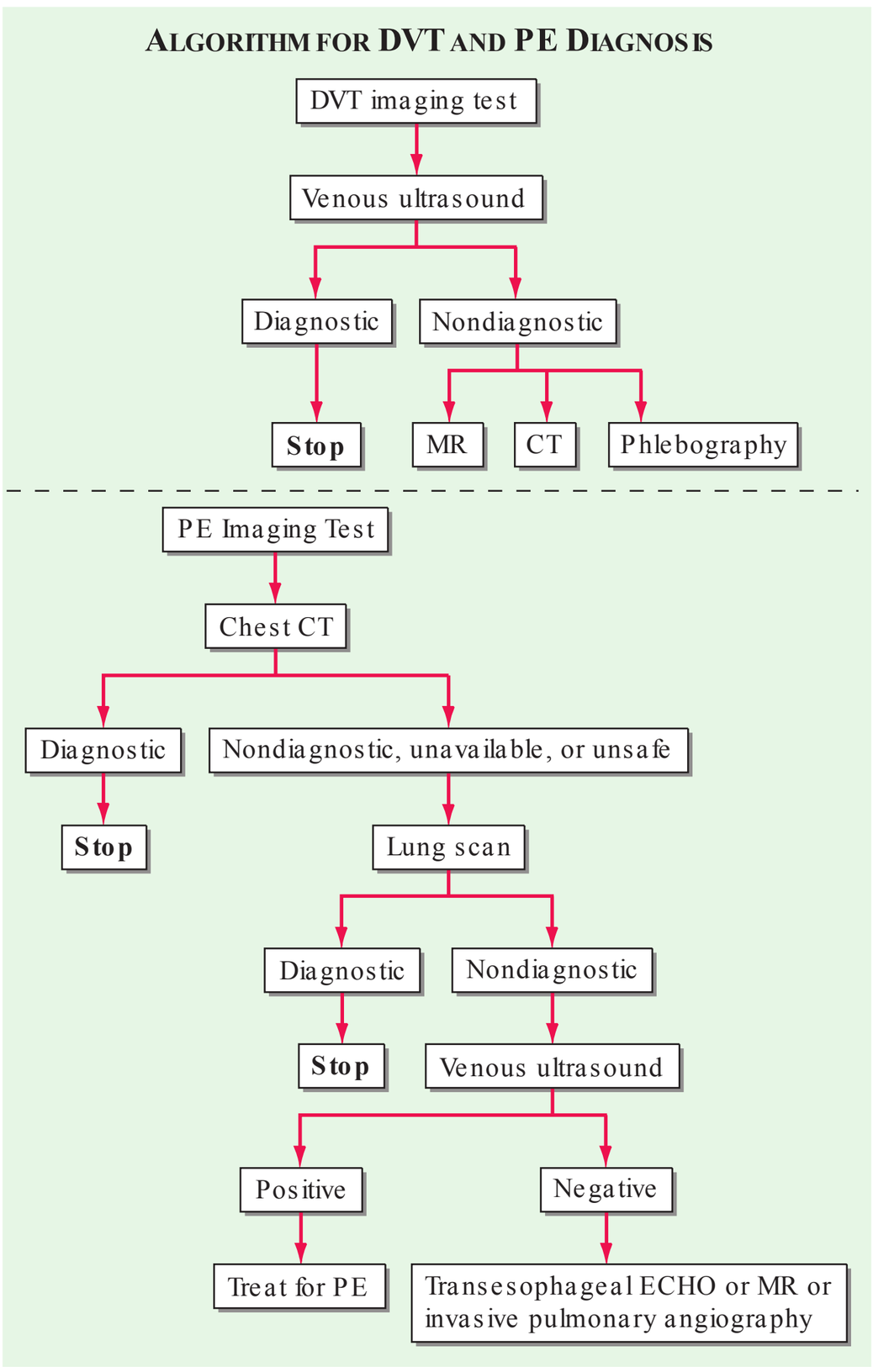

FIGURE 23-6
Imaging tests to diagnose DVT and PE. ECHO, echocardiography.

TREATMENT Deep Venous Thrombosis

PRIMARY THERAPY Primary therapy consists of clot dissolution with pharmacomechanical therapy that usually includes low-dose catheter-directed thrombolysis. T is approach is reserved for patients with extensive femoral, iliofemoral, or upper extremity DVT. T e open vein hypothesis postulates that patients who receive primary therapy will sustain less long-term damage to venous valves, with consequent lower rates of postthrombotic syndrome. A National Heart, Lung, and Blood Institute–sponsored randomized controlled trial called ATTRACT (NCT00790335) is testing this hypothesis.

SECONDARY PREVENTION Anticoagulation or placement of an inferior vena caval filter constitutes secon*d*ary prevention of VTE. To lessen the severity of postthrombotic syndrome of the legs, below-knee graduated compression stockings may be prescribed, 30–40 mmHg, for 2 years after the DVT episode. T ey should be replaced every 3 months because they lose their elasticity.

TREATMENT Pulmonary Embolism

RISK STRATIFICATION Hemodynamic instability, RV dysfunction on echocardiography, RV enlargement on chest CT, or elevation of the troponin level due to RV microinfarction portend a high risk of an adverse clinical outcome. When RV function remains normal in a hemodynamically stable patient, a good clinical outcome is highly likely with anticoagulation alone **(Fig. 23-7)**.

ANTICOAGULATION Effective anticoagulation is the foundation for successful treatment of DVT and PE. T ere are three options: (1) the conventional strategy of parenteral therapy "bridged" to warfarin, (2) parenteral therapy "bridged" to a

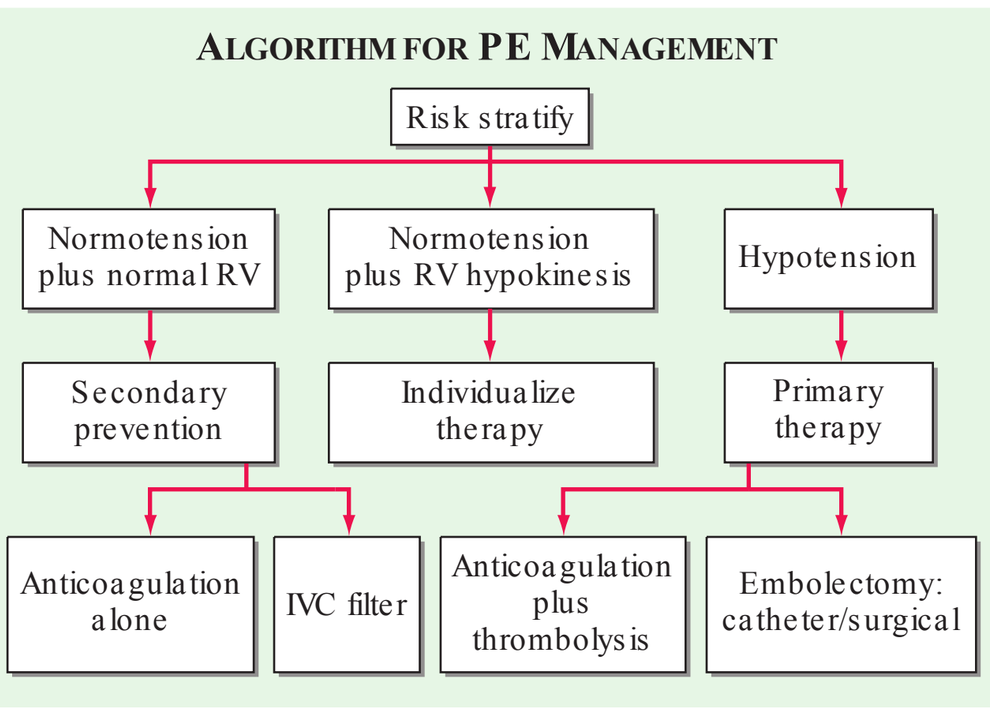

FIGURE 23-7
Acute management of pulmonary thromboembolism. RV, right ventricular; IVC, inferior vena cava.

novel oral anticoagulant such as dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent), or (3) oral anticoagulation with rivaroxaban or apixaban (both are anti-Xa agents) with a loading dose followed by a maintenance dose as monotherapy without parenteral anticoagulation.

The three heparin-based parenteral anticoagulants are (1) unfractionated heparin (UFH), (2) low-molecular-weight heparin (LMWH), and (3) fondaparinux. For patients with suspected or proven heparin-induced thrombocytopenia, there are two parenteral direct thrombin inhibitors: argatroban and bivalirudin **(Table 23-3)**.

Unfractionated Heparin UFH anticoagulates by binding to and accelerating the activity of antithrombin, thus preventing additional thrombus formation. UFH is dosed to achieve a target activated partial thromboplastin time (aPTT) of 60–80 s. The most popular nomogram uses an initial bolus of 80 U/kg, followed by an initial infusion rate of 18 U/kg per h.

The major advantage of UFH is its short half-life, which is especially useful in patients in whom hour-to-hour control of the intensity of anticoagulation is desired.

Low-Molecular-Weight Heparins These fragments of UFH exhibit less binding to plasma proteins and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than does UFH. No monitoring or dose adjustment is needed unless the patient is markedly obese or has chronic kidney disease.

Fondaparinux Fondaparinux, an anti-Xa pentasaccharide, is administered as a weight-based once-daily subcutaneous injection in a prefilled syringe. No laboratory monitoring is required. Fondaparinux is synthesized in a laboratory and, unlike LMWH or UFH, is not derived from animal products. It does not cause heparin-induced thrombocytopenia. The dose must be adjusted downward for patients with renal dysfunction.

Warfarin This vitamin K antagonist prevents carboxylation activation of coagulation factors II, VII, IX, and X. The full effect of warfarin requires at least 5 days, even if the prothrombin time, used for monitoring, becomes elevated more rapidly. If warfarin is initiated as monotherapy during an acute thrombotic illness, a paradoxical exacerbation of hypercoagulability increases the likelihood of thrombosis. Overlapping UFH, LMWH, fondaparinux, or parenteral direct thrombin inhibitors with warfarin for at least 5 days will nullify the early procoagulant effect of warfarin.

Warfarin Dosing In an average-size adult, warfarin is often initiated in a dose of 5 mg. The prothrombin time is standardized by calculating the international normalized ratio (INR), which assesses the anticoagulant effect of warfarin **(Chap. 3)**. The target INR is usually 2.5, with a range of 2.0–3.0.

The warfarin dose is usually titrated empirically to achieve the target INR. Proper dosing is difficult because hundreds of drug-drug and drug-food interactions affect warfarin metabolism. Increasing age and systemic illness reduce the required warfarin dose. Pharmacogenomics may provide more precise initial dosing of warfarin. CYP2C9 variant alleles impair the hydroxylation of S-warfarin, thereby lowering the dose requirement. Variants in the gene encoding the vitamin K epoxide reductase complex 1 (VKORC1) can predict whether patients require low, moderate, or high warfarin doses.

Centralized anticoagulation clinics have improved the efficacy and safety of warfarin dosing. Patients can self-monitor their INR with a home point-of-care fingerstick machine and can occasionally be taught to self-dose their warfarin.

Novel Oral Anticoagulants Novel oral anticoagulants are administered in a fixed dose, establish effective anticoagulation within hours of ingestion, require no laboratory coagulation monitoring, and have few of the drug-drug or drug-food interactions that make warfarin so difficult to dose. Rivaroxaban, a factor Xa inhibitor, is approved for treatment of acute DVT and acute PE as monotherapy, without a parenteral "bridging" anticoagulant. Apixaban is likely to receive similar approval for oral monotherapy. Dabigatran, a direct thrombin inhibitor, and edoxaban, a factor Xa inhibitor, are likely to be approved for treatment of VTE after an initial course of parenteral anticoagulation.

Complications of Anticoagulants The most serious adverse effect of anticoagulation is hemorrhage. For life-threatening or

TABLE 23-3

ANTICOAGULATION OF VTE

Immediate Anticoagulation
Unfractionated heparin, bolus and continuous infusion, to achieve aPTT 2–3 times the upper limit of the laboratory normal, or
Enoxaparin 1 mg/kg twice daily with normal renal function, or
Dalteparin 200 U/kg once daily or 100 U/kg twice daily, with normal renal function, or
Tinzaparin 175 U/kg once daily with normal renal function, or
Fondaparinux weight-based once daily; adjust for impaired renal function
Direct thrombin inhibitors: argatroban or bivalirudin
Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily with the dinner meal thereafter
Apixaban (not yet licensed)
Warfarin Anticoagulation
Requires 5–10 days of administration to achieve effectiveness as monotherapy
(Unfractionated heparin, low-molecular-weight heparin, and fondaparinux are the usual immediately effective "bridging agents" used when initiating warfarin)
Usual start dose is 5 mg
Titrate to INR, target 2.0–3.0
Continue parenteral anticoagulation for a minimum of 5 days and until two sequential INR values, at least 1 day apart, achieve the target INR range
Novel Oral Anticoagulants for Extended-Duration Anticoagulation following Initial Parenteral Anticoagulation
Edoxaban (not yet licensed)
Dabigatran (not yet licensed)

intracranial hemorrhage due to heparin or LMWH, protamine sulfate can be administered. Heparin-induced thrombocytopenia is less common with LMWH than with UFH. There is no specific reversal agent for bleeding caused by fondaparinux, direct thrombin inhibitors, or factor Xa inhibitors.

Major bleeding from warfarin is best managed with prothrombin complex concentrate. With serious but non–life-threatening bleeding, fresh-frozen plasma or intravenous vitamin K can be used. Recombinant human coagulation factor VIIa (rFVIIa) is an off-label option to manage catastrophic bleeding from warfarin, but prothrombin complex concentrate is a better choice. Oral vitamin K is effective for managing minor bleeding or an excessively high INR in the absence of bleeding.

Duration of Anticoagulation For DVT isolated to an upper extremity or calf that has been provoked by surgery, trauma, estrogen, or an indwelling central venous catheter or pacemaker, 3 months of anticoagulation usually suffice. For an initial episode of provoked proximal leg DVT or PE, 3 to 6 months of anticoagulation are considered sufficient. For patients with cancer and VTE, prescribe LMWH as monotherapy without warfarin and continue anticoagulation indefinitely unless the patient is rendered cancer-free.

Among patients with idiopathic, unprovoked VTE, the recurrence rate is high after cessation of anticoagulation. VTE that occurs during long-haul air travel is considered unprovoked. Unprovoked VTE may be caused by an exacerbation of an underlying inflammatory state and can be conceptualized as a chronic illness, with latent periods between flares of recurrent episodes. American College of Chest Physicians (ACCP) guidelines recommend considering anticoagulation for an indefinite duration with a target INR between 2 and 3 for patients with idiopathic VTE. An alternative approach after the first 6 months of anticoagulation is to reduce the intensity of anticoagulation and to lower the target INR range to between 1.5 and 2.

Counterintuitively, the presence of genetic mutations such as heterozygous factor V Leiden and prothrombin gene mutation does not appear to increase the risk of recurrent VTE. However, patients with antiphospholipid antibody syndrome may warrant indefinite-duration anticoagulation, even if the initial VTE was provoked by trauma or surgery.

INFERIOR VENA CAVAL (IVC) FILTERS The two principal indications for insertion of an IVC filter are (1) active bleeding that precludes anticoagulation and (2) recurrent venous thrombosis despite intensive anticoagulation. Prevention of recurrent PE in patients with right heart failure who are not candidates for fibrinolysis and prophylaxis of extremely high-risk patients are "softer" indications for filter placement. The filter itself may fail by permitting the passage of small-to medium-size clots. Large thrombi may embolize to the pulmonary arteries via collateral veins that develop. A more common complication is caval thrombosis with marked bilateral leg swelling.

Paradoxically, by providing a nidus for clot formation, filters increase the DVT rate, even though they usually prevent PE (over the short term). Retrievable filters can now be placed for patients with an anticipated temporary bleeding disorder or for patients at temporary high risk of PE, such as individuals undergoing bariatric surgery who have a prior history of perioperative PE. The filters can be retrieved up to several months after insertion unless thrombus forms and is trapped within the filter. The retrievable filter becomes permanent if it remains in place or if, for technical reasons such as rapid endothelialization, it cannot be removed.

MANAGEMENT OF MASSIVE PE For patients with massive PE and hypotension, replete volume with 500 mL of normal saline. Additional fluid should be infused with extreme caution because excessive fluid administration exacerbates RV wall stress, causes more profound RV ischemia, and worsens LV compliance and filling by causing further interventricular septal shift toward the LV. Dopamine and dobutamine are first-line inotropic agents for treatment of PE-related shock. Maintain a low threshold for initiating these pressors. Often, a "trial-and-error" approach works best; other agents that may be effective include norepinephrine, vasopressin, or phenylephrine.

FIBRINOLYSIS Successful fibrinolytic therapy rapidly reverses right heart failure and may result in a lower rate of death and recurrent PE by (1) dissolving much of the anatomically obstructing pulmonary arterial thrombus, (2) preventing the continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension, and (3) lysing much of the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent PE.

The preferred fibrinolytic regimen is 100 mg of recombinant tissue plasminogen activator (tPA) administered as a continuous peripheral intravenous infusion over 2 h. The sooner thrombolysis is administered, the more effective it is. However, this approach can be used for at least 14 days after the PE has occurred.

Contraindications to fibrinolysis include intracranial disease, recent surgery, and trauma. The overall major bleeding rate is about 10%, including a 1–3% risk of intracranial hemorrhage. Careful screening of patients for contraindications to fibrinolytic therapy is the best way to minimize bleeding risk.

The only Food and Drug Administration–approved indication for PE fibrinolysis is massive PE. For patients with submassive PE, who have preserved systolic blood pressure but moderate or severe RV dysfunction, use of fibrinolysis remains controversial. Results of a 1006-patient European multicentered randomized trial of submassive PE, using the thrombolytic agent tenecteplase, were published in 2014. Death or hemodynamic collapse within 7 days of randomization was reduced by 56% in the tenecteplase group. However, hemorrhagic stroke occurred in 2% of tenecteplase patients versus 0.2% in patients who only received heparin.

PHARMACOMECHANICAL CATHETER-DIRECTED THERAPY Many patients have relative contraindications to full-dose thrombolysis. Pharmacomechanical catheter-directed therapy usually

combines physical fragmentation or pulverization of thrombus with catheter-directed low-dose thrombolysis. Mechanical techniques include catheter maceration and intentional embolization of clot more distally, suction thrombectomy, rheolytic hydrolysis, and low-energy ultrasound-facilitated thrombolysis. The dose of alteplase can be markedly reduced, usually to a range of 20 to 25 mg instead of the peripheral intravenous systemic dose of 100 mg.

PULMONARY EMBOLECTOMY The risk of major hemorrhage with systemically administered fibrinolysis has prompted a renaissance of interest in surgical embolectomy, an operation that had almost become extinct. More rapid referral before the onset of irreversible multisystem organ failure and improved surgical technique have resulted in a high survival rate.

PULMONARY THROMBOENDARTERECTOMY Chronic thromboembolic pulmonary hypertension develops in 2–4% of acute PE patients. Therefore, PE patients who have initial pulmonary hypertension (usually diagnosed with Doppler echocardiography) should be followed up at about 6 weeks with a repeat echocardiogram to determine whether pulmonary arterial pressure has normalized. Patients impaired by dyspnea due to chronic thromboembolic pulmonary hypertension should be considered for pulmonary thromboendarterectomy, which, if successful, can markedly reduce, and sometimes even cure, pulmonary hypertension. The operation requires median sternotomy, cardiopulmonary bypass, deep hypothermia, and periods of hypothermic circulatory arrest. The mortality rate at experienced centers is approximately 5%. Inoperable patients should be managed with pulmonary vasodilator therapy.

EMOTIONAL SUPPORT Patients with VTE may feel overwhelmed when they learn that they are suffering from PE or DVT. Some have never previously encountered serious cardiovascular illness. They wonder whether they will be able to adapt to the new limitations imposed by anticoagulation. They worry about the health of their families and the genetic implications of their illness. Those who are advised to discontinue anticoagulation may feel especially vulnerable about the potential for suffering recurrent VTE. At Brigham and Woman's Hospital, a physician-nurse–facilitated PE support group was initiated to address these concerns and has met monthly for more than 20 years.

PREVENTION OF VTE

Prevention of DVT and PE **(Table 23-4)** is of paramount importance because VTE is difficult to detect and poses a profound medical and economic burden. Low-dose UFH or LMWH is the most common form of in-hospital prophylaxis. Computerized reminder systems can increase the use of preventive measures and, at Brigham and Women's Hospital, have reduced the symptomatic VTE rate by more than 40%. Audits of hospitals to ensure that prophylaxis protocols are being used will also increase utilization of preventive measures. Duration of prophylaxis is an important consideration. Extended-duration prophylaxis has not been shown to be both effective and safe in medically ill patients after hospital discharge in separate large trials that have tested enoxaparin, apixaban, and rivaroxaban. There is an ongoing trial of a novel oral anticoagulant, betrixaban, for extended-duration VTE prophylaxis in medically ill patients.

Patients who have undergone total hip or knee replacement or cancer surgery will benefit from extended pharmacologic VTE prophylaxis after hospital discharge. For hip replacement or extensive cancer surgery, the duration of prophylaxis is usually at least 1 month.

TABLE 23-4

PREVENTION OF VENOUS THROMBOEMBOLISM AMONG HOSPITALIZED PATIENTS

CONDITION	PROPHYLAXIS STRATEGY
High-risk nonorthopedic surgery	Unfractionated heparin 5000 units SC bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily
Cancer surgery, including gynecologic cancer surgery	Enoxaparin 40 mg daily, consider 1 month of prophylaxis
Major orthopedic surgery	Warfarin (target INR 2.0–3.0) Enoxaparin 40 mg daily Enoxaparin 30 mg bid Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily Rivaroxaban 10 mg daily Aspirin 81–325 mg daily Dabigatran 220 mg daily (not in the United States) Apixaban 2.5 mg bid (not in the United States) Intermittent pneumatic compression (with or without pharmacologic prophylaxis)
Medically ill patients, especially if immobilized, with a history of prior VTE, with an indwelling central venous catheter, or with cancer (but without active gastroduodenal ulcer, major bleeding within 3 months, or platelet count <50,000)	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily
Anticoagulation contraindicated	Intermittent pneumatic compression devices (but whether graduated compression stockings are effective in medical patients is controversial)

CHAPTER 24

ANTIPLATELET, ANTICOAGULANT, AND FIBRINOLYTIC DRUGS

Jeffrey I. Weitz

Thromboembolic disorders are major causes of morbidity and mortality. Thrombosis can occur in arteries or veins. Arterial thrombosis is the most common cause of acute myocardial infarction (MI), ischemic stroke, and limb gangrene. Venous thromboembolism encompasses deep vein thrombosis (DVT), which can lead to postthrombotic syndrome, and pulmonary embolism (PE), which can be fatal or can result in chronic thromboembolic pulmonary hypertension.

Most arterial thrombi are superimposed on disrupted atherosclerotic plaque because plaque rupture exposes thrombogenic material in the plaque core to the blood. This material then triggers platelet aggregation and fibrin formation, which results in the generation of a platelet-rich thrombus that can temporarily or permanently occlude blood flow. In contrast, venous thrombi rarely form at sites of obvious vascular disruption. Although they can develop after surgical trauma to veins or secondary to indwelling venous catheters, venous thrombi usually originate in the valve cusps of the deep veins of the calf or in the muscular sinuses. Sluggish blood flow reduces the oxygen supply to the avascular valve cusps. Endothelial cells lining these valve cusps become activated and express adhesion molecules on their surface. Tissue factor–bearing leukocytes and microparticles adhere to these activated cells and induce coagulation. DNA extruded from neutrophils forms neutrophil extracelluar traps (NETs) that provide a scaffold that traps red blood cells, promotes platelet adhesion and activation, and augments coagulation. Local thrombus formation is exacerbated by reduced clearance of activated clotting factors as a result of impaired blood flow. If the thrombi extend from the calf veins into the popliteal and more proximal veins of the leg, thrombus fragments can dislodge, travel to the lungs, and produce a PE.

Arterial and venous thrombi are composed of platelets, fibrin, and trapped red blood cells, but the proportions differ. Arterial thrombi are rich in platelets because of the high shear in the injured arteries. In contrast, venous thrombi, which form under low shear conditions, contain relatively few platelets and are predominantly composed of fibrin and trapped red cells. Because of the predominance of platelets, arterial thrombi appear white, whereas venous thrombi are red in color, reflecting the trapped red cells.

Antithrombotic drugs are used for prevention and treatment of thrombosis. Targeting the components of thrombi, these agents include (1) antiplatelet drugs, (2) anticoagulants, and (3) fibrinolytic agents **(Fig. 24-1)**. With the predominance of platelets in arterial thrombi, strategies to attenuate arterial thrombosis focus mainly on antiplatelet agents, although, in the acute setting, often include anticoagulants and fibrinolytic agents. Anticoagulants are the mainstay of prevention and treatment of venous thromboembolism because fibrin is the predominant component of venous thrombi. Antiplatelet drugs are less effective than anticoagulants in this setting because of the limited platelet content of venous thrombi. Fibrinolytic therapy is used in selected patients with venous thromboembolism. For example, patients with massive or submassive PE can benefit from systemic or catheter-directed fibrinolytic therapy. Pharmaco-mechanical therapy also is used to restore blood flow in patients with extensive DVT involving the iliac and/or femoral veins.

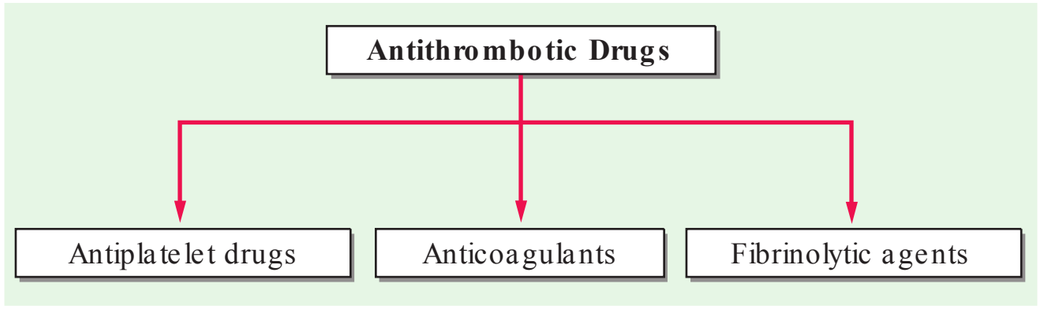

FIGURE 24-1
Classification of antithrombotic drugs.

ANTIPLATELET DRUGS

ROLE OF PLATELETS IN ARTERIAL THROMBOSIS

In healthy vasculature, circulating platelets are maintained in an inactive state by nitric oxide (NO) and prostacyclin released by endothelial cells lining the blood vessels. In addition, endothelial cells also express CD39 on their surface, a membrane-associated ecto-adenosine diphosphatase (ADPase) that degrades ADP released from activated platelets. When the vessel wall is damaged, release of these substances is impaired and subendothelial matrix is exposed. Platelets adhere to exposed collagen via $\alpha_2\beta_1$ and glycoprotein (Gp) V1 and to von Willebrand factor (VWF) via Gp Ibα and Gp IIb/IIIa ($\alpha_{IIb}\beta_3$)—receptors that are constitutively expressed on the platelet surface. Adherent platelets undergo a change in shape, secrete ADP from their dense granules, and synthesize and release thromboxane A_2. Released ADP and thromboxane A_2, which are platelet agonists, activate ambient platelets and recruit them to the site of vascular injury **(Fig. 24-2)**.

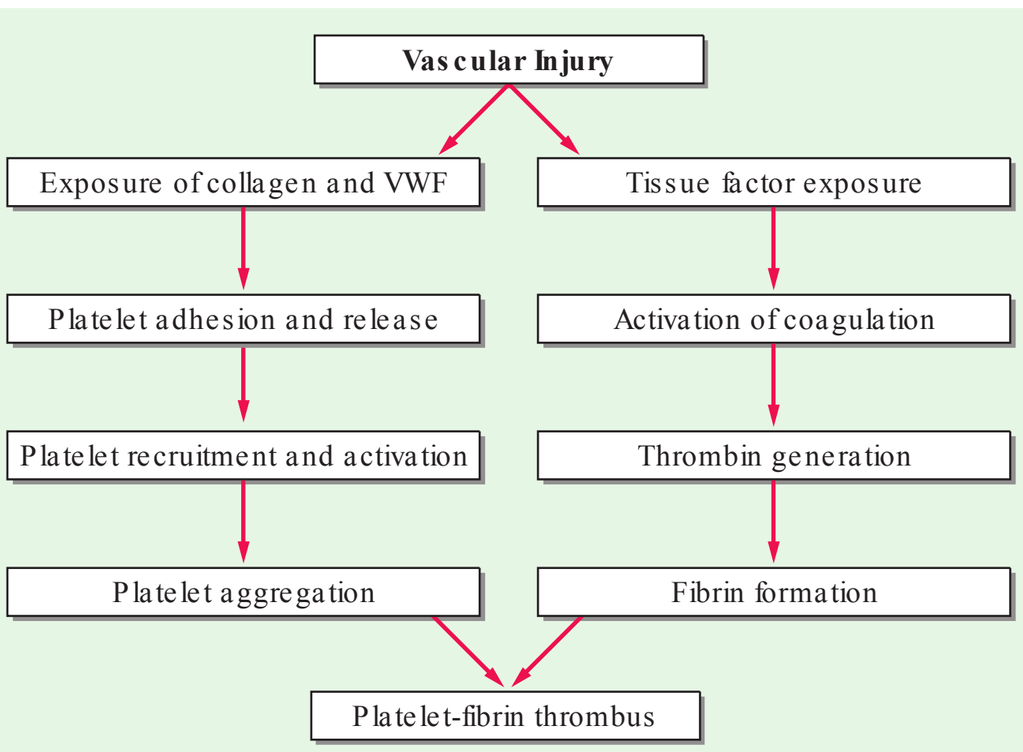

FIGURE 24-2
Coordinated role of platelets and the coagulation system in thrombogenesis. Vascular injury simultaneously triggers platelet activation and aggregation and activation of the coagulation system. Platelet activation is initiated by exposure of subendothelial collagen and von Willebrand factor (VWF), onto which platelets adhere. Adherent platelets become activated and release ADP and thromboxane A_2, platelet agonists that activate ambient platelets and recruit them to the site of injury. When platelets are activated, glycoprotein IIb/IIIa on their surface undergoes a conformational change that enables it to ligate fibrinogen and/or VWF and mediate platelet aggregation. Coagulation is triggered by tissue factor exposed at the site of injury. Tissue factor triggers thrombin generation. As a potent platelet agonist, thrombin amplifies platelet recruitment to the site of injury. Thrombin also converts fibrinogen to fibrin, and the fibrin strands then weave the platelet aggregates together to form a platelet/fibrin thrombus.

Disruption of the vessel wall also exposes tissue factor–expressing cells to the blood. Tissue factor binds factor VIIa and initiates coagulation. Activated platelets potentiate coagulation by providing a surface that binds clotting factors and supports the assembly of activation complexes that enhance thrombin generation. In addition to converting fibrinogen to fibrin, thrombin serves as a potent platelet agonist and recruits more platelets to the site of vascular injury. Thrombin also amplifies its own generation by feedback activation of factors V, VIII, and XI and solidifies the fibrin network by activating factor XIII, which then cross-links the fibrin strands.

When platelets are activated, Gp IIb/IIIa, the most abundant receptor on the platelet surface, undergoes a conformational change that enables it to bind fibrinogen and, under high shear conditions, VWF. Divalent fibrinogen or multivalent VWF molecules bridge adjacent platelets together to form platelet aggregates. Fibrin strands, generated through the action of thrombin, then weave these aggregates together to form a platelet/fibrin mesh.

Antiplatelet drugs target various steps in this process. The commonly used drugs include aspirin, ADP receptor inhibitors, which include the thienopyridines (clopidogrel and prasugrel) and ticagrelor, dipyridamole, and Gp IIb/IIIa antagonists.

ASPIRIN

The most widely used antiplatelet agent worldwide is aspirin. As a cheap and effective antiplatelet drug, aspirin serves as the foundation of most antiplatelet strategies.

Mechanism of action

Aspirin produces its antithrombotic effect by irreversibly acetylating and inhibiting platelet cyclooxygenase (COX)-1 **(Fig. 24-3)**, a critical enzyme in the biosynthesis of thromboxane A_2. At high doses (~1 g/d), aspirin also inhibits COX-2, an inducible COX isoform found in endothelial cells and inflammatory cells. In endothelial cells, COX-2 initiates the synthesis of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation.

Indications

Aspirin is widely used for secondary prevention of cardiovascular events in patients with coronary artery, cerebrovascular, or peripheral vascular disease. Compared with placebo, aspirin produces a 25% reduction in the risk of cardiovascular death, MI, or stroke. Aspirin is also used for primary prevention in patients whose estimated annual risk of MI is >1%, a point where its benefits are likely to outweigh harms. This is

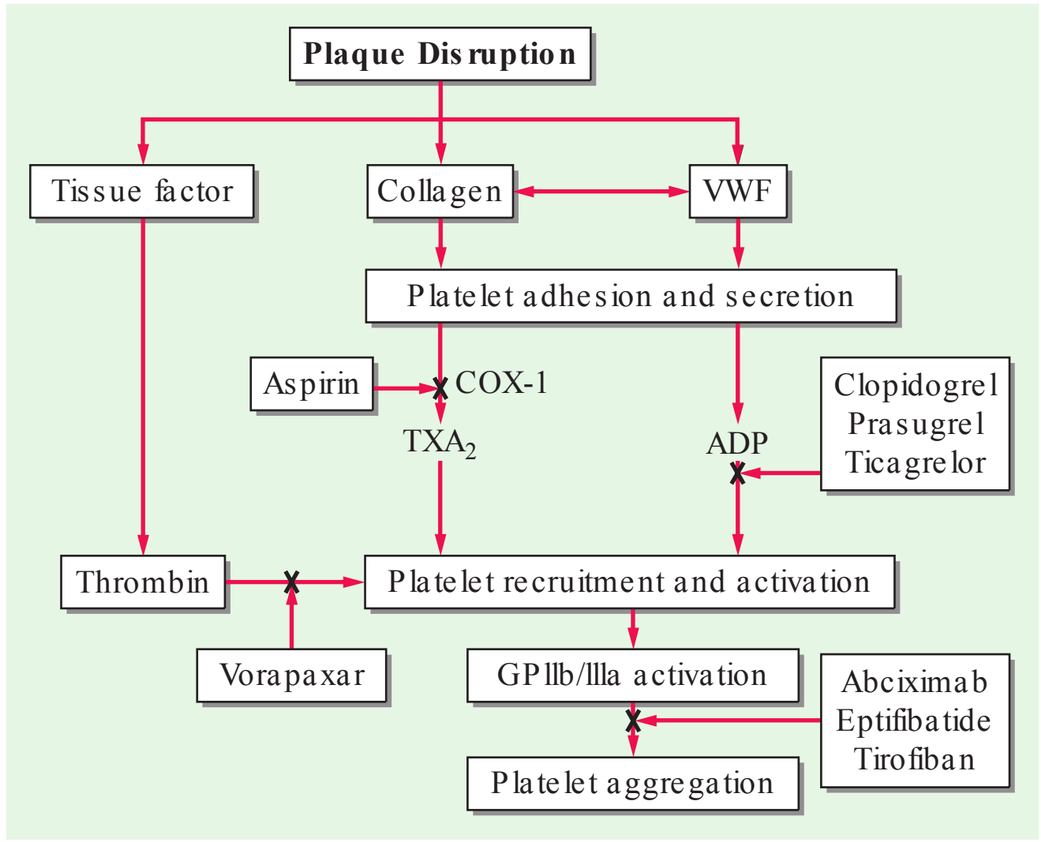

FIGURE 24-3
Site of action of antiplatelet drugs. Aspirin inhibits thromboxane A_2 (TXA_2) synthesis by irreversibly acetylating cyclooxygenase-1 (COX-1). Reduced TXA_2 release attenuates platelet activation and recruitment to the site of vascular injury. Clopidogrel and prasugrel irreversibly block $P2Y_{12}$, a key ADP receptor on the platelet surface; cangrelor and ticagrelor are reversible inhibitors of $P2Y_{12}$. Abciximab, eptifibatide, and tirofiban inhibit the final common pathway of platelet aggregation by blocking fibrinogen and von Willebrand factor binding to activated glycoprotein (Gp) IIb/IIIa. Vorapaxar inhibits thrombin-mediated platelet activation by targeting protease-activated receptor-1 (PAR-1), the major thrombin receptor on human platelets.

includes patients older than age 40 years with two or more major risk factors for cardiovascular disease or men older than age 45 years and women over the age of 55 years with one or more such risk factors. Aspirin is equally effective in men and women. In men, aspirin mainly reduces the risk of MI, whereas in women, aspirin lowers the risk of stroke.

Dosages

Aspirin is usually administered at doses of 75–325 mg once daily. Higher doses of aspirin are not more effective than lower aspirin doses, and some analyses suggest reduced efficacy with higher doses. Because the side effects of aspirin are dose-related, daily aspirin doses of 75–100 mg are recommended for most indications. When rapid platelet inhibition is required, an initial aspirin dose of at least 160 mg should be given.

Side effects

The most common side effects are gastrointestinal and range from dyspepsia to erosive gastritis or peptic ulcers with bleeding and perforation. These side effects are dose-related. Use of enteric-coated or buffered aspirin in place of plain aspirin does not eliminate gastrointestinal side effects. The overall risk of major bleeding with aspirin is 1–3% per year. The risk of bleeding is increased two- to threefold when aspirin is given in conjunction with other antiplatelet drugs, such as clopidogrel, or with anticoagulants, such as warfarin. When dual or triple therapy is prescribed, low-dose aspirin should be given (75–100 mg daily). Eradication of Helicobacter pylori infection and administration of proton pump inhibitors may reduce the risk of aspirin-induced upper gastrointestinal bleeding in patients with peptic ulcer disease.

Aspirin should not be administered to patients with a history of aspirin allergy characterized by bronchospasm. This problem occurs in ~0.3% of the general population but is more common in those with chronic urticaria or asthma, particularly in individuals with nasal polyps or chronic rhinitis. Hepatic and renal toxicity are observed with aspirin overdose.

Aspirin resistance

Clinical aspirin resistance is defined as the failure of aspirin to protect patients from ischemic vascular events. This is not a helpful definition because it is made after the event occurs. Furthermore, it is not realistic to expect aspirin, which only blocks thromboxane A_2–induced platelet activation, to prevent all vascular events.

Aspirin resistance has also been described biochemically as failure of the drug to produce its expected inhibitory effects on tests of platelet function, such as thromboxane A_2 synthesis or arachidonic acid-induced platelet aggregation. Potential causes of aspirin resistance include poor compliance, reduced absorption, drug-drug interaction with ibuprofen, and overexpression of COX-2. Unfortunately, the tests for aspirin resistance have not been well standardized, and there is little evidence that they identify patients at increased risk of recurrent vascular events, or that resistance can be reversed by giving higher doses of aspirin or by adding other antiplatelet drugs. Until such information is available, testing for aspirin resistance remains a research tool.

ADP RECEPTOR ANTAGONISTS

The ADP receptor antagonists include the thienopyridines (clopidogrel and prasugrel) and ticagrelor. All of these drugs target $P2Y_{12}$, the key ADP receptor on platelets.

Thienopyridines

Mechanism of action

The thienopyridines are structurally related drugs that selectively inhibit ADP-induced platelet aggregation by irreversibly blocking $P2Y_{12}$ (Fig. 24-3). Clopidogrel and prasugrel are prodrugs that require metabolic activation

by the hepatic cytochrome P450 (CYP) enzyme system. Prasugrel is about 10-fold more potent than clopidogrel and has a more rapid onset of action because of better absorption and more streamlined metabolic activation.

Indications

When compared with aspirin in patients with recent ischemic stroke, recent MI, or a history of peripheral arterial disease, clopidogrel reduced the risk of cardiovascular death, MI, and stroke by 8.7%. T erefore, clopidogrel is more effective than aspirin but is also more expensive. In some patients, clopidogrel and aspirin are combined to capitalize on their capacity to block complementary pathways of platelet activation. For example, the combination of aspirin plus clopidogrel is recommended for at least 4 weeks after implantation of a bare metal stent in a coronary artery and for at least a year in those with a drug-eluting stent. Concerns about late in-stent thrombosis with drug-eluting stents have led some experts to recommend long-term use of clopidogrel plus aspirin for the latter indication. However, these recommendations are likely to change because the risk of late stent thrombosis is decreasing with the newer generation of drug-eluting coronary stents.

T e combination of clopidogrel and aspirin is also effective in patients with unstable angina. T us, in 12,562 such patients, the risk of cardiovascular death, MI, or stroke was 9.3% in those randomized to the combination of clopidogrel and aspirin and 11.4% in those given aspirin alone. T is 20% relative risk reduction with combination therapy was highly statistically significant. However, combining clopidogrel with aspirin increases the risk of major bleeding to about 2% per year. T is bleeding risk persists even if the daily dose of aspirin is ≤100 mg. T erefore, the combination of clopidogrel and aspirin should only be used when there is a clear benefit. For example, this combination has not proven to be superior to clopidogrel alone in patients with acute ischemic stroke or to aspirin alone for primary prevention in those at risk for cardiovascular events.

Prasugrel was compared with clopidogrel in 13,608 patients with acute coronary syndromes who were scheduled to undergo percutaneous coronary intervention. T e incidence of the primary ef cacy endpoint, a composite of cardiovascular death, MI, or stroke, was significantly lower with prasugrel than with clopidogrel (9.9% and 12.1%, respectively), mainly reflecting a reduction in the incidence of nonfatal MI. T e incidence of stent thrombosis also was significantly lower with prasugrel (1.1% and 2.4%, respectively). However, these advantages were at the expense of significantly higher rates of fatal bleeding (0.4% and 0.1%, respectively) and life-threatening bleeding (1.4% and 0.9%, respectively) with prasugrel. Because patients older than age 75 years and those with a history of prior stroke or transient ischemic attack have a particularly high risk of bleeding, prasugrel should generally be avoided in older patients, and the drug is contraindicated in those with a history of cerebrovascular disease. Caution is required if prasugrel is used in patients weighing less than 60 kg or in those with renal impairment.

When prasugrel was compared with clopidogrel in 7243 patients with unstable angina or MI without ST-segment elevation, prasugrel failed to reduce the rate of the primary ef cacy endpoint, which was a composite of cardiovascular death, MI, and stroke. Because of the negative results of this study, prasugrel is reserved for patients undergoing percutaneous coronary intervention. In this setting, prasugrel is usually given in conjunction with aspirin. To reduce the risk of bleeding, the daily aspirin dose should be ≤100 mg.

Dosing

Clopidogrel is given once daily at a dose of 75 mg. Loading doses of clopidogrel are given when rapid ADP receptor blockade is desired. For example, patients undergoing coronary stenting are often given a loading dose of 300 mg, which produces inhibition of ADP-induced platelet aggregation in about 6 h; loading doses of 600 or 900 mg produce an even more rapid effect. After a loading dose of 60 mg, prasugrel is given once daily at a dose of 10 mg. Patients older than age 75 years or weighing less than 60 kg should receive a lower daily prasugrel dose of 5 mg.

Side ef ects

T e most common side effect of clopidogrel and prasugrel is bleeding. Because of its greater potency, bleeding is more common with prasugrel than clopidogrel. To reduce the risk of bleeding, clopidogrel and prasugrel should be stopped 5–7 days before major surgery. In patients taking clopidogrel or prasugrel who present with serious bleeding, platelet transfusion may be helpful.

Hematologic side effects, including neutropenia, thrombocytopenia, and thrombotic thrombocytopenic purpura, are rare.

Thienopyridine resistance

T e capacity of clopidogrel to inhibit ADP-induced platelet aggregation varies among subjects. T is variability reflects, at least in part, genetic polymorphisms in the CYP isoenzymes involved in the metabolic activation of clopidogrel. Most important of these is CYP2C19. Clopidogrel-treated patients with the loss-of-function CYP2C19*2 allele exhibit reduced platelet inhibition compared with those with the wild-type CYP2C19*1 allele and experience a higher rate of cardiovascular events. T is is important because estimates suggest that up to 25% of whites, 30% of African Americans, and 50% of Asians carry the loss-of-function allele, which would render them resistant to clopidogrel. Even patients with the reduced function CYP2C19*3, *4, or *5 alleles may derive less benefit from clopidogrel than

those with the full-function CYP2C19*1 allele. Concomitant administration of clopidogrel with proton pump inhibitors, which are inhibitors of CYP2C19, produces a small reduction in the inhibitory effects of clopidogrel on ADP-induced platelet aggregation. The extent to which this interaction increases the risk of cardiovascular events remains controversial.

In contrast to their effect on the metabolic activation of clopidogrel, CYP2C19 polymorphisms appear to be less important determinants of the activation of prasugrel. Thus, no association was detected between the loss-of-function allele and decreased platelet inhibition or increased rate of cardiovascular events with prasugrel. The observation that genetic polymorphisms affecting clopidogrel absorption or metabolism influence clinical outcomes raises the possibilities that pharmacogenetic profiling may be useful to identify clopidogrel-resistant patients and that point-of-care assessment of the extent of clopidogrel-induced platelet inhibition may help detect patients at higher risk for subsequent cardiovascular events. Clinical trials designed to evaluate these possibilities have thus far been negative. Although administration of higher doses of clopidogrel can overcome a reduced response to clopidogrel, the clinical benefit of this approach is uncertain. Instead, prasugrel or ticagrelor may be better choices for these patients.

Ticagrelor

As an orally active inhibitor of $P2Y_{12}$, ticagrelor differs from the thienopyridines in that ticagrelor does not require metabolic activation and it produces reversible inhibition of the ADP receptor.

Mechanism of action

Like the thienopyridines, ticagrelor inhibits $P2Y_{12}$. Because it does not require metabolic activation, ticagrelor has a more rapid onset and offset of action than clopidogrel, and it produces greater and more predictable inhibition of ADP-induced platelet aggregation than clopidogrel.

Indications

When compared with clopidogrel in patients with acute coronary syndromes, ticagrelor produced a greater reduction in the primary efficacy endpoint—a composite of cardiovascular death, MI, and stroke at 1 year—than clopidogrel (9.8% and 11.7%, respectively; p = .001). This difference reflected a significant reduction in both cardiovascular death (4.0% and 5.1%, respectively; p = .001) and MI (5.8% and 6.9%, respectively; p = .005) with ticagrelor compared with clopidogrel. Rates of stroke were similar with ticagrelor and clopidogrel (1.5% and 1.3%, respectively), and no difference in rates of major bleeding was noted. When minor bleeding was added to the major bleeding results, however, ticagrelor showed an increase relative to clopidogrel (16.1% and 14.6%, respectively; p = .008). Ticagrelor also was superior to clopidogrel in patients with acute coronary syndrome who underwent percutaneous coronary intervention or cardiac surgery. Based on these observations, some guidelines give ticagrelor preference over clopidogrel, particularly in higher risk patients.

Dosing

Ticagrelor is initiated with an oral loading dose of 180 mg followed by 90 mg twice daily. The dose does not require adjustment in patients with renal impairment, but the drug should be used with caution in patients with hepatic disease and in those receiving potent inhibitors or inducers of CYP3A4 because ticagrelor is metabolized in the liver via CYP3A4. Ticagrelor is usually administered in conjunction with aspirin; the daily aspirin dose should not exceed 100 mg.

Side effects

In addition to bleeding, the most common side effects of ticagrelor are dyspnea, which can occur in up to 15% of patients, and asymptomatic ventricular pauses. The dyspnea, which tends to occur soon after initiating ticagrelor, is usually self-limiting and mild in intensity. The mechanism responsible for this side effect is unknown.

To reduce the risk of bleeding, ticagrelor should be stopped 5–7 days prior to major surgery. Platelet transfusions are unlikely to be of benefit in patients with ticagrelor-related bleeding because the drug will bind to $P2Y_{12}$ on the transfused platelets.

DIPYRIDAMOLE

Dipyridamole is a relatively weak antiplatelet agent on its own, but an extended-release formulation of dipyridamole combined with low-dose aspirin, a preparation known as Aggrenox, is used for prevention of stroke in patients with transient ischemic attacks.

Mechanism of action

By inhibiting phosphodiesterase, dipyridamole blocks the breakdown of cyclic adenosine monophosphate (AMP). Increased levels of cyclic AMP reduce intracellular calcium and inhibit platelet activation. Dipyridamole also blocks the uptake of adenosine by platelets and other cells. This produces a further increase in local cyclic AMP levels because the platelet adenosine A_2 receptor is coupled to adenylate cyclase **(Fig. 24-4)**.

Indications

Dipyridamole plus aspirin was compared with aspirin or dipyridamole alone, or with placebo, in patients with an ischemic stroke or transient ischemic attack. The combination reduced the risk of stroke by 22.1% compared with aspirin and by 24.4% compared with

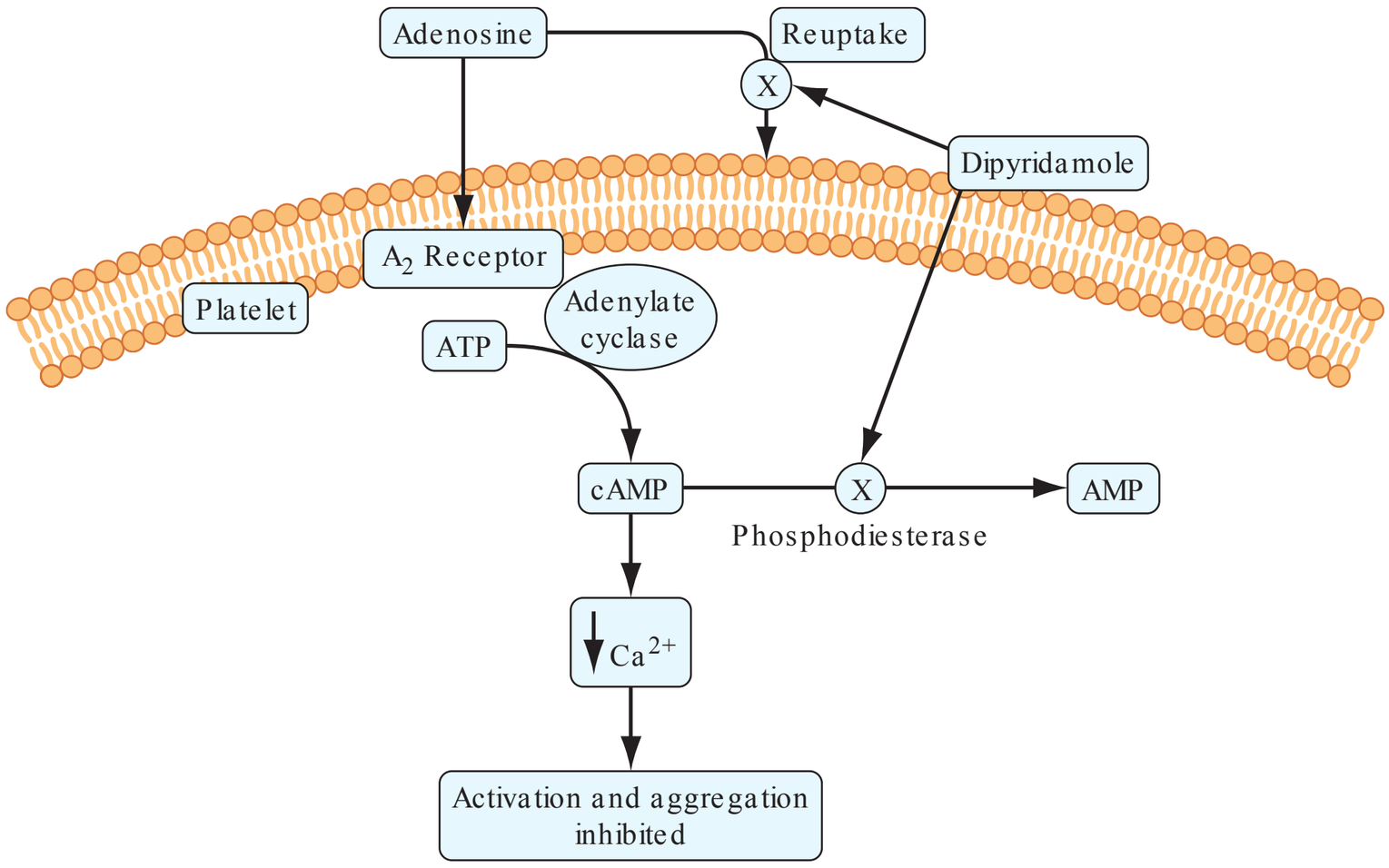

FIGURE 24-4
Mechanism of action of dipyridamole. Dipyridamole increases levels of cyclic AMP (cAMP) in platelets by (1) blocking the reuptake of adenosine and (2) inhibiting phosphodiesterase-mediated cyclic AMP degradation. By promoting calcium uptake, cyclic AMP reduces intracellular levels of calcium. This, in turn, inhibits platelet activation and aggregation.

dipyridamole. A second trial compared dipyridamole plus aspirin with aspirin alone for secondary prevention in patients with ischemic stroke. Vascular death, stroke, or MI occurred in 13% of patients given combination therapy and in 16% of those treated with aspirin alone. Another trial randomized 20,332 patients with noncardioembolic ischemic stroke to either Aggrenox or clopidogrel. The primary efficacy endpoint of recurrent stroke occurred in 9.0% of those given Aggrenox and in 8.8% of patients treated with clopidogrel. Although this difference was not statistically significant, the study failed to meet the prespecified margin to claim noninferiority of Aggrenox relative to clopidogrel. These results have dampened enthusiasm for the use of Aggrenox.

Because of its vasodilatory effects and the paucity of data supporting the use of dipyridamole in patients with symptomatic coronary artery disease, Aggrenox should not be used for stroke prevention in such patients. Clopidogrel is a better choice in this setting.

Dosing

Aggrenox is given twice daily. Each capsule contains 200 mg of extended-release dipyridamole and 25 mg of aspirin.

Side effects

Because dipyridamole has vasodilatory effects, it must be used with caution in patients with coronary artery disease. Gastrointestinal complaints, headache, facial flushing, dizziness, and hypotension can also occur. These symptoms often subside with continued use of the drug.

GP IIB/IIIA RECEPTOR ANTAGONISTS

As a class, parenteral Gp IIb/IIIa receptor antagonists have an established niche in patients with acute coronary syndromes. The three agents in this class are abciximab, eptifibatide, and tirofiban.

Mechanism of action

A member of the integrin family of adhesion receptors, Gp IIb/IIIa is found on the surface of platelets and megakaryocytes. With about 80,000 copies per platelet, Gp IIb/IIIa is the most abundant receptor. Consisting of a noncovalently linked heterodimer, Gp IIb/IIIa is inactive on resting platelets. When platelets are activated, inside-outside signal transduction pathways trigger a conformational activation of the receptor. Once activated, Gp IIb/IIIa binds adhesive molecules, such as fibrinogen and, under high shear conditions, VWF. Binding is mediated by the Arg-Gly-Asp (RGD) sequence found on the α chains of fibrinogen and on VWF, and by the Lys-Gly-Asp (KGD) sequence located within a unique dodecapeptide domain on the γ chains of fibrinogen. Once bound, fibrinogen and/or VWF bridge adjacent platelets together to induce platelet aggregation.

Although abciximab, eptifibatide, and tirofiban all target the Gp IIb/IIIa receptor, they are structurally

TABLE 24-1

FEATURES OF GPIIB/IIIA ANTAGONISTS

FEATURE	ABCIXIMAB	EPTIFIBATIDE	TIROFIBAN
Description	Fab fragment of humanized mouse monoclonal antibody	Cyclical KGD-containing heptapeptide	Nonpeptidic RGD mimetic
Specific for Gp IIb/IIIa	No	Yes	Yes
Plasma half-life	Short (min)	Long (2.5 h)	Long (2.0 h)
Platelet-bound half-life	Long (days)	Short (s)	Short (s)
Renal clearance	No	Yes	Yes

and pharmacologically distinct **(Table 24-1)**. Abciximab is a Fab fragment of a humanized murine monoclonal antibody directed against the activated form of Gp IIb/IIIa. Abciximab binds to the activated receptor with high af nity and blocks the binding of adhesive molecules. In contrast, eptifibatide and tirofiban are synthetic small molecules. Eptifibatide is a cyclic heptapeptide that binds Gp IIb/IIIa because it incorporates the KGD motif, whereas tirofiban is a nonpeptidic tyrosine derivative that acts as an RGD mimetic. Abciximab has a long half-life and can be detected on the surface of platelets for up to 2 weeks; eptifibatide and tirofiban have short half-lives.

Whereas eptifibatide and tirofiban are specific for Gp IIb/IIIa, abciximab also inhibits the closely related $\alpha_v\beta_3$ receptor, which binds vitronectin, and $\alpha_M\beta_2$, a leukocyte integrin. Inhibition of $\alpha_v\beta_3$ and $\alpha_M\beta_2$ may endow abciximab with anti-inflammatory and/or antiproliferative properties that extend beyond platelet inhibition.

Indications

Abciximab and eptifibatide are used in patients undergoing percutaneous coronary interventions, particularly those who have not been pretreated with an ADP receptor antagonist. Tirofiban is used in high-risk patients with unstable angina. Eptifibatide also can be used for this indication.

Dosing

All of the Gp IIb/IIIa antagonists are given as an IV bolus followed by an infusion. T e recommended dose of abciximab is a bolus of 0.25 mg/kg followed by an infusion of 0.125 μg/kg per minute to a maximum of 10 μg/kg for 12 h. Eptifibatide is given as two 180 μg/kg boluses given 10 min apart, followed by an infusion of 2.0 μg/kg per minute for 18–24 h. Tirofiban is started at a rate of 0.4 μg/kg per minute for 30 min; the drug is then continued at a rate of 0.1 μg/kg per minute for up to 18 h. Because these agents are cleared by the kidneys, the doses of eptifibatide and tirofiban must be reduced in patients with renal insuf ciency. T us, the eptifibatide infusion is reduced to 1 μg/kg per minute in patients with a creatinine clearance below 50 mL/min, whereas the dose of tirofiban is cut in half for patients with a creatinine clearance below 30 mL/min.

Side ef ects

In addition to bleeding, thrombocytopenia is the most serious complication. T rombocytopenia is immune-mediated and is caused by antibodies directed against neoantigens on Gp IIb/IIIa that are exposed upon antagonist binding. With abciximab, thrombocytopenia occurs in up to 5% of patients. T rombocytopenia is severe in ~1% of these individuals. T rombocytopenia is less common with the other two agents, occurring in ~1% of patients.

NEW ANTIPLATELET AGENTS

New agents in advanced stages of development include cangrelor, a parenteral, rapidly acting, reversible inhibitor of $P2Y_{12}$, and vorapaxar, an orally active inhibitor of protease-activated receptor 1 (PAR-1), the major thrombin receptor on platelets (Fig. 24-3).

Cangrelor

An adenosine analogue, cangrelor binds reversibly to $P2Y_{12}$ and inhibits its activity. T e drug has a half-life of 3–6 min and is given IV as a bolus followed by an infusion. When stopped, platelet function recovers within 60 min. A trial comparing cangrelor with placebo during percutaneous coronary interventions and a study comparing cangrelor with clopidogrel after such procedures revealed little or no advantage of cangrelor. A third trial compared cangrelor (given as an IV bolus of 30 μg/kg followed by an infusion of 4 μg/kg per minute for at least 2 h, or for the duration of the procedure, whichever was longer) with a loading dose of clopidogrel (300 or 600 mg) in 11,145 patients undergoing urgent or elective percutaneous coronary intervention. T e rate of the primary ef cacy endpoint, a composite of death, MI, ischemia-driven revascularization, and stent thrombosis,

was 4.7% in the cangrelor group and 5.9% in the clopidogrel group (p = .005). T e rates of severe bleeding, the primary safety endpoint, were 0.16% and 0.11% in the cangrelor and clopidogrel groups, respectively. Using the same ef cacy endpoint, a prespecified meta-analysis of the three trials revealed a relative risk reduction of 19% with cangrelor compared with clopidogrel (3.8% and 4.7%, respectively) and a 40% reduction in stent thrombosis (0.5% and 0.8%, respectively) with no significant increase in serious bleeding. Based on these data, cangrelor is currently under regulatory review.

Vorapaxar

An orally active PAR-1 antagonist, vorapaxar is slowly eliminated with a half-life of about 200 h. When compared with placebo in 12,944 patients with acute coronary syndrome without ST-segment elevation, vorapaxar failed to significantly reduce the primary ef - cacy endpoint, a composite of cardiovascular death, MI, stroke, recurrent ischemia requiring rehospitalization, and urgent coronary revascularization. Moreover, vorapaxar was associated with increased rates of bleeding, including intracranial bleeding.

In a second trial, vorapaxar was compared with placebo for secondary prevention in 26,449 patients with prior MI, ischemic stroke, or peripheral arterial disease. Overall, vorapaxar reduced the risk for cardiovascular death, MI, or stroke by 13%, but doubled the risk of intracranial bleeding. In the prespecified subgroup of 17,779 patients with prior MI, however, vorapaxar reduced the risk for cardiovascular death, MI, or stroke by 20% compared with placebo (from 9.7% to 8.1%, respectively). T e rate of intracranial hemorrhage was higher with vorapaxar than with placebo (0.6% and 0.4%, respectively; p = .076) as was the rate of moderate or severe bleeding (3.4% and 2.1%, respectively; P <0.0001). Based on these data, the drug is under consideration for regulatory approval in MI patients under the age of 75 years who have no history of stroke or transient ischemic attack and have a weight over 60 kg.

ANTICOAGULANTS

T ere are both parenteral and oral anticoagulants. T e parenteral anticoagulants include heparin, low-molecular-weight heparin (LMWH), fondaparinux (a synthetic pentasaccharide), lepirudin, desirudin, bivalirudin, and argatroban. Currently available oral anticoagulants include warfarin; dabigatran etexilate, an oral thrombin inhibitor; and rivaroxaban and apixaban, oral factor Xa inhibitors. Edoxaban, a third oral factor Xa inhibitor, is undergoing regulatory review.

PARENTERAL ANTICOAGULANTS

Heparin

A sulfated polysaccharide, heparin is isolated from mammalian tissues rich in mast cells. Most commercial heparin is derived from porcine intestinal mucosa and is a polymer of alternating d-glucuronic acid and N-acetyl-d-glucosamine residues.

Mechanism of action

Heparin acts as an anticoagulant by activating antithrombin (previously known as antithrombin III) and accelerating the rate at which antithrombin inhibits clotting enzymes, particularly thrombin and factor Xa. Antithrombin, the obligatory plasma cofactor for heparin, is a member of the serine protease inhibitor (serpin) superfamily. Synthesized in the liver and circulating in plasma at a concentration of 2.6 ± 0.4 μM, antithrombin acts as a suicide substrate for its target enzymes.

To activate antithrombin, heparin binds to the serpin via a unique pentasaccharide sequence that is found on one-third of the chains of commercial heparin **(Fig. 24-5)**. Heparin chains without this pentasaccharide sequence have little or no anticoagulant activity. Once bound to antithrombin, heparin induces a conformational change in the reactive center loop of antithrombin that renders it more readily accessible to its target proteases. T is conformational change enhances the rate at which antithrombin inhibits factor Xa by at least two orders of magnitude but has little effect on the rate of thrombin inhibition. To catalyze thrombin inhibition, heparin serves as a template that binds antithrombin and thrombin simultaneously. Formation of this ternary complex brings the enzyme in close apposition to the inhibitor, thereby promoting the formation of a stable covalent thrombin-antithrombin complex.

Only pentasaccharide-containing heparin chains composed of at least 18 saccharide units (which correspond to a molecular weight of 5400) are of suf cient length to bridge thrombin and antithrombin together. With a mean molecular weight of 15,000, and a range of 5000–30,000, almost all of the chains of unfractionated heparin are long enough to do so. Consequently, by definition, heparin has equal capacity to promote the inhibition of thrombin and factor Xa by antithrombin and is assigned an anti-factor Xa to anti-factor IIa (thrombin) ratio of 1:1.

Heparin causes the release of tissue factor pathway inhibitor (TFPI) from the endothelium. A factor Xa–dependent inhibitor of tissue factor–bound factor VIIa, TFPI may contribute to the antithrombotic activity of heparin. Longer heparin chains induce the release of more TFPI than shorter ones.

Pharmacology

Heparin must be given parenterally. It is usually administered SC or by continuous IV infusion. When used

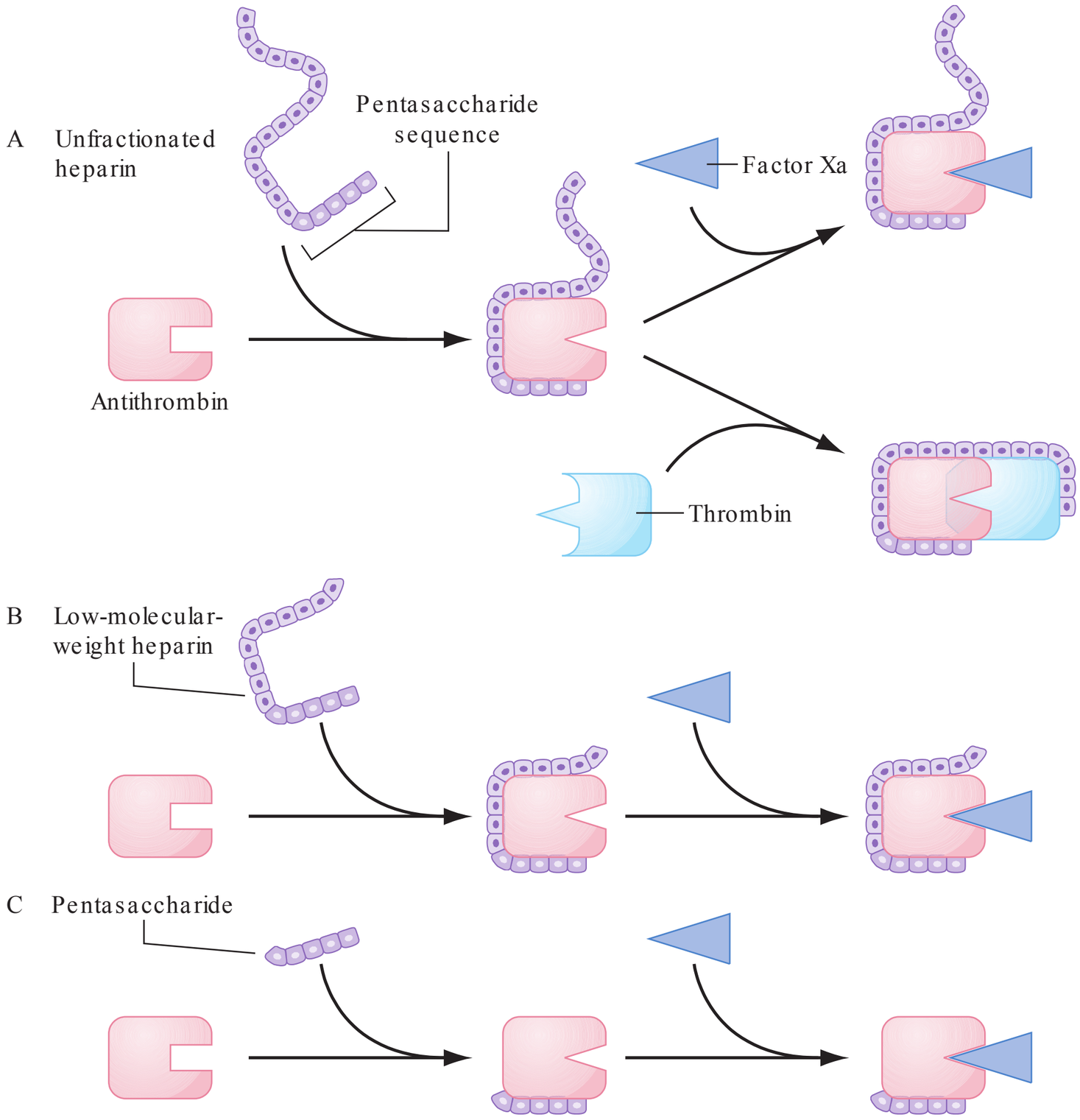

FIGURE 24-5

Mechanism of action of heparin, low-molecular-weight heparin (LMWH), and fondaparinux, a synthetic pentasaccharide. A. Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. Only heparin chains composed of at least 18 saccharide units, which corresponds to a molecular weight of 5400, are of sufficient length to perform this bridging function. With a mean molecular weight of 15,000, all of the heparin chains are long enough to do this. B. LMWH has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin because, with a mean molecular weight of 4500–5000, at least half of the LMWH chains are too short to bridge antithrombin to thrombin. C. The pentasaccharide only accelerates factor Xa inhibition by antithrombin because the pentasaccharide is too short to bridge antithrombin to thrombin.

for therapeutic purposes, the IV route is most often employed. If heparin is given SC for treatment of thrombosis, the dose of heparin must be high enough to overcome the limited bioavailability associated with this method of delivery.

In the circulation, heparin binds to the endothelium and to plasma proteins other than antithrombin. Heparin binding to endothelial cells explains its dose-dependent clearance. At low doses, the half-life of heparin is short because it binds rapidly to the endothelium. With higher doses of heparin, the half-life is longer because heparin is cleared more slowly once the endothelium is saturated. Clearance is mainly extrarenal; heparin binds to macrophages, which internalize and depolymerize the long heparin chains and secrete shorter chains back into the circulation. Because of its dose-dependent clearance mechanism, the plasma half-life of heparin ranges from 30 to 60 min with bolus IV doses of 25 and 100 units/kg, respectively.

Once heparin enters the circulation, it binds to plasma proteins other than antithrombin, a phenomenon that reduces its anticoagulant activity. Some of the heparin-binding proteins found in plasma are acute-phase reactants whose levels are elevated in ill patients. Others, such as high-molecular-weight multimers of VWF, are released from activated platelets or

endothelial cells. Activated platelets also release platelet factor 4 (PF4), a highly cationic protein that binds heparin with high af nity. T e large amounts of PF4 found in the vicinity of platelet-rich arterial thrombi can neutralize the anticoagulant activity of heparin. T is phenomenon may attenuate heparin's capacity to suppress thrombus growth.

Because the levels of heparin-binding proteins in plasma vary from person to person, the anticoagulant response to fixed or weight-adjusted doses of heparin is unpredictable. Consequently, coagulation monitoring is essential to ensure that a therapeutic response is obtained. T is is particularly important when heparin is administered for treatment of established thrombosis because a subtherapeutic anticoagulant response may render patients at risk for recurrent thrombosis, whereas excessive anticoagulation increases the risk of bleeding.

Monitoring the anticoagulant ef ect

Heparin therapy can be monitored using the activated partial thromboplastin time (aPTT) or anti-factor Xa level. Although the aPTT is the test most often used for this purpose, there are problems with this assay. aPTT reagents vary in their sensitivity to heparin, and the type of coagulometer used for testing can influence the results. Consequently, laboratories must establish a therapeutic aPTT range with each reagent-coagulometer combination by measuring the aPTT and anti-factor Xa level in plasma samples collected from heparin-treated patients. For most of the aPTT reagents and coagulometers in current use, therapeutic heparin levels are achieved with a two- to threefold prolongation of the aPTT.

Anti-factor Xa levels also can be used to monitor heparin therapy. With this test, therapeutic heparin levels range from 0.3 to 0.7 units/mL. Although this test is gaining in popularity, anti-factor Xa assays have yet to be standardized, and results can vary widely between laboratories.

Up to 25% of heparin-treated patients with venous thromboembolism require >35,000 units/d to achieve a therapeutic aPTT. T ese patients are considered heparin resistant. It is useful to measure anti-factor Xa levels in heparin-resistant patients because many will have a therapeutic anti-factor Xa level despite a subtherapeutic aPTT. T is dissociation in test results occurs because elevated plasma levels of fibrinogen and factor VIII, both of which are acute-phase proteins, shorten the aPTT but have no effect on anti-factor Xa levels. Heparin therapy in patients who exhibit this phenomenon is best monitored using anti-factor Xa levels instead of the aPTT. Patients with congenital or acquired antithrombin deficiency and those with elevated levels of heparin-binding proteins may also need high doses of heparin to achieve a therapeutic aPTT or anti-factor Xa level. If there is good correlation between the aPTT and the anti-factor Xa levels, either test can be used to monitor heparin therapy.

Dosing

For prophylaxis, heparin is usually given in fixed doses of 5000 units SC two or three times daily. With these low doses, coagulation monitoring is unnecessary. In contrast, monitoring is essential when the drug is given in therapeutic doses. Fixed-dose or weight-based heparin nomograms are used to standardize heparin dosing and to shorten the time required to achieve a therapeutic anticoagulant response. At least two heparin nomograms have been validated in patients with venous thromboembolism and reduce the time required to achieve a therapeutic aPTT. Weight-adjusted heparin nomograms have also been evaluated in patients with acute coronary syndromes. After an IV heparin bolus of 5000 units or 70 units/kg, a heparin infusion rate of 12–15 units/kg per hour is usually administered. In contrast, weight-adjusted heparin nomograms for patients with venous thromboembolism use an initial bolus of 5000 units or 80 units/kg, followed by an infusion of 18 units/kg per h. T us, patients with venous thromboembolism appear to require higher doses of heparin to achieve a therapeutic aPTT than do patients with acute coronary syndromes. T is may reflect differences in the thrombus burden. Heparin binds to fibrin, and the amount of fibrin in patients with extensive DVT is greater than that in those with coronary thrombosis.

Heparin manufacturers in North America have traditionally measured heparin potency in USP units, with a unit defined as the concentration of heparin that prevents 1 mL of citrated sheep plasma from clotting for 1 h after calcium addition. In contrast, manufacturers in Europe measure heparin potency with anti-Xa assays using an international heparin standard for comparison. Because of problems with heparin contamination with oversulfated chondroitin sulfate, which the USP assay system does not detect, North American heparin manufacturers now use the anti-Xa assay to assess heparin potency. T e use of international units in place of USP units results in a 10% reduction in heparin doses, which is a difference unlikely to affect patient care because monitoring will help to ensure that a therapeutic anticoagulant response has been achieved.

Limitations

Heparin has pharmacokinetic and biophysical limitations **(Table 24-2)**. T e pharmacokinetic limitations reflect heparin's propensity to bind in a pentasaccharide-independent fashion to cells and plasma proteins. Heparin binding to endothelial cells explains its dose-dependent clearance, whereas binding to plasma proteins results in a variable anticoagulant response and can lead to heparin resistance.

T e biophysical limitations of heparin reflect the inability of the heparin-antithrombin complex to inhibit factor Xa when it is incorporated into the prothrombinase complex, the complex that converts prothrombin

TABLE 24-2

PHARMACOKINETIC AND BIOPHYSICAL LIMITATIONS OF HEPARIN

LIMITATIONS	MECHANISM
Poor bioavailability at low doses	Binds to endothelial cells and macrophages
Dose-dependent clearance	Binds to macrophages
Variable anticoagulant response	Binds to plasma proteins whose levels vary from patient to patient
Reduced activity in the vicinity of platelet-rich thrombi	Neutralized by platelet factor 4 released from activated platelets
Limited activity against factor Xa incorporated in the prothrombinase complex and thrombin bound to fibrin	Reduced capacity of heparin-antithrombin complex to inhibit factor Xa bound to activated platelets and thrombin bound to fibrin

to thrombin, and to inhibit thrombin bound to fibrin. Consequently, factor Xa bound to activated platelets within platelet-rich thrombi has the potential to generate thrombin, even in the face of heparin. Once this thrombin binds to fibrin, it too is protected from inhibition by the heparin-antithrombin complex. Clot-associated thrombin can then trigger thrombus growth by locally activating platelets and amplifying its own generation through feedback activation of factors V, VIII, and XI. Further compounding the problem is the potential for heparin neutralization by the high concentrations of PF4 released from activated platelets within the platelet-rich thrombus.

Side effects

The most common side effect of heparin is bleeding. Other complications include thrombocytopenia, osteoporosis, and elevated levels of transaminases.

Bleeding

The risk of bleeding rises as the dose of heparin is increased. Concomitant administration of drugs that affect hemostasis, such as antiplatelet or fibrinolytic agents, increases the risk of bleeding, as does recent surgery or trauma. Heparin-treated patients with serious bleeding can be given protamine sulfate to neutralize the heparin. Protamine sulfate, a mixture of basic polypeptides isolated from salmon sperm, binds heparin with high affinity, and the resultant protamine-heparin complexes are then cleared. Typically, 1 mg of protamine sulfate neutralizes 100 units of heparin. Protamine sulfate is given IV. Anaphylactoid reactions to protamine sulfate can occur, and drug administration by slow IV infusion is recommended to reduce the risk.

Thrombocytopenia

Heparin can cause thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is an antibody-mediated process that is triggered by antibodies directed against neoantigens on PF4 that are exposed when heparin binds to this protein. These antibodies, which are usually of the IgG isotype, bind simultaneously to the heparin-PF4 complex and to platelet Fc receptors. Such binding activates the platelets and generates platelet microparticles. Circulating microparticles are prothrombotic because they express anionic phospholipids on their surface and can bind clotting factors and promote thrombin generation.

The clinical features of HIT are illustrated in **Table 24-3**. Typically, HIT occurs 5–14 days after initiation of heparin therapy, but it can manifest earlier if the patient has received heparin within the past 3 months. A platelet count below 100,000/μL or a 50% decrease in the platelet count from the pretreatment value should raise the suspicion of HIT in those receiving heparin. HIT is more common in surgical patients than in medical patients and, like many autoimmune disorders, occurs more frequently in females than in males.

HIT can be associated with thrombosis, either arterial or venous. Venous thrombosis, which manifests as DVT and/or PE, is more common than arterial thrombosis. Arterial thrombosis can manifest as ischemic stroke or acute MI. Rarely, platelet-rich thrombi in the distal aorta or iliac arteries can cause critical limb ischemia.

The diagnosis of HIT is established using enzyme-linked assays to detect antibodies against heparin-PF4 complexes or with platelet activation assays. Enzyme-linked assays are sensitive but can be positive in the absence of any clinical evidence of HIT. The most specific diagnostic test is the serotonin release assay. This test is performed by quantifying serotonin release when

TABLE 24-3

FEATURES OF HEPARIN-INDUCED THROMBOCYTOPENIA

FEATURES	DETAILS
Thrombocytopenia	Platelet count of ≤100,000/μL or a decrease in platelet count of ≥50%
Timing	Platelet count falls 5–10 days after starting heparin
Type of heparin	More common with unfractionated heparin than low-molecular-weight heparin
Type of patient	More common in surgical patients and patients with cancer than general medical patients; more common in women than in men
Thrombosis	Venous thrombosis more common than arterial thrombosis

TABLE 24-4

MANAGEMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA
Stop all heparin.
Give an alternative anticoagulant, such as lepirudin, argatroban, bivalirudin, or fondaparinux.
Do not give platelet transfusions.
Do not give warfarin until the platelet count returns to its baseline level. If warfarin was administered, give vitamin K to restore the INR to normal.
Evaluate for thrombosis, particularly deep vein thrombosis.

Abbreviation: INR, international normalized ratio.

washed platelets loaded with labeled serotonin are exposed to patient serum in the absence or presence of varying concentrations of heparin. If the patient serum contains the HIT antibody, heparin addition induces platelet activation and serotonin release.

Management of HIT is outlined in **Table 24-4**. Heparin should be stopped in patients with suspected or documented HIT, and an alternative anticoagulant should be administered to prevent or treat thrombosis. The agents most often used for this indication are parenteral direct thrombin inhibitors, such as lepirudin, argatroban, or bivalirudin, or factor Xa inhibitors, such as fondaparinux.

Patients with HIT, particularly those with associated thrombosis, often have evidence of increased thrombin generation that can lead to consumption of protein C. If these patients are given warfarin without a concomitant parenteral anticoagulant to inhibit thrombin or thrombin generation, the further decrease in protein C levels induced by the vitamin K antagonist can trigger skin necrosis. To avoid this problem, patients with HIT should be treated with a direct thrombin inhibitor or fondaparinux until the platelet count returns to normal levels. At this point, low-dose warfarin therapy can be introduced, and the thrombin inhibitor can be discontinued when the anticoagulant response to warfarin has been therapeutic for at least 2 days.

Osteoporosis

Treatment with therapeutic doses of heparin for >1 month can cause a reduction in bone density. This complication has been reported in up to 30% of patients given long-term heparin therapy, and symptomatic vertebral fractures occur in 2–3% of these individuals.

Heparin causes bone loss both by decreasing bone formation and by enhancing bone resorption. Thus, heparin affects the activity of both osteoblasts and osteoclasts.

Elevated levels of transaminases

Therapeutic doses of heparin are frequently associated with modest elevations in the serum levels of hepatic transaminases without a concomitant increase in the level of bilirubin. The levels of transaminases rapidly return to normal when the drug is stopped. The mechanism responsible for this phenomenon is unknown.

Low-molecular-weight heparin

Consisting of smaller fragments of heparin, LMWH is prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. The mean molecular weight of LMWH is about 5000, one-third the mean molecular weight of unfractionated heparin. LMWH has advantages over heparin **(Table 24-5)** and has replaced heparin for most indications.

Mechanism of action

Like heparin, LMWH exerts its anticoagulant activity by activating antithrombin. With a mean molecular weight of 5000, which corresponds to about 17 saccharide units, at least half of the pentasaccharide-containing chains of LMWH are too short to bridge thrombin to antithrombin (Fig. 24-5). However, these chains retain the capacity to accelerate factor Xa inhibition by antithrombin because this activity is largely the result of the conformational changes in antithrombin evoked by pentasaccharide binding. Consequently, LMWH catalyzes factor Xa inhibition by antithrombin more than thrombin inhibition. Depending on their unique molecular weight distributions, LMWH preparations have anti-factor Xa to anti-factor IIa ratios ranging from 2:1 to 4:1.

Pharmacology

Although usually given SC, LMWH also can be administered IV if a rapid anticoagulant response is needed. LMWH has pharmacokinetic advantages over heparin. These advantages reflect the fact that shorter heparin chains bind less avidly to endothelial cells, macrophages, and heparin-binding plasma proteins. Reduced binding to endothelial cells and

TABLE 24-5

ADVANTAGES OF LMWH OVER HEPARIN	
ADVANTAGE	CONSEQUENCE
Better bioavailability and longer half-life after subcutaneous injection	Can be given subcutaneously once or twice daily for both prophylaxis and treatment
Dose-independent clearance	Simplified dosing
Predictable anticoagulant response	Coagulation monitoring is unnecessary in most patients
Lower risk of heparin-induced thrombocytopenia	Safer than heparin for short- or long-term administration
Lower risk of osteoporosis	Safer than heparin for extended administration

Abbreviation: LMWH, low-molecular-weight heparin.

macrophages eliminates the rapid, dose-dependent, and saturable mechanism of clearance that is a characteristic of unfractionated heparin. Instead, the clearance of LMWH is dose-independent and its plasma half-life is longer. Based on measurement of anti-factor Xa levels, LMWH has a plasma half-life of ~4 h. LMWH is cleared almost exclusively by the kidneys, and the drug can accumulate in patients with renal insuf ciency.

LMWH exhibits about 90% bioavailability after SC injection. Because LMWH binds less avidly to heparin-binding proteins in plasma than heparin, LMWH produces a more predictable dose response, and resistance to LMWH is rare. With a longer half-life and more predictable anticoagulant response, LMWH can be given SC once or twice daily without coagulation monitoring, even when the drug is given in treatment doses. T ese properties render LMWH more convenient than unfractionated heparin. Capitalizing on this feature, studies in patients with venous thromboembolism have shown that home treatment with LMWH is as effective and safe as in-hospital treatment with continuous IV infusions of heparin. Outpatient treatment with LMWH streamlines care, reduces health care costs, and increases patient satisfaction.

Monitoring

In the majority of patients, LMWH does not require coagulation monitoring. If monitoring is necessary, anti-factor Xa levels must be measured because most LMWH preparations have little effect on the aPTT. T erapeutic anti-factor Xa levels with LMWH range from 0.5 to 1.2 units/mL when measured 3–4 h after drug administration. When LMWH is given in prophylactic doses, peak anti-factor Xa levels of 0.2–0.5 units/mL are desirable.

Indications for LMWH monitoring include renal insuf ciency and obesity. LMWH monitoring in patients with a creatinine clearance of ≤50 mL/min is advisable to ensure that there is no drug accumulation. Although weight-adjusted LMWH dosing appears to produce therapeutic anti-factor Xa levels in patients who are overweight, this approach has not been extensively evaluated in those with morbid obesity. It may also be advisable to monitor the anticoagulant activity of LMWH during pregnancy because dose requirements can change, particularly in the third trimester. Monitoring should also be considered in high-risk settings, such as in patients with mechanical heart valves who are given LMWH for prevention of valve thrombosis, and when LMWH is used in treatment doses in infants or children.

Dosing

T e doses of LMWH recommended for prophylaxis or treatment vary depending on the LMWH preparation. For prophylaxis, once-daily SC doses of 4000–5000 units are often used, whereas doses of 2500–3000 units are given when the drug is administered twice daily. For treatment of venous thromboembolism, a dose of 150–200 units/kg is given if the drug is administered once daily. If a twice-daily regimen is used, a dose of 100 units/kg is given. In patients with unstable angina, LMWH is given SC on a twice-daily basis at a dose of 100–120 units/kg.

Side ef ects

T e major complication of LMWH is bleeding. Meta-analyses suggest that the risk of major bleeding is lower with LMWH than with unfractionated heparin. HIT and osteoporosis are less common with LMWH than with unfractionated heparin.

Bleeding

Like the situation with heparin, bleeding with LMWH is more common in patients receiving concomitant therapy with antiplatelet or fibrinolytic drugs. Recent surgery, trauma, or underlying hemostatic defects also increase the risk of bleeding with LMWH.

Although protamine sulfate can be used as an antidote for LMWH, protamine sulfate incompletely neutralizes the anticoagulant activity of LMWH because it only binds the longer chains of LMWH. Because longer chains are responsible for catalysis of thrombin inhibition by antithrombin, protamine sulfate completely reverses the anti-factor IIa activity of LMWH. In contrast, protamine sulfate only partially reverses the anti-factor Xa activity of LMWH because the shorter pentasaccharide-containing chains of LMWH do not bind to protamine sulfate. Consequently, patients at high risk for bleeding may be more safely treated with continuous IV unfractionated heparin than with SC LMWH.

Thrombocytopenia

T e risk of HIT is about fivefold lower with LMWH than with heparin. LMWH binds less avidly to platelets and causes less PF4 release. Furthermore, with lower af nity for PF4 than heparin, LMWH is less likely to induce the conformational changes in PF4 that trigger the formation of HIT antibodies.

LMWH should not be used to treat HIT patients because most HIT antibodies exhibit cross-reactivity with LMWH. T is in vitro cross-reactivity is not simply a laboratory phenomenon because there are case reports of thrombosis when HIT patients were switched from heparin to LMWH.

Osteoporosis

Because the risk of osteoporosis is lower with LMWH than with heparin, LMWH is the better choice for extended treatment.

Fondaparinux

A synthetic analogue of the antithrombin-binding pentasaccharide sequence, fondaparinux differs from LMWH

TABLE 24-6

COMPARISON OF LMWH AND FONDAPARINUX

FEATURES	LMWH	FONDAPARINUX
Number of saccharide units	15–17	5
Catalysis of factor Xa inhibition	Yes	Yes
Catalysis of thrombin inhibition	Yes	No
Bioavailability after subcutaneous administration (%)	90	100
Plasma half-life (h)	4	17
Renal excretion	Yes	Yes
Induces release of tissue factor pathway inhibitor	Yes	No
Neutralized by protamine sulfate	Partially	No

in several ways **(Table 24-6)**. Fondaparinux is licensed for thromboprophylaxis in general medical or surgical patients and in high-risk orthopedic patients and as an alternative to heparin or LMWH for initial treatment of patients with established venous thromboembolism. Although widely used in Europe, as an alternative to heparin or LMWH in patients with acute coronary syndromes, fondaparinux is not licensed for this indication in the United States.

Mechanism of action

As a synthetic analogue of the antithrombin-binding pentasaccharide sequence found in heparin and LMWH, fondaparinux has a molecular weight of 1728. Fondaparinux binds only to antithrombin (Fig. 24-5) and is too short to bridge thrombin to antithrombin. Consequently, fondaparinux catalyzes factor Xa inhibition by antithrombin and does not enhance the rate of thrombin inhibition.

Pharmacology

Fondaparinux exhibits complete bioavailability after SC injection. With no binding to endothelial cells or plasma proteins, the clearance of fondaparinux is dose independent and its plasma half-life is 17 h. The drug is given SC once daily. Because fondaparinux is cleared unchanged via the kidneys, it is contraindicated in patients with a creatinine clearance <30 mL/min and should be used with caution in those with a creatinine clearance <50 mL/min.

Fondaparinux produces a predictable anticoagulant response after administration in fixed doses because it does not bind to plasma proteins. The drug is given at a dose of 2.5 mg once daily for prevention of venous thromboembolism. For initial treatment of established venous thromboembolism, fondaparinux is given at a dose of 7.5 mg once daily. The dose can be reduced to 5 mg once daily for those weighing <50 kg and increased to 10 mg for those >100 kg. When given in these doses, fondaparinux is as effective as heparin or LMWH for initial treatment of patients with DVT or PE and produces similar rates of bleeding.

Fondaparinux is used at a dose of 2.5 mg once daily in patients with acute coronary syndromes. When this prophylactic dose of fondaparinux was compared with treatment doses of enoxaparin in patients with non-ST-segment elevation acute coronary syndrome, there was no difference in the rate of cardiovascular death, MI, or stroke at 9 days. However, the rate of major bleeding was 50% lower with fondaparinux than with enoxaparin, a difference that likely reflects the fact that the dose of fondaparinux was lower than that of enoxaparin. In acute coronary syndrome patients who require percutaneous coronary intervention, there is a risk of catheter thrombosis with fondaparinux unless adjunctive heparin is given.

Side effects

Fondaparinux does not cause HIT because it does not bind to PF4. In contrast to LMWH, there is no cross-reactivity of fondaparinux with HIT antibodies. Consequently, fondaparinux appears to be effective for treatment of HIT patients, although large clinical trials supporting its use are lacking.

The major side effect of fondaparinux is bleeding. There is no antidote for fondaparinux. Protamine sulfate has no effect on the anticoagulant activity of fondaparinux because it fails to bind to the drug. Recombinant activated factor VII reverses the anticoagulant effects of fondaparinux in volunteers, but it is unknown whether this agent controls fondaparinux-induced bleeding.

Parenteral direct thrombin inhibitors

Direct thrombin inhibitors bind directly to thrombin and block its interaction with its substrates. Approved parenteral direct thrombin inhibitors include recombinant hirudins (lepirudin and desirudin), argatroban, and bivalirudin **(Table 24-7)**. Lepirudin and argatroban are licensed for treatment of patients with HIT, desirudin is licensed for thromboprophylaxis after elective hip arthroplasty, and bivalirudin is approved as an alternative to heparin in patients undergoing percutaneous coronary intervention, including those with HIT.

Lepirudin and desirudin

Recombinant forms of hirudin, lepirudin, and desirudin are bivalent direct thrombin inhibitors that interact with the active site and exosite 1, the substrate-binding site on thrombin. For rapid anticoagulation, lepirudin is given by continuous IV infusion, but the drug can be given SC. Lepirudin has a plasma half-life of 60 min after IV infusion and is cleared by the kidneys. Consequently, lepirudin accumulates in

TABLE 24-7

COMPARISON OF THE PROPERTIES OF LEPIRUDIN, BIVALIRUDIN, AND ARGATROBAN

	LEPIRUDIN/ DESIRUDIN	BIVALIRUDIN	ARGATROBAN
Molecular mass	7000	1980	527
Site(s) of interaction with thrombin	Active site and exosite 1	Active site and exosite 1	Active site
Renal clearance	Yes	No	No
Hepatic metabolism	No	No	Yes
Plasma half-life (min)	60 (IV) 120–180 (SC)	25	45

patients with renal insuf ciency. For thromboprophylaxis, desirudin is given SC twice daily in fixed doses; the half-life of desirudin is 2–3 h after SC injection.

A high proportion of lepirudin-treated patients develop antibodies against the drug; antibody formation is rare with SC desirudin. Although lepirudin-directed antibodies rarely cause problems, in a small subset of patients, they can delay lepirudin clearance and enhance its anticoagulant activity. Serious bleeding has been reported in some of these patients.

Lepirudin is usually monitored using the aPTT, and the dose is adjusted to maintain an aPTT that is 1.5–2.5 times the control. T e aPTT is not an ideal test for monitoring lepirudin therapy because the clotting time plateaus with higher drug concentrations. Although the clotting time with ecarin, a snake venom that converts prothrombin to meizothrombin, provides a better index of lepirudin dose than the aPTT, the ecarin clotting time has yet to be standardized. When used for thromboprophylaxis, desirudin does not require monitoring.

Argatroban

A univalent inhibitor that targets the active site of thrombin, argatroban is metabolized in the liver. Consequently, this drug must be used with caution in patients with hepatic insuf ciency. Argatroban is not cleared via the kidneys, so this drug is safer than lepirudin for HIT patients with renal insuf ciency.

Argatroban is administered by continuous IV infusion and has a plasma half-life of ~45 min. T e aPTT is used to monitor its anticoagulant effect, and the dose is adjusted to achieve an aPTT 1.5–3 times the baseline value, but not to exceed 100 s. Argatroban also prolongs the international normalized ratio (INR), a feature that can complicate the transitioning of patients to warfarin. T is problem can be circumvented by using the levels of factor X to monitor warfarin in place of the INR. Alternatively, argatroban can be stopped for 2–3 h before INR determination.

Bivalirudin

A synthetic 20-amino-acid analogue of hirudin, bivalirudin is a divalent thrombin inhibitor. T us, the N-terminus of bivalirudin interacts with the active site of thrombin, whereas its C-terminus binds to exosite 1. Bivalirudin has a plasma half-life of 25 min, the shortest half-life of all the parenteral direct thrombin inhibitors. Bivalirudin is degraded by peptidases and is partially excreted via the kidneys. When given in high doses in the cardiac catheterization laboratory, the anticoagulant activity of bivalirudin is monitored using the activated clotting time. With lower doses, its activity can be assessed using the aPTT.

Bivalirudin is licensed as an alternative to heparin in patients undergoing percutaneous coronary intervention. Bivalirudin also has been used successfully in HIT patients who require percutaneous coronary intervention or cardiac bypass surgery.

ORAL ANTICOAGULANTS

Current oral anticoagulant practice dates back almost 60 years to when the vitamin K antagonists were discovered as a result of investigations into the cause of hemorrhagic disease in cattle. Characterized by a decrease in prothrombin levels, this disorder is caused by ingestion of hay containing spoiled sweet clover. Hydroxycoumarin, which was isolated from bacterial contaminants in the hay, interferes with vitamin K metabolism, thereby causing a syndrome similar to vitamin K deficiency. Discovery of this compound provided the impetus for development of other vitamin K antagonists, including warfarin.

For many years, the vitamin K antagonists were the only available oral anticoagulants. T is situation changed with the introduction of new oral anticoagulants, including dabigatran, which targets thrombin, and rivaroxaban, apixaban, and edoxaban, which target factor Xa.

Warfarin

A water-soluble vitamin K antagonist initially developed as a rodenticide, warfarin is the coumarin derivative most often prescribed in North America. Like other vitamin K antagonists, warfarin interferes with the synthesis of the vitamin K–dependent clotting proteins, which include prothrombin (factor II) and factors VII, IX, and X. T e synthesis of the vitamin K–dependent anticoagulant proteins, proteins C and S, is also reduced by vitamin K antagonists.

Mechanism of action

All of the vitamin K–dependent clotting factors possess glutamic acid residues at their N termini. A posttranslational modification adds a carboxyl group to the

γ-carbon of these residues to generate γ-carboxyglutamic acid. T is modification is essential for expression of the activity of these clotting factors because it permits their calcium-dependent binding to negatively charged phospholipid surfaces. T e γ-carboxylation process is catalyzed by a vitamin K–dependent carboxylase. T us, vitamin K from the diet is reduced to vitamin K hydroquinone by vitamin K reductase **(Fig. 24-6)**. Vitamin K hydroquinone serves as a cofactor for the carboxylase enzyme, which in the presence of carbon dioxide replaces the hydrogen on the γ-carbon of glutamic acid residues with a carboxyl group. During this process, vitamin K hydroquinone is oxidized to vitamin K epoxide, which is then reduced to vitamin K by vitamin K epoxide reductase.

Warfarin inhibits vitamin K epoxide reductase (VKOR), thereby blocking the γ-carboxylation process. T is results in the synthesis of vitamin K–dependent clotting proteins that are only partially γ-carboxylated. Warfarin acts as an anticoagulant because these partially γ-carboxylated proteins have reduced or absent biologic activity. T e onset of action of warfarin is delayed until the newly synthesized clotting factors with reduced activity gradually replace their fully active counterparts.

T e antithrombotic effect of warfarin depends on a reduction in the functional levels of factor X and prothrombin, clotting factors that have half-lives of 24 and 72 h, respectively. Because the antithrombotic effect of warfarin is delayed, patients with established thrombosis or at high risk for thrombosis require concomitant treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux, for at least 5 days.

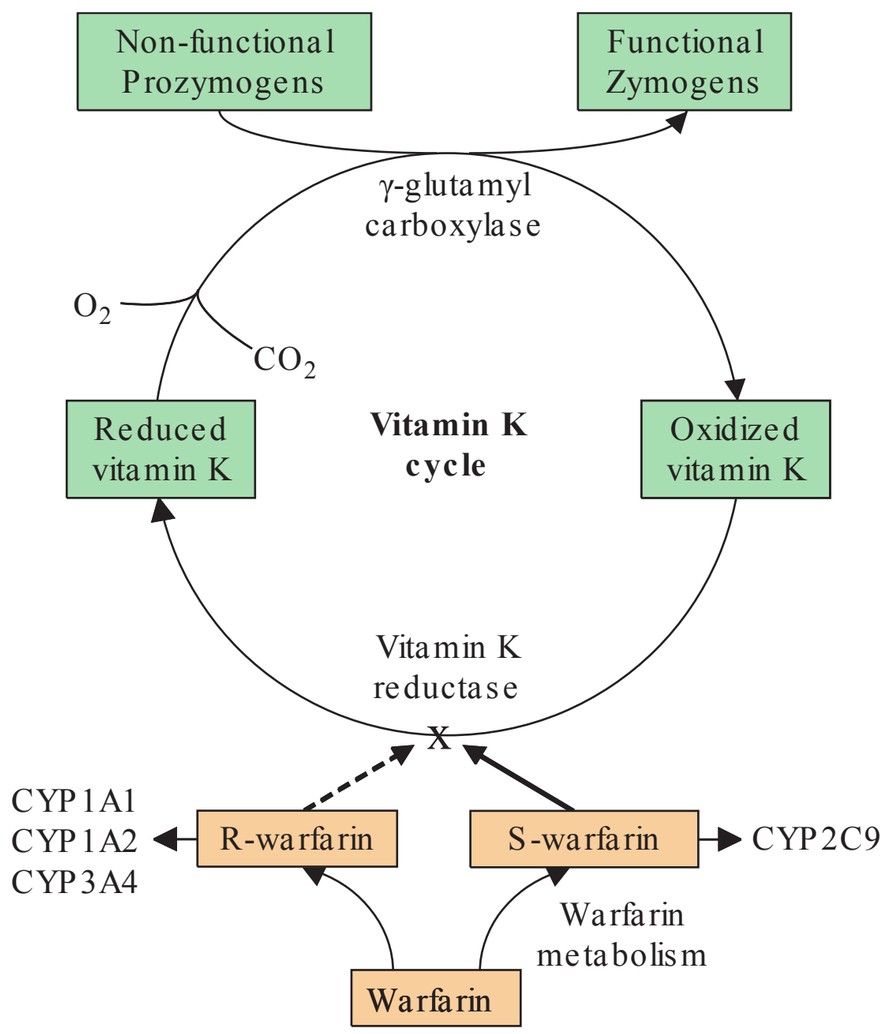

FIGURE 24-6

Mechanism of action of warfarin. A racemic mixture of S- and R-enantiomers, S-warfarin is most active. By blocking vitamin K epoxide reductase, warfarin inhibits the conversion of oxidized vitamin K into its reduced form. This inhibits vitamin K–dependent γ-carboxylation of factors II, VII, IX, and X because reduced vitamin K serves as a cofactor for a γ-glutamyl carboxylase that catalyzes the γ-carboxylation process, thereby converting prozymogens to zymogens capable of binding calcium and interacting with anionic phospholipid surfaces. S-warfarin is metabolized by CYP2C9. Common genetic polymorphisms in this enzyme can influence warfarin metabolism. Polymorphisms in the C1 subunit of vitamin K reductase (VKORC1) also can affect the susceptibility of the enzyme to warfarin-induced inhibition, thereby influencing warfarin dosage requirements.

Pharmacology

Warfarin is a racemic mixture of R and S isomers. Warfarin is rapidly and almost completely absorbed from the gastrointestinal tract. Levels of warfarin in the blood peak about 90 min after drug administration. Racemic warfarin has a plasma half-life of 36–42 h, and more than 97% of circulating warfarin is bound to albumin. Only the small fraction of unbound warfarin is biologically active.

Warfarin accumulates in the liver where the two isomers are metabolized via distinct pathways. CYP2C9 mediates oxidative metabolism of the more active S isomer (Fig. 24-6). Two relatively common variants, CYP2C9*2 and CYP2C9*3, encode an enzyme with reduced activity. Patients with these variants require lower maintenance doses of warfarin. Approximately 25% of Caucasians have at least one variant allele of CYP2C9*2 or CYP2C9*3, whereas those variant alleles are less common in African Americans and Asians **(Table 24-8)**. Heterozygosity for CYP2C9*2 or CYP2C9*3 decreases the warfarin dose requirement by 20–30% relative to that required in subjects with the wild-type CYP2C9*1/*1 alleles, whereas homozygosity for the CYP2C9*2 or CYP2C9*3 alleles reduces the warfarin dose requirement by 50–70%.

Consistent with their decreased warfarin dose requirement, subjects with at least one CYP2C9 variant allele are at increased risk for bleeding. Compared with individuals with no variant alleles, the relative risks for warfarin-associated bleeding in CYP2C9*2 or CYP2C9*3 carriers are 1.9 and 1.8, respectively.

Polymorphisms in VKORC1 also can influence the anticoagulant response to warfarin. Several genetic variations of VKORC1 are in strong linkage disequilibrium and have been designated as non-A haplotypes. VKORC1 variants are more prevalent than variants of CYP2C9. Asians have the highest prevalence of VKORC1 variants, followed by Caucasians and African Americans (Table 24-8). Polymorphisms in VKORC1 likely

TABLE 24-8

FREQUENCIES OF CYP2C9 ENOTYPES AND VKORC1 HAPLOTYPES IN DIFFERENT POPULATIONS AND THEIR EFFECT ON WARFARIN DOSE REQUIREMENTS

	FREQUENCY, %			
GENOTYPE/HAPLOTYPE	CAUCASIANS	AFRICAN AMERICANS (A/A)	ASIANS (A)	DOSE REDUCTION COMPARED WITH WILD-TYPE
CYP2C9				
*1/*1	70	90	95	–
*1/*2	17	2	0	22
*1/*3	9	3	4	34
*2/*2	2	0	0	43
*2/*3	1	0	0	53
*3/*3	0	0	1	76
VKORC1				
Non-A/non-A	37	82	7	–
Non-A/A	45	12	30	26
A/A	18	6	63	50

explain 30% of the variability in warfarin dose requirements. Compared with VKORC1 non-A/non-A homozygotes, the warfarin dose requirement decreases by 25 and 50% in A haplotype heterozygotes and homozygotes, respectively. T ese findings prompted the Food and Drug Administration to amend the prescribing information for warfarin to indicate that lower initiation doses should be considered for patients with CYP2C9 and VKORC1 genetic variants. In addition to genotype data, other pertinent patient information has been incorporated into warfarin dosing algorithms. Although such algorithms help predict suitable warfarin doses, it remains unclear whether better dose identification improves patient outcome in terms of reducing hemorrhagic complications or recurrent thrombotic events.

In addition to genetic factors, the anticoagulant effect of warfarin is influenced by diet, drugs, and various disease states. Fluctuations in dietary vitamin K intake affect the activity of warfarin. A wide variety of drugs can alter absorption, clearance, or metabolism of warfarin. Because of the variability in the anticoagulant response to warfarin, coagulation monitoring is essential to ensure that a therapeutic response is obtained.

Monitoring

Warfarin therapy is most often monitored using the prothrombin time, a test that is sensitive to reductions in the levels of prothrombin, factor VII, and factor X. T e test is performed by adding thromboplastin, a reagent that contains tissue factor, phospholipid, and calcium, to citrated plasma and determining the time to clot formation. T romboplastins vary in their sensitivity to reductions in the levels of the vitamin K–dependent clotting factors. T us, less sensitive thromboplastins will trigger the administration of higher doses of warfarin to achieve a target prothrombin time. T is is problematic because higher doses of warfarin increase the risk of bleeding.

T e INR was developed to circumvent many of the problems associated with the prothrombin time. To calculate the INR, the patient's prothrombin time is divided by the mean normal prothrombin time, and this ratio is then multiplied by the international sensitivity index (ISI), which is an index of the sensitivity of the thromboplastin used for prothrombin time determination to reductions in the levels of the vitamin K–dependent clotting factors. Highly sensitive thromboplastins have an ISI of 1.0. Most current thromboplastins have ISI values that range from 1.0 to 1.4.

Although the INR has helped to standardize anticoagulant practice, problems persist. T e precision of INR determination varies depending on reagent-coagulometer combinations. T is leads to variability in the INR results. Also complicating INR determination is unreliable reporting of the ISI by thromboplastin manufacturers. Furthermore, every laboratory must establish the mean normal prothrombin time with each new batch of thromboplastin reagent. To accomplish this, the prothrombin time must be measured in fresh plasma samples from at least 20 healthy volunteers using the same coagulometer that is used for patient samples.

For most indications, warfarin is administered in doses that produce a target INR of 2.0–3.0. An exception is patients with mechanical heart valves, particularly those in the mitral position or older ball and cage valves in the aortic position, where a target INR of

2.5–3.5 is recommended. Studies in atrial fibrillation demonstrate an increased risk of cardioembolic stroke when the INR falls to <1.7 and an increase in bleeding with INR values >4.5. T ese findings highlight the fact that vitamin K antagonists have a narrow therapeutic window. In support of this concept, a study in patients receiving long-term warfarin therapy for unprovoked venous thromboembolism demonstrated a higher rate of recurrent venous thromboembolism with a target INR of 1.5–1.9 compared with a target INR of 2.0–3.0.

Dosing

Warfarin is usually started at a dose of 5–10 mg. Lower doses are used for patients with CYP2C9 or VKORC1 polymorphisms, which affect the pharmacodynamics or pharmacokinetics of warfarin and render patients more sensitive to the drug. T e dose is then titrated to achieve the desired target INR. Because of its delayed onset of action, patients with established thrombosis or those at high risk for thrombosis are given concomitant initial treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux. Early prolongation of the INR reflects reduction in the functional levels of factor VII. Consequently, concomitant treatment with the parenteral anticoagulant should be continued until the INR has been therapeutic for at least 2 consecutive days. A minimum 5-day course of parenteral anticoagulation is recommended to ensure that the levels of factor Xa and prothrombin have been reduced into the therapeutic range with warfarin.

Because warfarin has a narrow therapeutic window, frequent coagulation monitoring is essential to ensure that a therapeutic anticoagulant response is maintained. Even patients with stable warfarin dose requirements should have their INR determined every 3–4 weeks. More frequent monitoring is necessary when new medications are introduced because so many drugs enhance or reduce the anticoagulant effects of warfarin.

Side ef ects

Like all anticoagulants, the major side effect of warfarin is bleeding. A rare complication is skin necrosis. Warfarin crosses the placenta and can cause fetal abnormalities. Consequently, warfarin should not be used during pregnancy.

Bleeding

At least half of the bleeding complications with warfarin occur when the INR exceeds the therapeutic range. Bleeding complications may be mild, such as epistaxis or hematuria, or more severe, such as retroperitoneal or gastrointestinal bleeding. Life-threatening intracranial bleeding can also occur.

To minimize the risk of bleeding, the INR should be maintained in the therapeutic range. In asymptomatic patients whose INR is between 3.5 and 10, warfarin should be withheld until the INR returns to the therapeutic range. If the INR is over 10, oral vitamin K should be administered, at a dose of 2.5–5 mg, although there is no evidence that doing so reduces the bleeding risk. Higher doses of oral vitamin K (5–10 mg) produce more rapid reversal of the INR but may render patients temporarily resistant to warfarin when the drug is restarted. Patients with serious bleeding need more aggressive treatment. T ese patients should be given 5–10 mg of vitamin K by slow IV infusion. Additional vitamin K should be given until the INR is in the normal range. Treatment with vitamin K should be supplemented with fresh-frozen plasma as a source of the vitamin K–dependent clotting proteins. Four factor prothrombin complex concentrates, which contain all four vitamin K–dependent clotting proteins, are the treatment of choice for (1) life-threatening bleeds, (2) rapid restoration of the INR into the normal range in patients requiring urgent surgery or intervention, and (3) patients who cannot tolerate the volume load of fresh-frozen plasma.

Warfarin-treated patients who experience bleeding when their INR is in the therapeutic range require investigation into the cause of the bleeding. T ose with gastrointestinal or genitourinary bleeding often have an underlying lesion.

Skin necrosis

A rare complication of warfarin, skin necrosis usually is seen 2–5 days after initiation of therapy. Well-demarcated erythematous lesions form on the thighs, buttocks, breasts, or toes. Typically, the center of the lesion becomes progressively necrotic. Examination of skin biopsies taken from the border of these lesions reveals thrombi in the microvasculature.

Warfarin-induced skin necrosis is seen in patients with congenital or acquired deficiencies of protein C or protein S. Initiation of warfarin therapy in these patients produces a precipitous fall in plasma levels of proteins C or S, thereby eliminating this important anticoagulant pathway before warfarin exerts an antithrombotic effect through lowering of the functional levels of factor X and prothrombin. T e resultant procoagulant state triggers thrombosis. Why the thrombosis is localized to the microvasculature of fatty tissues is unclear.

Treatment involves discontinuation of warfarin and reversal with vitamin K, if needed. An alternative anticoagulant, such as heparin or LMWH, should be given in patients with thrombosis. Protein C concentrate can be given to protein C–deficient patients to accelerate healing of the skin lesions; fresh-frozen plasma may be of value if protein C concentrate is unavailable and for those with protein S deficiency. Occasionally, skin grafting is necessary when there is extensive skin loss.

Because of the potential for skin necrosis, patients with known protein C or protein S deficiency require overlapping treatment with a parenteral anticoagulant when initiating warfarin therapy. Warfarin should be

started in low doses in these patients, and the parenteral anticoagulant should be continued until the INR is therapeutic for at least 2–3 consecutive days.

Pregnancy

Warfarin crosses the placenta and can cause fetal abnormalities or bleeding. The fetal abnormalities include a characteristic embryopathy, which consists of nasal hypoplasia and stippled epiphyses. The risk of embryopathy is highest if warfarin is given in the first trimester of pregnancy. Central nervous system abnormalities can also occur with exposure to warfarin at any time during pregnancy. Finally, maternal administration of warfarin produces an anticoagulant effect in the fetus that can cause bleeding. This is of particular concern at delivery when trauma to the head during passage through the birth canal can lead to intracranial bleeding. Because of these potential problems, warfarin is contraindicated in pregnancy, particularly in the first and third trimesters. Instead, heparin, LMWH, or fondaparinux can be given during pregnancy for prevention or treatment of thrombosis.

Warfarin does not pass into the breast milk. Consequently, warfarin can safely be given to nursing mothers.

Special problems

Patients with a lupus anticoagulant and those who need urgent or elective surgery present special challenges. Although observational studies suggested that patients with thrombosis complicating the antiphospholipid antibody syndrome required higher intensity warfarin regimens to prevent recurrent thromboembolic events, two randomized trials showed that targeting an INR of 2.0–3.0 is as effective as higher intensity treatment and produces less bleeding. Monitoring warfarin therapy can be problematic in patients with antiphospholipid antibody syndrome if the lupus anticoagulant prolongs the baseline INR; factor X levels can be used instead of the INR in such patients.

There is no need to stop warfarin before procedures associated with a low risk of bleeding; these include dental cleaning, simple dental extraction, cataract surgery, or skin biopsy. For procedures associated with a moderate or high risk of bleeding, warfarin should be stopped 5 days before the procedure to allow the INR to return to normal levels. Patients at high risk for thrombosis, such as those with mechanical heart valves, can be bridged with once- or twice-daily SC injections of LMWH when the INR falls to <2.0. The last dose of LMWH should be given 12–24 h before the procedure, depending on whether LMWH is administered twice or once daily. After the procedure, treatment with warfarin can be restarted.

New oral anticoagulants

New oral anticoagulants are now available as alternatives to warfarin. These include dabigatran, which targets thrombin, and rivaroxaban, apixaban, and edoxaban, which target factor Xa. All of these drugs have a rapid onset and offset of action and have half-lives that permit once- or twice-daily administration. Designed to produce a predictable level of anticoagulation, the new oral agents are more convenient to administer than warfarin because they are given in fixed doses without routine coagulation monitoring.

Mechanism of action

The new oral anticoagulants are small molecules that bind reversibly to the active site of their target enzyme. **Table 24-9** summarizes the distinct pharmacologic properties of these agents.

Indications

The new oral anticoagulants have been compared with warfarin for stroke prevention in patients with nonvalvular atrial fibrillation in four randomized trials that enrolled 71,683 patients. A meta-analysis of these data demonstrates that compared with warfarin, the new agents significantly reduce stroke or systemic embolism by 19% ($p = .001$), primarily driven by a 51% reduction in hemorrhagic stroke ($p < .0001$), and are associated with a

TABLE 24-9

COMPARISON OF THE PHARMACOLOGIC PROPERTIES OF THE NEW ORAL ANTICOAGULANTS

CHARACTERISTIC	RIVAROXABAN	APIXABAN	EDOXABAN	DABIGATRAN
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	No	Yes
Bioavailability	80%	60%	50%	6%
Dosing	qd (bid)	bid	qd	bid (qd)
Half-life	7–11 h	12 h	9–11 h	12–17 h
Renal	33% (66%)	25%	35%	80%
Monitoring	No	No	No	No
Interactions	3A4/P-gp	3A4/P-gp	P-gp	P-gp

Abbreviations: bid, twice a day; P-gp, P-glycoprotein; qd., once a day.

10% reduction in mortality (p <.0001). New oral anticoagulants reduce intracranial hemorrhage by 52% compared with warfarin (p <.0001), but increase gastrointestinal bleeding by about 24% (p = .04). Overall, the new agents demonstrate a favorable benefit-to-risk profile compared with warfarin, and their relative ef cacy and safety are maintained across a wide spectrum of atrial fibrillation patients, including those over the age of 75 years and those with a prior history of stroke. Based on these findings, dabigatran, rivaroxaban, and apixaban are licensed as alternatives to warfarin for stroke prevention in nonvalvular atrial fibrillation, and edoxaban is under regulatory consideration for this indication. Nonvalvular atrial fibrillation is defined as that occurring in patients without mechanical heart valves or severe rheumatic valvular disease, particularly mitral stenosis and/or regurgitation.

Dabigatran, rivaroxaban, and apixaban have been compared with enoxaparin for thromboprophylaxis after elective hip or knee arthroplasty. Currently, only rivaroxaban and apixaban are licensed for this indication in the United States. Rivaroxaban and dabigatran are also licensed for treatment of DVT or PE. Apixaban and edoxaban have also been investigated for treatment of patients with venous thromboembolism, but have not yet been approved for this indication. Rivaroxaban is licensed in Europe for prevention of recurrent ischemic events in patients who have been stabilized after an acute coronary syndrome. In this setting, rivaroxaban is usually administered in conjunction with dual antiplatelet therapy with aspirin and clopidogrel.

Dosing

For stroke prevention in patients with nonvalvular atrial fibrillation, rivaroxaban is given at a dose of 20 mg once daily with a dose reduction to 15 mg once daily in patients with a creatinine clearance of 15–49 mL/min; dabigatran is given at a dose of 150 mg twice daily with a dose reduction to 75 mg twice daily in those with a creatinine clearance of 15–30 mL/min; and apixaban is given at a dose of 5 mg twice daily with a dose reduction to 2.5 mg twice daily for patients with a creatinine >1.5 g/dL, for those 80 years of age or older, or for patients who weigh <60 kg.

For thromboprophylaxis after elective hip or knee replacement surgery, rivaroxaban is given at a dose of 10 mg once daily, whereas apixaban is given at a dose of 2.5 mg twice daily. For treatment of patients with DVT or PE, rivaroxaban is started at a dose of 15 mg twice daily for 3 weeks; the dose is then reduced to 20 mg once daily thereafter. After a minimum of a 5 day course of treatment with heparin or LMWH, dabigatran is given at a dose of 150 mg twice daily.

Monitoring

Although designed to be administered without routine monitoring, there are situations where determination of the anticoagulant activity of the new oral anticoagulants can be helpful. T ese include assessment of adherence, detection of accumulation or overdose, identification of bleeding mechanisms, and determination of activity prior to surgery or intervention. For qualitative assessment of anticoagulant activity, the prothrombin time can be used for factor Xa inhibitors and the aPTT for dabigatran. Rivaroxaban and edoxaban prolong the prothrombin time more than apixaban. In fact, because apixaban has such a limited effect on the prothrombin time, anti-factor Xa assays are needed to assess its activity. T e effect of the drugs on tests of coagulation varies depending on the time that the blood is drawn relative to the timing of the last dose of the drug and the reagents used to perform the tests. Chromogenic anti-factor Xa assays and a dilute thrombin clotting time with appropriate calibrators provide quantitative assays to measure the plasma levels of the factor Xa inhibitors and dabigatran, respectively.

Side ef ects

Like all anticoagulants, bleeding is the most common side effect of the new oral anticoagulants. T e new agents are associated with less intracranial bleeding than warfarin. T e increased risk of intracranial bleeding with warfarin likely reflects the reduction in functional levels of factor VII, which precludes ef cient thrombin generation at sites of microvascular bleeding in the brain. Because the new oral anticoagulants target downstream coagulation enzymes, they produce less impairment of hemostatic plug formation at sites of vascular injury.

A downside of the new oral anticoagulants is the increased risk of gastrointestinal bleeding. T is likely occurs because unabsorbed active drug in the gut exacerbates bleeding from lesions. Although dabigatran etexilate is a prodrug, only 7% is absorbed. Although the remainder passes through the gut, at least two-thirds is metabolically activated to dabigatran by gut esterases.

Dyspepsia occurs in up to 10% of patients treated with dabigatran; this problem improves with time and can be minimized by administering the drug with food. Dyspepsia is rare with rivaroxaban, apixaban, and edoxaban.

Periprocedural management

Like warfarin, the new oral anticoagulants must be stopped before procedures associated with a moderate or high risk of bleeding. T e drugs should be held for 1–2 days, or longer if renal function is impaired. Assessment of residual anticoagulant activity before procedures associated with a high bleeding risk is prudent.

Management of bleeding

T ere are no specific antidotes for the new oral anticoagulants. With minor bleeding, holding one or two doses of drug is usually suf cient. T e approach to serious bleeding is similar to that with warfarin except that vitamin K administration is of no benefit. T us, the

anticoagulant and antiplatelet drugs should be held, the patient should be resuscitated with fluids and blood products as necessary, and, if possible, the bleeding site should be identified and managed. Coagulation testing will determine the extent of anticoagulation. and renal function should be assessed so that the half-life of the drug can be calculated. Timing of the last dose of anticoagulant is important; administration of oral activated charcoal may help to prevent absorption of drug administered in the past 2–4 h. If bleeding continues or is life-threatening, procoagulants, such as prothrombin complex concentrate (either unactivated or activated) or factor VIIa, can be administered, although the evidence of their effectiveness is limited. Dialysis removes dabigatran from the circulation in patients with renal impairment; dialysis does not remove rivaroxaban, apixaban, or edoxaban because unlike dabigatran, these drugs are highly protein-bound.

Pregnancy

As small molecules, the new oral anticoagulants can all pass through the placenta. Consequently, these agents are contraindicated in pregnancy, and when used by women of childbearing potential, appropriate contraception is important.

Ongoing investigations

Although the lack of antidotes has created concern about the risk of bleeding events in patients taking the new oral anticoagulants, emerging postmarketing data suggest that the rates of bleeding in the real-world setting are similar to those reported in the trials. Nonetheless, specific antidotes are under development. T ese include a humanized mouse monoclonal antibody fragment against dabigatran and a recombinant variant of factor Xa that serves as a decoy for the oral factor Xa inhibitors. Neither agent is currently available for clinical use.

FIBRINOLYTIC DRUGS

ROLE OF FIBRINOLYTIC THERAPY

Fibrinolytic drugs can be used to degrade thrombi and are administered systemically or can be delivered via catheters directly into the substance of the thrombus. Systemic delivery is used for treatment of acute MI, acute ischemic stroke, and most cases of massive PE. T e goal of therapy is to produce rapid thrombus dissolution, thereby restoring antegrade blood flow. In the coronary circulation, restoration of blood flow reduces morbidity and mortality rates by limiting myocardial damage, whereas in the cerebral circulation, rapid thrombus dissolution decreases the neuronal death and brain infarction that produce irreversible brain injury. For patients with massive PE, the goal of thrombolytic therapy is to restore pulmonary artery perfusion.

Peripheral arterial thrombi and thrombi in the proximal deep veins of the leg are most often treated using catheter-directed thrombolytic therapy. Catheters with multiple side holes can be used to enhance drug delivery. In some cases, intravascular devices that fragment and extract the thrombus are used to hasten treatment. T ese devices can be used alone or in conjunction with fibrinolytic drugs.

MECHANISM OF ACTION

Currently approved fibrinolytic agents include streptokinase; acylated plasminogen streptokinase activator complex (anistreplase); urokinase; recombinant tissue-type plasminogen activator (rtPA), which is also known as alteplase or activase; and two recombinant derivatives of rtPA, tenecteplase and reteplase. All of these agents act by converting plasminogen, the zymogen, to plasmin, the active enzyme **(Fig. 24-7)**. Plasmin then degrades the fibrin matrix of thrombi and produces soluble fibrin degradation products.

Endogenous fibrinolysis is regulated at two levels. Plasminogen activator inhibitors, particularly the type 1 form (PAI-1), prevent excessive plasminogen activation by regulating the activity of tPA and urokinase-type plasminogen activator (uPA). Once plasmin is generated, it is regulated by plasmin inhibitors, the most important of which is α_2-antiplasmin. T e plasma concentration of plasminogen is twofold higher than that of α_2-antiplasmin. Consequently, with pharmacologic doses of plasminogen activators, the concentration of plasmin that is generated can exceed that of α_2-antiplasmin. In addition to degrading fibrin, unregulated plasmin can also degrade fibrinogen and other clotting factors. T is process, which is known as the systemic lytic state, reduces the hemostatic potential of the blood and increases the risk of bleeding.

T e endogenous fibrinolytic system is geared to localize plasmin generation to the fibrin surface. Both

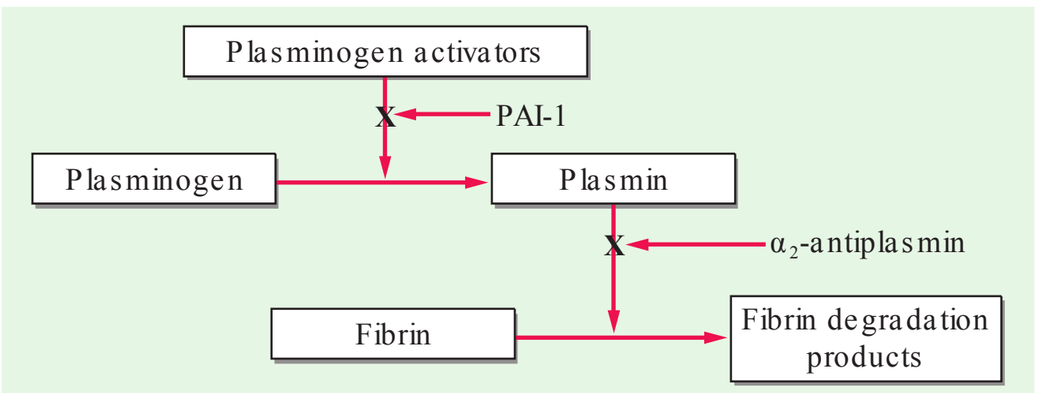

FIGURE 24-7
The f brinolytic system and its regulation. Plasminogen activators convert plasminogen to plasmin. Plasmin then degrades fibrin into soluble fibrin degradation products. The system is regulated at two levels. Type 1 plasminogen activator inhibitor (PAI-1) regulates the plasminogen activators, whereas α_2-antiplasmin serves as the major inhibitor of plasmin.

plasminogen and tPA bind to fibrin to form a ternary complex that promotes ef cient plasminogen activation. In contrast to free plasmin, plasmin generated on the fibrin surface is relatively protected from inactivation by α_2-antiplasmin, a feature that promotes fibrin dissolution. Furthermore, C-terminus lysine residues, exposed as plasmin degrades fibrin, serve as binding sites for additional plasminogen and tPA molecules. T is creates a positive feedback that enhances plasmin generation. When used pharmacologically, the various plasminogen activators capitalize on these mechanisms to a lesser or greater extent.

Plasminogen activators that preferentially activate fibrin-bound plasminogen are considered fibrin-specific. In contrast, nonspecific plasminogen activators do not discriminate between fibrin-bound and circulating plasminogen. Activation of circulating plasminogen results in the generation of unopposed plasmin that can trigger the systemic lytic state. Alteplase and its derivatives are fibrin-specific plasminogen activators, whereas streptokinase, anistreplase, and urokinase are nonspecific agents.

STREPTOKINASE

Unlike other plasminogen activators, streptokinase is not an enzyme and does not directly convert plasminogen to plasmin. Instead, streptokinase forms a 1:1 stoichiometric complex with plasminogen. Formation of this complex induces a conformational change in plasminogen that exposes its active site **(Fig. 24-8)**. T e streptokinase-plasminogen complex then converts additional plasminogen to plasmin.

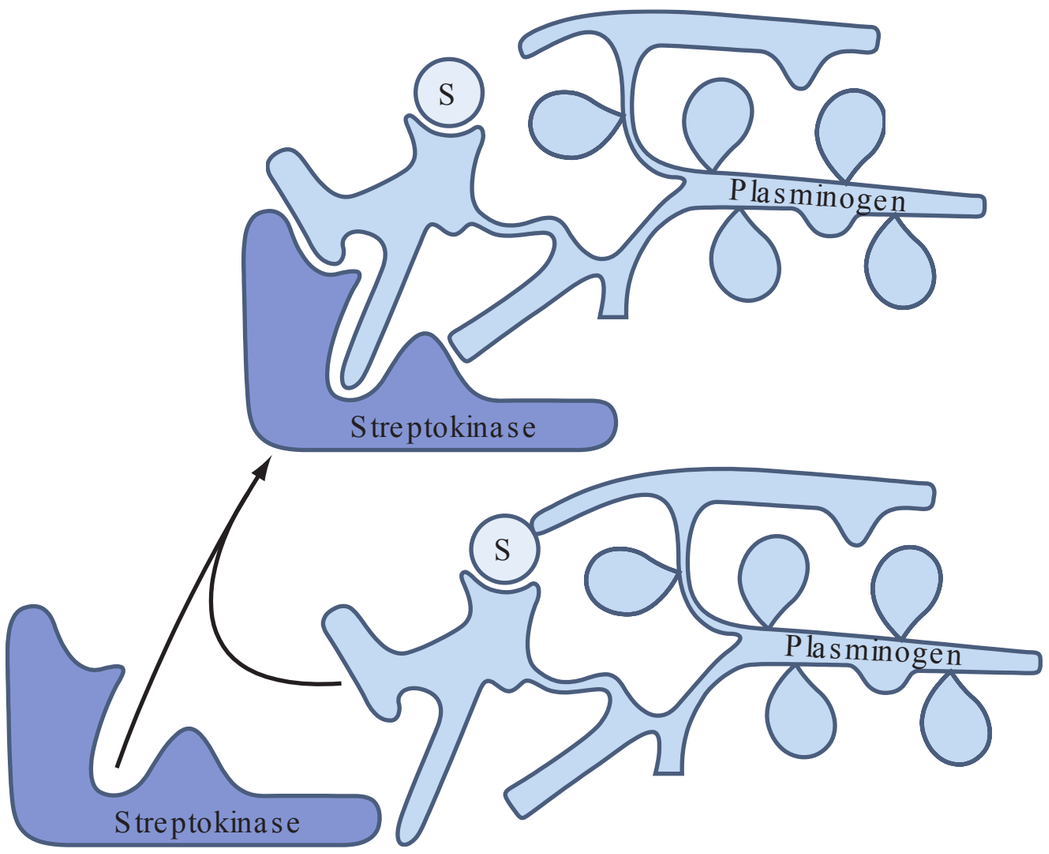

FIGURE 24-8
Mechanism of action of streptokinase. Streptokinase binds to plasminogen and induces a conformational change in plasminogen that exposes its active site. The streptokinase/plasmin(ogen) complex then serves as the activator of additional plasminogen.

Streptokinase has no af nity for fibrin, and the streptokinase-plasminogen complex activates both free and fibrin-bound plasminogen. Activation of circulating plasminogen generates suf cient amounts of plasmin to overwhelm α_2-antiplasmin. Unopposed plasmin not only degrades fibrin in the occlusive thrombus but also induces a systemic lytic state.

When given systemically to patients with acute MI, streptokinase reduces mortality. For this indication, the drug is usually given as an IV infusion of 1.5 million units over 30–60 min. Patients who receive streptokinase can develop antibodies against the drug, as can patients with prior streptococcal infection. T ese antibodies can reduce the effectiveness of streptokinase.

Allergic reactions occur in ~5% of patients treated with streptokinase. T ese may manifest as a rash, fever, chills, and rigors. Although anaphylactic reactions can occur, these are rare. Transient hypotension is common with streptokinase and has been attributed to plasmin-mediated release of bradykinin from kininogen. T e hypotension usually responds to leg elevation and administration of IV fluids and low doses of vasopressors, such as dopamine or norepinephrine.

ANISTREPLASE

To generate this drug, streptokinase is combined with equimolar amounts of Lys-plasminogen, a plasmin-cleaved form of plasminogen with a Lys residue at its N terminus. T e active site of Lys-plasminogen that is exposed upon combination with streptokinase is then masked with an anisoyl group. After IV infusion, the anisoyl group is slowly removed by deacylation, giving the complex a half-life of ~100 min. T is allows drug administration via a single bolus infusion.

Although it is more convenient to administer, anistreplase offers few mechanistic advantages over streptokinase. Like streptokinase, anistreplase does not distinguish between fibrin-bound and circulating plasminogen. Consequently, it too produces a systemic lytic state. Likewise, allergic reactions and hypotension are just as frequent with anistreplase as they are with streptokinase.

When anistreplase was compared with alteplase in patients with acute MI, reperfusion was obtained more rapidly with alteplase than with anistreplase. Improved reperfusion was associated with a trend toward better clinical outcomes and reduced mortality rate with alteplase. T ese results and the high cost of anistreplase have dampened the enthusiasm for its use.

UROKINASE

Urokinase is a two-chain serine protease derived from cultured fetal kidney cells with a molecular weight of 34,000. Urokinase converts plasminogen to plasmin

directly by cleaving the Arg560-Val561 bond. Unlike streptokinase, urokinase is not immunogenic and allergic reactions are rare. Urokinase produces a systemic lytic state because it does not discriminate between fibrin-bound and circulating plasminogen.

Despite many years of use, urokinase has never been systemically evaluated for coronary thrombolysis. Instead, urokinase is often employed for catheter-directed lysis of thrombi in the deep veins or the peripheral arteries. Because of production problems, the availability of urokinase is limited.

ALTEPLASE

A recombinant form of single-chain tPA, alteplase has a molecular weight of 68,000. Alteplase is rapidly converted into its two-chain form by plasmin. Although single- and two-chain forms of tPA have equivalent activity in the presence of fibrin, in its absence, single-chain tPA has tenfold lower activity.

Alteplase consists of five discrete domains **(Fig. 24-9)**; the N-terminus A chain of two-chain alteplase contains four of these domains. Residues 4 through 50 make up the finger domain, a region that resembles the finger domain of fibronectin; residues 50 through 87 are homologous with epidermal growth factor, whereas residues 92 through 173 and 180 through 261, which have homology to the kringle domains of plasminogen, are designated as the first and second kringle, respectively. T e fifth alteplase domain is the protease domain; it is located on the C-terminus B chain of two-chain alteplase.

T e interaction of alteplase with fibrin is mediated by the finger domain and, to a lesser extent, by the second kringle domain. T e af nity of alteplase for fibrin is considerably higher than that for fibrinogen. Consequently, the catalytic ef ciency of plasminogen activation by alteplase is two to three orders of magnitude higher in the presence of fibrin than in the presence of fibrinogen. T is phenomenon helps to localize plasmin generation to the fibrin surface.

Although alteplase preferentially activates plasminogen in the presence of fibrin, alteplase is not as fibrin-selective as was first predicted. Its fibrin specificity is limited because like fibrin, (DD)E, the major soluble degradation product of cross-linked fibrin, binds alteplase and plasminogen with high af nity. Consequently, (DD)E is as potent as fibrin as a stimulator of plasminogen activation by alteplase. Whereas plasmin generated on the fibrin surface results in thrombolysis, plasmin generated on the surface of circulating (DD)E degrades fibrinogen. Fibrinogen degradation results in the accumulation of fragment X, a high-molecular-weight clottable fibrinogen degradation product. Incorporation of fragment X into hemostatic plugs formed at sites of vascular injury renders them susceptible to lysis. T is phenomenon may contribute to alteplase-induced bleeding.

A trial comparing alteplase with streptokinase for treatment of patients with acute MI demonstrated significantly lower mortality with alteplase than with streptokinase, although the absolute difference was small. T e greatest benefit was seen in patients age <75 years with anterior MI who presented <6 h after symptom onset.

For treatment of acute MI or acute ischemic stroke, alteplase is given as an IV infusion over 60–90 min. T e total dose of alteplase usually ranges from 90 to 100 mg. Allergic reactions and hypotension are rare, and alteplase is not immunogenic.

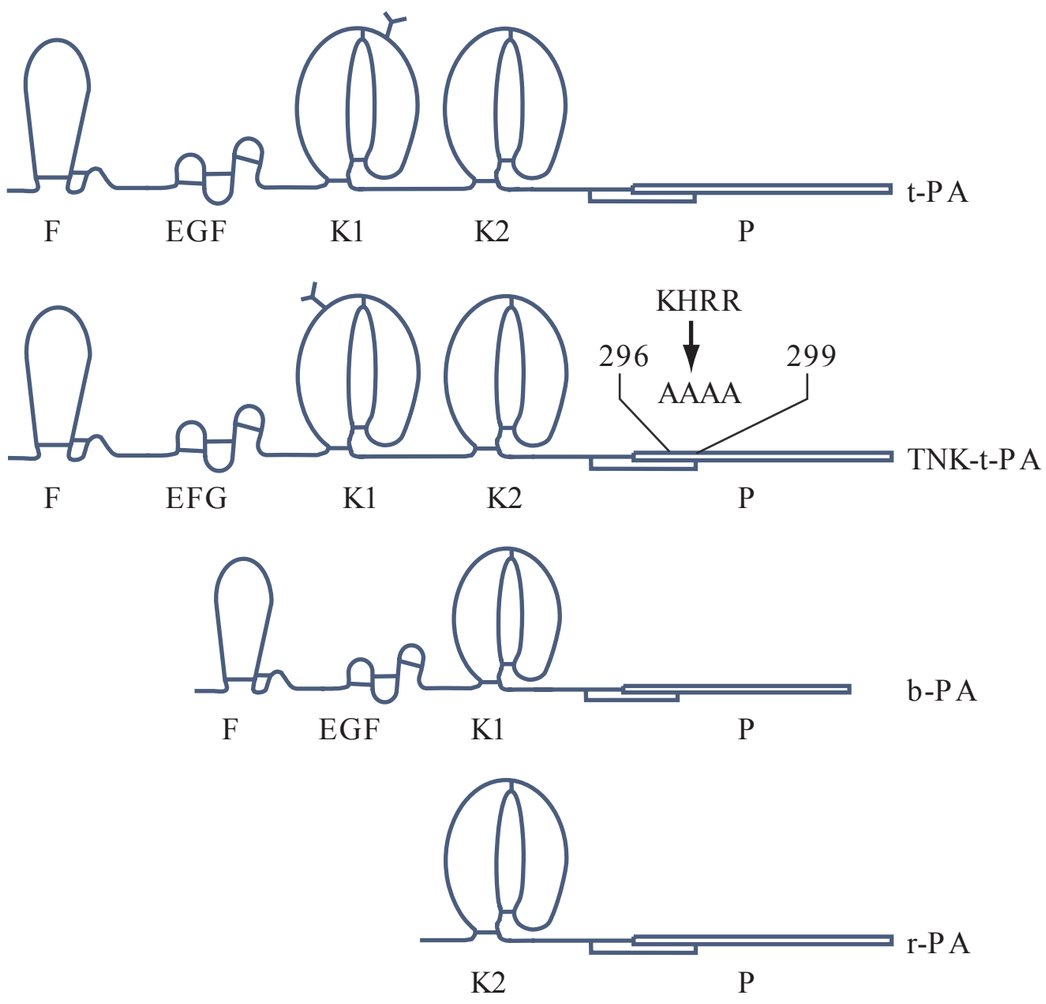

FIGURE 24-9

Domain structures of alteplase (tPA), tenecteplase (TNK-tPA), desmoteplase (b-PA), and reteplase (r-PA). The finger (F), epidermal growth factor (EGF), first and second kringles (K1 and K2, respectively), and protease (P) domains are illustrated. The glycosylation site (Y) on K1 has been repositioned in tenecteplase to endow it with a longer half-life. In addition, a tetra-alanine substitution in the protease domain renders tenecteplase resistant to type 1 plasminogen activator inhibitor (PAI-1) inhibition. Desmoteplase dif ers from alteplase and tenecteplase in that it lacks a K2 domain. Reteplase is a truncated variant that lacks the F, EGF, and K1 domains.

TENECTEPLASE

Tenecteplase is a genetically engineered variant of tPA and was designed to have a longer half-life than tPA and to be resistant to inactivation by PAI-1. To prolong its half-life, a new glycosylation site was added to the first kringle domain (Fig. 24-9). Because addition of this extra carbohydrate side chain reduced fibrin af nity, the existing glycosylation site on the first kringle domain was removed. To render the molecule resistant to inhibition

by PAI-1, a tetra-alanine substitution was introduced at residues 296–299 in the protease domain, the region responsible for the interaction of tPA with PAI-1.

Tenecteplase is more fibrin-specific than tPA. Although both agents bind to fibrin with similar af nity, the af nity of tenecteplase for (DD)E is significantly lower than that of tPA. Consequently, (DD)E does not stimulate systemic plasminogen activation by tenecteplase to the same extent as tPA. As a result, tenecteplase produces less fibrinogen degradation than tPA.

For coronary thrombolysis, tenecteplase is given as a single IV bolus. In a large phase III trial that enrolled >16,000 patients, the 30-day mortality rate with single-bolus tenecteplase was similar to that with accelerated-dose tPA. Although rates of intracranial hemorrhage were also similar with both treatments, patients given tenecteplase had fewer noncerebral bleeds and a reduced need for blood transfusions than those treated with tPA. T e improved safety profile of tenecteplase likely reflects its enhanced fibrin specificity.

RETEPLASE

Reteplase is a is a single-chain, recombinant tPA derivative that lacks the finger, epidermal growth factor, and first kringle domains (Fig. 24-9). T is truncated derivative has a molecular weight of 39,000. Reteplase binds fibrin more weakly than tPA because it lacks the finger domain. Because it is produced in Escherichia coli, reteplase is not glycosylated. T is endows it with a plasma half-life longer than that of tPA. Consequently, reteplase is given as two IV boluses, which are separated by 30 min. Clinical trials have demonstrated that reteplase is at least as effective as streptokinase for treatment of acute MI, but the agent is not superior to tPA.

NEWER FIBRINOLYTIC AGENTS

Two new drugs are under investigation. T ese include desmoteplase (Fig. 24-9), a recombinant form of the full-length plasminogen activator isolated from the saliva of the vampire bat, and alfimeprase, a truncated form of fibrolase, an enzyme isolated from the venom of the southern copperhead snake. Clinical studies with these agents have been disappointing. Desmoteplase, which is more fibrin-specific than tPA, was investigated for treatment of acute ischemic stroke. Patients presenting 3–9 h after symptom onset were randomized to one of two doses of desmoteplase or to placebo. Overall response rates were low and no different with desmoteplase than with placebo. T e mortality rate was higher in the desmoteplase arms.

Alfimeprase is a metalloproteinase that degrades fibrin and fibrinogen in a plasmin-independent fashion. In the circulation, alfimeprase is rapidly inhibited by α_2-macroglobulin. Consequently, the drug must be delivered via a catheter directly into the thrombus. Studies of alfimeprase for treatment of peripheral arterial occlusion or for restoration of flow in blocked central venous catheters were stopped due to lack of ef cacy. T e disappointing results with desmoteplase and alfimeprase highlight the challenges of introducing new fibrinolytic drugs.

CONCLUSIONS AND FUTURE DIRECTIONS

T rombosis involves a complex interplay among the vessel wall, platelets, the coagulation system, and the fibrinolytic pathways. Activation of coagulation also triggers inflammatory pathways that may exacerbate thrombosis. A better understanding of the biochemistry of blood coagulation and advances in structure-based drug design have identified new targets and resulted in the development of novel antithrombotic drugs. Well-designed clinical trials have provided detailed information on which drugs to use and when to use them. Despite these advances, however, thromboembolic disorders remain a major cause of morbidity and mortality. T erefore, the search for better targets and more potent antiplatelet, anticoagulant, and fibrinolytic drugs continues.

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SECTION VII

BIOLOGY OF CANCER

CHAPTER 25

CANCER GENETICS

Pat J. Morin ■ Jeffrey M. Trent ■ Francis S. Collins ■ Bert Vogelstein

CANCER IS A GENETIC DISEASE

Cancer arises through a series of somatic alterations in DNA that result in unrestrained cellular proliferation. Most of these alterations involve actual sequence changes in DNA (i.e., mutations). They may originate as a consequence of random replication errors, exposure to carcinogens (e.g., radiation), or faulty DNA repair processes. While most cancers arise sporadically, familial clustering of cancers occurs in certain families that carry a germline mutation in a cancer gene.

HISTORICAL PERSPECTIVE

The idea that cancer progression is driven by sequential somatic mutations in specific genes has only gained general acceptance in the past 25 years. Before the advent of the microscope, cancer was believed to be composed of aggregates of mucus or other noncellular matter. By the middle of the nineteenth century, it became clear that tumors were masses of cells and that these cells arose from the normal cells of the tissue from which the cancer originated. However, the molecular basis for the uncontrolled proliferation of cancer cells was to remain a mystery for another century. During that time, a number of theories for the origin of cancer were postulated. The great biochemist Otto Warburg proposed the combustion theory of cancer, which stipulated that cancer was due to abnormal oxygen metabolism. In addition, some believed that all cancers were caused by viruses, and that cancer was in fact a contagious disease.

In the end, observations of cancer occurring in chimney sweeps, studies of x-rays, and the overwhelming data demonstrating cigarette smoke as a causative agent in lung cancer, together with Ames's work on chemical mutagenesis, provided convincing evidence that cancer originated through changes in DNA. Although the viral theory of cancer did not prove to be generally accurate (with the exception of human papillomaviruses, which can cause cervical and other cancers in human), the study of retroviruses led to the discovery of the first human oncogenes in the late 1970s. Soon after, the study of families with genetic predisposition to cancer was instrumental in the discovery of tumor-suppressor genes. The field that studies the type of mutations, as well as the consequence of these mutations in tumor cells, is now known as cancer genetics.

THE CLONAL ORIGIN AND MULTISTEP NATURE OF CANCER

Nearly all cancers originate from a single cell; this clonal origin is a critical discriminating feature between neoplasia and hyperplasia. Multiple cumulative mutational events are invariably required for the progression of a tumor from normal to fully malignant phenotype. The process can be seen as Darwinian microevolution in which, at each successive step, the mutated cells gain a growth advantage resulting in an increased representation relative to their neighbors **(Fig. 25-1)**. Based on observations of cancer frequency increases during aging, as well as molecular genetics work, it is believed that 5 to 10 accumulated mutations are necessary for a cell to progress from the normal to the fully malignant phenotype.

We are beginning to understand the precise nature of the genetic alterations responsible for some malignancies and to get a sense of the order in which they occur. The best-studied example is colon cancer, in which analyses of DNA from tissues extending from normal colon epithelium through adenoma to carcinoma have identified some of the genes mutated in the process **(Fig. 25-2)**. Other malignancies are believed to progress in a similar stepwise fashion, although the order and identity of genes affected may be different.

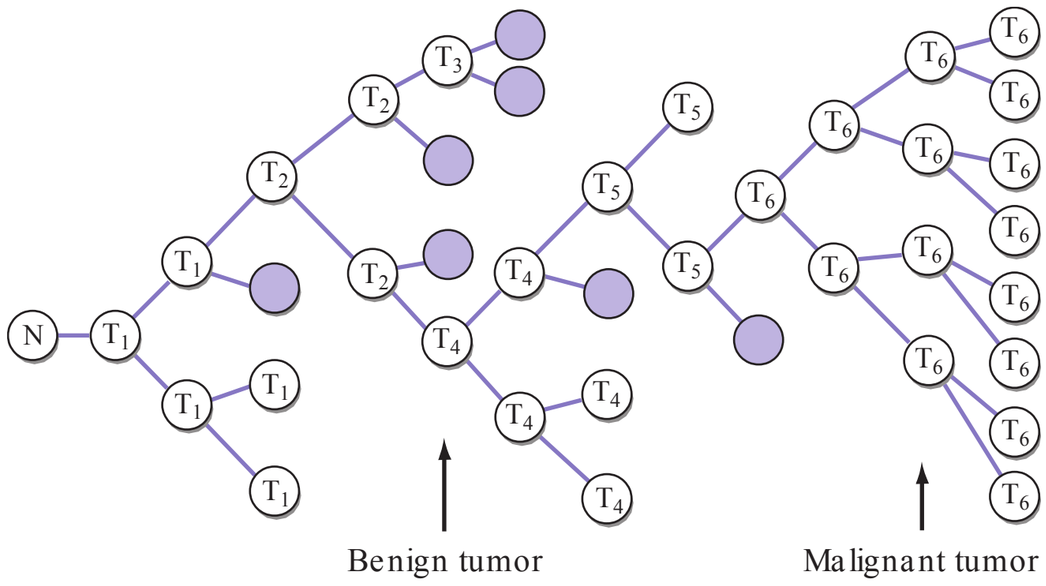

FIGURE 25-1

Multistep clonal development of malignancy. In this diagram a series of five cumulative mutations (T_1, T_2, T_4, T_5, T_6), each with a modest growth advantage acting alone, eventually results in a malignant tumor. Note that not all such alterations result in progression; for example, the T_3 clone is a dead end. The actual number of cumulative mutations necessary to transform from the normal to the malignant state is unknown in most tumors. (After P Nowell: Science 194:23, 1976, with permission.)

TWO TYPES OF CANCER GENES: ONCOGENES AND TUMOR-SUPPRESSOR GENES

T ere are two major types of cancer genes. T e first type comprises genes that positively influence tumor formation and are known as oncogenes. T e second type of cancer genes negatively impact tumor growth and have been named tumor-suppressor genes. Both oncogenes and tumor-suppressor genes exert their effects on tumor growth through their ability to control cell division (cell birth) or cell death (apoptosis), although the mechanisms can be extremely complex. While tightly regulated in normal cells, oncogenes acquire mutations in cancer cells, and the mutations typically relieve this control and lead to increased activity of the gene products. T is mutational event typically occurs in a single allele of the oncogene and acts in a dominant fashion. In contrast, the normal function of tumor-suppressor genes is usually to restrain cell growth, and this function is lost in cancer. Because of the diploid nature of mammalian cells, both alleles must be inactivated for a cell to completely lose the function of a tumor-suppressor gene, leading to a recessive mechanism at the cellular level. From these ideas and studies on the inherited form of retinoblastoma, Knudson and others formulated the two-hit hypothesis, which in its modern version states that both copies of a tumor-suppressor gene must be inactivated in cancer.

T ere is a subset of tumor-suppressor genes, the caretaker genes, that do not affect cell growth directly, but rather control the ability of the cell to maintain the integrity of its genome. Cells with a deficiency in these genes have an increased rate of mutations throughout their genomes, including in oncogenes and tumor-suppressor genes. T is "mutator" phenotype was first hypothesized by Loeb to explain how the multiple mutational events required for tumorigenesis can occur in the lifetime of an individual. A mutator phenotype has now been observed in some forms of cancer, such as those associated with deficiencies in DNA mismatch repair. T e great majority of cancers, however, do not harbor repair deficiencies, and their rate of mutation is similar to that observed in normal cells. Many of these cancers, however, appear to harbor a different kind of genetic instability, affecting the loss or gains of whole chromosomes or large parts thereof (as explained in more detail below).

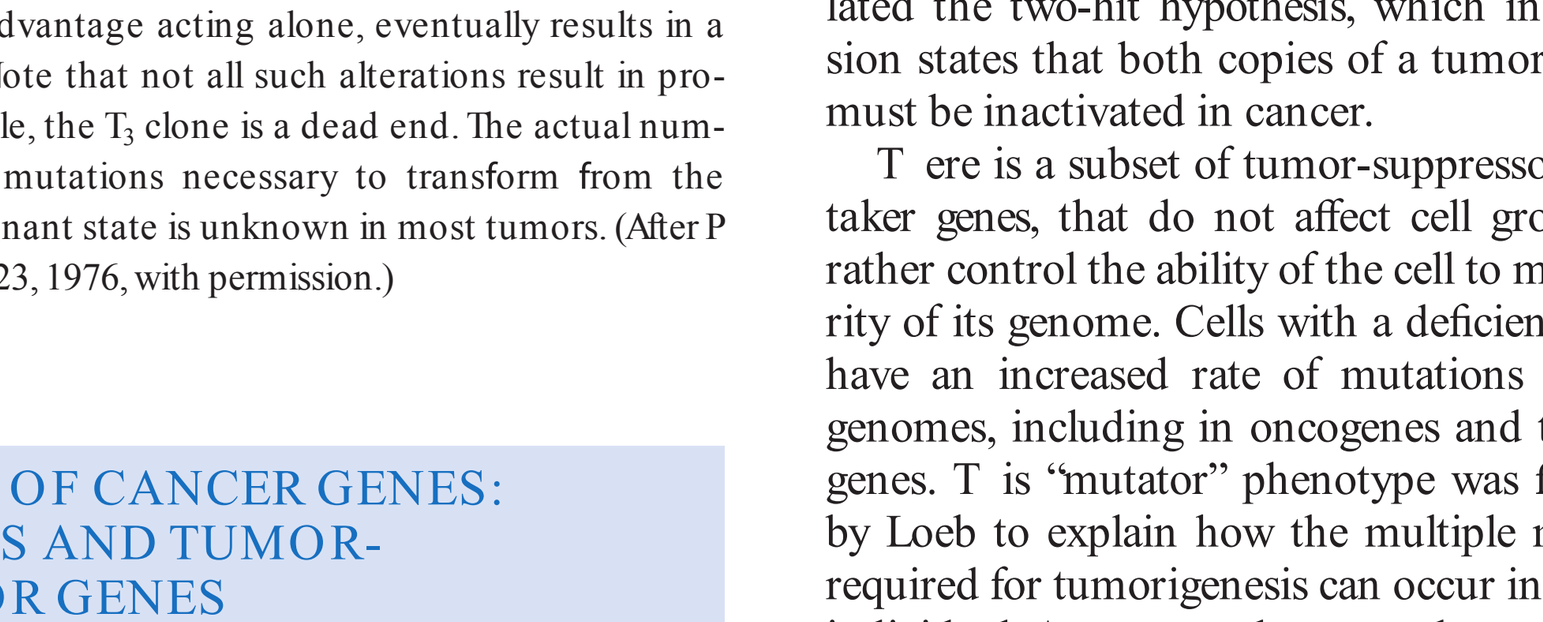

FIGURE 25-2

Progressive somatic mutational steps in the development of colon carcinoma. The accumulation of alterations in a number of different genes results in the progression from normal epithelium through adenoma to full-blown carcinoma. Genetic instability (microsatellite or chromosomal) accelerates the progression by increasing the likelihood of mutation at each step. Patients with familial polyposis are already one step into this pathway, because they inherit a germline alteration of the APC gene. TGF, transforming growth factor.

ONCOGENES IN HUMAN CANCER

Work by Peyton Rous in the early 1900s revealed that a chicken sarcoma could be transmitted from animal to animal in cell-free extracts, suggesting that cancer could be induced by an agent acting positively to promote tumor formation. T e agent responsible for the transmission of the cancer was a retrovirus (Rous sarcoma virus, RSV) and the oncogene responsible was identified 75 years later as v-src. Other oncogenes were also discovered through their presence in the genomes of retroviruses that are capable of causing cancers in chickens, mice, and rats. T e cellular homologues of these viral genes are called protooncogenes and are often targets of mutation or aberrant regulation in human cancer. Whereas many oncogenes were discovered because of their presence in retroviruses, other oncogenes, particularly those involved in translocations characteristic of particular leukemias and lymphomas, were isolated through genomic approaches. Investigators cloned the sequences surrounding the chromosomal translocations observed cytogenetically and then deduced the nature of the genes that were the targets of these translocations (see below). Some of these were oncogenes known from retroviruses (like ABL, involved in chronic myeloid leukemia [CML]), whereas others were new (like BCL2, involved in B cell lymphoma). In the normal cellular environment, protooncogenes have crucial roles in cell proliferation and differentiation. **Table 25-1** is a partial list of oncogenes known to be involved in human cancer.

T e normal growth and differentiation of cells is controlled by growth factors that bind to receptors on the surface of the cell. T e signals generated by the membrane receptors are transmitted inside the cells through signaling cascades involving kinases, G proteins, and other regulatory proteins. Ultimately, these signals affect the activity of transcription factors in the nucleus, which regulate the expression of genes crucial in cell proliferation, cell differentiation, and cell death. Oncogene products have been found to function at critical steps in these pathways (**Chap. 26**), and inappropriate activation of these pathways can lead to tumorigenesis.

MECHANISMS OF ONCOGENE ACTIVATION

POINT MUTATION

Point mutation is a common mechanism of oncogene activation. For example, mutations in one of the RAS genes (HRAS, KRAS, or NRAS) are present in up to 85% of pancreatic cancers and 45% of colon cancers but are less common in other cancer types, although they can occur at significant frequencies in leukemia, lung, and thyroid cancers. Remarkably—and in contrast to the diversity of mutations found in tumor-suppressor genes

TABLE 25-1

COMMON ONCOGENES ALTERED IN HUMAN CANCERS

ONCOGENE	FUNCTION	ALTERATION IN CANCER	NEOPLASM
AKT1	Serine/threonine kinase	Amplification	Stomach
AKT2	Serine/threonine kinase	Amplification	Ovarian, breast, pancreatic
BRAF	Serine/threonine kinase	Point mutation	Melanoma, lung, colorectal
CDK4	Cyclin-dependent kinase	Point mutation, amplification	Breast, melanoma, myeloma, others
CTNNB1	Signal transduction	Point mutation	Colon, prostate, melanoma, skin, others
FOS	Transcription factor	Overexpression	Osteosarcomas
ERBB2	Receptor tyrosine kinase	Point mutation, amplification	Breast, ovary, stomach, neuroblastoma
JUN	Transcription factor	Overexpression	Lung
MET	Receptor tyrosine kinase	Point mutation, rearrangement	Osteocarcinoma, kidney, glioma
MYB	Transcription factor	Amplification	AML, CML, colorectal, melanoma
C-MYC	Transcription factor	Amplification	Breast, colon, gastric, lung
L-MYC	Transcription factor	Amplification	Lung, bladder
N-MYC	Transcription factor	Amplification	Neuroblastoma, lung
PIK3A	Phosphoinositol-3-kinase	Point Mutation	Multiple cancers
HRAS	GTPase	Point mutation	Colon, lung, pancreas
KRAS	GTPase	Point mutation	Melanoma, colorectal, AML
NRAS	GTPase	Point mutation	Various carcinomas, melanoma
REL	Transcription factor	Rearrangement, amplification	Lymphomas
WNT1	Growth factor	Amplification	Retinoblastoma

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia.

(see below)—most of the activated RAS genes contain point mutations in codons 12, 13, or 61 (these mutations reduce RAS GTPase activity, leading to constitutive activation of the mutant RAS protein). T e restricted pattern of mutations observed in oncogenes compared to that of tumor-suppressor genes reflects the fact that gain-of-function mutations are less likely to occur than mutations that simply lead to loss of activity. Indeed, inactivation of a gene can in theory be accomplished through the introduction of a stop codon anywhere in the coding sequence, whereas activations require precise substitutions at residues that can somehow lead to an increase in the activity of the encoded protein. Importantly, the specificity of oncogene mutations provides diagnostic opportunities, as tests that identify mutations at defined positions are easier to design than tests aimed at detecting random changes in a gene.

DNA AMPLIFICATION

T e second mechanism for activation of oncogenes is DNA sequence amplification, leading to overexpression of the gene product. T is increase in DNA copy number may cause cytologically recognizable chromosome alterations referred to as homogeneous staining regions (HSRs) if integrated within chromosomes, or double minutes (dmins) if extrachromosomal. T e recognition of DNA amplification is accomplished through various cytogenetic techniques such as comparative genomic hybridization (CGH) or fluorescence in situ hybridization (FISH), which allow the visualization of chromosomal aberrations using fluorescent dyes. In addition, noncytogenetic, microarray-based approaches are now available for identifying changes in copy number at high resolution. Newer short-tag–based sequencing approaches have been used to evaluate amplifications. When paired with next-generation sequencing, this approach offers the highest degree of resolution and quantification available. With both microarray and sequencing technologies, the entire genome can be surveyed for gains and losses of DNA sequences, thus pinpointing chromosomal regions likely to contain genes important in the development or progression of cancer.

Numerous genes have been reported to be amplified in cancer. Several of these genes, including NMYC and LMYC, were identified through their presence within the amplified DNA sequences of a tumor and had homology to known oncogenes. Because the region amplified often includes hundreds of thousands of base pairs, multiple oncogenes may be amplified in a single amplicon in some cancers (particularly in sarcomas). Indeed, MDM2, GLI, CDK4, and SAS at chromosomal location 12q13-15 have been shown to be simultaneously amplified in several types of sarcomas and other tumors. Amplification of a cellular gene is often a predictor of poor prognosis; for example, ERBB2/HER2 and NMYC are often amplified in aggressive breast cancers and neuroblastoma, respectively.

CHROMOSOMAL REARRANGEMENT

Chromosomal alterations provide important clues to the genetic changes in cancer. T e chromosomal alterations in human solid tumors such as carcinomas are heterogeneous and complex and occur as a result of the frequent chromosomal instability (CIN) observed in these tumors (see below). In contrast, the chromosome alterations in myeloid and lymphoid tumors are often simple translocations, i.e., reciprocal transfers of chromosome arms from one chromosome to another. Consequently, many detailed and informative chromosome analyses have been performed on hematopoietic cancers. T e breakpoints of recurring chromosome abnormalities usually occur at the site of cellular oncogenes. **Table 25-2** lists representative examples of recurring chromosome alterations in malignancy and the associated gene(s) rearranged or deregulated by the chromosomal rearrangement. Translocations are particularly common in lymphoid tumors, probably because these cell types have the capability to rearrange their DNA to generate antigen receptors. Indeed, antigen receptor genes are commonly involved in the translocations, implying that an imperfect regulation of receptor gene rearrangement may be involved in the pathogenesis. An interesting example is Burkitt's lymphoma, a B cell tumor characterized by a reciprocal translocation between chromosomes 8 and 14. Molecular analysis of Burkitt's lymphomas demonstrated that the breakpoints occurred within or near the MYC locus on chromosome 8 and within the immunoglobulin heavy chain locus on chromosome 14, resulting in the transcriptional activation of MYC. Enhancer activation by translocation, although not universal, appears to play an important role in malignant progression. In addition to transcription factors and signal transduction molecules, translocation may result in the overexpression of cell cycle regulatory proteins or proteins such as cyclins and of proteins that regulate cell death.

T e first reproducible chromosome abnormality detected in human malignancy was the Philadelphia chromosome detected in CML. T is cytogenetic abnormality is generated by reciprocal translocation involving the ABL oncogene on chromosome 9, encoding a tyrosine kinase, being placed in proximity to the BCR (breakpoint cluster region) gene on chromosome 22. **Figure 25-3** illustrates the generation of the translocation and its protein product. T e consequence of expression of the BCR-ABL gene product is the activation of signal transduction pathways leading to cell growth independent of normal external signals. Imatinib (marketed as Gleevec), a drug that

TABLE 25-2

REPRESENTATIVE ONCOGENES AT CHROMOSOMAL TRANSLOCATIONS

GENE (CHROMOSOME)	TRANSLOCATION	MALIGNANCY
ABL (9q34.1)–BCR (22q11)	(9;22)(q34;q11)	Chronic myeloid leukemia
ATF1 (12q13)–EWS (22q12)	(12;22)(q13;q12)	Malignant melanoma of soft parts
BCL1 (11q13.3)–IgH (14q32)	(11;14)(q13;q32)	Mantle cell lymphoma
BCL2 (18q21.3)–IgH (14q32)	(14;18)(q32;q21)	Follicular lymphoma
FLI1 (11q24)–EWS (22q12)	(11;22)(q24;q12)	Ewing's sarcoma
LCK (1p34)–TCRB (7q35)	(1;7)(p34;q35)	T cell acute lymphocytic leukemia
MYC (8q24)–IgH (14q32)	(8;14)(q24;q32)	Burkitt's lymphoma, B cell acute lymphocytic leukemia
PAX3 (2q35)–FKHR/ALV (13q14)	(2;13)(q35;q14)	Alveolar rhabdomyosarcoma
PAX7 (1p36)–KHR/ALV (13q14)	(1;13)(p36;q14)	Alveolar rhabdomyosarcoma
REL (2p13)–NRG (2p11.2-14)	Inv(2(p13;p11.2-14)	Non-Hodgkin's lymphoma
RET (10q11.2)–PKAR1A (17q23)	(10;17)(q11.2;q23)	Thyroid carcinoma
TAL1 (1p32)–TCTA (3p21)	(1;3)(p34;p21)	Acute T cell leukemia
TRK (1q23-1q24)–TPM3 (1q31)	Inv1(q23;q31)	Colon carcinoma
WT1 (11p13)–EWS (22q12)	(11;22)(p13;q12)	Desmoplastic small round cell tumor

Source: From R Hesketh: The Oncogene and Tumour Suppressor Gene Facts Book, 2nd ed. San Diego, Academic Press, 1997; with permission.

specifically blocks the activity of Abl tyrosine kinase, has shown remarkable efficacy with little toxicity in patients with CML. It is hoped that knowledge of genetic alterations in other cancers will likewise lead to mechanism-based design and development of a new generation of chemotherapeutic agents.

CHROMOSOMAL INSTABILITY IN SOLID TUMORS

Solid tumors are generally highly aneuploid, containing an abnormal number of chromosomes; these chromosomes also exhibit structural alterations such as

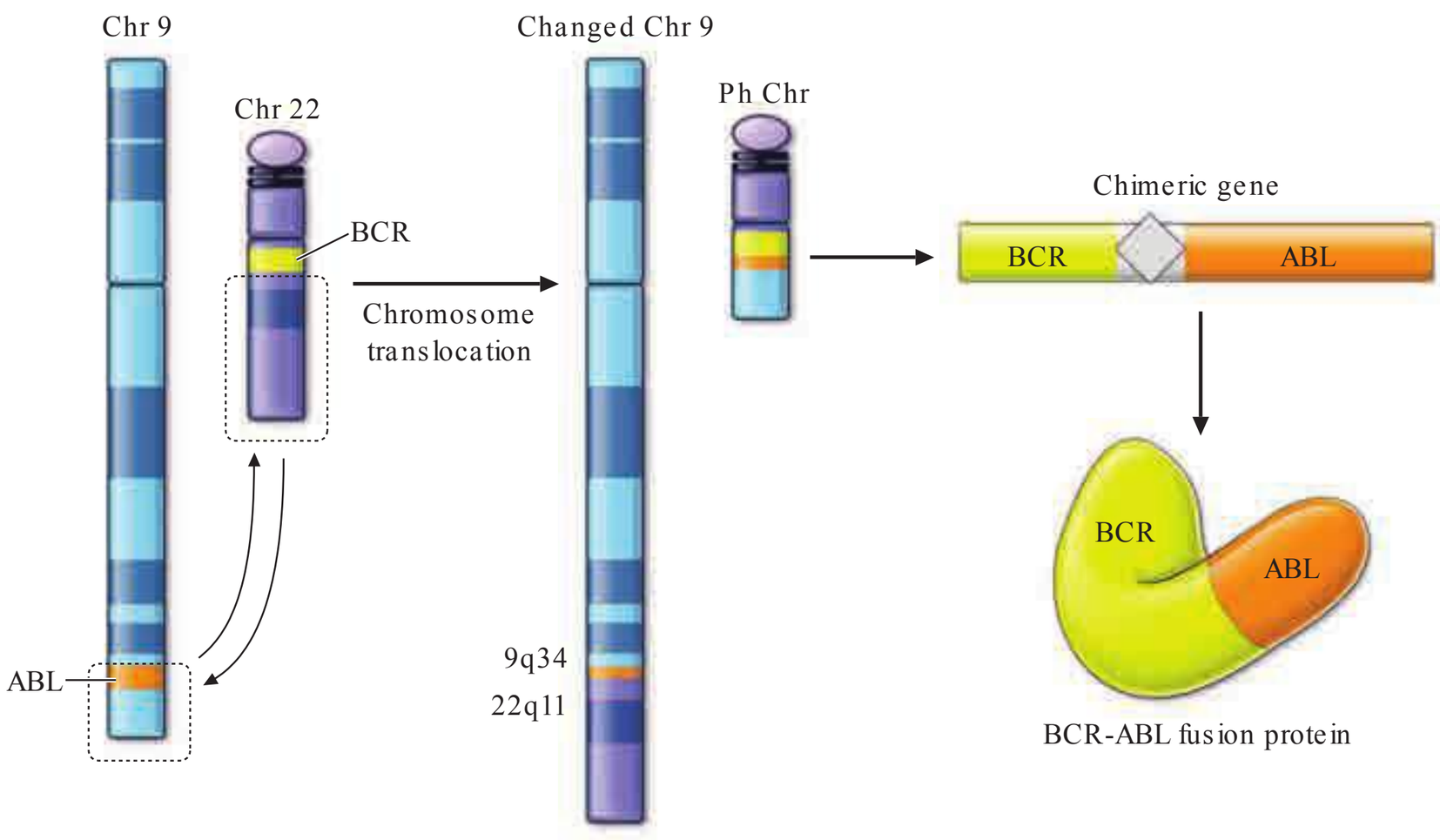

FIGURE 25-3

Specific translocation seen in chronic myeloid leukemia (CML). The Philadelphia chromosome (Ph) is derived from a reciprocal translocation between chromosomes 9 and 22 with the breakpoint joining the sequences of the ABL oncogene with the BCR gene. The fusion of these DNA sequences allows the generation of an entirely novel fusion protein with modified function.

translocations, deletions, and amplifications. T ese abnormalities are collectively referred to as chromosomal instability (CIN). Normal cells possess several cell cycle checkpoints, essentially quality-control requirements that have to be met before subsequent events are allowed to take place. T e mitotic checkpoint, which ensures proper chromosome attachment to the mitotic spindle before allowing the sister chromatids to separate, is altered in certain cancers. T e molecular basis of CIN remains unclear, although a number of mitotic checkpoint genes are found mutated or abnormally expressed in various tumors. T e exact effects of these changes on the mitotic checkpoint are unknown, and both weakening and overactivation of the checkpoint have been proposed. T e identification of the cause of CIN in tumors will likely be a formidable task, considering that several hundred genes are thought to control the mitotic checkpoint and other cellular processes ensuring proper chromosome segregation. Regardless of the mechanisms underlying CIN, the measurement of the number of chromosomal alterations present in tumors is now possible with both cytogenetic and molecular techniques, and several studies have shown that this information can be useful for prognostic purposes. In addition, because the mitotic checkpoint is essential for cellular viability, it may become a target for novel therapeutic approaches.

TUMOR-SUPPRESSOR GENE INACTIVATION IN CANCER

T e first indication of the existence of tumor-suppressor genes came from experiments showing that fusion of mouse cancer cells with normal mouse fibroblasts led to a nonmalignant phenotype in the fused cells. T e normal role of tumor-suppressor genes is to restrain cell growth, and the function of these genes is inactivated in cancer. T e two major types of somatic lesions observed in tumor-suppressor genes during tumor development are point mutations and large deletions. Point mutations in the coding region of tumor-suppressor genes will frequently lead to truncated protein products or otherwise nonfunctional proteins. Similarly, deletions lead to the loss of a functional product and sometimes encompass the entire gene or even the entire chromosome arm, leading to loss of heterozygosity (LOH) in the tumor DNA compared to the corresponding normal tissue DNA **(Fig. 25-4)**. LOH in tumor DNA is considered a hallmark for the presence of a tumor-suppressor gene at a particular chromosomal location, and LOH studies have been useful in the positional cloning of many tumor-suppressor genes.

Gene silencing, an epigenetic change that leads to the loss of gene expression and occurs in conjunction with hypermethylation of the promoter and histone deacetylation, is another mechanism of tumor-suppressor gene inactivation. (An epigenetic modif cation refers to a change in the genome, heritable by cell progeny, that does not involve a change in the DNA sequence. T e inactivation of the second X chromosome in female cells is an example of an epigenetic silencing that prevents gene expression from the inactivated chromosome.) During embryologic development, regions of chromosomes from one parent are silenced and gene expression proceeds from the chromosome of the other parent. For most genes, expression occurs from both alleles or randomly from one allele or the other. T e preferential expression of a particular gene exclusively from the allele contributed by one parent is called parental imprinting and is thought to be regulated by covalent modifications of chromatin protein and DNA (often methylation) of the silenced allele.

T e role of epigenetic control mechanisms in the development of human cancer is unclear. However, a general decrease in the level of DNA methylation has been noted as a common change in cancer. In addition, numerous genes, including some tumor-suppressor genes, appear to become hypermethylated and silenced during tumorigenesis. VHL and p16INK4 are well-studied examples of such tumor-suppressor genes. Overall, epigenetic mechanisms may be responsible for reprogramming the expression of a large number of genes in cancer and, together with the mutation of specific genes, are likely to be crucial in the development of human malignancies. T e use of drugs that can reverse epigenetic changes in cancer cells may represent a novel therapeutic option in certain cancers or premalignant conditions. For example, demethylating agents (azacitidine or decitabine) are now approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with high-risk myelodysplastic syndrome (MDS).

FAMILIAL CANCER SYNDROMES

A small fraction of cancers occur in patients with a genetic predisposition. In these families, the affected individuals have a predisposing loss-of-function mutation in one allele of a tumor-suppressor gene. T e tumors in these patients show a loss of the remaining normal allele as a result of somatic events (point mutations or deletions), in agreement with the two-hit hypothesis (Fig. 25-4). T us, most cells of an individual with an inherited loss-of-function mutation in a tumor-suppressor gene are functionally normal, and only the rare cells that develop a mutation in the remaining normal allele will exhibit uncontrolled regulation.

Roughly 100 syndromes of familial cancer have been reported, although many are rare. T e majority are

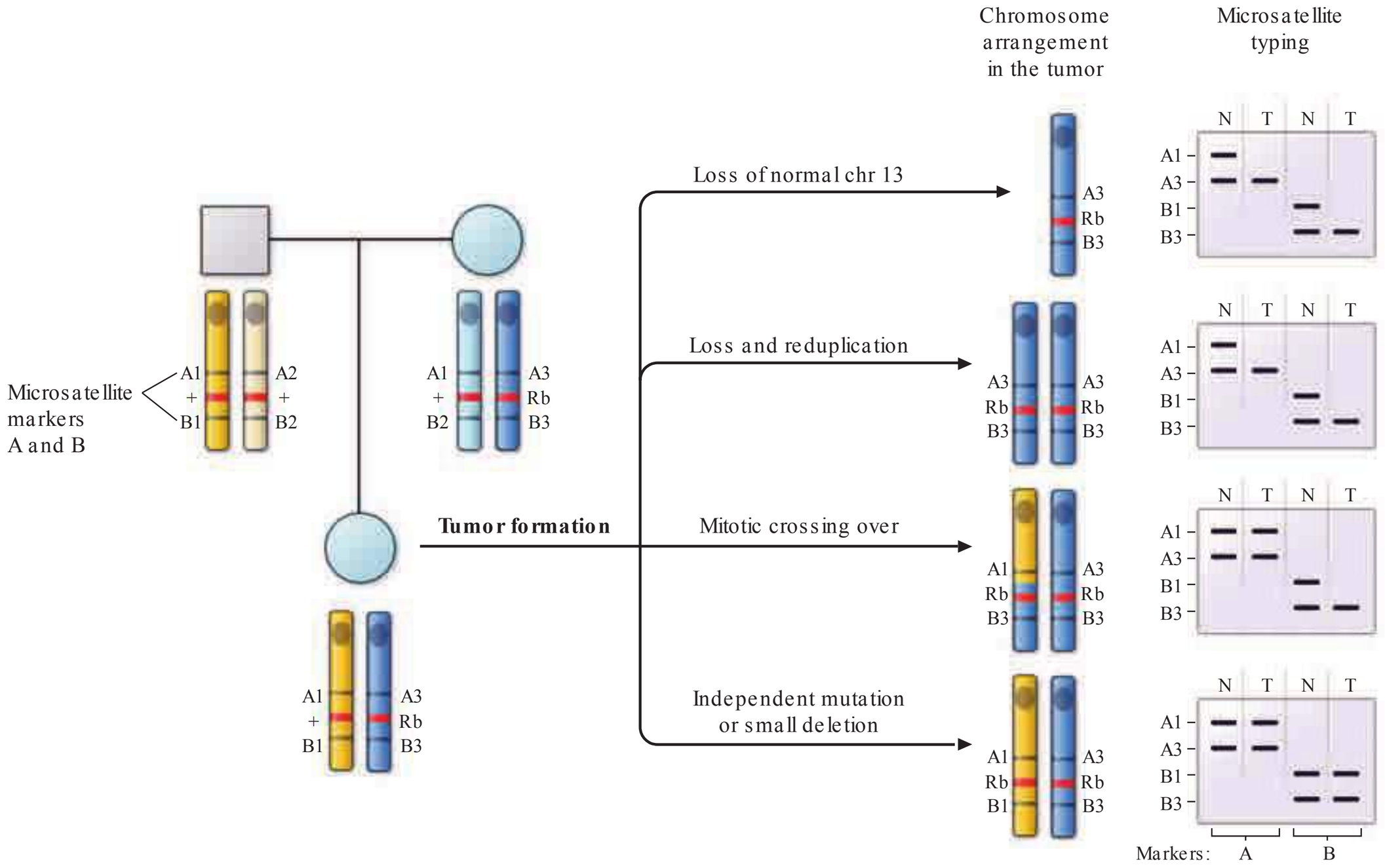

FIGURE 25-4

Diagram of possible mechanisms for tumor formation in an individual with hereditary (familial) retinoblastoma. On the left is shown the pedigree of an affected individual who has inherited the abnormal (Rb) allele from her affected mother. The normal allele is shown as a (+). The four chromosomes of her two parents are drawn to indicate their origin. Flanking the retinoblastoma locus are microsatellite markers (A and B) also analyzed in this family. Markers A3 and B3 are on the chromosome carrying the retinoblastoma disease gene. Tumor formation results when the normal allele, which this patient inherited from her father, is inactivated. On the right are shown four possible ways in which this could occur. In each case, the resulting chromosome 13 arrangement is shown, as well as the results of PCR typing using the microsatellite markers comparing normal tissue (N) with tumor tissue (T). Note that in the first three situations, the normal allele (B1) has been lost in the tumor tissue, which is referred to as loss of heterozygosity (LOH) at this locus.

inherited as autosomal dominant traits, although some of those associated with DNA repair abnormalities (xeroderma pigmentosum, Fanconi's anemia, ataxia telangiectasia) are autosomal recessive. **Table 25-3** shows a number of cancer predisposition syndromes and the responsible genes. The current paradigm states that the genes mutated in familial syndromes can also be targets for somatic mutations in sporadic (noninherited) tumors. The study of cancer syndromes has thus provided invaluable insights into the mechanisms of progression for many tumor types. This section examines the case of inherited colon cancer in detail, but similar lessons can be applied to many of the cancer syndromes listed in Table 25-3. In particular, the study of inherited colon cancer will clearly illustrate the difference between two types of tumor-suppressor genes: the gatekeepers, which directly regulate the growth of tumors, and the caretakers, which, when mutated, lead to genetic instability and therefore act indirectly on tumor growth.

Familial adenomatous polyposis (FAP) is a dominantly inherited colon cancer syndrome due to germline mutations in the adenomatous polyposis coli (APC) tumor-suppressor gene on chromosome 5. Patients with this syndrome develop hundreds to thousands of adenomas in the colon. Each of these adenomas has lost the normal remaining allele of APC but has not yet accumulated the required additional mutations to generate fully malignant cells (Fig. 25-2). The loss of the second functional APC allele in tumors from FAP families often occurs through loss of heterozygosity. However, out of these thousands of benign adenomas, several will invariably acquire further abnormalities and a subset will even develop into fully malignant cancers. APC is thus considered to be a gatekeeper for colon tumorigenesis: in the absence of mutation of this gatekeeper (or a gene acting within the same pathway), a colorectal tumor simply cannot form. **Figure 25-5** shows germline and somatic mutations found in the

TABLE 25-3

CANCER PREDISPOSITION SYNDROMES AND ASSOCIATED GENES

SYNDROME	GENE	CHROMOSOME	INHERITANCE	TUMORS
Ataxia telangiectasia	ATM	11q22-q23	AR	Breast
Autoimmune lymphoproliferative syndrome	FAS FASL	10q24 1q23	AD	Lymphomas
Bloom syndrome	BLM	15q26.1	AR	Several types
Cowden syndrome	PTEN	10q23	AD	Breast, thyroid
Familial adenomatous polyposis	APC	5q21	AD	Intestinal adenoma, colorectal
Familial melanoma	p16INK4	9p21	AD	Melanoma, pancreatic
Familial Wilms' tumor	WT1	11p13	AD	Kidney (pediatric)
Hereditary breast/ovarian cancer	BRCA1 BRCA2	17q21 13q12.3	AD	Breast, ovarian, colon, prostate
Hereditary diffuse gastric cancer	CDH1	16q22	AD	Stomach
Hereditary multiple exostoses	EXT1 EXT2	8q24 11p11-12	AD	Exostoses, chondrosarcoma
Hereditary prostate cancer	HPC1	1q24-25	AD	Prostate
Hereditary retinoblastoma	RB1	13q14.2	AD	Retinoblastoma, osteosarcoma
Hereditary nonpolyposis colon cancer (HNPCC)	MSH2 MLH1 MSH6 PMS2	2p16 3p21.3 2p16 7p22	AD	Colon, endometrial, ovarian, stomach, small bowel, ureter carcinoma
Hereditary papillary renal carcinoma	MET	7q31	AD	Papillary kidney
Juvenile polyposis	SMAD4	18q21	AD	Gastrointestinal, pancreatic
Li-Fraumeni	TP53	17p13.1	AD	Sarcoma, breast
Multiple endocrine neoplasia type 1	MEN1	11q13	AD	Parathyroid, endocrine, pancreas, and pituitary
Multiple endocrine neoplasia type 2a	RET	10q11.2	AD	Medullary thyroid carcinoma, pheochromocytoma
Neurofibromatosis type 1	NF1	17q11.2	AD	Neurofibroma, neurofibrosarcoma, brain
Neurofibromatosis type 2	NF2	22q12.2	AD	Vestibular schwannoma, meningioma, spine
Nevoid basal cell carcinoma syndrome (Gorlin's syndrome)	PTCH	9q22.3	AD	Basal cell carcinoma, medulloblastoma, jaw cysts
Tuberous sclerosis	TSC1 TSC2	9q34 16p13.3	AD	Angiofibroma, renal angiomyolipoma
von Hippel–Lindau	VHL	3p25-26	AD	Kidney, cerebellum, pheochromocytoma

Abbreviations: AD, autosomal dominant; AR, autosomal recessive

APC gene. The function of the APC protein is still not completely understood, but it likely provides differentiation and apoptotic cues to colonic cells as they migrate up the crypts. Defects in this process may lead to abnormal accumulation of cells that should normally undergo apoptosis.

In contrast to patients with FAP, patients with hereditary nonpolyposis colon cancer (HNPCC, or Lynch's syndrome) do not develop multiple polyposis, but instead develop only one or a small number of adenomas that rapidly progress to cancer. Most HNPCC cases are due to mutations in one of four DNA mismatch repair genes (Table 25-3), which are components of a repair system that is normally responsible for correcting errors in freshly replicated DNA. Germline mutations in MSH2 and MLH1 account for more than 90% of HNPCC cases, whereas mutations in MSH6 and PMS2 are much less frequent. When a somatic mutation inactivates the remaining wild-type allele of a mismatch repair gene, the cell develops a hypermutable phenotype characterized by profound genomic instability, especially for the short repeated sequences called

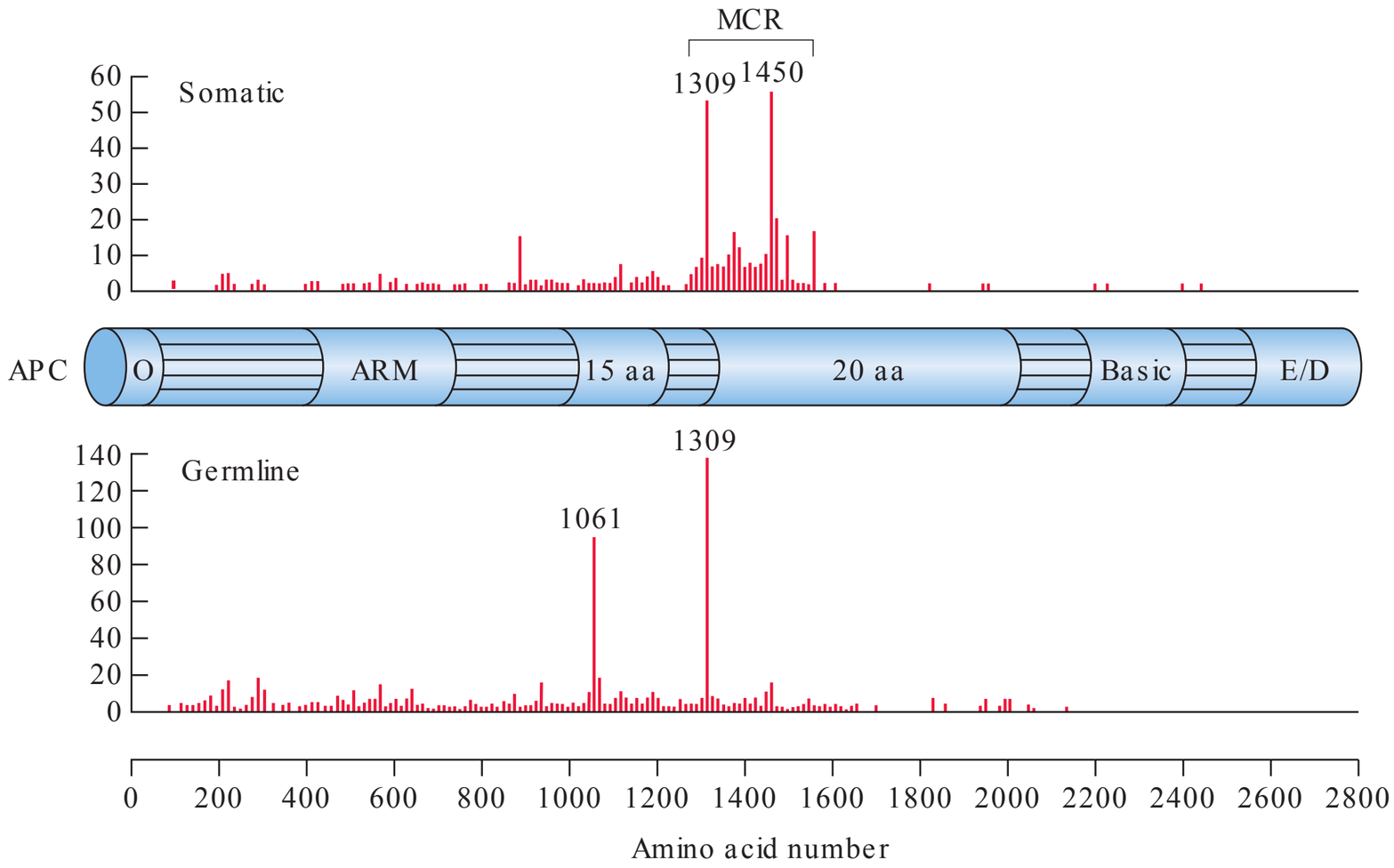

FIGURE 25-5

Germline and somatic mutations in the tumor-suppressor gene APC. APC encodes a 2843-amino-acid protein with six major domains: an oligomerization region (O), armadillo repeats (ARM), 15-amino-acid repeats (15 aa), 20-amino-acid repeats (20 aa), a basic region, and a domain involved in binding EB1 and the Drosophila discs large homologue (E/D). Shown are the positions within the APC gene of a total of 650 somatic and 826 germline mutations (from the APC database at http://www.umd.be/APC/). The vast majority of these mutations result in the truncation of the APC protein. Germline mutations are found to be relatively evenly distributed up to codon 1600 except for two mutation hotspots at amino acids 1061 and 1309, which together account for one-third of the mutations found in familial adenomatous polyposis (FAP) families. Somatic APC mutations in colon tumors cluster in an area of the gene known as the mutation cluster region (MCR). The location of the MCR suggests that the 20-amino-acid domain plays a crucial role in tumor suppression.

microsatellites. T is microsatellite instability (MSI) favors the development of cancer by increasing the rate of mutations in many genes, including oncogenes and tumor-suppressor genes (Fig. 25-2). T ese genes can thus be considered caretakers. Interestingly, CIN can also be found in colon cancer, but MSI and CIN appear to be mutually exclusive, suggesting that they represent alternative mechanisms for the generation of a mutator phenotype in this cancer (Fig. 25-2). Other cancer types rarely exhibit MSI, but most exhibit CIN.

Although most autosomal dominant inherited cancer syndromes are due to mutations in tumor-suppressor genes (Table 25-3), there are a few interesting exceptions. Multiple endocrine neoplasia type 2, a dominant disorder characterized by pituitary adenomas, medullary carcinoma of the thyroid, and (in some pedigrees) pheochromocytoma, is due to gain-of-function mutations in the protooncogene RET on chromosome 10. Similarly, gain-of-function mutations in the tyrosine kinase domain of the MET oncogene lead to hereditary papillary renal carcinoma. Interestingly, loss-of-function mutations in the RET gene cause a completely different disease, Hirschsprung's disease (aganglionic megacolon **[Chap. 52]**).

Although the Mendelian forms of cancer have taught us much about the mechanisms of growth control, most forms of cancer do not follow simple patterns of inheritance. In many instances (e.g., lung cancer), a strong environmental contribution is at work. Even in such circumstances, however, some individuals may be more genetically susceptible to developing cancer, given the appropriate exposure, due to the presence of modifier alleles.

GENETIC TESTING FOR FAMILIAL CANCER

T e discovery of cancer susceptibility genes raises the possibility of DNA testing to predict the risk of cancer in individuals of affected families. An algorithm for cancer risk assessment and decision making in high-risk families using genetic testing is shown in **Fig. 25-6**. Once a mutation is discovered in a family, subsequent testing of asymptomatic family members can be crucial in patient management. A negative gene test in these individuals can prevent years of anxiety in the knowledge that their cancer risk is no higher than

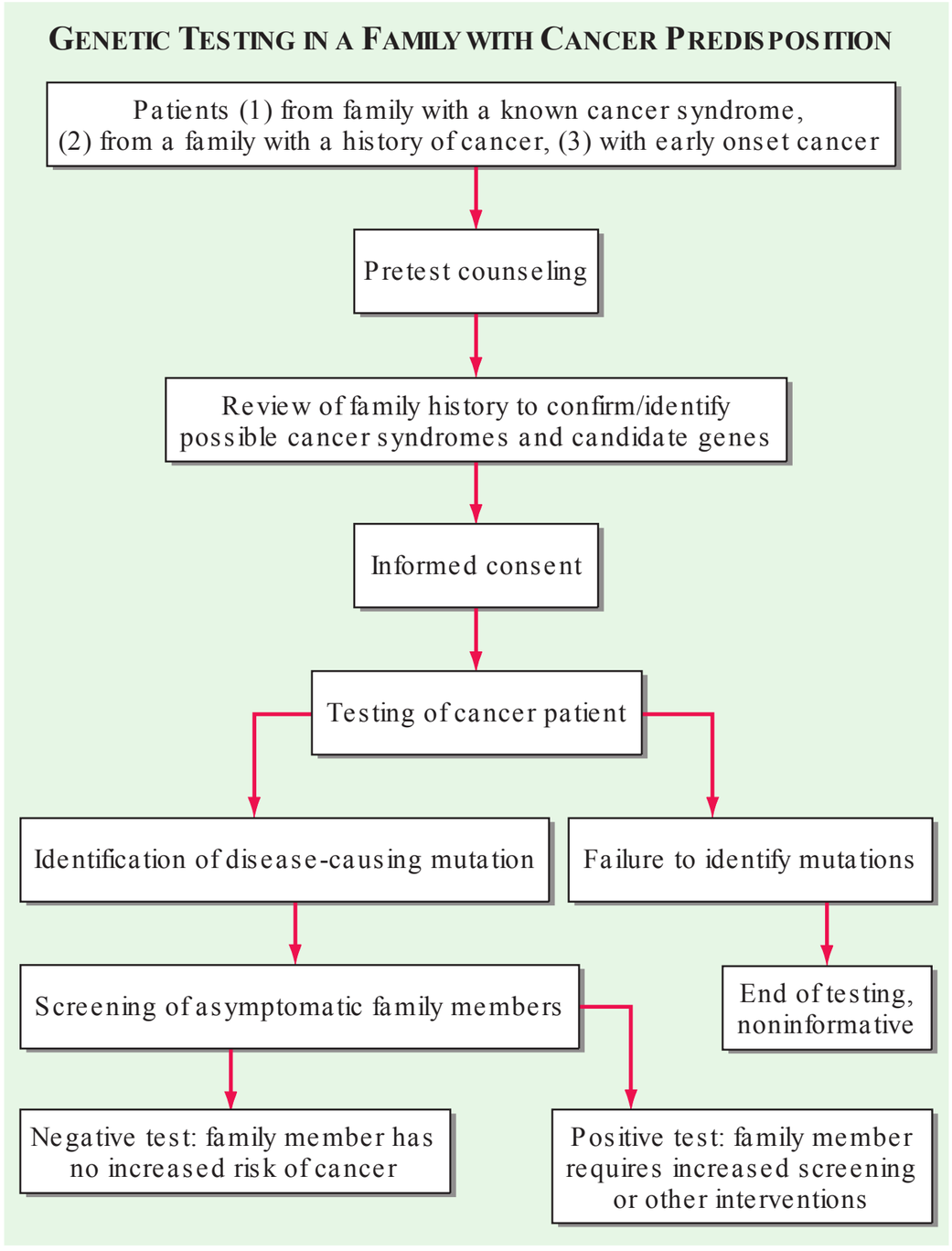

FIGURE 25-6

Algorithm for genetic testing in a family with cancer predisposition. The key step is the identification of a mutation in a cancer patient, which allows testing of asymptomatic family members. Asymptomatic family members who test positive may require increased screening or surgery, whereas others are at no greater risk for cancer than the general population.

that of the general population. On the other hand, a positive test may lead to alteration of clinical management, such as increased frequency of cancer screening and, when feasible and appropriate, prophylactic surgery. Potential negative consequences of a positive test result include psychological distress (anxiety, depression) and discrimination, although the Genetic Information Nondiscrimination Act (GINA) makes it illegal for predictive genetic information to be used to discriminate in health insurance or employment. Testing should therefore not be conducted without counseling before and after disclosure of the test result. In addition, the decision to test should depend on whether effective interventions exist for the particular type of cancer to be tested. Despite these caveats, genetic cancer testing for some cancer syndromes already appears to have greater benefits than risks. Companies offer genetic testing for many of the cancer syndromes listed in Table 25-3, including FAP (APC gene), hereditary breast and ovarian cancer syndrome (BRCA1 and BRCA2 genes), Lynch's syndrome (mismatch repair genes), Li-Fraumeni syndrome (TP53 gene), Cowden syndrome (PTEN gene), hereditary retinoblastoma (RB1 gene), and others.

Because of the inherent problems of genetic testing such as cost, specificity, and sensitivity, it is not yet appropriate to offer these tests to the general population. However, testing may be appropriate in some subpopulations with a known increased risk, even without a defined family history. For example, two mutations in the breast cancer susceptibility gene BRCA1, 185delAG and 5382insC, exhibit a suf ciently high frequency in the Ashkenazi Jewish population that genetic testing of an individual of this ethnic group may be warranted.

As noted above, it is important that genetic test results be communicated to families by trained genetic counselors, especially for high-risk high-penetrance conditions such as the hereditary breast and ovarian cancer syndrome (BRCA1/BRCA2). To ensure that the families clearly understand its advantages and disadvantages and the impact it may have on disease management and psyche, genetic testing should never be done before counseling. Significant expertise is needed to communicate the results of genetic testing to families. For example, one common mistake is to misinterpret the result of negative genetic tests. For many cancer predisposition genes, the sensitivity of genetic testing is less than 70% (i.e., of 100 kindreds tested, disease-causing mutations can be identified in 70 at most). T erefore, such testing should in general begin with an affected member of the kindred (the youngest family member still alive who has had the cancer of interest). If a mutation is not identified in this individual, then the test should be reported as noninformative (Fig. 25-6) rather than negative (because it is possible that, for technical reasons, the mutation in this individual is not detectable by standard genetic assays). On the other hand, if a mutation can be identified in this individual, then testing of other family members can be performed, and the sensitivity of such subsequent tests will be 100% (because the mutation in the family is in this case known to be detectable by the method used).

MICRORNAS AND CANCER

MicroRNAs (miRNAs) are small noncoding RNAs 20–22 nucleotides in length that are involved in post-transcriptional gene regulation. Studies in chronic lymphocytic leukemia first suggested a link between miRNAs and cancer when miR-15 and miR-16 were found to be deleted or downregulated in the vast majority of tumors. Various miRNAs have since been found

abnormally expressed in several human malignancies. Aberrant expression of miRNAs in cancer has been attributed to several mechanisms, such as chromosomal rearrangements, genomic copy number change, epigenetic modifications, defects in miRNA biogenesis pathway, and regulation by transcriptional factors. Somatic mutations of miRNAs have been identified in many cancers, but the exact functional consequences of these changes on cancer development remain to be determined. T e SomaMir database (http://compbio.uthsc.edu/SomamiR) catalogs somatic and germline miRNA mutations that have been identified in cancer.

Functionally, miRNAs have been suggested to contribute to tumorigenesis through their ability to regulate oncogenic signaling pathways. For example, miR-15 and miR-16 have been shown to target the BCL2 oncogene, leading to its downregulation in leukemic cells and apoptosis. As another example of miRNAs' involvement in oncogenic pathways, the p53 tumor suppressor can transcriptionally induce miR-34 following genotoxic stress, and this induction is important in mediating p53 function. T e expression of miRNAs is extremely specific, and there is evidence that miRNA expression patterns may be useful in distinguishing lineage and differentiation state, as well as cancer diagnosis and outcome prediction.

VIRUSES IN HUMAN CANCER

Certain human malignancies are associated with viruses. Examples include Burkitt's lymphoma (Epstein-Barr virus), hepatocellular carcinoma (hepatitis viruses), cervical cancer (human papillomavirus [HPV]), and T cell leukemia (retroviruses). T e mechanisms of action of these viruses are varied but always involve activation of growth-promoting pathways or inhibition of tumor-suppressor products in the infected cells. For example, HPV proteins E6 and E7 bind and inactivate cellular tumor suppressors p53 and pRB, respectively. T ere are several HPV types, and some of these types have been associated with the development of several malignancies, including cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancer. Viruses are not suf cient for cancer development, but constitute one alteration in the multistep process of cancer progression.

GENE EXPRESSION IN CANCER

The tumorigenesis process, driven by alterations in tumor suppressors, oncogenes, and epigenetic regulation, is accompanied by changes in gene expression. The advent of powerful techniques for high-throughput gene expression profiling, based on sequencing or microarrays, has allowed the comprehensive study of gene expression in neoplastic cells. It is indeed possible to identify the expression levels of thousands of genes expressed in normal and cancer tissues. **Figure 25-7** shows a typical microarray experiment examining gene expression in cancer. This global knowledge of gene expression allows the identification of differentially expressed genes and, in principle, the understanding of the complex molecular circuitry regulating normal and neoplastic behaviors. Such studies have led to molecular profiling of tumors, which has suggested general methods for distinguishing tumors of various biologic behaviors (molecular classification), elucidating pathways relevant to the development of tumors, and identifying molecular targets for the detection and therapy of cancer. The first practical applications of this technology have suggested that global gene expression profiling can provide prognostic information not

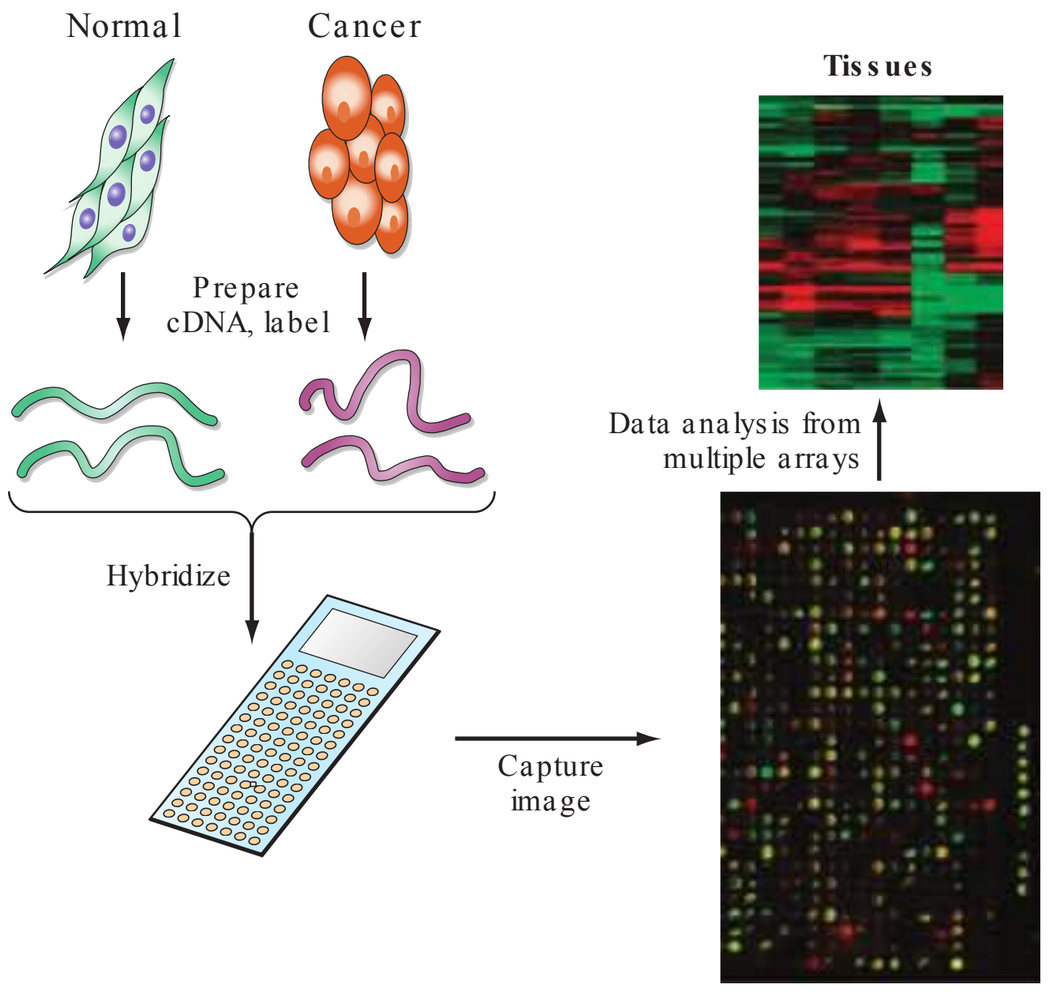

FIGURE 25-7

A microarray experiment. RNA is prepared from cells, reverse transcribed to cDNA, and labeled with fuorescent dyes (typically green for normal cells and red for cancer cells). The fuorescent probes are mixed and hybridized to a cDNA array. Each spot on the array is an oligonucleotide (or cDNA fragment) that represents a different gene. The image is then captured with a fuorescence camera; red spots indicate higher expression in tumor cells compared with reference, while green spots represent the lower expression in tumor cells. Yellow signals indicate equal expression levels in normal and tumor specimens. After clustering analysis of multiple arrays, the results are typically represented graphically using a visualization software, which shows, for each sample, a color-coded representation of gene expression for every gene on the array.

evident from other clinical or laboratory tests. The Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) is a searchable online repository for expression profiling data.

GENOMEWIDE MUTATIONAL PROFILING IN CANCER

With the completion of the Human Genome Project and advances in sequencing technologies, systematic mutational analysis of the cancer genome has become possible. In fact, whole genome sequencing of cancer cells is now possible, and this technology has the potential to revolutionize our approach to cancer prevention, diagnosis, and treatment. The International Cancer Genome Consortium (http://icgc.org/) was developed by leading cancer agencies worldwide, genome and cancer scientists, and statisticians with the goal to launch and coordinate cancer genomics research projects worldwide and to disseminate the data. Hundreds of cancer genomes from at least 25 cancer types have been sequenced through various collaborative efforts. In addition, exome sequencing (sequencing all the coding regions of the genome) has also been performed on a large number of tumors. These sequencing data have been used to elucidate the mutational profile of cancer, including the identification of driver mutations that are functionally involved in tumor development. There are generally 40 to 100 genetic alterations that affect protein sequence in a typical cancer, although statistical analyses suggest that only 8–15 are functionally involved in tumorigenesis. The picture that emerges from these studies is that most genes found mutated in tumors are actually mutated at relatively low frequencies (<5%), whereas a small number of genes (such as p53, KRAS) are mutated in a large proportion of tumors **(Fig. 25-8)**. In the past, the focus of research has been on the frequently mutated genes, but it appears that the large number of genes that are infrequently mutated in cancer are major contributors to the cancer phenotype. Understanding the signaling pathways altered by mutations in these genes, as well as the functional relevance of these different mutations, represents the next challenge in the field. Moreover, a detailed knowledge of the genes altered in a particular tumor may allow for a new era of personalized treatment in cancer medicine (see below). A major effort in the United States, The Cancer Genome Atlas (http://cancergenome.nih.gov) is a coordinated effort from the National Cancer Institute and the National Human Genome Research Institute to systematically characterize the entire spectrum of genomic changes involved in human cancers. Similarly, COSMIC (Catalogue of Somatic Mutations in Cancer) is an initiative from the Welcome Trust Sanger Institute to store and display somatic mutation information and related details regarding human cancers (http://cancer.sanger.ac.uk/).

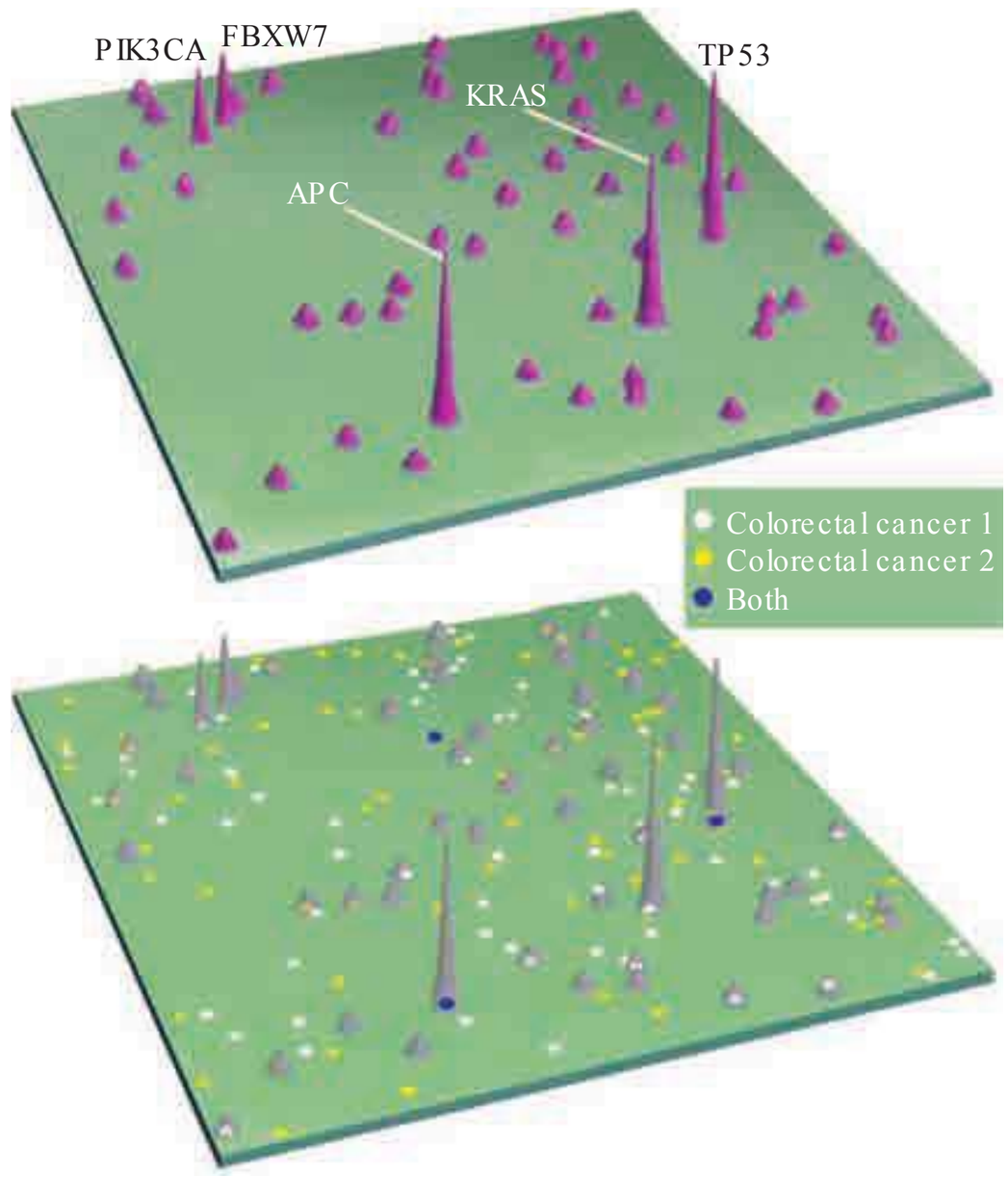

FIGURE 25-8

A two-dimensional maps of genes mutated in colorectal cancer. The two-dimensional landscape represents the positions of the RefSeq genes along the chromosomes and the height of the peaks represents the mutation frequency. On the top map, the taller peaks represent the genes that are commonly mutated in colon cancer, while the large number of smaller hills indicates the genes that are mutated at lower frequency. On the lower map, the mutations of two individual tumors are indicated. Note that there is little overlap between the mutated genes of the two colorectal tumors shown. These differences may represent the basis for the heterogeneity in terms of behavior and responsiveness to therapy observed in human cancer. (From LD Wood et al: Science 318:1108, 2007, with permission.)

PERSONALIZED CANCER TREATMENT BASED ON MOLECULAR PROFILES: PRECISION THERAPY

Gene expression profiling and genomewide sequencing approaches have allowed for an unprecedented understanding of cancer at the molecular level. It has been suggested that individualized knowledge of pathways or genes deregulated in a given tumor (personalized genomics) may provide a guide for therapeutic options on the tumor, thus leading to personalized therapy

(also called precision medicine). Because tumor behavior is highly heterogeneous, even within a tumor type, personalized information-based medicine will likely supplement or perhaps one day supplant the current histology-based therapy, especially in the case of tumors resistant to conventional therapeutic approaches. Molecular nosology has revealed similarities in tumors of diverse histotype. T e success of this approach will be dependent on the identification of suf cient actionable changes (mutations or pathways that can be targeted with a specific drug). Examples of currently actionable changes include mutations in BRAF (targeted by the drug vemurafenib) and RET (targeted by sunitinib and sorafenib), and ALK rearrangements (targeted by crizotinib). Interestingly, studies have reported that 20% of triple-negative breast cancers and 60% of lung cancers have potentially actionable genetic changes. Gene expression also offers the potential to predict drug sensitivities as well as provide prognostic information. Commercial diagnostic tests, such as Mammaprint and Oncotype DX for breast cancer, are available to help the patients and their physicians make treatment decisions. Personalized medicine is an exciting new avenue for cancer treatment based on matching the unique features of a tumor to an effective therapy, and this concept is in the process of changing our approach to cancer therapy in fundamental ways. On a cautionary note, gene expression can vary enormously within a single person's cancer and at different anatomic sites in the patient. We have not yet determined whether such clonal variation within an individual tumor will interfere with the goal tailoring therapy to a particular patient's tumor.

THE FUTURE

A revolution in cancer genetics has occurred in the past 25 years. Identification of cancer genes has led to a deep understanding of the tumorigenesis process and has had important repercussions on all fields of cancer biology. In particular, the advancement of powerful techniques for genomewide expression profiling and mutation analyses has provided a detailed picture of the molecular defects present in individual tumors. Individualized treatment based on the specific genetic alterations within a given tumor has already become possible. Although these advances have not yet translated into overall changes in cancer prevention, prognosis, or treatment, it is expected that breakthroughs in these areas will continue to emerge and be applicable to an ever-increasing number of cancers.

CHAPTER 26

CANCER CELL BIOLOGY

Jeffrey W. Clark ■ Dan L. Longo

Cancers are characterized by unregulated cell division, avoidance of cell death, tissue invasion, and the ability to metastasize. A neoplasm is benign when it grows in an unregulated fashion without tissue invasion. The presence of unregulated growth and tissue invasion is characteristic of malignant neoplasms. Cancers are named based on their origin: those derived from epithelial tissue are called carcinomas, those derived from mesenchymal tissues are sarcomas, and those derived from hematopoietic tissue are leukemias, lymphomas, and plasma cell dyscrasias (including multiple myeloma).

Cancers nearly always arise as a consequence of genetic alterations, the vast majority of which begin in a single cell and therefore are monoclonal in origin. However, because a wide variety of genetic and epigenetic changes can occur in different cells within malignant tumors over time, most cancers are characterized by marked heterogeneity in the populations of cells. This heterogeneity significantly complicates the treatment of most cancers because it is likely that there are subsets of cells that will be resistant to therapy and will therefore survive and proliferate even if the majority of cells are killed.

A few cancers appear to, at least initially, be primarily driven by an alteration in a dominant gene that produces uncontrolled cell proliferation. Examples include chronic myeloid leukemia (abl), about half of melanomas (braf), Burkitt's lymphoma (c-myc), and subsets of lung adenocarcinomas (egfr, alk, ros1, and ret). The genes that can promote cell growth when altered are often called oncogenes. They were first identified as critical elements of viruses that cause animal tumors; it was subsequently found that the viral genes had normal counterparts with important functions in the cell and had been captured and mutated by viruses as they passed from host to host.

However, the vast majority of human cancers are characterized by a multiple-step process involving many genetic abnormalities, each of which contributes to the loss of control of cell proliferation and differentiation and the acquisition of capabilities, such as tissue invasion, the ability to metastasize, and angiogenesis. These properties are not found in the normal adult cell from which the tumor is derived. Indeed, normal cells have a large number of safeguards against uncontrolled proliferation and invasion. Many cancers go through recognizable steps of progressively more abnormal phenotypes: hyperplasia, to adenoma, to dysplasia, to carcinoma in situ, to invasive cancer with the ability to metastasize **(Table 26-1)**. For most cancers, these changes occur over a prolonged period of time, usually many years.

In most organs, only primitive undifferentiated cells are capable of proliferating and the cells lose the capacity to proliferate as they differentiate and acquire functional capability. The expansion of the primitive cells is linked to some functional need in the host through receptors that receive signals from the local environment or through hormonal and other influences delivered by the vascular supply. In the absence of such signals, the cells are at rest. The signals that keep the primitive cells at rest remain incompletely understood. These signals must be environmental, based on the observations that a regenerating liver stops growing when it has replaced the portion that has been surgically removed after partial hepatectomy and regenerating bone marrow stops growing when the peripheral blood counts return to normal. Cancer cells clearly have lost responsiveness to such controls and do not recognize when they have overgrown the niche normally occupied by the organ from which they are derived. A better understanding of the mechanisms of growth regulation is evolving.

CELL CYCLE CHECKPOINTS

Normal cells have a number of control mechanisms that are targeted by specific genetic alterations in cancer. Critical proteins in these control processes that are frequently mutated or otherwise inactivated in cancers are called tumor-suppressor genes. Examples include p53 and Rb (discussed below). The progression of a cell

TABLE 26-1

PHENOTYPIC CHARACTERISTICS OF MALIGNANT CELLS

Deregulated cell proliferation: Loss of function of negative growth regulators (tumor-suppressor genes, i.e., Rb, p53), and increased action of positive growth regulators (oncogenes, i.e., Ras, Myc). Leads to aberrant cell cycle control and includes loss of normal checkpoint responses.

Failure to differentiate: Arrest at a stage before terminal differentiation. May retain stem cell properties. (Frequently observed in leukemias due to transcriptional repression of developmental programs by the gene products of chromosomal translocations.)

Loss of normal apoptosis pathways: Inactivation of p53, increases in Bcl-2 family members. This defect enhances the survival of cells with oncogenic mutations and genetic instability and allows clonal expansion and diversification within the tumor without activation of physiologic cell death pathways.

Genetic instability: Defects in DNA repair pathways leading to either single-nucleotide or oligonucleotide mutations (as in microsatellite instability, MIN) or more commonly chromosomal instability (CIN) leading to aneuploidy. Caused by loss of function of p53, BRCA1/2, mismatch repair genes, DNA repair enzymes, and the spindle checkpoint. Leads to accumulation of a variety of mutations in different cells within the tumor and heterogeneity.

Loss of replicative senescence: Normal cells stop dividing in vitro after 25–50 population doublings. Arrest is mediated by the Rb, $p16^{INK4a}$, and p53 pathways. Further replication leads to telomere loss, with crisis. Surviving cells often harbor gross chromosomal abnormalities. Relevance to human in vivo cancer remains uncertain. Many human cancers express telomerase.

Nonresponsiveness to external growth-inhibiting signals: Cancer cells have lost responsiveness to signals normally present to stop proliferating when they have overgrown the niche normally occupied by the organ from which they are derived. We know very little about this mechanism of growth regulation.

Increased angiogenesis: Due to increased gene expression of proangiogenic factors (VEGF, FGF, IL-8) by tumor or stromal cells, or loss of negative regulators (endostatin, tumstatin, thrombospondin).

Invasion: Loss of cell-cell contacts (gap junctions, cadherins) and increased production of matrix metalloproteinases (MMPs). Often takes the form of epithelial-to-mesenchymal transition (EMT), with anchored epithelial cells becoming more like motile fibroblasts.

Metastasis: Spread of tumor cells to lymph nodes or distant tissue sites. Limited by the ability of tumor cells to survive in a foreign environment.

Evasion of the immune system: Downregulation of MHC class I and II molecules; induction of T cell tolerance; inhibition of normal dendritic cell and/or T cell function; antigenic loss variants and clonal heterogeneity; increase in regulatory T cells.

Shift in cell metabolism: Energy generation shifts to aerobic glycolysis.

Abbreviations: FGF, fibroblast growth factor; IL, interleukin; MHC, major histocompatibility complex; VEGF, vascular endothelial growth factor.

through the cell division cycle is regulated at a number of checkpoints by a wide array of genes. In the first phase, G_1, preparations are made to replicate the genetic material. The cell stops before entering the DNA synthesis phase, or S phase, to take inventory. Are we ready to replicate our DNA? Is the DNA repair machinery in place to fix any mutations that are detected? Are the DNA replicating enzymes available? Is there an adequate supply of nucleotides? Is there sufficient energy? The main brake on the process is the retinoblastoma protein, Rb. When the cell determines that it is prepared to move ahead, sequential activation of cyclin-dependent kinases (CDKs) results in the inactivation of the brake, Rb, by phosphorylation. Phosphorylated Rb releases the S phase–regulating transcription factor, E2F/DP1, and genes required for S phase progression are expressed. If the cell determines that it is unready to move ahead with DNA replication, a number of inhibitors are capable of blocking the action of the CDKs, including $p21^{Cip2/Waf1}$, $p16^{Ink4a}$, and $p27^{Kip1}$. Nearly every cancer has one or more genetic lesions in the G_1 checkpoint that permits progression to S phase.

At the end of S phase, when the cell has exactly duplicated its DNA content, a second inventory is taken at the S checkpoint. Have all of the chromosomes been fully duplicated? Were any segments of DNA copied more than once? Do we have the right number of chromosomes and the right amount of DNA? If so, the cell proceeds to G_2, in which the cell prepares for division by synthesizing mitotic spindle and other proteins needed to produce two daughter cells. When DNA damage is detected, the p53 pathway is normally activated. Called the guardian of the genome, p53 is a transcription factor that is normally present in the cell in very low levels. Its level is generally regulated through its rapid turnover. Normally, p53 is bound to mdm2, a ubiquitin ligase, that both inhibits p53 transcriptional activation and also targets p53 for degradation in the proteasome. When damage is sensed, the ATM (ataxia-telangiectasia mutated) pathway is activated; ATM phosphorylates mdm2, which no longer binds to p53, and p53 then stops cell cycle progression, directs the synthesis of repair enzymes, or if the damage is too great, initiates apoptosis of the cell to prevent the propagation of a damaged cell **(Fig. 26-1)**.

A second method of activating p53 involves the induction of $p14^{ARF}$ by hyperproliferative signals from oncogenes. $p14^{ARF}$ competes with p53 for binding to mdm2, allowing p53 to escape the effects of mdm2 and accumulate in the cell. Then p53 stops cell cycle progression by activating CDK inhibitors such as p21 and/or initiating the apoptosis pathway. Not surprisingly given its critical role in controlling cell cycle progression, mutations in the gene for p53 on chromosome 17p are found in more than 50% of human

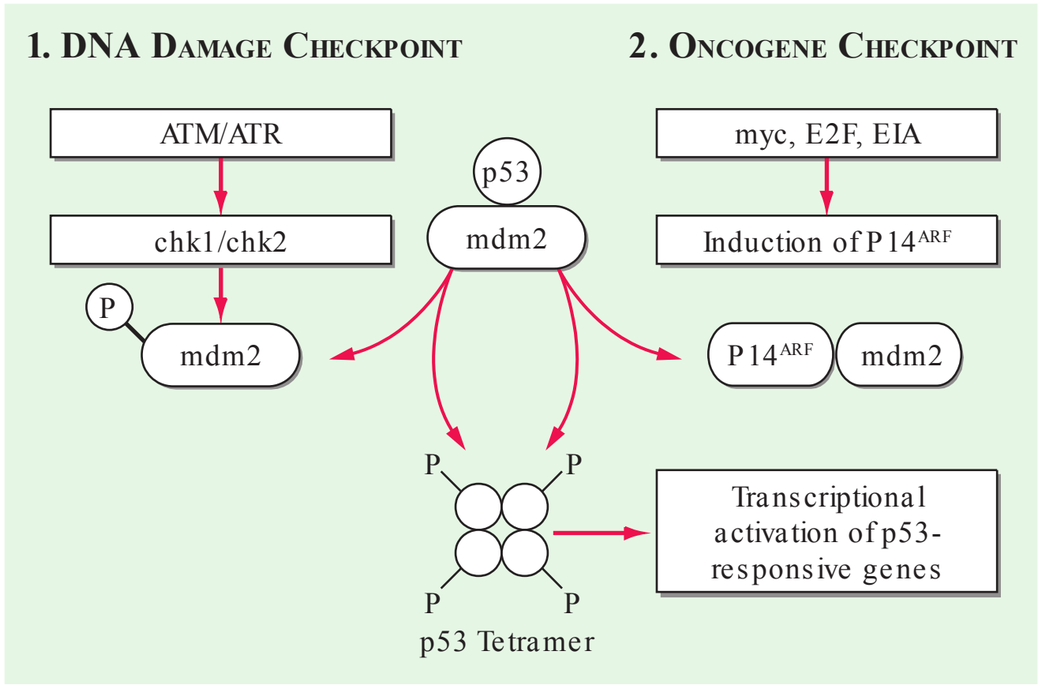

FIGURE 26-1
Induction of p53 by the DNA damage and oncogene checkpoints. In response to noxious stimuli, p53 and mdm2 are phosphorylated by the ataxia-telangiectasia mutated (ATM) and related (ATR) serine/threonine kinases, as well as the immediate downstream checkpoint kinases, Chk1 and Chk2. This causes dissociation of p53 from mdm2, leading to increased p53 protein levels and transcription of genes leading to cell cycle arrest ($p21^{Cip1/Waf1}$) or apoptosis (e.g., the proapoptotic Bcl-2 family members Noxa and Puma). Inducers of p53 include hypoxemia, DNA damage (caused by ultraviolet radiation, gamma irradiation, or chemotherapy), ribonucleotide depletion, and telomere shortening. A second mechanism of p53 induction is activated by oncogenes such as Myc, which promote aberrant G_1/S transition. This pathway is regulated by a second product of the Ink4a locus, $p14^{ARF}$ (p19 in mice), which is encoded by an alternative reading frame of the same stretch of DNA that codes for $p16^{Ink4a}$. Levels of ARF are upregulated by Myc and E2F, and ARF binds to mdm2 and rescues p53 from its inhibitory effect. This oncogene checkpoint leads to the death or senescence (an irreversible arrest in G_1 of the cell cycle) of renegade cells that attempt to enter S phase without appropriate physiologic signals. Senescent cells have been identified in patients whose premalignant lesions harbor activated oncogenes, for instance, dysplastic nevi that encode an activated form of BRAF (see below), demonstrating that induction of senescence is a protective mechanism that operates in humans to prevent the outgrowth of neoplastic cells.

cancers. Most commonly these mutations are acquired in the malignant tissue in one allele and the second allele is deleted, leaving the cell unprotected from DNA-damaging agents or oncogenes. Some environmental exposures produce signature mutations in p53; for example, aflatoxin exposure leads to mutation of arginine to serine at codon 249 and leads to hepatocellular carcinoma. In rare instances, p53 mutations are in the germline (Li-Fraumeni syndrome) and produce a familial cancer syndrome. The absence of p53 leads to chromosome instability and the accumulation of DNA damage including the acquisition of properties that give the abnormal cell a proliferative and survival advantage. Like Rb dysfunction, most cancers have mutations that disable the p53 pathway. Indeed, the importance of p53 and Rb in the development of cancer is underscored by the neoplastic transformation mechanism of human papillomavirus. The virus has two main oncogenes, E6 and E7. E6 acts to increase the rapid turnover of p53, and E7 acts to inhibit Rb function; inhibition of these two targets is required for transformation of epithelial cells.

Another cell cycle checkpoint exists when the cell is undergoing division, the spindle checkpoint. The details of this checkpoint are still being discovered; however, it appears that if the spindle apparatus does not properly align the chromosomes for division, if the chromosome number is abnormal (i.e., greater or less than 4n), or if the centromeres are not properly paired with their duplicated partners, then the cell initiates a cell death pathway to prevent the production of aneuploid progeny (having an altered number of chromosomes). Abnormalities in the spindle checkpoint facilitate the development of aneuploidy. In some tumors, aneuploidy is a predominant genetic feature. In others, a defect in the cells' ability to repair errors in the DNA due to mutations in genes coding for the proteins critical for mismatched DNA repair is the primary genetic lesion. This is usually detected by finding alterations in repeat sequences of DNA (called microsatellites) or microsatellite instability in malignant cells. In general, tumors either have defects in chromosome number or microsatellite instability, but not both. Defects that lead to cancer include abnormal cell cycle checkpoints, inadequate DNA repair, and failure to preserve genome integrity.

Efforts are under way to therapeutically restore the defects in cell cycle regulation that characterize cancer, although this remains a challenging problem because it is much more difficult to restore normal biologic function than to inhibit abnormal function of proteins driving cell proliferation, such as oncogenes.

CANCER AS AN ORGAN THAT IGNORES ITS NICHE

The fundamental cellular defects that create a malignant neoplasm act at the cellular level. However, that is not the entire story. Cancers behave as organs that have lost their specialized function and stopped responding to signals that normally limit their growth. Human cancers usually become clinically detectable when a primary mass is at least 1 cm in diameter—such a mass consists of about 10^9 cells. More commonly, patients present with tumors that are 10^{10} cells or greater. A lethal tumor burden is about 10^{12} to 10^{13} cells. If all tumor cells were dividing at the time of diagnosis, patients would reach a lethal tumor burden in a very short time. However, human tumors grow by Gompertzian kinetics—this means that not every

daughter cell produced by a cell division is itself capable of dividing. T e growth fraction of a tumor declines exponentially with time. T e growth fraction of the first malignant cell is 100%, and by the time a patient presents for medical care, the growth fraction is 2–3% or less. T is fraction is similar to the growth fraction of normal bone marrow and normal intestinal epithelium, the most highly proliferative normal tissues in the human body, a fact that may explain the dose-limiting toxicities of agents that target dividing cells.

T e implication of these data is that the tumor is slowing its own growth over time. How does it do this? T e tumor cells have multiple genetic lesions that tend to promote proliferation, yet by the time the tumor is clinically detectable, its capacity for proliferation has declined. We need to better understand how a tumor slows its own growth. A number of factors are known to contribute to the failure of tumor cells to proliferate in vivo. Some cells are hypoxemic and have inadequate supply of nutrients and energy. Some have sustained too much genetic damage to complete the cell cycle but have lost the capacity to undergo apoptosis and therefore survive but do not proliferate. However, an important subset is not actively dividing but retains the capacity to divide and can start dividing again under certain conditions such as when the tumor mass is reduced by treatments. Just as the bone marrow increases its rate of proliferation in response to bone marrow–damaging agents, the tumor also seems to sense when tumor cell numbers have been reduced and can respond by increasing growth rate. However, the critical difference is that the marrow stops growing when it has reached its production goals, whereas tumors do not.

Additional tumor cell vulnerabilities are likely to be detected when we learn more about how normal cells respond to "stop" signals from their environment and why and how tumor cells fail to heed such signals.

IS IN VITRO SENESCENCE RELEVANT TO CARCINOGENESIS?

When normal cells are placed in culture in vitro, most are not capable of sustained growth. Fibroblasts are an exception to this rule. When they are cultured, fibroblasts may divide 30–50 times and then they undergo what has been termed a "crisis" during which the majority of cells stop dividing (usually due to an increase in p21 expression, a CDK inhibitor), many die, and a small fraction emerge that have acquired genetic changes that permit their uncontrolled growth. T e cessation of growth of normal cells in culture has been termed "senescence," and whether this phenomenon is relevant to any physiologic event in vivo is debated.

Among the cellular changes during in vitro propagation is telomere shortening. DNA polymerase is unable to replicate the tips of chromosomes, resulting in the loss of DNA at the specialized ends of chromosomes (called telomeres) with each replication cycle. At birth, human telomeres are 15- to 20-kb pairs long and are composed of tandem repeats of a six-nucleotide sequence (TTAGGG) that associates with specialized telomere-binding proteins to form a T-loop structure that protects the ends of chromosomes from being mistakenly recognized as damaged. T e loss of telomeric repeats with each cell division cycle causes gradual telomere shortening, leading to growth arrest (called senescence) when one or more critically short telomeres trigger a p53-regulated DNA-damage checkpoint response. Cells can bypass this growth arrest if pRb and p53 are nonfunctional, but cell death usually ensues when the unprotected ends of chromosomes lead to chromosome fusions or other catastrophic DNA rearrangements. T e ability to bypass telomere-based growth limitations is thought to be a critical step in the evolution of most malignancies. T is occurs by the reactivation of telomerase expression in cancer cells. Telomerase is an enzyme that adds TTAGGG repeats onto the 3′ ends of chromosomes. It contains a catalytic subunit with reverse transcriptase activity (hTERT) and an RNA component that provides the template for telomere extension. Most normal somatic cells do not express sufficient telomerase to prevent telomere attrition with each cell division. Exceptions include stem cells (such as those found in hematopoietic tissues, gut and skin epithelium, and germ cells) that require extensive cell division to maintain tissue homeostasis. More than 90% of human cancers express high levels of telomerase that prevent telomere shortening to critical levels and allow indefinite cell proliferation. In vitro experiments indicate that inhibition of telomerase activity leads to tumor cell apoptosis. Major efforts are under way to develop methods to inhibit telomerase activity in cancer cells. For example, the protein component of telomerase (hTERT) may act as one of the most widely expressed tumor-associated antigens and be targeted by vaccine approaches.

Although most of the functions of telomerase relate to cell division, it also has several other effects including interfering with the differentiated functions of at least certain stem cells, although the impact on differentiated function of normal non-stem cells is less clear. Nevertheless, a major growth industry in medical research has been discovering an association between short telomeres and human diseases ranging from diabetes and coronary artery disease to Alzheimer's disease. T e picture is further complicated by the fact that rare genetic defects in the telomerase enzyme seem to cause pulmonary fibrosis, aplastic anemia, or dyskeratosis congenita (characterized by abnormalities in skin, nails, and oral mucosa with increased risk for certain malignancies) but not defects in nutrient absorption in the gut, a site that might be presumed to be highly sensitive to

defective cell proliferation. Much remains to be learned about how telomere shortening and telomere maintenance are related to human illness in general and cancer in particular.

SIGNAL TRANSDUCTION PATHWAYS IN CANCER CELLS

Signals that affect cell behavior come from adjacent cells, the stroma in which the cells are located, hormonal signals that originate remotely, and from the cells themselves (autocrine signaling). T ese signals generally exert their influence on the receiving cell through activation of signal transduction pathways that have as their end result the induction of activated transcription factors that mediate a change in cell behavior or function or the acquisition of effector machinery to accomplish a new task. Although signal transduction pathways can lead to a wide variety of outcomes, many such pathways rely on cascades of signals that sequentially activate different proteins or glycoproteins and lipids or glycolipids, and the activation steps often involve the addition or removal of one or more phosphate groups on a downstream target. Other chemical changes can result from signal transduction pathways, but phosphorylation and dephosphorylation play a major role. T e proteins that add phosphate groups to proteins are called kinases. T ere are two major distinct classes of kinases; one class acts on tyrosine residues, and the other acts on serine/threonine residues. T e tyrosine kinases often play critical roles in signal transduction pathways; they may be receptor tyrosine kinases, or they may be linked to other cell-surface receptors through associated docking proteins **(Fig. 26-2)**.

Normally, tyrosine kinase activity is short-lived and reversed by protein tyrosine phosphatases (PTPs). However, in many human cancers, tyrosine kinases or components of their downstream pathways are activated by mutation, gene amplification, or chromosomal translocations. Because these pathways regulate proliferation, survival, migration, and angiogenesis, they have been identified as important targets for cancer therapeutics.

Inhibition of kinase activity is effective in the treatment of a number of neoplasms. Lung cancers with mutations in the epidermal growth factor receptor are highly responsive to erlotinib and gefitinib **(Table 26-2)**. Lung cancers with activation of anaplastic lymphoma kinase (ALK) or ROS1 by translocations respond to crizotinib, an ALK and ROS1 inhibitor. A BRAF inhibitor is highly effective in melanomas and thyroid cancers in which BRAF is mutated. Targeting a protein (MEK) downstream of BRAF also has activity against BRAF mutant melanomas. Janus kinase inhibitors are active in myeloproliferative syndromes in which JAK2 activation is a pathogenetic event. Imatinib (which targets a number of tyrosine kinases) is an effective agent in tumors that have translocations of the c-Abl and BCR gene (such as chronic myeloid leukemia), mutant c-Kit (gastrointestinal stromal cell tumors), or mutant platelet-derived growth factor receptor (PDGFR; chronic myelomonocytic leukemia); second-generation inhibitors of BCR-Abl, dasatinib, and nilotinib are even more effective. T e third-generation agent bosutinib has activity in some patients who have progressed on other inhibitors, whereas the third-generation agent ponatinib has activity against the T315I mutation, which is resistant to the other agents. Sorafenib and sunitinib, agents that inhibit a large number of kinases, have shown antitumor activity in a number of malignancies, including renal cell cancer (RCC) (both), hepatocellular carcinoma (sorafenib), thyroid cancer (sorafenib), gastrointestinal stromal tumor (GIST) (sunitinib), and pancreatic neuroendocrine tumors (sunitinib). Inhibitors of the mammalian target of rapamycin (mTOR) are active in RCC, pancreatic neuroendocrine tumors, and breast cancer. T e list of active agents and treatment indications is growing rapidly. T ese new agents have ushered in a new era of personalized therapy. It is becoming more routine for resected tumors to be assessed for specific molecular changes that predict response and to have clinical decision-making guided by those results.

However, none of these therapies has yet been curative by themselves for any malignancy, although prolonged periods of disease control lasting many years frequently occur in chronic myeloid leukemia. T e reasons for the failure to cure are not completely defined, although resistance to the treatment ultimately develops in most patients. In some tumors, resistance to kinase inhibitors is related to an acquired mutation in the target kinase that inhibits drug binding. Many of these kinase inhibitors act as competitive inhibitors of the ATP-binding pocket. ATP is the phosphate donor in these phosphorylation reactions. Mutation in the BCR-ABL kinase in the ATP-binding pocket (such as the threonine to isoleucine change at codon 315 [T315I]) can prevent imatinib binding. Other resistance mechanisms include altering other signal transduction pathways to bypass the inhibited pathway. As resistance mechanisms become better defined, rational strategies to overcome resistance will emerge. In addition, many kinase inhibitors are less specific for an oncogenic target than was hoped, and toxicities related to off-target inhibition of kinases limit the use of the agent at a dose that would optimally inhibit the cancer-relevant kinase.

Targeted agents can also be used to deliver highly toxic compounds. An important component of the technology for developing effective conjugates is the design of the linker between the two, which needs to be stable. Currently approved antibody drug

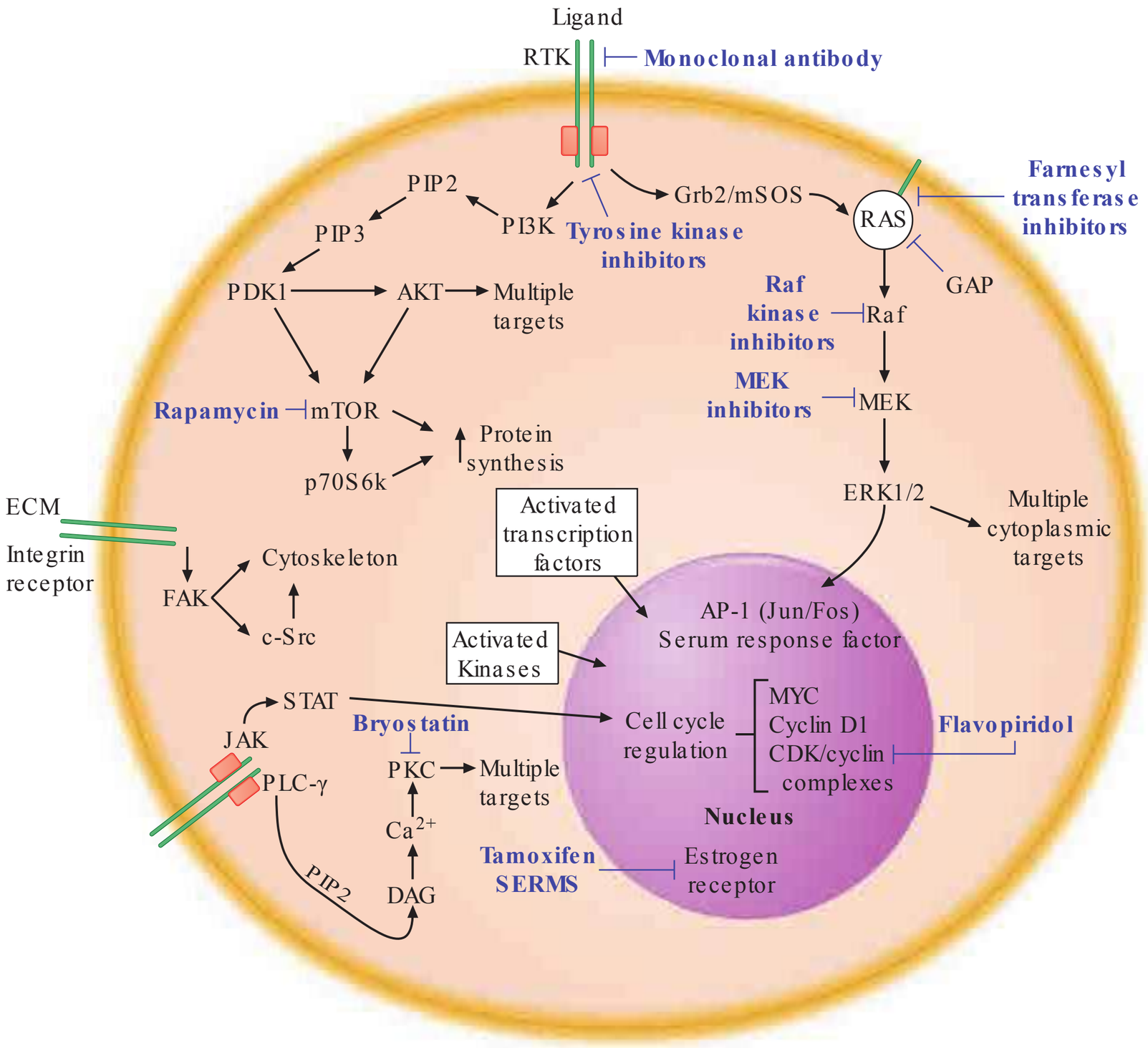

FIGURE 26-2

Therapeutic targeting of signal transduction pathways in cancer cells. Three major signal transduction pathways are activated by receptor tyrosine kinases (RTK). 1. The protooncogene Ras is activated by the Grb2/mSOS guanine nucleotide exchange factor, which induces an association with Raf and activation of downstream kinases (MEK and ERK1/2). 2. Activated PI3K phosphorylates the membrane lipid PIP_2 to generate PIP_3, which acts as a membrane-docking site for a number of cellular proteins including the serine/threonine kinases PDK1 and Akt. PDK1 has numerous cellular targets, including Akt and mTOR. Akt phosphorylates target proteins that promote resistance to apoptosis and enhance cell cycle progression, whereas mTOR and its target p70S6K upregulate protein synthesis to potentiate cell growth. 3. Activation of PLC-γ leads to the formation of diacylglycerol (DAG) and increased intracellular calcium, with activation of multiple isoforms of PKC and other enzymes regulated by the calcium/calmodulin system. Other important signaling pathways involve non-RTKs that are activated by cytokine or integrin receptors. Janus kinases (JAK) phosphorylate STAT (signal transducer and activator of transcription) transcription factors, which translocate to the nucleus and activate target genes. Integrin receptors mediate cellular interactions with the extracellular matrix (ECM), inducing activation of FAK (focal adhesion kinase) and c-Src, which activate multiple downstream pathways, including modulation of the cell cytoskeleton. Many activated kinases and transcription factors migrate into the nucleus, where they regulate gene transcription, thus completing the path from extracellular signals, such as growth factors, to a change in cell phenotype, such as induction of differentiation or cell proliferation. The nuclear targets of these processes include transcription factors (e.g., Myc, AP-1, and serum response factor) and the cell cycle machinery (CDKs and cyclins). Inhibitors of many of these pathways have been developed for the treatment of human cancers. Examples of inhibitors that are currently being evaluated in clinical trials are shown in purple type.

conjugates include brentuximab vedotin, which links the microtubule toxin monomethyl auristatin E (MMAE) to an antibody targeting the cell surface antigen CD30, which is expressed on a number of malignant cells but especially in Hodgkin's disease and anaplastic lymphoma. The linker in this case is cleavable, which allows diffusion of the drug out of the cell after delivery. The second approved conjugate is ado-trastuzumab emtansine, which links the microtubule formation inhibitor mertansine and the monoclonal antibody trastuzumab targeted against human epidermal growth factor receptor 2 (HER2) on breast cancer cells. In this case, the linker is noncleavable, thus trapping the chemotherapeutic agent within the cells.

TABLE 26-2

SOME FDA-APPROVED MOLECULARLY TARGETED AGENTS FOR THE TREATMENT OF CANCER

DRUG	MOLECULAR TARGET	DISEASE	MECHANISM OF ACTION
All-trans retinoic acid	PML-RARα oncogene	Acute promyelocytic leukemia M3 AML; t(15;17)	Inhibits transcriptional repression by PML-RARα
Imatinib	Bcr-Abl, c-Abl, c-Kit, PDGFR-α/β	Chronic myeloid leukemia; GIST	Blocks ATP binding to tyrosine kinase active site
Dasatinib, nilotinib, ponatinib, bosutinib	Bcr-Abl (primarily)	Chronic myeloid leukemia	Blocks ATP binding to tyrosine kinase active site
Sunitinib	c-Kit, VEGFR-2, PDGFR-β, Flt-3	GIST; renal cell cancer	Inhibits activated c-Kit and PDGFR in GIST; inhibits VEGFR in RCC
Sorafenib	RAF, VEGFR-2, PDGFR-α/β, Flt-3, c-Kit	RCC; hepatocellular carcinoma; TC	Targets VEGFR pathways in RCC. Possible activity against BRAF in thyroid cancer
Regorafenib	VEGFR-1 to -3, TIE-2, FGFR1, KIT, RET, PDGFR	Colorectal cancer; GIST	Competitive inhibitor of ATP binding site of tyrosine kinase domain multiple kinases
Axitinib	VEGFR-1 to -3	RCC	Competitive inhibitor of ATP binding site of tyrosine kinase domain VEGF receptors
Erlotinib	EGFR	Non-small-cell lung cancer; pancreatic cancer	Competitive inhibitor of the ATP-binding site of the EGFR
Afatinib	EGFR (and other HER family)	Non-small-cell lung cancer	Irreversible inhibitor of ATP-binding site of HER family members
Lapatinib	HER2/neu	Breast cancer	Competitive inhibitor of the ATP binding site of HER2
Crizotinib (Xalkori)	ALK	Non-small-cell lung cancer	Inhibitor of ALK tyrosine kinase
Bortezomib, carfilzomib	Proteasome	Multiple myeloma	Inhibits proteolytic degradation of multiple cellular proteins
Vemurafenib, dabrafenib	BRAF	Melanoma	Inhibitor of serine-threonine kinase domain of V600E mutant of BRAF
Trametinib	MEK	Melanoma	Inhibitor of serine-threonine kinase domain of V600E mutant of MEK
Cabozantinib	RET, MET, VEGFR	MTC	Competitive inhibitor of ATP binding site of tyrosine kinase domain multiple kinases
Vandetanib	RET, VEGFR, EGFR	MTC	Competitive inhibitor of ATP binding site of tyrosine kinase domain multiple kinases
Temsirolimus	mTOR	RCC	Competitive inhibitor of mTOR serine-threonine kinase
Everolimus	mTOR	RCC; breast cancer	Binds to immuophilin FK binding protein-12, which forms complex that inhibits mTOR kinase
Vorinostat, romidepsin	HDAC	CTCL	HDAC inhibitor
Ruxolitinib	JAK-1, -2	Myelofibrosis	Competitive inhibitor of tyrosine kinase
Vismodegib	Hedgehog pathway	Basel cell cancer (skin)	Inhibits smoothened in hedgehog pathway
Monoclonal Antibodies Alone			
Trastuzumab	HER2/neu (ERBB2)	Breast cancer	Binds HER2 on tumor cell surface and induces receptor internalization
Pertuzumab	HER2/neu (ERBB2)	Breast cancer	Binds HER2 on tumor cell surface at distinct site from trastuzumab and prevents binding to other receptors
Cetuximab	EGFR	Colon cancer, squamous cell carcinoma of the head and neck	Binds extracellular domain of EGFR and blocks binding of EGF and TGF-α; induces receptor internalization; potentiates the efficacy of chemotherapy and radiotherapy
Panitumumab	EGFR	Colon cancer	Similar to cetuximab but fully humanized rather than chimeric
Rituximab	CD20	B cell lymphomas and leukemias that express CD20	Multiple potential mechanisms, including direct induction of tumor cell apoptosis and immune mechanisms
Alemtuzumab	CD52	Chronic lymphocytic leukemia and CD52-expressing lymphoid tumors	Immune mechanisms

(continued)

TABLE 26-2

SOME FDA-APPROVED MOLECULARLY TARGETED AGENTS FOR THE TREATMENT OF CANCER (CONTINUED)

DRUG	MOLECULAR TARGET	DISEASE	MECHANISM OF ACTION
Bevacizumab	VEGF	Colorectal, lung cancers, RCC, glioblastoma, cervical cancer	Inhibits angiogenesis by high-affinity binding to VEGF
Ziv-aflibercept	VEGF-A, VEGF-B, PLGF	Colorectal cancers	Inhibits angiogenesis by high-affinity binding to VEGF-A, VEGF-B, and PLGF
Ipilimumab	CTLA-4	Melanoma	Blocks CTLA-4, preventing interaction with CD80/86 and T cell inhibition
Denosumab	RANK ligand	Breast, prostate cancer	Inhibits RANK ligand, the primary signal for bone removal
Pembrolizumab	PD-1	Melanoma	Blocks PD-1 preventing interaction with PD-L1 T cell inhibition
Antibody-Chemotherapy Conjugates			
Brentuximab vedotin	CD30	Hodgkin's disease, anaplastic lymphoma	Delivery of chemotherapeutic agent (MMAE) to CD30-expressing tumor cells
Ado-trastuzumab emtansine	HER2	Breast cancer	Delivery of chemotherapeutic agent emtansine to HER2-expressing breast cancer cells

Abbreviations: AML, acute myeloid leukemia; CTCL, cutaneous T cell lymphoma; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; Flt-3, fms-like tyrosine kinase-3; GIST, gastrointestinal stromal tumor; MTC, medullary thyroid cancer; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; PLGF, placental growth factor; PML-RARα, promyelocytic leukemia-retinoic acid receptor-alpha; RCC, renal cell cancer; t(15;17), translocation between chromosomes 15 and 17; TC, thyroid cancer; TGF-α, transforming growth factor-alpha; VEGFR, vascular endothelial growth factor receptor.

There are theoretical pluses and minuses to having either cleavable or noncleavable linkers, and it is likely that both will be used in future developments of antibody-drug conjugates.

Another strategy to enhance the antitumor effects of targeted agents is to use them in rational combinations with each other and in empiric combinations with chemotherapy agents that kill cells in ways distinct from targeted agents. Combinations of trastuzumab (a monoclonal antibody that targets the HER2 receptor [member of the epidermal growth factor receptor (EGFR) family]) with chemotherapy have significant activity against breast and stomach cancers that have high levels of expression of the HER2 protein. The activity of trastuzumab and chemotherapy can be enhanced further by combinations with another targeted monoclonal antibody (pertuzumab), which prevents dimerization of the HER2 receptor with other HER family members including HER3.

Although targeted therapies have not yet resulted in cures when used alone, their use in the adjuvant setting and when combined with other effective treatments has substantially increased the fraction of patients cured. For example, the addition of rituximab, an anti-CD20 antibody, to combination chemotherapy in patients with diffuse large B cell lymphoma improves cure rates by 15–20%. The addition of trastuzumab, antibody to HER2, to combination chemotherapy in the adjuvant treatment of HER2-positive breast cancer reduces relapse rates by 50%.

A major effort is under way to develop targeted therapies for mutations in the ras family of genes, which are the most common mutations in oncogenes in cancers (especially kras) but have proved to be very difficult targets for a number of reasons related to how RAS proteins are activated and inactivated. Targeted therapies against proteins downstream of RAS (including mitogen-activated protein [MAP] kinase and ERK) are currently being studied, both individually and in combination. A large number of inhibitors of phospholipid signaling pathways such as the phosphatidylinositol-3-kinase (PI3K) and phospholipase C-gamma pathways, which are involved in a large number of cellular processes that are important in cancer development and progression, are being evaluated. The targeting of a variety of other pathways that are activated in malignant cells, such as the MET pathway, hedgehog pathway, and various angiogenesis pathways, is also being explored.

One of the strategies for new drug development is to take advantage of so-called oncogene addiction. This situation **(Fig. 26-3)** is created when a tumor cell develops an activating mutation in an oncogene that becomes a dominant pathway for survival and growth with reduced contributions from other pathways, even when there may be abnormalities in those pathways. This dependency on a single pathway creates a cell that is vulnerable to inhibitors of that oncogene pathway. For example, cells harboring mutations in BRAF are very sensitive to MEK inhibitors that inhibit downstream signaling in the BRAF pathway.

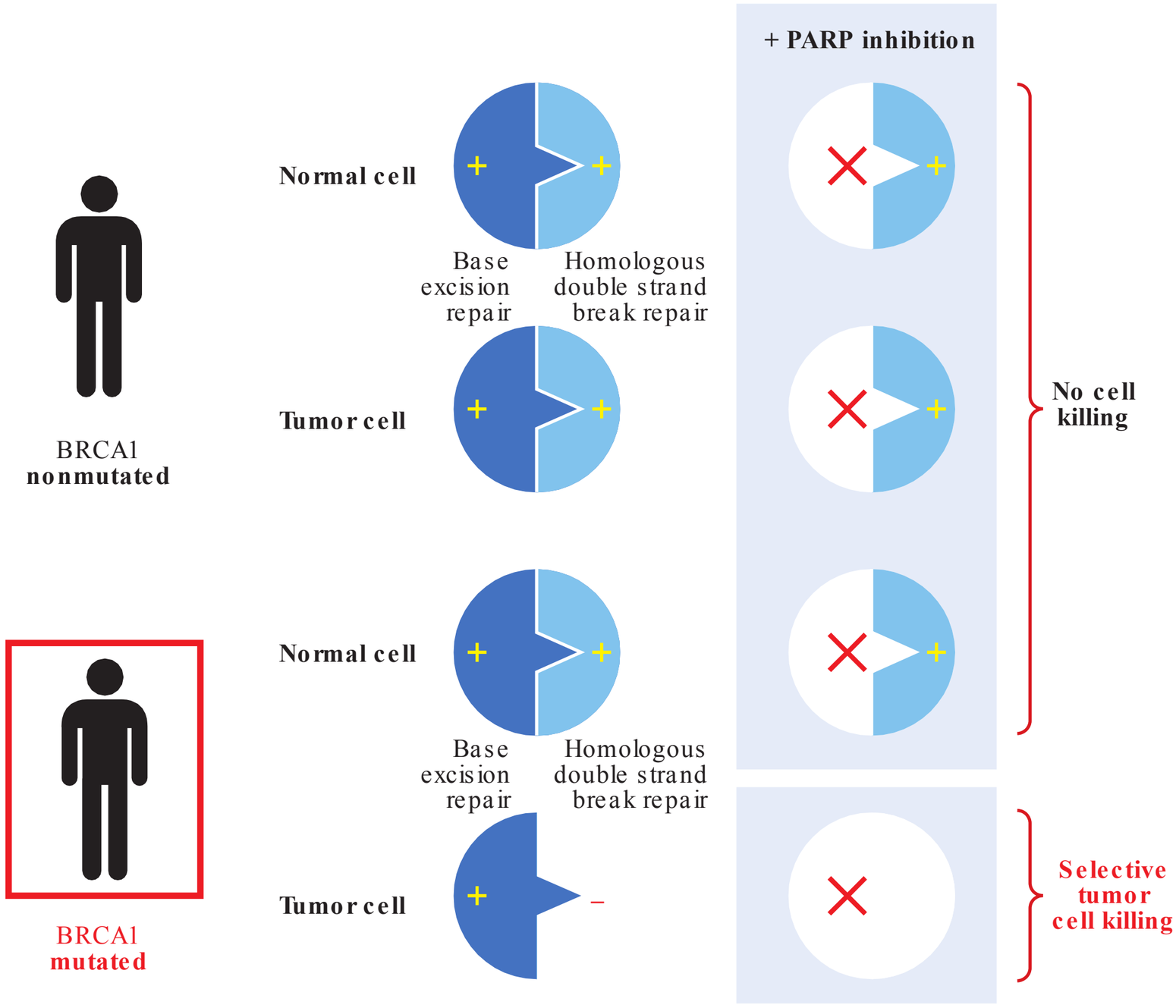

FIGURE 26-3

Synthetic lethality. Genes are said to have a synthetic lethal relationship when mutation of either gene alone is tolerated by the cell but mutation of both genes leads to lethality, as originally noted by Bridges and later named by Dobzhansky. Thus, mutant gene a and gene b have a synthetic lethal relationship, implying that the loss of one gene makes the cell dependent on the function of the other gene. In cancer cells, loss of function of a DNA repair gene like BRCA1, which repairs double-strand breaks, makes the cell dependent on base excision repair mediated in part by PARP. If the PARP gene product is inhibited, the cell attempts to repair the break using the error-prone nonhomologous end-joining method, which results in tumor cell death. High-throughput screens can now be performed using isogenic cell line pairs in which one cell line has a defined defect in a DNA repair pathway. Compounds can be identified that selectively kill the mutant cell line; targets of these compounds have a synthetic lethal relationship to the repair pathway and are potentially important targets for future therapeutics.

Targeting proteins critical for transcription of proteins vital for malignant cell survival or proliferation provides another potential target for treating cancers. T e transcription factor nuclear factor-κB (NF-κB) is a heterodimer composed of p65 and p50 subunits that associate with an inhibitor, IκB, in the cell cytoplasm. In response to growth factor or cytokine signaling, a multi-subunit kinase called IKK (IκB kinase) phosphorylates IκB and directs its degradation by the ubiquitin/proteasome system. NF-κB, free of its inhibitor, translocates to the nucleus and activates target genes, many of which promote the survival of tumor cells. Novel drugs called proteasome inhibitors block the proteolysis of IκB, thereby preventing NF-κB activation. For unexplained reasons, this is selectively toxic to tumor cells. T e antitumor effects of proteasome inhibitors are more complicated and involve the inhibition of the degradation of multiple cellular proteins. Proteasome inhibitors (e.g., bortezomib [Velcade]) have activity in patients with multiple myeloma, including partial and complete remissions. Inhibitors of IKK are also in development, with the hope of more selectively blocking the degradation of IκB, thus "locking" NF-κB in an inhibitory complex and rendering the cancer cell more susceptible to apoptosis-inducing agents. Many other transcription factors are activated by phosphorylation, which can be prevented by tyrosine kinase inhibitors or serine/threonine kinase inhibitors, a number of which are currently in clinical trials.

Estrogen receptors (ERs) and androgen receptors (ARs), members of the steroid hormone family of nuclear receptors, are targets of inhibition by drugs used to treat breast and prostate cancers, respectively. Tamoxifen, a partial agonist and antagonist of ER

function, can mediate tumor regression in metastatic breast cancer and can prevent disease recurrence in the adjuvant setting. Tamoxifen binds to the ER and modulates its transcriptional activity, inhibiting activity in the breast but promoting activity in bone and uterine epithelium. Selective ER modulators (SERMs) have been developed with the hope of a more beneficial modulation of ER activity, i.e., antiestrogenic activity in the breast, uterus, and ovary, but estrogenic for bone, brain, and cardiovascular tissues. Aromatase inhibitors, which block the conversion of androgens to estrogens in breast and subcutaneous fat tissues, have demonstrated improved clinical efficacy compared with tamoxifen and are often used as first-line therapy in patients with ER-positive disease. A number of approaches have been developed for blocking androgen stimulation of prostate cancer, including decreasing production (e.g., orchiectomy, luteinizing hormone–releasing hormone agonists or antagonists, estrogens, ketoconazole, and inhibitors of enzymes such as CYP17 involved in androgen production) and AR blockers **(Chap. 38)**.

ONCOGENE ADDICTION AND SYNTHETIC LETHALITY

T e concepts of oncogene addiction and synthetic lethality have spurred new drug development targeting oncogene- and tumor-suppressor pathways. As discussed earlier in this chapter and outlined in Fig. 26-3, cancer cells can become dependent on signaling pathways containing activated oncogenes; this can effect proliferation (i.e., mutated Kras, Braf, overexpressed Myc, or activated tyrosine kinases), DNA repair (loss of BRCA1 or BRCA2 gene function), survival (overexpression of Bcl-2 or NF-κB), cell metabolism (as occurs when mutant Kras enhances glucose uptake and aerobic glycolysis), and perhaps angiogenesis (production of VEGF in response to HIF-2α in RCC). In such cases, targeted inhibition of the pathway can lead to specific killing of the cancer cells. However, targeting defects in tumor-suppressor genes has been much more difficult, both because the target of mutation is often deleted and because it is much more difficult to restore normal function than to inhibit abnormal function of a protein. Synthetic lethality occurs when loss of function in either of two genes alone has limited effects on cell survival but loss of function in both genes leads to cell death. Identifying genes that have a synthetic lethal relationship to tumor-suppressor pathways that have been mutated in tumor cells may allow targeting of proteins required uniquely by those cells (Fig. 26-3). Several examples of this have been identified. For instance, cells with mutations in the BRCA1 or BRCA2 tumor-suppressor genes (e.g., a subset of breast and ovarian cancers) are unable to repair DNA damage by homologous recombination. PARP are a family of proteins important for single-strand break (SSB) DNA repair. PARP inhibition results in selective killing of cancer cells with BRCA1 or BRCA2 loss. Preliminary trials have suggested some effectiveness of PARP inhibition, especially in combination with chemotherapy; clinical trials are ongoing. T e concept of synthetic lethality provides a framework for genetic screens to identify other synthetic lethal combinations involving known tumor-suppressor genes and development of novel therapeutic agents to target dependent pathways.

EPIGENETIC INFLUENCES ON CANCER GENE TRANSCRIPTION

Chromatin structure regulates the hierarchical order of sequential gene transcription that governs differentiation and tissue homeostasis. Disruption of chromatin remodeling (the process of modifying chromatin structure to control exposure of specific genes to transcriptional proteins, thereby controlling the expression of those genes) leads to aberrant gene expression and can induce proliferation of undifferentiated cells. Epigenetics is defined as changes that alter the pattern of gene expression that persist across at least one cell division but are not caused by changes in the DNA code. Epigenetic changes include alterations of chromatin structure mediated by methylation of cytosine residues in CpG dinucleotides, modification of histones by acetylation or methylation, or changes in higher-order chromosome structure **(Fig. 26-4)**. T e transcriptional regulatory regions of active genes often contain a high frequency of CpG dinucleotides (referred to as CpG islands), which are normally unmethylated. Expression of these genes is controlled by transient association with repressor or activator proteins that regulate transcriptional activation. However, hypermethylation of promoter regions is a common mechanism by which tumor-suppressor loci are epigenetically silenced in cancer cells. T us one allele may be inactivated by mutation or deletion (as occurs in loss of heterozygosity), while expression of the other allele is epigenetically silenced, usually by methylation.

Acetylation of the amino terminus of the core histones H3 and H4 induces an open chromatin conformation that promotes transcription initiation. Histone acetylases are components of coactivator complexes recruited to promoter/enhancer regions by sequence-specific transcription factors during the activation of genes (Fig. 26-4). Histone deacetylases (HDACs; at least 17 are encoded in the human genome) are recruited to genes by transcriptional repressors and prevent the initiation of gene transcription. Methylated cytosine residues in promoter regions become associated with methyl cytosine–binding proteins that recruit protein complexes with HDAC activity. T e balance between permissive and inhibitory chromatin structure is therefore largely

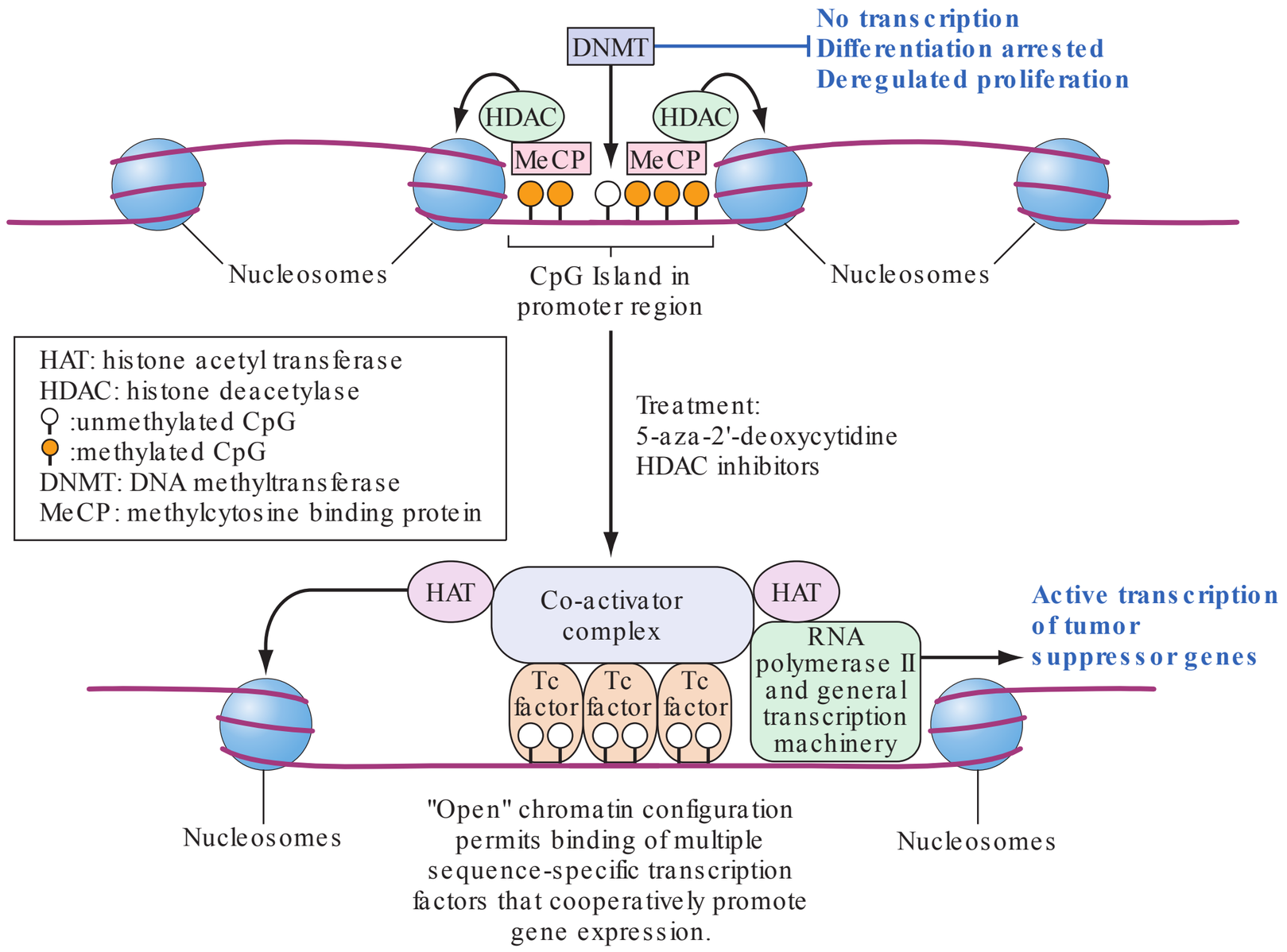

FIGURE 26-4

Epigenetic regulation of gene expression in cancer cells. Tumor-suppressor genes are often epigenetically silenced in cancer cells. In the upper portion, a CpG island within the promoter and enhancer regions of the gene has been methylated, resulting in the recruitment of methyl-cytosine binding proteins (MeCP) and complexes with histone deacetylase (HDAC) activity. Chromatin is in a condensed, nonpermissive conformation that inhibits transcription. Clinical trials are under way using the combination of demethylating agents such as 5-aza-2′-deoxycytidine plus HDAC inhibitors, which together confer an open, permissive chromatin structure (lower portion). Transcription factors bind to specific DNA sequences in promoter regions and, through protein-protein interactions, recruit coactivator complexes containing histone acetyl transferase (HAT) activity. This enhances transcription initiation by RNA polymerase II and associated general transcription factors. The expression of the tumor-suppressor gene commences, with phenotypic changes that may include growth arrest, differentiation, or apoptosis.

determined by the activity of transcription factors in modulating the "histone code" and the methylation status of the genetic regulatory elements of genes.

The pattern of gene transcription is aberrant in all human cancers, and in many cases, epigenetic events are responsible. Unlike genetic events that alter DNA primary structure (e.g., deletions), epigenetic changes are potentially reversible and appear amenable to therapeutic intervention. In certain human cancers, including pancreatic cancer and multiple myeloma, the $p16^{Ink4a}$ promoter is inactivated by methylation, thus permitting the unchecked activity of CDK4/cyclin D and rendering pRb nonfunctional. In sporadic forms of renal, breast, and colon cancer, the von Hippel–Lindau (VHL), breast cancer 1 (BRCA1), and serine/threonine kinase 11 (*STK11*) genes, respectively, are epigenetically silenced. Other targeted genes include the $p15^{Ink4b}$ CDK inhibitor, glutathione-S-transferase (which detoxifies reactive oxygen species), and the E-cadherin molecule (important for junction formation between epithelial cells). Epigenetic silencing can occur in premalignant lesions and can affect genes involved in DNA repair, thus predisposing to further genetic damage. Examples include MLH1 (mut L homologue) in hereditary nonpolyposis colon cancer (HNPCC, also called Lynch's syndrome), which is critical for repair of mismatched bases that occur during DNA synthesis, and O^6-methylguanine-DNA methyltransferase, which removes alkylated guanine adducts from DNA and is often silenced in colon, lung, and lymphoid tumors.

Human leukemias often have chromosomal translocations that code for novel fusion proteins with enzymatic activities that alter chromatin structure. The promyelocytic leukemia–retinoic acid receptor (PML-RAR) fusion protein, generated by the t(15;17) observed in most cases of acute promyelocytic leukemia (APL), binds to promoters containing retinoic acid response elements and recruits HDAC to these promoters, effectively inhibiting gene expression. This arrests differentiation at the promyelocyte stage and promotes tumor cell proliferation and survival. Treatment with pharmacologic doses of all-trans retinoic

acid (ATRA), the ligand for RARα, results in the release of HDAC activity and the recruitment of coactivators, which overcome the differentiation block. T is induced differentiation of APL cells has improved treatment of these patients but also has led to a novel treatment toxicity when newly differentiated tumor cells infiltrate the lungs. However, ATRA represents a treatment paradigm for the reversal of epigenetic changes in cancer. For other leukemia-associated fusion proteins, such as acute myeloid leukemia (AML)-eight-twenty-one (ETO) and the MLL fusion proteins seen in AML and acute lymphocytic leukemia, no ligand is known. T erefore, efforts are ongoing to determine the structural basis for interactions between translocation fusion proteins and chromatin-remodeling proteins and to use this information to rationally design small molecules that will disrupt specific protein-protein associations, although this has proven to be technically difficult. Drugs that block the enzymatic activity of HDAC are being tested. HDAC inhibitors have demonstrated antitumor activity in clinical studies against cutaneous T cell lymphoma (e.g., vorinostat) and some solid tumors. HDAC inhibitors may target cancer cells via a number of mechanisms, including upregulation of death receptors (DR4/5, FAS, and their ligands) and $p21^{Cip1/Waf1}$, as well as inhibition of cell cycle checkpoints.

Efforts are also under way to reverse the hypermethylation of CpG islands that characterizes many malignancies. Drugs that induce DNA demethylation, such as 5-aza-2′-deoxycytidine, can lead to reexpression of silenced genes in cancer cells with restoration of function, and 5-aza-2′-deoxycytidine is approved for use in myelodysplastic syndrome (MDS). However, 5-aza-2′-deoxycytidine has limited aqueous solubility and is myelosuppressive. Other inhibitors of DNA methyltransferases are in development. In ongoing clinical trials, inhibitors of DNA methylation are being combined with HDAC inhibitors. T e hope is that by reversing coexisting epigenetic changes, the deregulated patterns of gene transcription in cancer cells will be at least partially reversed.

Epigenetic gene regulation can also occur via micro-RNAs or long non-coding RNAs (lncRNAs). MicroRNAs are short (average 22 nucleotides in length) RNA molecules that silence gene expression after transcription by binding and inhibiting the translation or promoting the degradation of mRNA transcripts. It is estimated that more than 1000 microRNAs are encoded in the human genome. Each tissue has a distinctive repertoire of microRNA expression, and this pattern is altered in specific ways in cancers. However, specific correlations between microRNA expression and tumor biology and clinical behavior are just now emerging. T erapies targeting microRNAs are not currently at hand but represent a novel area of treatment development. lncRNAs are longer than 200 nucleotides and compose the largest group of noncoding RNAs. Some of them have been shown to play important roles in gene regulation. T e potential for altering these RNAs for therapeutic benefit is an area of active investigation, although much more needs to be learned before this will be feasible.

APOPTOSIS AND OTHER MECHANISMS OF CELL DEATH

Tissue homeostasis requires a balance between the death of aged, terminally differentiated cells or severely damaged cells and their renewal by proliferation of committed progenitors. Genetic damage to growth-regulating genes of stem cells could lead to catastrophic results for the host as a whole. T us, genetic events causing activation of oncogenes or loss of tumor suppressors, which would be predicted to lead to unregulated cell proliferation unless corrected, usually activate signal transduction pathways that block aberrant cell proliferation. T ese pathways can lead to a form of programmed cell death (apoptosis) or irreversible growth arrest (senescence). Much as a panoply of intra- and extracellular signals impinge upon the core cell cycle machinery to regulate cell division, so too are these signals transmitted to a core enzymatic machinery that regulates cell death and survival.

Apoptosis is induced by two main pathways **(Fig. 26-5)**. T e extrinsic pathway of apoptosis is activated by cross-linking members of the tumor necrosis factor (TNF) receptor superfamily, such as CD95 (Fas) and death receptors DR4 and DR5, by their ligands, Fas ligand or TRAIL (TNF-related apoptosis-inducing ligand), respectively. T is induces the association of FADD (Fas-associated death domain) and procaspase-8 to death domain motifs of the receptors. Caspase-8 is activated and then cleaves and activates effector caspases-3 and -7, which then target cellular constituents (including caspase-activated DNAse, cytoskeletal proteins, and a number of regulatory proteins), inducing the morphologic appearance characteristic of apoptosis, which pathologists term "karyorrhexis." T e intrinsic pathway of apoptosis is initiated by the release of cytochrome c and SMAC (second mitochondrial activator of caspases) from the mitochondrial intermembrane space in response to a variety of noxious stimuli, including DNA damage, loss of adherence to the extracellular matrix (ECM), oncogene-induced proliferation, and growth factor deprivation. Upon release into the cytoplasm, cytochrome c associates with dATP, procaspase-9, and the adaptor protein APAF-1, leading to the sequential activation of caspase-9 and effector caspases. SMAC binds to and blocks the function of inhibitor of apoptosis proteins (IAP), negative regulators of caspase activation.

T e release of apoptosis-inducing proteins from the mitochondria is regulated by pro- and antiapoptotic members of the Bcl-2 family. Antiapoptotic members (e.g., Bcl-2, Bcl-XL, and Mcl-1) associate with the mitochondrial outer membrane via their carboxyl termini,

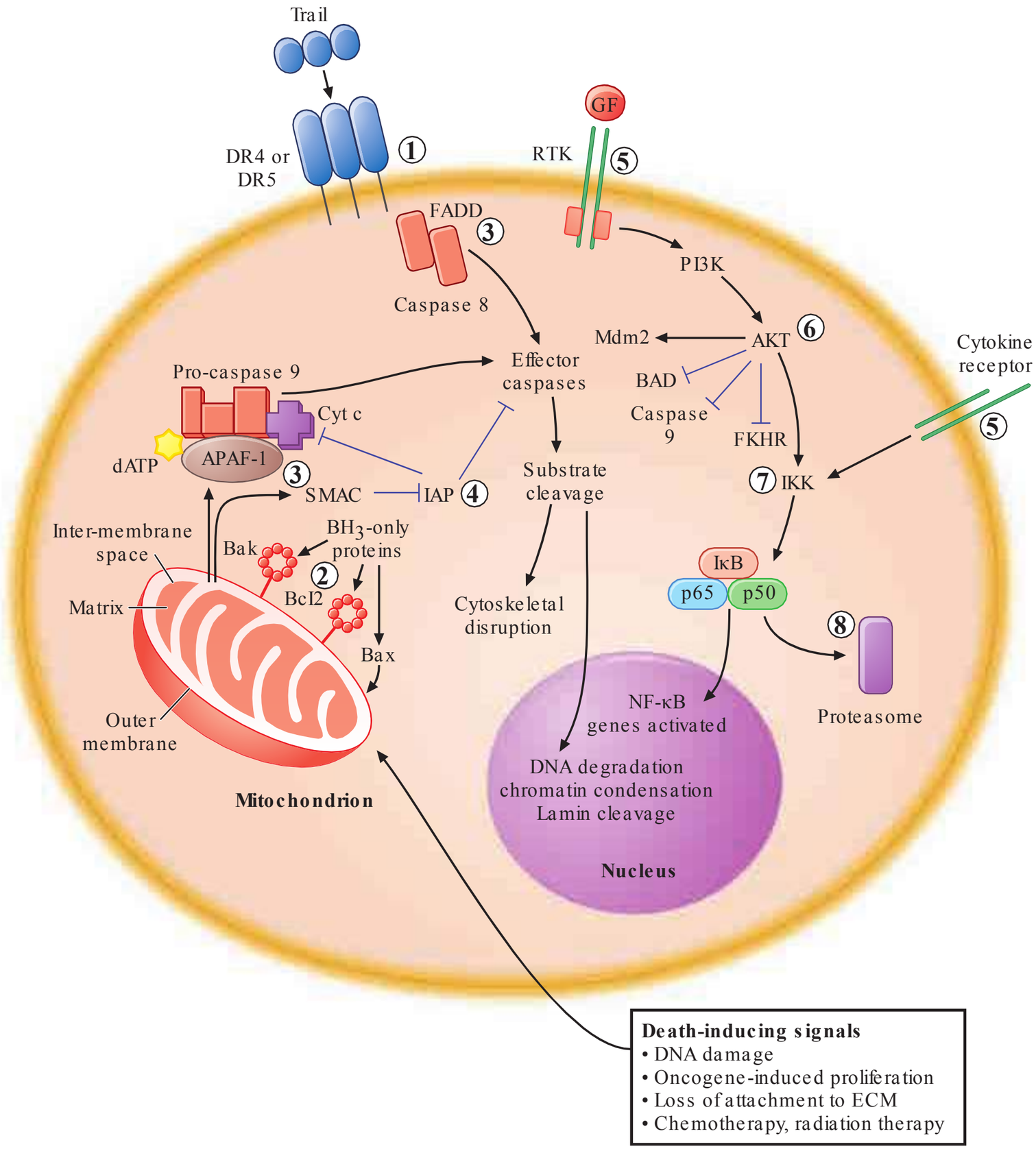

FIGURE 26-5

Therapeutic strategies to overcome aberrant survival pathways in cancer cells. 1. The extrinsic pathway of apoptosis can be selectively induced in cancer cells by TRAIL (the ligand for death receptors 4 and 5) or by agonistic monoclonal antibodies. 2. Inhibition of antiapoptotic Bcl-2 family members with antisense oligonucleotides or inhibitors of the BH_3-binding pocket will promote formation of Bak- or Bax-induced pores in the mitochondrial outer membrane. 3. Epigenetic silencing of APAF-1, caspase-8, and other proteins can be overcome using demethylating agents and inhibitors of histone deacetylases. 4. Inhibitor of apoptosis proteins (IAP) blocks activation of caspases; small-molecule inhibitors of IAP function (mimicking SMAC action) should lower the threshold for apoptosis. 5. Signal transduction pathways originating with activation of receptor tyrosine kinase receptors (RTKs) or cytokine receptors promote survival of cancer cells by a number of mechanisms. Inhibiting receptor function with monoclonal antibodies, such as trastuzumab or cetuximab, or inhibiting kinase activity with small-molecule inhibitors can block the pathway. 6. The Akt kinase phosphorylates many regulators of apoptosis to promote cell survival; inhibitors of Akt may render tumor cells more sensitive to apoptosis-inducing signals; however, the possibility of toxicity to normal cells may limit the therapeutic value of these agents. 7 and 8. Activation of the transcription factor NF-κB (composed of p65 and p50 subunits) occurs when its inhibitor, IκB, is phosphorylated by IκB kinase (IKK), with subsequent degradation of IκB by the proteasome. Inhibition of IKK activity should selectively block the activation of NF-κB target genes, many of which promote cell survival. Inhibitors of proteasome function are Food and Drug Administration approved and may work in part by preventing destruction of IκB, thus blocking NF-κB nuclear localization. NF-κB is unlikely to be the only target for proteasome inhibitors.

exposing to the cytoplasm a hydrophobic binding pocket composed of Bcl-2 homology (BH) domains 1, 2, and 3 that is crucial for their activity. Perturbations of normal physiologic processes in specific cellular compartments lead to the activation of BH3-only proapoptotic family members (such as Bad, Bim, Bid, Puma, Noxa, and others) that can alter the conformation of the outer-membrane proteins Bax and Bak, which then oligomerize to form pores in the mitochondrial outer membrane resulting in cytochrome c release.

If proteins composed only of BH3 domains are sequestered by Bcl-2, Bcl-XL, or Mcl-1, pores do not form and apoptosis-inducing proteins are not released from the mitochondria. The ratio of levels of antiapoptotic Bcl-2 family members and the levels of proapoptotic BH3-only proteins at the mitochondrial membrane determines the activation state of the intrinsic pathway. The mitochondrion must therefore be recognized not only as an organelle with vital roles in intermediary metabolism and oxidative phosphorylation but also as a central regulatory structure of the apoptotic process.

The evolution of tumor cells to a more malignant phenotype requires the acquisition of genetic changes that subvert apoptosis pathways and promote cancer cell survival and resistance to anticancer therapies. However, cancer cells may be more vulnerable than normal cells to therapeutic interventions that target the apoptosis pathways that cancer cells depend on. For instance, overexpression of Bcl-2 as a result of the t(14;18) translocation contributes to follicular lymphoma. Upregulation of Bcl-2 expression is also observed in prostate, breast, and lung cancers and melanoma. Targeting of antiapoptotic Bcl-2 family members has been accomplished by the identification of several low-molecular-weight compounds that bind to the hydrophobic pockets of either Bcl-2 or Bcl-XL and block their ability to associate with death-inducing BH3-only proteins. These compounds inhibit the antiapoptotic activities of Bcl-2 and Bcl-XL at nanomolar concentrations in the laboratory and are entering clinical trials.

Preclinical studies targeting death receptors DR4 and DR5 have demonstrated that recombinant, soluble, human TRAIL or humanized monoclonal antibodies with agonist activity against DR4 or DR5 can induce apoptosis of tumor cells while sparing normal cells. The mechanisms for this selectivity may include expression of decoy receptors or elevated levels of intracellular inhibitors (such as FLIP, which competes with caspase-8 for FADD) by normal cells but not tumor cells. Synergy has been shown between TRAIL-induced apoptosis and chemotherapeutic agents. For instance, some colon cancers encode mutated Bax protein as a result of mismatch repair (MMR) defects and are resistant to TRAIL. However, upregulation of Bak by chemotherapy restores the ability of TRAIL to activate the mitochondrial pathway of apoptosis. However, clinical studies have not yet shown significant activity of approaches targeting the TRAIL pathway.

Many of the signal transduction pathways perturbed in cancer promote tumor cell survival (Fig. 26-5). These include activation of the PI3K/Akt pathway, increased levels of the NF-κB transcription factor, and epigenetic silencing of genes such as APAF-1 and caspase-8. Each of these pathways is a target for therapeutic agents that, in addition to affecting cancer cell proliferation or gene expression, may render cancer cells more susceptible to apoptosis, thus promoting synergy when combined with other chemotherapeutic agents.

Some tumor cells resist drug-induced apoptosis by expression of one or more members of the ABC family of ATP-dependent efflux pumps that mediate the multidrug-resistance (MDR) phenotype. The prototype, P-glycoprotein (PGP), spans the plasma membrane 12 times and has two ATP-binding sites. Hydrophobic drugs (e.g., anthracyclines and vinca alkaloids) are recognized by PGP as they enter the cell and are pumped out. Numerous clinical studies have failed to demonstrate that drug resistance can be overcome using inhibitors of PGP. However, ABC transporters have different substrate specificities, and inhibition of a single family member may not be sufficient to overcome the MDR phenotype. Efforts to reverse PGP-mediated drug resistance continue.

Cells, including cancer cells, can also undergo other mechanisms of cell death including autophagy (degradation of proteins and organelles by lysosomal proteases) and necrosis (digestion of cellular components and rupturing of the cell membrane). Necrosis usually occurs in response to external forces resulting in release of cellular components, which leads to inflammation and damage to surrounding tissues. Although necrosis was thought to be unprogrammed, evidence now suggests that at least some aspects may be programmed. The exact role of necrosis in cancer cell death in various settings is still being determined. In addition to its role in cell death, autophagy can serve as a homeostatic mechanism to promote survival for the cell by recycling cellular components to provide necessary energy. The mechanisms that control the balance between enhancing survival versus leading to cell death are still not fully understood. Autophagy appears to play conflicting roles in the development and survival of cancer. Early in the carcinogenic process, it can act as a tumor suppressor by preventing the cell from accumulating abnormal proteins and organelles. However, in established tumors, it may serve as a mechanism of survival for cancer cells when they are stressed by damage such as from chemotherapy. Inhibition of this process can enhance the sensitivity of cancer cells to chemotherapy. Better understanding of the factors that control the survival-promoting versus death-inducing aspects of autophagy is required in order to know how to best manipulate it for therapeutic benefit.

METASTASIS

The metastatic process accounts for the vast majority of deaths from solid tumors, and therefore, an understanding of this process is critical. The biology of metastasis is complex and requires multiple steps. The three major features of tissue invasion are cell adhesion to the basement membrane, local proteolysis of the membrane, and movement of the cell through the rent in the membrane and the ECM. Cells that lose contact with the ECM normally undergo programmed cell death (anoikis), and this process has to be suppressed in cells

that metastasize. Another process important for metastasizing epithelial cancer cells is epithelial-mesenchymal transition (EMT). T is is a process by which cells lose their epithelial properties and gain mesenchymal properties. T is normally occurs during the developmental process in embryos, allowing cells to migrate to their appropriate destinations in the embryo. It also occurs in wound healing, tissue regeneration, and fibrotic reactions, but in all of these processes, cells stop proliferating when the process is complete. Malignant cells that metastasize undergo EMT as an important step in that process but retain the capacity for unregulated proliferation. Malignant cells that gain access to the circulation must then repeat those steps at a remote site, find a hospitable niche in a foreign tissue, avoid detection by host defenses, and induce the growth of new blood vessels. T e rate-limiting step for metastasis is the ability for tumor cells to survive and expand in the novel microenvironment of the metastatic site, and multiple host-tumor interactions determine the ultimate outcome **(Fig. 26-6)**. Few drugs have been developed to attempt to directly target the process of

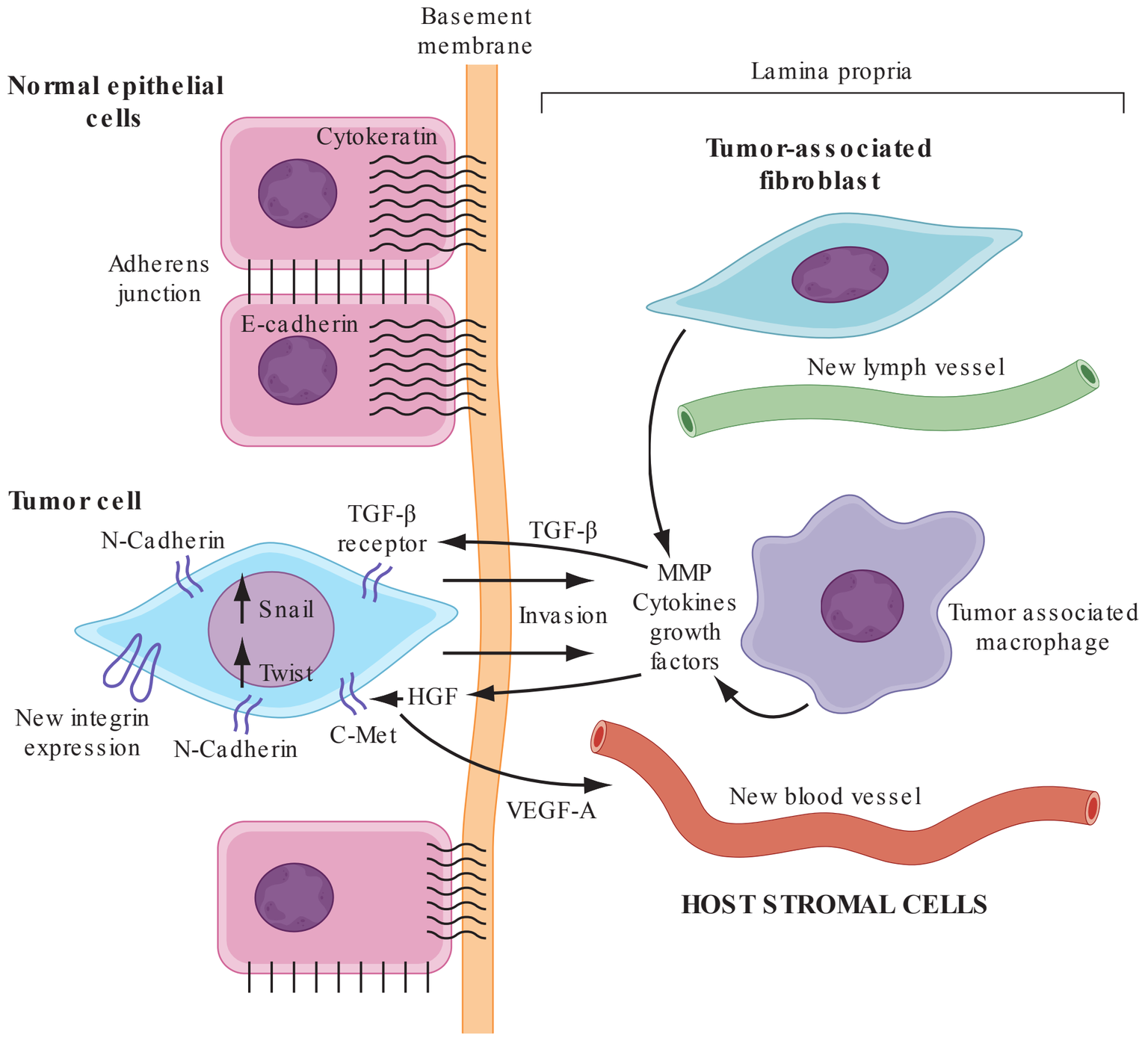

FIGURE 26-6

Oncogene signaling pathways are activated during tumor progression and promote metastatic potential. This figure shows a cancer cell that has undergone epithelial to mesenchymal transition (EMT) under the inf uence of several environmental signals. Critical components include activated transforming growth factor β (TGF-β) and the hepatocyte growth factor (HGF)/c-Met pathways, as well as changes in the expression of adhesion molecules that mediate cell-cell and cell–extracellular matrix interactions. Important changes in gene expression are mediated by the Snail and Twist family of transcriptional repressors (whose expression is induced by the oncogenic pathways), leading to reduced expression of E-cadherin, a key component of adherens junctions between epithelial cells. This, in conjunction with upregulation of N-cadherin, a change in the pattern of expression of integrins (which mediate cell–extracellular matrix associations that are important for cell motility), and a switch in intermediate filament expression from cytokeratin to vimentin, results in the phenotypic change from adherent highly organized epithelial cells to motile and invasive cells with a fibroblast or mesenchymal morphology. EMT is thought to be an important step leading to metastasis in some human cancers. Host stromal cells, including tumor-associated fibroblasts and macrophages, play an important role in modulating tumor cell behavior through secretion of growth factors and proangiogenic cytokines, and matrix metalloproteinases that degrade the basement membrane. VEGF-A, -C, and -D are produced by tumor cells and stromal cells in response to hypoxemia or oncogenic signals and induce production of new blood vessels and lymphatic channels through which tumor cells metastasize to lymph nodes or tissues.

metastasis, in part because the specifics of the critical steps in the process that would be potentially good targets for drugs are still being identified. However, a number of potential targets are known. HER2 can enhance the metastatic potential of breast cancer cells, and as discussed above, the monoclonal antibody trastuzumab, which targets HER2, improves survival in the adjuvant setting for HER2-positive breast cancer patients. Other potential targets that increase metastatic potential of cells in preclinical studies include HIF-1 and -2, transcription factors induced by hypoxia within tumors; growth factors (e.g., cMET and VEGFR); oncogenes (e.g., SRC); adhesion molecules (e.g., focal adhesion kinase [FAK]); ECM proteins (e.g., matrix metalloproteinases-1 and -2); and inflammatory molecules (e.g., COX-2).

T e metastatic phenotype is likely restricted to a small fraction of tumor cells (Fig. 26-6). A number of genetic and epigenetic changes are required for tumor cells to be able to metastasize, including activation of metastasis-promoting genes and inhibition of genes that suppress the metastatic ability. Cells with metastatic capability frequently express chemokine receptors that are likely important in the metastatic process. A number of candidate metastasis-suppressor genes have been identified, including genes coding for proteins that enhance apoptosis, suppress cell division, are involved in the interactions of cells with each other or the ECM, or suppress cell migration. T e loss of function of these genes enhances metastasis. Gene expression profiling is being used to study the metastatic process and other properties of tumor cells that may predict susceptibilities.

An example of the ability of malignant cells to survive and grow in a novel microenvironment is bone metastasis. Bone metastases are extremely painful, cause fractures of weight-bearing bones, can lead to hypercalcemia, and are a major cause of morbidity for cancer patients. Osteoclasts and their monocyte-derived precursors express the surface receptor RANK (receptor activator of NF-κB), which is required for terminal differentiation and activation of osteoclasts. Osteoblasts and other stromal cells express RANK ligand (RANKL), as both a membrane-bound and soluble cytokine. Osteoprotegerin (OPG), a soluble receptor for RANKL produced by stromal cells, acts as a decoy receptor to inhibit RANK activation. T e relative balance of RANKL and OPG determines the activation state of RANK on osteoclasts. Many tumors increase osteoclast activity by secretion of substances such as parathyroid hormone (PTH), PTH-related peptide, interleukin (IL)-1, or Mip1 that perturb the homeostatic balance of bone remodeling by increasing RANK signaling. One example is multiple myeloma, where tumor cell–stromal cell interactions activate osteoclasts and inhibit osteoblasts, leading to the development of multiple lytic bone lesions. Inhibition of RANKL by an antibody (denosumab) can prevent further bone destruction. Bisphosphonates are also effective inhibitors of osteoclast function that are used in the treatment of cancer patients with bone metastases.

CANCER STEM CELLS

Only a small proportion of the cells within a tumor are capable of initiating colonies in vitro or forming tumors at high efficiency when injected into immunocompromised NOD/SCID mice. Acute and chronic myeloid leukemias (AML and CML) have a small population of cells (<1%) that have properties of stem cells, such as unlimited self-renewal and the capacity to cause leukemia when serially transplanted in mice. T ese cells have an undifferentiated phenotype (T y1−CD34+CD38– and do not express other differentiation markers) and resemble normal stem cells in many ways, but are no longer under homeostatic control **(Fig. 26-7)**. Solid tumors may also contain a population of stem cells. Cancer stem cells, like their normal counterparts, have unlimited proliferative capacity and paradoxically traverse the cell cycle at a very slow rate; cancer growth occurs largely due to expansion of the stem cell pool, the unregulated proliferation of an amplifying population, and failure of apoptosis pathways (Fig. 26-7). Slow cell cycle progression and high levels of expression of antiapoptotic Bcl-2 family members and drug ef ux pumps of the MDR family render cancer stem cells less vulnerable to cancer chemotherapy or radiation therapy. Implicit in the cancer stem cell hypothesis is the idea that failure to cure most human cancers is due to the fact that current therapeutic agents do not kill the stem cells. If cancer stem cells can be identified and isolated, then aberrant signaling pathways that distinguish these cells from normal tissue stem cells can be identified and targeted. Evidence that cells with stem cell properties can arise from other epithelial cells within the cancer by processes such as epithelial mesenchymal transition also implies that it is essential to treat all of the cancer cells, and not just those with current stem cell-like properties, in order to eliminate the self-renewing cancer cell population. T e exact nature of cancer stem cells remains an area of investigation. One of the unanswered questions is the exact origin of cancer stem cells for the different cancers.

PLASTICITY AND RESISTANCE

Cancer cells, and especially stem cells, have the capacity for significant plasticity, allowing them to alter multiple aspects of cell biology in response to external factors (e.g., chemotherapy, inflammation, immune response).

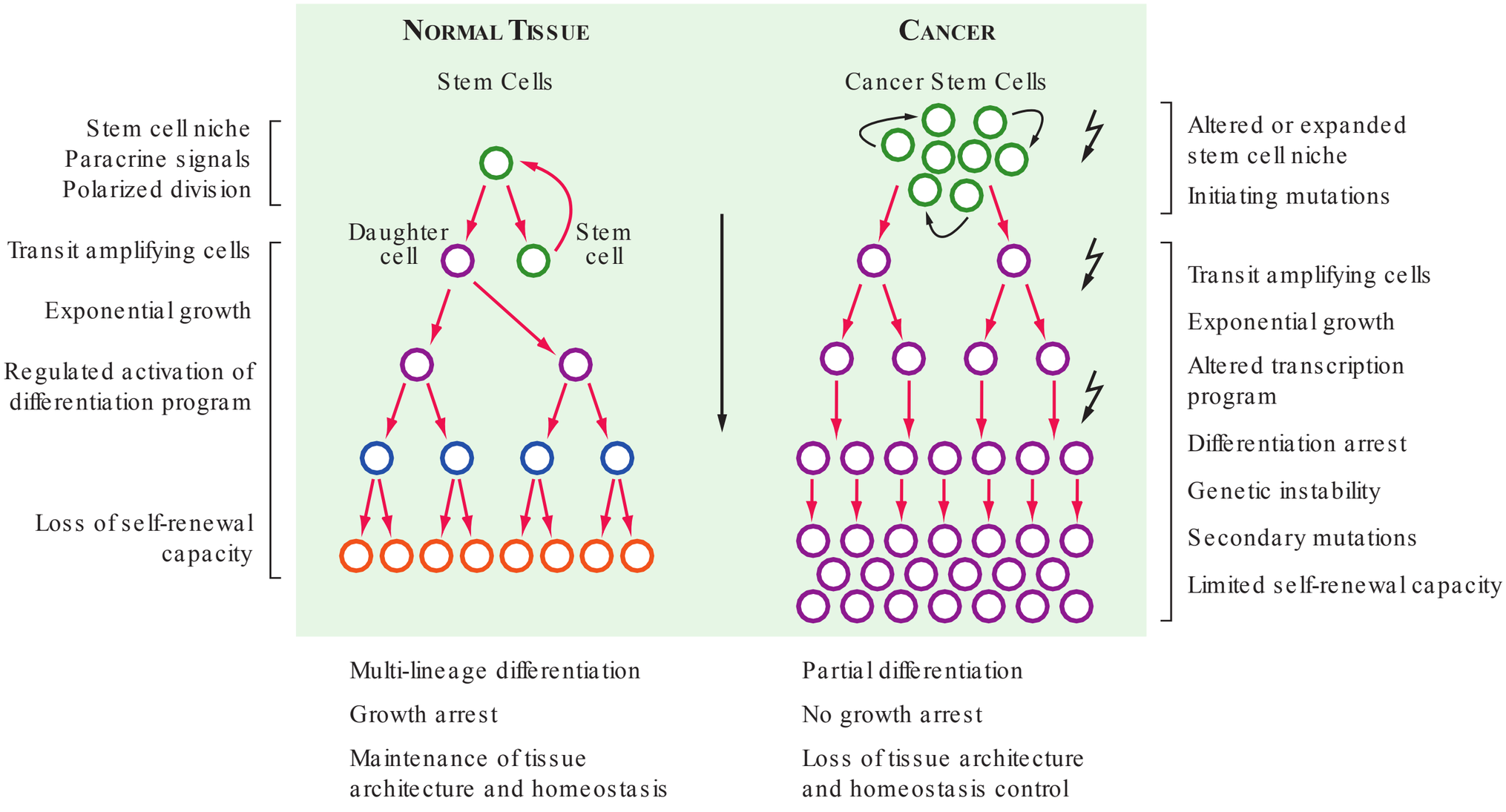

FIGURE 26-7

Cancer stem cells play a critical role in the initiation, progression, and resistance to therapy of malignant neoplasms. In normal tissues (left), homeostasis is maintained by asymmetric division of stem cells, leading to one progeny cell that will differentiate and one cell that will maintain the stem cell pool. This occurs within highly specific niches unique to each tissue, such as in close apposition to osteoblasts in bone marrow, or at the base of crypts in the colon. Here, paracrine signals from stromal cells, such as sonic hedgehog or Notch ligands, as well as upregulation of β-catenin and telomerase, help to maintain stem cell features of unlimited self-renewal while preventing differentiation or cell death. This occurs in part through upregulation of the transcriptional repressor Bmi-1 and inhibition of the $p16^{Ink4a}$/Arf and p53 pathways. Daughter cells leave the stem cells niche and enter a proliferative phase (referred to as transit-amplifying) for a specified number of cell divisions, during which time a developmental program is activated, eventually giving rise to fully differentiated cells that have lost proliferative potential. Cell renewal equals cell death, and homeostasis is maintained. In this hierarchical system, only stem cells are long-lived. The hypothesis is that cancers harbor stem cells that make up a small fraction (i.e., 0.001–1%) of all cancer cells. These cells share several features with normal stem cells, including an undifferentiated phenotype, unlimited self-renewal potential, and a capacity for some degree of differentiation; however, due to initiating mutations (mutations are indicated by lightning bolts), they are no longer regulated by environmental cues. The cancer stem cell pool is expanded, and rapidly proliferating progeny, through additional mutations, may attain stem cell properties, although most of this population is thought to have a limited proliferative capacity. Differentiation programs are dysfunctional due to reprogramming of the pattern of gene transcription by oncogenic signaling pathways. Within the cancer transit-amplifying population, genomic instability generates aneuploidy and clonal heterogeneity as cells attain a fully malignant phenotype with metastatic potential. The cancer stem cell hypothesis has led to the idea that current cancer therapies may be effective at killing the bulk of tumor cells but do not kill tumor stem cells, leading to a regrowth of tumors that is manifested as tumor recurrence or disease progression. Research is in progress to identify unique molecular features of cancer stem cells that can lead to their direct targeting by novel therapeutic agents.

T us, a major problem in cancer therapy is that malignancies have a wide spectrum of mechanisms for both initial and adaptive resistance to treatments. T ese include inhibiting drug delivery to the cancer cells, blocking drug uptake and retention, increasing drug metabolism, altering levels of target proteins, acquiring mutations in target proteins, modifying metabolism and cell signaling pathways, using alternate signaling pathways, adjusting the cell replication process including mechanisms by which the cell deals with DNA damage, inhibiting apoptosis, and evading the immune system. T us, most metastatic cancers (except those curable with chemotherapy such as germ cell tumors) eventually become resistant to the therapy being used. Overcoming resistance is a major area of research.

CANCER METABOLISM

One of the distinguishing characteristics of cancer cells is that they have altered metabolism as compared with

normal cells in supporting survival and their high rates of proliferation. T ese cells must focus a significant fraction of their energy resources on synthesis of proteins and other molecules while still maintaining sufficient ATP production to survive and grow. Although normal proliferating cells also have similar needs, there are differences in how cancer cells metabolize glucose and a number of other compounds, including glutamine, as compared to normal cells. Many cancer cells use aerobic glycolysis (the Warburg effect) **(Fig. 26-8)** to metabolize glucose, leading to increased lactic acid production, whereas normal cells use oxidative phosphorylation in mitochondria under aerobic conditions, a much more efficient process. One consequence is increased glucose uptake by cancer cells, a fact used in fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning to detect tumors. A number of proteins in cancer cells, including CMYC, HIF1, RAS, p53, pRB, and AKT, are all involved in modulating glycolytic processes and controlling the Warburg effect. Although these pathways remain difficult to target therapeutically, both the PI3 kinase pathway with signaling through mTOR and the AMP-activated kinase (AMPK) pathway, which inhibits mTOR complex 1 (mTORC1; a protein complex that includes mTOR), are important in controlling the glycolytic process and thus provide potential targets for inhibiting this process. T e inefficient utilization of glucose also leads to a need for alternative metabolic pathways for other compounds as well, one of which is glutamine. Similar to glucose, this provides both a source for structural molecules as well as energy production. Glutamine is also inefficiently used by cancer cells.

Mutations in genes involved in the metastatic process occur in a number of cancers. Among the most frequently found to date are mutations in isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2). These have been most commonly seen in gliomas, AML, and intrahepatic cholangiocarcinomas. These mutations lead to the production of an oncometabolite (2-hydroxyglutarate [2HG]) instead of the normal product α-ketoglutarate. Although the exact mechanisms of oncogenesis by 2HG are still being elucidated, α-ketoglutarate is a key cofactor for a number of dioxygenases involved in controlling DNA methylation. 2HG can act as a competitive inhibitor for α-ketoglutarate, leading to alterations in methylation status (primarily hypermethylation) of genes (epigenetic changes) that can have profound effects on a number of cellular processes including differentiation. Inhibitors of mutant IDH1 and IDH2 are being developed.

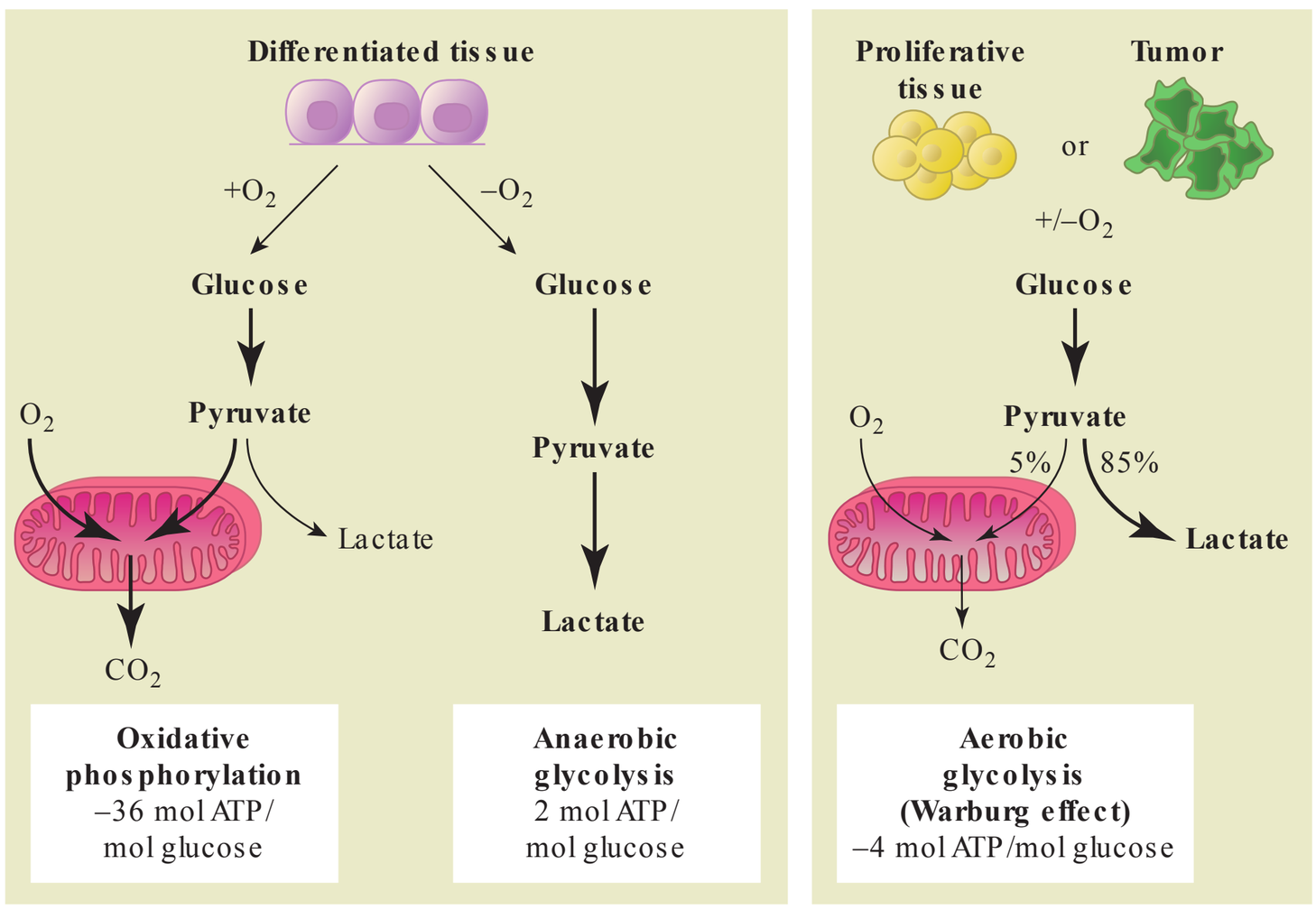

FIGURE 26-8

Warburg ef ect versus oxidative phosphorylation. In most normal tissues, the vast majority of cells are differentiated and dedicated to a particular function within the organ in which they reside. The metabolic needs are mainly for energy and not for building blocks for new cells. In these tissues, ATP is generated by oxidative phosphorylation that efficiently generates about 36 molecules of ATP for each molecule of glucose metabolized. By contrast, proliferative tumor tissues, especially in the setting of hypoxia, a typical condition within tumors, use aerobic glycolysis to generate energy for cell survival and generation of building blocks for new cells.

Much needs to be learned about the specific differences in metabolism between cancer cells and normal cells; however, modulators of metabolism are being tested clinically. T e first of these is the antidiabetic agent metformin, both alone and in combination with chemotherapeutic agents. Metformin inhibits gluconeogenesis and may have direct effects on tumor cells by activating the 5′-adenosine monophosphate-activated kinase (AMPK), a serine/threonine protein kinase that is downstream of the LKB1 tumor suppressor, and thus inhibiting mTORC1. T is leads to decreased protein synthesis and proliferation. A second approach being tested involves dichloracetate (DCA), an inhibitor of pyruvate dehydrogenase kinase (PDK). PDK inhibits pyruvate dehydrogenase in cancer cells, leading to a switch from mitochondrial oxidative phosphorylation of glucose to cytoplasmic glycolysis (the Warburg effect). By blocking PDK, DCA inhibits glycolysis. Additional approaches targeting tumor metabolism will likely emerge.

TUMOR MICROENVIRONMENT, ANGIOGENESIS, AND IMMUNE EVASION

Tumors consist not only of malignant cells but also of a complex microenvironment including many other types of cells (e.g., inflammatory cells), ECM, secreted factors (e.g., growth factors), reactive oxygen and nitrogen species, mechanical factors, blood vessels, and lymphatics. T is microenvironment is not static but rather is dynamic and continually evolving. Both the complexity and dynamic nature of the microenvironment enhance the difficulty of treating tumors. T ere are also a number of mechanisms by which the microenvironment can contribute to resistance to anticancer therapies.

One of the critical elements of tumor cell proliferation is delivery of oxygen, nutrients, and circulating factors important for growth and survival. T e diffusion limit for oxygen in tissues is ~100–200 μm, and thus, a critical aspect in the growth of tumors is the development of new blood vessels, or angiogenesis. T e growth of primary and metastatic tumors to larger than a few millimeters requires the recruitment of blood vessels and vascular endothelial cells to support their metabolic requirements. T us, a critical element in growth of primary tumors and formation of metastatic sites is the angiogenic switch: the ability of the tumor to promote the formation of new capillaries from preexisting host vessels. T e angiogenic switch is a phase in tumor development when the dynamic balance of pro- and antiangiogenic factors is tipped in favor of vessel formation by the effects of the tumor on its immediate environment. Stimuli for tumor angiogenesis include hypoxemia, inflammation, and genetic lesions in oncogenes or tumor suppressors that alter tumor cell gene expression. Angiogenesis consists of several steps, including the stimulation of endothelial cells (ECs) by growth factors, degradation of the ECM by proteases, proliferation and migration of ECs into the tumor, and the eventual formation of new capillary tubes.

Tumor blood vessels are not normal; they have chaotic architecture and blood flow. Due to an imbalance of angiogenic regulators such as VEGF and angiopoietins (see below), tumor vessels are tortuous and dilated with an uneven diameter, excessive branching, and shunting. Tumor blood flow is variable, with areas of hypoxemia and acidosis leading to the selection of variants that are resistant to hypoxemia-induced apoptosis (often due to the loss of p53 expression). Tumor vessel walls have numerous openings, widened interendothelial junctions, and discontinuous or absent basement membrane; this contributes to the high vascular permeability of these vessels and, together with lack of functional intratumoral lymphatics, causes increased interstitial pressure within the tumor (which also interferes with the delivery of therapeutics to the tumor; **Figs. 26-9**, **26-10**, and **26-11**). Tumor blood vessels lack perivascular cells such as pericytes and smooth-muscle cells that normally regulate flow in response to tissue metabolic needs.

Unlike normal blood vessels, the vascular lining of tumor vessels is not a homogeneous layer of ECs but often consists of a mosaic of ECs and tumor cells with upregulated genes seen in ECs and vessel formation that can occur in hypoxic conditions because of their plasticity; the concept of cancer cell–derived vascular channels, which may be lined by ECM secreted by the tumor cells, is referred to as vascular mimicry. During tumor angiogenesis, ECs are highly proliferative and express a number of plasma membrane proteins that are characteristic of activated endothelium, including growth factor receptors and adhesion molecules such as integrins.

MECHANISMS OF TUMOR VESSEL FORMATION

Tumors use a number of mechanisms to promote vascularization, subverting normal angiogenic processes for this purpose (Fig. 26-9). Primary or metastatic tumor cells sometimes arise in proximity to host blood vessels and grow around these vessels, parasitizing nutrients by co-opting the local blood supply. However, most tumor blood vessels arise by the process of sprouting, in which tumors secrete trophic angiogenic molecules, the most potent being vascular endothelial growth factors (VEGF), that induce the proliferation and migration of host ECs into the tumor. Sprouting in normal and pathogenic angiogenesis is regulated by three families of transmembrane receptor tyrosine kinases (RTKs) expressed on ECs and their ligands

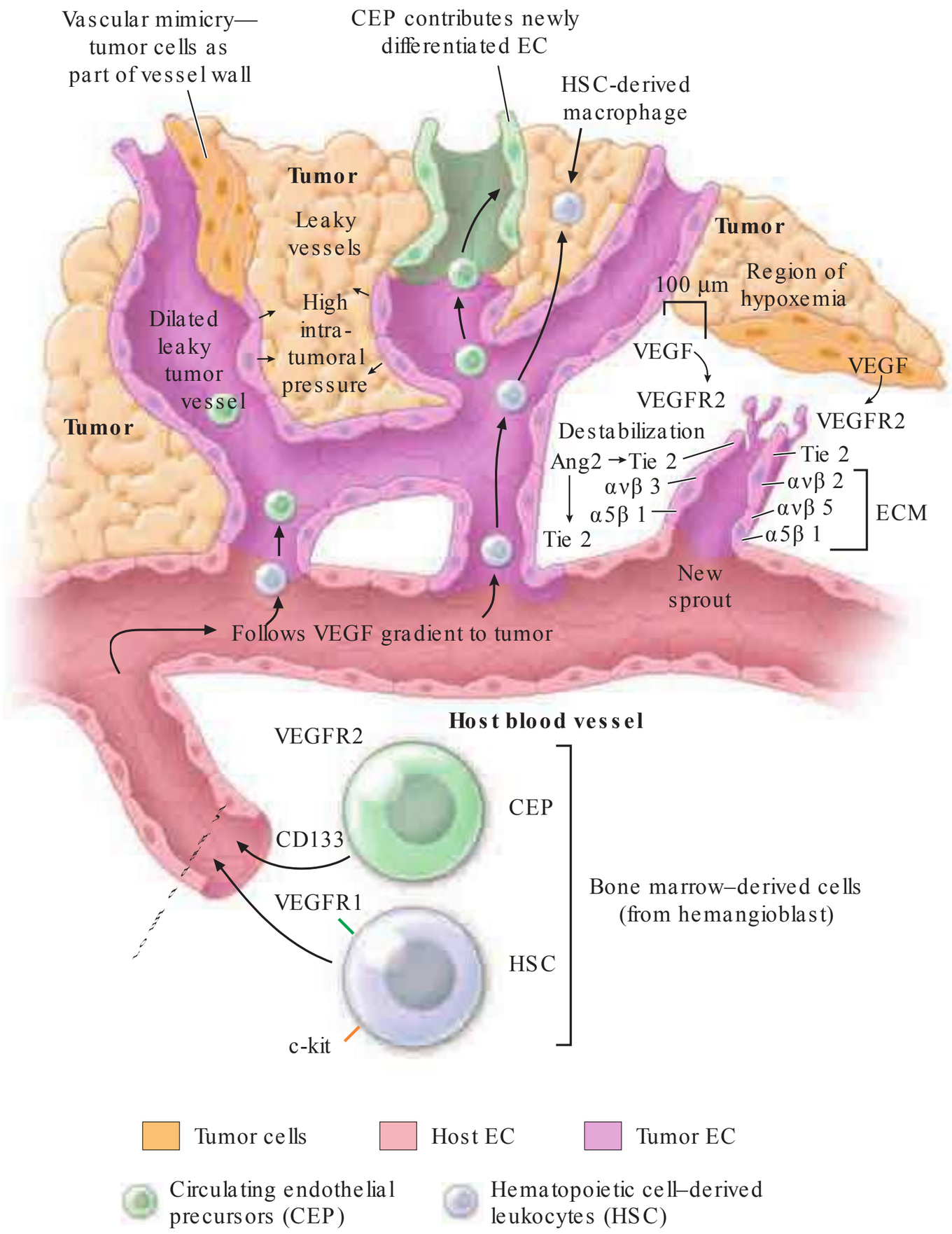

FIGURE 26-9

Tumor angiogenesis is a complex process involving many different cell types that must proliferate, migrate, invade, and differentiate in response to signals from the tumor microenvironment. Endothelial cells (ECs) sprout from host vessels in response to VEGF, bFGF, Ang2, and other proangiogenic stimuli. Sprouting is stimulated by VEGF/VEGFR2, Ang2/Tie2, and integrin/extracellular matrix (ECM) interactions. Bone marrow–derived circulating endothelial precursors (CEPs) migrate to the tumor in response to VEGF and differentiate into ECs, while hematopoietic stem cells differentiate into leukocytes, including tumor-associated macrophages that secrete angiogenic growth factors and produce matrix metalloproteinases (MMPs) that remodel the ECM and release bound growth factors. Tumor cells themselves may directly form parts of vascular channels within tumors. The pattern of vessel formation is haphazard: vessels are tortuous, dilated, and leaky and branch in random ways. This leads to uneven blood flow within the tumor, with areas of acidosis and hypoxemia (which stimulate release of angiogenic factors) and high intratumoral pressures that inhibit delivery of therapeutic agents.

(VEGFs, angiopoietins, ephrins; Fig. 26-10), which are produced by tumor cells, inflammatory cells, or stromal cells in the tumor microenvironment.

When tumor cells arise in or metastasize to an avascular area, they grow to a size limited by hypoxemia and nutrient deprivation. Hypoxemia, a key regulator of tumor angiogenesis, causes the transcriptional induction of the gene encoding VEGF. VEGF and its receptors are required for embryonic vasculogenesis (development of new blood vessels when none preexist) and normal (wound healing, corpus luteum formation) and pathologic angiogenesis (tumor angiogenesis, inflammatory conditions such as rheumatoid arthritis). VEGF-A is a heparin-binding glycoprotein with at least

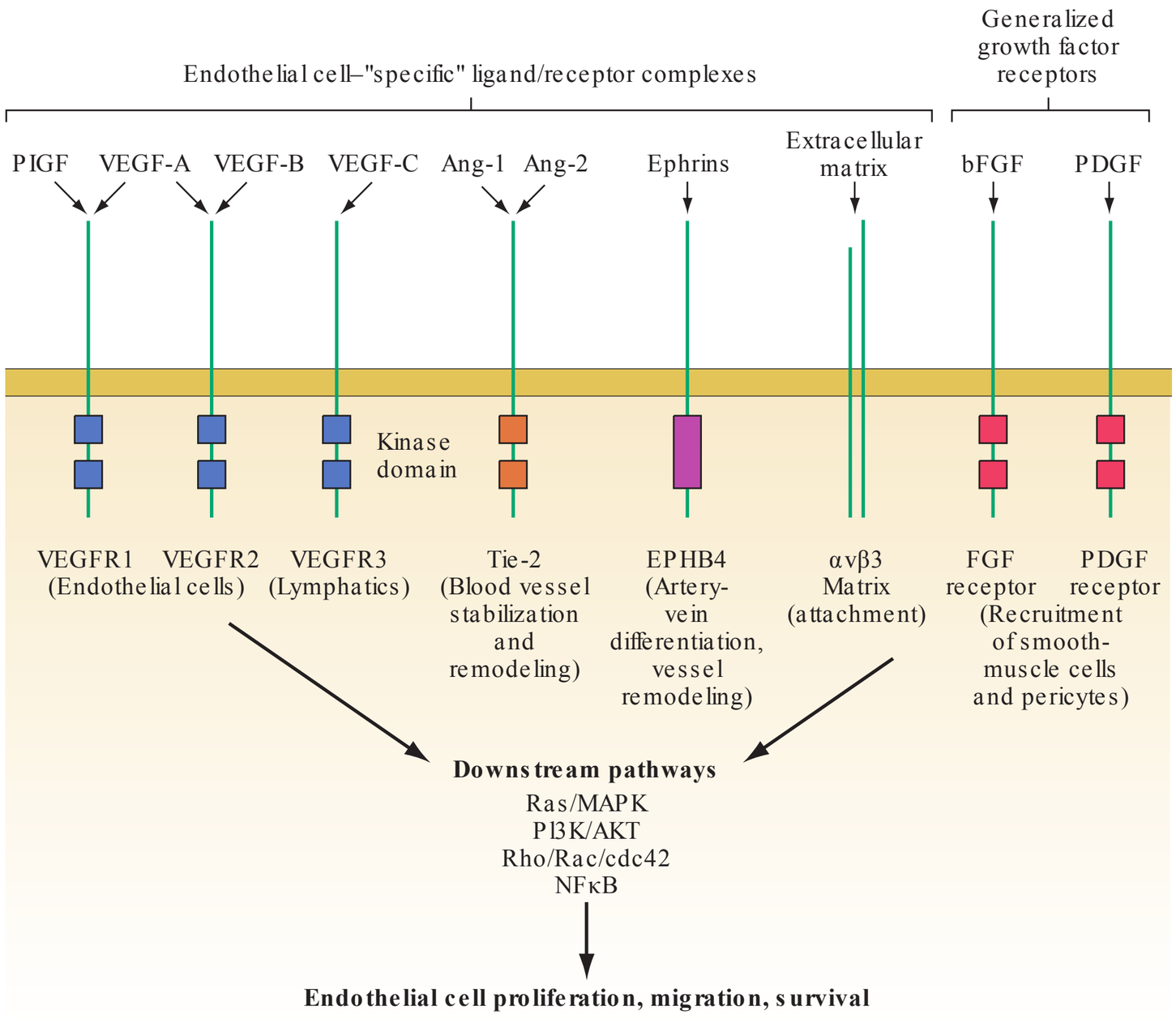

FIGURE 26-10

Critical molecular determinants of endothelial cell biology. Angiogenic endothelium expresses a number of receptors not found on resting endothelium. These include receptor tyrosine kinases (RTKs) and integrins that bind to the extracellular matrix and mediate endothelial cell (EC) adhesion, migration, and invasion. ECs also express RTK (i.e., the FGF and PDGF receptors) that are found on many other cell types. Critical functions mediated by activated RTK include proliferation, migration, and enhanced survival of endothelial cells, as well as regulation of the recruitment of perivascular cells and bloodborne circulating endothelial precursors and hematopoietic stem cells to the tumor. Intracellular signaling via EC-specific RTK uses molecular pathways that may be targets for future antiangiogenic therapies.

four isoforms (splice variants) that regulates blood vessel formation by binding to the RTKs VEGFR1 and VEGFR2, which are expressed on all ECs in addition to a subset of hematopoietic cells (Fig. 26-9). VEGFR2 regulates EC proliferation, migration, and survival, whereas VEGFR1 may act as an antagonist of R2 in ECs but is probably also important for angioblast differentiation during embryogenesis. Tumor vessels may be more dependent on VEGFR signaling for growth and survival than normal ECs. Although VEGF signaling is a critical initiator of angiogenesis, this is a complex process regulated by additional signaling pathways (Fig. 26-10). The angiopoietin, Ang1, produced by stromal cells, binds to the EC RTK Tie2 and promotes the interaction of ECs with the ECM and perivascular cells, such as pericytes and smooth-muscle cells, to form tight, nonleaky vessels. Platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) help to recruit these perivascular cells. Ang1 is required for maintaining the quiescence and stability of mature blood vessels and prevents the vascular permeability normally induced by VEGF and inflammatory cytokines.

For tumor cell–derived VEGF to initiate sprouting from host vessels, the stability conferred by the Ang1/Tie2 pathway must be perturbed; this occurs by the secretion of Ang2 by ECs that are undergoing active remodeling. Ang2 binds to Tie2 and is a competitive inhibitor of Ang1 action: under the influence of Ang2, preexisting blood vessels become more responsive to remodeling signals, with less adherence of ECs to stroma and associated perivascular cells and more responsiveness to VEGF. Therefore, Ang2 is required at early stages of tumor angiogenesis for destabilizing the vasculature by making host ECs more sensitive to angiogenic signals. Because tumor ECs are blocked by Ang2, there is no stabilization by the Ang1/Tie2 interaction, and tumor blood vessels are leaky, hemorrhagic, and have poor association of ECs with underlying stroma. Sprouting tumor ECs express high levels of the transmembrane protein ephrin-B2 and its receptor, the RTK EPH, whose signaling appears to work with the angiopoietins during vessel remodeling. During

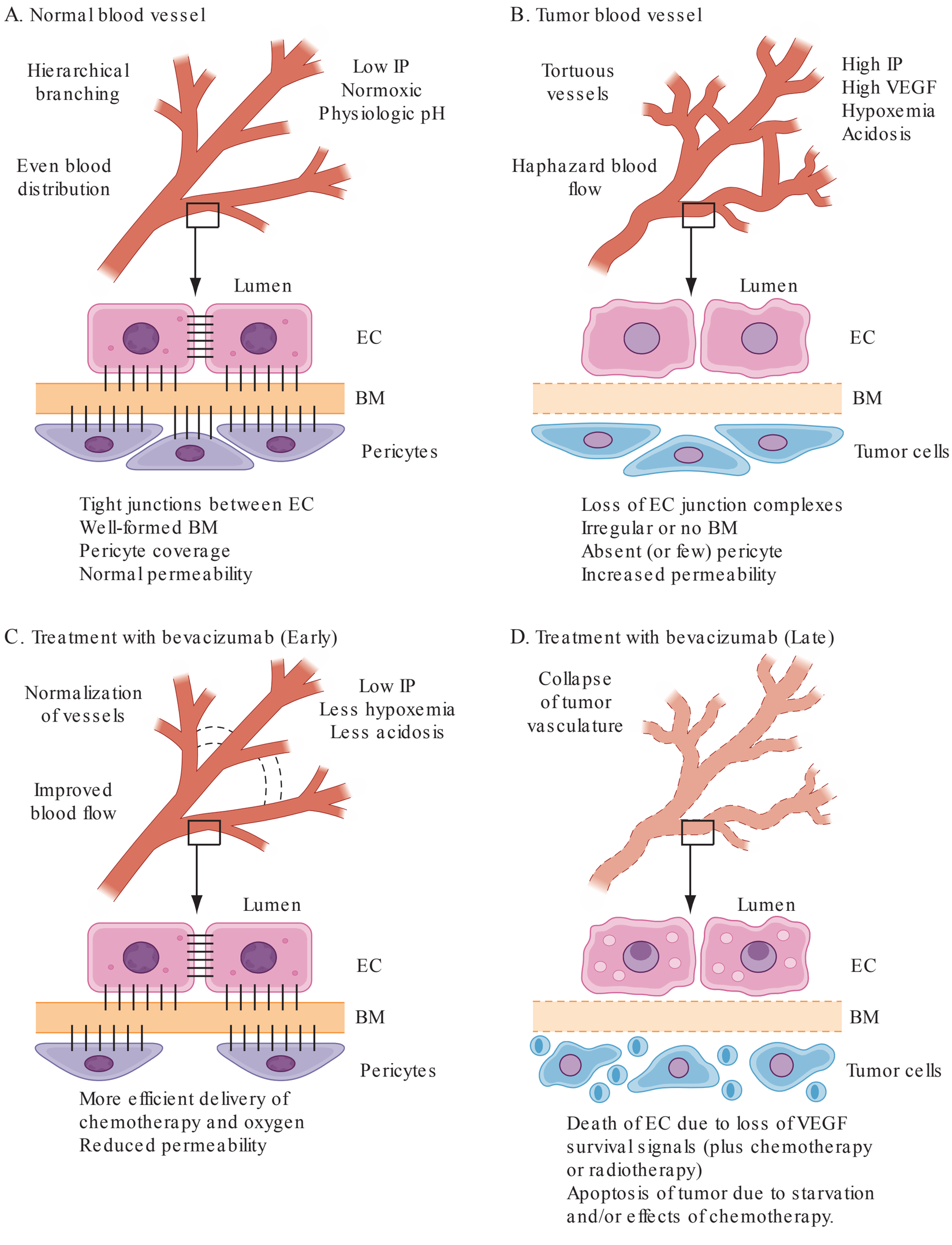

FIGURE 26-11

Normalization of tumor blood vessels due to inhibition of VEGF signaling. A. Blood vessels in normal tissues exhibit a regular hierarchical branching pattern that delivers blood to tissues in a spatially and temporally efficient manner to meet the metabolic needs of the tissue (top). At the microscopic level, tight junctions are maintained between endothelial cells (ECs), which are adherent to a thick and evenly distributed basement membrane (BM). Pericytes form a surrounding layer that provides trophic signals to the EC and helps maintain proper vessel tone. Vascular permeability is regulated, interstitial fluid pressure is low, and oxygen tension and pH are physiologic. B. Tumors have abnormal vessels with tortuous branching and dilated, irregular interconnecting branches, causing uneven blood flow with areas of hypoxemia and acidosis. This harsh environment selects genetic events that result in resistant tumor variants, such as the loss of p53. High levels of VEGF (secreted by tumor cells) disrupt gap junction communication, tight junctions, and adherens junctions between EC via src-mediated phosphorylation of proteins such as connexin 43, zonula occludens-1, VE-cadherin, and α/β-catenins. Tumor vessels have thin, irregular BM, and pericytes are sparse or absent. Together, these molecular abnormalities result in a vasculature that is permeable to serum macromolecules, leading to high tumor interstitial pressure, which can prevent the delivery of drugs to the tumor cells. This is made worse by the binding and activation of platelets at sites of exposed BM, with release of stored VEGF and microvessel clot formation, creating more abnormal blood flow and regions of hypoxemia. C. In experimental systems, treatment with bevacizumab or blocking antibodies to

embryogenesis, EPH receptors are expressed on the endothelium of primordial venous vessels while the transmembrane ligand ephrin-B2 is expressed by cells of primordial arteries; the reciprocal expression may regulate differentiation and patterning of the vasculature.

A number of ubiquitously expressed host molecules play critical roles in normal and pathologic angiogenesis. Proangiogenic cytokines, chemokines, and growth factors secreted by stromal cells or inflammatory cells make important contributions to neovascularization, including bFGF, transforming growth factor α (TGF-α), TNF-α, and IL-8. In contrast to normal endothelium, angiogenic endothelium overexpresses specific members of the integrin family of ECM-binding proteins that mediate EC adhesion, migration, and survival. Specifically, expression of integrins $\alpha_v\beta_3$, $\alpha_v\beta_5$, and $\alpha_5\beta_1$ mediates spreading and migration of ECs and is required for angiogenesis induced by VEGF and bFGF, which in turn can upregulate EC integrin expression. T e $\alpha_v\beta_3$ integrin physically associates with VEGFR2 in the plasma membrane and promotes signal transduction from each receptor to promote EC proliferation (via focal adhesion kinase, src, PI3K, and other pathways) and survival (by inhibition of p53 and increasing the Bcl-2/Bax expression ratio). In addition, $\alpha_v\beta_3$ forms cell-surface complexes with matrix metalloproteinases (MMPs), zinc-requiring proteases that cleave ECM proteins, leading to enhanced EC migration and the release of heparin-binding growth factors, including VEGF and bFGF. EC adhesion molecules can be upregulated (i.e., by VEGF, TNF-α) or downregulated (by TGF-β); this, together with chaotic blood flow, explains poor leukocyte-endothelial interactions in tumor blood vessels and may help tumor cells avoid immune surveillance.

Lymphatic vessels also exist within tumors. Development of tumor lymphatics is associated with expression of VEGFR3 and its ligands VEGF-C and VEGF-D. T e role of these vessels in tumor cell metastasis to regional lymph nodes remains to be determined. However, VEGF-C levels correlate significantly with metastasis to regional lymph nodes in lung, prostate, and colorectal cancers.

ANTIANGIOGENIC THERAPY

Angiogenesis inhibitors function by targeting the critical molecular pathways involved in EC proliferation, migration, and/or survival, many of which are unique to the activated endothelium in tumors. Inhibition of growth factor and adhesion-dependent signaling pathways can induce EC apoptosis with concomitant inhibition of tumor growth. Different types of tumors can use distinct combinations of molecular mechanisms to activate the angiogenic switch. T erefore, it is doubtful that a single antiangiogenic strategy will suffice for all human cancers; rather, a number of agents or combinations of agents will be needed, depending on distinct programs of angiogenesis used by different human cancers. Despite this, experimental data indicate that for some tumor types, blockade of a single growth factor (e.g., VEGF) may inhibit tumor-induced vascular growth.

Bevacizumab, an antibody that binds VEGF, appears to potentiate the effects of a number of different types of active chemotherapeutic regimens used to treat a variety of different tumor types including colon cancer, lung cancer, cervical cancer, and RCC.

Bevacizumab is administered IV every 2–3 weeks (its half-life is nearly 20 days) and is generally well tolerated. Hypertension is the most common side effect of inhibitors of VEGF (or its receptors), but can be treated with antihypertensive agents and rarely requires discontinuation of therapy. Rare but serious potential risks include arterial thromboembolic events, including stroke and myocardial infarction, and hemorrhage. Another serious complication is bowel perforation, which has been observed in 1–3% of patients (mainly those with colon and ovarian cancers). Inhibition of wound healing is also seen.

Several small-molecule inhibitors (SMIs) that target VEGFR tyrosine kinase activity but are also inhibitory to other kinases have also been approved to treat certain cancers. Sunitinib (see above and Table 26-2) has activity directed against mutant c-Kit receptors (approved for GIST), but also targets VEGFR and PDGFR, and has shown significant antitumor activity against metastatic RCC, presumably on the basis of its antiangiogenic activity. Similarly, sorafenib, originally developed as a Raf kinase inhibitor but with potent activity against VEGFR and PDGFR, has activity against RCC, thyroid cancer, and hepatocellular cancer. Other inhibitors of VEGFR approved for the treatment of RCC include axitinib and pazopanib.

VEGFR2 leads to changes in the tumor vasculature that has been termed vessel normalization. During the first week of treatment, abnormal vessels are eliminated or pruned (dotted lines), leaving a more normal branching pattern. ECs partially regain features such as cell-cell junctions, adherence to a more normal BM, and pericyte coverage. These changes lead to a decrease in vascular permeability, reduced interstitial pressure, and a transient increase in blood f ow within the tumor. Note that in murine models, this normalization period lasts only for ~5–6 days. D. After continued anti-VEGF/VEGFR therapy (which is often combined with chemo- or radiotherapy), ECs die, leading to tumor cell death (either due to direct effects of the chemotherapy or lack of blood f ow).

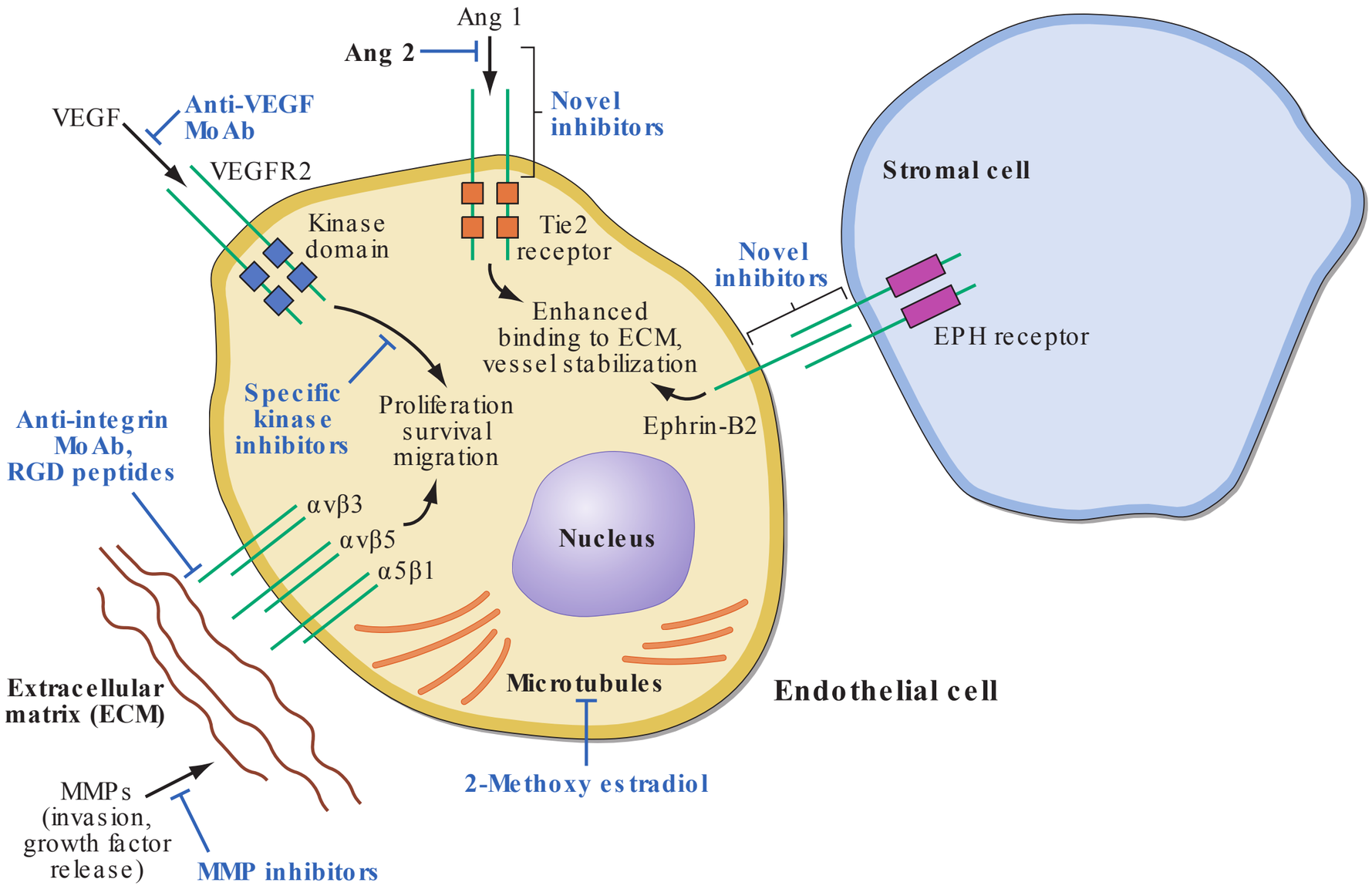

FIGURE 26-12

Knowledge of the molecular events governing tumor angiogenesis has led to a number of therapeutic strategies to block tumor blood vessel formation. The successful therapeutic targeting of VEGF is described in the text. Other endothelial cell–specific receptor tyrosine kinase pathways (e.g., angiopoietin/Tie2 and ephrin/EPH) are likely targets for the future. Ligation of the $\alpha_v\beta_3$ integrin is required for endothelial cell (EC) survival. Integrins are also required for EC migration and are important regulators of matrix metalloproteinase (MMP) activity, which modulates EC movement through the extracellular matrix (ECM) as well as release of bound growth factors. Targeting of integrins includes development of blocking antibodies, small peptide inhibitors of integrin signaling, and arg-gly-asp–containing peptides that prevent integrin:ECM binding. Peptides derived from normal proteins by proteolytic cleavage, including endostatin and tumstatin, inhibit angiogenesis by mechanisms that include interfering with integrin function. Signal transduction pathways that are dysregulated in tumor cells indirectly regulate EC function. Inhibition of EGF-family receptors, whose signaling activity is upregulated in a number of human cancers (e.g., breast, colon, and lung cancers), results in downregulation of VEGF and IL-8, while increasing expression of the antiangiogenic protein thrombospondin-1. The Ras/MAPK, PI3K/Akt, and Src kinase pathways constitute important antitumor targets that also regulate the proliferation and survival of tumor-derived EC. The discovery that ECs from normal tissues express tissue-specific "vascular addressins" on their cell surface suggests that targeting specific EC subsets may be possible.

The success in targeting tumor angiogenesis has led to enhanced enthusiasm for the development of drugs that target other aspects of the angiogenic process; some of these therapeutic approaches are outlined in **Fig. 26-12**.

EVASION OF THE IMMUNE SYSTEM BY CANCERS

Cancers have a number of mechanisms that allow them to evade detection and elimination by the immune system. These include downregulation of cell surface proteins involved in immune recognition (including MHC proteins and tumor-specific antigens), expression of other cell surface proteins that inhibit immune function (including members of the B7 family of proteins such as PD-L1), secretion of proteins and other molecules that are immunosuppressive, recruitment and expansion of immunosuppressive cells such as regulatory T cells, and induction of T cell tolerance. In addition, the inflammatory effects of some of the immune mediator cells in the tumor microenvironment (especially tissue-associated macrophages and myeloid-derived suppressor cells) can suppress T cell responses to the tumor as well as stimulate inflammation that can enhance tumor growth.

Immunotherapy approaches to treat cancer aimed at activating the immune response against tumors using immunostimulatory molecules such as interferons, IL-2, and monoclonal antibodies have had some successes. Another approach that has shown particular clinical promise is the targeting of proteins or cells

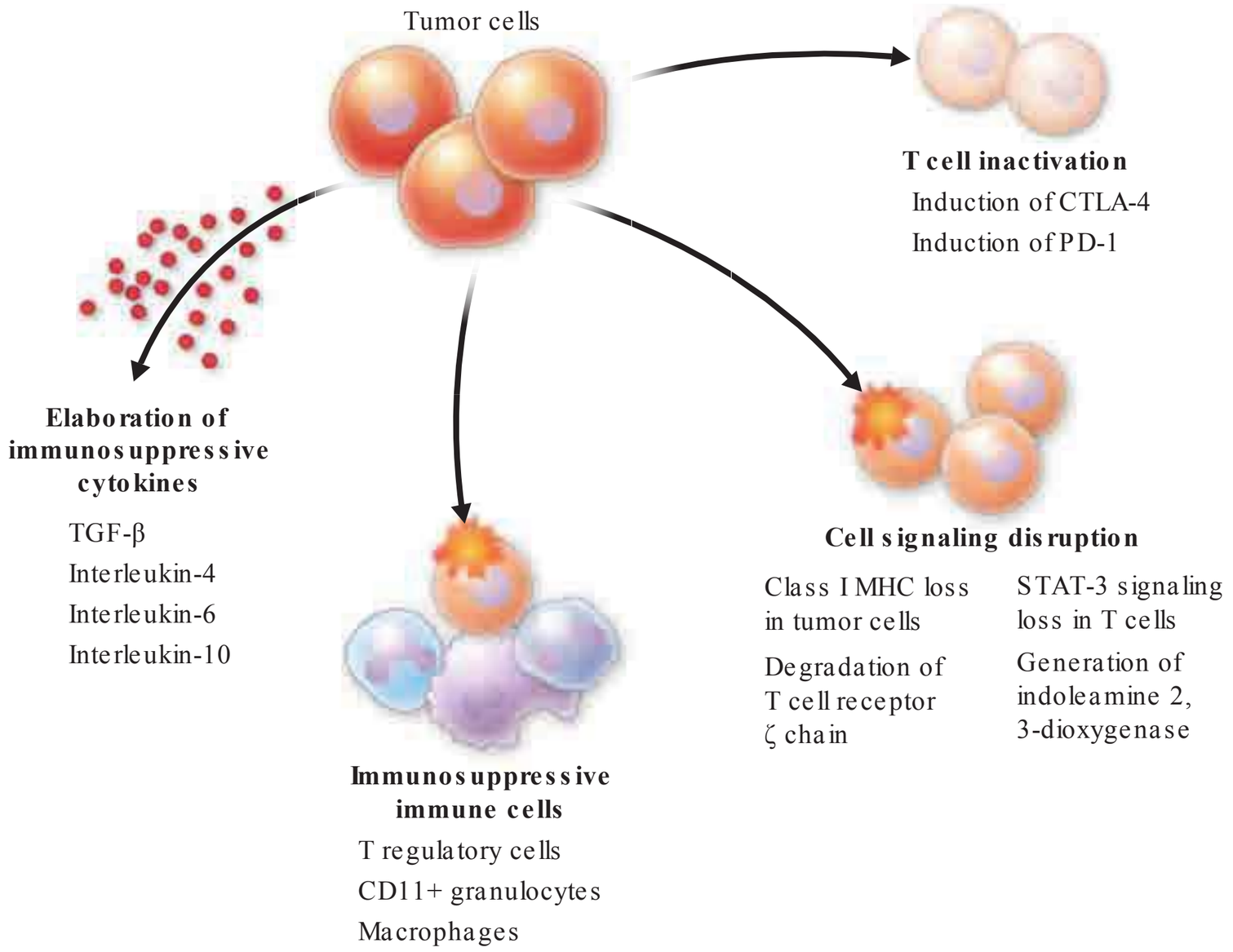

FIGURE 26-13
Tumor-host interactions that suppress the immune response to the tumor.

(such as regulatory T cells) involved in normal homeostatic control to prevent autoimmune damage to the host but that malignant cells and their stroma can also use to inhibit the immune response directed against them. T e approach that is furthest along clinically has involved targeting CTLA-4, PD-1, and PDL-1, co-inhibitory molecules that are expressed on the surface of cancer cells, cells of the immune system, and/or stromal cells and are involved in inhibiting the immune response against cancer **(Fig. 26-13)**. Monoclonal antibodies directed against CTLA-4 and PD-1 are approved for the treatment of melanoma, and additional antibodies targeting PD-1 or PDL-1 have shown activity against melanoma, RCC, and lung cancer and continue to be evaluated against other malignancies as well. Combination approaches targeting more than one protein or involving other anticancer approaches (targeted agents, chemotherapy, radiation therapy) are also being explored and have shown promise in early studies. An important aspect of these approaches is balancing sufficient release of the negative control of the immune response to allow immune-mediated attack on the tumors while not allowing too much release and inducing severe autoimmune effects (such as against skin, thyroid, pituitary gland, or the gastrointestinal tract).

SUMMARY

T e explosion of information on tumor cell biology, metastasis, and tumor-host interactions (including angiogenesis and immune evasion by tumors) has ushered in a new era of rational targeted therapy for cancer. Furthermore, it has become clear that specific molecular factors detected in individual tumors (specific gene mutations, gene-expression profiles, microRNA expression, overexpression of specific proteins) can be used to tailor therapy and maximize antitumor effects.

Acknowledgment
Robert G. Fenton contributed to this chapter in prior editions, and important material from those prior chapters has been included here.

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SECTION VIII

PRINCIPLES OF CANCER PREVENTION AND TREATMENT

CHAPTER 27

APPROACH TO THE PATIENT WITH CANCER

Dan L. Longo

The application of current treatment techniques (surgery, radiation therapy, chemotherapy, and biologic therapy) results in the cure of nearly two of three patients diagnosed with cancer. Nevertheless, patients experience the diagnosis of cancer as one of the most traumatic and revolutionary events that has ever happened to them. Independent of prognosis, the diagnosis brings with it a change in a person's self-image and in his or her role in the home and workplace. The prognosis of a person who has just been found to have pancreatic cancer is the same as the prognosis of the person with aortic stenosis who develops the first symptoms of congestive heart failure (median survival, ~8 months). However, the patient with heart disease may remain functional and maintain a self-image as a fully intact person with just a malfunctioning part, a diseased organ ("a bum ticker"). By contrast, the patient with pancreatic cancer has a completely altered self-image and is viewed differently by family and anyone who knows the diagnosis. He or she is being attacked and invaded by a disease that could be anywhere in the body. Every ache or pain takes on desperate significance. Cancer is an exception to the coordinated interaction among cells and organs. In general, the cells of a multicellular organism are programmed for collaboration. Many diseases occur because the specialized cells fail to perform their assigned task. Cancer takes this malfunction one step further. Not only is there a failure of the cancer cell to maintain its specialized function, but it also strikes out on its own; the cancer cell competes to survive using natural mutability and natural selection to seek advantage over normal cells in a recapitulation of evolution. One consequence of the traitorous behavior of cancer cells is that the patient feels betrayed by his or her body. The cancer patient feels that he or she, and not just a body part, is diseased.

THE MAGNITUDE OF THE PROBLEM

No nationwide cancer registry exists; therefore, the incidence of cancer is estimated on the basis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which tabulates cancer incidence and death figures from 13 sites, accounting for about 10% of the U.S. population, and from population data from the U.S. Census Bureau. In 2014, 1.665 million new cases of invasive cancer (855,220 men, 810,320 women) were diagnosed, and 585,720 persons (310,010 men, 275,710 women) died from cancer. The percent distribution of new cancer cases and cancer deaths by site for men and women is shown in **Table 27-1**. Cancer incidence has been declining by about 2% each year since 1992. Cancer is the cause of one in four deaths in the United States.

The most significant risk factor for cancer overall is age; two-thirds of all cases were in those older than age 65 years. Cancer incidence increases as the third, fourth, or fifth power of age in different sites. For the interval between birth and age 49 years, 1 in 29 men and 1 in 19 women will develop cancer; for the interval between ages 50 and 59 years, 1 in 15 men and 1 in 17 women will develop cancer; for the interval between ages 60 and 69 years, 1 in 6 men and 1 in 10 women will develop cancer; and for people age 70 and older, 1 in 3 men and 1 in 4 women will develop cancer. Overall, men have a 44% risk of developing cancer at some time during their lives; women have a 38% lifetime risk.

Cancer is the second leading cause of death behind heart disease. Deaths from heart disease have declined 45% in the United States since 1950 and continue to decline. Cancer has overtaken heart disease as the number one cause of death in persons younger than age 85 years. Incidence trends over time are shown in **Fig. 27-1**. After a 70-year period of increase, cancer

TABLE 27-1

DISTRIBUTION OF CANCER INCIDENCE AND DEATHS FOR 2014

MALE			FEMALE		
SITES	%	NUMBER	SITES	%	NUMBER
Cancer Incidence					
Prostate	27	233,000	Breast	29	232,670
Lung	14	116,000	Lung	13	108,210
Colorectal	8	71,830	Colorectal	8	65,000
Bladder	7	56,390	Endometrial	6	52,630
Melanoma	5	43,890	Thyroid	6	47,790
Kidney	4	39,140	Lymphoma	4	32,530
Lymphoma	4	38,270	Melanoma	4	32,210
Oral cavity	4	30,220	Kidney	3	24,780
Leukemia	4	30,100	Pancreas	3	22,890
Liver	3	24,600	Leukemia	3	22,280
All others	20	171,780	All others	21	169,330
All sites	100	855,220	All sites	100	810,320
Cancer Deaths					
Lung	28	86,930	Lung	26	72,330
Prostate	10	29,480	Breast	15	40,000
Colorectal	8	26,270	Colorectal	9	24,040
Pancreas	7	20,170	Pancreas	7	19,420
Liver	5	15,870	Ovary	5	14,270
Leukemia	5	14,040	Leukemia	4	10,050
Esophagus	4	12,450	Endometrial	3	8,590
Bladder	4	11,170	Lymphoma	3	8,520
Lymphoma	3	10,470	Liver	3	7,130
Kidney	3	8,900	CNS	2	6,230
All others	23	74,260	All others	23	65,130
All sites	100	310,010	All sites	100	275,710

Source: From R Siegel et al: Cancer statistics, 2014. CA Cancer J Clin 64:9, 2014.

deaths began to decline in 1990–1991 **(Fig. 27-2)**. Between 1990 and 2010, cancer deaths decreased by 21% among men and 12.3% among women. The magnitude of the decline is illustrated in **Fig. 27-3**. The five leading causes of cancer deaths are shown for various populations in **Table 27-2**. The 5-year survival for white patients was 39% in 1960–1963 and 69% in 2003–2009. Cancers are more often deadly in blacks; the 5-year survival was 61% for the 2003–2009 interval; however, the racial differences are narrowing over time. Incidence and mortality vary among racial and ethnic groups **(Table 27-3)**. The basis for these differences is unclear.

CANCER AROUND THE WORLD

In 2008, 12.7 million new cancer cases and 7.6 million cancer deaths were estimated worldwide, according to estimates of GLOBOCAN 2008, developed by the International Agency for Research on Cancer (IARC). When broken down by region of the world, ~45% of cases were in Asia, 26% in Europe, 14.5% in North America, 7.1% in Central/South America, 6% in Africa, and 1% in Australia/New Zealand **(Fig. 27-4)**.

Lung cancer is the most common cancer and the most common cause of cancer death in the world. Its incidence is highly variable, affecting only 2 per 100,000 African women but as many as 61 per 100,000 North American men. Breast cancer is the second most common cancer worldwide; however, it ranks fifth as a cause of death behind lung, stomach, liver, and colorectal cancer. Among the eight most common forms of cancer, lung (2-fold), breast (3-fold), prostate (2.5-fold), and colorectal (3-fold) cancers are more common in more developed countries than in less developed countries. By contrast, liver (2-fold), cervical (2-fold), and esophageal (2- to 3-fold) cancers are more common in less developed countries. Stomach cancer incidence is similar in more and less developed countries but is much more common in Asia than North America or Africa. The most common cancers in Africa are cervical, breast, and liver cancers. It has been estimated that nine modifiable risk factors are responsible for more than one-third of cancers worldwide. These include smoking, alcohol consumption, obesity, physical inactivity, low fruit and vegetable consumption, unsafe sex, air pollution, indoor smoke from household fuels, and contaminated injections.

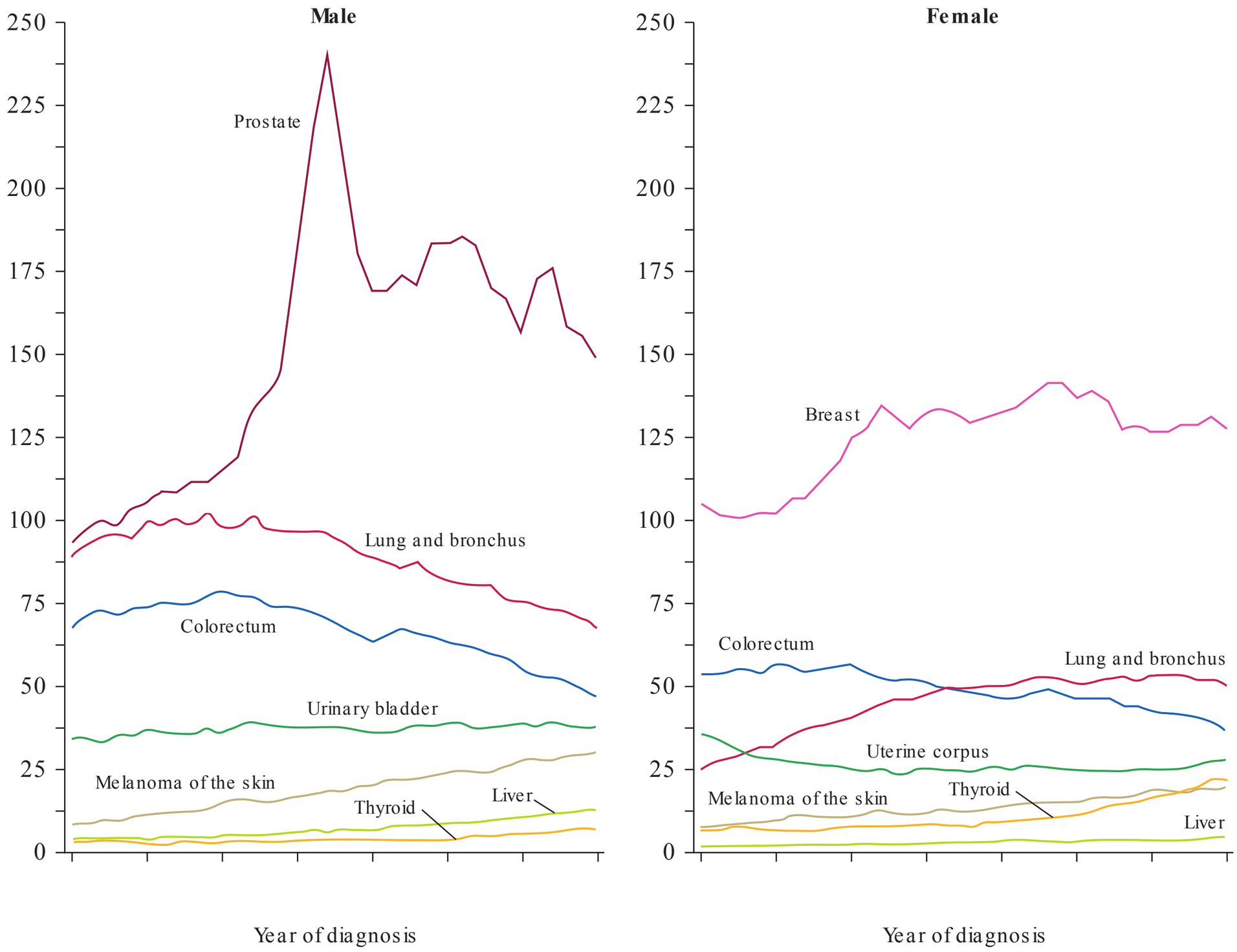


FIGURE 27-1
Incidence rates for particular types of cancer over the last 35 years in male (A) and female (B). (From R Siegel et al: CA Cancer J Clin 64:9, 2014.)

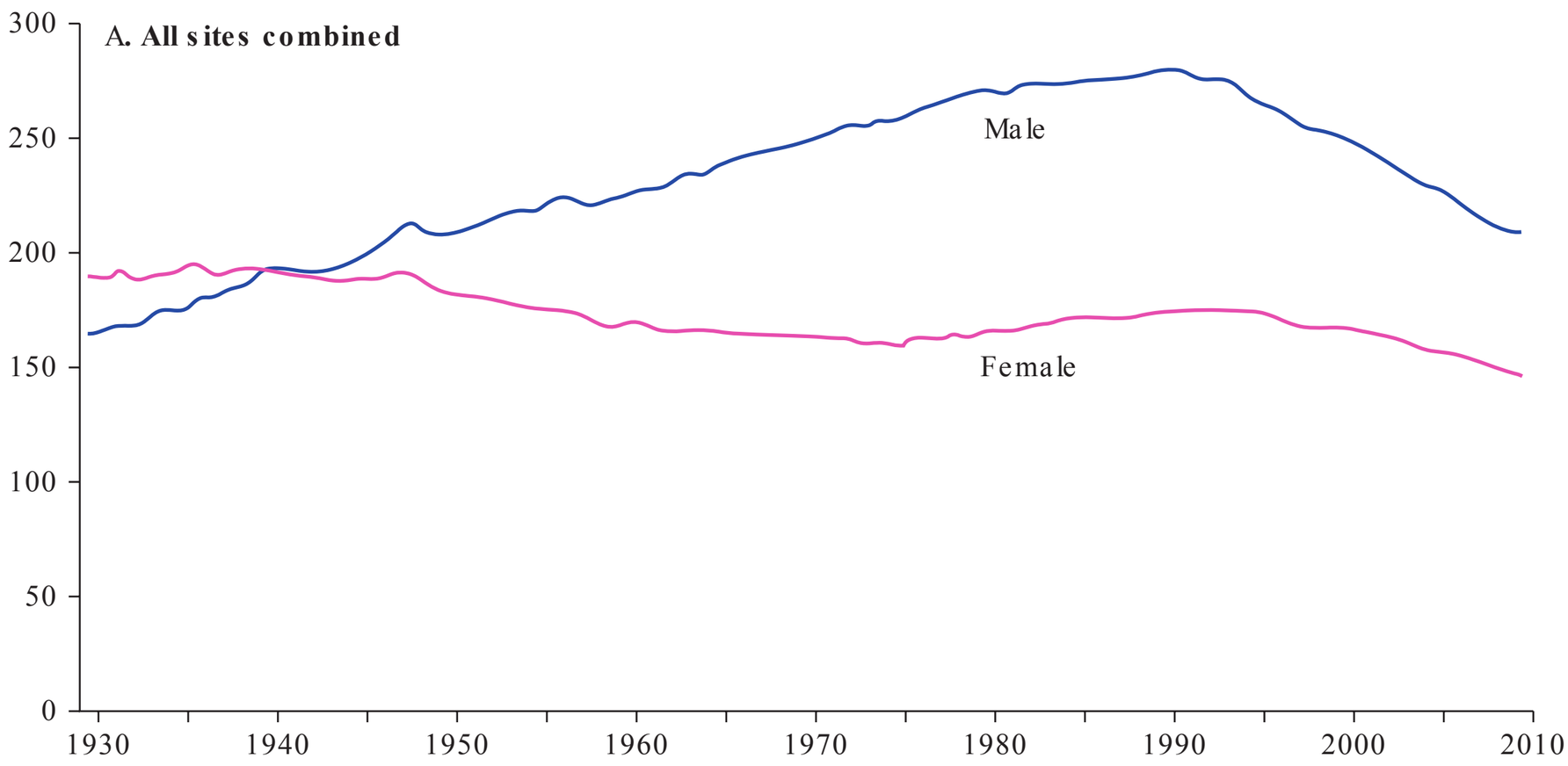
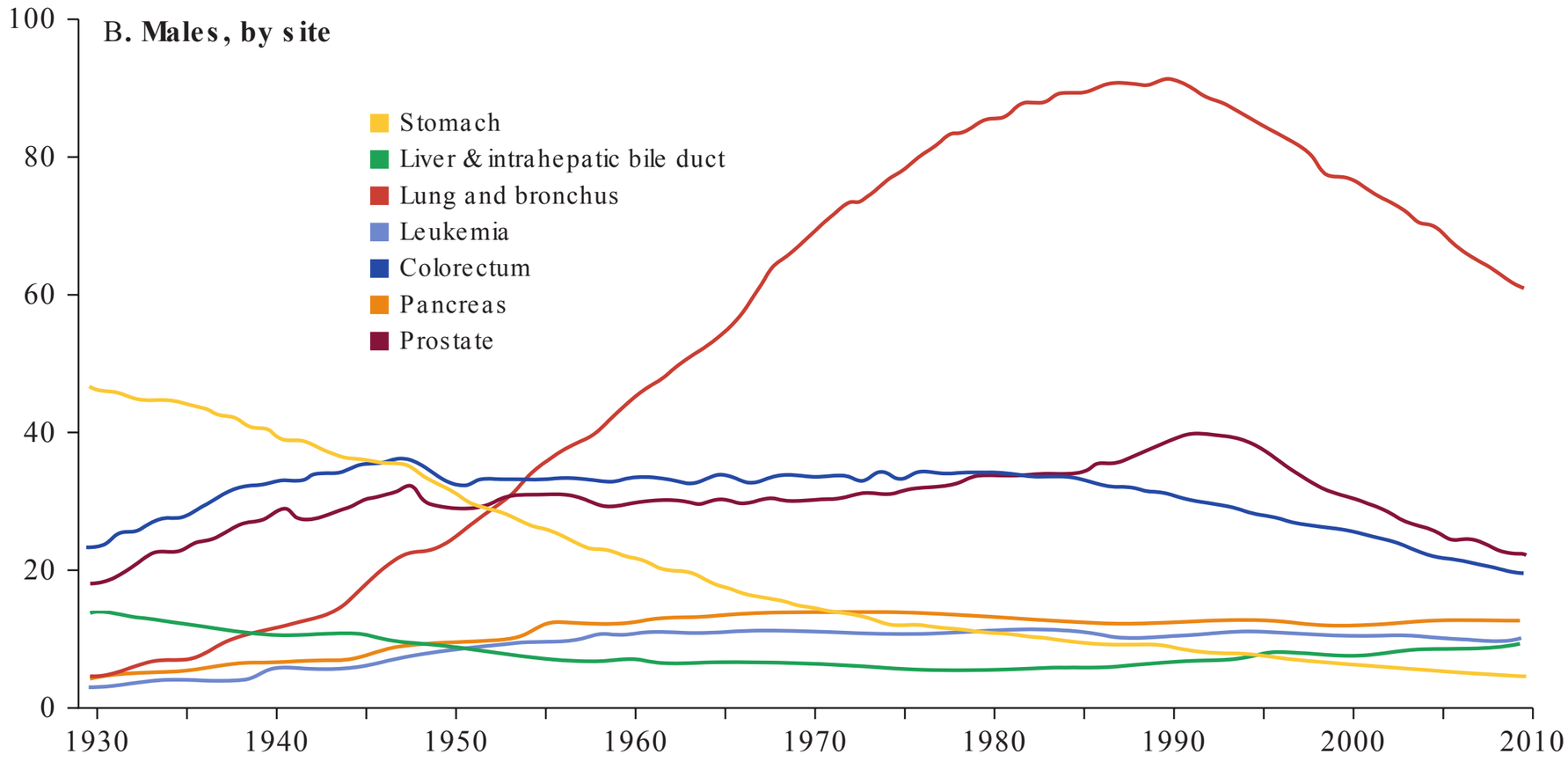


FIGURE 27-2
Eighty-year trend in cancer death rates for (A) female and (B) male by site in the United States, 1930–2010. Rates are per 100,000 age-adjusted to the 2000 U.S. standard population. All sites combined (A), individual sites in male (B) and individual sites in female (C) are shown. (From R Siegel et al: CA Cancer J Clin 64:9, 2014.)



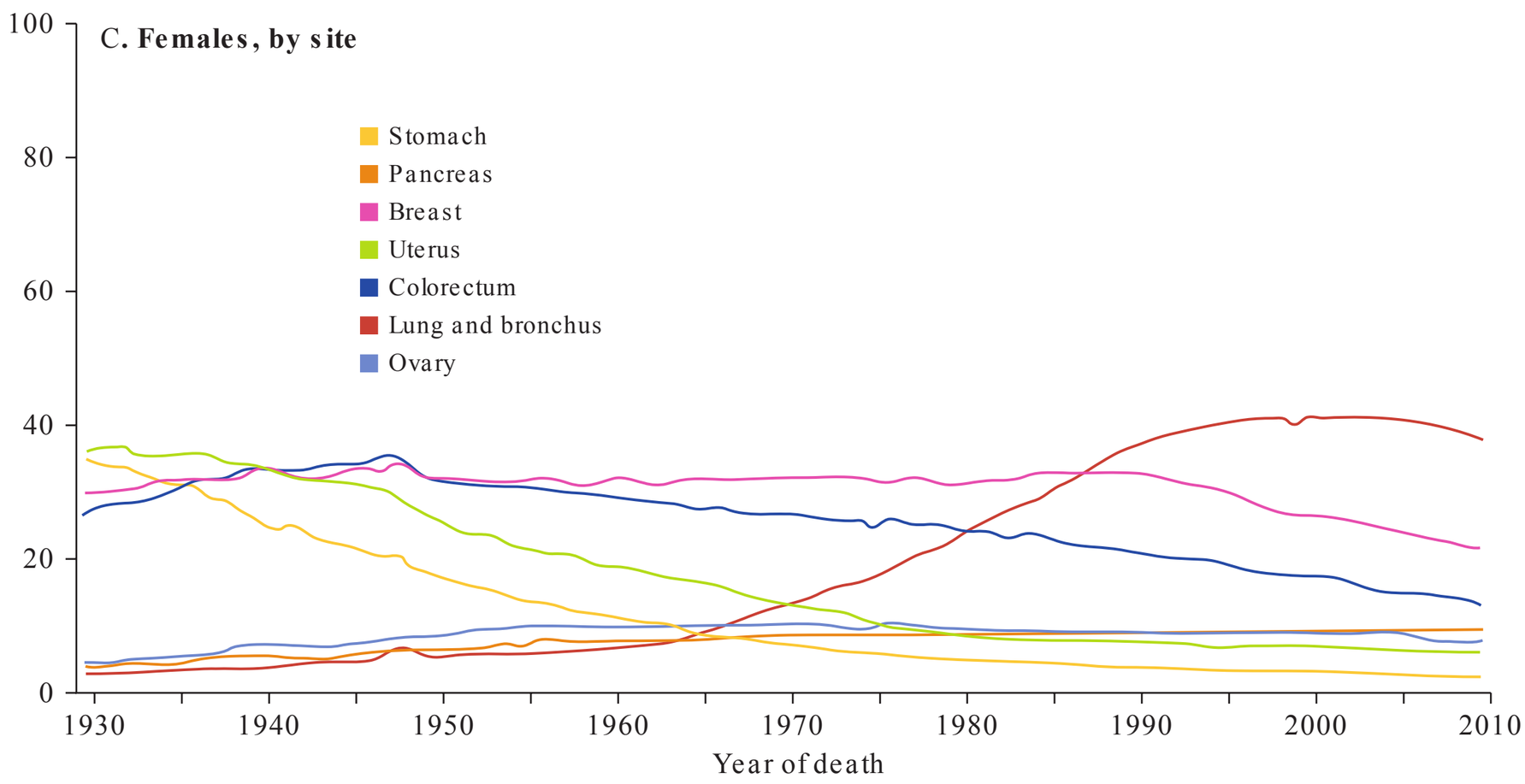


FIGURE 27-2
(Continued)

PATIENT MANAGEMENT

Important information is obtained from every portion of the routine history and physical examination. The duration of symptoms may reveal the chronicity of disease. The past medical history may alert the physician to the presence of underlying diseases that may affect the choice of therapy or the side effects of treatment. The social history may reveal occupational exposure to carcinogens or habits, such as smoking or alcohol consumption, that may influence the course of disease and its treatment. The family history may suggest an underlying familial cancer predisposition and point out the need to begin surveillance or other preventive therapy for unaffected siblings of the patient. The review of systems may suggest early symptoms of metastatic disease or a paraneoplastic syndrome.

DIAGNOSIS

The diagnosis of cancer relies most heavily on invasive tissue biopsy and should never be made without obtaining tissue; no noninvasive diagnostic test is sufficient to define a disease process as cancer. Although in rare clinical settings (e.g., thyroid nodules), fine-needle aspiration is an acceptable diagnostic procedure, the diagnosis generally depends on obtaining adequate tissue to permit careful evaluation of the histology of the tumor, its grade, and its invasiveness and to yield further molecular diagnostic information, such as the expression of cell-surface markers or intracellular proteins that typify a particular cancer, or the presence of a molecular marker, such as the t(8;14) translocation of Burkitt's lymphoma. Increasing evidence links the expression of certain genes with the prognosis and response to therapy **(Chaps. 25 and 26)**.

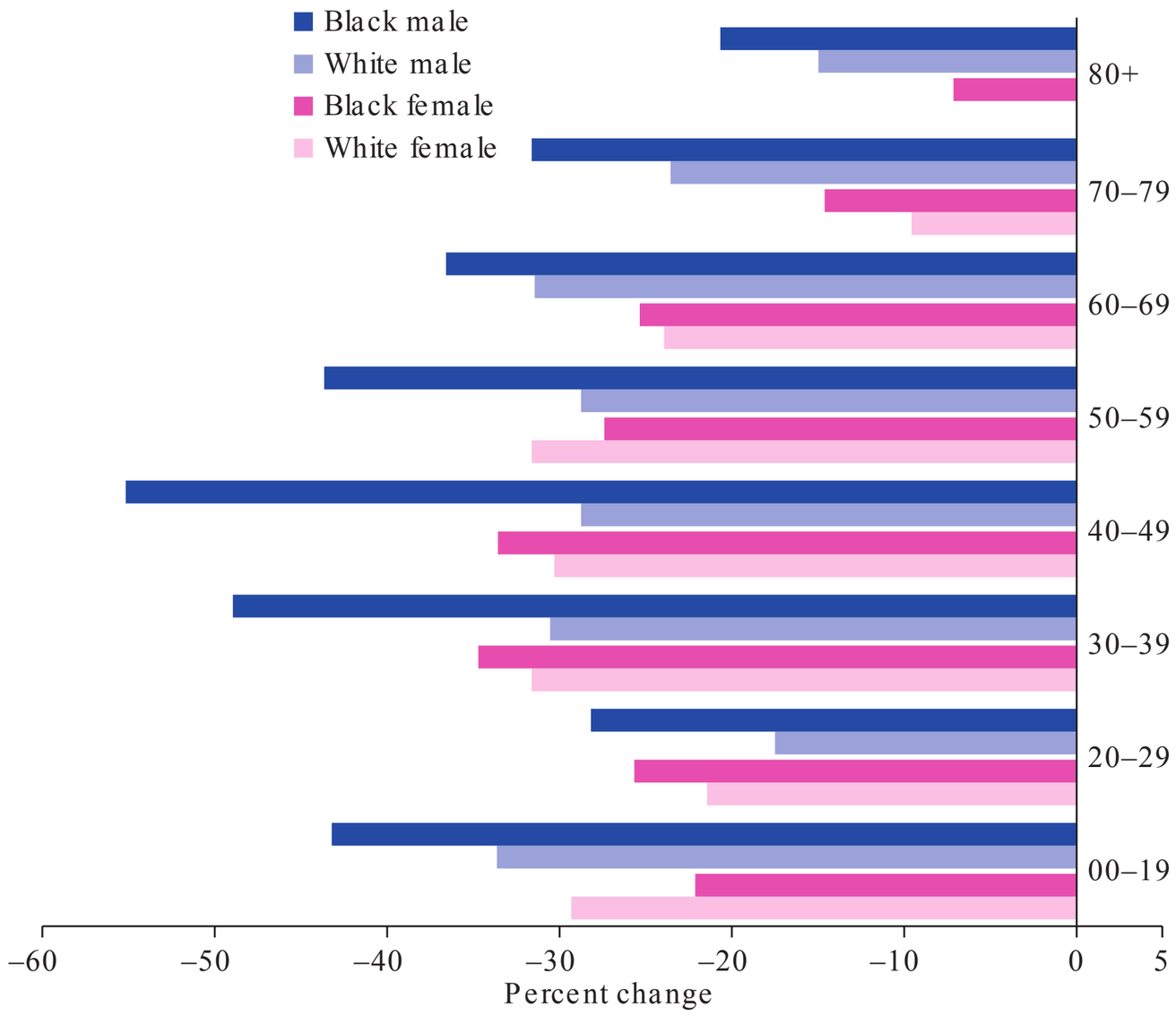


FIGURE 27-3
The decline in death rates from cancer is shown for different age ranges by sex and race for the 20-year period between 1991 and 2010 expressed as a percentage of the 1991 rate. (From R Siegel et al: CA Cancer J Clin 64:9, 2014.)

Occasionally a patient will present with a metastatic disease process that is defined as cancer on biopsy but has no apparent primary site of disease. Efforts should be made to define the primary site based on age, sex, sites of involvement, histology and tumor markers, and personal and family history. Particular attention should be focused on ruling out the most treatable causes **(Chap. 49)**.

Once the diagnosis of cancer is made, the management of the patient is best undertaken as a multidisciplinary collaboration among the primary care physician, medical oncologists, surgical oncologists, radiation oncologists, oncology nurse specialists, pharmacists, social workers, rehabilitation medicine specialists, and a number of other consulting professionals working closely with each other and with the patient and family.

DEFINING THE EXTENT OF DISEASE AND THE PROGNOSIS

The first priority in patient management after the diagnosis of cancer is established and shared with the

TABLE 27-2
THE FIVE LEADING PRIMARY TUMOR SITES FOR PATIENTS DYING OF CANCER BASED ON AGE AND SEX IN 2010

			AGE, YEARS				
RANK	SEX	ALL AGES	UNDER 20	20–39	40–59	60–79	>80
1	M	Lung	Leukemia	Leukemia	Lung	Lung	Lung
	F	Lung	Leukemia	Breast	Breast	Lung	Lung
2	M	Prostate	CNS	CNS	Colorectal	Colorectal	Prostate
	F	Breast	CNS	Cervix	Lung	Breast	Breast
3	M	Colorectal	Bone sarcoma	Colorectal	Liver	Prostate	Colorectal
	F	Colorectal	Bone sarcoma	Leukemia	Colorectal	Colorectal	Colorectal
4	M	Pancreas	Soft tissue sarcoma	Lymphoma	Pancreas	Pancreas	Bladder
	F	Pancreas	Soft tissue sarcoma	Colorectal	Ovary	Pancreas	Pancreas
5	M	Liver	Lymphoma	Lung	Esophagus	Liver	Pancreas
	F	Ovary	Liver	CNS	Pancreas	Ovary	Lymphoma

Abbreviations: CNS, central nervous system; F, female; M, male.
Source: From R Siegel et al: Cancer statistics, 2014. CA Cancer J Clin 64:9, 2014.

TABLE 27-3

CANCER INCIDENCE AND MORTALITY IN RACIAL AND ETHNIC GROUPS, UNITED STATES, 2006–2010

SITE	SEX	WHITE	BLACK	ASIAN/PACIFIC ISLANDER	AMERICAN INDIAN[a]	HISPANIC
Incidence per 100,000 Population						
All	M	548.1	601.0	326.1	441.1	426.8
	F	436.2	395.9	282.6	372.0	330.8
Breast		127.3	118.4	84.7	90.3	91.1
Colorectal	M	50.9	62.5	40.8	51.7	47.3
	F	38.6	46.7	31.0	42.7	32.6
Kidney	M	21.6	23.0	10.6	30.6	20.5
	F	11.2	12.2	5.1	17.5	11.5
Liver	M	8.7	14.9	21.3	17.8	11.5
	F	2.9	4.4	8.0	8.0	6.9
Lung	M	82.9	94.7	48.8	70.2	45.9
	F	57.1	50.7	27.6	41.3	26.5
Prostate		138.6	220.0	75.0	104.1	124.2
Cervix		7.2	10.3	6.7	9.7	10.9
Deaths per 100,000 Population						
All	M	217.3	276.6	132.4	191.0	152.2
	F	153.6	171.2	92.1	139.0	101.3
Breast		22.7	30.8	11.5	15.5	14.8
Colorectal	M	19.2	28.7	13.1	18.7	16.1
	F	13.6	19.0	9.7	15.4	10.2
Kidney	M	5.9	5.7	3.0	9.5	5.1
	F	2.6	2.6	1.2	4.4	2.3
Liver	M	7.1	11.8	14.4	13.2	12.3
	F	2.9	4.1	6.0	6.1	5.4
Lung	M	65.7	78.5	35.5	49.6	31.3
	F	42.7	37.2	18.4	33.1	14.1
Prostate		21.3	50.9	10.1	20.7	19.2
Cervix		2.1	4.2	1.9	3.5	2.9

[a]Based on Indian Health Service delivery areas.
Abbreviations: F, female; M, male.
Source: From R Siegel R et al: Cancer statistics, 2014. CA Cancer J Clin 64:9, 2014.

patient is to determine the extent of disease. The curability of a tumor usually is inversely proportional to the tumor burden. Ideally, the tumor will be diagnosed before symptoms develop or as a consequence of screening efforts **(Chap. 28)**. A very high proportion of such patients can be cured. However, most patients with cancer present with symptoms related to the cancer, caused either by mass effects of the tumor or by alterations associated with the production of cytokines or hormones by the tumor.

For most cancers, the extent of disease is evaluated by a variety of noninvasive and invasive diagnostic tests and procedures. This process is called staging. There are two types. Clinical staging is based on physical examination, radiographs, isotopic scans, computed tomography (CT) scans, and other imaging procedures; pathologic staging takes into account information obtained during a surgical procedure, which might include intraoperative palpation, resection of regional lymph nodes and/or tissue adjacent to the tumor, and inspection and biopsy of organs commonly involved in disease spread. Pathologic staging includes histologic examination of all tissues removed during the surgical procedure. Surgical procedures performed may include a simple lymph

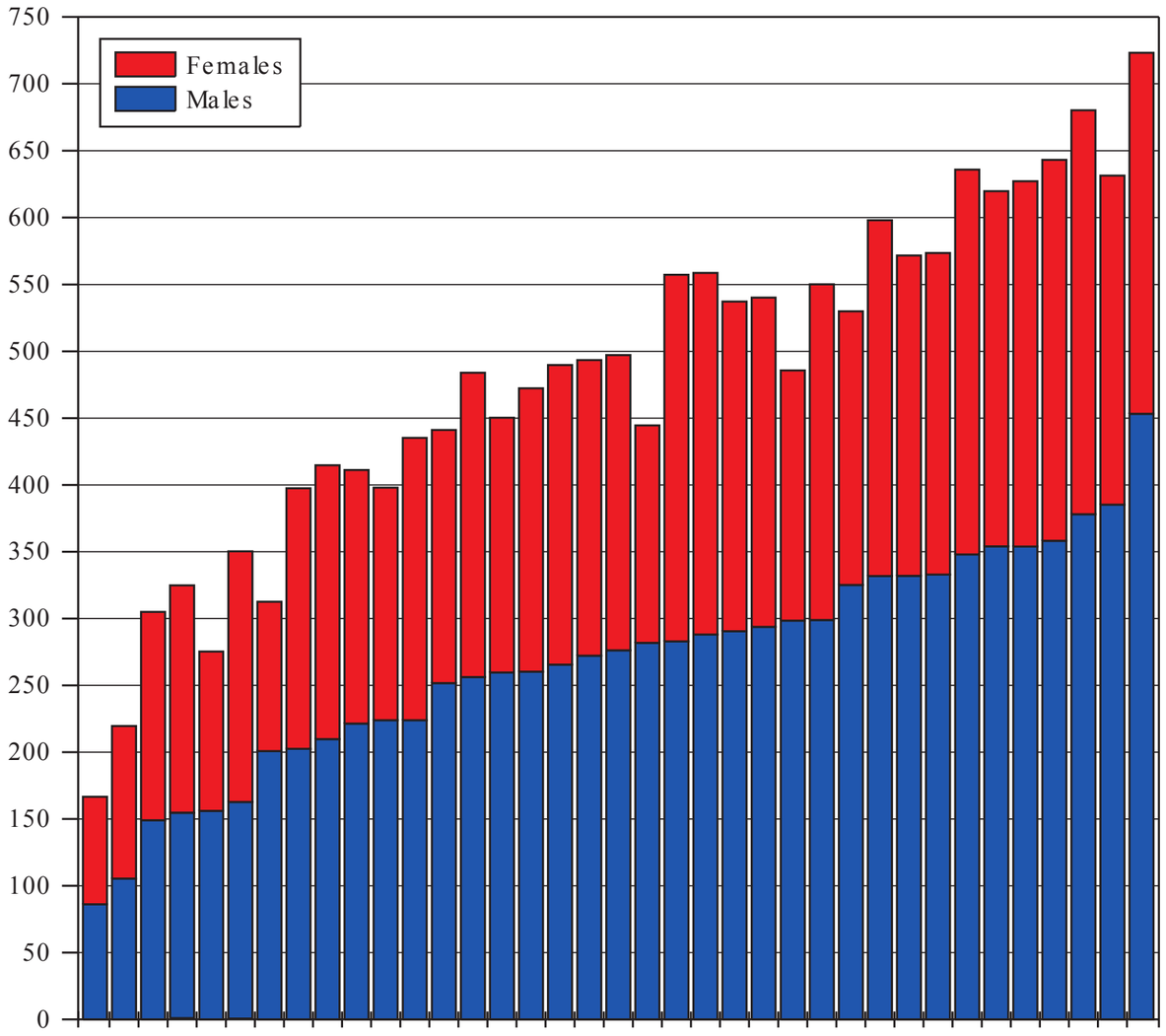


FIGURE 27-4
Worldwide overall annual cancer incidence, mortality, and 5-year prevalence for the period of 1993–2001. (Adapted from A Jemal et al: Cancer Epidemiol Biomarkers Prev 19:1893, 2010.)

node biopsy or more extensive procedures such as thoracotomy, mediastinoscopy, or laparotomy. Surgical staging may occur in a separate procedure or may be done at the time of definitive surgical resection of the primary tumor.

Knowledge of the predilection of particular tumors for spreading to adjacent or distant organs helps direct the staging evaluation.

Information obtained from staging is used to define the extent of disease as localized, as exhibiting spread outside of the organ of origin to regional but not distant sites, or as metastatic to distant sites. T e most widely used system of staging is the TNM (tumor, node, metastasis) system codified by the International Union Against Cancer and the American Joint Committee on Cancer. T e TNM classification is an anatomically based system that categorizes the tumor on the basis of the size of the primary tumor lesion (T1–4, where a higher number indicates a tumor of larger size), the presence of nodal involvement (usually N0 and N1 for the absence and presence, respectively, of involved nodes, although some tumors have more elaborate systems of nodal grading), and the presence of metastatic disease (M0 and M1 for the absence and presence, respectively, of metastases). T e various permutations of T, N, and M scores (sometimes including tumor histologic grade [G]) are then broken into stages, usually designated by the roman numerals I through IV. Tumor burden increases and curability decreases with increasing stage. Other anatomic staging systems are used for some tumors, e.g., the Dukes classification for colorectal cancers, the International Federation of Gynecologists and Obstetricians classification for gynecologic cancers, and the Ann Arbor classification for Hodgkin's disease.

Certain tumors cannot be grouped on the basis of anatomic considerations. For example, hematopoietic tumors such as leukemia, myeloma, and lymphoma are often disseminated at presentation and do not spread like solid tumors. For these tumors, other prognostic factors have been identified **(Chaps. 14, 15, 16, 17, and 18)**.

In addition to tumor burden, a second major determinant of treatment outcome is the physiologic reserve of the patient. Patients who are bedridden before developing cancer are likely to fare worse, stage for stage, than fully active patients. Physiologic reserve is a determinant of how a patient is likely to cope with the physiologic stresses imposed by the cancer and its treatment. T is factor is dif cult to assess directly. Instead,

TABLE 27-4

KARNOFSKY PERFORMANCE INDEX

PERFORMANCE STATUS	FUNCTIONAL CAPABILITY OF THE PATIENT
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 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	Very sick; hospitalization is necessary; active supportive treatment is necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

surrogate markers for physiologic reserve are used, such as the patient's age or Karnofsky performance status **(Table 27-4)** or Eastern Cooperative Oncology Group (ECOG) performance status **(Table 27-5)**. Older patients and those with a Karnofsky performance status <70 or ECOG performance status ≥3 have a poor prognosis unless the poor performance is a reversible consequence of the tumor.

TABLE 27-5

THE EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCALE

ECOG Grade 0: Fully active, able to carry on all predisease performance without restriction
ECOG Grade 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
ECOG Grade 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
ECOG Grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
ECOG Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
ECOG Grade 5: Dead

Source: From MM Oken et al: Am J Clin Oncol 5:649, 1982.

Increasingly, biologic features of the tumor are being related to prognosis. The expression of particular oncogenes, drug-resistance genes, apoptosis-related genes, and genes involved in metastasis is being found to influence response to therapy and prognosis. The presence of selected cytogenetic abnormalities may influence survival. Tumors with higher growth fractions, as assessed by expression of proliferation-related markers such as proliferating cell nuclear antigen, behave more aggressively than tumors with lower growth fractions. Information obtained from studying the tumor itself will increasingly be used to influence treatment decisions. Host genes involved in drug metabolism can influence the safety and efficacy of particular treatments.

Enormous heterogeneity has been noted by studying tumors; we have learned that morphology is not capable of discerning certain distinct subsets of patients whose tumors have different sets of abnormalities. Tumors that look the same by light microscopy can be very different. Similarly, tumors that look quite different from one another histologically can share genetic lesions that predict responses to treatments. Furthermore, tumor cells vary enormously within a single patient even though the cells share a common origin.

MAKING A TREATMENT PLAN

From information on the extent of disease and the prognosis and in conjunction with the patient's wishes, it is determined whether the treatment approach should be curative or palliative in intent. Cooperation among the various professionals involved in cancer treatment is of the utmost importance in treatment planning. For some cancers, chemotherapy or chemotherapy plus radiation therapy delivered before the use of definitive surgical treatment (so-called neoadjuvant therapy) may improve the outcome, as seems to be the case for locally advanced breast cancer and head and neck cancers. In certain settings in which combined-modality therapy is intended, coordination among the medical oncologist, radiation oncologist, and surgeon is crucial to achieving optimal results. Sometimes the chemotherapy and radiation therapy need to be delivered sequentially, and other times concurrently. Surgical procedures may precede or follow other treatment approaches. It is best for the treatment plan either to follow a standard protocol precisely or else to be part of an ongoing clinical research protocol evaluating new treatments. Ad hoc modifications of standard protocols are likely to compromise treatment results.

The choice of treatment approaches was formerly dominated by the local culture in both the university and the practice settings. However, it is now possible to gain access electronically to standard treatment

protocols and to every approved clinical research study in North America through a personal computer interface with the Internet.[1]

T e skilled physician also has much to offer the patient for whom curative therapy is no longer an option. Often a combination of guilt and frustration over the inability to cure the patient and the pressure of a busy schedule greatly limit the time a physician spends with a patient who is receiving only palliative care. Resist these forces. In addition to the medicines administered to alleviate symptoms (see below), it is important to remember the comfort that is provided by holding the patient's hand, continuing regular examinations, and taking time to talk.

MANAGEMENT OF DISEASE AND TREATMENT COMPLICATIONS

Because cancer therapies are toxic **(Chap. 29)**, patient management involves addressing complications of both the disease and its treatment as well as the complex psychosocial problems associated with cancer. In the short term during a course of curative therapy, the patient's functional status may decline. Treatment-induced toxicity is less acceptable if the goal of therapy is palliation. T e most common side effects of treatment are nausea and vomiting (see below), febrile neutropenia **(Chap. 30)**, and myelosuppression **(Chap. 29)**. Tools are now available to minimize the acute toxicity of cancer treatment.

New symptoms developing in the course of cancer treatment should always be assumed to be reversible until proven otherwise. T e fatalistic attribution of anorexia, weight loss, and jaundice to recurrent or progressive tumor could result in a patient dying from a reversible intercurrent cholecystitis. Intestinal obstruction may be due to reversible adhesions rather than progressive tumor. Systemic infections, sometimes with unusual pathogens, may be a consequence of the immunosuppression associated with cancer therapy. Some drugs used to treat cancer or its complications (e.g., nausea) may produce central nervous system symptoms that look like metastatic disease or may mimic paraneoplastic syndromes such as the syndrome of inappropriate antidiuretic hormone. A definitive diagnosis should be pursued and may even require a repeat biopsy.

A critical component of cancer management is assessing the response to treatment. In addition to a careful physical examination in which all sites of disease are physically measured and recorded in a flow chart by date, response assessment usually requires periodic repeating of imaging tests that were abnormal at the time of staging. If imaging tests have become normal, repeat biopsy of previously involved tissue is performed to document complete response by pathologic criteria. Biopsies are not usually required if there is macroscopic residual disease. A complete response is defined as disappearance of all evidence of disease, and a partial response as >50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions. T e determination of partial response may also be based on a 30% decrease in the sums of the longest diameters of lesions (Response Evaluation Criteria in Solid Tumors [RECIST]). Progressive disease is defined as the appearance of any new lesion or an increase of >25% in the sum of the products of the perpendicular diameters of all measurable lesions (or an increase of 20% in the sums of the longest diameters by RECIST). Tumor shrinkage or growth that does not meet any of these criteria is considered stable disease. Some sites of involvement (e.g., bone) or patterns of involvement (e.g., lymphangitic lung or diffuse pulmonary infiltrates) are considered unmeasurable. No response is complete without biopsy documentation of their resolution, but partial responses may exclude their assessment unless clear objective progression has occurred.

Tumor markers may be useful in patient management in certain tumors. Response to therapy may be dif cult to gauge with certainty. However, some tumors produce or elicit the production of markers that can be measured in the serum or urine, and in a particular patient, rising and falling levels of the marker are usually associated with increasing or decreasing tumor burden, respectively. Some clinically useful tumor markers are shown in **Table 27-6**. Tumor markers are not in themselves specific enough to permit a diagnosis of malignancy to be made, but once a malignancy has been diagnosed and shown to be associated with elevated levels of a tumor marker, the marker can be used to assess response to treatment.

T e recognition and treatment of depression are important components of management. T e incidence of depression in cancer patients is ~25% overall and may be greater in patients with greater debility. T is diagnosis is likely in a patient with a depressed mood (dysphoria) and/or a loss of interest in pleasure (anhedonia) for at least 2 weeks. In addition, three or more of the following symptoms are usually present: appetite change, sleep problems, psychomotor retardation or agitation, fatigue, feelings of guilt or worthlessness, inability to concentrate, and suicidal ideation. Patients with these symptoms should receive therapy. Medical therapy with a serotonin reuptake

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[1]T e National Cancer Institute maintains a database called PDQ (Physician Data Query) that is accessible on the Internet under the name CancerNet at www.cancer.gov/cancertopics/pdq/cancerdatabase. Information can be obtained through a facsimile machine using CancerFax by dialing 301-402-5874. Patient information is also provided by the National Cancer Institute in at least three formats: on the Internet via CancerNet at www.cancer.gov, through the CancerFax number listed above, or by calling 1-800-4-CANCER. T e quality control for the information provided through these services is rigorous.

TABLE 27-6

TUMOR MARKERS

TUMOR MARKERS	CANCER	NONNEOPLASTIC CONDITIONS
Hormones		
Human chorionic gonadotropin	Gestational trophoblastic disease, gonadal germ cell tumor	Pregnancy
Calcitonin	Medullary cancer of the thyroid	
Catecholamines	Pheochromocytoma	
Oncofetal Antigens		
α Fetoprotein	Hepatocellular carcinoma, gonadal germ cell tumor	Cirrhosis, hepatitis
Carcinoembryonic antigen	Adenocarcinomas of the colon, pancreas, lung, breast, ovary	Pancreatitis, hepatitis, inflammatory bowel disease, smoking
Enzymes		
Prostatic acid phosphatase	Prostate cancer	Prostatitis, prostatic hypertrophy
Neuron-specific enolase	Small-cell cancer of the lung, neuroblastoma	
Lactate dehydrogenase	Lymphoma, Ewing's sarcoma	Hepatitis, hemolytic anemia, many others
Tumor-Associated Proteins		
Prostate-specific antigen	Prostate cancer	Prostatitis, prostatic hypertrophy
Monoclonal immunoglobulin	Myeloma	Infection, MGUS
CA-125	Ovarian cancer, some lymphomas	Menstruation, peritonitis, pregnancy
CA 19-9	Colon, pancreatic, breast cancer	Pancreatitis, ulcerative colitis
CD30	Hodgkin's disease, anaplastic large-cell lymphoma	—
CD25	Hairy cell leukemia, adult T cell leukemia/lymphoma	—

Abbreviation: MGUS, monoclonal gammopathy of uncertain significance.

inhibitor such as fluoxetine (10–20 mg/d), sertraline (50–150 mg/d), or paroxetine (10–20 mg/d) or a tricyclic antidepressant such as amitriptyline (50–100 mg/d) or desipramine (75–150 mg/d) should be tried, allowing 4–6 weeks for response. Effective therapy should be continued at least 6 months after resolution of symptoms. If therapy is unsuccessful, other classes of antidepressants may be used. In addition to medication, psychosocial interventions such as support groups, psychotherapy, and guided imagery may be of benefit.

Many patients opt for unproven or unsound approaches to treatment when it appears that conventional medicine is unlikely to be curative. Those seeking such alternatives are often well educated and may be early in the course of their disease. Unsound approaches are usually hawked on the basis of unsubstantiated anecdotes and not only cannot help the patient but may be harmful. Physicians should strive to keep communications open and nonjudgmental, so that patients are more likely to discuss with the physician what they are actually doing. The appearance of unexpected toxicity may be an indication that a supplemental therapy is being taken.[2]

[2]Information about unsound methods may be obtained from the National Council Against Health Fraud, Box 1276, Loma Linda, CA 92354, or from the Center for Medical Consumers and Health Care Information, 237 Thompson Street, New York, NY 10012.

LONG-TERM FOLLOW-UP/LATE COMPLICATIONS

At the completion of treatment, sites originally involved with tumor are reassessed, usually by radiography or imaging techniques, and any persistent abnormality is biopsied. If disease persists, the multidisciplinary team discusses a new salvage treatment plan. If the patient has been rendered disease-free by the original treatment, the patient is followed regularly for disease recurrence. The optimal guidelines for follow-up care are not known. For many years, a routine practice has been to follow the patient monthly for 6–12 months, then every other month for a year, every 3 months for a year, every 4 months for a year, every 6 months for a year, and then annually. At each visit, a battery of laboratory and radiographic and imaging tests were obtained on the assumption that it is best to detect recurrent disease before it becomes symptomatic. However, where follow-up procedures have been examined, this assumption has been found to be untrue. Studies of breast cancer, melanoma, lung cancer, colon cancer, and lymphoma have all failed to support the notion that asymptomatic relapses are more readily cured by salvage therapy than symptomatic relapses. In view of the enormous cost of a full battery of diagnostic tests and their manifest lack of impact on survival, new guidelines are emerging for less frequent follow-up visits, during which the history and physical examination are the major investigations performed.

As time passes, the likelihood of recurrence of the primary cancer diminishes. For many types of cancer, survival for 5 years without recurrence is tantamount to cure. However, important medical problems can occur in patients treated for cancer and must be examined **(Chap. 57)**. Some problems emerge as a consequence of the disease and some as a consequence of the treatment. An understanding of these disease- and treatment-related problems may help in their detection and management.

Despite these concerns, most patients who are cured of cancer return to normal lives.

SUPPORTIVE CARE

In many ways, the success of cancer therapy depends on the success of the supportive care. Failure to control the symptoms of cancer and its treatment may lead patients to abandon curative therapy. Of equal importance, supportive care is a major determinant of quality of life. Even when life cannot be prolonged, the physician must strive to preserve its quality. Quality-of-life measurements have become common endpoints of clinical research studies. Furthermore, palliative care has been shown to be cost-effective when approached in an organized fashion. A credo for oncology could be to cure sometimes, to extend life often, and to comfort always.

Pain

Pain occurs with variable frequency in the cancer patient: 25–50% of patients present with pain at diagnosis, 33% have pain associated with treatment, and 75% have pain with progressive disease. The pain may have several causes. In ~70% of cases, pain is caused by the tumor itself—by invasion of bone, nerves, blood vessels, or mucous membranes or obstruction of a hollow viscus or duct. In ~20% of cases, pain is related to a surgical or invasive medical procedure, to radiation injury (mucositis, enteritis, or plexus or spinal cord injury), or to chemotherapy injury (mucositis, peripheral neuropathy, phlebitis, steroid-induced aseptic necrosis of the femoral head). In 10% of cases, pain is unrelated to cancer or its treatment.

Assessment of pain requires the methodical investigation of the history of the pain, its location, character, temporal features, provocative and palliative factors, and intensity **(Chap. 18)**; a review of the oncologic history and past medical history as well as personal and social history; and a thorough physical examination. The patient should be given a 10-division visual analogue scale on which to indicate the severity of the pain. The clinical condition is often dynamic, making it necessary to reassess the patient frequently. Pain therapy should not be withheld while the cause of pain is being sought.

A variety of tools are available with which to address cancer pain. About 85% of patients will have pain relief from pharmacologic intervention. However, other modalities, including antitumor therapy (such as surgical relief of obstruction, radiation therapy, and strontium-89 or samarium-153 treatment for bone pain), neurostimulatory techniques, regional analgesia, or neuroablative procedures, are effective in an additional 12% or so. Thus, very few patients will have inadequate pain relief if appropriate measures are taken. **A specific approach to pain relief is detailed in Chap. 33**.

Nausea

Emesis in the cancer patient is usually caused by chemotherapy **(Chap. 29)**. Its severity can be predicted from the drugs used to treat the cancer. Three forms of emesis are recognized on the basis of their timing with regard to the noxious insult. Acute emesis, the most common variety, occurs within 24 h of treatment. Delayed emesis occurs 1–7 days after treatment; it is rare, but, when present, usually follows cisplatin administration. Anticipatory emesis occurs before administration of chemotherapy and represents a conditioned response to visual and olfactory stimuli previously associated with chemotherapy delivery.

Acute emesis is the best understood form. Stimuli that activate signals in the chemoreceptor trigger zone in the medulla, the cerebral cortex, and peripherally in the intestinal tract lead to stimulation of the vomiting center in the medulla, the motor center responsible for coordinating the secretory and muscle contraction activity that leads to emesis. Diverse receptor types participate in the process, including dopamine, serotonin, histamine, opioid, and acetylcholine receptors. The serotonin receptor antagonists ondansetron and granisetron are the most effective drugs against highly emetogenic agents, but they are expensive.

As with the analgesia ladder, emesis therapy should be tailored to the situation. For mildly and moderately emetogenic agents, prochlorperazine, 5–10 mg PO or 25 mg PR, is effective. Its efficacy may be enhanced by administering the drug before the chemotherapy is delivered. Dexamethasone, 10–20 mg IV, is also effective and may enhance the efficacy of prochlorperazine. For highly emetogenic agents such as cisplatin, mechlorethamine, dacarbazine, and streptozocin, combinations of agents work best and administration should begin 6–24 h before treatment. Ondansetron, 8 mg PO every 6 h the day before therapy and IV on the day of therapy, plus dexamethasone, 20 mg IV before treatment, is an effective regimen. Addition of oral aprepitant (a substance P/neurokinin 1 receptor antagonist) to this regimen (125 mg on day 1, 80 mg on days 2 and 3) further decreases the risk of both acute and delayed vomiting. Like pain, emesis is easier to prevent than to alleviate.

Delayed emesis may be related to bowel inflammation from the therapy and can be controlled with oral

dexamethasone and oral metoclopramide, a dopamine receptor antagonist that also blocks serotonin receptors at high dosages. T e best strategy for preventing anticipatory emesis is to control emesis in the early cycles of therapy to prevent the conditioning from taking place. If this is unsuccessful, prophylactic antiemetics the day before treatment may help. Experimental studies are evaluating behavior modification.

Ef usions

Fluid may accumulate abnormally in the pleural cavity, pericardium, or peritoneum. Asymptomatic malignant effusions may not require treatment. Symptomatic effusions occurring in tumors responsive to systemic therapy usually do not require local treatment but respond to the treatment for the underlying tumor. Symptomatic effusions occurring in tumors unresponsive to systemic therapy may require local treatment in patients with a life expectancy of at least 6 months.

Pleural effusions due to tumors may or may not contain malignant cells. Lung cancer, breast cancer, and lymphomas account for ~75% of malignant pleural effusions. T eir exudative nature is usually gauged by an effusion/serum protein ratio of ≥0.5 or an effusion/serum lactate dehydrogenase ratio of ≥0.6. When the condition is symptomatic, thoracentesis is usually performed first. In most cases, symptomatic improvement occurs for <1 month. Chest tube drainage is required if symptoms recur within 2 weeks. Fluid is aspirated until the flow rate is <100 mL in 24 h. T en either 60 units of bleomycin or 1 g of doxycycline is infused into the chest tube in 50 mL of 5% dextrose in water; the tube is clamped; the patient is rotated on four sides, spending 15 min in each position; and, after 1–2 h, the tube is again attached to suction for another 24 h. T e tube is then disconnected from suction and allowed to drain by gravity. If <100 mL drains over the next 24 h, the chest tube is pulled, and a radiograph is taken 24 h later. If the chest tube continues to drain fluid at an unacceptably high rate, sclerosis can be repeated. Bleomycin may be somewhat more effective than doxycycline but is very expensive. Doxycycline is usually the drug of first choice. If neither doxycycline nor bleomycin is effective, talc can be used.

Symptomatic pericardial effusions are usually treated by creating a pericardial window or by stripping the pericardium. If the patient's condition does not permit a surgical procedure, sclerosis can be attempted with doxycycline and/or bleomycin.

Malignant ascites is usually treated with repeated paracentesis of small volumes of fluid. If the underlying malignancy is unresponsive to systemic therapy, peritoneovenous shunts may be inserted. Despite the fear of disseminating tumor cells into the circulation, widespread metastases are an unusual complication. T e major complications are occlusion, leakage, and fluid overload. Patients with severe liver disease may develop disseminated intravascular coagulation.

Nutrition

Cancer and its treatment may lead to a decrease in nutrient intake of suf cient magnitude to cause weight loss and alteration of intermediary metabolism. T e prevalence of this problem is dif cult to estimate because of variations in the definition of cancer cachexia, but most patients with advanced cancer experience weight loss and decreased appetite. A variety of both tumor-derived factors (e.g., bombesin, adrenocorticotropic hormone) and host-derived factors (e.g., tumor necrosis factor, interleukins 1 and 6, growth hormone) contribute to the altered metabolism, and a vicious cycle is established in which protein catabolism, glucose intolerance, and lipolysis cannot be reversed by the provision of calories.

It remains controversial how to assess nutritional status and when and how to intervene. Efforts to make the assessment objective have included the use of a prognostic nutritional index based on albumin levels, triceps skinfold thickness, transferrin levels, and delayed-type hypersensitivity skin testing. However, a simpler approach has been to define the threshold for nutritional intervention as <10% unexplained body weight loss, serum transferrin level <1500 mg/L (150 mg/dL), and serum albumin <34 g/L (3.4 g/dL).

T e decision is important, because it appears that cancer therapy is substantially more toxic and less effective in the face of malnutrition. Nevertheless, it remains unclear whether nutritional intervention can alter the natural history. Unless some pathology is affecting the absorptive function of the gastrointestinal tract, enteral nutrition provided orally or by tube feeding is preferred over parenteral supplementation. However, the risks associated with the tube may outweigh the benefits. Megestrol acetate, a progestational agent, has been advocated as a pharmacologic intervention to improve nutritional status. Research in this area may provide more tools in the future as cytokine-mediated mechanisms are further elucidated.

Psychosocial support

T e psychosocial needs of patients vary with their situation. Patients undergoing treatment experience fear, anxiety, and depression. Self-image is often seriously compromised by deforming surgery and loss of hair. Women who receive cosmetic advice that enables them to look better also feel better. Loss of control over how one spends time can contribute to the sense of vulnerability. Juggling the demands of work and family with the demands of treatment may create enormous stresses. Sexual dysfunction is highly prevalent and needs to be

discussed openly with the patient. An empathetic health care team is sensitive to the individual patient's needs and permits negotiation where such flexibility will not adversely affect the course of treatment.

Cancer survivors have other sets of dif culties. Patients may have fears associated with the termination of a treatment they associate with their continued survival. Adjustments are required to physical losses and handicaps, real and perceived. Patients may be preoccupied with minor physical problems. T ey perceive a decline in their job mobility and view themselves as less desirable workers. T ey may be victims of job and/or insurance discrimination. Patients may experience difficulty reentering their normal past life. T ey may feel guilty for having survived and may carry a sense of vulnerability to colds and other illnesses. Perhaps the most pervasive and threatening concern is the ever-present fear of relapse (the Damocles syndrome).

Patients in whom therapy has been unsuccessful have other problems related to the end of life.

Death and dying

T e most common causes of death in patients with cancer are infection (leading to circulatory failure), respiratory failure, hepatic failure, and renal failure. Intestinal blockage may lead to inanition and starvation. Central nervous system disease may lead to seizures, coma, and central hypoventilation. About 70% of patients develop dyspnea preterminally. However, many months usually pass between the diagnosis of cancer and the occurrence of these complications, and during this period, the patient is severely affected by the possibility of death. T e path of unsuccessful cancer treatment usually occurs in three phases. First, there is optimism at the hope of cure; when the tumor recurs, there is the acknowledgment of an incurable disease, and the goal of palliative therapy is embraced in the hope of being able to live with disease; finally, at the disclosure of imminent death, another adjustment in outlook takes place. T e patient imagines the worst in preparation for the end of life and may go through stages of adjustment to the diagnosis. T ese stages include denial, isolation, anger, bargaining, depression, acceptance, and hope. Of course, patients do not all progress through all the stages or proceed through them in the same order or at the same rate. Nevertheless, developing an understanding of how the patient has been affected by the diagnosis and is coping with it is an important goal of patient management.

It is best to speak frankly with the patient and the family regarding the likely course of disease. T ese discussions can be dif cult for the physician as well as for the patient and family. T e critical features of the interaction are to reassure the patient and family that everything that can be done to provide comfort will be done. T ey will not be abandoned. Many patients prefer to be cared for in their homes or in a hospice setting rather than a hospital. T e American College of Physicians has published a book called Home Care Guide for Cancer: How to Care for Family and Friends at Home that teaches an approach to successful problem-solving in home care. With appropriate planning, it should be possible to provide the patient with the necessary medical care as well as the psychological and spiritual support that will prevent the isolation and depersonalization that can attend in-hospital death.

T e care of dying patients may take a toll on the physician. A "burnout" syndrome has been described that is characterized by fatigue, disengagement from patients and colleagues, and a loss of self-fulfillment. Efforts at stress reduction, maintenance of a balanced life, and setting realistic goals may combat this disorder.

End-o*f*-li*f*e decisions

Unfortunately, a smooth transition in treatment goals from curative to palliative may not be possible in all cases because of the occurrence of serious treatment-related complications or rapid disease progression. Vigorous and invasive medical support for a reversible disease or treatment complication is assumed to be justified. However, if the reversibility of the condition is in doubt, the patient's wishes determine the level of medical care. T ese wishes should be elicited before the terminal phase of illness and reviewed periodically. Information about advance directives can be obtained from the American Association of Retired Persons, 601 E Street, NW, Washington, DC 20049, 202-434-2277, or Choice in Dying, 250 West 57th Street, New York, NY 10107, 212-366-5540. Some states allow physicians to assist patients who choose to end their lives. T is subject is challenging from an ethical and a medical point of view. Discussions of end-of-life decisions should be candid and involve clear informed consent, waiting periods, second opinions, and documentation. **A full discussion of end-of-life management is in Chap. 33**.

CHAPTER 28

PREVENTION AND EARLY DETECTION OF CANCER

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Improved understanding of carcinogenesis has allowed cancer prevention and early detection (also known as cancer control) to expand beyond the identification and avoidance of carcinogens. Specific interventions to prevent cancer in those at risk, and effective screening for early detection of cancer, are the goals.

Carcinogenesis is not an event but a process, a continuum of discrete tissue and cellular changes over time resulting in aberrant physiologic processes. Prevention concerns the identification and manipulation of the biologic, environmental, social, and genetic factors in the causal pathway of cancer.

EDUCATION AND HEALTHFUL HABITS

Public education on the avoidance of identified risk factors for cancer and encouraging healthy habits contributes to cancer prevention and control. T e clinician is a powerful messenger in this process. T e patient-provider encounter provides an opportunity to teach patients about the hazards of smoking, the features of a healthy lifestyle, use of proven cancer screening methods, and avoidance of excessive sun exposure.

SMOKING CESSATION

Tobacco smoking is a strong, modifiable risk factor for cardiovascular disease, pulmonary disease, and cancer. Smokers have an approximately 1 in 3 lifetime risk of dying prematurely from a tobacco-related cancer, cardiovascular, or pulmonary disease. Tobacco use causes more deaths from cardiovascular disease than from cancer. Lung cancer and cancers of the larynx, oropharynx, esophagus, kidney, bladder, pancreas, and stomach are all tobacco-related.

T e number of cigarettes smoked per day and the level of inhalation of cigarette smoke are correlated with risk of lung cancer mortality. Light- and low-tar cigarettes are not safer, because smokers tend to inhale them more frequently and deeply.

T ose who stop smoking have a 30–50% lower 10-year lung cancer mortality rate compared to those who continue smoking, despite the fact that some carcinogen-induced gene mutations persist for years after smoking cessation. Smoking cessation and avoidance would save more lives than any other public health activity.

T e risk of tobacco smoke is not limited to the smoker. Environmental tobacco smoke, known as secondhand or passive smoke, causes lung cancer and other cardiopulmonary diseases in nonsmokers.

Tobacco use prevention is a pediatric issue. More than 80% of adult American smokers began smoking before the age of 18 years. Approximately 20% of Americans in grades 9 through 12 have smoked a cigarette in the past month. Counseling of adolescents and young adults is critical to prevent smoking. A clinician's simple advice can be of benefit. Providers should query patients on tobacco use and offer smokers assistance in quitting.

Current approaches to smoking cessation recognize smoking as an addiction. T e smoker who is quitting goes through identifiable stages that include contemplation of quitting, an action phase in which the smoker quits, and a maintenance phase. Smokers who quit completely are more likely to be successful than those who gradually reduce the number of cigarettes smoked or change to lower-tar or lower-nicotine cigarettes. More than 90% of the Americans who have successfully quit smoking did so on their own, without participation in an organized cessation program, but cessation programs are helpful for some smokers. T e Community Intervention Trial for Smoking Cessation (COMMIT)

was a 4-year program showing that light smokers (<25 cigarettes per day) were more likely to benefit from simple cessation messages and cessation programs than those who did not receive an intervention. Quit rates were 30.6% in the intervention group and 27.5% in the control group. T e COMMIT interventions were unsuccessful in heavy smokers (<25 cigarettes per day). Heavy smokers may need an intensive broad-based cessation program that includes counseling, behavioral strategies, and pharmacologic adjuncts, such as nicotine replacement (gum, patches, sprays, lozenges, and inhalers), bupropion, and/or varenicline.

T e health risks of cigars are similar to those of cigarettes. Smoking one or two cigars daily doubles the risk for oral and esophageal cancers; smoking three or four cigars daily increases the risk of oral cancers more than eightfold and esophageal cancer fourfold. T e risks of occasional use are unknown.

Smokeless tobacco also represents a substantial health risk. Chewing tobacco is a carcinogen linked to dental caries, gingivitis, oral leukoplakia, and oral cancer. T e systemic effects of smokeless tobacco (including snuff) may increase risks for other cancers. Esophageal cancer is linked to carcinogens in tobacco dissolved in saliva and swallowed. T e net effects of e-cigarettes on health are poorly studied. Whether they aid in smoking cessation or serve as a "gateway" for nonsmoking children to acquire a smoking habit is debated.

PHYSICAL ACTIVITY

Physical activity is associated with a decreased risk of colon and breast cancer. A variety of mechanisms have been proposed. However, such studies are prone to confounding factors such as recall bias, association of exercise with other health-related practices, and effects of preclinical cancers on exercise habits (reverse causality).

DIET MODIFICATION

International epidemiologic studies suggest that diets high in fat are associated with increased risk for cancers of the breast, colon, prostate, and endometrium. T ese cancers have their highest incidence and mortalities in Western cultures, where fat composes an average of one-third of the total calories consumed.

Despite correlations, dietary fat has not been proven to cause cancer. Case-control and cohort epidemiologic studies give conflicting results. In addition, diet is a highly complex exposure to many nutrients and chemicals. Low-fat diets are associated with many dietary changes beyond simple subtraction of fat. Other lifestyle changes are also associated with adherence to a low-fat diet.

In observational studies, dietary fiber is associated with a reduced risk of colonic polyps and invasive cancer of the colon. However, cancer-protective effects of increasing fiber and lowering dietary fat have not been proven in the context of a prospective clinical trial. T e putative protective mechanisms are complex and speculative. Fiber binds oxidized bile acids and generates soluble fiber products, such as butyrate, that may have differentiating properties. Fiber does not increase bowel transit times. Two large prospective cohort studies of >100,000 health professionals showed no association between fruit and vegetable intake and risk of cancer.

T e Polyp Prevention Trial randomly assigned 2000 elderly persons, who had polyps removed, to a low-fat, high-fiber diet versus routine diet for 4 years. No differences were noted in polyp formation.

T e U.S. National Institutes of Health Women's Health Initiative, launched in 1994, was a long-term clinical trial enrolling >100,000 women age 45–69 years. It placed women in 22 intervention groups. Participants received calcium/vitamin D supplementation; hormone replacement therapy; and counseling to increase exercise, eat a low-fat diet with increased consumption of fruits, vegetables, and fiber, and cease smoking. T e study showed that although dietary fat intake was lower in the diet intervention group, invasive breast cancers were not reduced over an 8-year follow-up period compared to the control group. No reduction was seen in the incidence of colorectal cancer in the dietary intervention arm. T e difference in dietary fat averaged ~10% between the two groups. Evidence does not currently establish the anticarcinogenic value of vitamin, mineral, or nutritional supplements in amounts greater than those provided by a balanced diet.

ENERGY BALANCE

Risk of cancer appears to increase as body mass index increases beyond 25 kg/m^2. Obesity is associated with increased risk for cancers of the colon, breast (female postmenopausal), endometrium, kidney (renal cell), and esophagus, although causality has not been established.

In observational studies, relative risks of colon cancer are increased in obesity by 1.5–2 for men and 1.2–1.5 for women. Obese postmenopausal women have a 30–50% increased relative risk of breast cancer. An unproven hypothesis for the association is that adipose tissue serves as a depot for aromatase that facilitates estrogen production.

SUN AVOIDANCE

Nonmelanoma skin cancers (basal cell and squamous cell) are induced by cumulative exposure to ultraviolet (UV) radiation. Intermittent acute sun exposure and sun damage have been linked to melanoma, but

the evidence is inconsistent. Sunburns, especially in childhood and adolescence, may be associated with an increased risk of melanoma in adulthood. Reduction of sun exposure through use of protective clothing and changing patterns of outdoor activities can reduce skin cancer risk. Sunscreens decrease the risk of actinic keratoses, the precursor to squamous cell skin cancer, but melanoma risk may not be reduced. Sunscreens prevent burning, but they may encourage more prolonged exposure to the sun and may not filter out wavelengths of energy that cause melanoma.

Educational interventions to help individuals assess their risk of developing skin cancer have some impact. In particular, appearance-focused behavioral interventions in young women can decrease indoor tanning use and other UV exposures. Self-examination for skin pigment characteristics associated with skin cancer, such as freckling, may be useful in identifying people at high risk. T ose who recognize themselves as being at risk tend to be more compliant with sun-avoidance recommendations. Risk factors for melanoma include a propensity to sunburn, a large number of benign melanocytic nevi, and atypical nevi.

CANCER CHEMOPREVENTION

Chemoprevention involves the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of invasive malignancy.

Cancer develops through an accumulation of tissue abnormalities associated with genetic and epigenetic changes, and growth regulatory pathways that are potential points of intervention to prevent cancer. T e initial changes are termed initiation. T e alteration can be inherited or acquired through the action of physical, infectious, or chemical carcinogens. Like most human diseases, cancer arises from an interaction between genetics and environmental exposures **(Table 28-1)**. Influences that cause the initiated cell and its surrounding tissue microenvironment to progress through the carcinogenic process and change phenotypically are termed promoters. Promoters include hormones such as androgens, linked to prostate cancer, and estrogen, linked to breast and endometrial cancer. T e distinction between an initiator and promoter is indistinct; some components of cigarette smoke are "complete carcinogens," acting as both initiators and promoters. Cancer can be prevented or controlled through interference with the factors that cause cancer initiation, promotion, or progression. Compounds of interest in chemoprevention often have antimutagenic, hormone modulation, anti-inflammatory, antiproliferative, or proapoptotic activity (or a combination).

TABLE 28-1

SUSPECTED CARCINOGENS

CARCINOGENS[a]	ASSOCIATED CANCER OR NEOPLASM
Alkylating agents	Acute myeloid leukemia, bladder cancer
Androgens	Prostate cancer
Aromatic amines (dyes)	Bladder cancer
Arsenic	Cancer of the lung, skin
Asbestos	Cancer of the lung, pleura, peritoneum
Benzene	Acute myelocytic leukemia
Chromium	Lung cancer
Diethylstilbestrol (prenatal)	Vaginal cancer (clear cell)
Epstein-Barr virus	Burkitt's lymphoma, nasal T cell lymphoma
Estrogens	Cancer of the endometrium, liver, breast
Ethyl alcohol	Cancer of the breast, liver, esophagus, head and neck
Helicobacter pylori	Gastric cancer, gastric MALT lymphoma
Hepatitis B or C virus	Liver cancer
Human immunodeficiency virus	Non-Hodgkin's lymphoma, Kaposi's sarcoma, squamous cell carcinomas (especially of the urogenital tract)
Human papilloma virus	Cancers of the cervix, anus, oropharynx
Human T cell lymphotropic virus type 1 (HTLV-1)	Adult T cell leukemia/lymphoma
Immunosuppressive agents (azathioprine, cyclosporine, glucocorticoids)	Non-Hodgkin's lymphoma
Ionizing radiation (therapeutic or diagnostic)	Breast, bladder, thyroid, soft tissue, bone, hematopoietic, and many more
Nitrogen mustard gas	Cancer of the lung, head and neck, nasal sinuses
Nickel dust	Cancer of the lung, nasal sinuses
Diesel exhaust	Lung cancer (miners)
Phenacetin	Cancer of the renal pelvis and bladder
Polycyclic hydrocarbons	Cancer of the lung, skin (especially squamous cell carcinoma of scrotal skin)
Radon gas	Lung cancer
Schistosomiasis	Bladder cancer (squamous cell)
Sunlight (ultraviolet)	Skin cancer (squamous cell and melanoma)
Tobacco (including smokeless)	Cancer of the upper aerodigestive tract, bladder
Vinyl chloride	Liver cancer (angiosarcoma)

[a] Agents that are thought to act as cancer initiators and/or promoters.

CHEMOPREVENTION OF CANCERS OF THE UPPER AERODIGESTIVE TRACT

Smoking causes diffuse epithelial injury in the oral cavity, neck, esophagus, and lung. Patients cured of squamous cell cancers of the lung, esophagus, oral cavity, and neck are at risk (as high as 5% per year) of developing second cancers of the upper aerodigestive tract. Cessation of cigarette smoking does not markedly decrease the cured cancer patient's risk of second malignancy, even though it does lower the cancer risk in those who have never developed a malignancy. Smoking cessation may halt the early stages of the carcinogenic process (such as metaplasia), but it may have no effect on late stages of carcinogenesis. T is "field carcinogenesis" hypothesis for upper aerodigestive tract cancer has made "cured" patients an important population for chemoprevention of second malignancies.

Oral human papilloma virus (HPV) infection, particularly HPV-16, increases the risk for cancers of the oropharynx. T is association exists even in the absence of other risk factors such as smoking or alcohol use (although the magnitude of increased risk appears greater than additive when HPV infection and smoking are both present). Oral HPV infection is believed to be largely sexually acquired. Although no direct evidence currently exists to confirm the hypothesis, the introduction of the HPV vaccine may eventually reduce oropharyngeal cancer rates.

Oral leukoplakia, a premalignant lesion commonly found in smokers, has been used as an intermediate marker of chemopreventive activity in smaller shorter-duration, randomized, placebo-controlled trials. Response was associated with upregulation of retinoic acid receptor-β (RAR-β). T erapy with high, relatively toxic doses of isotretinoin (13-cis-retinoic acid) causes regression of oral leukoplakia. However, the lesions recur when the therapy is withdrawn, suggesting the need for long-term administration. More tolerable doses of isotretinoin have not shown benefit in the prevention of head and neck cancer. Isotretinoin also failed to prevent second malignancies in patients cured of early-stage non-small cell lung cancer; mortality rates were actually increased in current smokers.

Several large-scale trials have assessed agents in the chemoprevention of lung cancer in patients at high risk. In the α-tocopherol/β-carotene (ATBC) Lung Cancer Prevention Trial, participants were male smokers, age 50–69 years at entry. Participants had smoked an average of one pack of cigarettes per day for 35.9 years. Participants received α-tocopherol, β-carotene, and/or placebo in a randomized, two-by-two factorial design. After median follow-up of 6.1 years, lung cancer incidence and mortality were statistically significantly increased in those receiving β-carotene. α-Tocopherol had no effect on lung cancer mortality, and no evidence suggested interaction between the two drugs. Patients receiving α-tocopherol had a higher incidence of hemorrhagic stroke.

T e β-Carotene and Retinol Ef cacy Trial (CARET) involved 17,000 American smokers and workers with asbestos exposure. Entrants were randomly assigned to one of four arms and received β-carotene, retinol, and/or placebo in a two-by-two factorial design. T is trial also demonstrated harm from β-carotene: a lung cancer rate of 5 per 1000 subjects per year for those taking placebo and of 6 per 1000 subjects per year for those taking β-carotene.

T e ATBC and CARET results demonstrate the importance of testing chemoprevention hypotheses thoroughly before their widespread implementation because the results contradict a number of observational studies. T e Physicians' Health Trial showed no change in the risk of lung cancer for those taking β-carotene; however, fewer of its participants were smokers than those in the ATBC and CARET studies.

CHEMOPREVENTION OF COLON CANCER

Many colon cancer prevention trials are based on the premise that most colorectal cancers develop from adenomatous polyps. T ese trials use adenoma recurrence or disappearance as a surrogate endpoint (not yet validated) for colon cancer prevention. Early clinical trial results suggest that nonsteroidal anti-inflammatory drugs (NSAIDs), such as piroxicam, sulindac, and aspirin, may prevent adenoma formation or cause regression of adenomatous polyps. T e mechanism of action of NSAIDs is unknown, but they are presumed to work through the cyclooxygenase pathway. Although two randomized controlled trials (the Physicians' Health Study and the Women's Health Study) did not show an effect of aspirin on colon cancer or adenoma incidence in persons with no previous history of colonic lesions after 10 years of therapy, these trials did show an approximately 18% relative risk reduction for colonic adenoma incidence in persons with a previous history of adenomas after 1 year. Pooled findings from observational cohort studies do demonstrate a 22% and 28% relative reduction in colorectal cancer and adenoma incidence, respectively, with regular aspirin use, and a well-conducted meta-analysis of four randomized controlled trials (albeit primarily designed to examine aspirin's effects on cardiovascular events) found that aspirin at doses of at least 75 mg resulted in a 24% relative reduction in colorectal cancer incidence after 20 years, with no clear increase in ef cacy at higher doses. Cyclooxygenase-2 (COX-2) inhibitors have also been considered for colorectal cancer and polyp prevention. Trials with COX-2 inhibitors were initiated, but an increased risk of cardiovascular events

in those taking the COX-2 inhibitors was noted, suggesting that these agents are not suitable for chemoprevention in the general population.

Epidemiologic studies suggest that diets high in calcium lower colon cancer risk. Calcium binds bile and fatty acids, which cause proliferation of colonic epithelium. It is hypothesized that calcium reduces intraluminal exposure to these compounds. T e randomized controlled Calcium Polyp Prevention Study found that calcium supplementation decreased the absolute risk of adenomatous polyp recurrence by 7% at 4 years; extended observational follow-up demonstrated a 12% absolute risk reduction 5 years after cessation of treatment. However, in the Women's Health Initiative, combined use of calcium carbonate and vitamin D twice daily did not reduce the incidence of invasive colorectal cancer compared with placebo after 7 years.

T e Women's Health Initiative demonstrated that postmenopausal women taking estrogen plus progestin have a 44% lower relative risk of colorectal cancer compared to women taking placebo. Of >16,600 women randomized and followed for a median of 5.6 years, 43 invasive colorectal cancers occurred in the hormone group and 72 in the placebo group. T e positive effect on colon cancer is mitigated by the modest increase in cardiovascular and breast cancer risks associated with combined estrogen plus progestin therapy.

A case-control study suggested that statins decrease the incidence of colorectal cancer; however, several subsequent case-control and cohort studies have not demonstrated an association between regular statin use and a reduced risk of colorectal cancer. No randomized controlled trials have addressed this hypothesis. A meta-analysis of statin use showed no protective effect of statins on overall cancer incidence or death.

CHEMOPREVENTION OF BREAST CANCER

Tamoxifen is an antiestrogen with partial estrogen agonistic activity in some tissues, such as endometrium and bone. One of its actions is to upregulate transforming growth factor β, which decreases breast cell proliferation. In randomized placebo-controlled trials to assess tamoxifen as adjuvant therapy for breast cancer, tamoxifen reduced the number of new breast cancers in the opposite breast by more than a third. In a randomized placebo-controlled prevention trial involving >13,000 pre- and postmenopausal women at high risk, tamoxifen decreased the risk of developing breast cancer by 49% (from 43.4 to 22 per 1000 women) after a median follow-up of nearly 6 years. Tamoxifen also reduced bone fractures; a small increase in risk of endometrial cancer, stroke, pulmonary emboli, and deep vein thrombosis was noted. T e International Breast Cancer Intervention Study (IBIS-I) and the Italian Randomized Tamoxifen Prevention Trial also demonstrated a reduction in breast cancer incidence with tamoxifen use. A trial comparing tamoxifen with another selective estrogen receptor modulator, raloxifene, in postmenopausal women showed that raloxifene is comparable to tamoxifen in cancer prevention. T is trial only included postmenopausal women. Raloxifene was associated with more invasive breast cancers and a trend toward more noninvasive breast cancers, but fewer thromboembolic events than tamoxifen; the drugs are similar in risks of other cancers, fractures, ischemic heart disease, and stroke. Both tamoxifen and raloxifene (the latter for postmenopausal women only) have been approved by the U.S. Food and Drug Administration (FDA) for reduction of breast cancer in women at high risk for the disease (1.66% risk at 5 years based on the Gail risk model: http://www.cancer.gov/bcrisktool/).

Because the aromatase inhibitors are even more effective than tamoxifen in adjuvant breast cancer therapy, it has been hypothesized that they would be more effective in breast cancer prevention. A randomized, placebo-controlled trial of exemestane reported a 65% relative reduction (from 5.5 to 1.9 per 1000 women) in the incidence of invasive breast cancer in women at elevated risk after a median follow-up of about 3 years. Common adverse effects included arthralgias, hot flashes, fatigue, and insomnia. No trial has directly compared aromatase inhibitors with selective estrogen receptor modulators for breast cancer chemoprevention.

CHEMOPREVENTION OF PROSTATE CANCER

Finasteride and dutasteride are 5-α-reductase inhibitors. T ey inhibit conversion of testosterone to dihydrotestosterone (DHT), a potent stimulator of prostate cell proliferation. T e Prostate Cancer Prevention Trial (PCPT) randomly assigned men age 55 years or older at average risk of prostate cancer to finasteride or placebo. All men in the trial were being regularly screened with prostate-specific antigen (PSA) levels and digital rectal examination. After 7 years of therapy, the incidence of prostate cancer was 18.4% in the finasteride arm, compared with 24.4% in the placebo arm, a statistically significant difference. However, the finasteride group had more patients with tumors of Gleason score 7 and higher compared with the placebo arm (6.4 vs 5.1%). Reassuringly, long-term (10–15 years) follow-up did not reveal any statistically significant differences in overall mortality between all men in the finasteride and placebo arms or in men diagnosed with prostate cancer; differences in prostate cancer in favor of finasteride persisted.

Dutasteride has also been evaluated as a preventive agent for prostate cancer. T e Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial was a

randomized double-blind trial in which approximately 8200 men with an elevated PSA (2.5–10 ng/mL for men age 50–60 years and 3–10 ng/mL for men age 60 years or older) and negative prostate biopsy on enrollment received daily 0.5 mg of dutasteride or placebo. T e trial found a statistically significant 23% relative risk reduction in the incidence of biopsy-detected prostate cancer in the dutasteride arm at 4 years of treatment (659 cases vs 858 cases, respectively). Overall, across years 1 through 4, there was no difference between the arms in the number of tumors with a Gleason score of 7 to 10; however, during years 3 and 4, there was a statistically significant difference in tumors with Gleason score of 8 to 10 in the dutasteride arm (12 tumors vs 1 tumor, respectively).

T e clinical importance of the apparent increased incidence of higher-grade tumors in the 5-α-reductase inhibitor arms of these trials is controversial. It may likely represent an increased sensitivity of PSA and digital rectal exam for high-grade tumors in men receiving these agents. T e FDA has analyzed both trials, and it determined that the use of a 5-α-reductase inhibitor for prostate cancer chemoprevention would result in one additional high-grade (Gleason score 8 to 10) prostate cancer for every three to four lower-grade (Gleason score <6) tumors averted. Although it acknowledged that detection bias may have accounted for the finding, it stated that it could not conclusively dismiss a causative role for 5-α-reductase inhibitors. T ese agents are therefore not FDA-approved for prostate cancer prevention.

Because all men in both the PCPT and REDUCE trials were being screened and because screening approximately doubles the rate of prostate cancer, it is not known if finasteride or dutasteride decreases the risk of prostate cancer in men who are not being screened.

Several favorable laboratory and observational studies led to the formal evaluation of selenium and α-tocopherol (vitamin E) as potential prostate cancer preventives. T e Selenium and Vitamin E Cancer Prevention Trial (SELECT) assigned 35,533 men to receive 200 μg/d selenium, 400 IU/d α-tocopherol, selenium plus vitamin E, or placebo. After a median follow-up of 7 years, a trend toward an increased risk of developing prostate cancer was observed for those men taking vitamin E alone as compared to the placebo arm (hazard ratio 1.17; 95% confidence interval, 1.004–1.36).

VACCINES AND CANCER PREVENTION

A number of infectious agents cause cancer. Hepatitis B and C are linked to liver cancer; some HPV strains are linked to cervical, anal, and head and neck cancer; and Helicobacter pylori is associated with gastric adenocarcinoma and gastric lymphoma. Vaccines to protect against these agents may reduce the risk of their associated cancers.

T e hepatitis B vaccine is effective in preventing hepatitis and hepatomas due to chronic hepatitis B infection.

A quadrivalent HPV vaccine (covering HPV strains 6, 11, 16, and 18) and a bivalent vaccine (covering HPV strains 16 and 18) are available for use in the United States. HPV types 16 and 18 cause cervical and anal cancer; reduction in these HPV types could prevent >70% of cervical cancers worldwide. HPV types 6 and 11 cause genital papillomas. For individuals not previously infected with these HPV strains, the vaccines demonstrate high ef cacy in preventing persistent strain-specific HPV infections; however, the trials and substudies that evaluated the vaccines' ability to prevent cervical and anal cancer relied on surrogate outcome measures (cervical or anal intraepithelial neoplasia [CIN/AIN] I, II, and III), and the degree of durability of the immune response beyond 5 years is not currently known. T e vaccines do not appear to impact preexisting infections and the ef cacy appears to be markedly lower for populations that had previously been exposed to vaccine-specific HPV strains. T e vaccine is recommended in the United States for females and males age 9–26 years.

SURGICAL PREVENTION OF CANCER

Some organs in some individuals are at such high risk of developing cancer that surgical removal of the organ at risk may be considered. Women with severe cervical dysplasia are treated with laser or loop electrosurgical excision or conization and occasionally even hysterectomy. Colectomy is used to prevent colon cancer in patients with familial polyposis or ulcerative colitis.

Prophylactic bilateral mastectomy may be chosen for breast cancer prevention among women with genetic predisposition to breast cancer. In a prospective series of 139 women with BRCA1 and BRCA2 mutations, 76 chose to undergo prophylactic mastectomy and 63 chose close surveillance. At 3 years, no cases of breast cancer had been diagnosed in those opting for surgery, but eight patients in the surveillance group had developed breast cancer. A larger (n = 639) retrospective cohort study reported that three patients developed breast cancer after prophylactic mastectomy compared with an expected incidence of 30–53 cases: a 90–94% reduction in breast cancer risk. Postmastectomy breast cancer–related deaths were reduced by 81–94% for high-risk women compared with sister controls and by 100% for moderate-risk women when compared with expected rates.

Prophylactic oophorectomy may also be employed for the prevention of ovarian and breast cancers among high-risk women. A prospective cohort study evaluating the outcomes of BRCA mutation carriers demonstrated a statistically significant association between prophylactic oophorectomy and a reduced incidence of ovarian

or primary peritoneal cancer (36% relative risk reduction, or a 4.5% absolute difference). Studies of prophylactic oophorectomy for prevention of breast cancer in women with genetic mutations have shown relative risk reductions of approximately 50%; the risk reduction may be greatest for women having the procedure at younger (i.e., <50 years) ages.

All of the evidence concerning the use of prophylactic mastectomy and oophorectomy for prevention of breast and ovarian cancer in high-risk women has been observational in nature; such studies are prone to a variety of biases, including case selection bias, family relationships between patients and controls, and inadequate information about hormone use. T us, they may give an overestimate of the magnitude of benefit.

CANCER SCREENING

Screening is a means of detecting disease early in asymptomatic individuals, with the goal of decreasing morbidity and mortality. While screening can potentially reduce disease-specific deaths and has been shown to do so in cervical, colon, lung, and breast cancer, it is also subject to a number of biases that can suggest a benefit when actually there is none. Biases can even mask net harm. Early detection does not in itself confer benefit. Cause-specific mortality, rather than survival after diagnosis, is the preferred endpoint (see below).

Because screening is done on asymptomatic, healthy persons, it should offer substantial likelihood of benefit that outweighs harm. Screening tests and their appropriate use should be carefully evaluated before their use is widely encouraged in screening programs, as a matter of public policy.

A large and increasing number of genetic mutations and nucleotide polymorphisms have been associated with an increased risk of cancer. Testing for these genetic mutations could in theory define a high-risk population. However, most of the identified mutations have very low penetrance and individually provide minimal predictive accuracy. T e ability to predict the development of a particular cancer may some day present therapeutic options as well as ethical dilemmas. It may eventually allow for early intervention to prevent a cancer or limit its severity. People at high risk may be ideal candidates for chemoprevention and screening; however, ef cacy of these interventions in the high-risk population should be investigated. Currently, persons at high risk for a particular cancer can engage in intensive screening. While this course is clinically reasonable, it is not known if it reduces mortality in these populations.

The accuracy of screening

A screening test's accuracy or ability to discriminate disease is described by four indices: sensitivity, specificity, positive predictive value, and negative predictive value **(Table 28-2)**. Sensitivity, also called the true-positive rate, is the proportion of persons with the disease who test positive in the screen (i.e., the ability of the test to detect disease when it is present). Specificity, or 1 minus the false-positive rate, is the proportion of persons who do not have the disease that test negative in the screening test (i.e., the ability of a test to correctly identify that the disease is not present). T e positive predictive value is the proportion of persons who test positive that actually have the disease. Similarly, negative predictive value is the proportion testing negative that do not have the disease. T e sensitivity and specificity of a test are independent of the underlying prevalence (or risk) of the disease in the population screened, but the predictive values depend strongly on the prevalence of the disease.

Screening is most beneficial, ef cient, and economical when the target disease is common in the population being screened. Specificity is at least as important to the ultimate feasibility and success of a screening test as sensitivity.

TABLE 28-2

ASSESSMENT OF THE VALUE OF A DIAGNOSTIC TEST[a]

	CONDITION PRESENT	CONDITION ABSENT
Positive test	a	b
Negative test	c	d
a = true positive b = false positive c = false negative d = true negative		
Sensitivity	The proportion of persons with the condition who test positive: a /(a + c)	
Specificity	The proportion of persons without the condition who test negative: d /(b + d)	
Positive predictive value (PPV)	The proportion of persons with a positive test who have the condition: a /(a + b)	
Negative predictive value	The proportion of persons with a negative test who do not have the condition: d /(c + d)	
Prevalence, sensitivity, and specificity determine PPV $PPV = \frac{\text{prevalence} \times \text{sensitivity}}{(\text{prevalence} \times \text{sensitivity}) + (1 - \text{prevalence})(1 - \text{specificity})}$		

[a]For diseases of low prevalence, such as cancer, poor specificity has a dramatic adverse effect on PPV such that only a small fraction of positive tests are true positives.

Potential biases of screening tests

Common biases of screening are lead time, length-biased sampling, and selection. T ese biases can make a screening test seem beneficial when actually it is not

(or even causes net harm). Whether beneficial or not, screening can create the false impression of an epidemic by increasing the number of cancers diagnosed. It can also produce a shift in the proportion of patients diagnosed at an early stage and inflate survival statistics without reducing mortality (i.e., the number of deaths from a given cancer relative to the number of those at risk for the cancer). In such a case, the apparent duration of survival (measured from date of diagnosis) increases without lives being saved or life expectancy changed.

Lead-time bias occurs whether or not a test influences the natural history of the disease; the patient is merely diagnosed at an earlier date. Survival appears increased even if life is not really prolonged. T e screening test only prolongs the time the subject is aware of the disease and spends as a patient.

Length-biased sampling occurs because screening tests generally can more easily detect slow-growing, less aggressive cancers than fast-growing cancers. Cancers diagnosed due to the onset of symptoms between scheduled screenings are on average more aggressive, and treatment outcomes are not as favorable. An extreme form of length bias sampling is termed overdiagnosis, the detection of "pseudo disease." T e reservoir of some undetected slow-growing tumors is large. Many of these tumors fulfill the histologic criteria of cancer but will never become clinically significant or cause death. T is problem is compounded by the fact that the most common cancers appear most frequently at ages when competing causes of death are more frequent.

Selection bias must be considered in assessing the results of any screening effort. T e population most likely to seek screening may differ from the general population to which the screening test might be applied. In general, volunteers for studies are more health conscious and likely to have a better prognosis or lower mortality rate, irrespective of the screening result. T is is termed the healthy volunteer ef ect.

Potential drawbacks of screening

Risks associated with screening include harm caused by the screening intervention itself, harm due to the further investigation of persons with positive tests (both true and false positives), and harm from the treatment of persons with a true-positive result, whether or not life is extended by treatment (e.g., even if a screening test reduces relative cause-specific mortality by 20–30%, 70–80% of those diagnosed still go on to die of the target cancer). T e diagnosis and treatment of cancers that would never have caused medical problems can lead to the harm of unnecessary treatment and give patients the anxiety of a cancer diagnosis. T e psychosocial impact of cancer screening can also be substantial when applied to the entire population.

Assessment of screening tests

Good clinical trial design can offset some biases of screening and demonstrate the relative risks and benefits of a screening test. A randomized controlled screening trial with cause-specific mortality as the endpoint provides the strongest support for a screening intervention. Overall mortality should also be reported to detect an adverse effect of screening and treatment on other disease outcomes (e.g., cardiovascular disease). In a randomized trial, two like populations are randomly established. One is given the usual standard of care (which may be no screening at all) and the other receives the screening intervention being assessed. T e two populations are compared over time. Ef cacy for the population studied is established when the group receiving the screening test has a better cause-specific mortality rate than the control group. Studies showing a reduction in the incidence of advanced-stage disease, improved survival, or a stage shift are weaker (and possibly misleading) evidence of benefit. T ese latter criteria are early indicators but not suf cient to establish the value of a screening test.

Although a randomized, controlled screening trial provides the strongest evidence to support a screening test, it is not perfect. Unless the trial is population-based, it does not remove the question of generalizability to the target population. Screening trials generally involve thousands of persons and last for years. Less definitive study designs are therefore often used to estimate the effectiveness of screening practices. However, every nonrandomized study design is subject to strong confounders. In descending order of strength, evidence may also be derived from the findings of internally controlled trials using intervention allocation methods other than randomization (e.g., allocation by birth date, date of clinic visit); the findings of analytic observational studies; or the results of multiple time series studies with or without the intervention.

Screening for specif c cancers

Screening for cervical, colon, and breast cancer is beneficial for certain age groups. Depending on age and smoking history, lung cancer screening can also be beneficial in specific settings. Special surveillance of those at high risk for a specific cancer because of a family history or a genetic risk factor may be prudent, but few studies have assessed the influence on mortality. A number of organizations have considered whether or not to endorse routine use of certain screening tests. Because these groups have not used the same criteria to judge whether a screening test should be endorsed, they have arrived at different recommendations. T e American Cancer Society (ACS) and the U.S. Preventive Services Task Force (USPSTF) publish screening guidelines **(Table 28-3)**; the American Academy of Family

TABLE 28-3

SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a]

CANCER TYPE	TEST OR PROCEDURE	USPSTF	ACS
Breast	Self-examination	"D"	Women ≥20 years: Breast self-exam is an option
	Clinical examination	Women ≥40 years: "I" (as a stand-alone without mammography)	Women 20–39 years: Perform every 3 years Women ≥40 years: Perform annually
	Mammography	Women 40–49 years: The decision should be an individual one, and take patient context/values into account ("C") Women 50–74 years: Every 2 years ("B") Women ≥75 years: "I"	Women ≥40 years: Screen annually for as long as the woman is in good health
	Magnetic resonance imaging (MRI)	"I"	Women with >20% lifetime risk of breast cancer: Screen with MRI plus mammography annually Women with 15–20% lifetime risk of breast cancer: Discuss option of MRI plus mammography annually Women with <15% lifetime risk of breast cancer: Do not screen annually with MRI
Cervical	Pap test (cytology)	Women 21–65 years: Screen every 3 years ("A") Women <21 years: "D" Women >65 years, with adequate, normal prior Pap screenings: "D" Women after total hysterectomy for noncancerous causes: "D"	Women 21–29 years: Screen every 3 years Women 30–65 years: Acceptable approach to screen with cytology every 3 years (see HPV test below) Women <21 years: No screening Women >65 years: No screening following adequate negative prior screening Women after total hysterectomy for noncancerous causes: Do not screen
	HPV test	Women 30–65 years: Screen in combination with cytology every 5 years if woman desires to lengthen the screening interval (see Pap test, above) ("A") Women <30 years: "D" Women >65 years, with adequate, normal prior Pap screenings: "D" Women after total hysterectomy for noncancerous causes: "D"	Women 30–65 years: Preferred approach to screen with HPV and cytology co-testing every 5 years (see Pap test above) Women <30 years: Do not use HPV testing Women >65 years: No screening following adequate negative prior screening Women after total hysterectomy for noncancerous causes: Do not screen
Colorectal	Sigmoidoscopy	Adults 50–75 years: every 5 years in combination with high-sensitivity FOBT every 3 years ("A")[b] Adults 76–85 years: "C" Adults ≥85 years: "D"	Adults ≥50 years: Screen every 5 years
	Fecal occult blood testing (FOBT)	Adults 50–75 years: Annually, for high-sensitivity FOBT ("A") Adults 76–85 years: "C" Adults ≥85 years: "D"	Adults ≥50 years: Screen every year
	Colonoscopy	Adults 50–75 years: every 10 years ("A") Adults 76–85 years: "C" Adults ≥85 years: "D"	Adults ≥50 years: Screen every 10 years
	Fecal DNA testing	"I"	Adults ≥50 years: Screen, but interval uncertain
	Fecal immunochemical testing (FIT)	"I"	Adults ≥50 years: Screen every year
	CT colonography	"I"	Adults ≥50 years: Screen every 5 years

(continued)

TABLE 28-3

SCREENING RECOMMENDATIONS FOR ASYMPTOMATIC SUBJECTS NOT KNOWN TO BE AT INCREASED RISK FOR THE TARGET CONDITION[a] (Continued)

CANCER TYPE	TEST OR PROCEDURE	USPSTF	ACS
Lung	Low-dose computed tomography (CT) scan	Adults 55–80 years, with a ≥30 pack-year smoking history, still smoking or have quit within past 15 years. Discontinue once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability to have curative lung surgery: "B"	Men and women, 55–74 years, with ≥30 pack-year smoking history, still smoking or have quit within past 15 years: Discuss benefits, limitations, and potential harms of screening; only perform screening in facilities with the right type of CT scanner and with high expertise/specialists
Ovarian	CA-125 Transvaginal ultrasound	"D" "D"	There is no sufficiently accurate test proven effective in the early detection of ovarian cancer. For women at high risk of ovarian cancer and/or who have unexplained, persistent symptoms, the combination of CA-125 and transvaginal ultrasound with pelvic exam may be offered.
Prostate	Prostate-specific antigen (PSA)	Men, all ages: "D"	Starting at age 50, men should talk to a doctor about the pros and cons of testing so they can decide if testing is the right choice for them. If African American or have a father or brother who had prostate cancer before age 65, men should have this talk starting at age 45. How often they are tested will depend on their PSA level.
	Digital rectal examination (DRE)	No individual recommendation	As for PSA; if men decide to be tested, they should have the PSA blood test with or without a rectal exam
Skin	Complete skin examination by clinician or patient	"I"	Self-examination monthly; clinical exam as part of routine cancer-related checkup

[a]Summary of the screening procedures recommended for the general population by the USPSTF and the ACS. These recommendations refer to asymptomatic persons who are not known to have risk factors, other than age or gender, for the targeted condition.
[b]USPSTF lettered recommendations are defined as follows: "A": The USPSTF recommends the service, because there is high certainty that the net benefit is substantial; "B": The USPSTF recommends the service, because there is high certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial; "C": The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences; there is at least moderate certainty that the net benefit is small; "D": The USPSTF recommends against the service because there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; "I": The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service.
Abbreviations: ACS, American Cancer Society; USPSTF, U.S. Preventive Services Task Force.

Practitioners (AAFP) generally follow/endorse the USPSTF recommendations; and the American College of Physicians (ACP) develops recommendations based on structured reviews of other organizations' guidelines.

Breast cancer

Breast self-examination, clinical breast examination by a caregiver, mammography, and magnetic resonance imaging (MRI) have all been variably advocated as useful screening tools.

A number of trials have suggested that annual or biennial screening with mammography or mammography plus clinical breast examination in normal-risk women older than age 50 years decreases breast cancer mortality. Each trial has been criticized for design flaws. In most trials, breast cancer mortality rate is decreased by 15–30%. Experts disagree on whether average-risk women age 40–49 years should receive regular screening (Table 28-3). The U.K. Age Trial, the only randomized trial of breast cancer screening to specifically evaluate the impact of mammography in women age 40–49 years, found no statistically significant difference in breast cancer mortality for screened women versus controls after about 11 years of follow-up (relative risk 0.83; 95% confidence interval 0.66–1.04); however, <70% of women received screening in the intervention arm, potentially diluting the observed effect. A meta-analysis of eight large randomized trials showed a 15% relative reduction in mortality (relative risk 0.85; 95% confidence interval 0.75–0.96) from mammography

screening for women age 39–49 years after 11–20 years of follow-up. T is is equivalent to a number needed to invite to screening of 1904 over 10 years to prevent one breast cancer death. At the same time, nearly half of women age 40–49 years screened annually will have false-positive mammograms necessitating further evaluation, often including biopsy. Estimates of overdiagnosis range from 10 to 40% of diagnosed invasive cancers. In the United States, widespread screening over the last several decades has not been accompanied by a reduction in incidence of metastatic breast cancer despite a large increase in early-stage disease, suggesting a substantial amount of overdiagnosis at the population level.

No study of breast self-examination has shown it to decrease mortality. A randomized controlled trial of approximately 266,000 women in China demonstrated no difference in breast cancer mortality between a group that received intensive breast self-exam instruction and reinforcement/reminders and controls at 10 years of follow-up. However, more benign breast lesions were discovered and more breast biopsies were performed in the self-examination arm.

Genetic screening for BRCA1 and BRCA2 mutations and other markers of breast cancer risk has identified a group of women at high risk for breast cancer. Unfortunately, when to begin and the optimal frequency of screening have not been defined. Mammography is less sensitive at detecting breast cancers in women carrying BRCA1 and BRCA2 mutations, possibly because such cancers occur in younger women, in whom mammography is known to be less sensitive. MRI screening may be more sensitive than mammography in women at high risk due to genetic predisposition or in women with very dense breast tissue, but specificity may be lower. An increase in overdiagnosis may accompany the higher sensitivity. T e impact of MRI on breast cancer mortality with or without concomitant use of mammography has not been evaluated in a randomized controlled trial.

Cervical cancer

Screening with Papanicolaou (Pap) smears decreases cervical cancer mortality. T e cervical cancer mortality rate has fallen substantially since the widespread use of the Pap smear. With the onset of sexual activity comes the risk of sexual transmission of HPV, the fundamental etiologic factor for cervical cancer. Screening guidelines recommend regular Pap testing for all women who have reached the age of 21 (prior to this age, even in individuals that have begun sexual activity, screening may cause more harm than benefit). T e recommended interval for Pap screening is 3 years. Screening more frequently adds little benefit but leads to important harms, including unnecessary procedures and overtreatment of transient lesions. Beginning at age 30, guidelines also offer the alternative of combined Pap smear and HPV testing for women. T e screening interval for women who test normal using this approach may be lengthened to 5 years.

An upper age limit at which screening ceases to be effective is not known, but women age 65 years with no abnormal results in the previous 10 years may choose to stop screening. Screening should be discontinued in women who have undergone a hysterectomy for noncancerous reasons.

Although the ef cacy of the Pap smear in reducing cervical cancer mortality has never been directly confirmed in a randomized, controlled setting, a clustered randomized trial in India evaluated the impact of one-time cervical visual inspection and immediate colposcopy, biopsy, and/or cryotherapy (where indicated) versus counseling on cervical cancer deaths in women age 30–59 years. After 7 years of follow-up, the age-standardized rate of death due to cervical cancer was 39.6 per 100,000 person-years in the intervention group versus 56.7 per 100,000 person-years in controls.

Colorectal cancer

Fecal occult blood testing (FOBT), digital rectal examination (DRE), rigid and flexible sigmoidoscopy, colonoscopy, and computed tomography (CT) colonography have been considered for colorectal cancer screening. A meta-analysis of four randomized controlled trials demonstrated a 15% relative reduction in colorectal cancer mortality with FOBT. T e sensitivity for FOBT is increased if specimens are rehydrated before testing, but at the cost of lower specificity. T e false-positive rate for rehydrated FOBT is high; 1–5% of persons tested have a positive test. Only 2–10% of those with occult blood in the stool have cancer. T e high false-positive rate of FOBT dramatically increases the number of colonoscopies performed.

Fecal immunochemical tests appear to have higher sensitivity for colorectal cancer than nonrehydrated FOBT tests. Fecal DNA testing is an emerging testing modality; it may have increased sensitivity and comparable specificity to FOBT and could potentially reduce harms associated with follow-up of false-positive tests. T e body of evidence on the operating characteristics and effectiveness of fecal DNA tests in reducing colorectal cancer mortality is limited.

Two meta-analyses of five randomized controlled trials of sigmoidoscopy (i.e., the NORCCAP, SCORE, PLCO, Telemark, and U.K. trials) found an 18% relative reduction in colorectal cancer incidence and a 28% relative reduction in colorectal cancer mortality. Participant ages ranged from 50 to 74 years, with follow-up ranging from 6 to 13 years. Diagnosis of adenomatous polyps by sigmoidoscopy should lead to evaluation of the entire colon with colonoscopy. T e most ef cient interval for screening sigmoidoscopy is unknown, but an interval of 5 years is often recommended. Case-control studies suggest that intervals of up to 15 years may confer

benefit; the U.K. trial demonstrated benefit with one-time screening.

One-time colonoscopy detects ~25% more advanced lesions (polyps >10 mm, villous adenomas, adenomatous polyps with high-grade dysplasia, invasive cancer) than one-time FOBT with sigmoidoscopy; comparative programmatic performance of the two modalities over time is not known. Perforation rates are about 3/1000 for colonoscopy and 1/1000 for sigmoidoscopy. Debate continues on whether colonoscopy is too expensive and invasive and whether suf cient provider capacity exists to be recommended as the preferred screening tool in standard-risk populations. Some observational studies suggest that ef cacy of colonoscopy to decrease colorectal cancer mortality is primarily limited to the left side of the colon.

CT colonography, if done at expert centers, appears to have a sensitivity for polyps ≥6 mm comparable to colonoscopy. However, the rate of extracolonic findings of abnormalities of uncertain significance that must nevertheless be worked up is high (~15–30%); the long-term cumulative radiation risk of repeated colonography screenings is also a concern.

Lung cancer

Chest x-ray and sputum cytology have been evaluated in several randomized lung cancer screening trials. T e most recent and largest (n = 154,901) of these, one substudy of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, found that, compared with usual care, annual chest x-ray did not reduce the risk of dying from lung cancer (relative risk 0.99; 95% confidence interval 0.87–1.22) after 13 years. Low-dose CT has also been evaluated in several randomized trials. T e largest and longest of these, the National Lung Screening Trial (NLST), was a randomized controlled trial of screening for lung cancer in approximately 53,000 persons age 55–74 years with a 30+ pack-year smoking history. It demonstrated a statistically significant relative reduction of about 15–20% in lung cancer mortality in the CT arm compared to the chest x-ray arm (or about 3 fewer deaths per 1000 people screened with CT). However, the harms include the potential radiation risks associated with multiple scans, the discovery of incidental findings of unclear significance, and a high rate of false-positive test results. Both incidental findings and false-positive tests can lead to invasive diagnostic procedures associated with anxiety, expense, and complications (e.g., pneumo- or hemothorax after lung biopsy). T e NLST was performed at experienced screening centers, and the balance of benefits and harms may differ in the community setting at less experienced centers.

Ovarian cancer

Adnexal palpation, transvaginal ultrasound (TVUS), and serum CA-125 assay have been considered for ovarian cancer screening. A large randomized controlled trial has shown that an annual screening program of TVUS and CA-125 in average-risk women does not reduce deaths from ovarian cancer (relative risk 1.21; 95% confidence interval 0.99–1.48). Adnexal palpation was dropped early in the study because it did not detect any ovarian cancers that were not detected by either TVUS or CA-125. T e risks and costs associated with the high number of false-positive results are impediments to routine use of these modalities for screening. In the PLCO trial, 10% of participants had a false-positive result from TVUS or CA-125, and one-third of these women underwent a major surgical procedure; the ratio of surgeries to screen-detected ovarian cancer was approximately 20:1.

Prostate cancer

T e most common prostate cancer screening modalities are DRE and serum PSA assay. An emphasis on PSA screening has caused prostate cancer to become the most common nonskin cancer diagnosed in American males. T is disease is prone to lead-time bias, length bias, and overdiagnosis, and substantial debate continues among experts as to whether screening should be offered unless the patient specifically asks to be screened. Virtually all organizations stress the importance of informing men about the uncertainty regarding screening ef cacy and the harms associated with screening. Prostate cancer screening clearly detects many asymptomatic cancers, but the ability to distinguish tumors that are lethal but still curable from those that pose little or no threat to health is limited, and randomized trials indicate that the effect of PSA screening on prostate cancer mortality across a population is, at best, small. Men older than age 50 years have a high prevalence of indolent, clinically insignificant prostate cancers (about 30–50% of men, increasing further as men age).

Two major randomized controlled trials of the impact of PSA screening on prostate cancer mortality have been published. T e PLCO Cancer Screening Trial was a multicenter U.S. trial that randomized almost 77,000 men age 55–74 years to receive either annual PSA testing for 6 years or usual care. At 13 years of follow-up, no statistically significant difference in the number of prostate cancer deaths were noted between the arms (rate ratio 1.09; 95% confidence interval 0.87–1.36). Approximately 50% of men in the control arm received at least one PSA test during the trial, which may have potentially diluted a small effect.

T e European Randomized Study of Screening for Prostate Cancer (ERSPC) was a multinational study that randomized approximately 182,000 men between age 50 and 74 years (with a predefined "core" screening group of men age 55–69 years) to receive PSA testing or no screening. Recruitment and randomization procedures, as well as actual frequency of PSA testing, varied

by country. After a median follow-up of 11 years, a 20% relative reduction in the risk of prostate cancer death in the screened arm was noted in the "core" screening group. T e trial found that 1055 men would need to be invited to screening, and 37 cases of prostate cancer detected, to avert 1 death from prostate cancer. Of the seven countries included in the mortality analysis, two demonstrated statistically significant reductions in prostate cancer deaths, whereas five did not. T ere was also an imbalance in treatment between the two study arms, with a higher proportion of men with clinically localized cancer receiving radical prostatectomy in the screening arm and receiving it at experienced referral centers.

Treatments for low-stage prostate cancer, such as surgery and radiation therapy, can cause significant morbidity, including impotence and urinary incontinence. In a trial conducted in the United States after the initiation of widespread PSA testing, random assignment to radical prostatectomy compared with "watchful waiting" did not result in a statistically significant decrease in prostate cancer deaths (absolute risk reduction 2.7%; 95% confidence interval–1.3 to 6.2%).

Skin cancer

Visual examination of all skin surfaces by the patient or by a health care provider is used in screening for basal and squamous cell cancers and melanoma. No prospective randomized study has been performed to look for a mortality decrease. Unfortunately, screening is associated with a substantial rate of overdiagnosis.

CHAPTER 29

PRINCIPLES OF CANCER TREATMENT

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CANCER PRESENTATION

Cancer in a localized or systemic state is a frequent item in the differential diagnosis of a variety of common complaints. Although not all forms of cancer are curable at diagnosis, affording patients the greatest opportunity for cure or meaningful prolongation of life is greatly aided by diagnosing cancer at the earliest point possible in its natural history and defining treatments that prevent or retard its systemic spread. Indeed, certain forms of cancer, notably breast, colon, and possibly lung cancers in certain patients, can be prevented by screening appropriately selected asymptomatic patients; screening is arguably the earliest point in the spectrum of possible cancer-related interventions where cure is possible **(Table 29-1)**.

TABLE 29-1

SPECTRUM OF CANCER-RELATED INTERVENTIONS

- Screening for cancer in an asymptomatic patient
- Consideration of cancer in a differential diagnosis
- Physical examination, imaging, or endoscopy to define a possible tumor
- Diagnosis of cancer by biopsy or removal:
  - Routine histology
  - Specialized histology: immunohistochemistry
  - Molecular studies
  - Cytogenetic studies
- Staging the cancer: Where has it spread?
- Treatment
  - Localized
  - Systemic
- Supportive care
  - During treatment: related to tumor effects on patient
  - During treatment to counteract side effects of treatment
- Palliative and end of life
  - When useful treatments are not feasible or desired

DETECTION OF A CANCER

T e term cancer, as used here, is synonymous with the term tumor, whose original derivation from Latin simply meant "swelling," not otherwise specified. We now understand that the swelling that is a common physical manifestation of a tumor derives from increased interstitial fluid pressure and increased cellular and stromal mass per volume, compared to normal tissue. Tumors historically were referred to as carcinomas, or "crab-like" infiltrating tumors, or sarcomas, or "fleshy tumors," derived from the Greek terms for "crab" and "flesh," respectively. Leukemias are a special case of a cancer of the blood-forming tissues presenting in a disseminated form frequently without definable tumor masses. In addition to localized swelling, tumors present by altered function of the organ they afflict, such as dyspnea on exertion from the anemia caused by leukemia replacing normal hematopoietic cells, cough from lung cancers, jaundice from tumors disrupting the hepatobiliary tree, or seizures and neurologic signs from brain tumors. Hemorrhage is also a frequent presenting sign of tumors involving hollow viscera, as are decreases in the number of platelets and inappropriate inhibition of blood coagulation. T us, although statistically the fraction of patients with cancer underlying a particular presenting sign or symptom may be low, the implications for a patient with cancer of missing an early-stage tumor call for vigilance; therefore, persistent signs or symptoms should be evaluated as possibly coming from an early-stage tumor.

Evidence of a tumor's existence can objectively be established by careful physical examination, such as enlarged lymph nodes in lymphomas or a palpable mass in a breast or soft tissue site. A mass may also be detected or confirmed by an imaging modality, such as plain x-ray, computed tomography (CT) scan, ultrasound, positron emission tomography (PET) imaging, or nuclear magnetic resonance approaches. Sensitivity of these technologies varies considerably, and the index of suspicion for a tumor should match

the technology chosen. For example, low-dose helical CT scans are superior to plain chest radiographs in detecting lung cancers. Another way of initially establishing the existence of a possible tumor is through direct visualization of an afflicted organ by endoscopy.

ESTABLISHING A CANCER DIAGNOSIS

Once the existence of a likely tumor is defined, unequivocally establishing the diagnosis is the next step in the spectrum of correctly addressing a patient's needs. T is is usually accomplished by a biopsy procedure and the emergence after pathologic examination of an unequivocal statement that cancer is present. T e underlying principle in cancer diagnosis is to obtain as much tissue as safely as possible. Due to tumor heterogeneity, pathologists are better able to make the diagnosis when they have more tissue to examine. In addition to light microscopic inspection of a tumor for pattern of growth, degree of cellular atypia, invasiveness, and morphologic features that aid in the differential diagnosis, sufficient tissue is of value in searching for genetic abnormalities and protein expression patterns, such as hormone receptor expression in breast cancers, that may aid in the differential diagnosis or provide information about prognosis or likely response to treatment. Efforts to define "personalized" information from the biology of each patient's tumor and pertinent to each patient's treatment plan are becoming increasingly important in selecting treatment options. T e general internist should make sure that a patient's cancer biopsy is appropriately referred from the surgical suite for important molecular studies that can advise the best treatment **(Table 29-2)**.

Similar-appearing tumors by microscopic morphology may have very different gene expression patterns when assessed by such techniques as microarray analysis for gene expression patterns using gene chips, with important differences in biology and response to treatment. Such testing requires that the tissue be handled properly (e.g., immunologic detection of proteins is more effective in fresh-frozen tissue rather than in formalin-fixed tissue). Coordination among the surgeon, pathologist, and primary care physician is essential to ensure that the amount of information learned from the biopsy material is maximized. T ese goals are best met by an excisional biopsy in which the entire tumor mass is removed with a small margin of normal tissue surrounding it. If an excisional biopsy cannot be performed, incisional biopsy is the procedure of second choice. A wedge of tissue is removed, and an effort is made to include the majority of the cross-sectional diameter of the tumor in the biopsy to minimize sampling error. Biopsy techniques that involve cutting into tumor carry with them a risk of facilitating the spread of the tumor, and consideration of whether the biopsy might be the prelude to a curative surgery if certain diagnoses are established should inform the actual approach taken. Core-needle biopsy usually obtains considerably less tissue, but this procedure often provides enough information to plan a definitive surgical procedure. Fine-needle aspiration generally obtains only a suspension of cells from within a mass. T is procedure is minimally invasive, and if positive for cancer, it may allow inception of systemic treatment when metastatic disease is evident, or it can provide a basis for planning a more meticulous and extensive surgical procedure. However, a negative fine-needle aspiration for a neoplastic diagnosis cannot be taken as definitive evidence that a tumor is absent or make a definitive diagnosis in someone not known to have a cancer.

TABLE 29-2

DIAGNOSTIC BIOPSY: STANDARD OF CARE MOLECULAR AND SPECIAL STUDIES

- Breast cancer: primary and suspected metastatic
  - Hormone receptors: estrogen, progesterone
  - HER2/neu oncoprotein
- Lung cancer: primary and suspected metastatic
  - If nonsquamous non-small cell: epidermal growth factor receptor mutation; alk oncoprotein gene fusion
- Colon cancer: suspected metastatic
  - Ki-ras mutation
- Gastrointestinal stromal tumor
  - c-kit oncoprotein mutation
- Melanoma
  - B-raf oncoprotein mutation
  - c-kit expression and mutation
- Leukemia (peripheral blood mononuclear cells and/or bone marrow)
  - Cytogenetics
  - Flow cytometry
  - Treatment-defining chromosomal translocations
    - Bcr-Abl fusion protein
    - t(15,17)
    - inversion 16
    - t(8,21)
- Lymphoma
  - Immunohistochemistry for CD20, CD30, T cell markers
  - Treatment defining chromosomal translocations:
    - t(14,18)
    - t(8,14)

CANCER STAGING

An essential component of correct patient management in many cancer types is defining the extent of disease, because this information critically informs whether localized treatments, "combined-modality" approaches, or systemic treatments should initially be considered. Radiographic and other imaging tests can be helpful in defining the clinical stage; however, pathologic staging requires defining the extent of involvement by documenting the histologic presence of tumor in tissue

biopsies obtained through a surgical procedure. Axillary lymph node sampling in breast cancer and lymph node sampling at laparotomy for testicular, colon, and other intraabdominal cancers may provide crucial information for treatment planning and may determine the extent and nature of primary cancer treatment.

For tumors associated with a potential "primary site," staging systems have evolved to define a "T" component related to the size of the tumor or its invasion into local structures, an "N" component related to the number and nature of lymph node groups adjacent to the tumor with evidence of tumor spread, and an "M" component, based on the presence of local or distant metastatic sites. T e various "TNM" components are then aggregated to stages, usually stage I to III or IV, depending on the anatomic site. T e numerical stages reflect similar long-term survival outcomes of the aggregated TNM groupings in a numeric stage after treatment tailored to the stage. In general, stage I tumors are T1 (reflecting small size), N0 or N1 (reflecting no or minimal node spread), and M0 (no metastases). Such early-stage tumors are amenable to curative approaches with local treatments. On the other hand, stage IV tumors usually have metastasized to distant sites or locally invaded viscera in a nonresectable way and are dealt with using techniques that have palliative intent, except for those diseases with exceptional sensitivity to systemic treatments such as chemotherapy or immunotherapy. Also, the TNM staging system is not useful in diseases such as leukemia, where bone marrow infiltration is never really localized, or central nervous system tumors, where tumor histology and the extent of anatomically feasible resection are more important in driving prognosis.

CANCER TREATMENT

T e goal of cancer treatment is first to eradicate the cancer. If this primary goal cannot be accomplished, the goal of cancer treatment shifts to palliation, the amelioration of symptoms, and preservation of quality of life while striving to extend life. T e dictum primum non nocere may not always be the guiding principle of cancer therapy. When cure of cancer is possible, cancer treatments may be considered despite the certainty of severe and perhaps life-threatening toxicities. Every cancer treatment has the potential to cause harm, and treatment may be given that produces toxicity with no benefit. T e therapeutic index of many interventions may be quite narrow, with treatments given to the point of toxicity. Conversely, when the clinical goal is palliation, careful attention to minimizing the toxicity of potentially toxic treatments becomes a significant goal.

Cancer treatments are divided into two main types: local and systemic. Local treatments include surgery, radiation therapy (including photodynamic therapy), and ablative approaches, including radiofrequency and cryosurgical approaches. Systemic treatments include chemotherapy (including hormonal therapy and molecularly targeted therapy) and biologic therapy (including immunotherapy). T e modalities are often used in combination, and agents in one category can act by several mechanisms. For example, cancer chemotherapy agents can induce differentiation, and antibodies (a form of immunotherapy) can be used to deliver radiation therapy. Oncology, the study of tumors including treatment approaches, is a multidisciplinary effort with surgical, radiation, and internal medicine–related areas of oncologic expertise. Treatments for patients with hematologic malignancies are often shared by hematologists and medical oncologists.

In many ways, cancer mimics an organ attempting to regulate its own growth. However, cancers have not set an appropriate limit on how much growth should be permitted. Normal organs and cancers share the property of having (1) a population of cells actively progressing through the cell cycle with their division providing a basis for tumor growth, and (2) a population of cells not in cycle. In cancers, cells that are not dividing are heterogeneous; some have sustained too much genetic damage to replicate but have defects in their death pathways that permit their survival, some are starving for nutrients and oxygen, and some are out of cycle but poised to be recruited back into cycle and expand if needed (i.e., reversibly growth-arrested). Severely damaged and starving cells are unlikely to kill the patient. T e problem is that the cells that are reversibly not in cycle are capable of replenishing tumor cells physically removed or damaged by radiation and chemotherapy. T ese include cancer stem cells, whose properties are being elucidated, as they may serve as a basis for giving rise to tumor initiating or repopulating cells. T e stem cell fraction may define new targets for therapies that will retard their ability to reenter the cell cycle.

Tumors follow a Gompertzian growth curve **(Fig. 29-1)**, with the apparent growth fraction of a neoplasm being high with small tumor burdens and declining until, at the time of diagnosis, with a tumor burden of $1–5 \times 10^9$ tumor cells, the growth fraction is usually 1–4% for many solid tumors. By this view, the most rapid growth rate occurs before the tumor is detectable. An alternative explanation for such growth properties may also emerge from the ability of tumors at metastatic sites to recruit circulating tumor cells from the primary tumor or other metastases. An additional key feature of a successful tumor is the ability to stimulate the development of a new supporting stroma through angiogenesis and production of proteases to allow invasion through basement membranes and normal tissue barriers **(Chap. 26)**. Specific cellular mechanisms promote entry or withdrawal of tumorcells from the cell cycle. For example, when a tumor recurs after surgery or chemotherapy,

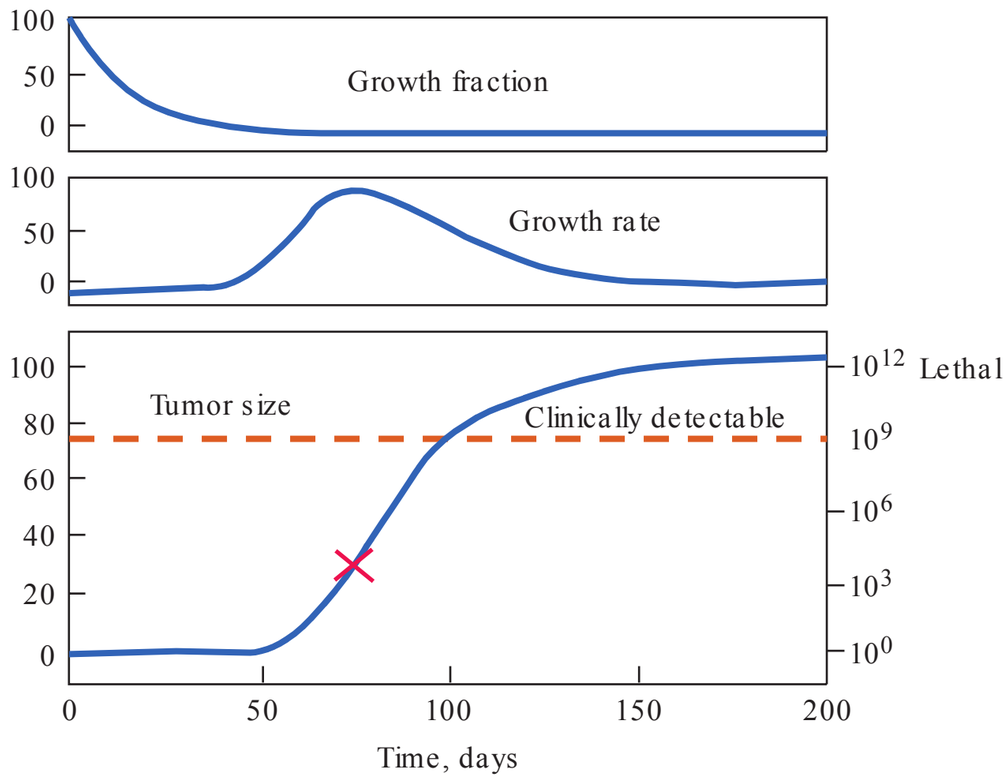


FIGURE 29-1
Gompertzian tumor growth. The growth fraction of a tumor declines exponentially over time (top). The growth rate of a tumor peaks before it is clinically detectable (middle). Tumor size increases slowly, goes through an exponential phase, and slows again as the tumor reaches the size at which limitation of nutrients or autoregulatory or host regulatory influences can occur. The maximum growth rate occurs at 1/e, the point at which the tumor is about 37% of its maximum size (marked with an X). Tumor becomes detectable at a burden of about 10^9 (1 cm^3) cells and kills the patient at a tumor cell burden of about 10^{12} (1 kg). Efforts to treat the tumor and reduce its size can result in an increase in the growth fraction and an increase in growth rate.

frequently its growth is accelerated and the growth fraction of the tumor is increased. This pattern is similar to that seen in regenerating organs. Partial resection of the liver results in the recruitment of cells into the cell cycle, and the resected liver volume is replaced. Similarly, chemotherapy-damaged bone marrow increases its growth to replace cells killed by chemotherapy. However, cancers do not recognize a limit on their expansion. Monoclonal gammopathy of uncertain significance may be an example of a clonal neoplasm with intrinsic features that stop its growth before a lethal tumor burden is reached. A fraction of patients with this disorder go on to develop fatal multiple myeloma, but probably this occurs because of the accumulation of additional genetic lesions. Elucidation of the mechanisms that regulate this "organ-like" behavior of tumors may provide additional clues to cancer control and treatment.

LOCALIZED CANCER TREATMENTS

SURGERY

Surgery is unquestionably the most effective means of treating cancer. Today at least 40% of cancer patients are cured by surgery. Unfortunately, a large fraction of patients with solid tumors (perhaps 60%) have metastatic disease that is not accessible for removal. However, even when the disease is not curable by surgery alone, the removal of tumor can obtain important benefits, including local control of tumor, preservation of organ function, debulking that permits subsequent therapy to work better, and staging information on extent of involvement. Cancer surgery aiming for cure is usually planned to excise the tumor completely with an adequate margin of normal tissue (the margin varies with the tumor and the anatomy), touching the tumor as little as possible to prevent vascular and lymphatic spread, and minimizing operative risk. Such a resection is defined as an R0 resection. R1 and R2 resections, in contrast, are imprecisely defined pathologically as having microscopic or macroscopic tumor at resection margins. Such outcomes may be necessitated by proximity of the tumor to vital structures or recognition only in the resected specimen of the extent of tumor involvement, and may be the basis for reoperation to obtain optimal margins if feasible. Extending the procedure to resect draining lymph nodes obtains prognostic information and may, in some anatomic locations, improve survival.

Increasingly, laparoscopic approaches are being used to address primary abdominal and pelvic tumors. Lymph node spread may be assessed using the sentinel node approach, in which the first draining lymph node a spreading tumor would encounter is defined by injecting a dye or radioisotope into the tumor site at operation and then resecting the first node to turn blue or collect label. The sentinel node assessment is continuing to undergo clinical evaluation but appears to provide reliable information without the risks (lymphedema, lymphangiosarcoma) associated with resection of all the regional nodes. Advances in adjuvant chemotherapy (chemotherapy given systemically after removal of all disease by operation and without evidence of active metastatic disease) and radiation therapy following surgery have permitted a substantial decrease in the extent of primary surgery necessary to obtain the best outcomes. Thus, lumpectomy with radiation therapy is as effective as modified radical mastectomy for breast cancer, and limb-sparing surgery followed by adjuvant radiation therapy and chemotherapy has replaced radical primary surgical procedures involving amputation and disarticulation for childhood rhabdomyosarcomas and osteosarcomas. More limited surgery is also being used to spare organ function, as in larynx and bladder cancer. The magnitude of operations necessary to optimally control and cure cancer has also been diminished by technical advances; for example, the circular anastomotic stapler has allowed narrower (<2 cm) margins in colon cancer without compromise of local control rates, and many patients who would have had colostomies are able to maintain normal anatomy.

In some settings (e.g., bulky testicular cancer or stage III breast cancer), surgery is not the first

treatment modality used. After an initial diagnostic biopsy, chemotherapy and/or radiation therapy is delivered to reduce the size of the tumor and clinically control undetected metastatic disease. Such therapy is followed by a surgical procedure to remove residual masses; this is called neoadjuvant therapy. Because the sequence of treatment is critical to success and is different from the standard surgery-first approach, coordination among the surgical oncologist, radiation oncologist, and medical oncologist is crucial.

Surgery may be curative in a subset of patients with metastatic disease. Patients with lung metastases from osteosarcoma may be cured by resection of the lung lesions. In patients with colon cancer who have fewer than five liver metastases restricted to one lobe and no extrahepatic metastases, hepatic lobectomy may produce long-term disease-free survival in 25% of selected patients. Surgery can also be associated with systemic antitumor effects. In the setting of hormonally responsive tumors, oophorectomy and/or adrenalectomy may eliminate estrogen production, and orchiectomy may reduce androgen production, hormones that drive certain breast and all prostate cancers, respectively; both procedures can have useful effects on metastatic tumor growth. If resection of the primary lesion takes place in the presence of metastases, acceleration of metastatic growth has also been described in certain cases, perhaps based on the removal of a source of angiogenesis inhibitors and mass-related growth regulators in the tumor.

In selecting a surgeon or center for primary cancer treatment, consideration must be given to the volume of cancer surgeries undertaken by the site. Studies in a variety of cancers have shown that increased annual procedure volume appears to correlate with outcome. In addition, facilities with extensive support systems—e.g., for joint thoracic and abdominal surgical teams with cardiopulmonary bypass, if needed—may allow resection of certain tumors that would otherwise not be possible.

Surgery is used in a number of ways for palliative or supportive care of the cancer patient, not related to the goal of curing the cancer. T ese include insertion and care of central venous catheters, control of pleural and pericardial effusions and ascites, caval interruption for recurrent pulmonary emboli, stabilization of cancer-weakened weight-bearing bones, and control of hemorrhage, among others. Surgical bypass of gastrointestinal, urinary tract, or biliary tree obstruction can alleviate symptoms and prolong survival. Surgical procedures may provide relief of otherwise intractable pain or reverse neurologic dysfunction (cord decompression). Splenectomy may relieve symptoms and reverse hypersplenism. Intrathecal or intrahepatic therapy relies on surgical placement of appropriate infusion portals. Surgery may correct other treatment-related toxicities such as adhesions or strictures. Surgical procedures are also valuable in rehabilitative efforts to restore health or function. Orthopedic procedures may be necessary to ensure proper ambulation. Breast reconstruction can make an enormous impact on the patient's perception of successful therapy. Plastic and reconstructive surgery can correct the effects of disfiguring primary treatment.

Surgery is also a tool valuable in the prevention of cancers in high-risk populations. Prophylactic mastectomy, colectomy, oophorectomy, and thyroidectomy are mainstays of prevention of genetic cancer syndromes. Resection of premalignant skin and uterine cervix lesions and colonic polyps prevents progression to frank malignancy.

RADIATION

Radiation biology and medicine

T erapeutic radiation is ionizing; it damages any tissue in its path. T e selectivity of radiation for causing cancer cell death may be due to defects in a cancer cell's ability to repair sublethal DNA and other damage. Ionizing radiation causes breaks in DNA and generates free radicals from cell water that may damage cell membranes, proteins, and organelles. Radiation damage is augmented by oxygen; hypoxic cells are more resistant. Augmentation of oxygen presence is one basis for radiation sensitization. Sulf ydryl compounds interfere with free radical generation and may act as radiation protectors. X-rays and gamma rays are the forms of ionizing radiation most commonly used to treat cancer. T ey are both electromagnetic, nonparticulate waves that cause the ejection of an orbital electron when absorbed. T is orbital electron ejection is called ionization. X-rays are generated by linear accelerators; gamma rays are generated from decay of atomic nuclei in radioisotopes such as cobalt and radium. T ese waves behave biologically as packets of energy, called photons. Particulate ionizing radiation using protons has also become available. Most radiation-induced cell damage is due to the formation of hydroxyl radicals from tissue water:

$$\text{Ionizing radiation} + H_2O \rightarrow H_3O^+ + e^-$$
$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH^*$$
$$OH^* \rightarrow \text{cell damage}$$

Radiation is quantitated based on the amount of radiation absorbed by the tumor in the patient; it is not based on the amount of radiation generated by the machine. T e International System (SI) unit for radiation absorbed is the Gray (Gy): 1 Gy refers to 1 J/kg of tissue; 1 Gy equals 100 centigrays (cGy) of absorbed dose. A historically used unit appearing in the oncology literature, the rad (radiation absorbed dose), is defined as 100 ergs of energy absorbed per gram of tissue and is equivalent to 1 cGy. Radiation dosage is defined by the energy absorbed per mass of tissue. Radiation dose

is measured by placing detectors at the body surface or based on radiating phantoms that resemble human form and substance, containing internal detectors. T e features that make a particular cell more sensitive or more resistant to the biologic effects of radiation are not completely defined and critically involve DNA repair proteins that, in their physiologic role, protect against environmentally related DNA damage.

Localized radiation therapy

Radiation effect is influenced by three determinants: total absorbed dose, number of fractions, and time of treatment. A frequent error is to omit the number of fractions and the duration of treatment. T is is analogous to saying that a runner completed a race in 20 s; without knowing how far he or she ran, the result is difficult to interpret. T e time could be very good for a 200-m race or very poor for a 100-m race. T us, a typical course of radiation therapy should be described as 4500 cGy delivered to a particular target (e.g., mediastinum) over 5 weeks in 180-cGy fractions. Most curative radiation treatment programs are delivered once a day, 5 days a week, in 150- to 200-cGy fractions.

A number of parameters influence the damage done to tissue (normal and tumor) by radiation. Hypoxic cells are relatively resistant. Nondividing cells are more resistant than dividing cells, and this is one rationale for delivering radiation in repeated fractions, to ultimately expose a larger number of tumor cells that have entered the division cycle. In addition to these biologic parameters, physical parameters of the radiation are also crucial. T e energy of the radiation determines its ability to penetrate tissue. Low-energy orthovoltage beams (150–400 kV) scatter when they strike the body, much like light diffuses when it strikes particles in the air. Such beams result in more damage to adjacent normal tissues and less radiation delivered to the tumor. Megavoltage radiation (>1 MeV) has very low lateral scatter; this produces a skin-sparing effect, more homogeneous distribution of the radiation energy, and greater deposit of the energy in the tumor, or target volume. T e tissues that the beam passes through to get to the tumor are called the transit volume. T e maximum dose in the target volume is often the cause of complications to tissues in the transit volume, and the minimum dose in the target volume influences the likelihood of tumor recurrence. Dose homogeneity in the target volume is the goal. Computational approaches and delivery of many beams to converge on a target lesion are the basis for "gamma knife" and related approaches to deliver high doses to small volumes of tumor, sparing normal tissue.

T erapeutic radiation is delivered in three ways: (1) teletherapy, with focused beams of radiation generated at a distance and aimed at the tumor within the patient; (2) brachytherapy, with encapsulated sources of radiation implanted directly into or adjacent to tumor tissues; and (3) systemic therapy, with radionuclides administered, for example, intravenously but targeted by some means to a tumor site. Teletherapy with x-ray or gamma-ray photons is the most commonly used form of radiation therapy. Particulate forms of radiation are also used in certain circumstances, such as the use of proton beams. T e difference between photons and protons relates to the volume in which the greatest delivery of energy occurs. Typically protons have a much narrower range of energy deposition, theoretically resulting in more precise delivery of radiation with improvement in the degree to which adjacent structures may be affected, in comparison to photons. Electron beams are a particulate form of radiation that, in contrast to photons and protons, have a very low tissue penetrance and are used to treat cutaneous tumors. Apart from sparing adjacent structures, particulate forms of radiation are in most applications not superior to x-rays or gamma rays in clinical studies reported thus far, but this is an active area of investigation.

Certain drugs used in cancer treatment may also act as radiation sensitizers. For example, compounds that incorporate into DNA and alter its stereochemistry (e.g., halogenated pyrimidines, cisplatin) augment radiation effects at local sites, as does hydroxyurea, another DNA synthesis inhibitor. T ese are important adjuncts to the local treatment of certain tumors, such as squamous head and neck, uterine cervix, and rectal cancers.

Toxicity of radiation therapy

Although radiation therapy is most often administered to a local region, systemic effects, including fatigue, anorexia, nausea, and vomiting, may develop that are related in part to the volume of tissue irradiated, dose fractionation, radiation fields, and individual susceptibility. Injured tissues release cytokines that act systemically to produce these effects. Bone is among the most radioresistant organs, with radiation effects being manifested mainly in children through premature fusion of the epiphyseal growth plate. By contrast, the male testis, female ovary, and bone marrow are the most sensitive organs. Any bone marrow in a radiation field will be eradicated by therapeutic irradiation. Organs with less need for cell renewal, such as heart, skeletal muscle, and nerves, are more resistant to radiation effects. In radiation-resistant organs, the vascular endothelium is the most sensitive component. Organs with more self-renewal as a part of normal homeostasis, such as the hematopoietic system and mucosal lining of the intestinal tract, are more sensitive. Acute toxicities include mucositis, skin erythema (ulceration in severe cases), and bone marrow toxicity. Often these can be alleviated by interruption of treatment.

Chronic toxicities are more serious. Radiation of the head and neck region often produces thyroid failure.

Cataracts and retinal damage can lead to blindness. Salivary glands stop making saliva, which leads to dental caries and poor dentition. Taste and smell can be affected. Mediastinal irradiation leads to a threefold increased risk of fatal myocardial infarction. Other late vascular effects include chronic constrictive pericarditis, lung fibrosis, viscus stricture, spinal cord transection, and radiation enteritis. A serious late toxicity is the development of second solid tumors in or adjacent to the radiation fields. Such tumors can develop in any organ or tissue and occur at a rate of about 1% per year beginning in the second decade after treatment. Some organs vary in susceptibility to radiation carcinogenesis. A woman who receives mantle field radiation therapy for Hodgkin's disease at age 25 years has a 30% risk of developing breast cancer by age 55 years. T is is comparable in magnitude to genetic breast cancer syndromes. Women treated after age 30 years have little or no increased risk of breast cancer. No data suggest that a threshold dose of therapeutic radiation exists below which the incidence of second cancers is decreased. High rates of second tumors occur in people who receive as little as 1000 cGy.

OTHER LOCALIZED CANCER TREATMENTS

Endoscopy techniques may allow the placement of stents to unblock viscera by mechanical means, palliating, for example, gastrointestinal or biliary obstructions. Radiofrequency ablation (RFA) refers to the use of focused microwave radiation to induce thermal injury within a volume of tissue. RFA can be useful in the control of metastatic lesions, particularly in liver, that may threaten biliary drainage (as one example) and threaten quality and duration of useful life in patients with otherwise unresectable disease. Cryosurgery uses extreme cold to sterilize lesions in certain sites, such as prostate and kidney, when at a very early stage, eliminating the need for modalities with more side effects such as surgery or radiation.

Some chemicals (porphyrins, phthalocyanines) are preferentially taken up by cancer cells by mechanisms not fully defined. When light, usually delivered by a laser, is shone on cells containing these compounds, free radicals are generated and the cells die. Hematoporphyrins and light (phototherapy) are being used with increasing frequency to treat skin cancer; ovarian cancer; and cancers of the lung, colon, rectum, and esophagus. Palliation of recurrent locally advanced disease can sometimes be dramatic and last many months.

Infusion of chemotherapeutic or biologic agents or radiation-bearing delivery devices such as isotope-coated glass spheres into local sites through catheters inserted into specific vascular sites such as liver or an extremity have been used in an effort to control disease limited to that site; in selected cases, prolonged control of truly localized disease has been possible.

SYSTEMIC CANCER TREATMENTS

T e concept that systemically administered agents may have a useful effect on cancers was historically derived from three sets of observations. Paul Ehrlich in the nineteenth century observed that different dyes reacted with different cell and tissue components. He hypothesized the existence of compounds that would be "magic bullets" that might bind to tumors, owing to the affinity of the agent for the tumor. A second observation was the toxic effects of certain mustard gas derivatives on the bone marrow during World War I, leading to the idea that smaller doses of these agents might be used to treat tumors of marrow-derived cells. Finally, the observation that certain tumors from hormone-responsive tissues, e.g., breast tumors, could shrink after oophorectomy led to the idea that endogenous substances promoting the growth of a tumor might be antagonized. Chemicals achieving each of the goals are actually or intellectually the forbearers of the currently used cancer chemotherapy agents.

Systemic cancer treatments are of four broad types. Conventional "cytotoxic" chemotherapy agents were historically derived by the empirical observation that these "small molecules" (generally with molecular mass <1500 Da) could cause major regression of experimental tumors growing in animals. T ese agents mainly target DNA structure or segregation of DNA as chromosomes in mitosis. Targeted agents refer to small molecules or "biologics" (generally macromolecules such as antibodies or cytokines) designed and developed to interact with a defined molecular target important in maintaining the malignant state or expressed by the tumor cells. As described in **Chap. 26**, successful tumors have activated biochemical pathways that lead to uncontrolled proliferation through the action of, e.g., oncogene products, loss of cell cycle inhibitors, or loss of cell death regulation, and have acquired the capacity to replicate chromosomes indefinitely, invade, metastasize, and evade the immune system. Targeted therapies seek to capitalize on the biology behind the aberrant cellular behavior as a basis for therapeutic effects. Hormonal therapies (the first form of targeted therapy) capitalize on the biochemical pathways underlying estrogen and androgen function and action as a therapeutic basis for approaching patients with tumors of breast, prostate, uterus, and ovarian origin. Biologic therapies are often macromolecules that have a particular target (e.g., anti-growth factor or cytokine antibodies) or may have the capacity to regulate growth of tumor cells or induce a

host immune response to kill tumor cells. T us, biologic therapies include not only antibodies but also cytokines and gene therapies.

CANCER CHEMOTHERAPY

Principles

T e usefulness of any drug is governed by the extent to which a given dose causes a useful result (therapeutic effect; in the case of anticancer agents, toxicity to tumor cells) as opposed to a toxic effect to the host. T e therapeutic index is the degree of separation between toxic and therapeutic doses. Really useful drugs have large therapeutic indices, and this usually occurs when the drug target is expressed in the disease-causing compartment as opposed to the normal compartment. Classically, selective toxicity of an agent for a tissue or cell type is governed by the differential expression of a drug's target in the "sensitive" cell type or by differential drug accumulation into or elimination from compartments where greater or lesser toxicity is experienced, respectively. Currently used chemotherapeutic agents have the unfortunate property that their targets are present in both normal and tumor tissues. T erefore, they have relatively narrow therapeutic indices.

Figure 29-2 illustrates steps in cancer drug development. Following demonstration of antitumor activity in animal models, potentially useful anticancer agents are further evaluated to define an optimal schedule of administration and arrive at a drug formulation designed for a given route of administration and schedule. Safety testing in two species on an analogous schedule of administration defines the starting dose for a phase 1 trial in humans, usually but not always in patients with cancer who have exhausted "standard" (already approved) treatments. T e initial dose is usually one-sixth to one-tenth of the dose just causing easily reversible toxicity in the more sensitive animal species. Escalating doses of the drug are then given during the human phase 1 trial until reversible toxicity is observed. Dose-limiting toxicity (DLT) defines a dose that conveys greater toxicity than would be acceptable in routine practice, allowing definition of a lower maximum-tolerated dose (MTD). T e occurrence of toxicity is, if possible, correlated with plasma drug concentrations. T e MTD or a dose just lower than the MTD is usually the dose suitable for phase 2 trials, where a fixed dose is administered to a relatively homogeneous set of patients with a particular tumor type in an effort to define whether the drug causes regression of tumors. In a phase 3 trial, evidence of improved overall survival or improvement in the time to progression of disease on the part of the new drug is sought in comparison to an appropriate control population, which is usually receiving an acceptable "standard of care" approach.

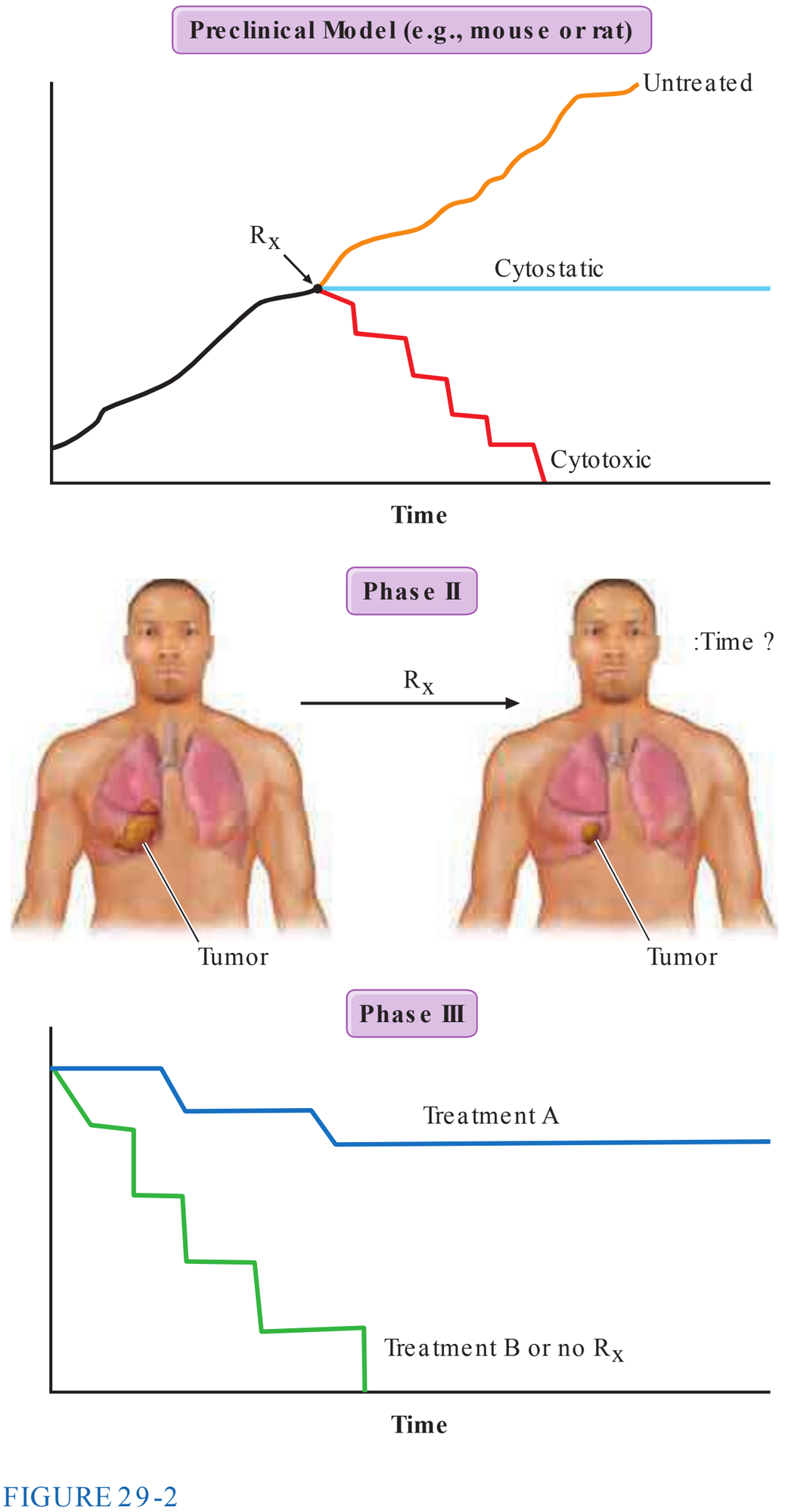


FIGURE 29-2
Steps in cancer drug discovery and development. Preclinical activity (top) in animal models of cancers may be used as evidence to support the entry of the drug candidate into phase 1 trials in humans to define a correct dose and observe any clinical antitumor effect that may occur. The drug may then be advanced to phase 2 trials directed against specific cancer types, with rigorous quantitation of antitumor effects (middle). Phase 3 trials then may reveal activity superior to standard or no treatment (bottom).

A favorable outcome of a phase 3 trial is the basis for application to a regulatory agency for approval of the new agent for commercial marketing as safe and possessing a measure of clinical effectiveness.

Response, defined as tumor shrinkage, is the most immediate indicator of drug effect. To be clinically valuable, responses must translate into clinical benefit. T is is conventionally established by a beneficial effect

on overall survival, or at least an increased time to further progression of disease. Karnofsky was among the first to champion the evaluation of a chemotherapeutic agent's benefit by carefully quantitating its effect on tumor size and using these measurements to objectively decide the basis for further treatment of a particular patient or further clinical evaluation of a drug's potential. A partial response (PR) is defined conventionally as a decrease by at least 50% in a tumor's bidimensional area; a complete response (CR) connotes disappearance of all tumor; progression of disease signifies an increase in size of existing lesions by >25% from baseline or best response or development of new lesions; and stable disease fits into none of the above categories. Newer evaluation systems, such as Response Evaluation Criteria in Solid Tumors (RECIST), use unidimensional measurement, but the intent is similar in rigorously defining evidence for the activity of the agent in assessing its value to the patient. An active chemotherapy agent conventionally has PR rates of at least 20–25% with reversible non-life-threatening side effects, and it may then be suitable for study in phase 3 trials to assess efficacy in comparison to standard or no therapy. Active efforts are being made to quantitate effects of anticancer agents on quality of life. Cancer drug clinical trials conventionally use a toxicity grading scale where grade 1 toxicities do not require treatment, grade 2 toxicities may require symptomatic treatment but are not life-threatening, grade 3 toxicities are potentially life-threatening if untreated, grade 4 toxicities are actually life-threatening, and grade 5 toxicities are those that result in the patient's death.

Development of targeted agents may proceed quite differently. While phase 1–3 trials are still conducted, molecular analysis of human tumors may allow the precise definition of target expression in a patient's tumor that is necessary for or relevant to the drug's action. T is information might then allow selection of patients expressing the drug target for participation in all trial phases. T ese patients may then have a greater chance of developing a useful response to the drug by virtue of expressing the target in the tumor. Clinical trials may be designed to incorporate an assessment of the behavior of the target in relation to the drug (pharmacodynamic studies). Ideally, the plasma concentration that affects the drug target is known, so escalation to MTD may not be necessary. Rather, the correlation of host toxicity while achieving an "optimal biologic dose" becomes a more relevant endpoint for phase 1 and early phase 2 trials with targeted agents.

Useful cancer drug treatment strategies using conventional chemotherapy agents, targeted agents, hormonal treatments, or biologics have one of two valuable outcomes. T ey can induce cancer cell death, resulting in tumor shrinkage with corresponding improvement in patient survival, or increase the time until the disease progresses. Another potential outcome is to induce cancer cell dif erentiation or dormancy with loss of tumor cell replicative potential and reacquisition of phenotypic properties resembling normal cells. A blocking in normal cellular differentiation may be a key feature in the pathogenesis of certain leukemias.

Cell death is a closely regulated process. Necrosis refers to cell death induced, for example, by physical damage with the hallmarks of cell swelling and membrane disruption. Apoptosis, or programmed cell death, refers to a highly ordered process whereby cells respond to defined stimuli by dying, and it recapitulates the necessary cell death observed during the ontogeny of the organism. Cancer chemotherapeutic agents can cause both necrosis and apoptosis. Apoptosis is characterized by chromatin condensation (giving rise to "apoptotic bodies"), cell shrinkage, and, in living animals, phagocytosis by surrounding stromal cells without evidence of inflammation. T is process is regulated either by signal transduction systems that promote a cell's demise after a certain level of insult is achieved or in response to specific cell-surface receptors that mediate physiologic cell death responses, such as occurs in the developing organism or in the normal function of immune cells. Influencing apoptosis by manipulation of signal transduction pathways has emerged as a basis for understanding the actions of drugs and designing new strategies to improve their use. Autophagy is a cellular response to injury where the cell does not initially die but catabolizes itself in a way that can lead to loss of replicative potential. A general view of how cancer treatments work is that the interaction of a chemotherapeutic drug with its target induces a "cascade" of further signaling steps. T ese signals ultimately lead to cell death by triggering an "execution phase" where proteases, nucleases, and endogenous regulators of the cell death pathway are activated **(Fig. 29-3)**.

Targeted agents differ from chemotherapy agents in that they do not indiscriminately cause macromolecular lesions but regulate the action of particular pathways. For example, the $p210^{bcr\text{-}abl}$ fusion protein tyrosine kinase drives chronic myeloid leukemia (CML), and HER2/neu stimulates the proliferation of certain breast cancers. T e tumor has been described as "addicted" to the function of these molecules in the sense that without the pathway's continued action, the tumor cell cannot survive. In this way, targeted agents directed at $p210^{bcr\text{-}abl}$ or HER2/neu may alter the "threshold" tumors driven by these molecules may have for undergoing apoptosis without actually creating any molecular lesions such as direct DNA strand breakage or altered membrane function.

While apoptotic mechanisms are important in regulating cellular proliferation and the behavior of tumor

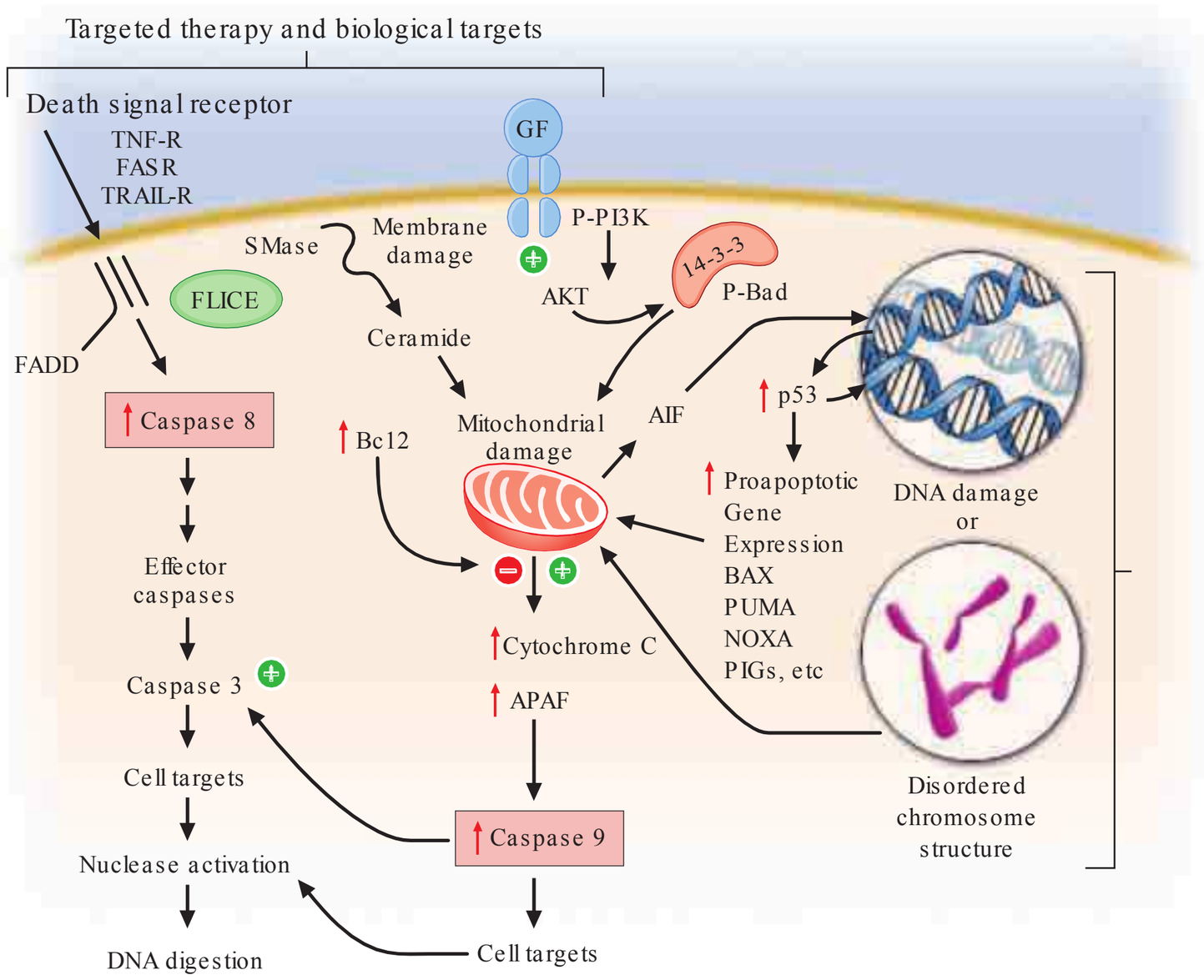


FIGURE 29-3

Integration of cell death responses. Cell death through an apoptotic mechanism requires active participation of the cell. In response to interruption of growth factor (GF) or propagation of certain cytokine death signals (e.g., tumor necrosis factor receptor [TNF-R]), there is activation of "upstream" cysteine aspartyl proteases (caspases), which then directly digest cytoplasmic and nuclear proteins, resulting in activation of "downstream" caspases; these cause activation of nucleases, resulting in the characteristic DNA fragmentation that is a hallmark of apoptosis. Chemotherapy agents that create lesions in DNA or alter mitotic spindle function seem to activate aspects of this process by damage ultimately conveyed to the mitochondria, perhaps by activating the transcription of genes whose products can produce or modulate the toxicity of free radicals. In addition, membrane damage with activation of sphingomyelinases results in the production of ceramides that can have a direct action at mitochondria. The antiapoptotic protein bcl2 attenuates mitochondrial toxicity, while proapoptotic gene products such as bax antagonize the action of bcl2. Damaged mitochondria release cytochrome C and apoptosis-activating factor (APAF), which can directly activate caspase 9, resulting in propagation of a direct signal to other downstream caspases through protease activation. Apoptosis-inducing factor (AIF) is also released from the mitochondrion and then can translocate to the nucleus, bind to DNA, and generate free radicals to further damage DNA. An additional proapoptotic stimulus is the bad protein, which can heterodimerize with bcl2 gene family members to antagonize apoptosis. Importantly, though, bad protein function can be retarded by its sequestration as phospho-bad through the 14-3-3 adapter proteins. The phosphorylation of bad is mediated by the action of the AKT kinase in a way that defines how growth factors that activate this kinase can retard apoptosis and promote cell survival.

cells in vitro, in vivo it is unclear whether all of the actions of chemotherapeutic agents to cause cell death can be attributed to apoptotic mechanisms. However, changes in molecules that regulate apoptosis are correlated with clinical outcomes (e.g., bcl2 overexpression in certain lymphomas conveys poor prognosis; proapoptotic bax expression is associated with a better outcome after chemotherapy for ovarian carcinoma). A better understanding of the relationship of cell death and cell survival mechanisms is needed.

Chemotherapy agents may be used for the treatment of active, clinically apparent cancer. T e goal of such treatment in some cases is cure of the cancer, that is, elimination of all clinical and pathologic evidence of cancer and return of the patient to an expected survival no different than the general population. **Table 29-3A** lists those tumors considered curable by conventionally available chemotherapeutic agents when used to address disseminated or metastatic cancers. If a tumor is localized to a single site, serious consideration of surgery or primary radiation therapy should be given, because these treatment modalities may be curative as local treatments. Chemotherapy may then be used after the failure of these modalities to eradicate a local tumor or as part of multimodality approaches to offer primary treatment to a clinically localized tumor. In this event, it can allow organ preservation when given with radiation, as in the larynx or other upper airway

TABLE 29-3

CURABILITY OF CANCERS WITH CHEMOTHERAPY

- A. Advanced Cancers with Possible Cure
  - Acute lymphoid and acute myeloid leukemia (pediatric/adult)
  - Hodgkin's disease (pediatric/adult)
  - Lymphomas—certain types (pediatric/adult)
  - Germ cell neoplasms
    - Embryonal carcinoma
    - Teratocarcinoma
    - Seminoma or dysgerminoma
    - Choriocarcinoma
  - Gestational trophoblastic neoplasia
  - Pediatric neoplasms
    - Wilms' tumor
    - Embryonal rhabdomyosarcoma
    - Ewing's sarcoma
    - Peripheral neuroepithelioma
    - Neuroblastoma
  - Small-cell lung carcinoma
  - Ovarian carcinoma
- B. Advanced Cancers Possibly Cured by Chemotherapy and Radiation
  - Squamous carcinoma (head and neck)
  - Squamous carcinoma (anus)
  - Breast carcinoma
  - Carcinoma of the uterine cervix
  - Non-small-cell lung carcinoma (stage III)
  - Small-cell lung carcinoma
- C. Cancers Possibly Cured with Chemotherapy as Adjuvant to Surgery
  - Breast carcinoma
  - Colorectal carcinoma[a]
  - Osteogenic sarcoma
  - Soft tissue sarcoma
- D. Cancers Possibly Cured with "High-Dose" Chemotherapy with Stem Cell Support
  - Relapsed leukemias, lymphoid and myeloid
  - Relapsed lymphomas, Hodgkin's and non-Hodgkin's
  - Chronic myeloid leukemia
  - Multiple myeloma
- E. Cancers Responsive with Useful Palliation, But Not Cure, by Chemotherapy
  - Bladder carcinoma
  - Chronic myeloid leukemia
  - Hairy cell leukemia
  - Chronic lymphocytic leukemia
  - Lymphoma—certain types
  - Multiple myeloma
  - Gastric carcinoma
  - Cervix carcinoma
  - Endometrial carcinoma
  - Soft tissue sarcoma
  - Head and neck cancer
  - Adrenocortical carcinoma
  - Islet cell neoplasms
  - Breast carcinoma
  - Colorectal carcinoma
  - Renal carcinoma
- F. Tumors Poorly Responsive in Advanced Stages to Chemotherapy
  - Pancreatic carcinoma
  - Biliary tract neoplasms
  - Thyroid carcinoma
  - Carcinoma of the vulva
  - Non-small-cell lung carcinoma
  - Prostate carcinoma
  - Melanoma (subsets)
  - Hepatocellular carcinoma
  - Salivary gland cancer

[a]Rectum also receives radiation therapy.

sites, or sensitize tumors to radiation when given, e.g., to patients concurrently receiving radiation for lung or cervix cancer **(Table 29-3B)**. Chemotherapy can be administered as an adjuvant, i.e., in addition to surgery or radiation **(Table 29-3C)**, even after all clinically apparent disease has been removed. T is use of chemotherapy has curative potential in breast and colorectal neoplasms, as it attempts to eliminate clinically unapparent tumor that may have already disseminated. As noted above, small tumors frequently have high growth fractions and therefore may be intrinsically more susceptible to the action of antiproliferative agents. Neoadjuvant chemotherapy refers to administration of chemotherapy prior to any surgery or radiation to a local tumor in an effort to enhance the effect of the local treatment.

Chemotherapy is routinely used in "conventional" dose regimens. In general, these doses produce reversible acute side effects, primarily consisting of transient myelosuppression with or without gastrointestinal toxicity (usually nausea), which are readily managed. "High-dose" chemotherapy regimens are predicated on the observation that the dose-response curve for many anticancer agents is rather steep, and increased dose can produce markedly increased therapeutic effect, although at the cost of potentially life-threatening complications that require intensive support, usually in the form of hematopoietic stem cell support from the patient (autologous) or from donors matched for histocompatibility loci (allogeneic), or pharmacologic "rescue" strategies to repair the effect of the high-dose chemotherapy on normal tissues. High-dose regimens have definite curative potential in defined clinical settings **(Table 29-3D)**.

If cure is not possible, chemotherapy may be undertaken with the goal of palliating some aspect of the tumor's effect on the host. In this usage, value is perceived by the demonstration of improved symptom relief, progression-free survival, or overall survival at a certain time from the inception of treatment in the treated population, compared to a relevant control population established as the result of clinical research protocol or other organized comparative study. Such clinical research protocols are the basis for U.S. Food and Drug Administration (FDA) approval of a particular cancer treatment as safe and effective and are the benchmark for an evidence-based approach to the use of chemotherapeutic agents. Common tumors that may be meaningfully addressed by chemotherapy with palliative intent are listed in **Table 29-3E**.

Usually, tumor-related symptoms manifest as pain, weight loss, or some local symptom related to the tumor's effect on normal structures. Patients treated with palliative intent should be aware of their diagnosis and the limitations of the proposed treatments, have access to supportive care, and have suitable "performance status," according to assessment algorithms such as the one developed by Karnofsky **(see Table 27-4)** or by the Eastern Cooperative Oncology Group (ECOG) **(see Table 27-5)**. ECOG performance status 0 (PS0) patients are without symptoms; PS1 patients are ambulatory but restricted in strenuous physical activity; PS2 patients are ambulatory but unable to work and are up and about 50% or more of the time; PS3 patients are capable of limited self-care and are up <50% of the time; and PS4 patients are totally confined to bed or chair and

incapable of self-care. Only PS0, PS1, and PS2 patients are generally considered suitable for palliative (non-curative) treatment. If there is curative potential, even poor–performance status patients may be treated, but their prognosis is usually inferior to that of good–performance status patients treated with similar regimens.

An important perspective the primary care provider may bring to patients and their families facing incurable cancer is that, given the limited value of chemotherapeutic approaches at some point in the natural history of most metastatic cancers, palliative care or hospice-based approaches, with meticulous and ongoing attention to symptom relief and with family, psychological, and spiritual support, should receive prominent attention as a valuable therapeutic plan **(Chaps. 27 and 33)**. Optimizing the quality of life rather than attempting to extend it becomes a valued intervention. Patients facing the impending progression of disease in a life-threatening way frequently choose to undertake toxic treatments of little to no potential value, and support provided by the primary caregiver in accessing palliative and hospice-based options in contrast to receiving toxic and ineffective regimen can be critical in providing a basis for patients to make sensible choices.

Cytotoxic chemotherapy agents

Table 29-4 lists commonly used cytotoxic cancer chemotherapy agents and pertinent clinical aspects of their use, with particular reference to adverse effects that might be encountered by the generalist in the care of patients. The drugs listed may be usefully grouped into two general categories: those affecting DNA and those affecting microtubules.

Direct DNA-interactive agents

DNA replication occurs during the synthesis or S-phase of the cell cycle, with chromosome segregation of the replicated DNA occurring in the M, or mitosis, phase. The G_1 and G_2 "gap phases" precede S and M, respectively. Historically, chemotherapeutic agents have been divided into "phase-nonspecific" agents, which can act in any phase of the cell cycle, and "phase-specific" agents, which require the cell to be at a particular cell cycle phase to cause greatest effect. Once the agent has acted, cells may progress to "checkpoints" in the cell cycle where the drug-related damage may be assessed and either repaired or allowed to initiate apoptosis. An important function of certain tumor-suppressor genes such as p53 may be to modulate checkpoint function.

Alkylating agents as a class are cell cycle phase–nonspecific agents. They break down, either spontaneously or after normal organ or tumor cell metabolism, to reactive intermediates that covalently modify bases in DNA. This leads to cross-linkage of DNA strands or the appearance of breaks in DNA as a result of repair efforts. "Broken" or cross-linked DNA is intrinsically unable to complete normal replication or cell division; in addition, it is a potent activator of cell cycle checkpoints and further activates cell-signaling pathways that can precipitate apoptosis. As a class, alkylating agents share similar toxicities: myelosuppression, alopecia, gonadal dysfunction, mucositis, and pulmonary fibrosis. They differ greatly in a spectrum of normal organ toxicities. As a class, they share the capacity to cause "second" neoplasms, particularly leukemia, many years after use, particularly when used in low doses for protracted periods.

Cyclophosphamide is inactive unless metabolized by the liver to 4-hydroxy-cyclophosphamide, which decomposes into an alkylating species, as well as to chloroacetaldehyde and acrolein. The latter causes chemical cystitis; therefore, excellent hydration must be maintained while using cyclophosphamide. If severe, the cystitis may be prevented from progressing or prevented altogether (if expected from the dose of cyclophosphamide to be used) by mesna (2-mercaptoethanesulfonate). Liver disease impairs cyclophosphamide activation. Sporadic interstitial pneumonitis leading to pulmonary fibrosis can accompany the use of cyclophosphamide, and high doses used in conditioning regimens for bone marrow transplant can cause cardiac dysfunction. Ifosfamide is a cyclophosphamide analogue also activated in the liver, but more slowly, and it requires coadministration of mesna to prevent bladder injury. Central nervous system (CNS) effects, including somnolence, confusion, and psychosis, can follow ifosfamide use; the incidence appears related to low body surface area or decreased creatinine clearance.

Several alkylating agents are less commonly used. Nitrogen mustard (mechlorethamine) is the prototypic agent of this class, decomposing rapidly in aqueous solution to potentially yield a bifunctional carbonium ion. It must be administered shortly after preparation into a rapidly flowing intravenous line. It is a powerful vesicant, and infiltration may be symptomatically ameliorated by infiltration of the affected site with 1/6 M thiosulfate. Even without infiltration, aseptic thrombophlebitis is frequent. It can be used topically as a dilute solution or ointment in cutaneous lymphomas, with a notable incidence of hypersensitivity reactions. It causes moderate nausea after intravenous administration. Bendamustine is a nitrogen mustard derivative with evidence of activity in chronic lymphocytic leukemia and certain lymphomas.

Chlorambucil causes predictable myelosuppression, azoospermia, nausea, and pulmonary side effects. Busulfan can cause profound myelosuppression, alopecia, and pulmonary toxicity but is relatively "lymphocyte sparing." Its routine use in treatment of CML has been curtailed in favor of imatinib (Gleevec) or dasatinib, but it is still used in transplant preparation regimens.

TABLE 29-4

CYTOTOXIC CHEMOTHERAPY AGENTS

DRUG	TOXICITY	INTERACTIONS, ISSUES
Direct DNA-Interacting Agents		
Alkylator		
Cyclophosphamide	Marrow (relative platelet sparing) Cystitis Common alkylator[a] Cardiac (high dose)	Liver metabolism required to activate to phosphoramide mustard + acrolein Mesna protects against "high-dose" bladder damage
Mechlorethamine	Marrow Vesicant Nausea	Topical use in cutaneous lymphoma
Chlorambucil	Marrow Common alkylator[a]	
Melphalan	Marrow (delayed nadir) GI (high dose)	Decreased renal function delays clearance
Carmustine (BCNU)	Marrow (delayed nadir) GI, liver (high dose) Renal	
Lomustine (CCNU)	Marrow (delayed nadir)	
Ifosfamide	Myelosuppressive Bladder Neurologic Metabolic acidosis	Analogue of cyclophosphamide Must use mesna Greater activity vs testicular neoplasms and sarcomas
Procarbazine	Marrow Nausea Neurologic Common alkylator[a]	Liver and tissue metabolism required Disulfiram-like effect with ethanol Acts as MAOI HBP after tyrosinase-rich foods
Dacarbazine (DTIC)	Marrow Nausea Flulike	Metabolic activation
Temozolomide	Nausea/vomiting Headache/fatigue Constipation	Infrequent myelosuppression
Altretamine (formerly hexamethylmelamine)	Nausea Neurologic (mood swing) Neuropathy Marrow (less)	Liver activation Barbiturates enhance/cimetidine diminishes
Cisplatin	Nausea Neuropathy Auditory Marrow platelets > WBCs Renal Mg^{2+}, Ca^{2+}	Maintain high urine flow; osmotic diuresis, monitor intake/output K^{+}, Mg^{2+} Emetogenic—prophylaxis needed Full dose if CrCl >60 mL/min and tolerate fluid push
Carboplatin	Marrow platelets > WBCs Nausea Renal (high dose)	Reduce dose according to CrCl: to AUC of 5–7 mg/mL per min (AUC = dose/[CrCl + 25])
Oxaliplatin	Nausea Anemia	Acute reversible neurotoxicity; chronic sensory neurotoxicity cumulative with dose; reversible laryngopharyngeal spasm
Antitumor Antibiotics and Topoisomerase Poisons		
Bleomycin	Pulmonary Skin effects Raynaud's Hypersensitivity	Inactivate by bleomycin hydrolase (decreased in lung/skin) O_2 enhances pulmonary toxicity Cisplatin-induced decrease in CrCl may increase skin/lung toxicity Reduce dose if CrCl <60 mL/min
Dactinomycin	Marrow Nausea Mucositis Vesicant Alopecia	Radiation recall

(continued)

TABLE 29-4

CYTOTOXIC CHEMOTHERAPY AGENTS (Continued)

DRUG	TOXICITY	INTERACTIONS, ISSUES
Etoposide (VP16-213)	Marrow (WBCs > platelet) Alopecia Hypotension Hypersensitivity (rapid IV) Nausea Mucositis (high dose)	Hepatic metabolism—renal 30% Reduce doses with renal failure Schedule-dependent (5-day schedule better than 1-day) Late leukemogenic Accentuate antimetabolite action
Topotecan	Marrow Mucositis Nausea Mild alopecia	Reduce dose with renal failure No liver toxicity
Irinotecan	Diarrhea: "early onset" with cramping, flushing, vomiting; "late onset" after several doses Marrow Alopecia Nausea Vomiting Pulmonary	Prodrug requires enzymatic clearance to active drug "SN 38" Early diarrhea likely due to biliary excretion Late diarrhea, use "high-dose" loperamide (2 mg q2–4 h)
Doxorubicin and daunorubicin	Marrow Mucositis Alopecia Cardiovascular acute/chronic Vesicant	Heparin aggregate; coadministration increases clearance Acetaminophen, BCNU increase liver toxicity Radiation recall
Idarubicin	Marrow Cardiac (less than doxorubicin)	None established
Epirubicin	Marrow Cardiac	None established
Mitoxantrone	Marrow Cardiac (less than doxorubicin) Vesicant (mild) Blue urine, sclerae, nails	Interacts with heparin Less alopecia, nausea than doxorubicin Radiation recall Less alopecia, nausea than doxorubicin
Indirectly DNA-Interacting Agents		
Antimetabolites		
Deoxycoformycin	Nausea Immunosuppression Neurologic Renal	Excretes in urine Reduce dose for renal failure Inhibits adenosine deaminase Reduce dose for renal failure
6-Mercaptopurine (6-MP)	Marrow Liver Nausea	Variable bioavailability Metabolize by xanthine oxidase Decrease dose with allopurinol Increased toxicity with thiopurine methyltransferase deficiency
6-Thioguanine	Marrow Liver Nausea	Variable bioavailability Increased toxicity with thiopurine methyltransferase deficiency
Azathioprine	Marrow Nausea Liver	Metabolizes to 6-MP; therefore, reduce dose with allopurinol Increase toxicity with thiopurine methyltransferase deficiency
2-Chlorodeoxy-adenosine	Marrow Renal Fever	Notable use in hairy cell leukemia
Hydroxyurea	Marrow Nausea Mucositis Skin changes Rare renal, liver, lung, CNS	Decrease dose with renal failure Augments antimetabolite effect

(continued)

TABLE 29-4

CYTOTOXIC CHEMOTHERAPY AGENTS (Continued)

DRUG	TOXICITY	INTERACTIONS, ISSUES
Methotrexate	Marrow Liver/lung Renal tubular Mucositis	Toxicity lessened by "rescue" with leucovorin Excreted in urine Decrease dose in renal failure; NSAIDs increase renal toxicity
5-Fluorouracil (5FU)	Marrow Mucositis Neurologic Skin changes	Toxicity enhanced by leucovorin by increasing "ternary complex" with thymidylate synthase; dihydropyrimidine dehydrogenase deficiency increases toxicity; metabolism in tissue
Capecitabine	Diarrhea Hand-foot syndrome	Prodrug of 5FU due to intratumoral metabolism
Cytosine arabinoside	Marrow Mucositis Neurologic (high dose) Conjunctivitis (high dose) Noncardiogenic pulmonary edema	Enhances activity of alkylating agents Metabolizes in tissues by deamination but renal excretion prominent at doses >500 mg; therefore, dose reduce in "high-dose" regimens in patients with decreased CrCl
Azacitidine	Marrow Nausea Liver Neurologic Myalgia	Use limited to leukemia Altered methylation of DNA alters gene expression
Gemcitabine	Marrow Nausea Hepatic Fever/"flu syndrome"	
Fludarabine phosphate	Marrow Neurologic Lung	Dose reduction with renal failure Metabolized to F-ara converted to F-ara ATP in cells by deoxycytidine kinase
Clofarabine	Myelosuppression Mucositis Rare cardiac/inflammatory	
Nelarabine	Myelosuppression Neurologic	T cell ALL; T cell lymphoblastic lymphoma
Asparaginase	Protein synthesis; indirect inhibition of DNA synthesis by decreased histone synthesis Clotting factors Glucose Albumin Hypersensitivity CNS Pancreatitis Hepatic	Blocks methotrexate action
Pemetrexed	Anemia Neutropenia Thrombocytopenia	Supplement folate/B_{12} Caution in renal failure
Pralatrexate	Myelosuppression Mucositis	Active in peripheral T cell lymphoma
Antimitotic Agents		
Vincristine	Vesicant Marrow Neurologic GI: ileus/constipation; bladder hypotoxicity; SIADH Cardiovascular	Hepatic clearance Dose reduction for bilirubin >1.5 mg/dL Prophylactic bowel regimen

(continued)

TABLE 29-4

CYTOTOXIC CHEMOTHERAPY AGENTS (Continued)

DRUG	TOXICITY	INTERACTIONS, ISSUES
Vinblastine	Vesicant Marrow Neurologic (less common but similar spectrum to other vincas) Hypertension Raynaud's	Hepatic clearance Dose reduction as with vincristine
Vinorelbine	Vesicant Marrow Allergic/bronchospasm (immediate) Dyspnea/cough (subacute) Neurologic (less prominent but similar spectrum to other vincas)	Hepatic clearance
Paclitaxel	Hypersensitivity Marrow Mucositis Alopecia Sensory neuropathy CV conduction disturbance Nausea—infrequent	Premedicate with steroids, H_1 and H_2 blockers Hepatic clearance Dose reduction as with vincas
Docetaxel	Hypersensitivity Fluid retention syndrome Marrow Dermatologic Sensory neuropathy Nausea infrequent Some stomatitis	Premedicate with steroids, H_1 and H_2 blockers
Estramustine phosphate	Nausea Vomiting Diarrhea CHF Thrombosis Gynecomastia	
Nab-paclitaxel (protein bound)	Neuropathy Anemia Neutropenia Thrombocytopenia	Caution in hepatic insuf ciency
Ixabepilone	Myelosuppression Neuropathy	

[a]Common allkylator: alopecia, pulmonary, infertility, plus teratogenesis.

Abbreviations: ALL, acute lymphocytic leukemia; AUC, area under the curve; CHF, congestive heart failure; CNS, central nervous system; CrCl, creatinine clearance; CV, cardiovascular; GI, gastrointestinal; HBP, high blood pressure; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Melphalan shows variable oral bioavailability and undergoes extensive binding to albumin and α_1-acidic glycoprotein. Mucositis appears more prominently; however, it has prominent activity in multiple myeloma.

Nitrosoureas break down to carbamylating species that not only cause a distinct pattern of DNA base pair–directed toxicity but also can covalently modify proteins. T ey share the feature of causing relatively delayed bone marrow toxicity, which can be cumulative and long-lasting. Procarbazine is metabolized in the liver and possibly in tumor cells to yield a variety of free radical and alkylating species. In addition to myelosuppression, it causes hypnotic and other CNS effects, including vivid nightmares. It can cause a disulfiram-like syndrome on ingestion of ethanol. Altretamine (formerly hexa-methylmelamine) and thiotepa can chemically give rise to alkylating species, although the nature of the DNA damage has not been well characterized in either case. Dacarbazine (DTIC) is activated in the liver to yield the highly reactive methyl diazonium cation. It causes only modest myelosuppression 21–25 days after a dose but causes prominent nausea on day 1. Temozolomide is structurally related to dacarbazine but was designed to be

activated by nonenzymatic hydrolysis in tumors and is bioavailable orally.

Cisplatin was discovered fortuitously by observing that bacteria present in electrolysis solutions with platinum electrodes could not divide. Only the cis diamine configuration is active as an antitumor agent. It is hypothesized that in the intracellular environment, a chloride is lost from each position, being replaced by a water molecule. T e resulting positively charged species is an efficient bifunctional interactor with DNA, forming Pt-based cross-links. Cisplatin requires administration with adequate hydration, including forced diuresis with mannitol to prevent kidney damage; even with the use of hydration, gradual decrease in kidney function is common, along with noteworthy anemia. Hypomagnesemia frequently attends cisplatin use and can lead to hypocalcemia and tetany. Other common toxicities include neurotoxocity with stocking-and-glove sensorimotor neuropathy. Hearing loss occurs in 50% of patients treated with conventional doses. Cisplatin is intensely emetogenic, requiring prophylactic antiemetics. Myelosuppression is less evident than with other alkylating agents. Chronic vascular toxicity (Raynaud's phenomenon, coronary artery disease) is a more unusual toxicity. Carboplatin displays less nephro-, oto-, and neurotoxicity. However, myelosuppression is more frequent, and because the drug is exclusively cleared through the kidney, adjustment of dose for creatinine clearance must be accomplished through use of various dosing nomograms. Oxaliplatin is a platinum analogue with noteworthy activity in colon cancers refractory to other treatments. It is prominently neurotoxic.

Antitumor antibiotics and topoisomerase poisons

Antitumor antibiotics are substances produced by bacteria that in nature appear to provide a chemical defense against other hostile microorganisms. As a class, they bind to DNA directly and can frequently undergo electron transfer reactions to generate free radicals in close proximity to DNA, leading to DNA damage in the form of single-strand breaks or cross-links. Topoisomerase poisons include natural products or semisynthetic species derived ultimately from plants, and they modify enzymes that regulate the capacity of DNA to unwind to allow normal replication or transcription. T ese include topoisomerase I, which creates single-strand breaks that then rejoin following the passage of the other DNA strand through the break. Topoisomerase II creates double-strand breaks through which another segment of DNA duplex passes before rejoining. DNA damage from these agents can occur in any cell cycle phase, but cells tend to arrest in S-phase or G_2 of the cell cycle in cells with p53 and Rb pathway lesions as the result of defective checkpoint mechanisms in cancer cells. Owing to the role of topoisomerase I in the procession of the replication fork, topoisomerase I poisons cause lethality if the topoisomerase I–induced lesions are made in S-phase.

Doxorubicin can intercalate into DNA, thereby altering DNA structure, replication, and topoisomerase II function. It can also undergo reduction reactions by accepting electrons into its quinone ring system, with the capacity to undergo reoxidation to form reactive oxygen radicals after reoxidation. It causes predictable myelosuppression, alopecia, nausea, and mucositis. In addition, it causes acute cardiotoxicity in the form of atrial and ventricular dysrhythmias, but these are rarely of clinical significance. In contrast, cumulative doses >550 mg/m^2 are associated with a 10% incidence of chronic cardiomyopathy. T e incidence of cardiomyopathy appears to be related to schedule (peak serum concentration), with low-dose, frequent treatment or continuous infusions better tolerated than intermittent higher-dose exposures. Cardiotoxicity has been related to iron-catalyzed oxidation and reduction of doxorubicin, and not to topoisomerase action. Cardiotoxicity is related to peak plasma dose; thus, lower doses and continuous infusions are less likely to cause heart damage. Doxorubicin's cardiotoxicity is increased when given together with trastuzumab (Herceptin), the anti-HER2/neu antibody. Radiation recall or interaction with concomitantly administered radiation to cause local site complications is frequent. T e drug is a powerful vesicant, with necrosis of tissue apparent 4–7 days after an extravasation; therefore, it should be administered into a rapidly flowing intravenous line. Dexrazoxane is an antidote to doxorubicin-induced extravasation. Doxorubicin is metabolized by the liver, so doses must be reduced by 50–75% in the presence of liver dysfunction. Daunorubicin is closely related to doxorubicin and was actually introduced first into leukemia treatment, where it remains part of curative regimens and has been shown preferable to doxorubicin owing to less mucositis and colonic damage. Idarubicin is also used in acute myeloid leukemia treatment and may be preferable to daunorubicin in activity. Encapsulation of daunorubicin into a liposomal formulation has attenuated cardiac toxicity and antitumor activity in Kaposi's sarcoma, other sarcomas, multiple myeloma, and ovarian cancer.

Bleomycin refers to a mixture of glycopeptides that have the unique feature of forming complexes with Fe^{2+} while also bound to DNA. It remains an important component of curative regimens for Hodgkin's disease and germ cell neoplasms. Oxidation of Fe^{2+} gives rise to superoxide and hydroxyl radicals. T e drug causes little, if any, myelosuppression. T e drug is cleared rapidly, but augmented skin and pulmonary toxicity in the presence of renal failure has led to the recommendation that doses be reduced by 50–75% in the face of a creatinine clearance <25 mL/min. Bleomycin is not a vesicant and can be administered intravenously, intramuscularly, or

subcutaneously. Common side effects include fever and chills, facial flush, and Raynaud's phenomenon. Hypertension can follow rapid intravenous administration, and the incidence of anaphylaxis with early preparations of the drug has led to the practice of administering a test dose of 0.5–1 unit before the rest of the dose. T e most feared complication of bleomycin treatment is pulmonary fibrosis, which increases in incidence at >300 cumulative units administered and is minimally responsive to treatment (e.g., glucocorticoids). T e earliest indicator of an adverse effect is usually a decline in the carbon monoxide diffusing capacity (DL_{co}) or coughing, although cessation of drug immediately upon documentation of a decrease in DL_{co} may not prevent further decline in pulmonary function. Bleomycin is inactivated by a bleomycin hydrolase, whose concentration is diminished in skin and lung. Because bleomycin-dependent electron transport is dependent on O_2, bleomycin toxicity may become apparent after exposure to transient very high fraction of inspired oxygen (Fi_{o2}). T us, during surgical procedures, patients with prior exposure to bleomycin should be maintained on the lowest Fi_{o2} consistent with maintaining adequate tissue oxygenation.

Mitoxantrone is a synthetic compound that was designed to recapitulate features of doxorubicin but with less cardiotoxicity. It is quantitatively less cardiotoxic (comparing the ratio of cardiotoxic to therapeutically effective doses) but is still associated with a 10% incidence of cardiotoxicity at cumulative doses of >150 mg/m^2. It also causes alopecia. Cases of acute promyelocytic leukemia (APL) have arisen shortly after exposure of patients to mitoxantrone, particularly in the adjuvant treatment of breast cancer. Although chemotherapy-associated leukemia is generally of the acute myeloid type, APL arising in the setting of prior mitoxantrone treatment had the typical t(15;17) chromosome translocation associated with APL, but the breakpoints of the translocation appeared to be at topoisomerase II sites that would be preferred sites of mitoxantrone action, clearly linking the action of the drug to the generation of the leukemia.

Etoposide was synthetically derived from the plant product podophyllotoxin; it binds directly to topoisomerase II and DNA in a reversible ternary complex. It stabilizes the covalent intermediate in the enzyme's action where the enzyme is covalently linked to DNA. T is "alkali-labile" DNA bond was historically a first hint that an enzyme such as a topoisomerase might exist. T e drug therefore causes a prominent G_2 arrest, reflecting the action of a DNA damage checkpoint. Prominent clinical effects include myelosuppression, nausea, and transient hypotension related to the speed of administration of the agent. Etoposide is a mild vesicant but is relatively free from other large-organ toxicities. When given at high doses or very frequently, topoisomerase II inhibitors may cause acute leukemia associated with chromosome 11q23 abnormalities in up to 1% of exposed patients.

Camptothecin was isolated from extracts of a Chinese tree and had notable antileukemia activity in preclinical mouse models. Early human clinical studies with the sodium salt of the hydrolyzed camptothecin lactone showed evidence of toxicity with little antitumor activity. Identification of topoisomerase I as the target of camptothecins and the need to preserve lactone structure allowed additional efforts to identify active members of this series. Topoisomerase I is responsible for unwinding the DNA strand by introducing single-strand breaks and allowing rotation of one strand about the other. In S-phase, topoisomerase I–induced breaks that are not promptly resealed lead to progress of the replication fork off the end of a DNA strand. T e DNA damage is a potent signal for induction of apoptosis. Camptothecins promote the stabilization of the DNA linked to the enzyme in a so-called cleavable complex, analogous to the action of etoposide with topoisomerase II. Topotecan is a camptothecin derivative approved for use in gynecologic tumors and small-cell lung cancer. Toxicity is limited to myelosuppression and mucositis. CPT-11, or irinotecan, is a camptothecin with evidence of activity in colon carcinoma. In addition to myelosuppression, it causes a secretory diarrhea related to the toxicity of a metabolite called SN-38. Levels of SN-38 are particularly high in the setting of Gilbert's disease, characterized by defective glucuronyl transferase and indirect hyperbilirubinemia, a condition that affects about 10% of the white population in the United States. T e diarrhea can be treated effectively with loperamide or octreotide.

Indirect modulators of nucleic acid function: antimetabolites

A broad definition of antimetabolites would include compounds with structural similarity to precursors of purines or pyrimidines, or compounds that interfere with purine or pyrimidine synthesis. Some antimetabolites can cause DNA damage indirectly, through misincorporation into DNA, abnormal timing or progression through DNA synthesis, or altered function of pyrimidine and purine biosynthetic enzymes. T ey tend to convey greatest toxicity to cells in S-phase, and the degree of toxicity increases with duration of exposure. Common toxic manifestations include stomatitis, diarrhea, and myelosuppression. Second malignancies are not associated with their use.

Methotrexate inhibits dihydrofolate reductase, which regenerates reduced folates from the oxidized folates produced when thymidine monophosphate is formed from deoxyuridine monophosphate. Without reduced folates, cells die a "thymine-less" death. N5-Tetrahydrofolate or N5-formyltetrahydrofolate (leucovorin) can bypass this block and rescue cells from methotrexate,

which is maintained in cells by polyglutamylation. T e drug and other reduced folates are transported into cells by the folate carrier, and high concentrations of drug can bypass this carrier and allow diffusion of drug directly into cells. T ese properties have suggested the design of "high-dose" methotrexate regimens with leucovorin rescue of normal marrow and mucosa as part of curative approaches to osteosarcoma in the adjuvant setting and hematopoietic neoplasms of children and adults. Methotrexate is cleared by the kidney via both glomerular filtration and tubular secretion, and toxicity is augmented by renal dysfunction and drugs such as salicylates, probenecid, and nonsteroidal anti-inflammatory agents that undergo tubular secretion. With normal renal function, 15 mg/m^2 leucovorin will rescue 10^{-8} to 10^{-6} M methotrexate in three to four doses. However, with decreased creatinine clearance, doses of 50–100 mg/m^2 are continued until methotrexate levels are $<5 \times 10^{-8}$ M. In addition to bone marrow suppression and mucosal irritation, methotrexate can cause renal failure itself at high doses owing to crystallization in renal tubules; therefore, high-dose regimens require alkalinization of urine with increased flow by hydration. Methotrexate can be sequestered in third-space collections and diffuse back into the general circulation, causing prolonged myelosuppression. Less frequent adverse effects include reversible increases in transaminases and hypersensitivity-like pulmonary syndrome. Chronic low-dose methotrexate can cause hepatic fibrosis. When administered to the intrathecal space, methotrexate can cause chemical arachnoiditis and CNS dysfunction.

Pemetrexed is a novel folate-directed antimetabolite. It is "multitargeted" in that it inhibits the activity of several enzymes, including thymidylate synthetase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, thereby affecting the synthesis of both purine and pyrimidine nucleic acid precursors. To avoid significant toxicity to the normal tissues, patients receiving pemetrexed should also receive low-dose folate and vitamin B_{12} supplementation. Pemetrexed has notable activity against certain lung cancers and, in combination with cisplatin, also against mesotheliomas. Pralatrexate is an antifolate approved for use in T cell lymphoma that is very efficiently transported into cancer cells.

5-Fluorouracil (5FU) represents an early example of "rational" drug design in that it originated from the observation that tumor cells incorporate radiolabeled uracil more efficiently into DNA than normal cells, especially gut. 5FU is metabolized in cells to 5′FdUMP, which inhibits thymidylate synthetase (TS). In addition, misincorporation can lead to single-strand breaks, and RNA can aberrantly incorporate FUMP. 5FU is metabolized by dihydropyrimidine dehydrogenase, and deficiency of this enzyme can lead to excessive toxicity from 5FU. Oral bioavailability varies unreliably, but orally administered analogues of 5FU such as capecitabine have been developed that allow at least equivalent activity to many parenteral 5FU-based approaches. Intravenous administration of 5FU leads to bone marrow suppression after short infusions but to stomatitis after prolonged infusions. Leucovorin augments the activity of 5FU by promoting formation of the ternary covalent complex of 5FU, the reduced folate, and TS. Less frequent toxicities include CNS dysfunction, with prominent cerebellar signs, and endothelial toxicity manifested by thrombosis, including pulmonary embolus and myocardial infarction.

Cytosine arabinoside (ara-C) is incorporated into DNA after formation of ara-CTP, resulting in S-phase–related toxicity. Continuous infusion schedules allow maximal efficiency, with uptake maximal at 5–7 μM. Ara-C can be administered intrathecally. Adverse effects include nausea, diarrhea, stomatitis, chemical conjunctivitis, and cerebellar ataxia. Gemcitabine is a cytosine derivative that is similar to ara-C in that it is incorporated into DNA after anabolism to the triphosphate, rendering DNA susceptible to breakage and repair synthesis, which differs from that in ara-C in that gemcitabine-induced lesions are very inefficiently removed. In contrast to ara-C, gemcitabine appears to have useful activity in a variety of solid tumors, with limited nonmyelosuppressive toxicities.

6-T ioguanine and 6-mercaptopurine (6MP) are used in the treatment of acute lymphoid leukemia. Although administered orally, they display variable bioavailability. 6MP is metabolized by xanthine oxidase and therefore requires dose reduction when used with allopurinol. 6MP is also metabolized by thiopurine methyltransferase; genetic deficiency of thiopurine methyltransferase results in excessive toxicity.

Fludarabine phosphate is a prodrug of F-adenine arabinoside (F-ara-A), which in turn was designed to diminish the susceptibility of ara-A to adenosine deaminase. F-ara-A is incorporated into DNA and can cause delayed cytotoxicity even in cells with low growth fraction, including chronic lymphocytic leukemia and follicular B cell lymphoma. CNS and peripheral nerve dysfunction and T cell depletion leading to opportunistic infections can occur in addition to myelosuppression. 2-Chlorodeoxyadenosine is a similar compound with activity in hairy cell leukemia. 2-Deoxycoformycin inhibits adenosine deaminase, with resulting increase in dATP levels. T is causes inhibition of ribonucleotide reductase as well as augmented susceptibility to apoptosis, particularly in T cells. Renal failure and CNS dysfunction are notable toxicities in addition to immunosuppression. Hydroxyurea inhibits ribonucleotide reductase, resulting in S-phase block. It is orally bioavailable and useful for the acute management of myeloproliferative states.

Asparaginase is a bacterial enzyme that causes breakdown of extracellular asparagine required for protein synthesis in certain leukemic cells. T is effectively stops tumor cell DNA synthesis, as DNA synthesis requires concurrent protein synthesis. T e outcome of asparaginase action is therefore very similar to the result of the small-molecule antimetabolites. Because asparaginase is a foreign protein, hypersensitivity reactions are common, as are effects on organs such as pancreas and liver that normally require continuing protein synthesis. T is may result in decreased insulin secretion with hyperglycemia, with or without hyperamylasemia and clotting function abnormalities. Close monitoring of clotting functions should accompany use of asparaginase. Paradoxically, owing to depletion of rapidly turning over anticoagulant factors, thromboses particularly affecting the CNS may also be seen with asparaginase.

Mitotic spindle inhibitors

Microtubules are cellular structures that form the mitotic spindle, and in interphase cells, they are responsible for the cellular "scaffolding" along which various motile and secretory processes occur. Microtubules are composed of repeating noncovalent multimers of a heterodimer of α and β isoform of the protein tubulin. Vincristine binds to the tubulin dimer with the result that microtubules are disaggregated. T is results in the block of growing cells in M-phase; however, toxic effects in G_1 and S-phase are also evident, reflecting effects on normal cellular activities of microtubules. Vincristine is metabolized by the liver, and dose adjustment in the presence of hepatic dysfunction is required. It is a powerful vesicant, and infiltration can be treated by local heat and infiltration of hyaluronidase. At clinically used intravenous doses, neurotoxicity in the form of glove-and-stocking neuropathy is frequent. Acute neuropathic effects include jaw pain, paralytic ileus, urinary retention, and the syndrome of inappropriate antidiuretic hormone secretion. Myelosuppression is not seen. Vinblastine is similar to vincristine, except that it tends to be more myelotoxic, with more frequent thrombocytopenia and also mucositis and stomatitis. Vinorelbine is a vinca alkaloid that appears to have differences in resistance patterns in comparison to vincristine and vinblastine; it may be administered orally.

T e taxanes include paclitaxel and docetaxel. T ese agents differ from the vinca alkaloids in that the taxanes stabilize microtubules against depolymerization. T e "stabilized" microtubules function abnormally and are not able to undergo the normal dynamic changes of microtubule structure and function necessary for cell cycle completion. Taxanes are among the most broadly active antineoplastic agents for use in solid tumors, with evidence of activity in ovarian cancer, breast cancer, Kaposi's sarcoma, and lung tumors. T ey are administered intravenously, and paclitaxel requires use of a Cremophor-containing vehicle that can cause hypersensitivity reactions. Premedication with dexamethasone (8–16 mg orally or intravenously 12 and 6 h before treatment) and diphenhydramine (50 mg) and cimetidine (300 mg), both 30 min before treatment, decreases but does not eliminate the risk of hypersensitivity reactions to the paclitaxel vehicle. Docetaxel uses a polysorbate 80 formulation, which can cause fluid retention in addition to hypersensitivity reactions, and dexamethasone premedication with or without antihistamines is frequently used. A protein-bound formulation of paclitaxel (called nab-paclitaxel) has at least equivalent antineoplastic activity and decreased risk of hypersensitivity reactions. Paclitaxel may also cause hypersensitivity reactions, myelosuppression, neurotoxicity in the form of glove-and-stocking numbness, and paresthesia. Cardiac rhythm disturbances were observed in phase 1 and 2 trials, most commonly asymptomatic bradycardia but also, much more rarely, varying degrees of heart block. T ese have not emerged as clinically significant in the majority of patients. Docetaxel causes comparable degrees of myelosuppression and neuropathy. Hypersensitivity reactions, including bronchospasm, dyspnea, and hypotension, are less frequent but occur to some degree in up to 25% of patients. Fluid retention appears to result from a vascular leak syndrome that can aggravate preexisting effusions. Rash can complicate docetaxel administration, appearing prominently as a pruritic maculopapular rash affecting the forearms, but it has also been associated with fingernail ridging, breakdown, and skin discoloration. Stomatitis appears to be somewhat more frequent than with paclitaxel. Cabazitaxel is a taxane with somewhat better activity in prostate cancers than earlier generations of taxanes, perhaps due to superior delivery to sites of disease.

Resistance to taxanes has been related to the emergence of efficient efflux of taxanes from tumor cells through the p170 P-glycoprotein (mdr gene product) or the presence of variant or mutant forms of tubulin. Epothilones represent a class of novel microtubule-stabilizing agents that have been conscientiously optimized for activity in taxane-resistant tumors. Ixabepilone has clear evidence of activity in breast cancers resistant to taxanes and anthracyclines such as doxorubicin. It retains acceptable expected side effects, including myelosuppression, and can also cause peripheral sensory neuropathy. Eribulin is a microtubule-directed agent with activity in patients who have had progression of disease on taxanes and is more similar to vinca alkaloids in its action but has similar side effects as vinca alkaloids and taxanes.

Estramustine was originally synthesized as a mustard derivative that might be useful in neoplasms that

possessed estrogen receptors. However, no evidence of interaction with DNA was observed. Surprisingly, the drug caused metaphase arrest, and subsequent study revealed that it binds to microtubule-associated proteins, resulting in abnormal microtubule function. Estramustine binds to estramustine-binding proteins (EMBPs), which are notably present in prostate tumor tissue, where the drug is used. Gastrointestinal and cardiovascular adverse effects related to the estrogen moiety occur in up to 10% of patients, including worsened heart failure and thromboembolic phenomena. Gynecomastia and nipple tenderness can also occur.

Targeted chemotherapy

Hormone receptor–directed therapy

Steroid hormone receptor–related molecules have emerged as prominent targets for small molecules useful in cancer treatment. When bound to their cognate ligands, these receptors can alter gene transcription and, in certain tissues, induce apoptosis. T e pharmacologic effect is a mirror or parody of the normal effects of the agents acting on nontransformed normal tissues, although the effects on tumors are mediated by indirect effects in some cases. While in some cases, such as breast cancer, demonstration of the target hormone receptor is necessary, in other cases such prostate cancer (androgen receptor) and lymphoid neoplasms (glucocorticoid receptor), the relevant receptor is always present in the tumor.

Glucocorticoids are generally given in "pulsed" high doses in leukemias and lymphomas, where they induce apoptosis in tumor cells. Cushing's syndrome and inadvertent adrenal suppression on withdrawal from high-dose glucocorticoids can be significant complications, along with infections common in immunosuppressed patients, in particular Pneumocystis pneumonia, which classically appears a few days after completing a course of high-dose glucocorticoids.

Tamoxifen is a partial estrogen receptor antagonist; it has a 10-fold greater antitumor activity in breast cancer patients whose tumors express estrogen receptors than in those who have low or no levels of expression. It might be considered the prototypic "molecularly targeted" agent. Owing to its agonistic activities in vascular and uterine tissue, side effects include a somewhat increased risk of cardiovascular complications, such as thromboembolic phenomena, and a small increased incidence of endometrial carcinoma, which appears after chronic use (usually >5 years). Progestational agents—including medroxyprogesterone acetate, androgens including fluoxymesterone (Halotestin), and, paradoxically, estrogens—have approximately the same degree of activity in primary hormonal treatment of breast cancers that have elevated expression of estrogen receptor protein. Estrogen itself is not used often owing to prominent cardiovascular and uterotropic activity.

Aromatase refers to a family of enzymes that catalyze the formation of estrogen in various tissues, including the ovary and peripheral adipose tissue and some tumor cells. Aromatase inhibitors are of two types, the irreversible steroid analogues such as exemestane and the reversible inhibitors such as anastrozole or letrozole. Anastrozole is superior to tamoxifen in the adjuvant treatment of breast cancer in postmenopausal patients with estrogen receptor–positive tumors. Letrozole treatment affords benefit following tamoxifen treatment. Adverse effects of aromatase inhibitors may include an increased risk of osteoporosis.

Prostate cancer is classically treated by androgen deprivation. Diethylstilbestrol (DES) acting as an estrogen at the level of the hypothalamus to downregulate hypothalamic luteinizing hormone (LH) production results in decreased elaboration of testosterone by the testicle. For this reason, orchiectomy is equally as effective as moderate-dose DES, inducing responses in 80% of previously untreated patients with prostate cancer but without the prominent cardiovascular side effects of DES, including thrombosis and exacerbation of coronary artery disease. In the event that orchiectomy is not accepted by the patient, testicular androgen suppression can also be effected by luteinizing hormone–releasing hormone (LHRH) agonists such as leuprolide and goserelin. T ese agents cause tonic stimulation of the LHRH receptor, with the loss of its normal pulsatile activation resulting in decreased output of LH by the anterior pituitary. T erefore, as primary hormonal manipulation in prostate cancer, one can choose orchiectomy or leuprolide, but not both. T e addition of androgen receptor blockers, including flutamide or bicalutamide, is of uncertain additional benefit in extending overall response duration; the combined use of orchiectomy or leuprolide plus flutamide is referred to as total androgen blockade. Enzalutamide also binds to the androgen receptor and antagonizes androgen action in a mechanistically distinct way. Somewhat analogous to inhibitors of aromatase, agents have been derived that inhibit testosterone and other androgen synthesis in the testis, adrenal gland, and prostate tissue. Abiraterone inhibits 17 α-hydroxylase/C17,20 lyase (CYP 17A1) and has been shown to be active in prostate cancer patients experiencing progression despite androgen blockade.

Tumors that respond to a primary hormonal manipulation may frequently respond to second and third hormonal manipulations. T us, breast tumors that had previously responded to tamoxifen have, on relapse, notable response rates to withdrawal of tamoxifen itself or to subsequent addition of an aromatase inhibitor or progestin. Likewise, initial treatment of prostate cancers with leuprolide plus flutamide may be followed

after disease progression by response to withdrawal of flutamide. T ese responses may result from the removal of antagonists from mutant steroid hormone receptors that have come to depend on the presence of the antagonist as a growth-promoting influence.

Additional strategies to treat refractory breast and prostate cancers that possess steroid hormone receptors may also address adrenal capacity to produce androgens and estrogens, even after orchiectomy or oophorectomy, respectively. T us, aminoglutethimide or ketoconazole can be used to block adrenal synthesis by interfering with the enzymes of steroid hormone metabolism. Administration of these agents requires concomitant hydrocortisone replacement and additional glucocorticoid doses administered in the event of physiologic stress.

Humoral mechanisms can also result in complications from an underlying malignancy producing the hormone. Adrenocortical carcinomas can cause Cushing's syndrome as well as syndromes of androgen or estrogen excess. Mitotane can counteract these by decreasing synthesis of steroid hormones. Islet cell neoplasms can cause debilitating diarrhea, treated with the somatostatin analogue octreotide. Prolactin-secreting tumors can be effectively managed by the dopaminergic agonist bromocriptine.

Diagnostically guided therapy

T e basis for discovery of drugs of this type was the prior knowledge of the importance of the drugs' molecular target to drive tumors in different contexts. **Figure 29-4** summarizes how FDA-approved targeted agents act. In the case of diagnostically guided targeted chemotherapy, prior demonstration of a specific target is necessary to guide the rational use of the agent, while in the case of targeted agents directed at oncogenic pathways, specific diagnosis of pathway activation is not yet necessary or in some cases feasible, although this is an area of ongoing clinical research. **Table 29-5** lists currently approved targeted chemotherapy agents, with features of their use.

In hematologic tumors, the prototypic agent of this type is imatinib, which targets the ATP binding site of the $p210^{bcr\text{-}abl}$ protein tyrosine kinase that is formed as the result of the chromosome 9;22 translocation producing the Philadelphia chromosome in CML. Imatinib is superior to interferon plus chemotherapy in the initial treatment of the chronic phase of this disorder. It has lesser activity in the blast phase of CML, where the cells may have acquired additional mutations in $p210^{bcr\text{-}abl}$ itself or other genetic lesions. Its side effects are relatively tolerable in most patients and include hepatic dysfunction, diarrhea, and fluid retention. Rarely, patients receiving imatinib have decreased cardiac function, which may persist after discontinuation of the drug. T e quality of response to imatinib enters into the decision about when to refer patients with CML for consideration

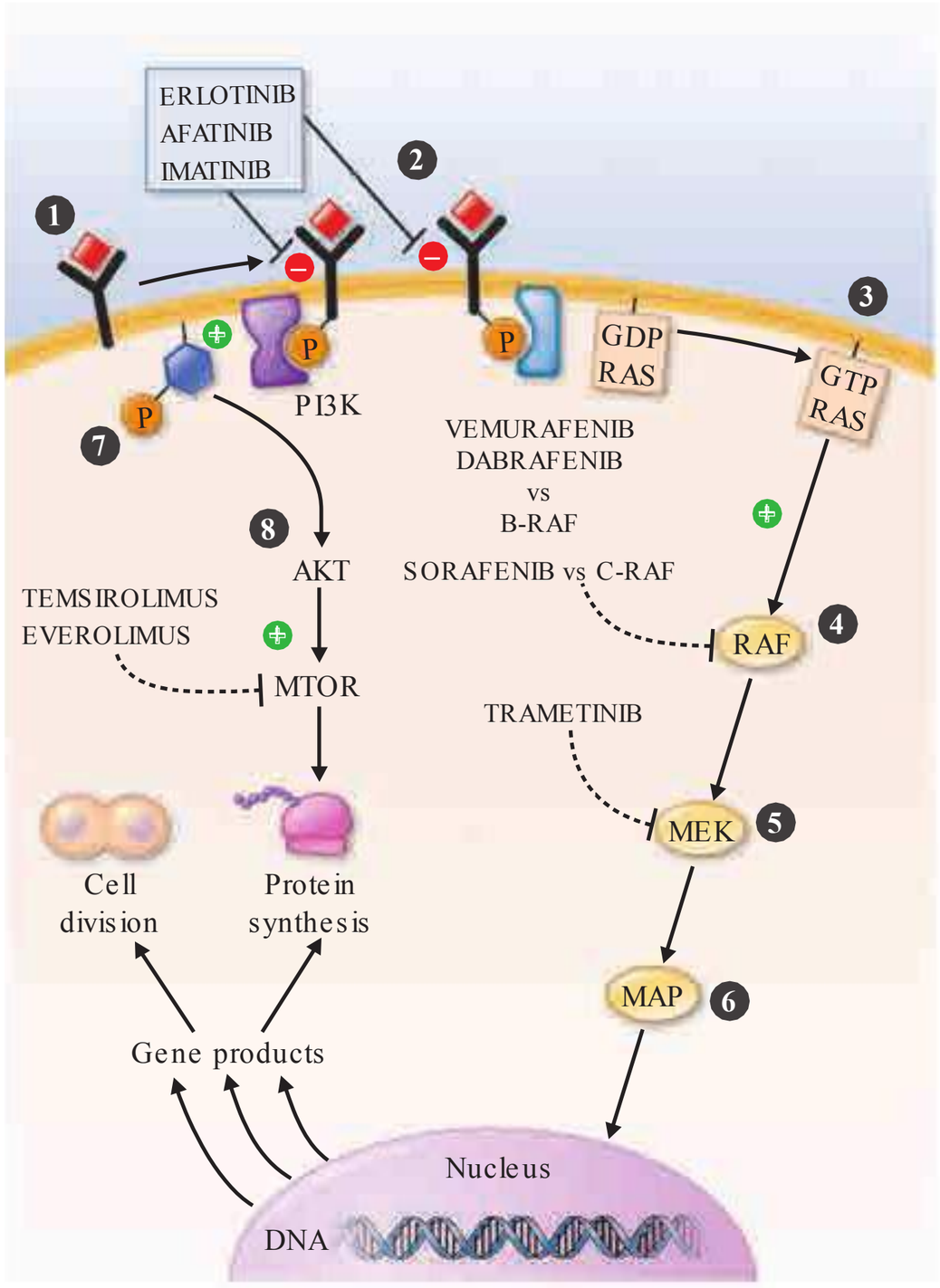


FIGURE 29-4

Targeted chemotherapeutic agents act in most instances by interrupting cell growth factor-mediated signaling pathways. After a growth factor binds to its cognate receptor (1), in many cases there is activation of tyrsosine kinase activity particularly after dimerization of the receptors (2). This leads to autophosphorylation of the receptor and docking of "adaptor" proteins. One important pathway activated occurs after exchange of GDP for GTP in the RAS family of proto-oncogene products (3). GTP-RAS activates the RAF proto-oncogene kinase (4), leading to a phosphorylation cascade of kinases (5, 6) that ultimately impart signals to regulators of gene function to produce transcripts which activate cell cycle progression and increase protein synthesis. In parallel, tyrosine phosphorylated receptors can activate the phosphatidylinositol-3-kinase to produce the phosphorylated lipid phosphatidyl-inositol-3- phosphate (7). This leads to the activation of the AKT kinase (8) which in turn stimulates the mammalian "Target of Rapamycin" kinase (mTOR), which directly increases the translation of key mRNAs for gene products regulating cell growth. Erlotinib and afatinib, are examples of Epidermal Growth Factor receptor tyrosine kinase inhibitors; imatinib can act on the nonreceptor tyrosine kinase bcr-abl or c-KIT membrane bound tyrosine kinase. Vemurafenib and Dabrafenib act on the B isoform of RAF uniquely in melanoma, and c-RAF is inhibited by sorafenib. Trametinib acts on MEK. Temsirolimus and everolimus inhibit mTOR kinase to downregulate translation of oncogenic mRNAs.

TABLE 29-5

MOLECULARLY TARGETED AGENTS

DRUG	TARGET	ADVERSE EVENTS	NOTES
Diagnostically Guided Protein Kinase Antagonists			
Imatinib	Bcr-Abl fusion protein (CML/ALL); c-kit mutants, PDGFR variants (GI stromal tumor; eosinophilic syndromes)	Nausea Periorbital edema Rare CHF QTc prolongation	Myelosuppression not frequent in solid tumor indications
Nilotinib	Bcr-Abl fusion protein (CML) and some imatinib-resistant variants	Interaction with CYP3A4-metabolized drugs CHF Hepatotoxicity Hypothyroidism	Chronic phase and in patients resistant to imatinib
Dasatinib	Bcr-Abl fusion protein (CML/ALL); wild-type and imatinib-resistant mutants	Myelosuppression (bleeding, infection) Pulmonary hypertension CHF Fluid retention QTc prolongation	Chronic phase and imatinib or nilotinib resistant
Bosutinib	Bcr-Abl fusion protein (CML); wild-type and imatinib-resistant mutants	Myelosuppression Hepatic QTc prolongation	Chronic phase and imatinib or nilotinib resistant
Ponatinib	T315I mutation of Bcr-Abl fusion protein (CML)	Clotting Hepatic CHF Pancreatitis Neuropathy Rash	
Gefitinib	First-line treatment of NSCLC with ATP site mutation of EGFR	Diarrhea Interstitial pneumonitis	In United States, only with prior documented benefit in second-line treatment of NSCLC
Erlotinib	First-line treatment of NSCLC with ATP site mutation of EGFR; second-line treatment of wild-type EGFR NSCLC	Rash Diarrhea Rare interstitial pneumonitis	1 h before, 2 h after meals
Afatinib	First-line treatment of NSCLC with ATP site mutation of EGFR	Diarrhea Cutaneous	Interacts with Pgp inhibitors
Crizotinib	EML4-Alk fusion protein	Interstitial pneumonitis Hepatic QTc prolongation Bradycardia	
Vemurafenib	BRAF V600E in melanoma	Nausea Rash Cutaneous Second cutaneous neoplasms	
Dabrafenib	BRAF V600E in melanoma	Cutaneous Second cutaneous neoplasms	
Trametinib	BRAF V600E in melanoma (both as single agent and in combination with dabrafenib)	Rash Diarrhea Lymphedema	In combination with dabrafenib, second neoplasms, hemorrhage, venous thrombosis, CHF, ocular, hyperglycemia

DRUG	**INDICATION**	**ADVERSE EVENTS**	**NOTES**
Diagnostically Guided Retinoid			
Tretinoin	APL t(15,17)	Teratogenic Cutaneous	APL differentiation syndrome: pulmonary dysfunction/infiltrate, pleural/pericardial effusion, fever

(continued)

TABLE 29-5

MOLECULARLY TARGETED AGENTS (Continued)			
DRUG	INDICATION	ADVERSE EVENTS	NOTES
NONDIAGNOSTICALLY GUIDED AGENTS			
Retinoid			
Bexarotene	Cutaneous T cell lymphoma	Hypercholesterolemia Hypertriglyceridemia Cutaneous Teratogenic	Central hypothyroidism
Multikinase inhibitors			
Sorafenib	Renal cell, hepatocellular, differentiated thyroid carcinoma	Diarrhea Hand-foot syndrome Other rash Hypertension CHF	Targets c-raf, VEGFR
Pazopanib	Renal cell carcinoma, soft tissue sarcoma	Fatigue Diarrhea/GI Hypertension Thromboses QTc	Target VEGFR, c-kit, PDGFR
Regorafenib	Second-line colorectal cancer; GI stromal tumor	Hypertension Hand-foot syndrome Thromboses Perforations	VEGFR/TIE2
Sunitinib	Renal cell carcinoma, pancreatic neuroendocrine tumor, GI stromal tumor	Fatigue Diarrhea Neutropenia	Target VEGFR
Vandetanib	Medullary thyroid cancer	Diarrhea Rash Hypertension Prolonged QTc Thromboses	Target VEGFR, ret, EGFR
Cabozantinib	Medullary thyroid cancer	Hypertension Wound healing Fistulas Osteonecrosis Proteinuria	Target VEGFR, c-met
Axitinib	Renal cell carcinoma, second line	Diarrhea/other GI Fatigue Hand-foot syndrome	Target VEGFR, PDGFR, c-kit
Proteasome Inhibitors			
Bortezomib	Multiple myeloma, mantle cell lymphoma	Neuropathy Thrombocytopenia GI	
Carfilzomib	Multiple myeloma, second line	Infusion reaction CHF Thrombocytopenia Pulmonary Tumor lysis	
Histone Deacetylase Inhibitors			
Vorinostat	Cutaneous T cell lymphoma, second line	Fatigue Diarrhea Thrombocytopenia Embolism	
Romidepsin	Cutaneous T cell lymphoma, second line	Nausea Vomiting Cytopenias Cardiac conduction	

(continued)

TABLE 29-5

MOLECULARLY TARGETED AGENTS (Continued)

DRUG	INDICATION	ADVERSE EVENTS	NOTES
mTOR Inhibitors			
Temsirolimus	Renal cell carcinoma, second line or poor prognosis	Stomatitis Thrombocytopenia Nausea Anorexia, fatigue Metabolic (glucose, lipid)	
Everolimus	Renal cell carcinoma, advanced; subependymal giant-cell astrocytoma; breast cancer, hormone receptor positive, resistant to antiestrogen; pancreatic neuroendocrine	Stomatitis Fatigue	
Miscellaneous			
Arsenic trioxide	APL	↑ QT_c	APL differentiation syndrome (see under tretinoin)
Vismodegib	Metastatic basal cell carcinoma	GI Hair loss Fatigue Muscle spasm Dysgeusia	Target smoothened receptor in hedgehog pathway

Abbreviations: APL, acute promyelocytic leukemia; ALL, acute lymphocytic leukemia; CHF, congestive heart failure; CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor; GI, gastrointestinal; mTOR, mammalian target of rapamycin kinase; NSCLC, non-small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; Pgp, P-glycoprotein; VEGFR, vascular endothelial growth factor receptor.

of transplant approaches. Nilotinib is a tyrosine protein kinase inhibitor with a similar spectrum of activity to imatinib, but with increased potency and perhaps better tolerance by certain patients. Dasatinib, another inhibitor of the $p210^{bcr\text{-}abl}$ oncoproteins, is active in certain mutant variants of $p210^{bcr\text{-}abl}$ that are refractory to imatinib and arise during therapy with imatinib or are present de novo. Dasatinib also has inhibitory action against kinases belonging to the src tyrosine protein kinase family; this activity may contribute to its effects in hematopoietic tumors and suggest a role in solid tumors where src kinases are active. T e T315I mutant of $p210^{bcr\text{-}abl}$ is resistant to imatinib, nilotinib, bosutinib, and dasatinib; ponatinib has activity in patients with this $p210^{bcr\text{-}abl}$ variant, but ponatinib has noteworthy associated thromboembolic toxicity. Use of this class of targeted agents is thus critically guided not only by the presence of the $p210^{bcr\text{-}abl}$ tyrosine kinase, but also by the presence of different mutations in the ATP binding site.

All-trans-retinoic acid (ATRA) targets the PML-retinoic acid receptor (RAR) α fusion protein, which is the result of the chromosome 15;17 translocation pathogenic for most forms of APL. Administered orally, it causes differentiation of the neoplastic promyelocytes to mature granulocytes and attenuates the rate of hemorrhagic complications. Adverse effects include headache with or without pseudotumor cerebri and gastrointestinal and cutaneous toxicities.

In epithelial solid tumors, the small-molecule epidermal growth factor (EGF) antagonists act at the ATP binding site of the EGF receptor tyrosine kinase. In early clinical trials, gefitinib showed evidence of responses in a small fraction of patients with non-small-cell lung cancer (NSCLC). Side effects were generally acceptable, consisting mostly of rash and diarrhea. Subsequent analysis of responding patients revealed a high frequency of activating mutations in the EGF receptor. Patients with such activating mutations who initially responded to gefitinib but who then had progression of the disease then acquired additional mutations in the enzyme, analogous functionally to mutational variants responsible for imatinib resistance in CML. Erlotinib is another EGF receptor tyrosine kinase antagonist with a superior outcome in clinical trials in NSCLC; an overall survival advantage was demonstrated in subsets of patients who were treated after demonstrating progression of disease and who also had not been preselected for the presence of activating mutations. T us, although even patients with wild-type EGF receptors may benefit from erlotinib treatment, the presence of EGF receptor tyrosine kinase mutations has recently been shown to be a basis for recommending erlotinib and afatinib for first-line treatment of advanced NSCLC. Likewise, crizotinib targeting the alk protooncogene fusion protein has value in the initial treatment of alk-positive NSCLC. Lapatinib is a tyrosine kinase inhibitor with

both EGF receptor and HER2/neu antagonist activity, which is important in the treatment of breast cancers expressing the HER2/neu oncoprotein.

In addition to the $p210^{bcr\text{-}abl}$ kinase, imatinib also has activity against the c-kit tyrosine kinase (the receptor for the steel growth factor, also called stem cell factor) and the platelet-derived growth factor receptor (PDGFR), both of which can be expressed in gastrointestinal stromal sarcoma (GIST). Imatinib has found clinical utility in GIST, a tumor previously notable for its refractoriness to chemotherapeutic approaches. Imatinib's degree of activity varies with the specific mutational variant of kit or PDGFR present in a particular patient's tumor.

T e BRAF V600E mutation has been detected in a notable fraction of melanomas, thyroid tumors, and hairy cell leukemia, and preclinical models supported the concept that BRAF V600E drives oncogenic signaling in these tumors. Vemurafenib and dabrafenib, with selective capacity to inhibit the BRAF V600E serine kinase activity, were each shown to cause noteworthy responses in patients with BRAF V600E–mutated melanomas, although early relapse occurred in many patients treated with the drugs as single agents. Trametinib, acting downstream of BRAF V600E by directly inhibiting the MEK serine kinase by a non-ATP binding site mechanism, also displayed noteworthy responses in BRAF V600E–mutated melanomas, and the combination of trametinib and dabrafenib is even more active, by targeting the BRAF V600E–driven pathway at two points in the pathway leading to gene activation.

Oncogenically activated pathways

T is group of agents also targets specific regulatory molecules in promoting the viability of tumor cells, but they do not require the diagnostically verified presence of a particular target or target variant at this time.

"Multitargeted" kinase antagonists are small-molecule ATP site-directed antagonists that inhibit more than one protein kinase and have value in the treatment of several solid tumors. Drugs of this type with prominent activity against the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase have activity in renal cell carcinoma. Sorafenib is a VEGFR antagonist with activity against the ra*f* serine-threonine protein kinase, and regorafenib is a closely related drug with value in relapsed advanced colon cancer. Pazopanib also prominently targets VEGFR and has activity in renal carcinoma and soft tissue sarcomas. Sunitinib has anti-VEGFR, anti-PDGFR, and anti-c-kit activity. It causes prominent responses and stabilization of disease in renal cell cancers and GISTs. Side effects for agents with anti-VEGFR activity prominently include hypertension, proteinuria, and, more rarely, bleeding and clotting disorders and perforation of scarred gastrointestinal lesions. Also encountered are fatigue, diarrhea, and the hand-foot syndrome, with erythema and desquamation of the distal extremities, in some cases requiring dose modification, particularly with sorafenib.

Temsirolimus and everolimus are mammalian target of rapamycin (mTOR) inhibitors with activity in renal cancers. T ey produce stomatitis, fatigue, and some hyperlipidemia (10%), myelosuppression (10%), and rare lung toxicity. Everolimus is also useful in patients with hormone receptor–positive breast cancers displaying resistance to hormonal inhibition and in certain neuroendocrine and brain tumors, the latter arising in patients with sporadic or inherited mutations in the pathway activating mTOR.

In hematologic neoplasms, bortezomib is an inhibitor of the proteasome, the multisubunit assembly of protease activities responsible for the selective degradation of proteins important in regulating activation of transcription factors, including nuclear factor-κB (NF-κB) and proteins regulating cell cycle progression. It has activity in multiple myeloma and certain lymphomas. Adverse effects include neuropathy, orthostatic hypotension with or without hyponatremia, and reversible thrombocytopenia. Carfilzomib is a proteasome inhibitor chemically unrelated to bortezomib without prominent neuropathy, but with evidence of a cytokine release syndrome, which can be a cardiopulmonary stress. Other agents active in multiple myeloma and certain other hematologic neoplasms include the immunomodulatory agents related to thalidomide, including lenalidomide and pomalidomide. All these agents collectively inhibit aberrant angiogenesis in the bone marrow microenvironment, as well as influence stromal cell immune functions to alter the cytokine milieu supporting the growth of myeloma cells. T alidomide, although clinically active, has prominent cytopenic, neuropathic, procoagulant, and CNS toxicities that have been somewhat attenuated in the other drugs of the class, although use of these agents frequently entails concomitant anticoagulant prophylaxis.

Ibrutinib is representative a novel class of inhibitors directed at Bruton's tyrosine kinase, which is important in the function of B cells. Initially approved for use in mantle cell lymphoma, it is potentially applicable to a number of B cell neoplasms that depend on signals through the B cell antigen receptor. Janus kinases likewise function downstream of a variety of cytokine receptors to amplify cytokine signals, and Janus kinase inhibitors including ruxolitinib have approved activity in myelofibrosis to ameliorate splenomegaly and systemic symptoms.

Vorinostat is an inhibitor of histone deacetylases, which are responsible for maintaining the proper orientation of histones on DNA, with resulting capacity for transcriptional readiness. Acetylated histones allow access of transcription factors to target genes and therefore increase expression of genes that are selectively repressed in tumors. T e result can be differentiation

with the emergence of a more normal cellular phenotype, or cell cycle arrest with expression of endogenous regulators of cell cycle progression. Vorinostat is approved for clinical use in cutaneous T cell lymphoma, with dramatic skin clearing and very few side effects. Romidepsin is a distinct molecular class of histone deacetylase inhibitor also active in cutaneous T cell lymphoma. An active retinoid in cutaneous T cell lymphoma is the synthetic retinoid X receptor ligand bexarotene.

DNA methyltransferase inhibitors, including 5-azacytidine and 2′-deoxy-5-azacytidine (decitabine), can also increase transcription of genes "silenced" during the pathogenesis of a tumor by causing demethylation of the methylated cytosines that are acquired as an "epigenetic" (i.e., after the DNA is replicated) modification of DNA. These drugs were originally considered antimetabolites but have clinical value in myelodysplastic syndromes and certain leukemias when administered at low doses.

CANCER BIOLOGIC THERAPY

Principles

The goal of biologic therapy is to manipulate the host–tumor interaction in favor of the host, potentially at an optimum biologic dose that might be different than the MTD. As a class, biologic therapies may be distinguished from molecularly targeted agents in that many biologic therapies require an active response (e.g., reexpression of silenced genes or antigen expression) on the part of the tumor cell or on the part of the host (e.g., immunologic effects) to allow therapeutic effect. This is may be contrasted with the more narrowly defined antiproliferative or apoptotic response that is the ultimate goal of molecularly targeted agents discussed above. However, there is much commonality in the strategies to evaluate and use molecularly targeted and biologic therapies.

Immune cell–mediated therapies

Tumors have a variety of means of avoiding the immune system: (1) they are often only subtly different from their normal counterparts; (2) they are capable of downregulating their major histocompatibility complex antigens, effectively masking them from recognition by T cells; (3) they are inefficient at presenting antigens to the immune system; (4) they can cloak themselves in a protective shell of fibrin to minimize contact with surveillance mechanisms; and (5) they can produce a range of soluble molecules, including potential immune targets, that can distract the immune system from recognizing the tumor cell or can kill or inactivate the immune effector cells. Some of the cell products initially polarize the immune response away from cellular immunity (shifting from T_H1 to T_H2 responses) and ultimately lead to defects in T cells that prevent their activation and cytotoxic activity. Cancer treatment further suppresses host immunity. A variety of strategies are being tested to overcome these barriers.

Cell-mediated immunity

The strongest evidence that the immune system can exert clinically meaningful antitumor effects comes from allogeneic bone marrow transplantation. Adoptively transferred T cells from the donor expand in the tumor-bearing host, recognize the tumor as being foreign, and can mediate impressive antitumor effects (graft-versus-tumor effects). Three types of experimental interventions are being developed to take advantage of the ability of T cells to kill tumor cells.

1. Transfer *of* allogeneic T cells. This occurs in three major settings: in allogeneic bone marrow transplantation; as purified lymphocyte transfusions following bone marrow recovery after allogeneic bone marrow transplantation; and as pure lymphocyte transfusions following immunosuppressive (nonmyeloablative) therapy (also called minitransplants). In each of these settings, the effector cells are donor T cells that recognize the tumor as being foreign, probably through minor histocompatibility differences. The main risk of such therapy is the development of graft-versus-host disease because of the minimal difference between the cancer and the normal host cells. This is approach has been highly effective in certain hematologic cancers.
2. Transfer *of* autologous T cells. In this approach, the patient's own T cells are removed from the tumor-bearing host, manipulated in several ways in vitro, and given back to the patient. There are three major classes of autologous T-cell manipulation. First, tumor antigen–specific T cells can be developed and expanded to large numbers over many weeks ex vivo before administration. Second, the patient's T cells can be activated by exposure to polyclonal stimulators such as anti-CD3 and anti-CD28 after a short period ex vivo, and then amplified in the host after transfer by stimulation with IL-2, for example. Short periods removed from the patient permit the cells to overcome the tumor-induced T cell defects, and such cells traffic and home to sites of disease better than cells that have been in culture for many weeks. In a third approach, genes that encode for a T cell receptor specific for an antigen expressed by the tumor along with genes that facilitate T cell activation can be introduced into subsets of a patient's T cells, which, after transfer back into the patient, allow homing of cytotoxic T cells to tumor cells expressing the antigen.
3. Tumor vaccines aimed at boosting T cell immunity. The finding that mutant oncogenes that are expressed

only intracellularly can be recognized as targets of T cell killing greatly expanded the possibilities for tumor vaccine development. No longer is it difficult to find something different about tumor cells. However, major difficulties remain in getting the tumor-specific peptides presented in a fashion to prime the T cells. Tumors themselves are very poor at presenting their own antigens to T cells at the first antigen exposure (priming). Priming is best accomplished by professional antigen-presenting cells (dendritic cells). T us, a number of experimental strategies are aimed at priming host T cells against tumor-associated peptides. Vaccine adjuvants such as granulocyte-macrophage colony-stimulating factor (GM-CSF) appear capable of attracting antigen-presenting cells to a skin site containing a tumor antigen. Such an approach has been documented to eradicate microscopic residual disease in follicular lymphoma and give rise to tumor-specific T cells. Purified antigen-presenting cells can be pulsed with tumor, its membranes, or particular tumor antigens and delivered as a vaccine. One such vaccine, Sipuleucel-T, is approved for use in patients with hormone-independent prostate cancer. In this approach, the patient undergoes leukapheresis, wherein mononuclear cells (that include antigen-presenting cells) are removed from the patient's blood. T e cells are pulsed in a laboratory with an antigenic fusion protein comprising a protein frequently expressed by prostate cancer cells, prostate acid phosphatase, fused to GM-CSF, and matured to increase their capacity to present the antigen to immune effector cells. T e cells are then returned to the patient in a well-tolerated treatment. Although no objective tumor response was documented in clinical trials, median survival was increased by about 4 months. Tumor cells can also be transfected with genes that attract antigen-presenting cells.

Another important vaccine strategy is directed at infectious agents whose action ultimately is tied to the development of human cancer. Hepatitis B vaccine in an epidemiologic sense prevents hepatocellular carcinoma, and a tetravalent human papillomavirus vaccine prevents infection by virus types currently accounting for 70% of cervical cancer. Unfortunately, these vaccines are ineffective at treating patients who have developed a virus-induced cancer.

Antibody-mediated therapeutic approaches

In general, antibodies are not very effective at killing cancer cells. Because the tumor seems to influence the host toward making antibodies rather than generating cellular immunity, it is inferred that antibodies are easier for the tumor to fend off. Many patients can be shown to have serum antibodies directed at their tumors, but these do not appear to influence disease progression. However, the ability to grow very large quantities of high-affinity antibody directed at a tumor by the hybridoma technique has led to the application of antibodies in the treatment of cancer. In this approach, antibodies are derived where the antigen-combining regions are grafted onto human immunoglobulin gene products (chimerized or humanized) or derived de novo from mice bearing human immunoglobulin gene loci. T ree general strategies have emerged using antibodies. Tumor-regulatory antibodies target tumor cells directly or indirectly to modulate intracellular functions or attract immune or stromal cells. Immunoregulatory antibodies target antigens expressed on the tumor cells or host immune cells to modulate primarily the host's immune responsiveness to the tumor. Finally, antibody conjugates can be made with the antibody linked to drugs, toxins, or radioisotopes to target these "warheads" for delivery to the tumor. **Table 29-6** lists features of currently used or promising antibodies for cancer treatment.

Tumor-regulatory antibodies

Humanized antibodies against the CD20 molecule expressed on B cell lymphomas (rituximab and ofatumumab) are exemplary of antibodies that affect both signaling events driving lymphomagenesis as well as activating immune responses against B cell neoplasms. T ey are used as single agents and in combination with chemotherapy and radiation in the treatment of B cell neoplasms. Obinutuzumab is an antibody with an altered glycosylation that enhances its ability to fix complement; it is also directed against CD20 and is of value in chronic lymphocytic leukemia. It seems to be more effective in this setting than rituximab.

T e HER2/neu receptor overexpressed on epithelial cancers, especially breast cancer, was initially targeted by trastuzumab, with noteworthy activity in potentiating the action of chemotherapy in breast cancer as well as some evidence of single-agent activity. Trastuzumab also appears to interrupt intracellular signals derived from HER2/neu and to stimulate immune mechanisms. T e anti-HER2 antibody pertuzumab, specifically targeting the domain of HER2/neu responsible for dimerization with other HER2 family members, is more specifically directed against HER2 signaling function and augments the action of trastuzumab.

EGF receptor (EGFR)-directed antibodies (such as cetuximab and panitumumab) have activity in colorectal cancer refractory to chemotherapy, particularly when used to augment the activity of an additional chemotherapy program, and in the primary treatment of head and neck cancers treated with radiation therapy. T e mechanism of action is unclear. Direct effects on the tumor may mediate an antiproliferative effect

TABLE 29-6

ANTIBODIES USED IN CANCER TREATMENT

DRUG	TARGET	INDICATIONS AND FEATURES OF USE
Tumor Regulatory Antibodies		
Rituximab	CD20	B cell neoplasms (also emerging role in autoimmune disease); chimeric antibody with frequent mouse-derived sequences; frequent infusion reactions, particularly on initial doses; reactivation of infections, particularly hepatitis; progressive multifocal leukoencephalopathy; tumor lysis syndrome
Ofatumumab	CD20	active in CLL; fully human antibody with distinct binding site compared to rituximab; decreased intensity infusion reactions;
Trastuzumab	HER2/neu	Active in breast cancer and GI cancers expressing HER2/neu; cardiotoxicity, particularly in setting of prior anthracyclines, requires monitoring; infusion reactions
Pertuzumab	HER2/neu	Breast cancer; targets distinct binding site from trastuzumab, inhibiting dimerization of HER2 family members; infusion reactions; cardiac toxicity
Cetuximab	EGFR	Colorectal cancers with wild-type Ki-ras oncoprotein; head and neck cancers with radiation; rash, diarrhea, infusion reactions
Panitumumab	EGFR	Colorectal cancers with wild-type Ki-ras oncoprotein; fully humanized; decreased infusion reactions; different IgG subtype than cetuximab
Bevacizumab	VEGF	Metastatic colorectal cancer and non-small-cell lung cancer (nonsquamous) with chemotherapy; renal cancer and glioblastoma as single agents; prominent HBP, proteinuria, GI perforations, hemorrhage, thrombosis (venous and arterial)
Immunoregulatory Antibodies		
Alemtuzumab	CD52	CLL, T cell lymphomas; activates complement after binding to cell surface; infusion reactions, hypersensitivity, tumor lysis, activation of infections, cytopenias
Ipilimumab	CTLA4	Melanoma; inhibits the negative proliferative signal to T cells acting through CTLA4, resulting in prominent T cell activation; side effects include immune-mediated toxicity to liver, skin, pituitary, gut, which if severe calls for steroids, which inhibit antineoplastic effect
Pembrolizumab	PD-1	Melanoma unresectable or metastatic and if B-RAF V600 mutated, refractory to a B-RAF inhibitor; also can cause immune related colitis, hepatitis, hypophysitis, nephritis, and altered thyroid function; also consider steroids for treatment of severe adverse events

Abbreviations: CLL, chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor; GI, gastrointestinal; HBP, high blood pressure; VEGF, vascular endothelial growth factor.

as well as stimulate the participation of host mechanisms involving immune cell or complement-mediated response to tumor cell–bound antibody. Alternatively, the antibody may alter the release of paracrine factors promoting tumor cell survival.

The anti-VEGF antibody bevacizumab shows little evidence of antitumor effect when used alone, but when combined with chemotherapeutic agents, it improves the magnitude of tumor shrinkage and time to disease progression in colorectal and nonsquamous lung cancers. The mechanism for the effect is unclear and may relate to the capacity of the antibody to alter delivery and tumor uptake of the active chemotherapeutic agent. Ziv-aflibercept is not an antibody, but a solubilized VEGF receptor VEGF binding domain, and therefore may have a distinct mechanism of action with comparable side effects.

Unintended side effects of any antibody use include infusion-related hypersensitivity reactions, usually limited to the first infusion, which can be managed with glucocorticoid and/or antihistamine prophylaxis. In addition, distinct syndromes have emerged with different antibodies. Anti-EGFR antibodies produce an acneiform rash that poorly responds to glucocorticoid cream treatment. Trastuzumab (anti-HER2) can inhibit cardiac function, particularly in patients with prior exposure to anthracyclines. Bevacizumab has a number of side effects of medical significance, including hypertension, thrombosis, proteinuria, hemorrhage, and gastrointestinal perforations with or without prior surgeries; these adverse events also occur with small-molecule drugs modulating VEGFR function.

Immunoregulatory antibodies

Purely immunoregulatory antibodies stimulate immune responses to mediate tumor-directed cytotoxicity. First-generation approaches sought to activate complement and are exemplified by antibodies to CD52; these are active in chronic lymphoid leukemia and T cell malignancies. A more refined understanding of the tumor–host interface has defined that cytotoxic tumor-directed T cells are frequently inhibited by ligands upregulated in the tumor cells. The programmed death ligand 1 (PD-L1; also known as B7-homolog 1) was initially recognized as an entity that induced T cell death through a receptor present on T cells, termed the PD receptor **(Fig 29-5)**, which physiologically exists to regulate the intensity of

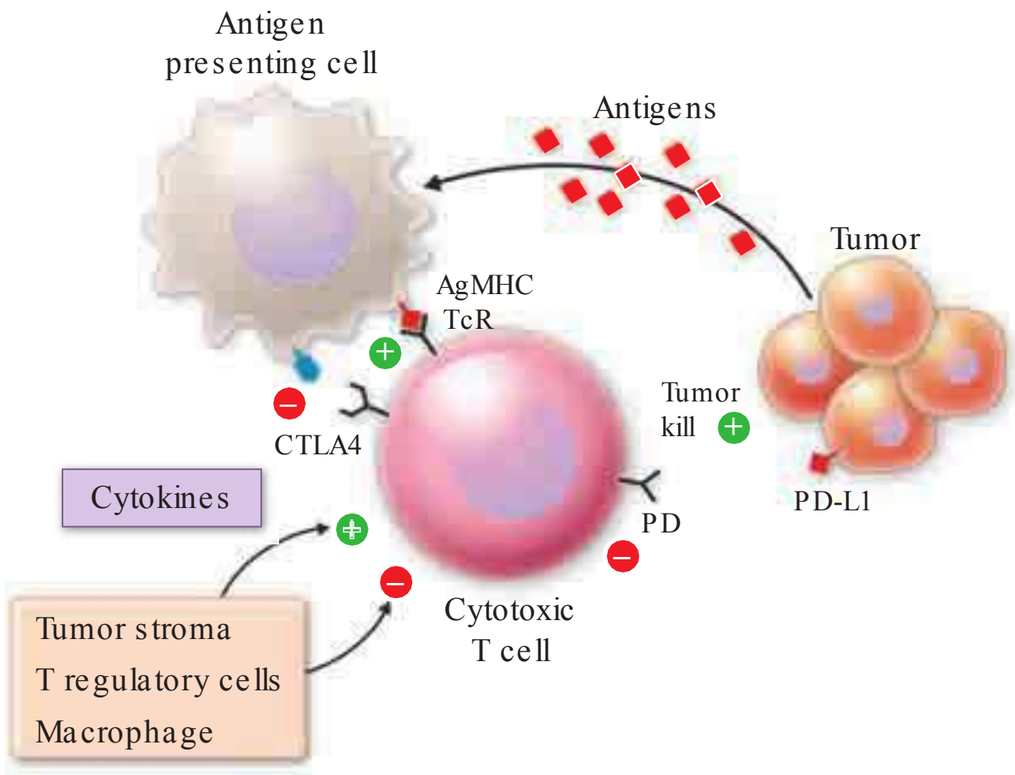


FIGURE 29-5
Tumors possess a microenvironment (tumor stroma) with immune cells including both helper T cells, suppressor T cells (both "regulatory" of other immune cell function), macrophages, and cytotoxic T cells. Cytokines found in the stroma and deriving from macrophages and regulatory T cells modulate the activities of cytotoxic T cells, which have the potential to kill tumor cells. Antigens released by tumor cells are taken up by Antigen Presenting Cells (APCs), also in the stroma. Antigens are processed by the APCs to peptides presented by the Major Histocompatibility Complex to T-cell antigen receptors, thus providing an (+) activation signal for the cytotoxic tumor cells to kill tumor cells bearing that antigen. Negative (–) signals inhibiting cytotoxic T cell action include the CTLA4 receptor (on T cells), interacting with the B7 family of negative regulatory signals from APCs, and the PD receptor (on T cells), interacting with the PD-L1 (–) signal coming from tumor cells expressing the PD-1 ligand (PD-l1). As both CTLA4 and PD1 signals attenuate the antitumor T cell response, strategies which inhibit CTLA4 and PD1 function are a means of stimulating cytotoxic T cell activity to kill tumor cells. Cytokines from other immune cells and macrophages can provide both (+) and (–) signals for T cell action, and are under investigation as novel immunoregulatory therapeutics.

the immune response. T e PD family of ligands and receptors also regulates macrophage function, present in tumor stroma. T ese actions raised the hypothesis that antibodies directed against the PD signaling axis (both anti-PD-L1 and anti-PD) might be useful in cancer treatment by allowing reactivation of the immune response against tumors. Indeed, nivolumab and lambrolizumab, both anti-PD antibodies, have shown evidence of important immune-mediated actions against certain solid tumors, including melanoma and lung cancers.

Already approved for clinical use in melanoma is ipilimumab, an antibody directed against the anti-CTLA4 (cytotoxic T lymphocyte antigen 4), which is expressed on T cells (not tumor cells), responds to signals from antigen-presenting cells (Fig. 29-5), and also downregulates the intensity of the T cell proliferative response to antigens derived from tumor cells. Indeed, manipulation of the CTLA4 axis was the first demonstration that purely immunoregulatory antibody strategies directed at T cell physiology could be safe and effective in the treatment of cancer, although it acts at a very early stage in T cell activation and can be considered somewhat nonspecific in its basis for T cell stimulation. Pembrolizumab, an anti-PD ligand blocking agent was also approved for melanoma, with a similar spectrum of potential adverse events, but acting in the tumor microenvironment. Indeed, prominent activation of autoimmune hepatic, endocrine, cutaneous, neurologic, and gastrointestinal responses is a basis for adverse events with the use of ipilimumab; the emergent use of glucocorticoids may be required to attenuate severe toxicities, which unfortunately can cause potential attenuation of antitumor effect. Importantly for the general internist, these events may occur late after exposure to ipilimumab while the patient may otherwise be enjoying sustained control of tumor growth owing to the beneficial actions of ipilimumab.

Another class of immunoregulatory antibody is the "bispecific" antibody blinatumomab, which was constructed to have an anti-CD19 antigen combining site as one valency of an antibody with anti-CD3 binding site as the other valency. T is antibody thus can bring T cells (with its anti-CD3 activity) close to B cells bearing the CD19 determinant. Blinatumomab is active in B cell neoplasms such as acute lymphocytic leukemia, which may not have prominent expression of the CD20 targeted by rituximab.

Antibody conjugates

Conjugates of antibodies with drugs and isotopes have also been shown to be effective in the treatment of cancer and have the intent of increasing the therapeutic index of the drug or isotope by delivering the toxic "warhead" directly to the tumor cell or tumor microenvironment. Ado-trastuzumab is a conjugate of the HER2/neu-directed trastuzumab and a highly toxic microtubule targeted drug (emtansine), which by itself is too toxic for human use; the antibody-drug conjugate shows valuable activity in patients with breast cancer who have developed resistance to the "naked" antibody. Brentuximab vedotin is an anti-CD30 antibody drug conjugate with a distinct microtubule poison with activity in neoplasms such as Hodgkin's lymphoma where the tumor cells frequently express CD30. Radioconjugates targeting CD20 on lymphomas have been approved for use (ibritumomab tiuxetan [Zevalin], using yttrium-90 or ^{131}I-tositumomab). Toxicity concerns have limited their use.

Cytokines

T ere are >70 separate proteins and glycoproteins with biologic effects in humans: interferon (IFN) α, β, and γ; interleukin (IL) 1 through 29 (so far); the tumor

necrosis factor (TNF) family (including lymphotoxin, TNF-related apoptosis-inducing ligand [TRAIL], CD40 ligand, and others); and the chemokine family. Only a fraction of these has been tested against cancer; only IFN-α and IL-2 are in routine clinical use.

About 20 different genes encode IFN-α, and their biologic effects are indistinguishable. IFN induces the expression of many genes, inhibits protein synthesis, and exerts a number of different effects on diverse cellular processes. T e two recombinant forms that are commercially available are IFN-α2a and -α2b. Interferon is not curative for any tumor but can induce partial responses in follicular lymphoma, hairy cell leukemia, CML, melanoma, and Kaposi's sarcoma. It has been used in the adjuvant setting in stage II melanoma, multiple myeloma, and follicular lymphoma, with uncertain effects on survival. It produces fever, fatigue, a flulike syndrome, malaise, myelosuppression, and depression and can induce clinically significant autoimmune disease. IFN-α is not generally the treatment of choice for any cancer.

IL-2 exerts its antitumor effects indirectly through augmentation of immune function. Its biologic activity is to promote the growth and activity of T cells and natural killer (NK) cells. High doses of IL-2 can produce tumor regression in certain patients with metastatic melanoma and renal cell cancer. About 2–5% of patients may experience complete remissions that are durable, unlike any other treatment for these tumors. IL-2 is associated with myriad clinical side effects, including intravascular volume depletion, capillary leak syndrome, adult respiratory distress syndrome, hypotension, fever, chills, skin rash, and impaired renal and liver function. Patients may require blood pressure support and intensive care to manage the toxicity. However, once the agent is stopped, most of the toxicities reverse completely within 3–6 days.

Ligand receptor–directed constructs

High-affinity receptors for cytokines have led to the design of cytokine-toxin recombinant fusion proteins, such as IL-2 expressed in frame with a fragment of diphtheria toxin. A commercially available construct has activity against certain T cell lymphomas. Likewise, the high-affinity folate receptor is the target for folate conjugated to chemotherapeutic agents. In both cases, the drug's utility derives from the internalization of the targeted receptor and cleavage of the active drug or toxin moiety.

SYSTEMIC RADIATION THERAPY

Although total-body irradiation has a role in preparing a patient to receive allogeneic stem cells, and antibodies as described above can specifically target radioisotopes, systemically administered isotopes of iodide salts have an important role in the treatment of thyroid neoplasms, owing to the selective upregulation of the iodide transporter in the tumor cell compartment. Likewise, isotopes of samarium and radium have been found useful in the palliation of symptoms from advanced bony metastases of prostate cancer owing to their selective deposition at the tumor–bone matrix interface, thereby potentially affecting the function of both tumor and stromal cells in the progressive growth of the metastatic deposit.

RESISTANCE TO CANCER TREATMENTS

Resistance mechanisms to the conventional cytotoxic agents were initially characterized in the late twentieth century as defects in drug uptake, metabolism, or export by tumor cells. T e multidrug resistance (mdr) gene defined in vitro in cell lines exposed to increasing concentrations of drugs led to the definition of a family of transport proteins that, when overexpressed, result in the facile transport of a variety of hydrophobic drugs out of the cancer cell. Although efforts to manipulate this transporter to promote drug residence in tumor cells have been pursued, none are clinically useful at this time. Drug-metabolizing enzymes such as cytidine deaminase are upregulated in resistant tumor cells, and this is the basis for so-called "high-dose cytarabine" regimens in the treatment of leukemia. Another resistance mechanism defined during this era involved increased expression of a drug's target, exemplified by amplification of the dihydrofolate reductase gene, in patients who had lost responsiveness to methotrexate, or mutation of topoisomerase II in tumors that relapsed after topoisomerase II modulator treatment.

A second class of resistance mechanisms involves loss of the cellular apoptotic mechanism activated after the engagement of a drug's target by the drug. T is occurs in a way that is heavily influenced by the biology of the particular tumor type. For example, decreased alkylguanine alkyltransferase defines a subset of glioblastoma patients with the prospect of greatest benefit from treatment with temozolomide, but has no predictive value for benefit from temozolomide in epithelial neoplasms. Likewise, ovarian cancers resistant to platinating agents have decreased expression of the proapoptotic gene bax. T ese types of findings have prompted the idea that responsive tumors to chemotherapeutic agents are populated by cells that express drug-related cell death controlling genes, creating in effect a state of "synthetic lethality" of the drug **(Chap. 26)** with the genes expressed in responsive tumors, analogous to the existence in yeast of mutations that are well tolerated in the absence of a physiologic stressor but become lethal in the presence of that stressor. In the case of tumors, the chemotherapy inducing the cell death response is the analogous physiologic stressor.

A third class of resistance mechanisms emerged from sequencing of the targets of agents directed at oncogenic

kinases. T us, patients with CML resistant to imatinib have acquired mutations in the ATP binding domain of $p210^{bcr\text{-}abl}$ in some cases, leading to the screening and design of agents with activity against the mutant proteins. Entirely analogous resistance mechanisms have emerged in patients with lung cancer treated with the EGFR antagonists gefitinib and erlotinib.

A final category of tumor resistance mechanisms to targeted agents includes the upregulation of alternate means of activating the pathway targeted by the agent. T us melanomas initially responsive to BRAF V600E antagonists such as vemurafenib may reactivate raf signaling by upregulating isoforms that can bypass the variant blocked by the drug. Likewise, inhibition of HER2/neu signaling in breast cancer cells can lead to the emergence of variants with distinct oncogenic signaling pathways such as PI3 kinase. Analogously in NSCLC, EGFR inhibitor treatment leads to the emergence of cells with a predominance of c-met protooncogene–dependent signaling in the resistant tumors.

T e susceptibility of a tumor to different treatments as a function of its expression of potential drug targets or their mutational profile has led to efforts to define the dominant pathways driving a patient's tumor by genomic techniques including whole exome sequencing. T e difficulty with applying such data to patient treatment is recognizing that these pathways may change during the natural history of a tumor and that different sites in a single patient may have tumors with different patterns of gene mutation.

SUPPORTIVE CARE DURING CANCER TREATMENT

MYELOSUPPRESSION

T e common cytotoxic chemotherapeutic agents almost invariably affect bone marrow function. Titration of this effect determines the MTD of the agent on a given schedule. T e normal kinetics of blood cell turnover influences the sequence and sensitivity of each of the formed elements. Polymorphonuclear leukocytes (PMNs; $t_{1/2}$ = 6–8 h), platelets ($t_{1/2}$ = 5–7 days), and red blood cells (RBCs; $t_{1/2}$ = 120 days) have most, less, and least susceptibility, respectively, to usually administered cytotoxic agents. T e nadir count of each cell type in response to classes of agents is characteristic. Maximal neutropenia occurs 6–14 days after conventional doses of anthracyclines, antifolates, and antimetabolites. Alkylating agents differ from each other in the timing of cytopenias. Nitrosoureas, DTIC, and procarbazine can display delayed marrow toxicity, first appearing 6 weeks after dosing.

Complications of myelosuppression result from the predictable sequelae of the missing cells' function. Febrile neutropenia refers to the clinical presentation of fever (one temperature ≥38.5°C or three readings ≥38°C but ≤38.5°C per 24 h) in a neutropenic patient with an uncontrolled neoplasm involving the bone marrow or, more usually, in a patient undergoing treatment with cytotoxic agents. Mortality from uncontrolled infection varies inversely with the neutrophil count. If the nadir neutrophil count is >1000/μL, there is little risk; if <500/μL, risk of death is markedly increased. Management of febrile neutropenia has conventionally included empirical coverage with antibiotics for the duration of neutropenia **(Chap. 30)**. Selection of antibiotics is governed by the expected association of infections with certain underlying neoplasms; careful physical examination (with scrutiny of catheter sites, dentition, mucosal surfaces, and perirectal and genital orifices by gentle palpation); chest x-ray; and Gram stain and culture of blood, urine, and sputum (if any) to define a putative site of infection. In the absence of any originating site, a broadly acting β-lactam with anti-Pseudomonas activity, such as ceftazidime, is begun empirically. T e addition of vancomycin to cover potential cutaneous sites of origin (until these are ruled out or shown to originate from methicillin-sensitive organisms) or metronidazole or imipenem for abdominal or other sites favoring anaerobes reflects modifications tailored to individual patient presentations. T e coexistence of pulmonary compromise raises a distinct set of potential pathogens, including Legionella, Pneumocystis, and fungal agents that may require further diagnostic evaluations, such as bronchoscopy with bronchoalveolar lavage. Febrile neutropenic patients can be stratified broadly into two prognostic groups. T e first, with expected short duration of neutropenia and no evidence of hypotension or abdominal or other localizing symptoms, may be expected to do well even with oral regimens, e.g., ciprofloxacin or moxifloxacin, or amoxicillin plus clavulanic acid. A less favorable prognostic group is patients with expected prolonged neutropenia, evidence of sepsis, and end organ compromise, particularly pneumonia. T ese patients require tailoring of their antibiotic regimen to their underlying presentation, with frequent empirical addition of antifungal agents if fever and neutropenia persists for 7 days without identification of an adequately treated organism or site.

Transfusion of granulocytes has no role in the management of febrile neutropenia, owing to their exceedingly short half-life, mechanical fragility, and clinical syndromes of pulmonary compromise with leukostasis after their use. Instead, colony-stimulating factors (CSFs) are used to augment bone marrow production of PMNs. Early-acting factors such as IL-1, IL-3, and stem cell factor have not been as useful clinically as late-acting, lineage-specific factors such as granulocyte colony-stimulating factor (G-CSF) or GM-CSF, erythropoietin (EPO), thrombopoietin, IL-6, and IL-11. CSFs may easily become overused in oncology practice. T e

settings in which their use has been proved effective are limited. G-CSF, GM-CSF, EPO, and IL-11 are currently approved for use. T e American Society of Clinical Oncology has developed practice guidelines for the use of G-CSF and GM-CSF **(Table 29-7)**.

TABLE 29-7

INDICATIONS FOR THE CLINICAL USE OF G-CSF OR GM-CSF

Preventive Uses
With the first cycle of chemotherapy (so-called primary CSF administration)
Not needed on a routine basis
Use if the probability of febrile neutropenia is ≥20%
Use if patient has preexisting neutropenia or active infection
Age >65 years treated for lymphoma with curative intent or other tumor treated by similar regimens
Poor performance status
Extensive prior chemotherapy
Dose-dense regimens in a clinical trial or with strong evidence of benefit
With subsequent cycles if febrile neutropenia has previously occurred (so-called secondary CSF administration)
Not needed after short-duration neutropenia without fever
Use if patient had febrile neutropenia in previous cycle
Use if prolonged neutropenia (even without fever) delays therapy
Therapeutic Uses
Afebrile neutropenic patients
No evidence of benefit
Febrile neutropenic patients
No evidence of benefit
May feel compelled to use in the face of clinical deterioration from sepsis, pneumonia, or fungal infection, but benefit unclear
In bone marrow or peripheral blood stem cell transplantation
Use to mobilize stem cells from marrow
Use to hasten myeloid recovery
In acute myeloid leukemia
G-CSF of minor or no benefit
GM-CSF of no benefit and may be harmful
In myelodysplastic syndromes
Not routinely beneficial
Use intermittently in subset with neutropenia and recurrent infection
What Dose and Schedule Should Be Used?
G-CSF: 5 mg/kg per day subcutaneously
GM-CSF: 250 mg/m^2 per day subcutaneously
Pegfilgrastim: one dose of 6 mg 24 h after chemotherapy
When Should Therapy Begin and End?
When indicated, start 24–72 h after chemotherapy
Continue until absolute neutrophil count is 10,000/μL
Do not use concurrently with chemotherapy or radiation therapy

Abbreviations: CSF, cerebrospinal fluid; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.
Source: From the American Society of Clinical Oncology: J Clin Oncol 24:3187, 2006.

Primary prophylaxis (i.e., shortly after completing chemotherapy to reduce the nadir) administers G-CSF to patients receiving cytotoxic regimens associated with a 20% incidence of febrile neutropenia. "Dose-dense" regimens, where cycling of chemotherapy is intended to be completed without delay of administered doses, may also benefit, but such patients should be on a clinical trial. Administration of G-CSF in these circumstances has reduced the incidence of febrile neutropenia in several studies by about 50%. Most patients, however, receive regimens that do not have such a high risk of expected febrile neutropenia, and therefore most patients initially should not receive G-CSF or GM-CSF. Special circumstances—such as a documented history of febrile neutropenia with the regimen in a particular patient or categories of patients at increased risk, such as patients older than age 65 years with aggressive lymphoma treated with curative chemotherapy regimens; extensive compromise of marrow by prior radiation or chemotherapy; or active, open wounds or deep-seated infection—may support primary treatment with G-CSF or GM-CSF. Administration of G-CSF or GM-CSF to afebrile neutropenic patients or to patients with low-risk febrile neutropenia is not recommended, and patients receiving concomitant chemoradiation treatment, particularly those with thoracic neoplasms, likewise are not generally recommended for treatment. In contrast, administration of G-CSF to high-risk patients with febrile neutropenia and evidence of organ compromise including sepsis syndrome, invasive fungal infection, concurrent hospitalization at the time fever develops, pneumonia, profound neutropenia ($<0.1 \times 10^9$/L), or age >65 years is reasonable.

Secondary prophylaxis refers to the administration of CSFs in patients who have experienced a neutropenic complication from a prior cycle of chemotherapy; dose reduction or delay may be a reasonably considered alternative. G-CSF or GM-CSF is conventionally started 24–72 h after completion of chemotherapy and continued until a PMN count of 10,000/μL is achieved, unless a "depot" preparation of G-CSF such as pegfilgrastim is used, where one dose is administered at least 14 days before the next scheduled administration of chemotherapy. Also, patients with myeloid leukemias undergoing induction therapy may have a slight reduction in the duration of neutropenia if G-CSF is commenced after completion of therapy and may be of particular value in elderly patients, but the influence on long-term outcome has not been defined. GM-CSF probably has a more restricted utility than G-CSF, with its use currently limited to patients after autologous bone marrow transplants, although proper head-to-head comparisons with G-CSF have not been conducted in most instances. GM-CSF may be associated with more systemic side effects.

Dangerous degrees of thrombocytopenia do not frequently complicate the management of patients with

solid tumors receiving cytotoxic chemotherapy (with the possible exception of certain carboplatin-containing regimens), but they are frequent in patients with certain hematologic neoplasms where marrow is infiltrated with tumor. Severe bleeding related to thrombocytopenia occurs with increased frequency at platelet counts <20,000/μL and is very prevalent at counts <5000/μL.

T e precise "trigger" point at which to transfuse patients has been defined as a platelet count of 10,000/μL or less in patients without medical comorbidities that may increase the risk of bleeding. T is issue is important not only because of the costs of frequent transfusion, but unnecessary platelet transfusions expose the patient to the risks of allosensitization and loss of value from subsequent transfusion owing to rapid platelet clearance, as well as the infectious and hypersensitivity risks inherent in any transfusion. Prophylactic transfusions to keep platelets >20,000/μL are reasonable in patients with leukemia who are stressed by fever or concomitant medical conditions (the threshold for transfusion is 10,000/μL in patients with solid tumors and no other bleeding diathesis or physiologic stressors such as fever or hypotension, a level that might also be reasonably considered for leukemia patients who are thrombocytopenic but not stressed or bleeding). In contrast, patients with myeloproliferative states may have functionally altered platelets despite normal platelet counts, and transfusion with normal donor platelets should be considered for evidence of bleeding in these patients. Careful review of medication lists to prevent exposure to nonsteroidal anti-inflammatory agents and maintenance of clotting factor levels adequate to support near-normal prothrombin and partial thromboplastin time tests are important in minimizing the risk of bleeding in the thrombocytopenic patient.

Certain cytokines in clinical investigation have shown an ability to increase platelets (e.g., IL-6, IL-1, thrombopoietin), but clinical benefit and safety are not yet proven. IL-11 (oprelvekin) is approved for use in the setting of expected thrombocytopenia, but its effects on platelet counts are small, and it is associated with side effects such as headache, fever, malaise, syncope, cardiac arrhythmias, and fluid retention. Eltrombopag and romiplostim are thrombopoietin agonists with demonstrated efficacy in certain thrombocytopenic states, but they have not been systematically studied in chemotherapy-induced thrombocytopenia.

Anemia associated with chemotherapy can be managed by transfusion of packed RBCs. Transfusion is not undertaken until the hemoglobin falls to <80 g/L (8 g/dL), compromise of end organ function occurs, or an underlying condition (e.g., coronary artery disease) calls for maintenance of hemoglobin >90 g/L (9 g/dL). Patients who are to receive therapy for >2 months on a "stable" regimen and who are likely to require continuing transfusions are also candidates for erythropoietin (EPO). Randomized trials in certain tumors have raised the possibility that EPO use may promote tumor-related adverse events. T is information should be considered in the care of individual patients. In the event EPO treatment is undertaken, maintenance of hemoglobin of 90–100 g/L (9–10 g/dL) should be the target. In the setting of adequate iron stores and serum EPO levels <100 ng/mL, EPO, 150 U three times a week, can produce a slow increase in hemoglobin over about 2 months of administration. Depot formulations can be administered less frequently. It is unclear whether higher hemoglobin levels, up to 110–120 g/L (11–12 g/dL), are associated with improved quality of life to a degree that justifies the more intensive EPO use. Efforts to achieve levels at or above 120 g/L (12 g/dL) have been associated with increased thromboses and mortality rates. EPO may rescue hypoxemic cells from death and contribute to tumor radioresistance.

NAUSEA AND VOMITING

T e most common side effect of chemotherapy administration is nausea, with or without vomiting. Nausea may be acute (within 24 h of chemotherapy), delayed (>24 h), or anticipatory of the receipt of chemotherapy. Patients may be likewise stratified for their risk of susceptibility to nausea and vomiting, with increased risk in young, female, heavily pretreated patients without a history of alcohol or drug use but with a history of motion or morning sickness. Antineoplastic agents vary in their capacity to cause nausea and vomiting. Highly emetogenic drugs (>90%) include mechlorethamine, streptozotocin, DTIC, cyclophosphamide at >1500 mg/m^2, and cisplatin; moderately emetogenic drugs (30–90% risk) include carboplatin, cytosine arabinoside (>1 mg/m^2), ifosfamide, conventional-dose cyclophosphamide, and anthracyclines; low-risk (10–30%) agents include 5FU, taxanes, etoposide, and bortezomib, with minimal risk (<10%) afforded by treatment with antibodies, bleomycin, busulfan, fludarabine, and vinca alkaloids. Emesis is a reflex caused by stimulation of the vomiting center in the medulla. Input to the vomiting center comes from the chemoreceptor trigger zone (CTZ) and afferents from the peripheral gastrointestinal tract, cerebral cortex, and heart. T e different emesis "syndromes" require distinct management approaches. In addition, a conditioned reflex may contribute to anticipatory nausea arising after repeated cycles of chemotherapy. Accordingly, antiemetic agents differ in their locus and timing of action. Combining agents from different classes or the sequential use of different classes of agent is the cornerstone of successful management of chemotherapy-induced nausea and vomiting. Of great importance are the prophylactic administration of agents and such psychological techniques as the maintenance of a supportive milieu, counseling, and relaxation to augment the action of antiemetic agents.

Serotonin antagonists (5-HT_3) and neurokinin 1 (NK1) receptor antagonists are useful in "high-risk" chemotherapy regimens. T e combination acts at both peripheral gastrointestinal and CNS sites that control nausea and vomiting. For example, the 5-HT_3 blocker dolasetron, 100 mg intravenously or orally; dexamethasone, 12 mg; and the NK1 antagonist aprepitant, 125 mg orally, are combined on the day of administration of severely emetogenic regimens, with repetition of dexamethasone (8 mg) and aprepitant (80 mg) on days 2 and 3 for delayed nausea. Alternate 5-HT_3 antagonists include ondansetron, given as 0.15 mg/kg intravenously for three doses just before and at 4 and 8 h after chemotherapy; palonosetron at 0.25 mg over 30 s, 30 min before chemotherapy; and granisetron, given as a single dose of 0.01 mg/kg just before chemotherapy. Emesis from moderately emetic chemotherapy regimens may be prevented with a 5-HT_3 antagonist and dexamethasone alone for patients not receiving doxorubicin and cyclophosphamide combinations; the latter combination requires the 5-HT_3/dexamethasone/aprepitant on day 1 but aprepitant alone on days 2 and 3. Emesis from low-emetic-risk regimens may be prevented with 8 mg of dexamethasone alone or with non-5-HT_3, non-NK1 antagonist approaches including the following.

Antidopaminergic phenothiazines act directly at the CTZ and include prochlorperazine (Compazine), 10 mg intramuscularly or intravenously, 10–25 mg orally, or 25 mg per rectum every 4–6 h for up to four doses; and thiethylperazine, 10 mg by potentially all of the above routes every 6 h. Haloperidol is a butyrophenone dopamine antagonist given at 1 mg intramuscularly or orally every 8 h. Antihistamines such as diphenhydramine have little intrinsic antiemetic capacity but are frequently given to prevent or treat dystonic reactions that can complicate use of the antidopaminergic agents. Lorazepam is a short-acting benzodiazepine that provides an anxiolytic effect to augment the effectiveness of a variety of agents when used at 1–2 mg intramuscularly, intravenously, or orally every 4–6 h. Metoclopramide acts on peripheral dopamine receptors to augment gastric emptying and is used in high doses for highly emetogenic regimens (1–2 mg/kg intravenously 30 min before chemotherapy and every 2 h for up to three additional doses as needed); intravenous doses of 10–20 mg every 4–6 h as needed or 50 mg orally 4 h before and 8 and 12 h after chemotherapy are used for moderately emetogenic regimens. 5-9-Tetrahydrocannabinol (Marinol) is a rather weak antiemetic compared to other available agents, but it may be useful for persisting nausea and is used orally at 10 mg every 3–4 h as needed.

DIARRHEA

Regimens that include 5FU infusions and/or irinotecan may produce severe diarrhea. Similar to the vomiting syndromes, chemotherapy-induced diarrhea may be immediate or can occur in a delayed fashion up to 48–72 h after the drugs. Careful attention to maintained hydration and electrolyte repletion, intravenously if necessary, along with antimotility treatments such as "high-dose" loperamide, commenced with 4 mg at the first occurrence of diarrhea, with 2 mg repeated every 2 h until 12 h without loose stools, not to exceed a total daily dose of 16 mg. Octreotide (100–150 μg), a somatostatin analogue, or opiate-based preparations may be considered for patients not responding to loperamide.

MUCOSITIS

Irritation and inflammation of the mucous membranes particularly afflicting the oral and anal mucosa, but potentially involving the gastrointestinal tract, may accompany cytotoxic chemotherapy. Mucositis is due to damage to the proliferating cells at the base of the mucosal squamous epithelia or in the intestinal crypts. Topical therapies, including anesthetics and barrier-creating preparations, may provide symptomatic relief in mild cases. Palifermin or keratinocyte growth factor, a member of the fibroblast growth factor family, is effective in preventing severe mucositis in the setting of high-dose chemotherapy with stem cell transplantation for hematologic malignancies. It may also prevent or ameliorate mucositis from radiation.

ALOPECIA

Chemotherapeutic agents vary widely in causing alopecia, with anthracyclines, alkylating agents, and topoisomerase inhibitors reliably causing near-total alopecia when given at therapeutic doses. Antimetabolites are more variably associated with alopecia. Psychological support and the use of cosmetic resources are to be encouraged, and "chemo caps" that reduce scalp temperature to decrease the degree of alopecia should be discouraged, particularly during treatment with curative intent of neoplasms, such as leukemia or lymphoma, or in adjuvant breast cancer therapy. T e richly vascularized scalp can certainly harbor micrometastatic or disseminated disease.

GONADAL DYSFUNCTION AND PREGNANCY

Cessation of ovulation and azoospermia reliably result from alkylating agent– and topoisomerase poison–containing regimens. T e duration of these effects varies with age and sex. Males treated for Hodgkin's disease with mechlorethamine- and procarbazine-containing regimens are effectively sterile, whereas fertility usually returns after regimens that include cisplatin, vinblastine, or etoposide and after bleomycin for testicular

cancer. Sperm banking before treatment may be considered to support patients likely to be sterilized by treatment. Females experience amenorrhea with anovulation after alkylating agent therapy; they are likely to recover normal menses if treatment is completed before age 30 but unlikely to recover menses after age 35. Even those who regain menses usually experience premature menopause. Because the magnitude and extent of decreased fertility can be difficult to predict, patients should be counseled to maintain effective contraception, preferably by barrier means, during and after therapy. Resumption of efforts to conceive should be considered in the context of the patient's likely prognosis. Hormone replacement therapy should be undertaken in women who do not have a hormonally responsive tumor. For patients who have had a hormone-sensitive tumor primarily treated by a local modality, conventional practice would counsel against hormone replacement, but this issue is under investigation.

Chemotherapy agents have variable effects on the success of pregnancy. All agents tend to have increased risk of adverse outcomes when administered during the first trimester, and strategies to delay chemotherapy, if possible, until after this milestone should be considered if the pregnancy is to continue to term. Patients in their second or third trimester can be treated with most regimens for the common neoplasms afflicting women in their childbearing years, with the exception of antimetabolites, particularly antifolates, which have notable teratogenic or fetotoxic effects throughout pregnancy. T e need for anticancer chemotherapy per se is infrequently a clear basis to recommend termination of a concurrent pregnancy, although each treatment strategy in this circumstance must be tailored to the individual needs of the patient.

SPECIAL ISSUES WITH TARGETED TREATMENTS

Treatment with EGFR-directed small molecules (e.g., erlotinib, afatinib, lapatinib), antibodies (e.g., cetuximab, panitumumab), and mTOR antagonists (e.g., everolimus, temsirolimus) reliably produces an acneiform rash that can be a source of distress to patients and can be ameliorated with topically applied clindamycin gels and low-potency corticosteroid creams. Diarrhea frequently accompanies tyrosine kinase inhibitor administration and may respond to antimotility agents such as loperamide or stool-bulking agents.

Anti-VEGFR-directed treatments, including the specific antibody bevacizumab, and the "multikinase" inhibitors with anti VEGFR activity, such as sorafenib, sunitinib, and pazopanib, reliably produce hypertension in a significant fraction of patients that typically can be treated with lisinopril, amlodipine, or clonidine alone or in combination. More difficult to treat is proteinuria with resultant azotemia; this can be a basis for discontinuing treatment depending on the clinical context. T yroid function is prominently affected by chronic exposure to this group of multikinase inhibitors including sorafenib and pazopanib, and periodic surveillance of thyroid-stimulating hormone and thyroxine (T_4) levels during treatment is reasonable. Gastrointestinal perforations, arterial thromboses, and hemorrhage likewise have no specific treatments and may be a basis to avoid this class of agents. Palmar-plantar dysesthesia ("hand-foot syndrome") can be seen after administration of these agents (as well as some cytotoxic agents including gemcitabine and liposomal preparations of doxorubicin) and is a basis for considering dose reduction if not responsive to topical emollients and analgesics.

Protein kinase antagonists as a class have been associated with poorly predicted hepatic and cardiac toxicities (imatinib, dasatinib, sorafenib, pazopanib) or cardiac conduction deficits including prolonged QT interval (pazopanib). T e occurrence of new cardiac or liver abnormalities in a patient receiving treatment with a protein kinase antagonist should lead to a consideration of the risk versus benefit and the possible relation of the agent to the new adverse event. T e existence of prior cardiac dysfunction is a relative contraindication to the use of certain targeted therapies (e.g., trastuzumab), although each patient's needs should be individualized. **Chronic ef ects of cancer treatment are reviewed in Chap. 57.**

CHAPTER 30

INFECTIONS IN PATIENTS WITH CANCER

Robert W. Finberg

Infections are a common cause of death and an even more common cause of morbidity in patients with a wide variety of neoplasms. Autopsy studies show that most deaths from acute leukemia and half of deaths from lymphoma are caused directly by infection. With more intensive chemotherapy, patients with solid tumors have also become more likely to die of infection. Fortunately, an evolving approach to prevention and treatment of infectious complications of cancer has decreased infection-associated mortality rates and will probably continue to do so. T is accomplishment has resulted from three major steps:

1. T e practice of using "early empirical" antibiotics reduced mortality rates among patients with leukemia and bacteremia from 84% in 1965 to 44% in 1972. Recent studies suggest that the mortality rate due to infection in febrile neutropenic patients dropped to <10% by 2013. T is dramatic improvement is attributed to early intervention with appropriate antimicrobial therapy.
2. "Empirical" antifungal therapy has also lowered the incidence of disseminated fungal infection, with dramatic decreases in mortality rates. An antifungal agent is administered—on the basis of likely fungal infection—to neutropenic patients who, after 4–7 days of antibiotic therapy, remain febrile but have no positive cultures.
3. Use of antibiotics for afebrile neutropenic patients as broad-spectrum prophylaxis against infections has decreased both mortality and morbidity even further. T e current approach to treatment of severely neutropenic patients (e.g., those receiving high-dose chemotherapy for leukemia or high-grade lymphoma) is based on initial prophylactic therapy at the onset of neutropenia, subsequent "empirical" antibacterial therapy targeting the organisms whose involvement is likely in light of physical findings (most often fever alone), and finally "empirical" antifungal therapy based on the known likelihood that fungal infection will become a serious issue after 4–7 days of broad-spectrum antibacterial therapy.

A physical predisposition to infection in patients with cancer **(Table 30-1)** can be a result of the neoplasm's production of a break in the skin. For example, a squamous cell carcinoma may cause local invasion of the epidermis, which allows bacteria to gain access to subcutaneous tissue and permits the development of cellulitis. T e artificial closing of a normally patent orifice can also predispose to infection; for example, obstruction of a ureter by a tumor can cause urinary tract infection, and obstruction of the bile duct can cause cholangitis. Part of the host's normal defense against infection depends on the continuous emptying of a viscus; without emptying, a few bacteria that are present as a result of bacteremia or local transit can multiply and cause disease.

A similar problem can affect patients whose lymph node integrity has been disrupted by radical surgery, particularly patients who have had radical node dissections. A common clinical problem following radical mastectomy is the development of cellulitis (usually caused by streptococci or staphylococci) because of lymphedema and/or inadequate lymph drainage. In most cases, this problem can be addressed by local measures designed to prevent fluid accumulation and breaks in the skin, but antibiotic prophylaxis has been necessary in refractory cases.

A life-threatening problem common to many cancer patients is the loss of the reticuloendothelial capacity to clear microorganisms after splenectomy, which may be performed as part of the management of hairy cell leukemia, chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML) and in Hodgkin's disease. Even after curative therapy for the underlying disease, the lack of a spleen predisposes such patients to rapidly fatal infections. T e loss of the spleen through trauma similarly predisposes the normal host to overwhelming

TABLE 30-1

DISRUPTION OF NORMAL BARRIERS THAT MAY PREDISPOSE TO INFECTIONS IN PATIENTS WITH CANCER

TYPE OF DEFENSE	SPECIFIC LESION	CELLS INVOLVED	ORGANISM	CANCER ASSOCIATION	DISEASE
Physical barrier	Breaks in skin	Skin epithelial cells	Staphylococci, streptococci	Head and neck, squamous cell carcinoma	Cellulitis, extensive skin infection
Emptying of fluid collections	Occlusion of orifices: ureters, bile duct, colon	Luminal epithelial cells	Gram-negative bacilli	Renal, ovarian, biliary tree, metastatic diseases of many cancers	Rapid, overwhelming bacteremia; urinary tract infection
Lymphatic function	Node dissection	Lymph nodes	Staphylococci, streptococci	Breast cancer surgery	Cellulitis
Splenic clearance of microorganisms	Splenectomy	Splenic reticuloendothelial cells	Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Babesia, Capnocytophaga canimorsus	Hodgkin's disease, leukemia	Rapid, overwhelming sepsis
Phagocytosis	Lack of granulocytes	Granulocytes (neutrophils)	Staphylococci, streptococci, enteric organisms, fungi	Acute myeloid and acute lymphocytic leukemias, hairy cell leukemia	Bacteremia
Humoral immunity	Lack of antibody	B cells	S. pneumoniae, H. influenzae, N. meningitidis	Chronic lymphocytic leukemia, multiple myeloma	Infections with encapsulated organisms, sinusitis, pneumonia
Cellular immunity	Lack of T cells	T cells and macrophages	Mycobacterium tuberculosis, Listeria, herpesviruses, fungi, intracellular parasites	Hodgkin's disease, leukemia, T cell lymphoma	Infections with intracellular bacteria, fungi, parasites; virus reactivation

infection throughout life. The splenectomized patient should be counseled about the risks of infection with certain organisms, such as the protozoan Babesia and Capnocytophaga canimorsus, a bacterium carried in the mouths of animals. Because encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis) are the organisms most commonly associated with postsplenectomy sepsis, splenectomized persons should be vaccinated (and revaccinated; **Table 30-2**) against the capsular polysaccharides of these organisms. Many clinicians recommend giving splenectomized patients a small supply of antibiotics effective against S. pneumoniae, N. meningitidis, and H. influenzae to avert rapid, overwhelming sepsis in the event that they cannot present for medical attention immediately after the onset of fever or other signs or symptoms of bacterial infection. A few tablets of amoxicillin/clavulanic acid (or levofloxacin if resistant strains of S. pneumoniae are prevalent locally) are a reasonable choice for this purpose.

The level of suspicion of infections with certain organisms should depend on the type of cancer diagnosed **(Table 30-3)**. Diagnosis of multiple myeloma or CLL should alert the clinician to the possibility of hypogammaglobulinemia. While immunoglobulin replacement therapy can be effective, in most cases prophylactic antibiotics are a cheaper, more convenient method of eliminating bacterial infections in CLL patients with hypogammaglobulinemia. Patients with acute lymphocytic leukemia (ALL), patients with non-Hodgkin's lymphoma, and all cancer patients treated with high-dose glucocorticoids (or glucocorticoid-containing chemotherapy regimens) should receive antibiotic prophylaxis for Pneumocystis infection (Table 30-3) for the duration of their chemotherapy. In addition to exhibiting susceptibility to certain infectious organisms, patients with cancer are likely to manifest their infections in characteristic ways. For example, fever—generally a sign of infection in normal hosts—continues to be a reliable indicator in neutropenic patients. In contrast, patients receiving glucocorticoids and agents that impair T cell function and cytokine secretion may have serious infections in the absence of fever. Similarly, neutropenic patients commonly present with cellulitis without purulence and with pneumonia without sputum or even x-ray findings (see below).

The use of monoclonal antibodies that target B and T cells as well as drugs that interfere with lymphocyte signal transduction events is associated with reactivation

TABLE 30-2

VACCINATION OF CANCER PATIENTS RECEIVING CHEMOTHERAPY[a]

	USE IN INDICATED PATIENTS		
VACCINE	INTENSIVE CHEMOTHERAPY	HODGKIN'S DISEASE	HEMATOPOIETIC STEM CELL TRANSPLANTATION
Diphtheria-tetanus[b]	Primary series and boosters as necessary	No special recommendation	3 doses given 6–12 months after transplantation
Poliomyelitis[c]	Complete primary series and boosters	No special recommendation	3 doses given 6–12 months after transplantation
Haemophilus influenzae type b conjugate	Primary series and booster for children	Single dose for adults	3 doses given 6–12 months after transplantation (separated by 1 month)
Human papillomavirus (HPV)	Quadrivalent HPV vaccine is approved for males and females 9–26 years of age. Check Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines) for updated recommendations.	Quadrivalent HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (www.cdc.gov/vaccines) for updated recommendations.	Quadrivalent HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (www.cdc.gov/vaccines) for updated recommendations.
Hepatitis A	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle
Hepatitis B	Same as for normal hosts	As indicated for normal hosts on the basis of occupation and lifestyle	3 doses given 6–12 months after transplantation
Pneumococcal conjugate vaccine (PCV13) Pneumococcal polysaccharide vaccine (PPSV23)[d]	Finish series prior to chemotherapy if possible	Patients with splenectomy should receive PPSV23.	Three doses of PCV13, beginning 3–6 months after transplantation, are followed by a dose of PPSV23 at least 8 weeks later. A second PPSV23 dose can be given 5 years later.
Quadrivalent meningococcal vaccine[e]	Should be administered to splenectomized patients and to patients living in endemic areas, including college students in dormitories	Should be administered to splenectomized patients and to patients living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years.	Should be administered to splenectomized patients and to patients living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years.
Influenza	Seasonal immunization	Seasonal immunization	Seasonal immunization (A seasonal dose is recommended and can be given as early as 4 months after transplantation; if given <6 months after transplantation, an additional dose is recommended.)
Measles/mumps/rubella	Contraindicated	Contraindicated during chemotherapy	After 24 months in patients without graft-versus-host disease
Varicella-zoster virus[f]	Contraindicated[g]	Contraindicated	Contraindicated (CDC recommends use on a case-by-case basis following reevaluation.)

[a]The latest recommendations by the Advisory Committee on Immunization Practices and the CDC guidelines can be found at http://www.cdc.gov/vaccines.
[b]A single dose of TDaP (tetanus–diphtheria–acellular pertussis), followed by a booster dose of Td (tetanus-diphtheria) every 10 years, is recommended for adults.
[c]Live-virus vaccine is contraindicated; inactivated vaccine should be used.
[d]Two types of vaccine are used to prevent pneumococcal disease. A conjugate vaccine active against 13 serotypes (13-valent pneumococcal conjugate vaccine, or PCV13) is currently administered in three separate doses to all children. A polysaccharide vaccine active against 23 serotypes (23-valent pneumococcal polysaccharide vaccine, or PPSV23) elicits titers of antibody lower than those achieved with the conjugate vaccine, and immunity may wane more rapidly. Because the ablative chemotherapy given to recipients of hematopoietic stem cell transplants (HSCTs) eradicates immunologic memory, revaccination is recommended for all such patients. Vaccination is much more effective once immunologic reconstitution has occurred; however, because of the need to prevent serious disease, pneumococcal vaccine should be administered 6–12 months after transplantation in most cases. Because PPSV23 includes serotypes not present in PCV13, HSCT recipients should receive a dose of PPSV23 at least 8 weeks after the last dose of PCV13. Although antibody titers from PPSV23 clearly decay, experience with multiple doses of PPSV23 is limited, as are data on the safety, toxicity, or efficacy of such a regimen. For this reason, the CDC currently recommends the administration of one additional dose of PPSV23 at least 5 years after the last dose to immunocompromised patients, including transplant recipients, as well as patients with Hodgkin's disease, multiple myeloma, lymphoma, or generalized malignancies. Beyond this single additional dose, further doses are not recommended at this time.
[e]Meningococcal conjugate vaccine MenACWY is recommended for adults ≤55 years old, and meningococcal polysaccharide vaccine (MPSV4) is recommended for those ≥56 years old.
[f]Includes both varicella vaccine for children and zoster vaccine for adults.
[g]Contact the manufacturer for more information on use in children with acute lymphocytic leukemia.

TABLE 30-3

INFECTIONS ASSOCIATED WITH SPECIFIC TYPES OF CANCER

CANCER	UNDERLYING IMMUNE ABNORMALITY	ORGANISMS CAUSING INFECTION
Multiple myeloma	Hypogammaglobulinemia	Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis
Chronic lymphocytic leukemia	Hypogammaglobulinemia	S. pneumoniae, H. influenzae, N. meningitidis
Acute myeloid or lymphocytic leukemia	Granulocytopenia, skin and mucous membrane lesions	Extracellular gram-positive and gram-negative bacteria, fungi
Hodgkin's disease	Abnormal T cell function	Intracellular pathogens (Mycobacterium tuberculosis, Listeria, Salmonella, Cryptococcus, Mycobacterium avium); herpesviruses
Non-Hodgkin's lymphoma and acute lymphocytic leukemia	Glucocorticoid chemotherapy, T and B cell dysfunction	Pneumocystis
Colon and rectal tumors	Local abnormalities[a]	Streptococcus bovis biotype 1 (bacteremia)
Hairy cell leukemia	Abnormal T cell function	Intracellular pathogens (M. tuberculosis, Listeria, Cryptococcus, M. avium)

[a]The reason for this association is not well defined.

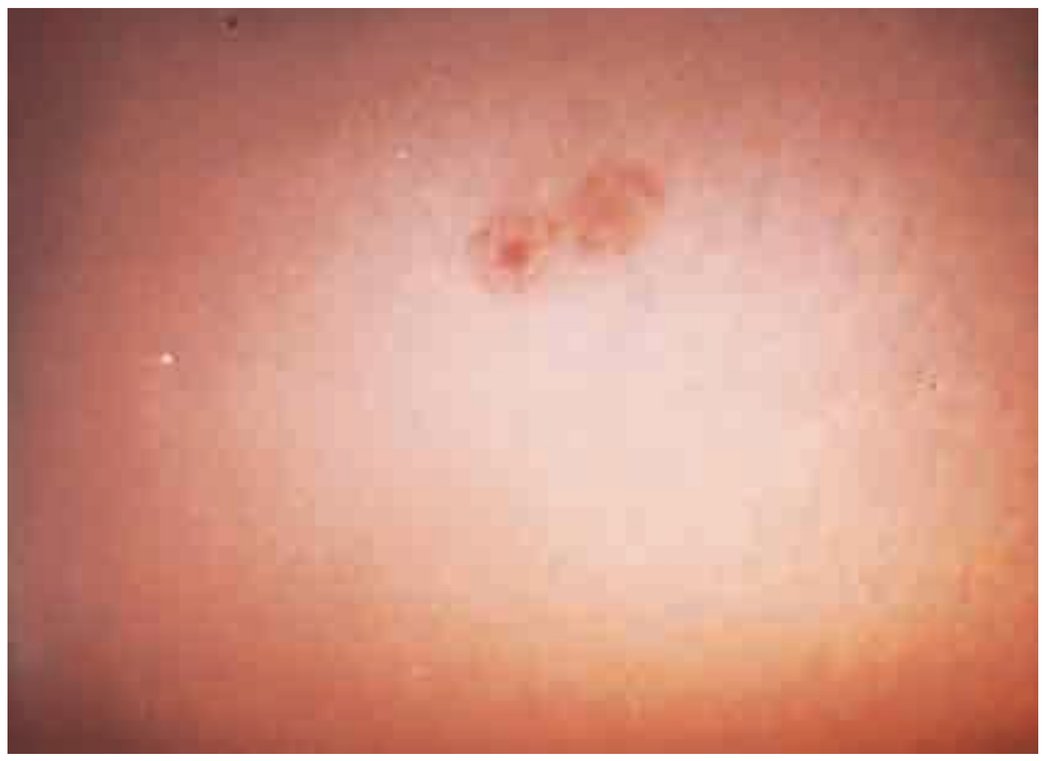
of latent infections. The use of rituximab, the antibody to CD20 (a B cell surface protein), is associated with the development of reactivation tuberculosis as well as other latent viral infections, including hepatitis B and cytomegalovirus (CMV) infection. Like organ transplant recipients, patients with latent bacterial disease (like tuberculosis) and latent viral disease (like herpes simplex or zoster) should be carefully monitored for reactivation disease.

SYSTEM-SPECIFIC SYNDROMES

SKIN-SPECIFIC SYNDROMES

Skin lesions are common in cancer patients, and the appearance of these lesions may permit the diagnosis of systemic bacterial or fungal infection. While cellulitis caused by skin organisms such as Streptococcus or Staphylococcus is common, neutropenic patients—i.e., those with <500 functional polymorphonuclear leukocytes (PMNs)/μL—and patients with impaired blood or lymphatic drainage may develop infections with unusual organisms. Innocent-looking macules or papules may be the first sign of bacterial or fungal sepsis in immunocompromised patients **(Fig. 30-1)**. In the neutropenic host, a macule progresses rapidly to ecthyma gangrenosum (see Fig. 25e-35), a usually painless, round, necrotic lesion consisting of a central black or gray-black eschar with surrounding erythema. Ecthyma gangrenosum, which is located in nonpressure areas (as distinguished from necrotic lesions associated with lack of circulation), is often associated with Pseudomonas aeruginosa bacteremia, but may be caused by other bacteria.

Candidemia is also associated with a variety of skin conditions and commonly presents as a maculopapular



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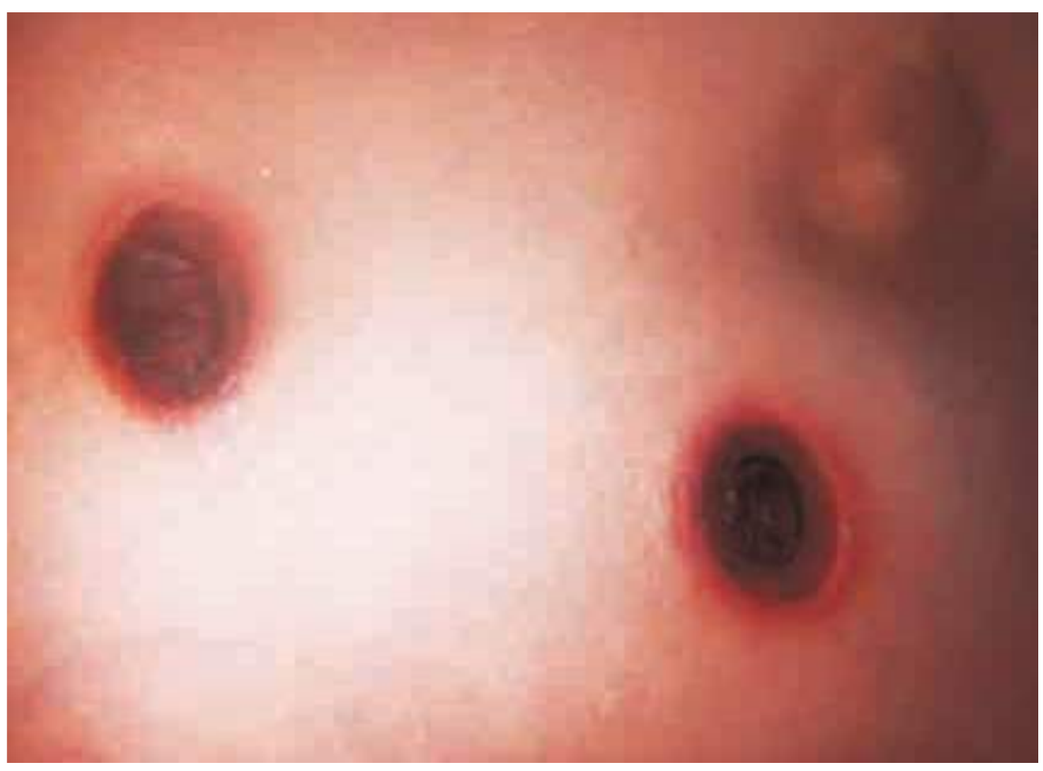

B

FIGURE 30-1

A. Papules related to Escherichia coli bacteremia in a patient with acute lymphocytic leukemia. B. The same lesions on the following day.

rash. Punch biopsy of the skin may be the best method for diagnosis.

Cellulitis, an acute spreading inflammation of the skin, is most often caused by infection with group A Streptococcus or Staphylococcus aureus, virulent organisms normally found on the skin. Although cellulitis tends to be circumscribed in normal hosts, it may spread rapidly in neutropenic patients. A tiny break in the skin may lead to spreading cellulitis, which is characterized by pain and erythema; in the affected patients, signs of infection (e.g., purulence) are often lacking. What might be a furuncle in a normal host may require amputation because of uncontrolled infection in a patient presenting with leukemia. A dramatic response to an infection that might be trivial in a normal host can mark the first sign of leukemia. Fortunately, granulocytopenic patients are likely to be infected with certain types of organisms **(Table 30-4)**; thus the selection of an antibiotic regimen is somewhat easier than it might otherwise be (see "Antibacterial T erapy," below). It is essential to recognize cellulitis early and to treat it aggressively. Patients who are neutropenic or who have previously received antibiotics for other reasons may develop cellulitis with unusual organisms (e.g., Escherichia coli, Pseudomonas, or fungi). Early treatment, even of innocent-looking lesions, is essential to prevent necrosis and loss of tissue. Debridement to prevent spread may sometimes be necessary early in the course of disease, but it can often be performed after chemotherapy, when the PMN count increases.

Sweet syndrome, or *f*ebrile neutrophilic dermatosis, was originally described in women with elevated white blood cell (WBC) counts. T e disease is characterized by the presence of leukocytes in the lower dermis, with edema of the papillary body. Ironically, this disease now is usually seen in neutropenic patients with cancer, most often in association with acute myeloid leukemia (AML) but also in association with a variety of other malignancies. Sweet syndrome usually presents as red or bluish-red papules or nodules that may coalesce and form sharply bordered plaques. T e edema may suggest vesicles, but on palpation the lesions are solid, and vesicles probably never arise in this disease. T e lesions are most common on the face, neck, and arms. On the legs, they may be confused with erythema nodosum. T e development of lesions is often accompanied by high fevers and an elevated erythrocyte sedimentation rate. Both the lesions and the temperature elevation respond dramatically to glucocorticoid administration. Treatment begins with high doses of glucocorticoids (prednisone, 60 mg/d) followed by tapered doses over the next 2–3 weeks.

Data indicate that erythema multi*f*orme with mucous membrane involvement is often associated with herpes simplex virus (HSV) infection and is distinct from Stevens-Johnson syndrome, which is associated with drugs and tends to have a more widespread distribution. Because cancer patients are both immunosuppressed (and therefore susceptible to herpes infections) and heavily treated with drugs (and therefore subject to Stevens-Johnson syndrome), both of these conditions are common in this population.

Cytokines, which are used as adjuvants or primary treatments for cancer, can themselves cause characteristic rashes, further complicating the differential diagnosis. T is phenomenon is a particular problem in bone marrow transplant recipients, who, in addition to having the usual chemotherapy-, antibiotic-, and cytokine-induced rashes, are plagued by graft-versus-host disease.

TABLE 30-4

ORGANISMS LIKELY TO CAUSE INFECTIONS IN GRANULOCYTOPENIC PATIENTS

Gram-Positive Cocci	
Staphylococcus epidermidis	Staphylococcus aureus
Viridans Streptococcus	Enterococcus *f*aecalis
Streptococcus pneumoniae	
Gram-Negative Bacilli	
Escherichia coli	Serratia spp.
Klebsiella spp.	Acinetobacter spp.[a]
Pseudomonas aeruginosa	Stenotrophomonas spp.
Enterobacter spp.	Citrobacter spp.
Non-aeruginosa Pseudomonas spp.[a]	
Gram-Positive Bacilli	
Diphtheroids	JK bacillus[a]
Fungi	
Candida spp.	Mucor/Rhizopus
Aspergillus spp.	

[a]Often associated with intravenous catheters.

CATHETER-RELATED INFECTIONS

Because IV catheters are commonly used in cancer chemotherapy and are prone to cause infection, they pose a major problem in the care of patients with cancer. Some catheter-associated infections can be treated with antibiotics, whereas in others the catheter must be removed **(Table 30-5)**. If the patient has a "tunneled" catheter (which consists of an entrance site, a subcutaneous tunnel, and an exit site), a red streak over the subcutaneous part of the line (the tunnel) is grounds for immediate device removal. Failure to remove catheters under these circumstances may result in extensive cellulitis and tissue necrosis.

More common than tunnel infections are exit-site infections, often with erythema around the area where the line penetrates the skin. Most authorities recommend treatment (usually with vancomycin) for an exit-site infection caused by coagulase-negative

TABLE 30-5

APPROACH TO CATHETER INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

CLINICAL PRESENTATION OR ISOLATED PATHOGEN	CATHETER REMOVAL	ANTIBIOTICS	COMMENTS
Evidence of Infection, Negative Blood Cultures			
Exit-site erythema	Not necessary if infection responds to treatment	Usually, begin treatment for gram-positive cocci.	Coagulase-negative staphylococci are most common.
Tunnel-site erythema	Required	Treat for gram-positive cocci pending culture results.	Failure to remove the catheter may lead to necrosis of the involved area requiring skin grafts in the future.
Blood Culture–Positive Infections			
Coagulase-negative staphylococci	Line removal optimal but may be unnecessary if patient is clinically stable and responds to antibiotics	Usually, start with vancomycin. Linezolid, quinupristin/dalfopristin, and daptomycin are alternative agents.	If there are no contraindications to line removal, this course of action is optimal. If the line is removed, antibiotics may not be necessary.
Other gram-positive cocci (e.g., Staphylococcus aureus, Enterococcus); gram-positive rods (Bacillus, Corynebacterium spp.)	Recommended	Treat with antibiotics to which the organism is sensitive, with duration based on the clinical setting.	The incidence of metastatic infections following S. aureus infection and the difficulty of treating enterococcal infection make line removal the recommended course of action. In addition, gram-positive rods do not respond readily to antibiotics alone.
Gram-negative bacteria	Recommended	Use an agent to which the organism is shown to be sensitive.	Organisms like Stenotrophomonas, Pseudomonas, and Burkholderia are notoriously hard to treat, as are carbapenem-resistant organisms.
Fungi	Recommended	—	Fungal infections of catheters are extremely difficult to treat.

Staphylococcus. Treatment of coagulase-positive staphylococcal infection is associated with a poorer outcome, and it is advisable to remove the catheter if possible. Similarly, most clinicians remove catheters associated with infections due to P. aeruginosa and Candida species, because such infections are difficult to treat and bloodstream infections with these organisms are likely to be deadly. Catheter infections caused by Burkholderia cepacia, Stenotrophomonas species, Agrobacterium species, Acinetobacter baumannii, Pseudomonas species other than aeruginosa, and carbapenem-resistant Enterobacteriaceae are likely to be very difficult to eradicate with antibiotics alone. Similarly, isolation of Bacillus, Corynebacterium, and Mycobacterium species should prompt removal of the catheter.

GASTROINTESTINAL TRACT–SPECIFIC SYNDROMES

Upper gastrointestinal tract disease

Infections of the mouth

The oral cavity is rich in aerobic and anaerobic bacteria that normally live in a commensal relationship with the host. The antimetabolic effects of chemotherapy cause a breakdown of mucosal host defenses, leading to ulceration of the mouth and the potential for invasion by resident bacteria. Mouth ulcerations afflict most patients receiving cytotoxic chemotherapy and have been associated with viridans streptococcal bacteremia. Candida infections of the mouth are very common. Fluconazole is clearly effective in the treatment of both local infections (thrush) and systemic infections (esophagitis) due to Candida albicans. Other azoles (e.g., voriconazole) as well as echinocandins offer similar efficacy as well as activity against the fluconazole-resistant organisms that are associated with chronic fluconazole treatment.

Noma (cancrum oris), commonly seen in malnourished children, is a penetrating disease of the soft and hard tissues of the mouth and adjacent sites, with resulting necrosis and gangrene. It has a counterpart in immunocompromised patients and is thought to be due to invasion of the tissues by Bacteroides, Fusobacterium, and other normal inhabitants of the mouth. Noma is associated with debility, poor oral hygiene, and immunosuppression.

Viruses, particularly HSV, are a prominent cause of morbidity in immunocompromised patients, in whom they are associated with severe mucositis. The use of acyclovir, either prophylactically or therapeutically, is of value.

Esophageal infections

The differential diagnosis of esophagitis (usually presenting as substernal chest pain upon swallowing) includes herpes simplex and candidiasis, both of which are readily treatable.

Lower gastrointestinal tract disease

Hepatic candidiasis results from seeding of the liver (usually from a gastrointestinal source) in neutropenic patients. It is most common among patients being treated for AML and usually presents symptomatically around the time the neutropenia resolves. The characteristic picture is that of persistent fever unresponsive to antibiotics, abdominal pain and tenderness or nausea, and elevated serum levels of alkaline phosphatase in a patient with hematologic malignancy who has recently recovered from neutropenia. The diagnosis of this disease (which may present in an indolent manner and persist for several months) is based on the finding of yeasts or pseudohyphae in granulomatous lesions. Hepatic ultrasound or CT may reveal bull's-eye lesions. MRI scans reveal small lesions not visible by other imaging modalities. The pathology (a granulomatous response) and the timing (with resolution of neutropenia and an elevation in granulocyte count) suggest that the host response to Candida is an important component of the manifestations of disease. In many cases, although organisms are visible, cultures of biopsied material may be negative. The designation hepatosplenic candidiasis or hepatic candidiasis is a misnomer because the disease often involves the kidneys and other tissues; the term chronic disseminated candidiasis may be more appropriate. Because of the risk of bleeding with liver biopsy, diagnosis is often based on imaging studies (MRI, CT). Treatment should be directed to the causative agent (usually C. albicans but sometimes Candida tropicalis or other less common Candida species).

Typhlitis

Typhlitis (also referred to as necrotizing colitis, neutropenic colitis, necrotizing enteropathy, ileocecal syndrome, and cecitis) is a clinical syndrome of fever and right-lower-quadrant (or generalized abdominal) tenderness in an immunosuppressed host. This syndrome is classically seen in neutropenic patients after chemotherapy with cytotoxic drugs. It may be more common among children than among adults and appears to be much more common among patients with AML or ALL than among those with other types of cancer. Physical examination reveals right-lower-quadrant tenderness, with or without rebound tenderness. Associated diarrhea (often bloody) is common, and the diagnosis can be confirmed by the finding of a thickened cecal wall on CT, MRI, or ultrasonography. Plain films may reveal a right-lower-quadrant mass, but CT with contrast or MRI is a much more sensitive means of diagnosis. Although surgery is sometimes attempted to avoid perforation from ischemia, most cases resolve with medical therapy alone. The disease is sometimes associated with positive blood cultures (which usually yield aerobic gram-negative bacilli), and therapy is recommended for a broad spectrum of bacteria (particularly gram-negative bacilli, which are likely to be found in the bowel flora). Surgery is indicated in the case of perforation.

Clostridium difficile–Induced diarrhea

Patients with cancer are predisposed to the development of C. difficile diarrhea as a consequence of chemotherapy alone. Thus, they may test positive for C. difficile even without receiving antibiotics. Obviously, such patients are also subject to C. difficile–induced diarrhea as a result of antibiotic pressure. C. difficile should always be considered as a possible cause of diarrhea in cancer patients who have received either chemotherapy or antibiotics.

CENTRAL NERVOUS SYSTEM–SPECIFIC SYNDROMES

Meningitis

The presentation of meningitis in patients with lymphoma or CLL and in patients receiving chemotherapy (particularly with glucocorticoids) for solid tumors suggests a diagnosis of cryptococcal or listerial infection. As noted previously, splenectomized patients are susceptible to rapid, overwhelming infection with encapsulated bacteria (including S. pneumoniae, H. influenzae, and N. meningitidis). Similarly, patients who are antibody-deficient (e.g., those with CLL, those who have received intensive chemotherapy, or those who have undergone bone marrow transplantation) are likely to have infections caused by these bacteria. Other cancer patients, however, because of their defective cellular immunity, are likely to be infected with other pathogens (Table 30-3). Central nervous system (CNS) tuberculosis should be considered, especially in patients from countries where tuberculosis is highly prevalent in the population.

Encephalitis

The spectrum of disease resulting from viral encephalitis is expanded in immunocompromised patients. A predisposition to infections with intracellular organisms similar to those encountered in patients with AIDS is seen in cancer patients receiving (1) high-dose cytotoxic chemotherapy, (2) chemotherapy affecting T cell function (e.g., fludarabine), or (3) antibodies that eliminate T cells (e.g.,

TABLE 30-6

DIFFERENTIAL DIAGNOSIS OF CENTRAL NERVOUS SYSTEM INFECTIONS IN PATIENTS WITH CANCER

	UNDERLYING PREDISPOSITION	
FINDINGS ON CT OR MRI	PROLONGED NEUTROPENIA	DEFECTS IN CELLULAR IMMUNITY[a]
Mass lesions	Aspergillus, Nocardia, or Cryptococcus brain abscess	Toxoplasmosis, Epstein-Barr virus lymphoma (rare)
Diffuse encephalitis	Progressive multifocal leukoencephalopathy (JC virus)	Infection with varicella-zoster virus, cytomegalovirus, herpes simplex virus, human herpesvirus type 6, JC virus, Listeria

[a]High-dose glucocorticoid therapy, cytotoxic chemotherapy.

TABLE 30-7

DIFFERENTIAL DIAGNOSIS OF CHEST INFILTRATES IN IMMUNOCOMPROMISED PATIENTS

	CAUSE OF PNEUMONIA	
INFILTRATE	INFECTIOUS	NONINFECTIOUS
Localized	Bacteria (including Legionella, mycobacteria)	Local hemorrhage or embolism, tumor
Nodular	Fungi (e.g., Aspergillus or Mucor), Nocardia	Recurrent tumor
Diffuse	Viruses (especially cytomegalovirus), Chlamydia, Pneumocystis, Toxoplasma gondii, mycobacteria	Congestive heart failure, radiation pneumonitis, drug-induced lung injury, lymphangitic spread of cancer

anti-CD3, alemtuzumab, anti-CD52) or cytokine activity (anti–tumor necrosis factor agents or interleukin 1 receptor antagonists). Infection with varicella-zoster virus (VZV) has been associated with encephalitis that may be caused by VZV-related vasculitis. Chronic viral infections may also be associated with dementia and encephalitic presentations. A diagnosis of progressive multifocal leukoencephalopathy should be considered when a patient who has received chemotherapy (rituximab in particular) presents with dementia **(Table 30-6)**. Other abnormalities of the CNS that may be confused with infection include normal-pressure hydrocephalus and vasculitis resulting from CNS irradiation. It may be possible to differentiate these conditions by MRI.

Brain Masses

Mass lesions of the brain most often present as headache with or without fever or neurologic abnormalities. Infections associated with mass lesions may be caused by bacteria (particularly Nocardia), fungi (particularly Cryptococcus or Aspergillus), or parasites (Toxoplasma). Epstein-Barr virus (EBV)–associated lymphoma may also present as single—or sometimes multiple—mass lesions of the brain. A biopsy may be required for a definitive diagnosis.

PULMONARY INFECTIONS

Pneumonia in immunocompromised patients may be difficult to diagnose because conventional methods of diagnosis depend on the presence of neutrophils. Bacterial pneumonia in neutropenic patients may present without purulent sputum—or, in fact, without any sputum at all—and may not produce physical findings suggestive of chest consolidation (rales or egophony).

In granulocytopenic patients with persistent or recurrent fever, the chest x-ray pattern may help to localize an infection and thus to determine which investigative tests and procedures should be undertaken and which therapeutic options should be considered **(Table 30-7)**. In this setting, a simple chest x-ray is a screening tool; because the impaired host response results in less evidence of consolidation or infiltration, high-resolution CT is recommended for the diagnosis of pulmonary infections. The difficulties encountered in the management of pulmonary infiltrates relate in part to the difficulties of performing diagnostic procedures on the patients involved. When platelet counts can be increased to adequate levels by transfusion, microscopic and microbiologic evaluation of the fluid obtained by endoscopic bronchial lavage is often diagnostic. Lavage fluid should be cultured for Mycoplasma, Chlamydia, Legionella, Nocardia, more common bacterial pathogens, fungi, and viruses. In addition, the possibility of Pneumocystis pneumonia should be considered, especially in patients with ALL or lymphoma who have not received prophylactic trimethoprim-sulfamethoxazole (TMP-SMX). The characteristics of the infiltrate may be helpful in decisions about further diagnostic and therapeutic maneuvers. Nodular infiltrates suggest fungal pneumonia (e.g., that caused by Aspergillus or Mucor). Such lesions may best be approached by visualized biopsy procedures. It is worth noting that while bacterial pneumonias classically present as lobar infiltrates in normal hosts, bacterial pneumonias in granulocytopenic hosts present with a paucity of signs, symptoms, or radiographic abnormalities; thus, the diagnosis is difficult.

Aspergillus species can colonize the skin and respiratory tract or cause fatal systemic illness. Although this fungus may cause aspergillomas in a previously existing cavity or may produce allergic bronchopulmonary

disease in some patients, the major problem posed by this genus in neutropenic patients is invasive disease, primarily due to Aspergillus *f*umigatus or Aspergillus *fl*avus. T e organisms enter the host following colonization of the respiratory tract, with subsequent invasion of blood vessels. T e disease is likely to present as a thrombotic or embolic event because of this ability of the fungi to invade blood vessels. T e risk of infection with Aspergillus correlates directly with the duration of neutropenia. In prolonged neutropenia, positive surveillance cultures for nasopharyngeal colonization with Aspergillus may predict the development of disease.

Patients with Aspergillus infection often present with pleuritic chest pain and fever, which are sometimes accompanied by cough. Hemoptysis may be an ominous sign. Chest x-rays may reveal new focal infiltrates or nodules. Chest CT may reveal a characteristic halo consisting of a mass-like infiltrate surrounded by an area of low attenuation. T e presence of a "crescent sign" on chest x-ray or chest CT, in which the mass progresses to central cavitation, is characteristic of invasive Aspergillus infection but may develop as the lesions are resolving.

In addition to causing pulmonary disease, Aspergillus may invade through the nose or palate, with deep sinus penetration. T e appearance of a discolored area in the nasal passages or on the hard palate should prompt a search for invasive Aspergillus. T is situation is likely to require surgical debridement. Catheter infections with Aspergillus usually require both removal of the catheter and antifungal therapy.

Diffuse interstitial infiltrates suggest viral, parasitic, or Pneumocystis pneumonia. If the patient has a diffuse interstitial pattern on chest x-ray, it may be reasonable, while considering invasive diagnostic procedures, to institute empirical treatment for Pneumocystis with TMP-SMX and for Chlamydia, Mycoplasma, and Legionella with a quinolone or azithromycin. Noninvasive procedures, such as staining of induced sputum smears for Pneumocystis, serum cryptococcal antigen tests, and urine testing for Legionella antigen, may be helpful. Serum galactomannan and β-d-glucan tests may be of value in diagnosing Aspergillus infection, but their utility is limited by their lack of sensitivity and specificity. T e presence of an elevated level of β-d-glucan in the serum of a patient being treated for cancer who is not receiving prophylaxis against Pneumocystis suggests the diagnosis of Pneumocystis pneumonia. Infections with viruses that cause only upper respiratory symptoms in immunocompetent hosts, such as respiratory syncytial virus (RSV), influenza viruses, and parainfluenza viruses, may be associated with fatal pneumonitis in immunocompromised hosts. CMV reactivation occurs in cancer patients receiving chemotherapy, but CMV pneumonia is most common among HSCT recipients. Polymerase chain reaction testing now allows rapid diagnosis of viral pneumonia, which can lead to treatment in some cases (e.g., influenza). Multiplex studies that can detect a wide array of viruses in the lung and upper respiratory tract are now available and will lead to specific diagnoses of viral pneumonias.

Bleomycin is the most common cause of chemotherapy-induced lung disease. Other causes include alkylating agents (such as cyclophosphamide, chlorambucil, and melphalan), nitrosoureas (carmustine [BCNU], lomustine [CCNU], and methyl-CCNU), busulfan, procarbazine, methotrexate, and hydroxyurea. Both infectious and noninfectious (drug- and/or radiation-induced) pneumonitis can cause fever and abnormalities on chest x-ray; thus, the differential diagnosis of an infiltrate in a patient receiving chemotherapy encompasses a broad range of conditions (Table 30-7). T e treatment of radiation pneumonitis (which may respond dramatically to glucocorticoids) or drug-induced pneumonitis is different from that of infectious pneumonia, and a biopsy may be important in the diagnosis. Unfortunately, no definitive diagnosis can be made in ~30% of cases, even after bronchoscopy.

Open-lung biopsy is the gold standard of diagnostic techniques. Biopsy via a visualized thoracostomy can replace an open procedure in many cases. When a biopsy cannot be performed, empirical treatment can be undertaken; a quinolone or an erythromycin derivative (azithromycin) and TMP-SMX are used in the case of diffuse infiltrates, and an antifungal agent is administered in the case of nodular infiltrates. T e risks should be weighed carefully in these cases. If inappropriate drugs are administered, empirical treatment may prove toxic or ineffective; either of these outcomes may be riskier than biopsy.

CARDIOVASCULAR INFECTIONS

Patients with Hodgkin's disease are prone to persistent infections by Salmonella, sometimes (and particularly often in elderly patients) affecting a vascular site. T e use of IV catheters deliberately lodged in the right atrium is associated with a high incidence of bacterial endocarditis, presumably related to valve damage followed by bacteremia. Nonbacterial thrombotic endocarditis (marantic endocarditis) has been described in association with a variety of malignancies (most often solid tumors) and may follow bone marrow transplantation as well. T e presentation of an embolic event with a new cardiac murmur suggests this diagnosis. Blood cultures are negative in this disease of unknown pathogenesis.

ENDOCRINE SYNDROMES

Infections of the endocrine system have been described in immunocompromised patients. Candida infection of the thyroid may be difficult to diagnose during the

neutropenic period. It can be defined by indium-labeled WBC scans or gallium scans after neutrophil counts increase. CMV infection can cause adrenalitis with or without resulting adrenal insufficiency. T e presentation of a sudden endocrine anomaly in an immunocompromised patient can be a sign of infection in the involved end organ.

MUSCULOSKELETAL INFECTIONS

Infection that is a consequence of vascular compromise, resulting in gangrene, can occur when a tumor restricts the blood supply to muscles, bones, or joints. T e process of diagnosis and treatment of such infection is similar to that in normal hosts, with the following caveats:

1. In terms *of* diagnosis, a lack of physical findings resulting from a lack of granulocytes in the granulocytopenic patient should make the clinician more aggressive in obtaining tissue rather than more willing to rely on physical signs.
2. In terms *of* therapy, aggressive debridement of infected tissues may be required. However, it is usually difficult to operate on patients who have recently received chemotherapy, both because of a lack of platelets (which results in bleeding complications) and because of a lack of WBCs (which may lead to secondary infection). A blood culture positive for Clostridium per*f*ringens—an organism commonly associated with gas gangrene—can have a number of meanings. Clostridium septicum bacteremia is associated with the presence of an underlying malignancy. Bloodstream infections with intestinal organisms such as Streptococcus bovis biotype 1 and C. per*f*ringens may arise spontaneously from lower gastrointestinal lesions (tumor or polyps); alternatively, these lesions may be harbingers of invasive disease. T e clinical setting must be considered in order to define the appropriate treatment for each case.

RENAL AND URETERAL INFECTIONS

Infections of the urinary tract are common among patients whose ureteral excretion is compromised (Table 30-1). Candida, which has a predilection for the kidney, can invade either from the bloodstream or in a retrograde manner (via the ureters or bladder) in immunocompromised patients. T e presence of "fungus balls" or persistent candiduria suggests invasive disease. Persistent funguria (with Aspergillus as well as Candida) should prompt a search for a nidus of infection in the kidney.

Certain viruses are typically seen only in immunosuppressed patients. BK virus (polyomavirus hominis 1) has been documented in the urine of bone marrow transplant recipients and, like adenovirus, may be associated with hemorrhagic cystitis.

ABNORMALITIES THAT PREDISPOSE TO INFECTION

THE LYMPHOID SYSTEM

It is beyond the scope of this chapter to detail how all the immunologic abnormalities that result from cancer or from chemotherapy for cancer lead to infections (Table 30-1). Disorders of the immune system are discussed in other sections of this book. As has been noted, patients with antibody deficiency are predisposed to overwhelming infection with encapsulated bacteria (including S. pneumoniae, H. in*fl*uenzae, and N. meningitidis). Infections that result from the lack of a functional cellular immune system are described in. It is worth mentioning, however, that patients undergoing intensive chemotherapy for any form of cancer will have not only defects due to granulocytopenia but also lymphocyte dysfunction, which may be profound. T us, these patients—especially those receiving glucocorticoid-containing regimens or drugs that inhibit either T cell activation (calcineurin inhibitors or drugs like fludarabine, which affect lymphocyte function) or cytokine induction—should be given prophylaxis for Pneumocystis pneumonia.

Patients receiving treatment that eliminates B cells (e.g., with anti-CD20 antibodies or rituximab) are especially vulnerable to intercurrent viral infections. T e incidence of progressive multifocal leukoencephalopathy (caused by JC virus) is elevated in these patients.

THE HEMATOPOIETIC SYSTEM

Initial studies in the 1960s revealed a dramatic increase in the incidence of infections (fatal and nonfatal) among cancer patients with a granulocyte count of <500/μL. T e use of prophylactic antibacterial agents has reduced the number of bacterial infections, but 35–78% of febrile neutropenic patients being treated for hematologic malignancies develop infections at some time during chemotherapy. Aerobic pathogens (both gram-positive and gram-negative) predominate in all series, but the exact organisms isolated vary from center to center. Infections with anaerobic organisms are uncommon. Geographic patterns affect the types of fungi isolated. Tuberculosis and malaria are common causes of fever in the developing world and may present in this setting as well.

Neutropenic patients are unusually susceptible to infection with a wide variety of bacteria; thus, antibiotic

therapy should be initiated promptly to cover likely pathogens if infection is suspected. Indeed, early initiation of antibacterial agents is mandatory to prevent deaths. Like most immunocompromised patients, neutropenic patients are threatened by their own microbial flora, including gram-positive and gram-negative organisms found commonly on the skin and mucous membranes and in the bowel (Table 30-4). Because treatment with narrow-spectrum agents leads to infection with organisms not covered by the antibiotics used, the initial regimen should target all pathogens likely to be the initial causes of bacterial infection in neutropenic hosts. As noted in the algorithm shown in **Fig. 30-2**, administration of antimicrobial agents is routinely continued until neutropenia resolves—i.e., the granulocyte count is sustained above 500 μL for at least 2 days. In some cases, patients remain febrile after resolution of neutropenia. In these instances, the risk of sudden death from overwhelming bacteremia is greatly reduced, and the following diagnoses should be seriously considered: (1) fungal infection, (2) bacterial abscesses or undrained foci of infection, and (3) drug fever (including reactions to antimicrobial agents as well as to chemotherapy or cytokines). In the proper setting, viral infection or graft-versus-host disease should be considered. In clinical practice, antibacterial therapy is usually discontinued when the patient is no longer neutropenic and all evidence of bacterial disease has been eliminated. Antifungal agents are then discontinued if there is no evidence of fungal disease.

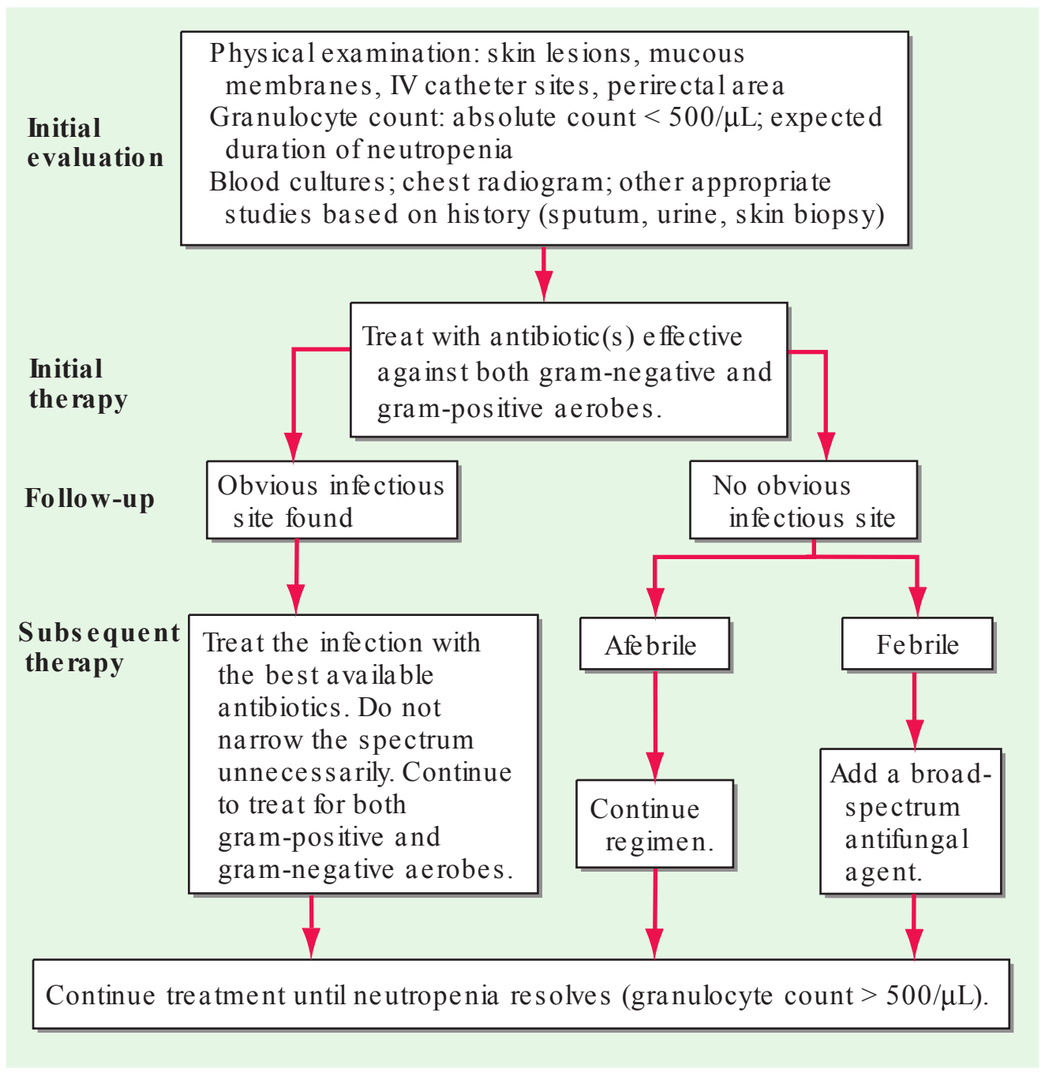

FIGURE 30-2
Algorithm for the diagnosis and treatment of fever and neutropenia.

If the patient remains febrile, a search for viral diseases or unusual pathogens is conducted while unnecessary cytokines and other drugs are systematically eliminated from the regimen.

TREATMENT Infections in Cancer Patients

ANTIBACTERIAL THERAPY Hundreds of antibacterial regimens have been tested for use in patients with cancer. The major risk of infection is related to the degree of neutropenia seen as a consequence of either the disease or the therapy. Many of the relevant studies have involved small populations in which the outcomes have generally been good, and most have lacked the statistical power to detect differences among the regimens studied. Each febrile neutropenic patient should be approached as a unique problem, with particular attention given to previous infections and recent antibiotic exposures. Several general guidelines are useful in the initial treatment of neutropenic patients with fever (**Fig. 30-2**):

1. In the initial regimen, it is necessary to use antibiotics active against both gram-negative and gram-positive bacteria (Table 30-4).
2. Monotherapy with an aminoglycoside or an antibiotic lacking good activity against gram-positive organisms (e.g., ciprofloxacin or aztreonam) is not adequate in this setting.
3. The agents used should reflect both the epidemiology and the antibiotic resistance pattern of the hospital.
4. If the pattern of resistance justifies its use, a single third-generation cephalosporin constitutes an appropriate initial regimen in many hospitals.
5. Most standard regimens are designed for patients who have not previously received prophylactic antibiotics. The development of fever in a patient who has received antibiotics affects the choice of subsequent therapy, which should target resistant organisms and organisms known to cause infections in patients being treated with the antibiotics already administered.
6. Randomized trials have indicated the safety of oral antibiotic regimens in the treatment of "low-risk" patients with fever and neutropenia. Outpatients who are expected to remain neutropenic for <10 days and who have no concurrent medical problems (such as hypotension, pulmonary compromise, or abdominal pain) can be classified as low risk and treated with a broad-spectrum oral regimen.
7. Several large-scale studies indicate that prophylaxis with a fluoroquinolone (ciprofloxacin or levofloxacin) decreases morbidity and mortality rates among afebrile patients who are anticipated to have neutropenia of long duration.

Commonly used antibiotic regimens for the treatment of febrile patients in whom prolonged neutropenia (>7 days) is anticipated include (1) ceftazidime or cefepime, (2) piperacillin/tazobactam, or (3) imipenem/cilastatin or meropenem. All three regimens have shown equal efficacy in large trials. All

three are active against P. aeruginosa and a broad spectrum of aerobic gram-positive and gram-negative organisms. Imipenem/cilastatin has been associated with an elevated rate of C. dif cile diarrhea, and many centers reserve carbapenem antibiotics for treatment of gram-negative bacteria that produce extended-spectrum β-lactamases; these limitations make carbapenems less attractive as an initial regimen. Despite the frequent involvement of coagulase-negative staphylococci, the initial use of vancomycin or its automatic addition to the initial regimen has not resulted in improved outcomes, and the antibiotic does exert toxic effects. For these reasons, only judicious use of vancomycin is recommended—for example, when there is good reason to suspect the involvement of coagulase-negative staphylococci (e.g., the appearance of erythema at the exit site of a catheter or a positive culture for methicillin-resistant S. aureus or coagulase-negative staphylococci). Because the sensitivities of bacteria vary from hospital to hospital, clinicians are advised to check their local sensitivities and to be aware that resistance patterns can change quickly, necessitating a change in approach to patients with fever and neutropenia. Similarly, infection control services should monitor for basic antibiotic resistance and for fungal infections. T e appearance of a large number of Aspergillus infections, in particular, suggests the possibility of an environmental source that requires further investigation and remediation.

T e initial antibacterial regimen should be refined on the basis of culture results (Fig. 30-2). Blood cultures are the most relevant basis for selection of therapy; surface cultures of skin and mucous membranes may be misleading. In the case of gram-positive bacteremia or another gram-positive infection, it is important that the antibiotic be optimal for the organism isolated. Once treatment with broad-spectrum antibiotics has begun, it is not desirable to discontinue all antibiotics because of the risk of failing to treat a potentially fatal bacterial infection; the addition of more and more antibacterial agents to the regimen is not appropriate unless there is a clinical or microbiologic reason to do so. Planned progressive therapy (the serial, empirical addition of one drug after another without culture data) is not efficacious in most settings and may have unfortunate consequences. Simply adding another antibiotic for fear that a gram-negative infection is present is a dubious practice. T e synergy exhibited by β-lactams and aminoglycosides against certain gram-negative organisms (especially P. aeruginosa) provides the rationale for using two antibiotics in this setting, but recent analyses suggest that efficacy is not enhanced by the addition of aminoglycosides, while toxicity may be increased. Mere "double coverage," with the addition of a quinolone or another antibiotic that is not likely to exhibit synergy, has not been shown to be of benefit and may cause additional toxicities and side effects. Cephalosporins can cause bone marrow suppression, and vancomycin is associated with neutropenia in some healthy individuals. Furthermore, the addition of multiple cephalosporins may induce β-lactamase production by some organisms; cephalosporins and double β-lactam combinations should probably be avoided altogether in Enterobacter infections.

ANTIFUNGAL THERAPY Fungal infections in cancer patients are most often associated with neutropenia. Neutropenic patients are predisposed to the development of invasive fungal infections, most commonly those due to Candida and Aspergillus species and occasionally those caused by Mucor, Rhizopus, Fusarium, Trichosporon, Bipolaris, and others. Cryptococcal infection, which is common among patients taking immunosuppressive agents, is uncommon among neutropenic patients receiving chemotherapy for AML. Invasive candidal disease is usually caused by C. albicans or C. tropicalis but can be caused by C. krusei, C. parapsilosis, and C. glabrata.

For decades, it has been common clinical practice to add amphotericin B to antibacterial regimens if a neutropenic patient remains febrile despite 4–7 days of treatment with antibacterial agents. T e rationale for this empirical addition is that it is difficult to culture fungi before they cause disseminated disease and that mortality rates from disseminated fungal infections in granulocytopenic patients are high. Before the introduction of newer azoles into clinical practice, amphotericin B was the mainstay of antifungal therapy. T e insolubility of amphotericin B has resulted in the marketing of several lipid formulations that are less toxic than the amphotericin B deoxycholate complex. Echinocandins (e.g., caspofungin) are useful in the treatment of infections caused by azole-resistant Candida strains as well as in therapy for aspergillosis and have been shown to be equivalent to liposomal amphotericin B for the empirical treatment of patients with prolonged fever and neutropenia. Newer azoles have also been demonstrated to be effective in this setting. Although fluconazole is efficacious in the treatment of infections due to many Candida species, its use against serious fungal infections in immunocompromised patients is limited by its narrow spectrum: it has no activity against Aspergillus or against several non-albicans Candida species. T e broad-spectrum azoles (e.g., voriconazole and posaconazole) provide another option for the treatment of Aspergillus infections, including CNS infection. Clinicians should be aware that the spectrum of each azole is somewhat different and that no drug can be assumed to be efficacious against all fungi. Aspergillus terreus is resistant to amphotericin B. Although voriconazole is active against Pseudallescheria boydii, amphotericin B is not; however, voriconazole has no activity against Mucor. Posaconazole, which is administered orally, is useful as a prophylactic agent in patients with prolonged neutropenia. Studies in progress are assessing the use of these agents in combinations.

ANTIVIRAL THERAPY T e availability of a variety of agents active against herpes-group viruses, including some new agents with a broader spectrum of activity, has heightened focus on the treatment of viral infections, which pose a major problem in cancer patients. Viral diseases caused by the herpes group are prominent. Serious (and sometimes fatal) infections due to HSV and VZV are well documented

in patients receiving chemotherapy. CMV may also cause serious disease, but fatalities from CMV infection are more common in HSCT recipients. T e roles of human herpesvirus (HHV)-6, HHV-7, and HHV-8 (Kaposi's sarcoma–associated herpesvirus) in cancer patients are still being defined. EBV lymphoproliferative disease (LPD) can occur in patients receiving chemotherapy but is much more common among transplant recipients. While clinical experience is most extensive with acyclovir, which can be used therapeutically or prophylactically, a number of derivative drugs offer advantages over this agent.

In addition to the herpes group, several respiratory viruses (especially RSV) may cause serious disease in cancer patients. Although influenza vaccination is recommended (see below), it may be ineffective in this patient population. T e availability of antiviral drugs with activity against influenza viruses gives the clinician additional options for the prophylaxis and treatment of these patients.

OTHER THERAPEUTIC MODALITIES Another way to address the problems posed by the febrile neutropenic patient is to replenish the neutrophil population. Although granulocyte transfusions may be effective in the treatment of refractory gram-negative bacteremia, they do not have a documented role in prophylaxis. Because of the expense, the risk of leukoagglutinin reactions (which has probably been decreased by improved cell-separation procedures), and the risk of transmission of CMV from unscreened donors (which has been reduced by the use of filters), granulocyte transfusion is reserved for patients whose condition is unresponsive to antibiotics. T is modality is efficacious for documented gram-negative bacteremia refractory to antibiotics, particularly in situations where granulocyte numbers will be depressed for only a short period. T e demonstrated usefulness of granulocyte colony-stimulating factor in mobilizing neutrophils and advances in preservation techniques may make this option more useful than in the past.

A variety of cytokines, including granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, enhance granulocyte recovery after chemotherapy and consequently shorten the period of maximal vulnerability to fatal infections. T e role of these cytokines in routine practice is still a matter of some debate. Most authorities recommend their use only when neutropenia is both severe and prolonged. T e cytokines themselves may have adverse effects, including fever, hypoxemia, and pleural effusions or serositis in other areas.

Once neutropenia has resolved, the risk of infection decreases dramatically. However, depending on what drugs they receive, patients who continue on chemotherapeutic protocols remain at high risk for certain diseases. Any patient receiving more than a maintenance dose of glucocorticoids (e.g., in many treatment regimens for diffuse lymphoma) should also receive prophylactic TMP-SMX because of the risk of Pneumocystis infection; those with ALL should receive such prophylaxis for the duration of chemotherapy.

PREVENTION OF INFECTION IN CANCER PATIENTS

EFFECT OF THE ENVIRONMENT

Outbreaks of fatal Aspergillus infection have been associated with construction projects and materials in several hospitals. T e association between spore counts and risk of infection suggests the need for a high-efficiency air-handling system in hospitals that care for large numbers of neutropenic patients. T e use of laminar-flow rooms and prophylactic antibiotics has decreased the number of infectious episodes in severely neutropenic patients. However, because of the expense of such a program and the failure to show that it dramatically affects mortality rates, most centers do not routinely use laminar flow to care for neutropenic patients. Some centers use "reverse isolation," in which health care providers and visitors to a patient who is neutropenic wear gowns and gloves. Since most of the infections these patients develop are due to organisms that colonize the patients' own skin and bowel, the validity of such schemes is dubious, and limited clinical data do not support their use. Hand washing by all staff caring for neutropenic patients should be required to prevent the spread of resistant organisms.

T e presence of large numbers of bacteria (particularly P. aeruginosa) in certain foods, especially fresh vegetables, has led some authorities to recommend a special "low-bacteria" diet. A diet consisting of cooked and canned food is satisfactory to most neutropenic patients and does not involve elaborate disinfection or sterilization protocols. However, there are no studies to support even this type of dietary restriction. Counseling of patients to avoid leftovers, deli foods, undercooked meat, and unpasteurized dairy products is recommended.

PHYSICAL MEASURES

Although few studies address this issue, patients with cancer are predisposed to infections resulting from anatomic compromise (e.g., lymphedema resulting from node dissections after radical mastectomy). Surgeons who specialize in cancer surgery can provide specific guidelines for the care of such patients, and patients benefit from common-sense advice about how to prevent infections in vulnerable areas.

IMMUNOGLOBULIN REPLACEMENT

Many patients with multiple myeloma or CLL have immunoglobulin deficiencies as a result of their disease, and all allogeneic bone marrow transplant recipients are hypogammaglobulinemic for a period after transplantation. However, current recommendations reserve intravenous immunoglobulin replacement therapy for

those patients with severe (<400 mg of total IgG/dL), prolonged hypogammaglobulinemia and a history of repeated infections. Antibiotic prophylaxis has been shown to be cheaper and is efficacious in preventing infections in most CLL patients with hypogammaglobulinemia. Routine use of immunoglobulin replacement is not recommended.

SEXUAL PRACTICES

The use of condoms is recommended for severely immunocompromised patients. Any sexual practice that results in oral exposure to feces is not recommended. Neutropenic patients should be advised to avoid any practice that results in trauma, as even microscopic cuts may result in bacterial invasion and fatal sepsis.

ANTIBIOTIC PROPHYLAXIS

Several studies indicate that the use of oral fluoroquinolones prevents infection and decreases mortality rates among severely neutropenic patients. Prophylaxis for Pneumocystis is mandatory for patients with ALL and for all cancer patients receiving glucocorticoid-containing chemotherapy regimens.

VACCINATION OF CANCER PATIENTS

In general, patients undergoing chemotherapy respond less well to vaccines than do normal hosts. Their greater need for vaccines thus leads to a dilemma in their management. Purified proteins and inactivated vaccines are almost never contraindicated and should be given to patients even during chemotherapy. For example, all adults should receive diphtheria–tetanus toxoid boosters at the indicated times as well as seasonal influenza vaccine. However, if possible, vaccination should not be undertaken concurrent with cytotoxic chemotherapy. If patients are expected to be receiving chemotherapy for several months and vaccination is indicated (e.g., influenza vaccination in the fall), the vaccine should be given midcycle—as far apart in time as possible from the antimetabolic agents that will prevent an immune response. The meningococcal and pneumococcal polysaccharide vaccines should be given to patients before splenectomy, if possible. The H. *influenzae* type b conjugate vaccine should be administered to all splenectomized patients.

In general, live virus (or live bacterial) vaccines should not be given to patients during intensive chemotherapy because of the risk of disseminated infection. Recommendations on vaccination are summarized in Table 30-2 (see www.cdc.gov/vaccine for updated recommendations).

CHAPTER 31

HEMATOPOIETIC CELL TRANSPLANTATION

Frederick R. Appelbaum

Bone marrow transplantation was the original term used to describe the collection and transplantation of hematopoietic stem cells, but with the demonstration that peripheral blood and umbilical cord blood are also useful sources of stem cells, hematopoietic cell transplantation has become the preferred generic term for this process. T e procedure is usually carried out for one of two purposes: (1) to replace an abnormal but nonmalignant lymphohematopoietic system with one from a normal donor or (2) to treat malignancy by allowing the administration of higher doses of myelosuppressive therapy than would otherwise be possible. T e use of hematopoietic cell transplantation has been increasing, both because of its efficacy in selected diseases and because of increasing availability of donors. T e Center for International Blood and Marrow Transplant Research (http://www.cibmtr.org) estimates that about 65,000 transplants are performed each year.

THE HEMATOPOIETIC STEM CELL

Several features of the hematopoietic stem cell make transplantation clinically feasible, including its remarkable regenerative capacity, its ability to home to the marrow space following intravenous injection, and the ability of the stem cell to be cryopreserved **(Chap. 1)**. Transplantation of a single stem cell can replace the entire lymphohematopoietic system of an adult mouse. In humans, transplantation of a small percentage of a donor's bone marrow volume regularly results in complete and sustained replacement of the recipient's entire lymphohematopoietic system, including all red cells, granulocytes, B and T lymphocytes, and platelets, as well as cells comprising the fixed macrophage population, including Kupffer cells of the liver, pulmonary alveolar macrophages, osteoclasts, Langerhans cells of the skin, and brain microglial cells. T e ability of the hematopoietic stem cell to home to the marrow following intravenous injection is mediated, in part, by an interaction between CXCL12, also known as stromal cell–derived factor 1, produced by marrow stromal cells and the alpha-chemokine receptor CXCR4 found on stem cells. Homing is also influenced by the interaction of cell-surface molecules, termed selectins, including E- and L-selectin, on bone marrow endothelial cells with ligands, termed integrins, such as VLA-4, on early hematopoietic cells. Human hematopoietic stem cells can survive freezing and thawing with little, if any, damage, making it possible to remove and store a portion of the patient's own bone marrow for later reinfusion following treatment of the patient with high-dose myelotoxic therapy.

CATEGORIES OF HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation can be described according to the relationship between the patient and the donor and by the anatomic source of stem cells. In ~1% of cases, patients have identical twins who can serve as donors. With the use of syngeneic donors, there is no risk of graft-versus-host disease (GVHD), which often complicates allogeneic transplantation, and unlike the use of autologous marrow, there is no risk that the stem cells are contaminated with tumor cells.

Allogeneic transplantation involves a donor and a recipient who are not genetically identical. Following allogeneic transplantation, immune cells transplanted with the stem cells or developing from them can react against the patient, causing GVHD. Alternatively, if the immunosuppressive preparative regimen used to treat the patient before transplant is inadequate, immunocompetent cells of the patient can cause graft rejection. T e risks of these complications are greatly influenced by the degree of matching between donor and recipient for antigens encoded by genes of the major histocompatibility complex.

T e human leukocyte antigen (HLA) molecules are responsible for binding antigenic proteins and presenting them to T cells. T e antigens presented by HLA molecules may derive from exogenous sources (e.g., during active infections) or may be endogenous proteins. If individuals are not HLA-matched, T cells from one individual will react strongly to the mismatched HLA, or "major antigens," of the second. Even if the individuals are HLA-matched, the T cells of the donor may react to differing endogenous or "minor antigens" presented by the HLA of the recipient. Reactions to minor antigens tend to be less vigorous. T e genes of major relevance to transplantation include HLA-A, -B, -C, and -D; they are closely linked and therefore tend to be inherited as haplotypes, with only rare crossovers between them. T us, the odds that any one full sibling will match a patient are one in four, and the probability that the patient has an HLA-identical sibling is $1 - (0.75)n$, where n equals the number of siblings.

With current techniques, the risk of graft rejection is 1–3%, and the risk of severe, life-threatening acute GVHD is ~15% following transplantation between HLA-identical siblings. T e incidence of graft rejection and GVHD increases progressively with the use of family member donors mismatched for one, two, or three antigens. Although survival following a one-antigen mismatched transplant is not markedly altered, survival following two- or three-antigen mismatched transplants is significantly reduced. Since the formation of the National Marrow Donor Program and other registries, it has become possible to identify HLA-matched unrelated donors for many patients. T e genes encoding HLA antigens are highly polymorphic, and thus the odds of any two unrelated individuals being HLA identical are extremely low, somewhat less than 1 in 10,000. However, by identifying and typing >20 million volunteer donors, HLA-matched donors can now be found for ~60% of patients for whom a search is initiated, with higher rates among whites and lower rates among minorities and patients of mixed race. It takes, on average, 3–4 months to complete a search and schedule and initiate an unrelated donor transplant. With improvements in HLA typing and supportive care measures, survival following matched unrelated donor transplantation is essentially the same as that seen with HLA-matched siblings.

Autologous transplantation involves the removal and storage of the patient's own stem cells with subsequent reinfusion after the patient receives high-dose myeloablative therapy. Unlike allogeneic transplantation, there is no risk of GVHD or graft rejection with autologous transplantation. On the other hand, autologous transplantation lacks a graft-versus-tumor (GVT) effect, and the autologous stem cell product can be contaminated with tumor cells, which could lead to relapse. A variety of techniques have been developed to "purge" autologous products of tumor cells. Some use antibodies directed at tumor-associated antigens plus complement, antibodies linked to toxins, or antibodies conjugated to immunomagnetic beads. Another technique is positive selection of stem cells using antibodies to CD34, with subsequent column adherence or flow techniques to select normal stem cells while leaving tumor cells behind. All of these approaches can reduce the number of tumor cells from 1000- to 10,000-fold and are clinically feasible; however, no prospective randomized trials have yet shown that any of these approaches results in a decrease in relapse rates or improvements in disease-free or overall survival.

Bone marrow aspirated from the posterior and anterior iliac crests initially was the source of hematopoietic stem cells for transplantation. Typically, anywhere from 1.5 to 5×10^8 nucleated marrow cells per kilogram are collected for allogeneic transplantation. Several studies have found improved survival in the settings of both matched sibling and unrelated transplantation by transplanting higher numbers of bone marrow cells.

Hematopoietic stem cells circulate in the peripheral blood but in very low concentrations. Following the administration of certain hematopoietic growth factors, including granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), and during recovery from intensive chemotherapy, the concentration of hematopoietic progenitor cells in blood, as measured either by colony-forming units or expression of the CD34 antigen, increases markedly. T is has made it possible to harvest adequate numbers of stem cells from the peripheral blood for transplantation. Donors are typically treated with 4 or 5 days of hematopoietic growth factor, following which stem cells are collected in one or two 4-h pheresis sessions. In the autologous setting, transplantation of $>2.5 \times 10^6$ CD34 cells per kilogram, a number that can be collected in most circumstances, leads to rapid and sustained engraftment in virtually all cases. In the 10–20% of patients who fail to mobilize sufficient CD34+ cells with growth factor alone, the addition of plerixafor, an antagonist of CXCR4, may be useful. Compared to the use of autologous marrow, use of peripheral blood stem cells results in more rapid hematopoietic recovery, with granulocytes recovering to 500/μL by day 12 and platelets recovering to 20,000/μL by day 14. Although this more rapid recovery diminishes the morbidity rate of transplantation, no studies show improved survival.

Hesitation in studying the use of peripheral blood stem cells for allogeneic transplantation occurred because peripheral blood stem cell products contain as much as 1 log more T cells than are contained in the typical marrow harvest; in animal models, the

incidence of GVHD is related to the number of T cells transplanted. Nonetheless, clinical trials have shown that the use of growth factor–mobilized peripheral blood stem cells from HLA-matched family members leads to faster engraftment without an increase in acute GVHD. Chronic GVHD may be increased with peripheral blood stem cells, but in trials conducted so far, this has been more than balanced by reductions in relapse rates and nonrelapse mortality rates, with the use of peripheral blood stem cells resulting in improved overall survival. However, in the setting of matched unrelated donor transplantation, use of peripheral blood results in more chronic GVHD without a compensatory survival advantage, favoring the use of bone marrow in this setting.

Umbilical cord blood contains a high concentration of hematopoietic progenitor cells, allowing for its use as a source of stem cells for transplantation. Cord blood transplantation from family members has been explored in the setting where the immediate need for transplantation precludes waiting the 9 or so months generally required for the baby to mature to the point of donating marrow. Use of cord blood results in slower engraftment and peripheral count recovery than seen with marrow but a lower incidence of GVHD, perhaps reflecting the low number of T cells in cord blood. Multiple cord blood banks have been developed to harvest and store cord blood for possible transplantation to unrelated patients from material that would otherwise be discarded. Currently more than 500,000 units are cryopreserved and available for use. T e advantages of unrelated cord blood are rapid availability and decreased immune reactivity allowing for the use of partially matched units, which is of particular importance for those without matched unrelated donors. T e risks of graft failure and transplant-related mortality are related to the dose of cord blood cells per kilogram, which previously limited the application of single cord blood transplantation to pediatric and smaller adult patients. Subsequent trials have found that the use of double cord transplants diminishes the risk of graft failure and early mortality even though only one of the donors ultimately engrafts. Survival rates are now similar with unrelated donor and cord blood transplantation.

THE TRANSPLANT PREPARATIVE REGIMEN

T e treatment regimen administered to patients immediately preceding transplantation is designed to eradicate the patient's underlying disease and, in the setting of allogeneic transplantation, immunosuppress the patient adequately to prevent rejection of the transplanted marrow. T e appropriate regimen therefore depends on the disease setting and source of marrow. For example, when transplantation is performed to treat severe combined immunodeficiency and the donor is a histocompatible sibling, no treatment is needed because no host cells require eradication and the patient is already too immunoincompetent to reject the transplanted marrow. For aplastic anemia, there is no large population of cells to eradicate, and high-dose cyclophosphamide plus antithymocyte globulin are sufficient to immunosuppress the patient adequately to accept the marrow graft. In the setting of thalassemia and sickle cell anemia, high-dose busulfan is frequently added to cyclophosphamide in order to eradicate hyperplastic host hematopoiesis. A variety of different regimens have been developed to treat malignant diseases. Most of these regimens include agents that have high activity against the tumor in question at conventional doses and have myelosuppression as their predominant dose-limiting toxicity. T erefore, these regimens commonly include busulfan, cyclophosphamide, melphalan, thiotepa, carmustine, etoposide, and total-body irradiation in various combinations.

Although high-dose treatment regimens have typically been used in transplantation, the understanding that much of the antitumor effect of transplantation derives from an immunologically mediated GVT response has led investigators to ask if reduced-intensity conditioning regimens might be effective and more tolerable. Evidence for a GVT effect comes from studies showing that posttransplant relapse rates are lowest in patients who develop acute and chronic GVHD, higher in those without GVHD, and higher still in recipients of T cell–depleted allogeneic or syngeneic marrow. T e demonstration that complete remissions can be obtained in many patients who have relapsed after transplant by simply administering viable lymphocytes from the original donor further strengthens the argument for a potent GVT effect. Accordingly, a variety of reduced-intensity regimens have been studied, ranging from the very minimum required to achieve engraftment (e.g., fludarabine plus 200 cGy total-body irradiation) to regimens of more immediate intensity (e.g., fludarabine plus melphalan). Studies to date document that engraftment can be readily achieved with less toxicity than seen with conventional transplantation. Furthermore, the severity of acute GVHD appears to be somewhat decreased. Complete sustained responses have been documented in many patients, particularly those with more indolent hematologic malignancies. In general, relapse rates are higher following reduced-intensity conditioning, but transplant-related mortality is lower, favoring the use of reduced-intensity conditioning in older patients and those with significant comorbidities. High-dose regimens are favored in younger, fitter patients.

THE TRANSPLANT PROCEDURE

Marrow is usually collected from the donor's posterior and sometimes anterior iliac crests, with the donor under general or spinal anesthesia. Typically, 10–15 mL/kg of marrow is aspirated, placed in heparinized media, and filtered through 0.3- and 0.2-mm screens to remove fat and bony spicules. The collected marrow may undergo further processing depending on the clinical situation, such as the removal of red cells to prevent hemolysis in ABO-incompatible transplants, the removal of donor T cells to prevent GVHD, or attempts to remove possible contaminating tumor cells in autologous transplantation. Marrow donation is safe, with only very rare complications reported.

Peripheral blood stem cells are collected by leukapheresis after the donor has been treated with hematopoietic growth factors or, in the setting of autologous transplantation, sometimes after treatment with a combination of chemotherapy and growth factors. Stem cells for transplantation are infused through a large-bore central venous catheter. Such infusions are usually well tolerated, although occasionally patients develop fever, cough, or shortness of breath. These symptoms typically resolve with slowing of the infusion. When the stem cell product has been cryopreserved using dimethyl sulfoxide, patients more often experience short-lived nausea or vomiting due to the odor and taste of the cryoprotectant.

ENGRAFTMENT

Peripheral blood counts usually reach their nadir several days to a week after transplant as a consequence of the preparative regimen; then cells produced by the transplanted stem cells begin to appear in the peripheral blood. The rate of recovery depends on the source of stem cells, the use of posttransplant growth factors, and the form of GVHD prophylaxis used. If marrow is the source of stem cells, recovery to 100 granulocytes/μL occurs on average by day 16 and to 500/μL by day 22. Use of G-CSF–mobilized peripheral blood stem cells speeds the rate of recovery by ~1 week when compared to marrow, whereas engraftment following cord blood transplantation is typically delayed by ~1 week compared to marrow. Use of a myeloid growth factor (G-CSF or GM-CSF) after transplant can accelerate recovery by 3–5 days, whereas use of methotrexate to prevent GVHD delays engraftment by a similar period. Following allogeneic transplantation, engraftment can be documented using fluorescence in situ hybridization of sex chromosomes if donor and recipient are sex-mismatched or by analysis of a variable number of tandem repeats or short tandem repeat polymorphisms after DNA amplification.

COMPLICATIONS FOLLOWING HEMATOPOIETIC CELL TRANSPLANT

Early direct chemoradiotoxicities

The transplant preparative regimen may cause a spectrum of acute toxicities that vary according to intensity of the regimen and the specific agents used, but frequently results in nausea, vomiting, and mild skin erythema **(Fig. 31-1)**. Regimens that include high-dose cyclophosphamide can result in hemorrhagic cystitis, which can usually be prevented by bladder irrigation or with the sulfydryl compound mercaptoethanesulfonate (MESNA); rarely, acute hemorrhagic carditis is seen. Most high-dose preparative regimens will result in oral mucositis, which typically develops 5–7 days after transplant and often requires narcotic analgesia. Use of a patient-controlled analgesic pump provides the greatest patient satisfaction and results in a lower cumulative dose of narcotic. Keratinocyte growth factor (palifermin) can shorten the duration of mucositis by several days following autologous transplantation. Patients begin losing their hair 5–6 days after transplant and by 1 week are usually profoundly pancytopenic.

Depending on the intensity of the conditioning regimen, 3–10% of patients will develop sinusoidal obstruction syndrome (SOS) of the liver (formerly called venoocclusive disease), a syndrome that results from direct cytotoxic injury to hepatic-venular and sinusoidal endothelium, with subsequent deposition of fibrin and the development of a local hypercoagulable state. This is chain of events leads to the clinical symptoms of tender hepatomegaly, ascites, jaundice, and

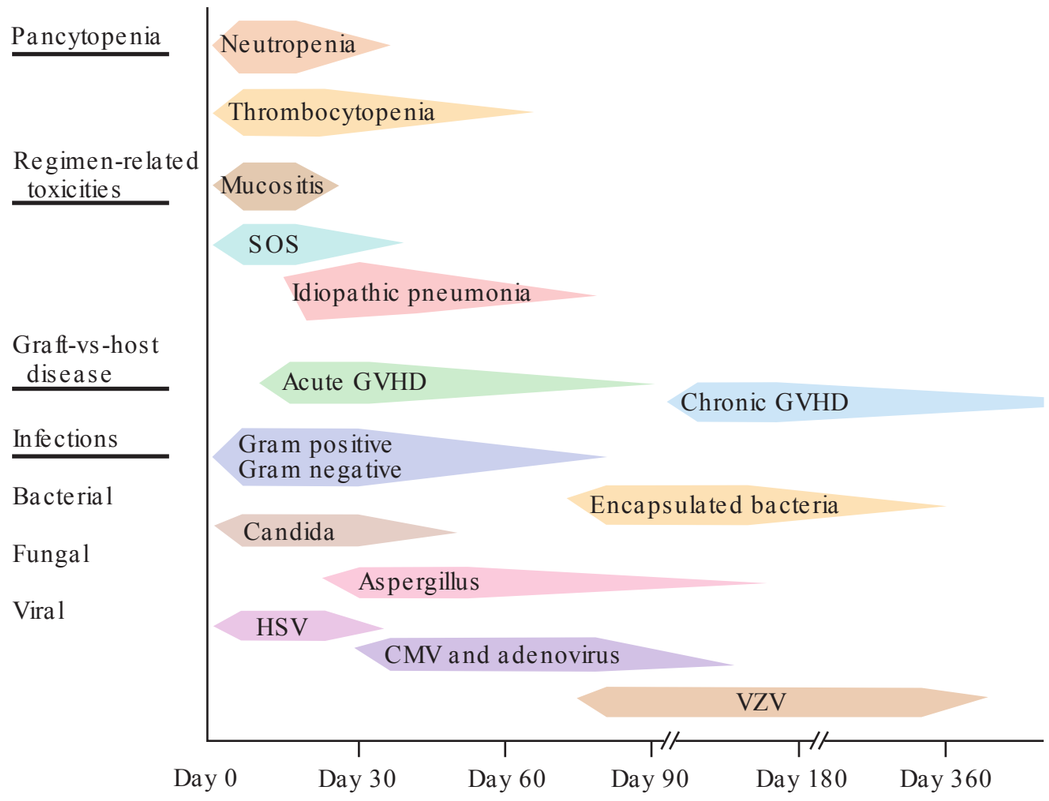

FIGURE 31-1
Major syndromes complicating marrow transplantation. CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; SOS, sinusoidal obstructive syndrome (formerly venoocclusive disease); VZV, varicella-zoster virus. The size of the shaded area roughly reflects the period of risk of the complication.

fluid retention. T ese symptoms can develop any time during the first month after transplant, with the peak incidence at day 16. Predisposing factors include prior exposure to intensive chemotherapy, pretransplant hepatitis of any cause, and use of more intense conditioning regimens. T e mortality rate of sinusoidal obstruction syndrome is ~30%, with progressive hepatic failure culminating in a terminal hepatorenal syndrome. Both thrombolytic and antithrombotic agents, such as tissue plasminogen activator, heparin, and prostaglandin E, have been studied as therapy, but none has proven of consistent major benefit in controlled trials, and all have significant toxicity. Studies with defibrotide, a polydeoxyribonucleotide, seem encouraging.

Although most pneumonias developing early after transplant are caused by infectious agents, in ~5% of patients a diffuse interstitial pneumonia will develop that is thought to be the result of direct toxicity of high-dose preparative regimens. Bronchoalveolar lavage usually shows alveolar hemorrhage, and biopsies are typically characterized by diffuse alveolar damage, although some cases may have a more clearly interstitial pattern. High-dose glucocorticoids or antitumor necrosis factor therapies are sometimes used as treatment, although randomized trials testing their utility have not been reported.

Late direct chemoradiotoxicities

Late complications of the preparative regimen include decreased growth velocity in children and delayed development of secondary sex characteristics. T ese complications can be partly ameliorated with the use of appropriate growth and sex hormone replacement. Most men become azoospermic, and most postpubertal women will develop ovarian failure, which should be treated. However, pregnancy is possible after transplantation, and patients should be counseled accordingly. T yroid dysfunction, usually well compensated, is sometimes seen. Cataracts develop in 10–20% of patients and are most common in patients treated with total-body irradiation and those who receive glucocorticoid therapy after transplant for treatment of GVHD. Aseptic necrosis of the femoral head is seen in 10% of patients and is particularly frequent in those receiving chronic glucocorticoid therapy. Both acute and late chemoradiotoxicities (except those due to glucocorticoids and other agents used to treat GVHD) are considerably less frequent in recipients of reduced-intensity compared to high-dose preparative regimens.

Graft failure

Although complete and sustained engraftment is usually seen after transplant, occasionally marrow function either does not return or, after a brief period of engraftment, is lost. Graft failure after autologous transplantation can be the result of inadequate numbers of stem cells being transplanted, damage during ex vivo treatment or storage, or exposure of the patient to myelotoxic agents after transplant. Infections with cytomegalovirus (CMV) or human herpesvirus type 6 have also been associated with loss of marrow function. Graft failure after allogeneic transplantation can also be due to immunologic rejection of the graft by immunocompetent host cells. Immunologically based graft rejection is more common following use of less immunosuppressive preparative regimens, in recipients of T cell–depleted stem cell products, and in patients receiving grafts from HLA-mismatched donors or cord blood.

Treatment of graft failure usually involves removing all potentially myelotoxic agents from the patient's regimen and attempting a short trial of a myeloid growth factor. Persistence of lymphocytes of host origin in allogeneic transplant recipients with graft failure indicates immunologic rejection. Reinfusion of donor stem cells in such patients is usually unsuccessful unless preceded by a second immunosuppressive preparative regimen. Standard high-dose preparative regimens are generally tolerated poorly if administered within 100 days of a first transplant because of cumulative toxicities. However, use of regimens combining, for example, fludarabine plus low-dose total-body irradiation, or cyclophosphamide plus antithymocyte globulin, has been effective in some cases.

Graft-versus-host disease

GVHD is the result of allogeneic T cells that are transferred with the donor's stem cell inoculum reacting with antigenic targets on host cells. Acute GVHD usually occurs within the first 3 months after transplant with a peak onset around 4 weeks and is characterized by an erythematous maculopapular rash; by persistent anorexia or diarrhea, or both; and by liver disease with increased serum levels of bilirubin, alanine and aspartate aminotransferase, and alkaline phosphatase. Because many conditions can mimic acute GVHD, the diagnosis usually requires skin, liver, or endoscopic biopsy for confirmation. In all these organs, endothelial damage and lymphocytic infiltrates are seen. In skin, the epidermis and hair follicles are damaged; in liver, the small bile ducts show segmental disruption; and in intestines, destruction of the crypts and mucosal ulceration may be noted. A commonly used rating system for acute GVHD is shown in **Table 31-1**. Grade I acute GVHD is of little clinical significance, does not affect the likelihood of survival, and does not require treatment. In contrast, grades II to IV GVHD are associated with significant symptoms and a poorer probability of survival, and they require aggressive therapy. T e incidence of acute GVHD is higher in recipients of stem cells from mismatched or unrelated donors, in older

TABLE 31-1

CLINICAL STAGING AND GRADING OF ACUTE GRAFT-VERSUS-HOST DISEASE

CLINICAL STAGE	SKIN	LIVER—BILIRUBIN, μmol/L (mg/dL)	GUT
1	Rash <25% body surface	34–51 (2–3)	Diarrhea 500–1000 mL/d
2	Rash 25–50% body surface	51–103 (3–6)	Diarrhea 1000–1500 mL/d
3	Generalized erythroderma	103–257 (6–15)	Diarrhea >1500 mL/d
4	Desquamation and bullae	>257 (>15)	Ileus
OVERALL CLINICAL GRADE	**SKIN STAGE**	**LIVER STAGE**	**GUT STAGE**
I	1–2	0	0
II	1–3	1	1
III	1–3	2–3	2–3
IV	2–4	2–4	2–4

patients, and in patients unable to receive full doses of drugs used to prevent the disease.

One general approach to the prevention of GVHD is the administration of immunosuppressive drugs early after transplant. Combinations of methotrexate and either cyclosporine or tacrolimus are among the most effective and widely used regimens. Prednisone, anti–T cell antibodies, mycophenolate mofetil, sirolimus, and other immunosuppressive agents have also been or are being studied in various combinations. A second general approach to GVHD prevention is removal of T cells from the stem cell inoculum. While effective in preventing GVHD, T cell depletion has been associated with an increased incidence of graft failure, infectious complications, and tumor recurrence after transplant; as yet, it is unsettled whether T cell depletion improves cure rates in any specific setting.

Despite prophylaxis, significant acute GVHD will develop in ~30% of recipients of stem cells from matched siblings and in as many as 60% of those receiving stem cells from unrelated donors. The disease is usually treated with glucocorticoids, additional immunosuppressants, or monoclonal antibodies targeted against T cells or T cell subsets.

Chronic GVHD occurs most commonly between 3 months and 2 years after allogeneic transplant, developing in 20–50% of recipients. The disease is more common in older patients, in recipients of mismatched or unrelated stem cells, and in those with a preceding episode of acute GVHD. The disease resembles an autoimmune disorder with malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, and bile duct degeneration and cholestasis. Single-agent prednisone or cyclosporine is standard treatment at present, although trials of other agents are under way. Mortality rates from chronic GVHD average around 15%, but range from 5–50% depending on severity. In most patients, chronic GVHD resolves, but it may require 1–3 years of immunosuppressive treatment before these agents can be withdrawn without the disease recurring. Because patients with chronic GVHD are susceptible to significant infection, they should receive prophylactic trimethoprim-sulfamethoxazole, and all suspected infections should be investigated and treated aggressively.

Although onset before or after 3 months after transplant is often used to discriminate between acute and chronic GVHD, occasional patients will develop signs and symptoms of acute GVHD after 3 months (late-onset acute GVHD), whereas others will exhibit signs and symptoms of both acute and chronic GVHD (overlap syndrome). There are as yet no data to suggest that these patients should be treated differently than those with classic acute or chronic GVHD.

From 3–5% of patients will develop an autoimmune disorder following allogeneic HCT, most commonly autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura. Unrelated donor source and chronic GVHD are risk factors, but autoimmune disorders have been reported in patients with no obvious GVHD. Treatment is with prednisone, cyclosporine, or rituximab.

Infection

Posttransplant patients, particularly recipients of allogeneic transplantation, require unique approaches to the problem of infection. Early after transplantation, patients are profoundly neutropenic, and because the risk of bacterial infection is so great, most centers initiate antibiotic treatment once the granulocyte count falls to <500/μL. Fluconazole prophylaxis at a dose of 200–400 mg/d reduces the risk of candidal infections. Patients seropositive for herpes simplex should receive acyclovir prophylaxis. One approach to infection prophylaxis is shown in **Table 31-2**. Despite these

TABLE 31-2

APPROACH TO INFECTION PROPHYLAXIS IN ALLOGENEIC TRANSPLANT RECIPIENTS

ORGANISM	AGENT	APPROACH
Bacterial	Levofloxacin	750 mg PO or IV daily
Fungal	Fluconazole	400 mg PO qd to day 75 posttransplant
Pneumocystis carinii	Trimethoprim-sulfamethoxazole	1 double-strength tablet PO bid 2 days/week until day 180 or off immunosuppression
Viral		
Herpes simplex	Acyclovir	800 mg PO bid to day 30
Varicella-zoster	Acyclovir	800 mg PO bid to day 365
Cytomegalovirus	Ganciclovir	5 mg/kg IV bid for 7 days, then 5 (mg/kg)/d 5 days/week to day 100

prophylactic measures, most patients will develop fever and signs of infection after transplant. T e management of patients who become febrile despite bacterial and fungal prophylaxis is a difficult challenge and is guided by individual aspects of the patient and by the institution's experience.

Once patients engraft, the incidence of bacterial infection diminishes; however, patients, particularly allogeneic transplant recipients, remain at significant risk of infection. During the period from engraftment until about 3 months after transplant, the most common causes of infection are gram-positive bacteria, fungi (particularly Aspergillus), and viruses including CMV. CMV infection, which in the past was frequently seen and often fatal, can be prevented in seronegative patients transplanted from seronegative donors by the use of either seronegative blood products or products from which the white blood cells have been removed. In seropositive patients or patients transplanted from seropositive donors, the use of ganciclovir, either as prophylaxis beginning at the time of engraftment or initiated when CMV first reactivates as evidenced by development of antigenemia or viremia, can significantly reduce the risk of CMV disease. Foscarnet is effective for some patients who develop CMV antigenemia or infection despite the use of ganciclovir or who cannot tolerate the drug.

Pneumocystis jiroveci pneumonia, once seen in 5–10% of patients, can be prevented by treating patients with oral trimethoprim-sulfamethoxazole for 1 week before transplant and resuming the treatment once patients have engrafted.

T e risk of infection diminishes considerably beyond 3 months after transplant unless chronic GVHD develops, requiring continuous immunosuppression. Most transplant centers recommend continuing trimethoprim-sulfamethoxazole prophylaxis while patients are receiving any immunosuppressive drugs and also recommend careful monitoring for late CMV reactivation. In addition, many centers recommend prophylaxis against varicella-zoster, using acyclovir for 1 year after transplant. Patients should be revaccinated against tetanus, diphtheria, Haemophilus inf uenzae, polio, and pneumococcal pneumonia starting at 12 months after transplant and against measles, mumps, and rubella (MMR), varicella-zoster virus, and possibly pertussis at 24 months.

TREATMENT OF SPECIFIC DISEASES USING HEMATOPOIETIC CELL TRANSPLANTATION

TREATMENT Nonmalignant Diseases

IMMUNODEFICIENCY DISORDERS By replacing abnormal stem cells with cells from a normal donor, hematopoietic cell transplantation can cure patients of a variety of immunodeficiency disorders including severe combined immunodeficiency, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. T e widest experience has been with severe combined immunodeficiency disease, where cure rates of 90% can be expected with HLA-identical donors and success rates of 50–70% have been reported using haplotype-mismatched parents as donors **(Table 31-3)**.

APLASTIC ANEMIA Transplantation from matched siblings after a preparative regimen of high-dose cyclophosphamide and antithymocyte globulin can cure up to 90% of patients age <40 years with severe aplastic anemia. Results in older patients and in recipients of mismatched family member or unrelated marrow are less favorable; therefore, a trial of immunosuppressive therapy is generally recommended for such patients before considering transplantation. Transplantation is effective in all forms of aplastic anemia including, for example, the syndromes associated with paroxysmal nocturnal hemoglobinuria and Fanconi's anemia. Patients with Fanconi's anemia are abnormally sensitive to the toxic effects of alkylating agents, and so less intensive preparative regimens must be used in their treatment **(Chap. 11)**.

TABLE 31-3

ESTIMATED 5-YEAR SURVIVAL RATES FOLLOWING TRANSPLANTATION[a]

DISEASE	ALLOGENEIC, %	AUTOLOGOUS, %
Severe combined immunodeficiency	90	N/A
Aplastic anemia	90	N/A
Thalassemia	90	N/A
Acute myeloid leukemia		
First remission	55–60	50
Second remission	40	30
Acute lymphocytic leukemia		
First remission	50	40
Second remission	40	30
Chronic myeloid leukemia		
Chronic phase	70	ID
Accelerated phase	40	ID
Blast crisis	15	ID
Chronic lymphocytic leukemia	50	ID
Myelodysplasia	45	ID
Multiple myeloma	30	35
Non-Hodgkin's lymphoma		
First relapse/ second remission	40	40
Hodgkin's disease		
First relapse/ second remission	40	50

[a]These estimates are generally based on data reported by the International Bone Marrow Transplant Registry. The analysis has not been reviewed by their Advisory Committee.
Abbreviations: ID, insuf cient data; N/A, not applicable.

HEMOGLOBINOPATHIES Marrow transplantation from an HLA-identical sibling following a preparative regimen of busulfan and cyclophosphamide can cure 80–90% of patients with thalassemia major. T e best outcomes can be expected if patients are transplanted before they develop hepatomegaly or portal fibrosis and if they have been given adequate iron chelation therapy. Among such patients, the probabilities of 5-year survival and disease-free survival are 95 and 90%, respectively. Although prolonged survival can be achieved with aggressive chelation therapy, transplantation is the only curative treatment for thalassemia. Transplantation is being studied as a curative approach to patients with sickle cell anemia. Two-year survival and disease-free survival rates of 90 and 80%, respectively, have been reported following matched sibling or cord blood transplantation. Decisions about patient selection and the timing of transplantation remain difficult, but transplantation represents a reasonable option for younger patients who suffer repeated crises or other significant complications and who have not responded to other interventions **(Chap. 8)**.

OTHER NONMALIGNANT DISEASES T eoretically, hematopoietic cell transplantation should be able to cure any disease that results from an inborn error of the lymphohematopoietic system. Transplantation has been used successfully to treat congenital disorders of white blood cells such as Kostmann's syndrome, chronic granulomatous disease, and leukocyte adhesion deficiency. Congenital anemias such as Blackfan-Diamond anemia can also be cured with transplantation. Infantile malignant osteopetrosis is due to an inability of the osteoclast to resorb bone, and because osteoclasts derive from the marrow, transplantation can cure this rare inherited disorder.

Hematopoietic cell transplantation has been used as treatment for a number of storage diseases caused by enzymatic deficiencies, such as Gaucher's disease, Hurler's syndrome, Hunter's syndrome, and infantile metachromatic leukodystrophy. Transplantation for these diseases has not been uniformly successful, but treatment early in the course of these diseases, before irreversible damage to extramedullary organs has occurred, increases the chance for success.

Transplantation is being explored as a treatment for severe acquired autoimmune disorders. T ese trials are based on studies demonstrating that transplantation can reverse autoimmune disorders in animal models and on the observation that occasional patients with coexisting autoimmune disorders and hematologic malignancies have been cured of both with transplantation.

TREATMENT Malignant Diseases

ACUTE LEUKEMIA Allogeneic hematopoietic cell transplantation cures 15–20% of patients who do not achieve complete response from induction chemotherapy for acute myeloid leukemia (AML) and is the only form of therapy that can cure such patients. Cure rates of 30–35% are seen when patients are transplanted in second remission or in first relapse. T e best results with allogeneic transplantation are achieved when applied during first remission, with disease-free survival rates averaging 55–60%. Meta-analyses of studies comparing matched related donor transplantation to chemotherapy for adult AML patients age <60 years show a survival advantage with transplantation. T is advantage is greatest for those with unfavorablerisk AML and is lost in those with favorable-risk disease. T e role of autologous transplantation in the treatment of AML is less well defined. T e rates of disease recurrence with autologous transplantation are higher than those seen after allogeneic transplantation, and cure rates are somewhat less.

Similar to patients with AML, adults with acute lymphocytic leukemia who do not achieve a complete response to induction chemotherapy can be cured in 15–20% of cases with immediate transplantation. Cure rates improve to 30–50% in second remission, and therefore transplantation can be recommended for adults who have persistent disease after induction chemotherapy or who have subsequently relapsed. Transplantation in first remission results in cure rates about 55%. Transplantation appears to offer a clear advantage over chemotherapy for patients with high-risk disease, such as those with Philadelphia chromosome–positive disease. Debate continues about whether adults with standard-risk disease should be transplanted in first remission or whether transplantation should be reserved until relapse. Autologous transplantation is associated with a higher relapse rate but a somewhat lower risk of nonrelapse mortality when compared to allogeneic transplantation. There is no obvious role of autologous transplantation for acute lymphocytic leukemia in first remission, and for second-remission patients, most experts recommend use of allogeneic stem cells if an appropriate donor is available.

CHRONIC LEUKEMIA Allogeneic hematopoietic cell transplantation is the only therapy shown to cure a substantial portion of patients with chronic myeloid leukemia (CML). Five-year disease-free survival rates are 15–20% for patients transplanted for blast crisis, 25–50% for accelerated-phase patients, and 60–70% for chronic-phase patients, with cure rates as high as 80% at selected centers. However, with the availability of imatinib mesylate and other highly active tyrosine kinase inhibitors (TKIs), transplantation is generally reserved for those who fail to achieve a complete cytogenetic response with a TKI, relapse after an initial response, or are intolerant of the drugs **(Chap. 15)**.

Allogeneic transplantation using a high-dose preparative regimen has rarely been used for chronic lymphocytic leukemia (CLL), in large part because of the chronic nature of the disease and because of the age profile of patients. In those cases where it was studied, complete remissions were achieved in the majority of patients, with disease-free survival rates of ~50% at 3 years, despite the advanced stage of the disease at the time of transplant. The marked antitumor effects have resulted in the increased use and study of allogeneic transplantation using reduced-intensity conditioning for the treatment of CLL.

MYELODYSPLASIA Between 20 and 65% of patients with myelodysplasia appear to be cured with allogeneic transplantation. Results are better among younger patients and those with less advanced disease. However, patients with early-stage myelodysplasia can live for extended periods without intervention, and so transplantation is generally reserved for patients with an International Prognostic Scoring System (IPSS) score of Int-2 or for selected patients with an IPSS score of Int-1 who have other poor prognostic features **(Chap. 11)**.

LYMPHOMA Patients with disseminated intermediate- or high-grade non-Hodgkin's lymphoma who have not been cured by first-line chemotherapy and are transplanted in first relapse or second remission can still be cured in 40–50% of cases. This represents a clear advantage over results obtained with conventional-dose salvage chemotherapy. It is unsettled whether patients with high-risk disease benefit from transplantation in first remission. Most experts favor the use of autologous rather than allogeneic transplantation for patients with intermediate- or high-grade non-Hodgkin's lymphoma, because fewer complications occur with this approach and survival appears equivalent. For patients with recurrent disseminated indolent non-Hodgkin's lymphoma, autologous transplantation results in high response rates and improved progression-free survival compared to salvage chemotherapy. However, late relapses are seen after transplantation. The role of autologous transplantation in the initial treatment of patients is debated. It may be indicated in the small subset of patients presenting with high-risk prognostic factors but is not clearly more effective in those in lower risk groups. Reduced-intensity conditioning regimens followed by allogeneic transplantation result in high response rates in patients with indolent lymphomas, but the exact role of this approach remains to be defined.

The role of transplantation in Hodgkin's disease is similar to that in intermediate- and high-grade non-Hodgkin's lymphoma. With transplantation, 5-year disease-free survival is 20–30% in patients who never achieve a first remission with standard chemotherapy and up to 70% for those transplanted in second remission. Transplantation has no defined role in first remission in Hodgkin's disease.

MYELOMA Patients with myeloma who have progressed on first-line therapy can sometimes benefit from allogeneic or autologous transplantation. Prospective randomized studies demonstrate that the inclusion of autologous transplantation as part of the initial therapy of patients results in improved disease-free survival and overall survival. Further benefit is seen with the use of lenalidomide maintenance therapy following transplantation. The use of autologous transplantation followed by nonmyeloablative allogeneic transplantation has yielded mixed results.

SOLID TUMORS Randomized trials evaluating autologous transplantation as treatment for primary or metastatic breast cancer have failed to show a consistent survival advantage with this approach, and therefore, there is no established role for transplantation in this disease.

Patients with testicular cancer in whom first-line platinum-containing chemotherapy has failed can still be cured in ~50% of cases if treated with high-dose chemotherapy with autologous stem cell support, an outcome better than that seen with low-dose salvage chemotherapy.

The use of high-dose chemotherapy with autologous stem cell support is being studied for several other solid tumors, including neuroblastoma and pediatric sarcomas. As in most other settings, the best results have been obtained in patients

with limited amounts of disease and where the remaining tumor remains sensitive to conventional-dose chemotherapy. Few randomized trials of transplantation in these diseases have been completed.

Partial and complete responses have been reported following nonmyeloablative allogeneic transplantation for some solid tumors, most notably renal cell cancers. The GVT effect, well documented in the treatment of hematologic malignancies, may apply to selected solid tumors under certain circumstances.

POSTTRANSPLANT RELAPSE Patients who relapse following autologous transplantation sometimes respond to further chemotherapy and may be candidates for possible allogeneic transplantation, particularly if the remission following the initial autologous transplant was long. Several options are available for patients who relapse following allogeneic transplantation. Of particular interest are the response rates seen with infusion of unirradiated donor lymphocytes. Complete responses in as many as 75% of patients with chronic myeloid leukemia, 40% in myelodysplasia, 25% in AML, and 15% in myeloma have been reported. Major complications of donor lymphocyte infusions include transient myelosuppression and the development of GVHD. These complications depend on the number of donor lymphocytes given and the schedule of infusions, with less GVHD seen with lower dose, fractionated schedules.

CHAPTER 32

NEOPLASIA DURING PREGNANCY

Michael F. Greene ■ Dan L. Longo

Cancer complicates ~1 in every 1000 pregnancies. Of all the cancers that occur in women, less than 1% complicate pregnancies. The four cancers that most commonly complicate pregnancies are cervical cancer, breast cancer, melanoma, and lymphomas (particularly Hodgkin's lymphoma); however, virtually every form of cancer has been reported in pregnant women **(Table 32-1)**. In addition to cancers developing in other organs of the mother, gestational trophoblastic tumors can arise from the placenta. The problem of cancer in a pregnant woman is complex. One must take into account (1) the possible influence of the pregnancy on the natural history of the cancer, (2) effects on the mother and fetus of complications from the malignancy (e.g., anorexia, nausea, vomiting, malnutrition), (3) potential effects of diagnostic and staging procedures, and (4) potential effects of cancer treatments on both the mother and the developing fetus. Generally, the management that optimizes maternal physiology is also best for the fetus. However, the dilemma occasionally arises that what is best for the mother may be harmful to the fetus, and what is best for the fetus may compromise the ultimate prognosis for the mother. The best way to approach management of a pregnant woman with cancer is to ask, "What would we do for this woman in this clinical situation if she was not pregnant? Now, which, if any, of those plans need to be modified because she is pregnant?"

Pregnancy is associated with a number of physiologic changes that frequently result in symptoms that may make it difficult to recognize symptoms or physical findings suggestive of a neoplasm. Increased sensitivity of central chemoreceptors to Pco_2 drives an increase in minute ventilation that many women perceive as dyspnea at rest or with minimal exertion. The combination of increased total body water, decreased colloid oncotic pressure, and some obstruction of venous return from the lower extremities causes demonstrable dependent edema in more than 50% of pregnant women. Decreased gastrointestinal motility due to high serum progesterone levels and mechanical compression from an enlarging uterus cause early satiety, gastroesophageal reflux, nausea, vomiting, and constipation. Hemorrhoids develop and often bleed. Breasts enlarge and increase in density and "lumpiness." These changes may result in delayed recognition and more advanced disease at diagnosis.

Physiologic changes in the maternal immune system necessary to facilitate retention of the fetal semiallograft raise concerns that the relationship of a cancer with its host may be altered to the detriment of the maternal host. One half of all the genes necessary to create a new individual by sexual reproduction come from each parent. This provides the opportunity for many antigenic differences between the conceptus and the mother. Mammalian placentation has been a very successful method of reproduction, but it has necessitated some combination of both fetal and maternal evolutionary immune adaptations. These mechanisms are incompletely understood and remain an area of active investigation. It does seem likely, however, that this has been accomplished without a general, nonspecific blunting of the maternal immune response, which would be maladaptive to the mother. The multiple mechanisms likely include some "masking" of fetal antigens from recognition by the maternal immune system, blunting the maternal inflammatory response locally at the placental–maternal interface and induction of fetal-specific maternal immune tolerance to avoid rejection. Attention has turned to a subset of CD4+ induced, peripherally produced regulatory T cells that express the X chromosome encoded transcription factor Foxp3 (so-called *T*regs). When these Foxp3 cells develop centrally in the thymus, they are termed "Tregs." When Foxp3-expressing cells develop peripherally, they are called "Pregs." These regulatory cells suppress the immune response against "self " and foreign antigens. They seem to be capable of suppressing the maternal response to paternal antigens expressed by the fetus and creating memory

TABLE 32-1

INCIDENCE OF MALIGNANT TUMORS DURING GESTATION

TUMOR TYPE	INCIDENCE PER 10,000 PREGNANCIES[a]	% OF CASES[b]
Breast cancer	1–3	25%
Cervical cancer	1.2–4.5	25%
Thyroid cancer	1.2	15%
Hodgkin's disease	1.6	10%
Melanoma	1–2.6	8%
Ovarian cancer	0.8	2%
All sites	10	100%

[a]These are estimates based on extrapolations from a review of more than 3 million pregnancies (LH Smith et al: Am J Obstet Gynecol 184:1504, 2001).
[b]Based on accumulating case reports from the literature; the precision of these data is not high.

TABLE 32-2

ESTIMATED FETAL EXPOSURE FROM SOME COMMON RADIOLOGIC PROCEDURES

PROCEDURE	FETAL EXPOSURE
Chest x-ray (2 views)	0.02–0.07 mrad
Abdominal film (single view)	100 mrad
Intravenous pyelography	≥1 rad[a]
Hip film (single view)	7–20 mrad
Barium enema or small bowel series	2–4 rad
CT scan of head or chest	<1 rad
CT scan of abdomen and lumbar spine	3.5 rad
CT pelvimetry	250 mrad

[a]Exposure depends on the number of films.
Abbreviation: CT, computed tomography.
Source: Data from FG Cunningham et al: General considerations and maternal evaluation. In Williams Obstetrics, 21st ed. New York: McGraw-Hill; 2001, pp. 1143–1158.

cells that retain tolerance to the same paternal antigens in subsequent pregnancies. Unfortunately, in a mouse model, the interleukin (IL) 10 produced by these cells enhanced susceptibility to infection by Listeria and Salmonella, while ironically not proving essential for retaining the fetal graft. Undoubtedly much remains to be learned about this critical immune balance.

RADIATION IN PREGNANCY

Exposure of developing fetuses to ionizing radiation may cause adverse fetal effects; awareness among physicians of this potential toxicity has resulted in a disproportionate aversion to diagnostic imaging in pregnancy. First, it must be stated that there are very useful imaging modalities (i.e., ultrasound and magnetic resonance imaging [MRI]) that do not use any ionizing radiation and are not associated with any demonstrable adverse fetal effects. There are three potential adverse fetal effects of ionizing radiation: teratogenesis (induction of anatomic birth defects), mutagenesis, and carcinogenesis. The fetus is most sensitive to teratogenesis during organogenesis in the first trimester. The dose of ionizing radiation necessary to induce birth defects in human fetuses is derived from studies of the survivors of the atomic bomb explosions and by extrapolation from controlled experiments in nonhuman mammals. From these data sources, it is clear that a minimum of 5 rem and more likely greater than 10 rem exposure is needed to induce birth defects in the first trimester. The fetal doses of radiation associated with some common diagnostic radiologic procedures are displayed in **Table 32-2**. The data in Table 32-2 show that no single procedure or selective combination of diagnostic procedures will exceed the very conservative 5 rem teratogenic threshold. Teratogenic effects later in pregnancy are largely limited to microcephaly and require exposures exceeding 25 rem. The reason for the disproportionate concern about radiation exposure and birth defects is that 2.5% of all fetuses are affected with birth defects without radiation exposure and, therefore, 2.5% of women undergoing any diagnostic imaging procedure will deliver malformed fetuses. Spontaneous mutations occur relatively infrequently, and high doses of radiation (>150 rem) are required to cause a demonstrable increase in that rate. The magnitude of the risk of carcinogenesis in offspring exposed as fetuses to diagnostic doses of radiation has been very difficult to measure due to the relative rarity of cancer in children and the long duration of follow-up that might credibly be needed to see the effect. The inconsistent results and small effect sizes observed from diagnostic exposures make it likely that, if there is an effect, it is very small and, if there is not a significant effect, it will be impossible to prove that fact to everyone's satisfaction. No imaging using ionizing radiation should be done without a compelling reason and due consideration to obtaining the necessary information by other imaging modalities. Exposure to diagnostic and therapeutic radionuclides, especially radioactive iodine, poses unique risks, but a full discussion of these is beyond the scope of this chapter. Radiation therapy uses radiation doses three orders of magnitude greater than diagnostic procedures, entails substantial risks if the fetus is in the radiation field, and is rarely appropriate in pregnancy. Finally, although difficult to prove, it is likely that more harm has come to pregnant women from failing to perform appropriate diagnostic procedures than has been done to their offspring from performing appropriate diagnostic procedures.

CHEMOTHERAPY IN PREGNANCY

There are a number of reasons why it is impossible to make many definitive statements regarding the safety and efficacy of chemotherapy in pregnancy. All of the available data in the literature are published as case reports or case series. The quality and completeness of the data are inconsistent and often poor. Reports may come from medical oncologists, obstetricians, pediatricians, or other treating physicians familiar with the information important to the report from their own perspective but missing information important for other specialty areas. Reports frequently lack critical details of drug administration, such as dose, duration, cumulative dose, and timing of exposure in gestation, and outcomes, including birth weight and gestational age at delivery, indication for or cause of premature delivery, and follow-up of offspring beyond the immediate neonatal period. There are a wide variety of agents available to treat cancer, and they are usually used in combinations. This results in the fact that every patient is almost unique (an experiment of one) in the combination of agents, doses, durations, and gestational ages of administration, making it very difficult to attribute what benefit or toxicity accrues to which agent. Fortunately, cancer in pregnant women is sufficiently rare that it takes quite a while to accumulate enough information for any one agent or combination of agents to be confident about what toxicities (including congenital malformations) are truly associated with which agents. There is such rapid progress in cancer chemotherapy that by the time there may seem to be enough information about the agents currently in use to use them intelligently and counsel patients meaningfully, the cancer community has moved on to newer, more efficacious, and hopefully less toxic agents for which there is little or no experience in pregnancy. Finally, for obvious reasons, there are no untreated controls for comparison. It may be very difficult to sort out the maternal consequences (nausea, vomiting, fever, weight loss, dehydration) that might result directly from the malignancy and cause adverse pregnancy outcomes from some of the toxicities of the chemotherapeutic agents used to treat the malignancy.

Generally, toxic chemotherapy should be avoided during pregnancy, if at all possible. It should virtually never be given in the first trimester. However, a variety of single agents and combinations have been given in the second and third trimesters, without a high frequency of toxic effects to the pregnancy or the fetus, but data on safety are sparse. Maternal factors that may influence the pharmacology of chemotherapeutic agents include the 50% increase in plasma volume, altered absorption and protein binding, increased glomerular filtration rate, increased hepatic mixed function oxidase activity, and third space created by amniotic fluid. The fetus is protected from some agents by placental expression of drug efflux pumps, but decreased fetal hepatic mixed function oxidase and glucuronidation activity may prolong the half-life of agents that do cross the placenta. A database on the risks associated with individual chemotherapy agents is available on the Internet (http://ntp.niehs.nih.gov/ntp/ohat/cancer_chemo_preg/chemopregnancy_monofnal_508.pdf).

Optimal management strategies have not been developed based on prospective clinical trials. Management of a malignancy complicating pregnancy will be critically determined by the gestational age when the malignancy is diagnosed and the anticipated natural history of the lesion, if left untreated. On one extreme, if the malignancy is slowly progressive, the patient is near her delivery date, and waiting until delivery to begin treatment would not be anticipated to compromise maternal prognosis, then treatment could be delayed until after delivery to avoid fetal exposure to chemotherapy. If there is a greater sense of urgency to begin definitive treatment to avoid compromising maternal prognosis, and the patient is beyond 24 weeks of gestation but remote from her delivery date, then treatment (surgical, medical, or both) might be initiated during pregnancy and plans made to deliver the fetus early to avoid exposure to more chemotherapy than absolutely necessary. Finally, if the patient is in her first trimester and toxic chemotherapy must be initiated promptly to avoid a very poor maternal outcome, then it may be necessary to consider therapeutic abortion to avoid maternal disaster and fetal survival with injury resulting in long-term morbid sequelae. No two cases are precisely alike, and inevitably, decision making must be individualized, preferably with consultation with a multidisciplinary team including medical oncology, surgical oncology if appropriate, maternal–fetal medicine, neonatology, and anesthesia. Pregnancy appears to have little or no impact on the natural history of malignancies, despite the hormonal influences. Spread of the mother's cancer to the fetus (so-called vertical transmission) is exceedingly rare.

CERVICAL CANCER DURING PREGNANCY

The incidence of cervical cancer in pregnant women is roughly comparable to that of age-matched controls who are not pregnant. Invasive cervical cancer complicates about 0.45 in 1000 live births, and carcinoma in situ is seen in 1 in 750 pregnancies. About 1% of women diagnosed with cervical cancer are pregnant at the time of diagnosis. Early signs of cervical cancer include vaginal spotting or discharge, pain, and postcoital bleeding, which are also common features of pregnancy.

Early visual changes in the cervix related to invasive cancer can be mistaken for cervical decidualization or ectropion (columnar epithelium on the cervix) due to pregnancy. Women diagnosed with cervical cancer during pregnancy report having had symptoms for 4.5 months on average.

Approximately 95% of all cervical cancer is caused by human papillomavirus (HPV) infections, with types 16 and 18 accounting for about 70% of cervical cancer. T e rate of carriage of these serotypes is highest among women in their early twenties and can be reduced with the use of vaccination before exposure. Women generally tend to clear the infection by age 30, with the risk of cervical cancer being highest among those who fail to clear the infection. Screening is recommended at the first prenatal visit and 6 weeks postpartum. T e rate of cytologic abnormalities on Pap smear in pregnant women is about 5–8% and is not much different than the rate in nonpregnant women of the same age.

In 2012, several sets of recommendations were published for screening for cervical cancer: one by the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP); a second by the U.S. Preventive Services Task Force (USPSTF); and a third by the American College of Obstetricians and Gynecologists (ACOG). Although the details of the recommendations for screening and management of abnormal results differ slightly among the three sets of guidelines, there is general consensus that cytology screening should start at age 21 and continue every 3 years through age 29. After age 30, cytology screening frequency may be reduced to every 5 years if accompanied by co-testing for HPV. Recommendations for management of abnormal cytology findings are complex and determined by the degree of abnormality of the cytology finding (e.g., atypical squamous cells of undetermined significance; atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; low-grade squamous intraepithelial lesion; or high-grade squamous intraepithelial lesion), the HPV status of the patient, the age of the patient, and whether this is the first abnormal finding or a persistent abnormality. A full discussion of all the treatment recommendations based on these factors is beyond the scope of this chapter. Some of the diagnostic procedures recommended for evaluation of nonpregnant women are contraindicated in pregnancy, and the indications for some procedures are modified in the setting of pregnancy. Suffice it to say that the evaluation of women with abnormal cervical cytology in pregnancy should be referred to knowledgeable and experienced gynecologists or gynecologic oncologists.

Cervical intraepithelial neoplasia is a slowly progressive lesion and has a low risk of progression to invasive cancer during pregnancy (~0.4%), and many low-grade lesions (36–70%) regress spontaneously. Accordingly, some physicians defer definitive diagnostic procedures in pregnant women until 6 weeks postpartum unless they are at high risk for invasive disease. If invasive disease is suspected and the pregnancy is between 16 and 20 weeks, a cone biopsy may be performed to make the diagnosis and may be curative for some lesions; however, the procedure may cause heavy bleeding due to the increased vasculature in the gravid cervix and increases the risk of premature rupture of membranes and preterm labor two- to threefold. Cone biopsy should not be done within 4 weeks of delivery. T e only indication for therapy of cervical neoplasia in pregnant women is the documentation of invasive cancer.

Management of invasive disease is guided by the stage of disease, the gestational age of the fetus, and the desire of the mother to have the baby. If the disease is in early stage and the pregnancy is desired, it is safe to delay treatment regardless of gestational age until fetal maturity allows for safe delivery. Abortion followed by definitive therapy is recommended for women with advanced, but potentially curable, cancer in the first or second trimester **(Chap. 46)**. If the disease is in an advanced stage in early pregnancy and the patient declines pregnancy termination to permit prompt definitive therapy, she must be informed of the fact that the maternal safety of delaying therapy is unproven. In women in the third trimester with advanced disease, the mother should be treated with betamethasone to accelerate fetal lung maturation and the baby should be delivered at the earliest possible gestational age followed immediately by stage-appropriate therapy. Most women with invasive cancer have early-stage disease. If the disease is microinvasive, vaginal delivery can take place and be followed by definitive treatment, usually conization. If a lesion is visible on the cervix, delivery is best done by caesarian section and followed by radical hysterectomy.

BREAST CANCER DURING PREGNANCY

Breast cancer complicates approximately 1 in 3000 to 10,000 live births. About 5% of all breast cancers occur in women age 40 years or younger. Among all premenopausal women with breast cancer, 25–30% were pregnant at the time of diagnosis. It has been recognized for some time that breast cancer associated with pregnancy generally seems to have a poorer prognosis for both overall survival and progression-free survival. T e definition of pregnancy-associated breast cancer (PABC) has differed in various publications, but a generally accepted definition is breast cancer diagnosed during pregnancy or within 1 year of delivery. T ere are likely several reasons for the observation of the poorer

prognosis. Breast cancers diagnosed during pregnancy are often diagnosed at a later stage of disease and so have a poorer outcome. T e late diagnosis is often due to the fact that early physical signs of the disease are missed or attributed to the changes that occur in the breast normally as a function of pregnancy. However, a discreet breast mass in a pregnant woman should never be assumed to be normal. Another reason is the more aggressive behavior of the cancer possibly related to the hormonal milieu (estrogen increases 100-fold; progesterone increases 1000-fold) of the pregnancy. However, about 70% of the breast cancers found in pregnancy are estrogen receptor–negative. About 28–58% of the tumors express HER2, a biologically more aggressive breast cancer subset. Another factor is that aggressive, definitive chemotherapy and radiation therapy are often delayed due to concerns about the consequences of those treatments for the fetus. Younger women with breast cancer have a higher likelihood of having mutations in BRCA1 or BRCA2.

Differences in presentation between PABC and breast cancers diagnosed in nonpregnant women are shown in **Table 32-3**. About 20% of breast cancers are detected in the first trimester, 45% in the second trimester, and 35% in the third trimester. Some argue that stage for stage, the outcome is the same for breast cancer diagnosed in pregnant and nonpregnant women. Primary tumors in pregnant women are 3.5 cm on average, compared to <2 cm in nonpregnant women. A dominant mass and a nipple discharge are the most common presenting signs, and they should prompt ultrasonography and breast MRI exam (if available) followed by lumpectomy if the mass is solid and aspiration if the mass is cystic. Mammography is less reliable in pregnancy due to the increased breast density. Needle aspirates of breast masses in pregnant women are often nondiagnostic or falsely positive. Even in pregnancy, most breast masses are benign (~80% are adenoma, lobular hyperplasia, milk retention cyst, fibrocystic disease, fibroadenoma, or other rarer entities).

TABLE 32-3

DIFFERENCES IN BREAST CANCERS IN PREGNANT AND NONPREGNANT WOMEN

	PREGNANT	NONPREGNANT
Tumor size	3.5 cm	2 cm
Estrogen receptor +	30%[a]	67%
HER2 +	Up to 58%	10–25%
Stage II, III	65–90%	45–66%
Lymph node +	56–89%	38–54%

[a]Lower measured levels could be in part artifactual due to the increased levels of estrogen in the milieu.

Many studies comparing outcomes among women with PABC to those of nonpregnant women have small sample sizes, and there is considerable heterogeneity among the study results, but a formal meta-analysis including multiple adjustments and sensitivity analyses confirms the clinical impression of poorer outcomes for women with PABC. T e hazard ratios were 1.44 for poorer overall survival and 1.60 for poorer disease-free survival.

Although having had a pregnancy is a protective factor against breast cancer in women in general, it is questionable as to whether it retains its protective effect in carriers of BRCA1 and BRCA2 mutations. Cullinane et al. (Int J Cancer 117:988, 2005) found a statistically insignificant difference (odds ratio 0.94) in breast cancer risk among BRCA1 carriers who had ever been pregnant versus those who never had a pregnancy. Stratifying the risk of breast cancer according to the number of prior pregnancies versus no pregnancies, no statistically significant protective trend was observed. For BRCA2 carriers, there was a marginally statistically significant increased risk of breast cancer among women with prior pregnancies. In an international study with more than 65,000 person-years of observation (Andrieu J: Natl Cancer Inst 98:535, 2006), there was no significant effect in either direction of pregnancy on breast cancer risk for carriers of either mutation. Staging the axillary lymph nodes is currently somewhat controversial. Sentinel lymph node sampling is not straightforward in pregnant women. Blue dye has been carcinogenic in rats, and fetuses cannot be shielded from administered radionuclides. For this reason, many surgeons favor axillary node dissection to stage the nodes. Largely due to the typical delay in diagnosis, axillary nodes are more often positive in pregnant than in nonpregnant women.

As with other types of cancer in pregnant women, counseling following diagnosis in the first trimester should include a discussion of pregnancy termination to allow definitive therapeutic intervention at the earliest possible time without the potential for permanent injury to a surviving fetus. While definitive local surgery can safely be performed in the first trimester, radiation therapy and chemotherapy are considerably more risky. Delay in administration of systemic therapy can increase the risk of axillary spread. In the second and third trimesters, chemotherapy (particularly anthracycline-based combinations) is both safe and effective **(Chap. 38)**. Lumpectomy followed by adjuvant chemotherapy is frequently used; fluorouracil and cyclophosphamide with either doxorubicin or epirubicin have been given without major risk to the fetus. Taxanes and gemcitabine are also beginning to be used; however, safety data are sparse. Methotrexate and other folate antagonists are to be avoided because of effects on the fetal nervous system. Myelotoxic therapy is generally

not administered after 33 or 34 weeks of gestation to allow 3 weeks off therapy before delivery for recovery of blood counts. Endocrine therapy and trastuzumab are unsafe during pregnancy. Experience with lapatinib is anecdotal, but no fetal malformations have been reported. Antiemetics and colony-stimulating factors are also considered safe. Women being treated into the postpartum period should not breast-feed their babies because of excretion of cancer chemotherapy agents, particularly alkylating agents, in milk.

Subsequent pregnancies following gestational breast cancer do not appear to influence relapse rate or overall survival. A meta-analysis found that pregnancy in breast cancer survivors was associated with a reduced the risk of dying from breast cancer by as much as 42%. T is finding, however, is heavily confounded by the "healthy survivor effect"; women with more extensive or advanced disease are more likely to avoid pregnancy.

MELANOMA DURING PREGNANCY

Speculation about melanoma occurring during pregnancy based largely on anecdotal evidence and small case series concluded that it occurred with increased frequency, was more aggressive in its natural history, and was caused in part by the hormonal changes that also produced hyperpigmentation (so-called melasma) during pregnancy. However, more complete epidemiologic data suggest that melanoma is no more frequent in pregnant women than in nonpregnant women in the same age group, that melanoma is not more aggressive during pregnancy, and that hormones seem to have little or nothing to do with the etiology. Pregnant and nonpregnant women do not differ in the location of primary tumor, depth of primary tumor, tumor ulceration, or vascular invasion.

Suspicious lesions should be looked for and managed definitively with excisional biopsy during pregnancy. Wide excision with sampling of regional lymph nodes is warranted. If lymph nodes are involved, the course of action is less clear. Several agents have demonstrated some activity in melanoma, but none have been used during pregnancy. Adjuvant interferon α is toxic, and its safety in pregnancy has not been documented. Agents active in advanced disease include dacarbazine, IL-2, ipilimumab (antibody to CTLA-4), and in those with BRAF mutation V600E, a BRAF kinase inhibitor. In the setting of metastatic disease, abortion may be indicated so that systemic therapy can be initiated as soon as possible **(Chap. 34)**.

Melanoma is one of the very few cancers that are well documented to metastasize transplacentally to the fetus, where it seems to have a predilection for the head and neck. It has a very grave prognosis in the offspring. Fortunately, transplacental spread is rare.

Pregnancy subsequent to the diagnosis and treatment of melanoma is not associated with an increased risk of melanoma recurrence.

HODGKIN'S DISEASE AND NON-HODGKIN'S LYMPHOMA DURING PREGNANCY

(See Chap. 16) Hodgkin's disease occurs mainly in the age range that coincides with child-bearing. However, Hodgkin's disease is not more common in pregnant than nonpregnant women. Hodgkin's disease is diagnosed in approximately 1 in 6000 pregnancies. It generally presents as a nontender lymph node swelling, most often in the left supraclavicular region. It may be accompanied by B symptoms (fever, night sweats, unexplained weight loss). Excisional biopsy is the preferred diagnostic procedure because fine-needle aspiration cannot reveal the architectural framework that is an essential component of Hodgkin's disease diagnosis. T e stage at presentation appears to be unaffected by pregnancy. Women diagnosed in the second and third trimester can be treated safely with combination chemotherapy, usually doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). In general, the patient in the first trimester is asymptomatic, and a woman with a desired pregnancy can be followed until the second or third trimester when definitive multiagent chemotherapy can be safely given. Radiation therapy is not given during pregnancy and is not necessary for optimal management of the pregnant patient. If symptoms requiring treatment appear during the first trimester, anecdotal evidence suggests that Hodgkin's disease symptoms can be controlled with weekly low-dose vinblastine. Such an approach has been safely used to avoid termination of pregnancy. Pregnancy does not have an adverse effect on treatment outcome.

Non-Hodgkin's lymphomas are more unusual in pregnancy (approximately 0.8 per 100,000 pregnancies), but are usually tumors with an aggressive natural history, such as diffuse large B cell lymphoma, Burkitt's lymphoma, or peripheral T cell lymphoma. Diagnosis relies on an excisional biopsy of a tumor mass, not fine-needle aspiration. Staging evaluation is generally limited to ultrasound or MRI examinations. Diagnosis in the first trimester should prompt termination of the pregnancy followed by definitive treatment with combination chemotherapy, because aggressive lymphomas are not likely to be held at bay with single-agent chemotherapy. Women diagnosed in the second or third trimesters can be treated with standard chemotherapy, such as with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). T e experience with rituximab in this setting is anecdotal. However, infants

born of mothers who have received rituximab may have transient delay in B cell development that typically normalizes by 6 months. T e treatment outcome is similar in lymphomas diagnosed in pregnant and nonpregnant women of the same clinical stage.

THYROID CANCER DURING PREGNANCY

(See Chap. 50) T yroid cancer, along with melanomas, brain tumors, and lymphomas, are cancers that are increasing in incidence in the general population. T yroid cancers are rising faster among women in North America than the other increasing tumor types. T e Endocrine Society has developed practice guidelines to inform the management of patients with thyroid disease during pregnancy (http://www.endocrine.org/~/media/endosociety/Files/Publications/Clinical%20Practice%20Guidelines/T yroid-Exec-Summ.pdf). T yroid nodules 1 cm or larger are approached by fine-needle aspiration. If a malignancy is diagnosed, surgery is generally recommended in the second and third trimesters. However, surgical complications appear to be twice as common when the patient is pregnant. Because the growth of thyroid tumors is often indolent, surgery can safely be postponed until after the first trimester. Patients with follicular cancer or early papillary cancer can be observed until the postpartum period. T e fetal thyroid begins trapping iodine by 12 weeks of gestation and does so with very high avidity. Even small doses of radioactive iodine given during pregnancy can completely ablate the fetal thyroid with serious consequences for the fetus and should be avoided throughout pregnancy. Radioactive iodine can be safely administered after delivery. Patients with a history of thyroid cancer who become pregnant should be maintained on thyroid hormone replacement during pregnancy because of the adverse impact of maternal hypothyroidism on the fetus. Women who are breast-feeding should not be treated with radioactive iodine, and women treated with radioactive iodine should not become pregnant for 6–12 months after treatment.

T e assessment of thyroid function during pregnancy is challenging because of the physiologic changes that occur during pregnancy. Women who have previously been treated for thyroid cancer are at risk of hypothyroidism. T e demand for thyroid hormone increases during pregnancy, and doses to maintain normal function may increase by 30–50%. Total T_4 levels are higher during pregnancy, but target therapeutic levels also increase **(Table 32-4)**. It is recommended that the upper and lower limits of the laboratory range be multiplied by 1.5 in the second and third trimester to establish a pregnancy-specific normal range. T e target thyroid-stimulating hormone (TSH) level is <2.5 mIU/L.

GESTATIONAL TROPHOBLASTIC DISEASE

(See Chap. 46) Gestational trophoblastic disease encompasses hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor, and assorted miscellaneous and unclassifiable trophoblastic tumors. Moles are the most common, occurring in 1 in 1500 pregnancies in the United States. T e incidence is higher in Asia. In general, if the serum level of β-human chorionic gonadotropin (β-hCG) returns to normal after surgical removal (evacuation) of the mole, the illness is considered gestational trophoblastic disease. By contrast, if the β-hCG level remains elevated after mole evacuation, the patient is considered to have gestational trophoblastic neoplasia. Choriocarcinoma occurs in 1 in 25,000 pregnancies. Maternal age >45 years and prior history of molar pregnancy are risk factors. A previous molar pregnancy makes choriocarcinoma about 1000 times more likely to occur (incidence 1–2%).

Hydatidiform moles are characterized by clusters of villi with hydropic changes, trophoblastic hyperplasia, and absence of fetal blood vessels. Invasive moles are distinguished by invasion of the myometrium. Placental site trophoblastic tumors are composed mainly of cytotrophoblast cells arising at the site of placental implantation. Choriocarcinomas contain anaplastic trophoblastic tissue with both cytotrophoblast and syncytiotrophoblast features and no identifiable villi.

Moles can be partial, typically associated with fetal tissue, or complete, typically not associated with any fetal or embryonic tissue. Partial moles have a distinct molecular origin and usually are smaller tumors with less hydropic villi and considerably less potential for persistent or malignant disease. Partial moles result

TABLE 32-4

THYROID FUNCTION TEST DURING PREGNANCY (MEAN LEVELS)

	NONPREGNANT	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Thyroid-stimulating hormone (mIU/L)	1.38	0.91	1.03	1.32
Total thyroxine (µg/dL)	7.35	10.98	11.88	11.08

Source: Based on the National Health and Nutrition Examination Survey III (NHANES III) (OP Soldin et al: Ther Drug Monit 17:303, 2007).

from fertilization of an egg by two sperm, resulting in diandric triploidy. Complete moles usually have a 46,XX genotype; 95% develop by a single male sperm fertilizing an empty egg and undergoing gene duplication (diandric diploidy); 5% develop from dispermic fertilization of an empty egg (diandric dispermy).

Women with molar gestations often present with first-trimester bleeding, disproportionately high serum β-hCG levels for menstrual age, unusually large uterine size for menstrual age, hyperemesis gravidarum, theca lutein cysts in the ovaries (due to β-hCG stimulation), and hyperthyroidism (due to cross-reactivity of β-hCG and TSH) and may develop preeclampsia before 20 weeks of menstrual age. Pelvic ultrasound imaging of complete moles shows absence of fetal parts, an enlarged echo-bright, hydropic placenta in an enlarged uterus, and enlarged multicystic ovaries. If the diagnosis is uncertain at the initial examination and the pregnancy is desired, then a serum β-hCG level should be obtained and the examination repeated in a week. If no embryo is seen within 7–10 days and the serum β-hCG is elevated, then this is a nonviable pregnancy that should be evacuated. Diagnosis of partial molar pregnancies can be more difficult because an embryo or fetus with visible heart motion is usually present, and the hydropic changes in the placenta, uterine enlargement, and elevations of β-hCG are not usually as dramatic. Although an embryo or fetus is present, it rarely grows normally with normal anatomy, and repeated ultrasound examinations usually make the diagnosis. Amniocentesis will also make the diagnosis by demonstration of triploidy.

Patients with molar pregnancies require prompt uterine evacuation with suction curettage, which may be complicated by very heavy bleeding. Following evacuation of complete moles, approximately 20% will result in persistent, invasive, or metastatic disease. Partial moles are considerably less likely (<5%) to result in persistent disease. Patients should be monitored with serial determinations of serum β-hCG until the values fall below the lower limit of the assay and remain low for at least 6 months. Patients should be advised not to become pregnant for at least 12 months.

A variety of criteria have been used to make the diagnosis of postmolar gestational trophoblastic disease, but current consensus guidelines as adopted by the International Federation of Gynecology and Obstetrics are listed below:

1. A β-hCG level plateau of four values plus or minus 10% recorded over a 3-week duration (days 1, 7, 14, and 21)
2. A β-hCG level increase of more than 10% in three values recorded over a 2-week duration (days 1, 7, and 14)
3. Persistence of detectable β-hCG for more than 6 months after molar evacuation

About half of choriocarcinomas develop after a molar pregnancy, and half develop after ectopic pregnancy or, rarely, after a normal full-term pregnancy. Disease is classified as stage I if it is confined to the uterus, stage II if disease is limited to genital structures (~30% have vaginal involvement), stage III if disease has spread to the lungs but no other organs, and stage IV if disease has spread to liver, brain, or other organs.

Patients without widely metastatic disease are generally managed with single-agent methotrexate (either 30 mg/m^2 IM weekly until β-hCG normalizes or 1 mg/kg IM every other day for four doses followed by leucovorin 0.1 mg/kg IV 24 h after methotrexate), which cures >90% of patients. Patients with very high β-hCG levels, presenting >4 months after a pregnancy, with brain or liver metastases, or failing to be cured by single-agent methotrexate are treated with combination chemotherapy. Etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine (EMA-CO) is the most commonly used regimen, producing long-term survival in >80% of patients. Brain metastases can usually be controlled with brain radiation therapy. T e vast majority of choriocarcinomas can be cured with chemotherapy alone. Hysterectomy is reserved for women who have completed their child-bearing, women with chemotherapy-resistant disease in the uterus, and women with rare placental site trophoblastic tumors confined to the uterus because these tumors are less reliably sensitive to chemotherapy. Women cured of trophoblastic disease who have not undergone hysterectomy do not appear to have increased risk of fetal abnormalities or maternal complications with subsequent pregnancies.

CHAPTER 33

PALLIATIVE AND END-OF-LIFE CARE

Ezekiel J. Emanuel

EPIDEMIOLOGY

In 2010, according to the Centers for Disease Control and Prevention, 2,468,435 individuals died in the United States **(Table 33-1)**. Approximately 73% of all deaths occur in those >65 years of age. T e epidemiology of mortality is similar in most developed countries; cardiovascular diseases and cancer are the predominant causes of death, a marked change since 1900, when heart disease caused ~8% of all deaths and cancer accounted for <4% of all deaths. In 2010, the year with the most recent available data, AIDS did not rank among the top 15 causes of death, causing just 8369 deaths. Even among people age 35–44, heart disease, cancer, chronic liver disease, and accidents all cause more deaths than AIDS.

It is estimated that in developed countries ~70% of all deaths are preceded by a disease or condition, making it reasonable to plan for dying in the foreseeable future. Cancer has served as the paradigm for terminal care, but it is not the only type of illness with a recognizable and predictable terminal phase. Because heart failure, chronic obstructive pulmonary disease (COPD), chronic liver failure, dementia, and many other conditions have recognizable terminal phases, a systematic approach to end-of-life care should be part of all medical specialties. Many patients with illness-related suffering also can benefit from palliative care regardless of prognosis. Ideally, palliative care should be considered part of comprehensive care for all patients. Palliative care can be improved by coordination between caregivers, doctors, and patients for advance care planning, as

TABLE 33-1

TEN LEADING CAUSES OF DEATH IN THE UNITED STATES AND BRITAIN

	UNITED STATES			BRITAIN	
CAUSE OF DEATH	NUMBER OF DEATHS	PERCENTAGE OF TOTAL	NUMBER OF DEATHS AMONG PEOPLE ≥65 YEARS OF AGE	NUMBER OF DEATHS	PERCENTAGE OF TOTAL
All deaths	2,468,435	100	1,798,276	499,331	100
Heart disease	597,689	24.2	477,338	141,362	28.3
Malignant neoplasms	574,743	23.3	396,670	142,107	28.5
Chronic lower respiratory diseases	138,080	5.6	118,031	27,132	5.4
Cerebrovascular diseases	129,476	5.2	109,990	35,846	7.2
Accidents	120,859	4.9	41,300	11,256	2.3
Alzheimer's disease	83,494	3.4	82,616	8859	1.8
Diabetes mellitus	69,071	2.8	49,191	4931	1.0
Nephritis, nephritic syndrome, nephrosis	50,476	2.0	41,994	4102	0.8
Influenza and pneumonia	50,097	2.0	42,846	26,138	5.2
Intentional self-harm	38,364	1.6	6008	3671	0.7

Source: National Center for Health Statistics (data for all age groups from 2010), http://www.cdc.gov/nchs; National Statistics (England and Wales, 2012), http://www.statistics.gov.uk.

well as dedicated teams of physicians, nurses, and other providers.

T e rapid increases in life expectancy in developed countries over the last century have been accompanied by new difficulties facing individuals, families, and society as a whole in addressing the needs of an aging population. T ese challenges include both more complicated conditions and technologies to address them at the end of life. T e development of technologies that can prolong life without restoring full health has led many Americans to seek out alternative end-of-life care settings and approaches that relieve suffering for those with terminal diseases. Over the last few decades in the United States, a significant change in the site of death has occurred that coincides with patient and family preferences. Nearly 60% of Americans died as inpatients in hospitals in 1980. By 2000, the trend was reversing, with ~31% of Americans dying as hospital inpatients **(Fig. 33-1)**. T is shift has been most dramatic for those dying from cancer and COPD and for younger and very old individuals. In the last decade, it has been associated with the increased use of hospice care; in 2008, approximately 39% of all decedents in the United States received such care. Cancer patients currently constitute ~36.9% of hospice users. About 79% of patients receiving hospice care die out of the hospital, and around 42% of those receiving hospice care die in a private residence. In addition, in 2008, for the first time, the American Board of Medical Specialties (ABMS) offered certification in hospice and palliative medicine. With shortening of hospital stays, many serious conditions are being treated at home or on an outpatient basis. Consequently, providing optimal palliative and end-of-life care requires ensuring that appropriate services are available in a variety of settings, including noninstitutional settings.

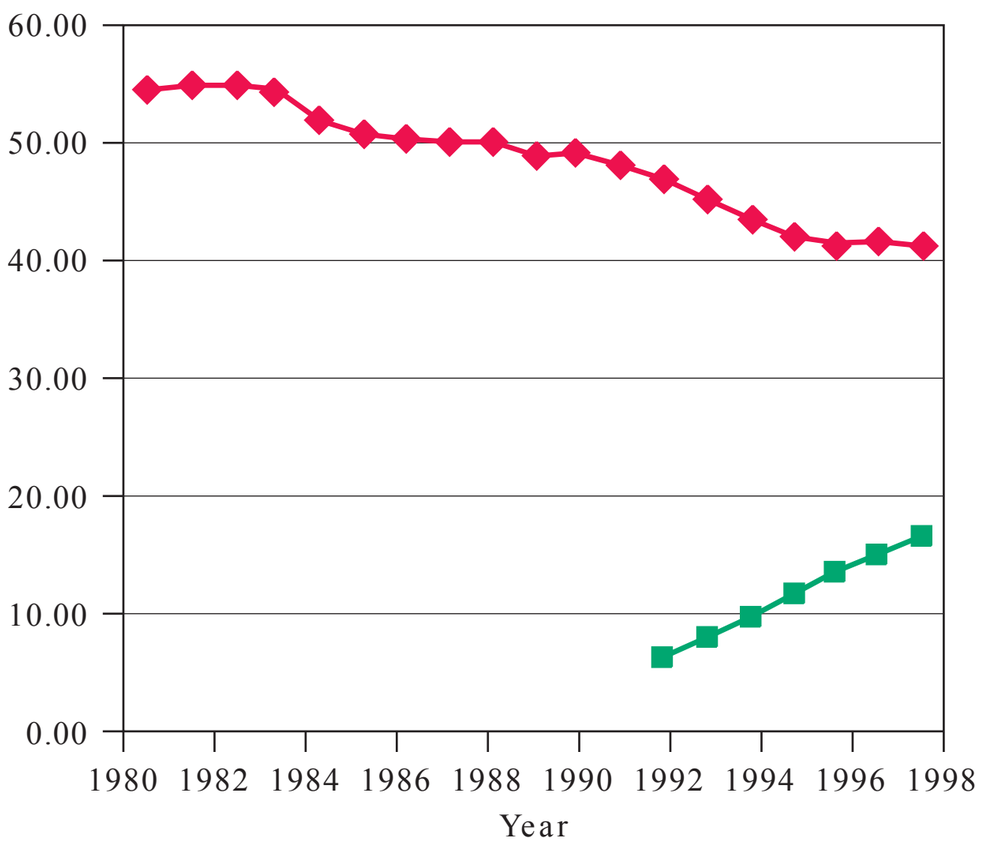

FIGURE 33-1
Graph showing trends in the site of death in the last two decades. ◆, percentage of hospital inpatient deaths; ■, percentage of decedents enrolled in a hospice.

HOSPICE AND THE PALLIATIVE CARE FRAMEWORK

Central to this type of care is an interdisciplinary team approach that typically encompasses pain and symptom management, spiritual and psychological care for the patient, and support for family caregivers during the patient's illness and the bereavement period.

Terminally ill patients have a wide variety of advanced diseases, often with multiple symptoms that demand relief, and require noninvasive therapeutic regimens to be delivered in f exible care settings. Fundamental to ensuring quality palliative and end-of-life care is a focus on four broad domains: (1) physical symptoms; (2) psychological symptoms; (3) social needs that include interpersonal relationships, caregiving, and economic concerns; and (4) existential or spiritual needs.

A comprehensive assessment screens for and evaluates needs in each of these four domains. Goals for care are established in discussions with the patient and/or family, based on the assessment in each of the domains. Interventions then are aimed at improving or managing symptoms and needs. Although physicians are responsible for certain interventions, especially technical ones, and for coordinating the interventions, they cannot be responsible for providing all of them. Because failing to address any one of the domains is likely to preclude a good death, a well-coordinated, effectively communicating interdisciplinary team takes on special importance in end-of-life care. Depending on the setting, critical members of the interdisciplinary team will include physicians, nurses, social workers, chaplains, nurse's aides, physical therapists, bereavement counselors, and volunteers.

ASSESSMENT AND CARE PLANNING

Comprehensive assessment

Standardized methods for conducting a comprehensive assessment focus on evaluating the patient's condition in all four domains affected by illness: physical, psychological, social, and spiritual. T e assessment of physical and mental symptoms should follow a modified version of the traditional medical history and physical examination that emphasizes symptoms. Questions should aim at elucidating symptoms and discerning sources of suffering and gauging how much those symptoms interfere with the patient's quality of life. Standardized assessment is critical. Currently, there are 21 symptom

assessment instruments for cancer alone. Further research on and validation of these assessment tools, especially taking into account patient perspectives, could improve their effectiveness. Instruments with good psychometric properties that assess a wide range of symptoms include the Memorial Symptom Assessment Scale (MSAS), the Rotterdam Symptom Checklist, the Worthing Chemotherapy Questionnaire, and the Computerized Symptom Assessment Instrument. T ese instruments are long and may be useful for initial clinical or for research assessments. Shorter instruments are useful for patients whose performance status does not permit comprehensive assessments. Suitable shorter instruments include the Condensed Memorial Symptom Assessment Scale, the Edmonton Symptom Assessment System, the M.D. Anderson Symptom Assessment Inventory, and the Symptom Distress Scale. Using such instruments ensures that the assessment is comprehensive and does not focus only on pain and a few other physical symptoms. Invasive tests are best avoided in end-of-life care, and even minimally invasive tests should be evaluated carefully for their benefit-to-burden ratio for the patient. Aspects of the physical examination that are uncomfortable and unlikely to yield useful information can be omitted.

Regarding social needs, health care providers should assess the status of important relationships, financial burdens, caregiving needs, and access to medical care. Relevant questions will include the following: How o*f*ten is there someone to *f*eel close to? How has this illness been *f*or your *f*amily? How has it a*ff*ected your relationships? How much help do you need with things like getting meals and getting around? How much trouble do you have getting the medical care you need? In the area of existential needs, providers should assess distress and the patient's sense of being emotionally and existentially settled and of finding purpose or meaning. Helpful assessment questions can include the following: How much are you able to f nd meaning since your illness began? What things are most important to you at this stage? In addition, it can be helpful to ask how the patient perceives his or her care: How much do you *f*eel your doctors and nurses respect you? How clear is the in*f*ormation *f*rom us about what to expect regarding your illness? How much do you *f*eel that the medical care you are getting f ts with your goals? If concern is detected in any of these areas, deeper evaluative questions are warranted.

Communica tion

Especially when an illness is life-threatening, there are many emotionally charged and potentially con- f ict-creating moments, collectively called "bad news" situations, in which empathic and effective communication skills are essential. T ose moments include communicating with the patient and/or family about a terminal diagnosis, the patient's prognosis, any treatment failures, deemphasizing efforts to cure and prolong life while focusing more on symptom management and palliation, advance care planning, and the patient's death. Although these conversations can be difficult and lead to tension, research indicates that end-of-life discussions can lead to earlier hospice referrals rather than overly aggressive treatment, benefiting quality of life for patients and improving the bereavement process for families.

Just as surgeons plan and prepare for major operations and investigators rehearse a presentation of research results, physicians and health care providers caring for patients with significant or advanced illness can develop a practiced approach to sharing important information and planning interventions. In addition, families identify as important both how well the physician was prepared to deliver bad news and the setting in which it was delivered. For instance, 27% of families making critical decisions for patients in an intensive care unit (ICU) desired better and more private physical space to communicate with physicians, and 48% found having clergy present reassuring.

An organized and effective seven-step procedure for communicating bad news goes by the acronym P-SPIKES: (1) **p**repare for the discussion, (2) **s**et up a suitable environment, (3) begin the discussion by finding out what the **p**atient and/or family understand, (4) determine how they will comprehend new **i**nformation best and how much they want to know, (5) provide needed new **k**nowledge accordingly, (6) allow for **e**motional responses, and (7) **s**hare plans for the next steps in care. **Table 33-2** provides a summary of these steps along with suggested phrases and underlying rationales for each one. Additional research that further considers the response of patients to systematic methods of delivering bad news could build the evidence base for even more effective communication procedures.

Continuous goal assessment

Major barriers to ensuring quality palliative and end-of-life care include difficulty providing an accurate prognosis and emotional resistance of patients and their families to accepting the implications of a poor prognosis. T ere are two practical solutions to these barriers. One is to integrate palliative care with curative care regardless of prognosis. With this approach, palliative care no longer conveys the message of failure, having no more treatments, or "giving up hope." Fundamental to integrating palliative care with curative therapy is to include continuous goal assessment as part of the routine patient reassessment that occurs at most patient-physician encounters. Alternatively, some practices may find it useful to implement a standard point in the

TABLE 33-2

ELEMENTS OF COMMUNICATING BAD NEWS—THE P-SPIKES APPROACH

ACRONYM	STEPS	AIM OF THE INTERACTION	PREPARATIONS, QUESTIONS, OR PHRASES
P	Preparation	Mentally prepare for the interaction with the patient and/or family.	Review what information needs to be communicated. Plan how you will provide emotional support. Rehearse key steps and phrases in the interaction.
S	Setting of the interaction	Ensure the appropriate setting for a serious and potentially emotionally charged discussion.	Ensure that patient, family, and appropriate social supports are present. Devote sufficient time. Ensure privacy and prevent interruptions by people or beeper. Bring a box of tissues.
P	Patient's perception and preparation	Begin the discussion by establishing the baseline and whether the patient and family can grasp the information. Ease tension by having the patient and family contribute.	Start with open-ended questions to encourage participation. Possible phrases to use: What do you understand about your illness? When you first had symptom X, what did you think it might be? What did Dr. X tell you when he or she sent you here? What do you think is going to happen?
I	Invitation and information needs	Discover what information needs the patient and/or family have and what limits they want regarding the bad information.	Possible phrases to use: If this condition turns out to be something serious, do you want to know? Would you like me to tell you all the details of your condition? If not, who would you like me to talk to?
K	Knowledge of the condition	Provide the bad news or other information to the patient and/or family sensitively.	Do not just dump the information on the patient and family. Check for patient and family understanding. Possible phrases to use: I feel badly to have to tell you this, but … Unfortunately, the tests showed … I'm afraid the news is not good …
E	Empathy and exploration	Identify the cause of the emotions—e.g., poor prognosis. Empathize with the patient and/or family's feelings. Explore by asking open-ended questions.	Strong feelings in reaction to bad news are normal. Acknowledge what the patient and family are feeling. Remind them such feelings are normal, even if frightening. Give them time to respond. Remind patient and family you won't abandon them. Possible phrases to use: I imagine this is very hard for you to hear. You look very upset. Tell me how you are feeling. I wish the news were different. We'll do whatever we can to help you.
S	Summary and planning	Delineate for the patient and the family the next steps, including additional tests or interventions.	It is the unknown and uncertain that can increase anxiety. Recommend a schedule with goals and landmarks. Provide your rationale for the patient and/or family to accept (or reject). If the patient and/or family are not ready to discuss the next steps, schedule a follow-up visit.

Source: Adapted from R Buckman: How to Break Bad News: A Guide for Health Care Professionals. Baltimore, Johns Hopkins University Press, 1992.

clinical course to address goals of care and advance care planning. For example, some oncology practices ask all patients whose Eastern Cooperative Oncology Group (ECOG) performance status is 3 or less—meaning they spend 50% or more of the day in bed—or those who develop metastatic disease about their goals of care and advance care preferences.

Goals for care are numerous, ranging from cure of a specific disease, to prolonging life, to relief of a symptom, to delaying the course of an incurable disease, to adapting to progressive disability without disrupting the family, to finding peace of mind or personal meaning, to dying in a manner that leaves loved ones with positive memories. Discernment of goals for care can be approached through a seven-step protocol: (1) ensure that medical and other information is as complete as reasonably possible and is understood by all relevant parties (see above); (2) explore what the

patient and/or family are hoping for while identifying relevant and realistic goals; (3) share all the options with the patient and family; (4) respond with empathy as they adjust to changing expectations; (5) make a plan, emphasizing what can be done toward achieving the realistic goals; (6) follow through with the plan; and (7) review and revise the plan periodically, considering at every encounter whether the goals of care should be reviewed with the patient and/or family. Each of these steps need not be followed in rote order, but together they provide a helpful framework for interactions with patients and their families about goals for care. It can be especially challenging if a patient or family member has difficulty letting go of an unrealistic goal. One strategy is to help them refocus on more realistic goals and also suggest that while hoping for the best, it is still prudent to plan for other outcomes as well.

Advance care planning

Practices

Advance care planning is a process of planning for future medical care in case the patient becomes incapable of making medical decisions. A 2010 study of adults 60 or older who died between 2000 and 2006 found that 42% required decision making about treatment in the final days of life but 70% lacked decision-making capacity. Among those lacking decision-making capacity, around one-third did not have advance planning directives. Ideally, such planning would occur before a health care crisis or the terminal phase of an illness. Diverse barriers prevent this. Polls suggest 80% of Americans endorse advance care planning and completing living wills. However, data suggest between 33 and 42% have actually completed one. Other countries have even lower completion rates. Most patients expect physicians to initiate advance care planning and will wait for physicians to broach the subject. Patients also wish to discuss advance care planning with their families. Yet patients with unrealistic expectations are significantly more likely to prefer aggressive treatments. Fewer than one-third of health care providers have completed advance care planning for themselves. Hence, a good first step is for health care providers to complete their own advance care planning. T is makes providers aware of the critical choices in the process and the issues that are especially charged and allows them to tell their patients truthfully that they personally have done advance planning. Lessons from behavioral economics suggest that setting this kind of social norming helps people view completing an advance directive as acceptable and even expected.

Steps in effective advance care planning center on (1) introducing the topic, (2) structuring a discussion, (3) reviewing plans that have been discussed by the patient and family, (4) documenting the plans, (5) updating them periodically, and (6) implementing the advance care directives **(Table 33-3)**. Two of the main barriers to advance care planning are problems in raising the topic and difficulty in structuring a succinct discussion. Raising the topic can be done efficiently as a routine matter, noting that it is recommended for all patients, analogous to purchasing insurance or estate planning. Many of the most difficult cases have involved unexpected, acute episodes of brain damage in young individuals.

Structuring a focused discussion is a central communication skill. Identify the health care proxy and recommend his or her involvement in the process of advance care planning. Select a worksheet, preferably one that has been evaluated and demonstrated to produce reliable and valid expressions of patient preferences, and orient the patient and proxy to it. Such worksheets exist for both general and disease-specific situations. Discuss with the patient and proxy one scenario as an example to demonstrate how to think about the issues. It is often helpful to begin with a scenario in which the patient is likely to have settled preferences for care, such as being in a persistent vegetative state. Once the patient's preferences for interventions in this scenario are determined, suggest that the patient and proxy discuss and complete the worksheet for the others. If appropriate, suggest that they involve other family members in the discussion. On a return visit, go over the patient's preferences, checking and resolving any inconsistencies. After having the patient and proxy sign the document, place it in the medical chart and be sure that copies are provided to relevant family members and care sites. Because patients' preferences can change, these documents have to be reviewed periodically.

Types of documents

Advance care planning documents are of three broad types. T e first includes living wills or instructional directives; these are advisory documents that describe the types of decisions that should direct care. Some are more specific, delineating different scenarios and interventions for the patient to choose from. Among these, some are for general use and others are designed for use by patients with a specific type of disease, such as cancer or HIV. A second type is a less specific directive that provides general statements of not wanting life-sustaining interventions or forms that describe the values that should guide specific discussions about terminal care. T ese can be problematic because, when critical decisions about specific treatments are needed, they require assessments by people other than the patient of whether a treatment fulfills a particular wish. T e third type of advance directive allows the designation of a health care proxy (sometimes also referred to as a durable attorney for health care), who is an individual selected by the patient to make decisions.

TABLE 33-3

STEPS IN ADVANCE CARE PLANNING

STEP	GOALS TO BE ACHIEVED AND MEASURES TO COVER	USEFUL PHRASES OR POINTS TO MAKE
Introducing advance care planning	Ask the patient what he or she knows about advance care planning and if he or she has already completed an advance care directive. Indicate that you as a physician have completed advance care planning. Indicate that you try to perform advance care planning with all patients regardless of prognosis. Explain the goals of the process as empowering the patient and ensuring that you and the proxy understand the patient's preferences. Provide the patient relevant literature, including the advance care directive that you prefer to use. Recommend the patient identify a proxy decision-maker who should attend the next meeting.	I'd like to talk with you about something I try to discuss with all my patients. It's called advance care planning. In *f*act, I *f*eel that this is such an important topic that I have done this myself. Are you *f*amiliar with advance care planning or living wills? Have you thought about the type o*f* care you would want i*f* you ever became too sick to speak *f*or yourself? That is the purpose o*f* advance care planning. There is no change in health that we have not discussed. I am bringing this up now because it is sensible *f*or everyone, no matter how well or ill, old or young. Have many copies of advance care directives available, including in the waiting room, for patients and families. Know resources for state-specific forms (available at www.nhpco.org).
Structured discussion of scenarios and patient	Affirm that the goal of the process is to follow the patient's wishes if the patient loses decision-making capacity. Elicit the patient's overall goals related to health care. Elicit the patient's preferences for specific interventions in a few salient and common scenarios. Help the patient define the threshold for withdrawing and withholding interventions. Define the patient's preference for the role of the proxy.	Use a structured worksheet with typical scenarios. Begin the discussion with persistent vegetative state and consider other scenarios, such as recovery from an acute event with serious disability, asking the patient about his or her preferences regarding specific interventions, such as ventilators, artificial nutrition, and CPR, and then proceeding to less invasive interventions, such as blood transfusions and antibiotics.
Review the patient's preferences	After the patient has made choices of interventions, review them to ensure they are consistent and the proxy is aware of them.	
Document the patient's preferences	Formally complete the advance care directive and have a witness sign it. Provide a copy for the patient and the proxy. Insert a copy into the patient's medical record and summarize in a progress note.	
Update the directive	Periodically, and with major changes in health status, review the directive with the patient and make any modifications.	
Apply the directive	The directive goes into ef ect only when the patient becomes unable to make medical decisions for himself or herself. Reread the directive to be sure about its content. Discuss your proposed actions based on the directive with the proxy.	

Abbreviation: CPR, cardiopulmonary resuscitation.

T e choice is not either/or; a combined directive that includes a living will and designates a proxy is often used, and the directive should indicate clearly whether the specified patient preferences or the proxy's choice takes precedence if they conf ict. T e Five Wishes and the Medical Directive are such combined forms. Some states have begun to put into practice a "Physician Orders for Life-Sustaining Treatment (POLST)" paradigm, which builds on communication between providers and patients to include guidance for end-of-life care in a color-coordinated form that follows the patient across treatment settings. T e procedures for completing advance care planning documents vary according to state law.

A potentially misleading distinction relates to statutory as opposed to advisory documents. Statutory

documents are drafted to fulfill relevant state laws. Advisory documents are drafted to reflect the patient's wishes. Both are legal, the first under state law and the latter under common or constitutional law.

Legal aspects

The U.S. Supreme Court has ruled that patients have a constitutional right to decide about refusing and terminating medical interventions, including life-sustaining interventions, and that mentally incompetent patients can exercise this right by providing "clear and convincing evidence" of their preferences. Because advance care directives permit patients to provide such evidence, commentators agree that they are constitutionally protected. Most commentators believe that a state is required to honor any clear advance care directive whether or not it is written on an "official" form. Many states have enacted laws explicitly to honor out-of-state directives. If a patient is not using a statutory form, it may be advisable to attach a statutory form to the advance care directive being used. State-specific forms are readily available free of charge for health care providers and patients and families through the National Hospice and Palliative Care Organization's "Caring Connections" website (http://www.caringinfo.org).

In January 2014, Texas judge R. H. Wallace ruled that a brain dead woman who was 23 weeks pregnant should be removed from life support. This was after several months of disagreement between the woman's family and the hospital providing care. The hospital cited Texas law that states that life-sustaining treatment must be administered to a pregnant woman, but the judge sided with the woman's family saying that the law did not apply because the patient was legally dead.

As of 2013, advance directives are legal in all states and the District of Columbia either through state specific legislation, state judicial rulings, or United States Supreme Court rulings. Many states have their own statutory forms. Massachusetts and Michigan do not have living will laws, although both have health care proxy laws. In 27 states, the laws state that the living will is not valid if a woman is pregnant. However, like all other states except Alaska, these states have enacted durable power of attorney for health care laws that permit patients to designate a proxy decision-maker with authority to terminate life-sustaining treatments. Only in Alaska does the law prohibit proxies from terminating life-sustaining treatments. The health reform legislation, the Affordable Care Act of 2010, raised substantial controversy when early versions of the law included Medicare reimbursement for advance care planning consultations. These provisions were withdrawn over accusations that they would lead to the rationing of care for the elderly.

INTERVENTIONS

PHYSICAL SYMPTOMS AND THEIR MANAGEMENT

Great emphasis has been placed on addressing dying patients' pain. Some institutions have made pain assessment a fifth vital sign to emphasize its importance. This is also has been advocated by large health care systems such as the Veterans' Administration and accrediting bodies such as the Joint Commission. Although this embrace of pain as the fifth vital sign has been symbolically important, no data document that it has improved pain management practices. Although good palliative care requires good pain management, it also requires more. The frequency of symptoms varies by disease and other factors. The most common physical and psychological symptoms among all terminally ill patients include pain, fatigue, insomnia, anorexia, dyspnea, depression, anxiety, and nausea and vomiting. In the last days of life, terminal delirium is also common. Assessments of patients with advanced cancer have shown that patients experienced an average of 11.5 different physical and psychological symptoms **(Table 33-4)**.

Evaluations to determine the etiology of these symptoms usually can be limited to the history and physical examination. In some cases, radiologic or other diagnostic examinations will provide sufficient benefit in directing optimal palliative care to warrant the risks, potential discomfort, and inconvenience, especially to a seriously ill patient. Only a few of the common

TABLE 33-4

COMMON PHYSICAL AND PSYCHOLOGICAL SYMPTOMS OF TERMINALLY ILL PATIENTS

PHYSICAL SYMPTOMS	PSYCHOLOGICAL SYMPTOMS
Pain	Anxiety
Fatigue and weakness	Depression
Dyspnea	Hopelessness
Insomnia	Meaninglessness
Dry mouth	Irritability
Anorexia	Impaired concentration
Nausea and vomiting	Confusion
Constipation	Delirium
Cough	Loss of libido
Swelling of arms or legs	
Itching	
Diarrhea	
Dysphagia	
Dizziness	
Fecal and urinary incontinence	
Numbness/tingling in hands/feet	

symptoms that present difficult management issues will be addressed in this chapter.

Pain

Frequency

The frequency of pain among terminally ill patients varies widely. Substantial pain occurs in 36–90% of patients with advanced cancer. In the SUPPORT study of hospitalized patients with diverse conditions and an estimated survival ≤6 months, 22% reported moderate to severe pain, and caregivers of those patients noted that 50% had similar levels of pain during the last few days of life. A meta-analysis found pain prevalence of 58–69% in studies that included patients characterized as having advanced, metastatic, or terminal cancer; 44–73% in studies that included patients characterized as undergoing cancer treatment; and 21–46% in studies that included posttreatment individuals.

Etiology

Nociceptive pain is the result of direct mechanical or chemical stimulation of nociceptors and normal neural signaling to the brain. It tends to be localized, aching, throbbing, and cramping. The classic example is bone metastases. Visceral pain is caused by nociceptors in gastrointestinal, respiratory, and other organ systems. It is a deep or colicky type of pain classically associated with pancreatitis, myocardial infarction, or tumor invasion of viscera. Neuropathic pain arises from disordered nerve signals. It is described by patients as burning, electrical, or shocklike pain. Classic examples are poststroke pain, tumor invasion of the brachial plexus, and herpetic neuralgia.

Assessment

Pain is a subjective experience. Depending on the patient's circumstances, perspective, and physiologic condition, the same physical lesion or disease state can produce different levels of reported pain and need for pain relief. Systematic assessment includes eliciting the following: (1) type: throbbing, cramping, burning, etc.; (2) periodicity: continuous, with or without exacerbations, or incident; (3) location; (4) intensity; (5) modifying factors; (6) effects of treatments; (7) functional impact; and (8) impact on patient. Several validated pain assessment measures may be used, such as the Visual Analogue Scale, the Brief Pain Inventory, and the pain component of one of the more comprehensive symptom assessment instruments. Frequent reassessments are essential to assess the effects of interventions.

Interventions

Interventions for pain must be tailored to each individual, with the goal of preempting chronic pain and relieving breakthrough pain. At the end of life, there is rarely reason to doubt a patient's report of pain. Pain medications are the cornerstone of management. If they are failing and nonpharmacologic interventions—including radiotherapy and anesthetic or neurosurgical procedures such as peripheral nerve blocks or epidural medications—are required, a pain consultation is appropriate.

Pharmacologic interventions follow the World Health Organization three-step approach involving nonopioid analgesics, mild opioids, and strong opioids, with or without adjuvants **(Chap. 18)**. Nonopioid analgesics, especially nonsteroidal anti-inflammatory drugs (NSAIDs), are the initial treatments for mild pain. They work primarily by inhibiting peripheral prostaglandins and reducing inflammation but also may have central nervous system (CNS) effects. They have a ceiling effect. Ibuprofen, up to a total dose of 1600 mg/d given in four doses of 400 mg each, has a minimal risk of causing bleeding and renal impairment and is a good initial choice. In patients with a history of severe gastrointestinal (GI) or other bleeding, it should be avoided. In patients with a history of mild gastritis or gastroesophageal reflux disease (GERD), acid-lowering therapy such as a proton pump inhibitor should be used. Acetaminophen is an alternative in patients with a history of GI bleeding and can be used safely at up to 4 g/d given in four doses of 1 g each. In patients with liver dysfunction due to metastases or other causes and in patients with heavy alcohol use, doses should be reduced.

If nonopioid analgesics are insufficient, opioids should be introduced. They work by interacting with μ opioid receptors in the CNS to activate pain-inhibitory neurons; most are receptor antagonists. The mixed agonist/antagonist opioids useful for postacute pain should not be used for the chronic pain in end-of-life care. Weak opioids such as codeine can be used initially. However, if they are escalated and fail to relieve pain, strong opioids such as morphine, 5–10 mg every 4 h, should be used. Nonopioid analgesics should be combined with opioids because they potentiate the effect of opioids.

For continuous pain, opioids should be administered on a regular, around-the-clock basis consistent with their duration of analgesia. They should not be provided only when the patient experiences pain; the goal is to prevent patients from experiencing pain. Patients also should be provided rescue medication, such as liquid morphine, for breakthrough pain, generally at 20% of the baseline dose. Patients should be informed that using the rescue medication does not obviate the need to take the next standard dose of pain medication. If after 24 h the patient's pain remains uncontrolled and recurs before the next dose, requiring the patient to use the rescue medication, the daily opioid dose can be increased by the total dose of rescue medications used by the patient, or by 50% for moderate pain and 100% for severe pain of the standing opioid daily dose.

It is inappropriate to start with extended-release preparations. Instead, an initial focus on using short-acting preparations to determine how much is required in the first 24–48 h will allow clinicians to determine opioid needs. Once pain relief is obtained with short-acting preparations, one should switch to extended-release preparations. Even with a stable extended-release preparation regimen, the patient may have incident pain, such as during movement or dressing changes. Short-acting preparations should be taken before such predictable episodes. Although less common, patients may have "end-of-dose failure" with long-acting opioids, meaning that they develop pain after 8 h in the case of an every-12-h medication. In these cases, a trial of giving an every-12-h medication every 8 h is appropriate.

Because of differences in opioid receptors, cross-tolerance among opioids is incomplete, and patients may experience different side effects with different opioids. T erefore, if a patient is not experiencing pain relief or is experiencing too many side effects, a change to another opioid preparation is appropriate. When switching, one should begin with 50–75% of the published equianalgesic dose of the new opioid.

Unlike NSAIDs, opioids have no ceiling effect; therefore, there is no maximum dose no matter how many milligrams the patient is receiving. T e appropriate dose is the dose needed to achieve pain relief. T is is an important point for clinicians to explain to patients and families. Addiction or excessive respiratory depression is extremely unlikely in the terminally ill; fear of these side effects should neither prevent escalating opioid medications when the patient is experiencing insufficient pain relief nor justify using opioid antagonists.

Opioid side effects should be anticipated and treated preemptively. Nearly all patients experience constipation that can be debilitating (see below). Failure to prevent constipation often results in noncompliance with opioid therapy. Methylnaltrexone is a drug that targets opioid-induced constipation by blocking peripheral opioid receptors but not central receptors for analgesia. In placebo-controlled trials, it has been shown to cause laxation within 24 h of administration. As with the use of opioids, about a third of patients using methylnaltrexone experience nausea and vomiting, but unlike constipation, tolerance develops, usually within a week. T erefore, when one is beginning opioids, an antiemetic such as metoclopramide or a serotonin antagonist often is prescribed prophylactically and stopped after 1 week. Olanzapine also has antinausea properties and can be effective in countering delirium or anxiety, with the advantage of some weight gain.

Drowsiness, a common side effect of opioids, also usually abates within a week. During this period, drowsiness can be treated with psychostimulants such as dextroamphetamine, methylphenidate, and modafinil. Modafinil has the advantage of everyday dosing. Pilot reports suggest that donepezil may also be helpful for opiate-induced drowsiness as well as relieving fatigue and anxiety. Metabolites of morphine and most opioids are cleared renally; doses may have to be adjusted for patients with renal failure.

Seriously ill patients who require chronic pain relief rarely if ever become addicted. Suspicion of addiction should not be a reason to withhold pain medications from terminally ill patients. Patients and families may withhold prescribed opioids for fear of addiction or dependence. Physicians and health care providers should reassure patients and families that the patient will not become addicted to opioids if they are used as prescribed for pain relief; this fear should not prevent the patient from taking the medications around the clock. However, diversion of drugs for use by other family members or illicit sale may occur. It may be necessary to advise the patient and caregiver about secure storage of opioids. Contract writing with the patient and family can help. If that fails, transfer to a safe facility may be necessary.

Tolerance is the need to increase medication dosage for the same pain relief without a change in disease. In the case of patients with advanced disease, the need for increasing opioid dosage for pain relief usually is caused by disease progression rather than tolerance. Physical dependence is indicated by symptoms from the abrupt withdrawal of opioids and should not be confused with addiction.

Adjuvant analgesic medications are nonopioids that potentiate the analgesic effects of opioids. T ey are especially important in the management of neuropathic pain. Gabapentin and pregabalin, calcium channel alpha 2-delta ligands, are now the first-line treatments for neuropathic pain from a variety of causes. Gabapentin is begun at 100–300 mg bid or tid, with 50–100% dose increments every 3 days. Usually 900–3600 mg/d in two or three doses is effective. T e combination of gabapentin and nortriptyline may be more effective than gabapentin alone. One potential side effect of gabapentin to be aware of is confusion and drowsiness, especially in the elderly. Pregabalin has the same mechanism of action as gabapentin but is absorbed more efficiently from the GI tract. It is started at 75 mg bid and increased to 150 mg bid. T e maximum dose is 225 mg bid. Carbamazepine, a first-generation agent, has been proved effective in randomized trials for neuropathic pain. Other potentially effective anticonvulsant adjuvants include topiramate (25–50 mg qd or bid, rising to 100–300 mg/d) and oxcarbazepine (75–300 mg bid, rising to 1200 mg bid). Glucocorticoids, preferably dexamethasone given once a day, can be useful in reducing inf ammation

that causes pain while elevating mood, energy, and appetite. Its main side effects include confusion, sleep difficulties, and fuid retention. Glucocorticoids are especially effective for bone pain and abdominal pain from distention of the GI tract or liver. Other drugs, including clonidine and baclofen, can be effective in pain relief. T ese drugs are adjuvants and generally should be used in conjunction with—not instead of—opioids. Methadone, carefully dosed because of its unpredictable half-life in many patients, has activity at the N-methyl-d-aspartamate (NMDA) receptor and is useful for complex pain syndromes and neuropathic pain. It generally is reserved for cases in which first-line opioids (morphine, oxycodone, hydromorphone) are either ineffective or unavailable.

Radiation therapy can treat bone pain from single metastatic lesions. Bone pain from multiple metastases can be amenable to radiopharmaceuticals such as strontium-89 and samarium-153. Bisphosphonates (such as pamidronate [90 mg every 4 weeks]) and calcitonin (200 IU intranasally once or twice a day) also provide relief from bone pain but have an onset of action of days.

Constipation

Frequency

Constipation is reported in up to 87% of patients requiring palliative care.

Etiology

Although hypercalcemia and other factors can cause constipation, it is most frequently a predictable consequence of the use of opioids for the relief of pain and dyspnea and of tricyclic antidepressants, from their anticholinergic effects, and of the inactivity and poor diet that are common among seriously ill patients. If untreated, constipation can cause substantial pain and vomiting and also is associated with confusion and delirium. Whenever opioids and other medications known to cause constipation are used, preemptive treatment for constipation should be instituted.

Assessment

T e physician should establish the patient's previous bowel habits, including the frequency, consistency, and volume. Abdominal and rectal examinations should be performed to exclude impaction or acute abdomen. A number of constipation assessment scales are available, although guidelines issued in the Journal *of* Palliative Medicine did not recommend them for routine practice. Radiographic assessments beyond a simple fat plate of the abdomen in cases in which obstruction is suspected are rarely necessary.

Intervention

Intervention to reestablish comfortable bowel habits and relieve pain and discomfort should be the goals of any measures to address constipation during end-of-life care. Although physical activity, adequate hydration, and dietary treatments with fiber can be helpful, each is limited in its effectiveness for most seriously ill patients, and fiber may exacerbate problems in the setting of dehydration and if impaired motility is the etiology. Fiber is contraindicated in the presence of opioid use. Stimulant and osmotic laxatives, stool softeners, fuids, and enemas are the mainstays of therapy **(Table 33-5)**. In preventing constipation from opioids and other medications, a combination of a laxative and a stool softener (such as senna and docusate) should be used. If after several days of treatment, a bowel movement has not occurred, a rectal examination to remove impacted stool and place a suppository is necessary. For patients with impending bowel obstruction or gastric stasis, octreotide to reduce secretions can be helpful. For patients in whom the suspected mechanism is dysmotility, metoclopramide can be helpful.

Nausea

Frequency

Up to 70% of patients with advanced cancer have nausea, defined as the subjective sensation of wanting to vomit.

Etiology

Nausea and vomiting are both caused by stimulation at one of four sites: the GI tract, the vestibular system, the chemoreceptor trigger zone (CTZ), and the cerebral cortex. Medical treatments for nausea are aimed at receptors at each of these sites: the GI tract contains mechanoreceptors, chemoreceptors, and 5-hydroxytryptamine type 3 (5-HT_3) receptors; the vestibular system probably contains histamine and acetylcholine receptors; and the CTZ contains chemoreceptors, dopamine type 2 receptors, and 5-HT_3 receptors. An example of nausea that most likely is mediated by the cortex is anticipatory nausea before a dose of chemotherapy or other noxious stimuli.

Specific causes of nausea include metabolic changes (liver failure, uremia from renal failure, hypercalcemia), bowel obstruction, constipation, infection, GERD, vestibular disease, brain metastases, medications (including antibiotics, NSAIDs, proton pump inhibitors, opioids, and chemotherapy), and radiation therapy. Anxiety can also contribute to nausea.

Intervention

Medical treatment of nausea is directed at the anatomic and receptor-mediated cause that a careful history and physical examination reveals. When a single specific

TABLE 33-5

MEDICATIONS FOR THE MANAGEMENT OF CONSTIPATION

INTERVENTION	DOSE	COMMENT
Stimulant laxatives		These agents directly stimulate peristalsis and may reduce colonic absorption of water.
Prune juice	120–240 mL/d	Work in 6–12 h.
Senna (Senokot)	2–8 tablets PO bid	
Bisacodyl	5–15 mg/d PO, PR	
Osmotic laxatives		These agents are not absorbed. They attract and retain water in the gastrointestinal tract.
Lactulose	15–30 mL PO q4–8h	Lactulose may cause flatulence and bloating.
Magnesium hydroxide (Milk of Magnesia)	15–30 mL/d PO	Lactulose works in 1 day, magnesium products in 6 h.
Magnesium citrate	125–250 mL/d PO	
Stool softeners		These agents work by increasing water secretion and as detergents, increasing water penetration into the stool.
Sodium docusate (Colace)	300–600 mg/d PO	Work in 1–3 days.
Calcium docusate	300–600 mg/d PO	
Suppositories and enemas		
Bisacodyl	10–15 PR qd	
Sodium phosphate enema	PR qd	Fixed dose, 4.5 oz, Fleet's.

cause is not found, many advocate beginning treatment with a dopamine antagonist such as haloperidol or prochlorperazine. Prochlorperazine is usually more sedating than haloperidol. When decreased motility is suspected, metoclopramide can be an effective treatment. When inf ammation of the GI tract is suspected, glucocorticoids such as dexamethasone are an appropriate treatment. For nausea that follows chemotherapy and radiation therapy, one of the 5-HT_3 receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron) is recommended. Studies suggest palonosetron has higher receptor binding affinity and clinical superiority to the other 5-HT_3 receptor antagonists. Clinicians should attempt prevention of postchemotherapy nausea rather than provide treatment after the fact. Current clinical guidelines recommend tailoring the strength of treatments to the specific emetic risk posed by a specific chemotherapy drug. When a vestibular cause (such as "motion sickness" or labyrinthitis) is suspected, antihistamines such as meclizine (whose primary side effect is drowsiness) or anticholinergics such as scopolamine can be effective. In anticipatory nausea, a benzodiazepine such as lorazepam is indicated. As with antihistamines, drowsiness and confusion are the main side effects.

Dyspnea

Frequency

Dyspnea is a subjective experience of being short of breath. Frequencies vary among causes of death, but it can affect 80–90% of dying patients with lung cancer, COPD, and heart disease. Dyspnea is among the most distressing physical symptoms and can be even more distressing than pain.

Assessment

As with pain, dyspnea is a subjective experience that may not correlate with objective measures of Po_2, Pco_2, or respiratory rate. Consequently, measurements of oxygen saturation through pulse oximetry or blood gases are rarely helpful in guiding therapy. Despite the limitations of existing assessment methods, physicians should regularly assess and document patients' experience of dyspnea and its intensity. Guidelines recommend visual or analogue dyspnea scales to assess the severity of symptoms and the effects of treatment. Potentially reversible or treatable causes of dyspnea include infection, pleural effusions, pulmonary emboli, pulmonary edema, asthma, and tumor encroachment on the airway. However, the risk-versus-benefit ratio of the diagnostic and therapeutic interventions for patients with little time left to live must be considered carefully before one undertakes diagnostic steps. Frequently, the specific etiology cannot be identified, and dyspnea is the consequence of progression of the underlying disease that cannot be treated. T e anxiety caused by dyspnea and the choking sensation can significantly exacerbate the underlying dyspnea in a negatively reinforcing cycle.

Interventions

When reversible or treatable etiologies are diagnosed, they should be treated as long as the side effects of

TABLE 33-6

MEDICATIONS FOR THE MANAGEMENT OF DYSPNEA

INTERVENTION	DOSE	COMMENTS
Weak opioids		For patients with mild dyspnea
Codeine (or codeine with 325 mg acetaminophen)	30 mg PO q4h	For opioid-naïve patients
Hydrocodone	5 mg PO q4h	
Strong opioids		For opioid-naïve patients with moderate to severe dyspnea
Morphine	5–10 mg PO q4h 30–50% of baseline opioid dose q4h	For patients already taking opioids for pain or other symptoms
Oxycodone	5–10 mg PO q4h	
Hydromorphone	1–2 mg PO q4h	
Anxiolytics		Give a dose every hour until the patient is relaxed, then provide a dose for maintenance
Lorazepam	0.5–2.0 mg PO/SL/IV qh then q4–6h	
Clonazepam	0.25–2.0 mg PO q12h	
Midazolam	0.5 mg IV q15min	

treatment, such as repeated drainage of effusions or anticoagulants, are less burdensome than the dyspnea itself. More aggressive treatments such as stenting a bronchial lesion may be warranted if it is clear that the dyspnea is due to tumor invasion at that site and if the patient and family understand the risks of such a procedure. Usually, treatment will be symptomatic **(Table 33-6)**. A dyspnea scale and careful monitoring should guide dose adjustment. Low-dose opioids reduce the sensitivity of the central respiratory center and the sensation of dyspnea. If patients are not receiving opioids, weak opioids can be initiated; if patients are already receiving opioids, morphine or other strong opioids should be used. Controlled trials do not support the use of nebulized opioids for dyspnea at the end of life. Phenothiazines and chlorpromazine may be helpful when combined with opioids. Benzodiazepines can be helpful if anxiety is present but should be neither used as first-line therapy nor used alone in the treatment of dyspnea. If the patient has a history of COPD or asthma, inhaled bronchodilators and glucocorticoids may be helpful. If the patient has pulmonary edema due to heart failure, diuresis with a medication such as furosemide is indicated. Excess secretions can be dried with scopolamine, transdermally or intravenously. Use of oxygen is controversial. There are conflicting data on its effectiveness for patients with proven hypoxemia. But there is no clear benefit of oxygen compared to room air for nonhypoxemic patients. Noninvasive positive-pressure ventilation using a facemask or nasal plugs may be used for some patients for symptom relief. For some families and patients, oxygen is distressing; for others, it is reassuring. More general interventions that medical staff can do include sitting the patient upright, removing smoke or other irritants such as perfume, ensuring a supply of fresh air with sufficient humidity, and minimizing other factors that can increase anxiety.

Fatigue

Frequency

More than 90% of terminally ill patients experience fatigue and/or weakness. Fatigue is one of the most commonly reported symptoms of cancer treatment as well as in the palliative care of multiple sclerosis, COPD, heart failure, and HIV. Fatigue frequently is cited as among the most distressing symptoms.

Etiology

The multiple causes of fatigue in the terminally ill can be categorized as resulting from the underlying disease; from disease-induced factors such as tumor necrosis factor and other cytokines; and from secondary factors such as dehydration, anemia, infection, hypothyroidism, and drug side effects. Apart from low caloric intake, loss of muscle mass and changes in muscle enzymes may play an important role in fatigue of terminal illness. The importance of changes in the CNS, especially the reticular activating system, have been hypothesized based on reports of fatigue in patients receiving cranial radiation, experiencing depression, or having chronic pain in the absence of cachexia or other physiologic changes. Finally, depression and other causes of psychological distress can contribute to fatigue.

Assessment

Like pain and dyspnea, fatigue is subjective. Objective changes, even in body mass, may be absent.

Consequently, assessment must rely on patient self-reporting. Scales used to measure fatigue, such as the Edmonton Functional Assessment Tool, the Fatigue Self-Report Scales, and the Rhoten Fatigue Scale, are usually appropriate for research rather than clinical purposes. In clinical practice, a simple performance assessment such as the Karnofsky Performance Status or the ECOG's question "How much of the day does the patient spend in bed?" may be the best measure. In this 0–4 performance status assessment, 0 = normal activity; 1 = symptomatic without being bedridden; 2 = requiring some, but <50%, bed time; 3 = bedbound more than half the day; and 4 = bedbound all the time. Such a scale allows for assessment over time and correlates with overall disease severity and prognosis. A 2008 review by the European Association of Palliative Care also described several longer assessment tools with 9–20 items, including the Piper Fatigue Inventory, the Multidimensional Fatigue Inventory, and the Brief Fatigue Inventory (BFI).

Interventions

For some patients, there are reversible causes such as anemia, but for most patients at the end of life, fatigue will not be "cured." T e goal is to ameliorate it and help patients and families adjust expectations. Behavioral interventions should be used to avoid blaming the patient for inactivity and to educate both the family and the patient that the underlying disease causes physiologic changes that produce low energy levels. Understanding that the problem is physiologic and not psychological can help alter expectations regarding the patient's level of physical activity. Practically, this may mean reducing routine activities such as housework and cooking or social events outside the house and making it acceptable to receive guests lying on a couch. At the same time, institution of exercise regimens and physical therapy can raise endorphins, reduce muscle wasting, and reduce the risk of depression. In addition, ensuring good hydration without worsening edema may help reduce fatigue. Discontinuing medications that worsen fatigue may help, including cardiac medications, benzodiazepines, certain antidepressants, or opioids if pain is well-controlled. As end-of-life care proceeds into its final stages, fatigue may protect patients from further suffering, and continued treatment could be detrimental.

T ere are woefully few pharmacologic interventions that target fatigue and weakness. Glucocorticoids can increase energy and enhance mood. Dexamethasone is preferred for its once-a-day dosing and minimal mineralocorticoid activity. Benefit, if any, usually is seen within the first month. Psychostimulants such as dextroamphetamine (5–10 mg PO) and methylphenidate (2.5–5 mg PO) may also enhance energy levels, although a randomized trial did not show methylphenidate beneficial compared with placebo in cancer fatigue. Doses should be given in the morning and at noon to minimize the risk of counterproductive insomnia. Modafinil, developed for narcolepsy, has shown some promise in the treatment of severe fatigue and has the advantage of once-daily dosing. Its precise role in fatigue at the end of life has not been determined. Anecdotal evidence suggests that l-carnitine may improve fatigue, depression, and sleep disruption. Similarly, some studies suggest ginseng can reduce fatigue.

PSYCHOLOGICAL SYMPTOMS AND THEIR MANAGEMENT

Depression

Frequency

Depression at the end of life presents an apparently paradoxical situation. Many people believe that depression is normal among seriously ill patients because they are dying. People frequently say, "Wouldn't you be depressed?" However, depression is not a necessary part of terminal illness and can contribute to needless suffering. Although sadness, anxiety, anger, and irritability are normal responses to a serious condition, they are typically of modest intensity and transient. Persistent sadness and anxiety and the physically disabling symptoms that they can lead to are abnormal and suggestive of major depression. Although as many as 75% of terminally ill patients experience emotional distress and depressive symptoms, <30% of terminally ill patients have major depression. Depression is not limited to cancer patients but found in patients with end-stage renal disease, Parkinson's disease, multiple sclerosis, and other terminal conditions.

Etiology

Previous history of depression, family history of depression or bipolar disorder, and prior suicide attempts are associated with increased risk for depression among terminally ill patients. Other symptoms, such as pain and fatigue, are associated with higher rates of depression; uncontrolled pain can exacerbate depression, and depression can cause patients to be more distressed by pain. Many medications used in the terminal stages, including glucocorticoids, and some anticancer agents, such as tamoxifen, interleukin 2, interferon α, and vincristine, also are associated with depression. Some terminal conditions, such as pancreatic cancer, certain strokes, and heart failure, have been reported to be associated with higher rates of depression, although this is controversial. Finally, depression may be attributable to grief over the loss of a role or function, social isolation, or loneliness.

Assessment

Diagnosing depression among seriously ill patients is complicated because many of the vegetative symptoms

in the DSM-V (Diagnostic and Statistical Manual *of* Mental Disorders) criteria for clinical depression—insomnia, anorexia and weight loss, fatigue, decreased libido, and difficulty concentrating—are associated with the dying process itself. T e assessment of depression in seriously ill patients therefore should focus on the dysphoric mood, helplessness, hopelessness, and lack of interest and enjoyment and concentration in normal activities. T e single questions "How often do you feel downhearted and blue?" (more than a good bit of the time or similar responses) and "Do you feel depressed most of the time?" are appropriate for screening. Visual Analog Scales can also be useful in screening.

Interventions

Physicians must treat any physical symptom, such as pain, that may be causing or exacerbating depression. Fostering adaptation to the many losses that the patient is experiencing can also be helpful. Nonpharmacologic interventions, including group or individual psychological counseling, and behavioral therapies such as relaxation and imagery can be helpful, especially in combination with drug therapy.

Pharmacologic interventions remain the core of therapy. T e same medications are used to treat depression in terminally ill as in non–terminally ill patients. Psychostimulants may be preferred for patients with a poor prognosis or for those with fatigue or opioid-induced somnolence. Psychostimulants are comparatively fast acting, working within a few days instead of the weeks required for selective serotonin reuptake inhibitors (SSRIs). Dextroamphetamine or methylphenidate should be started at 2.5–5.0 mg in the morning and at noon, the same starting doses used for treating fatigue. T e dose can be escalated up to 15 mg bid. Modafinil is started at 100 mg qd and can be increased to 200 mg if there is no effect at the lower dose. Pemoline is a nonamphetamine psychostimulant with minimal abuse potential. It is also effective as an antidepressant beginning at 18.75 mg in the morning and at noon. Because it can be absorbed through the buccal mucosa, it is preferred for patients with intestinal obstruction or dysphagia. If it is used for prolonged periods, liver function must be monitored. T e psychostimulants can also be combined with more traditional antidepressants while waiting for the antidepressants to become effective and then tapered after a few weeks if necessary. Psychostimulants have side effects, particularly initial anxiety, insomnia, and rarely paranoia, which may necessitate lowering the dose or discontinuing treatment.

Mirtazapine, an antagonist at the postsynaptic serotonin receptors, is a promising psychostimulant. It should be started at 7.5 mg before bed. It has sedating, antiemetic, and anxiolytic properties with few drug interactions. Its side effect of weight gain may be beneficial for seriously ill patients; it is available in orally disintegrating tablets.

For patients with a prognosis of several months or longer, SSRIs, including f uoxetine, sertraline, paroxetine, citalopram, escitalopram, and f uvoxamine, and serotonin-noradrenaline reuptake inhibitors such as venlafaxine, are the preferred treatment because of their efficacy and comparatively few side effects. Because low doses of these medications may be effective for seriously ill patients, one should use half the usual starting dose for healthy adults. T e starting dose for f uoxetine is 10 mg once a day. In most cases, once-a-day dosing is possible. T e choice of which SSRI to use should be driven by (1) the patient's past success or failure with the specific medication, (2) the most favorable side effect profile for that specific agent, and (3) the time it takes to reach steady-state drug levels. For instance, for a patient in whom fatigue is a major symptom, a more activating SSRI (f uoxetine) would be appropriate. For a patient in whom anxiety and sleeplessness are major symptoms, a more sedating SSRI (paroxetine) would be appropriate.

Atypical antidepressants are recommended only in selected circumstances, usually with the assistance of a specialty consultation. Trazodone can be an effective antidepressant but is sedating and can cause orthostatic hypotension and, rarely, priapism. T erefore, it should be used only when a sedating effect is desired and is often used for patients with insomnia, at a dose starting at 25 mg. In addition to its antidepressant effects, bupropion is energizing, making it useful for depressed patients who experience fatigue. However, it can cause seizures, preventing its use for patients with a risk of CNS neoplasms or terminal delirium. Finally, alprazolam, a benzodiazepine, starting at 0.25–1.0 mg tid, can be effective in seriously ill patients who have a combination of anxiety and depression. Although it is potent and works quickly, it has many drug interactions and may cause delirium, especially among very ill patients, because of its strong binding to the benzodiazepine–γ-aminobutyric acid (GABA) receptor complex.

Unless used as adjuvants for the treatment of pain, tricyclic antidepressants are not recommended. Similarly, monoamine oxidase (MAO) inhibitors are not recommended because of their side effects and dangerous drug interactions.

Delirium

Frequency

In the weeks or months before death, delirium is uncommon, although it may be significantly underdiagnosed. However, delirium becomes relatively common

in the hours and days immediately before death. Up to 85% of patients dying from cancer may experience terminal delirium.

Etiology

Delirium is a global cerebral dysfunction characterized by alterations in cognition and consciousness. It frequently is preceded by anxiety, changes in sleep patterns (especially reversal of day and night), and decreased attention. In contrast to dementia, delirium has an acute onset, is characterized by fluctuating consciousness and inattention, and is reversible, although reversibility may be more theoretical than real for patients near death. Delirium may occur in a patient with dementia; indeed, patients with dementia are more vulnerable to delirium.

Causes of delirium include metabolic encephalopathy arising from liver or renal failure, hypoxemia, or infection; electrolyte imbalances such as hypercalcemia; paraneoplastic syndromes; dehydration; and primary brain tumors, brain metastases, or leptomeningeal spread of tumor. Commonly, among dying patients, delirium can be caused by side effects of treatments, including radiation for brain metastases, and medications, including opioids, glucocorticoids, anticholinergic drugs, antihistamines, antiemetics, benzodiazepines, and chemotherapeutic agents. The etiology may be multifactorial; e.g., dehydration may exacerbate opioid-induced delirium.

Assessment

Delirium should be recognized in any terminally ill patient with new onset of disorientation, impaired cognition, somnolence, fluctuating levels of consciousness, or delusions with or without agitation. Delirium must be distinguished from acute anxiety and depression as well as dementia. The central distinguishing feature is altered consciousness, which usually is not noted in anxiety, depression, and dementia. Although "hyperactive" delirium characterized by overt confusion and agitation is probably more common, patients also should be assessed for "hypoactive" delirium characterized by sleep-wake reversal and decreased alertness.

In some cases, use of formal assessment tools such as the Mini-Mental Status Examination (which does not distinguish delirium from dementia) and the Delirium Rating Scale (which does distinguish delirium from dementia) may be helpful in distinguishing delirium from other processes. The patient's list of medications must be evaluated carefully. Nonetheless, a reversible etiologic factor for delirium is found in fewer than half of terminally ill patients. Because most terminally ill patients experiencing delirium will be very close to death and may be at home, extensive diagnostic evaluations such as lumbar punctures and neuroradiologic examinations are usually inappropriate.

Interventions

One of the most important objectives of terminal care is to provide terminally ill patients the lucidity to say goodbye to the people they love. Delirium, especially with agitation during the final days, is distressing to family and caregivers. A strong determinant of bereavement difficulties is witnessing a difficult death. Thus, terminal delirium should be treated aggressively.

At the first sign of delirium, such as day-night reversal with slight changes in mentation, the physician should let the family members know that it is time to be sure that everything they want to say has been said. The family should be informed that delirium is common just before death.

If medications are suspected of being a cause of the delirium, unnecessary agents should be discontinued. Other potentially reversible causes, such as constipation, urinary retention, and metabolic abnormalities, should be treated. Supportive measures aimed at providing a familiar environment should be instituted, including restricting visits only to individuals with whom the patient is familiar and eliminating new experiences; orienting the patient, if possible, by providing a clock and calendar; and gently correcting the patient's hallucinations or cognitive mistakes.

Pharmacologic management focuses on the use of neuroleptics and, in the extreme, anesthetics **(Table 33-7)**. Haloperidol remains first-line therapy. Usually, patients can be controlled with a low dose (1–3 mg/d), usually given every 6 h, although some may require as much as 20 mg/d. It can be administered PO, SC, or IV. IM injections should not be used, except when this is the only way to get a patient under control. Newer atypical neuroleptics, such as olanzapine, risperidone, and quetiapine, have shown significant effectiveness in

TABLE 33-7

MEDICATIONS FOR THE MANAGEMENT OF DELIRIUM

INTERVENTIONS	DOSE
Neuroleptics	
Haloperidol	0.5–5 mg q2–12h, PO/IV/SC/IM
Thioridazine	10–75 mg q4–8h, PO
Chlorpromazine	12.5–50 mg q4–12h, PO/IV/IM
Atypical neuroleptics	
Olanzapine	2.5–5 mg qd or bid, PO
Risperidone	1–3 mg q12h, PO
Quetiapine	50 mg qd, PO
Anxiolytics	
Lorazepam	0.5–2 mg q1–4h, PO/IV/IM
Midazolam	1–5 mg/h continuous infusion, IV/SC
Anesthetics	
Propofol	0.3–2.0 mg/h continuous infusion, IV

completely resolving delirium in cancer patients. T ese drugs also have fewer side effects than haloperidol, along with other beneficial effects for terminally ill patients, including antinausea, antianxiety, and weight gain. T ey are useful for patients with longer anticipated life expectancy because they are less likely to cause dysphoria and have a lower risk of dystonic reactions. Also, because they are metabolized through multiple pathways, they can be used in patients with hepatic and renal dysfunction. Olanzapine has the disadvantage that it is available only orally and that it takes a week to reach steady state. T e usual dose is 2.5–5 mg PO bid. Chlorpromazine (10–25 mg every 4–6 h) can be useful if sedation is desired and can be administered IV or PR in addition to PO. Dystonic reactions resulting from dopamine blockade are a side effect of neuroleptics, although they are reported to be rare when these drugs are used to treat terminal delirium. If patients develop dystonic reactions, benztropine should be administered. Neuroleptics may be combined with lorazepam to reduce agitation when the delirium is the result of alcohol or sedative withdrawal.

If no response to first-line therapy is seen, a specialty consultation should be obtained with a change to a different medication. If patients fail to improve after a second neuroleptic, sedation with an anesthetic such as propofol or continuous-infusion midazolam may be necessary. By some estimates, at the very end of life, as many as 25% of patients experiencing delirium, especially restless delirium with myoclonus or convulsions, may require sedation.

Physical restraints should be used with great reluctance and only when the patient's violence is threatening to self or others. If they are used, their appropriateness should be reevaluated frequently.

Insomnia

Frequency

Sleep disorders, defined as difficulty initiating sleep or maintaining sleep, sleep difficulty at least 3 nights a week, or sleep difficulty that causes impairment of daytime functioning, occur in 19–63% of patients with advanced cancer. Some 30–74% of patients with other end-stage conditions, including AIDS, heart disease, COPD, and renal disease, experience insomnia.

Etiology

Patients with cancer may have changes in sleep efficiency such as an increase in stage I sleep. Other etiologies of insomnia are coexisting physical illness such as thyroid disease and coexisting psychological illnesses such as depression and anxiety. Medications, including antidepressants, psychostimulants, steroids, and β agonists, are significant contributors to sleep disorders, as are caffeine and alcohol. Multiple over-the-counter medications contain caffeine and antihistamines, which can contribute to sleep disorders.

Assessment

Assessment should include specific questions concerning sleep onset, sleep maintenance, and early-morning wakening as these will provide clues to the causative agents and to management. Patients should be asked about previous sleep problems, screened for depression and anxiety, and asked about symptoms of thyroid disease. Caffeine and alcohol are prominent causes of sleep problems, and a careful history of the use of these substances should be obtained. Both excessive use and withdrawal from alcohol can be causes of sleep problems.

Interventions

T e mainstays of intervention include improvement of sleep hygiene (encouragement of regular time for sleep, decreased nighttime distractions, elimination of caffeine and other stimulants and alcohol), intervention to treat anxiety and depression, and treatment for the insomnia itself. For patients with depression who have insomnia and anxiety, a sedating antidepressant such as mirtazapine can be helpful. In the elderly, trazodone, beginning at 25 mg at nighttime, is an effective sleep aid at doses lower than those which cause its antidepressant effect. Zolpidem may have a decreased incidence of delirium in patients compared with traditional benzodiazepines, but this has not been clearly established. When benzodiazepines are prescribed, short-acting ones (such as lorazepam) are favored over longer-acting ones (such as diazepam). Patients who receive these medications should be observed for signs of increased confusion and delirium.

SOCIAL NEEDS AND THEIR MANAGEMENT

Financial burdens

Frequency

Dying can impose substantial economic strains on patients and families, causing distress. In the United States, with one of the least comprehensive health insurance systems among the developed countries, ~20% of terminally ill patients and their families spend >10% of family income on health care costs over and above health insurance premiums. Between 10 and 30% of families sell assets, use savings, or take out a mortgage to pay for the patient's health care costs. Nearly 40% of terminally ill patients in the United States report that the cost of their illness is a moderate or great economic hardship for their family.

T e patient is likely to reduce and eventually stop working. In 20% of cases, a family member of the terminally ill patient also stops working to provide care. T e major underlying causes of economic burden are

related to poor physical functioning and care needs, such as the need for housekeeping, nursing, and personal care. More debilitated patients and poor patients experience greater economic burdens.

Intervention

T is economic burden should not be ignored as a private matter. It has been associated with a number of adverse health outcomes, including preferring comfort care over life-prolonging care as well as consideration of euthanasia or physician-assisted suicide. Economic burdens increase the psychological distress of families and caregivers of terminally ill patients, and poverty is associated with many adverse health outcomes. Importantly, recent studies found that "patients with advanced cancer who reported having end-of-life conversations with physicians had significantly lower health care costs in their final week of life. Higher costs were associated with worse quality of death." Assistance from a social worker, early on if possible, to ensure access to all available benefits may be helpful. Many patients, families, and health care providers are unaware of options for long-term care insurance, respite care, the Family Medical Leave Act (FMLA), and other sources of assistance. Some of these options (such as respite care) may be part of a formal hospice program, but others (such as the FMLA) do not require enrollment in a hospice program.

Relationships

Frequency

Settling personal issues and closing the narrative of lived relationships are universal needs. When asked if sudden death or death after an illness is preferable, respondents often initially select the former but soon change to the latter as they ref ect on the importance of saying goodbye. Bereaved family members who have not had the chance to say goodbye often have a more difficult grief process.

Interventions

Care of seriously ill patients requires efforts to facilitate the types of encounters and time spent with family and friends that are necessary to meet those needs. Family and close friends may need to be accommodated with unrestricted visiting hours, which may include sleeping near the patient even in otherwise regimented institutional settings. Physicians and other health care providers may be able to facilitate and resolve strained interactions between the patient and other family members. Assistance for patients and family members who are unsure about how to create or help preserve memories, whether by providing materials such as a scrapbook or memory box or by offering them suggestions and informational resources, can be deeply appreciated. Taking photographs and creating videos can be especially helpful to terminally ill patients who have younger children or grandchildren.

Family caregivers

Frequency

Caring for seriously ill patients places a heavy burden on families. Families frequently are required to provide transportation and homemaking as well as other services. Typically, paid professionals such as home health nurses and hospice workers supplement family care; only about a quarter of all caregiving consists of exclusively paid professional assistance. T e trend toward more out-of-hospital deaths will increase reliance on families for end-of-life care. Increasingly, family members are being called upon to provide physical care (such as moving and bathing patients) and medical care (such as assessing symptoms and giving medications) in addition to emotional care and support.

T ree-quarters of family caregivers of terminally ill patients are women—wives, daughters, sisters, and even daughters-in-law. Because many are widowed, women tend to be able to rely less on family for caregiving assistance and may need more paid assistance. About 20% of terminally ill patients report substantial unmet needs for nursing and personal care. T e impact of caregiving on family caregivers is substantial: both bereaved and current caregivers have a higher mortality rate than that of non-caregiving controls.

Interventions

It is imperative to inquire about unmet needs and to try to ensure that those needs are met either through the family or by paid professional services when possible. Community assistance through houses of worship or other community groups often can be mobilized by telephone calls from the medical team to someone the patient or family identifies. Sources of support specifically for family caregivers should be identified through local sources or nationally through groups such as the National Family Caregivers Association (www.n*f*cacares.org), the American Cancer Society (www.cancer.org), and the Alzheimer's Association (www.alz.org).

EXISTENTIAL NEEDS AND THEIR MANAGEMENT

Frequency

Religion and spirituality are often important to dying patients. Nearly 70% of patients report becoming more religious or spiritual when they became terminally ill, and many find comfort in religious or spiritual practices such as prayer. However, ~20% of terminally ill patients become less religious, frequently feeling cheated or

betrayed by becoming terminally ill. For other patients, the need is for existential meaning and purpose that is distinct from and may even be antithetical to religion or spirituality. When asked, patients and family caregivers frequently report wanting their professional caregivers to be more attentive to religion and spirituality.

Assessment

Health care providers are often hesitant about involving themselves in the religious, spiritual, and existential experiences of their patients because it may seem private or not relevant to the current illness. But physicians and other members of the care team should be able at least to detect spiritual and existential needs. Screening questions have been developed for a physician's spiritual history taking. Spiritual distress can amplify other types of suffering and even masquerade as intractable physical pain, anxiety, or depression. T e screening questions in the comprehensive assessment are usually sufficient. Deeper evaluation and intervention are rarely appropriate for the physician unless no other member of a care team is available or suitable. Pastoral care providers may be helpful, whether from the medical institution or from the patient's own community.

Interventions

Precisely how religious practices, spirituality, and existential explorations can be facilitated and improve end-of-life care is not well established. What is clear is that for physicians, one main intervention is to inquire about the role and importance of spirituality and religion in a patient's life. T is will help a patient feel heard and help physicians identify specific needs. In one study, only 36% of respondents indicated that a clergy member would be comforting. Nevertheless, the increase in religious and spiritual interest among a substantial fraction of dying patients suggests inquiring of individual patients how this need can be addressed. Some evidence supports specific methods of addressing existential needs in patients, ranging from establishing a supportive group environment for terminal patients to individual treatments emphasizing a patient's dignity and sources of meaning.

MANAGING THE LAST STAGES

WITHDRAWING AND WITHHOLDING LIFE-SUSTAINING TREATMENT

Legal aspects

For centuries, it has been deemed ethical to withhold or withdraw life-sustaining interventions. T e current legal consensus in the United States and most developed countries is that patients have a moral as well as constitutional or common law right to refuse medical interventions. American courts also have held that incompetent patients have a right to refuse medical interventions. For patients who are incompetent and terminally ill and who have not completed an advance care directive, next of kin can exercise that right, although this may be restricted in some states, depending how clear and convincing the evidence is of the patient's preferences. Courts have limited families' ability to terminate life-sustaining treatments in patients who are conscious, incompetent, but not terminally ill. In theory, patients' right to refuse medical therapy can be limited by four countervailing interests: (1) preservation of life, (2) prevention of suicide, (3) protection of third parties such as children, and (4) preservation of the integrity of the medical profession. In practice, these interests almost never override the right of competent patients and incompetent patients who have left explicit and advance care directives.

For incompetent patients who either appointed a proxy without specific indications of their wishes or never completed an advance care directive, three criteria have been suggested to guide the decision to terminate medical interventions. First, some commentators suggest that ordinary care should be administered but extraordinary care could be terminated. Because the ordinary/extraordinary distinction is too vague, courts and commentators widely agree that it should not be used to justify decisions about stopping treatment. Second, many courts have advocated the use of the substituted-judgment criterion, which holds that the proxy decision-makers should try to imagine what the incompetent patient would do if he or she were competent. However, multiple studies indicate that many proxies, even close family members, cannot accurately predict what the patient would have wanted. T erefore, substituted judgment becomes more of a guessing game than a way of fulfilling the patient's wishes. Finally, the best-interests criterion holds that proxies should evaluate treatments by balancing their benefits and risks and select those treatments in which the benefits maximally outweigh the burdens of treatment. Clinicians have a clear and crucial role in this by carefully and dispassionately explaining the known benefits and burdens of specific treatments. Yet even when that information is as clear as possible, different individuals can have very different views of what is in the patient's best interests, and families may have disagreements or even overt conf icts. T is criterion has been criticized because there is no single way to determine the balance between benefits and burdens; it depends on a patient's personal values. For instance, for some people, being alive even if mentally incapacitated is a benefit, whereas for others, it may be the worst possible existence. As a matter of practice, physicians rely on family members to make decisions that they feel are best and object only if those

decisions seem to demand treatments that the physicians consider not beneficial.

Practices

Withholding and withdrawing acutely life-sustaining medical interventions from terminally ill patients are now standard practice. More than 90% of American patients die without cardiopulmonary resuscitation (CPR), and just as many forgo other potentially life-sustaining interventions. For instance, in ICUs in the period 1987–1988, CPR was performed 49% of the time, but it was performed only 10% of the time in 1992–1993. On average, 3.8 interventions, such as vasopressors and transfusions, were stopped for each dying ICU patient. However, up to 19% of decedents in hospitals received interventions such as extubation, ventilation, and surgery in the 48 h preceding death. However, practices vary widely among hospitals and ICUs, suggesting an important element of physician preferences rather than objective data.

Mechanical ventilation may be the most challenging intervention to withdraw. T e two approaches are terminal extubation, which is the removal of the endotracheal tube, and terminal weaning, which is the gradual reduction of the or ventilator rate. One-third of ICU physicians prefer to use the terminal weaning technique, and 13% extubate; the majority of physicians use both techniques. T e American T oracic Society's 2008 clinical policy guidelines note that there is no single correct process of ventilator withdrawal and that physicians use and should be proficient in both methods but that the chosen approach should carefully balance benefits and burdens as well as patient and caregiver preferences. Physicians' assessment of patients' likelihood of survival, their prediction of possible cognitive damage, and patients' preferences about the use of life support are primary factors in determining the likelihood of withdrawal of mechanical ventilation. Some recommend terminal weaning because patients do not develop upper airway obstruction and the distress caused by secretions or stridor; however, terminal weaning can prolong the dying process and not allow a patient's family to be with him or her unencumbered by an endotracheal tube. To ensure comfort for conscious or semiconscious patients before withdrawal of the ventilator, neuromuscular blocking agents should be terminated and sedatives and analgesics administered. Removing the neuromuscular blocking agents permits patients to show discomfort, facilitating the titration of sedatives and analgesics; it also permits interactions between patients and their families. A common practice is to inject a bolus of midazolam (2–4 mg) or lorazepam (2–4 mg) before withdrawal, followed by 5–10 mg of morphine and continuous infusion of morphine (50% of the bolus dose per hour) during weaning. In patients who have significant upper airway secretions, IV scopolamine at a rate of 100 μg/h can be administered. Additional boluses of morphine or increases in the infusion rate should be administered for respiratory distress or signs of pain. Higher doses will be needed for patients already receiving sedatives and opioids. Families need to be reassured about treatments for common symptoms after withdrawal of ventilatory support, such as dyspnea and agitation, and warned about the uncertainty of length of survival after withdrawal of ventilatory support: up to 10% of patients unexpectedly survive for 1 day or more after mechanical ventilation is stopped.

FUTILE CARE

Beginning in the late 1980s, some commentators argued that physicians could terminate futile treatments demanded by the families of terminally ill patients. Although no objective definition or standard of futility exists, several categories have been proposed. Physiologic futility means that an intervention will have no physiologic effect. Some have defined qualitative futility as applying to procedures that "fail to end a patient's total dependence on intensive medical care." Quantitative futility occurs "when physicians conclude (through personal experience, experiences shared with colleagues, or consideration of reported empiric data) that in the last 100 cases, a medical treatment has been useless." T e term conceals subjective value judgments about when a treatment is "not beneficial." Deciding whether a treatment that obtains an additional 6 weeks of life or a 1% survival advantage confers benefit depends on patients' preferences and goals. Furthermore, physicians' predictions of when treatments were futile deviated markedly from the quantitative definition. When residents thought CPR was quantitatively futile, more than one in five patients had a >10% chance of survival to hospital discharge. Most studies that purport to guide determinations of futility are based on insufficient data to provide statistical confidence for clinical decision making. Quantitative futility rarely applies in ICU settings. Many commentators reject using futility as a criterion for withdrawing care, preferring instead to consider futility situations as ones that represent con f ict that calls for careful negotiation between families and health care providers.

In the wake of a lack of consensus over quantitative measures of futility, many hospitals adopted process-based approaches to resolve disputes over futility and enhance communication with patients and surrogates, including focusing on interests and alternatives rather than opposing positions and generating a wide range of options. Some hospitals have enacted "unilateral do not resuscitate (DNR)" policies to allow clinicians to provide a DNR order in cases in which consensus cannot

be reached with families and medical opinion is that resuscitation would be futile if attempted. T is type of a policy is not a replacement for careful and patient communication and negotiation but recognizes that agreement cannot always be reached. Over the last 15 years, many states, such as Texas, Virginia, Maryland, and California, have enacted so-called medical futility laws that provide physicians a "safe harbor" from liability if they refuse a patient or family's request for life-sustaining interventions. For instance, in Texas when a disagreement about terminating interventions between the medical team and the family has not been resolved by an ethics consultation, the hospital is supposed to try to facilitate transfer of the patient to an institution willing to provide treatment. If this fails after 10 days, the hospital and physician may unilaterally withdraw treatments determined to be futile. T e family may appeal to a state court. Early data suggest that the law increases futility consultations for the ethics committee and that although most families concur with withdrawal, about 10–15% of families refuse to withdraw treatment. Approximately 12 cases have gone to court in Texas in the 7 years since the adoption of the law. As of 2007, there had been 974 ethics committee consultations on medical futility cases and 65 in which committees ruled against families and gave notice that treatment would be terminated. Treatment was withdrawn for 27 of those patients, and the remainder were transferred to other facilities or died while awaiting transfer.

EUTHANASIA AND PHYSICIAN-ASSISTED SUICIDE

Euthanasia and physician-assisted suicide are defined in **Table 33-8**. Terminating life-sustaining care and providing opioid medications to manage symptoms have long been considered ethical by the medical profession and legal by courts and should not be confused with euthanasia or physician-assisted suicide.

Legal aspects

Euthanasia is legal in the Netherlands, Belgium, and Luxembourg. It was legalized in the Northern Territory of Australia in 1995, but that legislation was repealed in 1997. Euthanasia is not legal in any state in the United States. With certain conditions, in Switzerland, a layperson can legally assist suicide. In the United States, physician-assisted suicide is legal in four states: Oregon, Vermont, and Washington State by legislation and Montana by court ruling. In jurisdictions where physician-assisted suicide is legal, physicians wishing to prescribe the necessary medication must fulfill multiple criteria and complete processes that include a waiting period. In other countries and all other states in the United States, physician-assisted suicide and euthanasia are illegal explicitly or by common law.

Practices

Fewer than 10–20% of terminally ill patients actually consider euthanasia and/or physician-assisted suicide for themselves. In the Netherlands and Oregon, >70% of patients using these interventions are dying of cancer; in Oregon, in 2013, just 1.2% of physician-assisted suicide cases involved patients with HIV/AIDS and 7.2% involved patients with amyotrophic lateral sclerosis. In the Netherlands, the share of deaths attributable to euthanasia or physician-assisted suicide declined from around 2.8% of all deaths in 2001 to around 1.8% in 2005. In 2013, the last year with complete data, around 71 patients in Oregon (just 0.2% of all deaths) died by physician-assisted suicide, although this may be an underestimate. In Washington State, between March 2009 (when the law allowing physician-assisted suicide went into force) and December 2009, 36 individuals died from prescribed lethal doses.

Pain is not a primary motivator for patients' requests for or interest in euthanasia and/or physician-assisted

TABLE 33-8

DEFINITIONS OF ASSISTED SUICIDE AND EUTHANASIA

TERM	DEFINITION	LEGAL STATUS
Voluntary active euthanasia	Intentionally administering medications or other interventions to cause the patient's death with the patient's informed consent	Netherlands, Belgium
Involuntary active euthanasia	Intentionally administering medications or other interventions to cause the patient's death when the patient was competent to consent but did not—e.g., the patient may not have been asked	Nowhere
Passive euthanasia	Withholding or withdrawing life-sustaining medical treatments from a patient to let him or her die (terminating life-sustaining treatments)	Everywhere
Physician-assisted suicide	A physician provides medications or other interventions to a patient with the understanding that the patient can use them to commit suicide	Oregon, Netherlands, Belgium, Switzerland

suicide. Fewer than 25% of all patients in Oregon cite inadequate pain control as the reason for desiring physician-assisted suicide. Depression, hopelessness, and, more profoundly, concerns about loss of dignity or autonomy or being a burden on family members appear to be primary factors motivating a desire for euthanasia or physician-assisted suicide. Over 75% cite loss of autonomy or dignity and inability to engage in enjoyable activities as the reason for wanting physician-assisted suicide. About 40% cite being a burden on family. A study from the Netherlands showed that depressed terminally ill cancer patients were four times more likely to request euthanasia and confirmed that uncontrolled pain was not associated with greater interest in euthanasia. Interestingly, despite the importance of emotional distress in motivating requests for euthanasia and physician-assisted suicide, few patients receive psychiatric care. For instance, in Oregon, only 5.9% of patients have been referred for psychiatric evaluation.

Euthanasia and physician-assisted suicide are no guarantee of a painless, quick death. Data from the Netherlands indicate that in as many as 20% of cases technical and other problems arose, including patients waking from coma, not becoming comatose, regurgitating medications, and experiencing a prolonged time to death. Data from Oregon indicate that between 1997 and 2013, 22 patients (~5%) regurgitated after taking prescribed medication, 1 patient awaked, and none experienced seizures. Problems were significantly more common in physician-assisted suicide, sometimes requiring the physician to intervene and provide euthanasia.

Whether practicing in a setting where euthanasia is legal or not, over a career, 12–54% of physicians receive a request for euthanasia or physician-assisted suicide from a patient. Competency in dealing with such a request is crucial. Although challenging, the request can also provide a chance to address intense suffering. After receiving a request for euthanasia and/or physician-assisted suicide, health care providers should carefully clarify the request with empathic, open-ended questions to help elucidate the underlying cause for the request, such as "What makes you want to consider this option?" Endorsing either moral opposition or moral support for the act tends to be counterproductive, giving an impression of being judgmental or of endorsing the idea that the patient's life is worthless. Health care providers must reassure the patient of continued care and commitment. T e patient should be educated about alternative, less controversial options, such as symptom management and withdrawing any unwanted treatments and the reality of euthanasia and/or physician-assisted suicide, because the patient may have misconceptions about their effectiveness as well as the legal implications of the choice. Depression, hopelessness, and other symptoms of psychological distress as well as physical suffering and economic burdens are likely factors motivating the request, and such factors should be assessed and treated aggressively. After these interventions and clarification of options, most patients proceed with another approach, declining life-sustaining interventions, possibly including refusal of nutrition and hydration.

CARE DURING THE LAST HOURS

Most laypersons have limited experiences with the actual dying process and death. T ey frequently do not know what to expect of the final hours and afterward. T e family and other caregivers must be prepared, especially if the plan is for the patient to die at home.

Patients in the last days of life typically experience extreme weakness and fatigue and become bedbound; this can lead to pressure sores. T e issue of turning patients who are near the end of life, however, must be balanced against the potential discomfort that movement may cause. Patients stop eating and drinking with drying of mucosal membranes and dysphagia. Careful attention to oral swabbing, lubricants for lips, and use of artificial tears can provide a form of care to substitute for attempts at feeding the patient. With loss of the gag ref ex and dysphagia, patients may also experience accumulation of oral secretions, producing noises during respiration sometimes called "the death rattle." Scopolamine can reduce the secretions. Patients also experience changes in respiration with periods of apnea or Cheyne-Stokes breathing. Decreased intravascular volume and cardiac output cause tachycardia, hypotension, peripheral coolness, and livedo reticularis (skin mottling). Patients can have urinary and, less frequently, fecal incontinence. Changes in consciousness and neurologic function generally lead to two different paths to death **(Fig. 33-2)**.

Each of these terminal changes can cause patients and families distress, requiring reassurance and targeted interventions **(Table 33-9)**. Informing families that these changes might occur and providing them with an information sheet can help preempt problems and minimize distress. Understanding that patients stop eating because they are dying, not dying because they have stopped eating, can reduce family and caregiver anxiety. Similarly, informing the family and caregivers that the "death rattle" may occur and that it is not indicative of suffocation, choking, or pain can reduce their worry from the breathing sounds.

Families and caregivers may also feel guilty about stopping treatments, fearing that they are "killing" the patient. T is may lead to demands for interventions, such as feeding tubes, that may be ineffective.

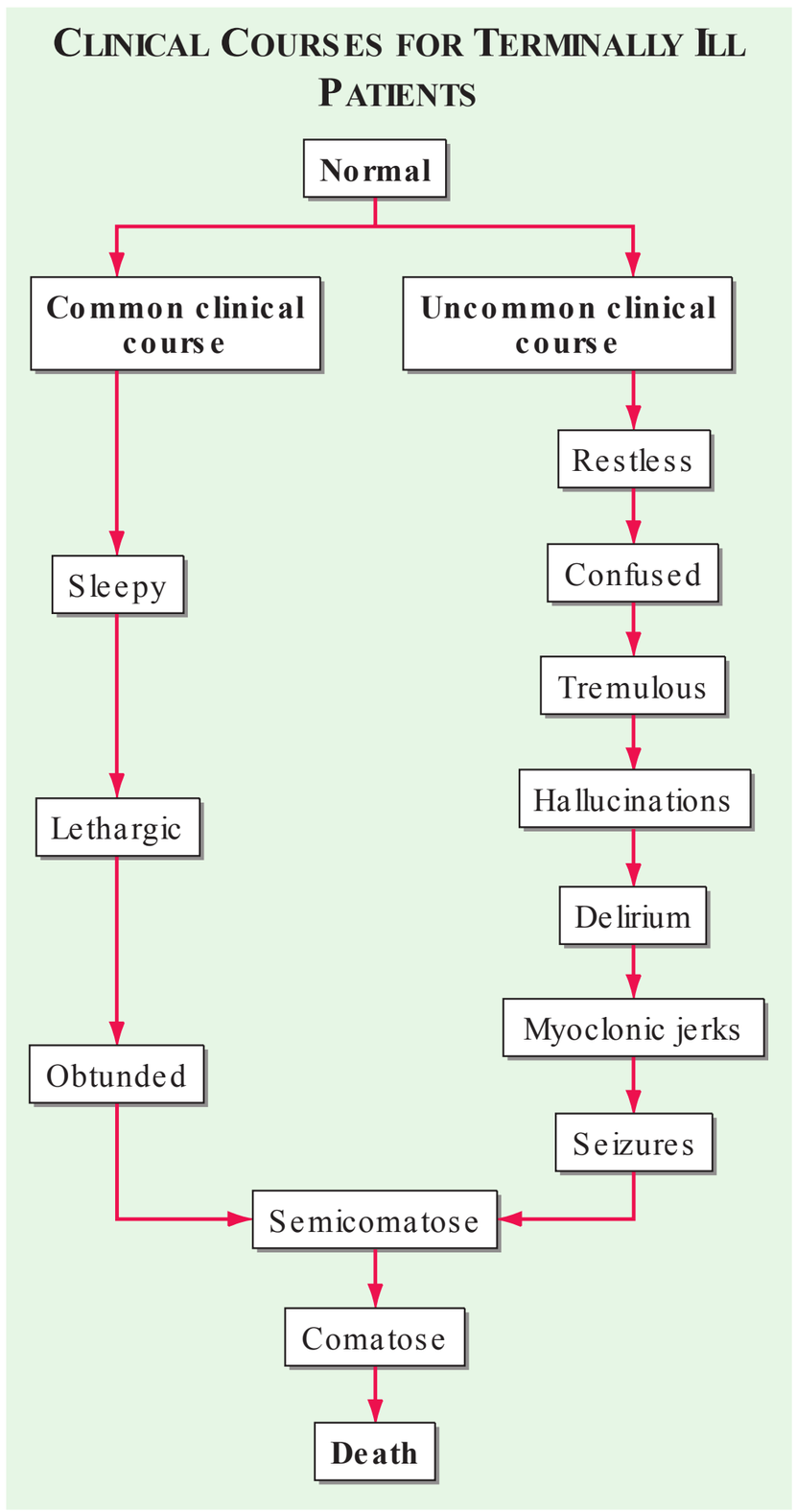

FIGURE 33-2
Common and uncommon clinical courses in the last days of terminally ill patients. (Adapted from FD Ferris et al: Module 4: Palliative care, in Comprehensive Guide for the Care of Persons with HIV Disease. Toronto: Mt. Sinai Hospital and Casey Hospice, 1995, http://www.cpsonline.info/content/resources/hivmodule/module4complete.pdf.)

In such cases, the physician should remind the family and caregivers about the inevitability of events and the palliative goals. Interventions may prolong the dying process and cause discomfort. Physicians also should emphasize that withholding treatments is both legal and ethical and that the family members are not the cause of the patient's death. This reassurance may have to be provided multiple times.

Hearing and touch are said to be the last senses to stop functioning. Whether this is the case or not, families and caregivers can be encouraged to communicate with the dying patient. Encouraging them to talk directly to the patient, even if he or she is unconscious, and hold the patient's hand or demonstrate affection in other ways can be an effective way to channel their urge "to do something" for the patient.

When the plan is for the patient to die at home, the physician must inform the family and caregivers how to determine that the patient has died. The cardinal signs are cessation of cardiac function and respiration; the pupils become fixed; the body becomes cool; muscles relax; and incontinence may occur. Remind the family and caregivers that the eyes may remain open even after the patient has died because the retroorbital fat pad may be depleted, permitting the orbit to fall posteriorly, which makes it difficult for the eyelids to cover the eyeball.

The physician should establish a plan for who the family or caregivers will contact when the patient is dying or has died. Without a plan, they may panic and call 911, unleashing a cascade of unwanted events, from arrival of emergency personnel and resuscitation to hospital admission. The family and caregivers should be instructed to contact the hospice (if one is involved), the covering physician, or the on-call member of the palliative care team. They should also be told that the medical examiner need not be called unless the state requires it for all deaths. Unless foul play is suspected, the health care team need not contact the medical examiner either.

Just after the patient dies, even the best-prepared family may experience shock and loss and be emotionally distraught. They need time to assimilate the event and be comforted. Health care providers are likely to find it meaningful to write a bereavement card or letter to the family. The purpose is to communicate about the patient, perhaps emphasizing the patient's virtues and the honor it was to care for the patient, and to express concern for the family's hardship. Some physicians attend the funerals of their patients. Although this is beyond any medical obligation, the presence of the physician can be a source of support to the grieving family and provides an opportunity for closure for the physician.

Death of a spouse is a strong predictor of poor health, and even mortality, for the surviving spouse. It may be important to alert the spouse's physician about the death so that he or she is aware of symptoms that might require professional attention.

PALLIATIVE CARE SERVICES: HOW AND WHERE

Determining the best approach to providing palliative care to patients will depend on patient preferences, the availability of caregivers and specialized services in close proximity, institutional resources, and reimbursement. Hospice is a leading, but not the only, model of palliative care services. In the United States, a plurality—41.5%—of hospice care is provided in residential homes. In 2012, just over 17% of hospice care

TABLE 33-9

MANAGING CHANGES IN THE PATIENT'S CONDITION DURING THE FINAL DAYS AND HOURS

CHANGES IN THE PATIENT'S CONDITION	POTENTIAL COMPLICATION	FAMILY'S POSSIBLE REACTION AND CONCERN	ADVICE AND INTERVENTION
Profound fatigue	Bedbound with development of pressure ulcers that are prone to infection, malodor, and pain, and joint pain	Patient is lazy and giving up.	Reassure family and caregivers that terminal fatigue will not respond to interventions and should not be resisted. Use an air mattress if necessary.
Anorexia	None	Patient is giving up; patient will suffer from hunger and will starve to death.	Reassure family and caregivers that the patient is not eating because he or she is dying; not eating at the end of life does not cause suffering or death. Forced feeding, whether oral, parenteral, or enteral, does not reduce symptoms or prolong life.
Dehydration	Dry mucosal membranes (see below)	Patient will suffer from thirst and die of dehydration.	Reassure family and caregivers that dehydration at the end of life does not cause suffering because patients lose consciousness before any symptom distress. Intravenous hydration can worsen symptoms of dyspnea by pulmonary edema and peripheral edema as well as prolong dying process.
Dysphagia	Inability to swallow oral medications needed for palliative care		Do not force oral intake. Discontinue unnecessary medications that may have been continued, including antibiotics, diuretics, antidepressants, and laxatives. If swallowing pills is difficult, convert essential medications (analgesics, antiemetics, anxiolytics, and psychotropics) to oral solutions, buccal, sublingual, or rectal administration.
"Death rattle"—noisy breathing		Patient is choking and suffocating.	Reassure the family and caregivers that this is caused by secretions in the oropharynx and the patient is not choking. Reduce secretions with scopolamine (0.2–0.4 mg SC q4h or 1–3 patches q3d). Reposition patient to permit drainage of secretions. Do not suction. Suction can cause patient and family discomfort and is usually ineffective.
Apnea, Cheyne-Stokes respirations, dyspnea		Patient is suffocating.	Reassure family and caregivers that unconscious patients do not experience suffocation or air hunger. Apneic episodes are frequently a premorbid change. Opioids or anxiolytics may be used for dyspnea. Oxygen is unlikely to relieve dyspneic symptoms and may prolong the dying process.
Urinary or fecal incontinence	Skin breakdown if days until death Potential transmission of infectious agents to caregivers	Patient is dirty, malodorous, and physically repellent.	Remind family and caregivers to use universal precautions. Frequent changes of bedclothes and bedding. Use diapers, urinary catheter, or rectal tube if diarrhea or high urine output.
Agitation or delirium	Day/night reversal Hurt self or caregivers	Patient is in horrible pain and going to have a horrible death.	Reassure family and caregivers that agitation and delirium do not necessarily connote physical pain. Depending on the prognosis and goals of treatment, consider evaluating for causes of delirium and modify medications. Manage symptoms with haloperidol, chlorpromazine, diazepam, or midazolam.
Dry mucosal membranes	Cracked lips, mouth sores, and candidiasis can also cause pain. Odor	Patient may be malodorous or physically repellent.	Use baking soda mouthwash or saliva preparation q15–30min. Use topical nystatin for candidiasis. Coat lips and nasal mucosa with petroleum jelly q60–90min. Use ophthalmic lubricants q4h or artificial tears q30min.

was provided in nursing homes. In the United States, Medicare pays for hospice services under Part A, the hospital insurance part of reimbursement. Two physicians must certify that the patient has a prognosis of ≤6 months if the disease runs its usual course. Prognoses are probabilistic by their nature; patients are not required to die within 6 months but rather to have a condition from which half the individuals with it would not be alive within 6 months. Patients sign a hospice enrollment form that states their intent to forgo curative services related to their terminal illness, but they can still receive medical services for other comorbid conditions. Patients also can withdraw enrollment and reenroll later; the hospice Medicare benefit can be revoked later to secure traditional Medicare benefits. Payments to the hospice are per diem (or capitated), not fee-for-service. Payments are intended to cover physician services for the medical direction of the care team; regular home care visits by registered nurses and licensed practical nurses; home health aid and homemaker services; chaplain services; social work services; bereavement counseling; and medical equipment, supplies, and medications. No specific therapy is excluded, and the goal is for each therapy to be considered for its symptomatic (as opposed to disease-modifying) effect. Additional clinical care, including services of the primary physician, is covered by Medicare Part B even while the hospice Medicare benefit is in place. T e health reform legislation signed into law in March 2010—the Affordable Care Act—directs the Secretary of Health and Human Services to gather data on Medicare hospice reimbursement with the goal of reforming payment rates to account for resource use over an entire episode of care. T e legislation also requires additional evaluations and reviews of eligibility for hospice care by hospice physicians or nurses. Finally, the legislation establishes a demonstration project for concurrent hospice care in Medicare, which would test and evaluate allowing patients to remain eligible for regular Medicare during hospice care.

By 2012, the mean length of enrollment in a hospice was around 71.8 days, with the median being 18.7 days. Such short stays create barriers to establishing high-quality palliative services in patients' homes and also place financial strains on hospice providers because the initial assessments are resource intensive. Physicians should initiate early referrals to the hospice to allow more time for patients to receive palliative care.

Hospice care has been the main method in the United States for securing palliative services for terminally ill patients. However, efforts are being made to ensure continuity of palliative care across settings and through time. Palliative care services are becoming available as consultative services and more rarely as palliative care units in hospitals, in day care and other outpatient settings, and in nursing homes. Palliative care consultations for nonhospice patients can be billed as for other consultations under Medicare Part B, the physician reimbursement part. Many believe palliative care should be offered to patients regardless of their prognosis. A patient, his or her family, and physicians should not have to make a "curative versus palliative care" decision because it is rarely possible to make such a decisive switch to embracing mortality.

FUTURE DIRECTIONS

OUTCOME MEASURES

Care near the end of life cannot be measured by most of the available validated outcome measures because palliative care does not consider death a bad outcome. Similarly, the family and patients receiving end-of-life care may not desire the elements elicited in current quality-of-life measurements. Symptom control, enhanced family relationships, and quality of bereavement are difficult to measure and are rarely the primary focus of carefully developed or widely used outcome measures. Nevertheless, outcomes are as important in end-of-life care as in any other field of medical care. Specific end-of-life care instruments are being developed both for assessment, such as T e Brief Hospice Inventory and NEST (needs near the end of life screening tool), and for outcome measures, such as the Palliative Care Outcomes Scale, as well as for prognosis, such as the Palliative Prognostic Index. T e field of end-of-life care is entering an era of evidence-based practice and continuous improvement through clinical trials.

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SECTION IX

NEOPLASTIC DISORDERS

CHAPTER 34

CANCER OF THE SKIN

Walter J. Urba ■ Brendan D. Curti

MELANOMA

Pigmented lesions are among the most common findings on skin examination. T e challenge is to distinguish cutaneous melanomas, which account for the overwhelming majority of deaths resulting from skin cancer, from the remainder, which are usually benign. Cutaneous melanoma can occur in adults of all ages, even young individuals, and people of all colors; its location on the skin and its distinct clinical features make it detectable at a time when complete surgical excision is possible. Examples of malignant and benign pigmented lesions are shown in **Fig. 34-1**.

EPIDEMIOLOGY

Melanoma is an aggressive malignancy of melanocytes, pigment-producing cells that originate from the neural crest and migrate to the skin, meninges, mucous membranes, upper esophagus, and eyes. Melanocytes in each of these locations have the potential for malignant transformation. Cutaneous melanoma is predominantly a malignancy of white-skinned people (98% of cases), and the incidence correlates with latitude of residence, providing strong evidence for the role of sun exposure. Men are affected slightly more than women (1.3:1), and the median age at diagnosis is the late fifties. Dark-skinned populations (such as those of India and Puerto Rico), blacks, and East Asians also develop melanoma, albeit at rates 10–20 times lower than those in whites. Cutaneous melanomas in these populations are diagnosed more often at a higher stage, and patients tend to have worse outcomes. Furthermore, in nonwhite populations, there is a much higher frequency of acral (subungual, plantar, palmar) and mucosal melanomas. In 2014, more than 76,000 individuals in the United States were expected to develop melanoma, and approximately 9700 were expected to die. T ere will be nearly 50,000 annual deaths worldwide as a result of melanoma. Data from the Connecticut Tumor Registry support an unremitting increase in the incidence and mortality of melanoma. In the past 60 years, there have been 17-fold and 9-fold increases in incidence for men and women, respectively. In the same six decades, there has been a tripling of mortality rates for men and doubling for women. Mortality rates begin to rise at age 55, with the greatest increase in men age >65 years. Of particular concern is the increase in rates among women <40 years of age. Much of this increase is believed to be associated with a greater emphasis on tanned skin as a marker of beauty, the increased availability and use of indoor tanning beds, and exposure to intense ultraviolet (UV) light in childhood. T ese statistics highlight the need to promote prevention and early detection.

RISK FACTORS

Presence of nevi

T e risk of developing melanoma is related to genetic, environmental, and host factors **(Table 34-1)**. T e strongest risk factors for melanoma are the presence of multiple benign or atypical nevi and a family or personal history of melanoma. T e presence of melanocytic nevi, common or dysplastic, is a marker for increased risk of melanoma. Nevi have been referred to as precursor lesions because they can transform into melanomas; however, the actual risk for any specific nevus is exceedingly low. About one-quarter of melanomas are histologically associated with nevi, but the majority arise de novo. T e number of clinically atypical moles may vary from one to several hundred, and they usually differ from one another in appearance. T e borders are often hazy and indistinct, and the pigment pattern is more highly varied than that in benign acquired nevi. Individuals with clinically atypical moles and a strong family history of melanoma have been reported to have a >50% lifetime risk for developing melanoma and warrant close follow-up with a

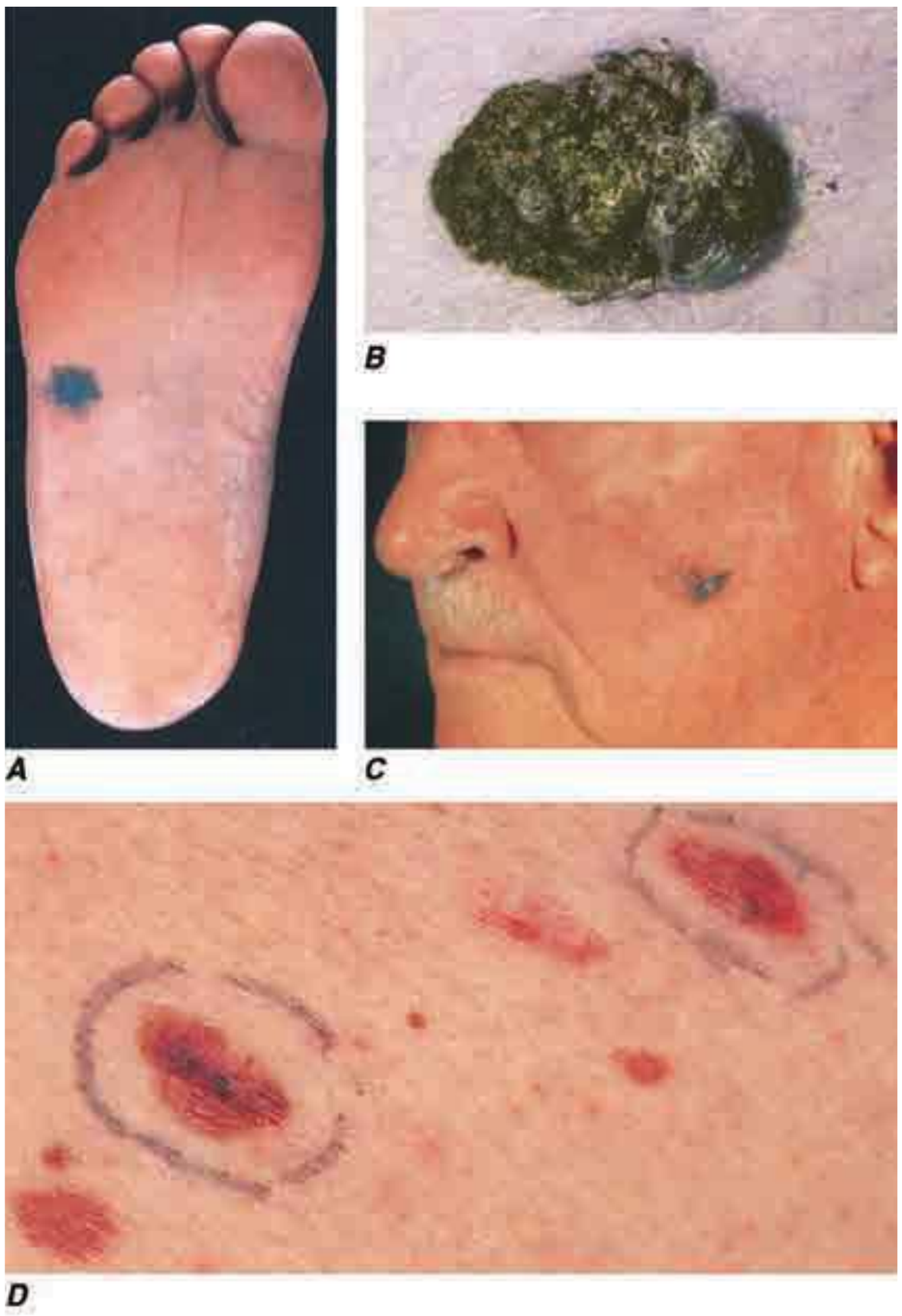

FIGURE 34-1
Atypical and malignant pigmented lesions. The most common melanoma is superficial spreading melanoma (not pictured). A. Acral lentiginous melanoma is the most common melanoma in blacks, Asians, and Hispanics and occurs as an enlarging hyperpigmented macule or plaque on the palms and soles. Lateral pigment diffusion is present. B. Nodular melanoma most commonly manifests as a rapidly growing, often ulcerated or crusted black nodule. C. Lentigo maligna melanoma occurs on sun-exposed skin as a large, hyperpigmented macule or plaque with irregular borders and variable pigmentation. D. Dysplastic nevi are irregularly pigmented and shaped nevomelanocytic lesions that may be associated with familial melanoma.

TABLE 34-1

FACTORS ASSOCIATED WITH INCREASED RISK OF MELANOMA
Total body nevi (higher number = higher risk)
Dysplastic nevi (10-fold increased risk)
Family or personal history
Ultraviolet exposure/sunburns/tanning booths
Light skin/hair/eye color
Poor tanning ability
Freckling
CDKN2A, CDK4, MITF mutations
MC1R variants

dermatologist. Of the 90% of patients whose disease is sporadic (i.e., who lack a family history of melanoma), ~40% have clinically atypical moles, compared with an estimated 5–10% of the population at large.

Congenital melanocytic nevi, which are classified as small (≤1.5 cm), medium (1.5–20 cm), and giant (>20 cm), can be precursors for melanoma. T e risk is highest for the giant melanocytic nevus, also called the bathing trunk nevus, a rare malformation that affects 1 in 30,000–100,000 individuals. Since the lifetime risk of melanoma development is estimated to be as high as 6%, prophylactic excision early in life is prudent. T is usually requires staged removal with coverage by split-thickness skin grafts. Surgery cannot remove all at-risk nevus cells, as some may penetrate into the muscles or central nervous system (CNS) below the nevus. Small- to medium-size congenital melanocytic nevi affect approximately 1% of persons; the risk of melanoma developing in these lesions is not known but appears to be relatively low. T e management of small- to medium-size congenital melanocytic nevi remains controversial.

Personal and family history

Once diagnosed, patients with melanoma require a lifetime of surveillance because their risk of developing another melanoma is 10 times that of the general population. First-degree relatives have a higher risk of developing melanoma than do individuals without a family history, but only 5–10% of all melanomas are truly familial. In familial melanoma, patients tend to be younger at first diagnosis, lesions are thinner, survival is improved, and multiple primary melanomas are common.

Genetic susceptibility

Approximately 20–40% of cases of hereditary melanoma (0.2–2% of all melanomas) are due to germline mutations in the cell cycle regulatory gene cyclin-dependent kinase inhibitor 2A (CDKN2A). In fact, 70% of all cutaneous melanomas have mutations or deletions affecting the CDKN2A locus on chromosome 9p21. T is locus encodes two distinct tumor-suppressor proteins from alternate reading frames: p16 and ARF ($p14^{ARF}$). T e p16 protein inhibits CDK4/6-mediated phosphorylation and inactivation of the retinoblastoma (RB) protein, whereas ARF inhibits MDM2 ubiquitin-mediated degradation of p53. T e end result of the loss of CDKN2A is inactivation of two critical tumor-suppressor pathways, RB and p53, which control entry of cells into the cell cycle. Several studies have shown an increased risk of pancreatic cancer among melanoma-prone families with CDKN2A mutations. A second high-risk locus for melanoma susceptibility,

CDK4, is located on chromosome 12q13 and encodes the kinase inhibited by p16. CDK4 mutations, which also inactivate the RB pathway, are much rarer than CDKN2A mutations. Germline mutations in the melanoma lineage-specific oncogene microphthalmia-associated transcription factor (MITF) predispose to both familial and sporadic melanomas.

T e melanocortin-1 receptor (MC1R) gene is a moderate-risk inherited melanoma susceptibility factor. Solar radiation stimulates the production of melanocortin (α-melanocyte-stimulating hormone [α-MSH]), the ligand for MC1R, which is a G-protein-coupled receptor that signals via cyclic AMP and regulates the amount and type of pigment produced. MC1R is highly polymorphic, and among its 80 variants are those that result in partial loss of signaling and lead to the production of red/yellow pheomelanins, which are not sun-protective and produce red hair, rather than brown/black eumelanins that are photoprotective. T is red hair color (RHC) phenotype is associated with fair skin, red hair, freckles, increased sun sensitivity, and increased risk of melanoma. In addition to its weak UV shielding capacity relative to eumelanin, increased pheomelanin production in patients with inactivating polymorphisms of MC1R also provides a UV-independent carcinogenic contribution to melanomagenesis via oxidative damage.

A number of other more common, low-penetrance polymorphisms that have small effects on melanoma susceptibility include other genes related to pigmentation, nevus count, immune responses, DNA repair, metabolism, and the vitamin D receptor.

PREVENTION AND EARLY DETECTION

Primary prevention of melanoma and nonmelanoma skin cancer (NMSC) is based on protection from the sun. Public health initiatives, such as the SunSmart program that started in Australia and now is operative in Europe and the United States, have demonstrated that behavioral change can decrease the incidence of NMSC and melanoma. Preventive measures should start early in life because damage from UV light begins early despite the fact that cancers develop years later. Biological factors are increasingly being understood, such as tanning addiction, which is postulated to involve stimulation of reward centers in the brain involving dopamine pathways, and cutaneous secretion of β-endorphins after UV exposure, and may represent another area for preventive intervention. Regular use of broad-spectrum sunscreens that block UVA and UVB with a sun protection factor (SPF) of at least 30 and protective clothing should be encouraged. Avoidance of tanning beds and midday (10:00 a.m. to 2:00 p.m.) sun exposure is recommended.

Secondary prevention comprises education, screening, and early detection. Patients should be educated in the clinical features of melanoma (ABCDEs; see following "Diagnosis" section) and advised to report any growth or other change in a pigmented lesion. Brochures are available from the American Cancer Society, the American Academy of Dermatology, the National Cancer Institute, and the Skin Cancer Foundation. Self-examination at 6- to 8-week intervals may enhance the likelihood of detecting change. Although the U.S. Preventive Services Task Force states that evidence is insufficient to recommend for or against skin cancer screening, a full-body skin exam seems to be a simple, practical way to approach reducing the mortality rate for skin cancer. Depending on the presence or absence of risk factors, strategies for early detection can be individualized. T is is particularly true for patients with clinically atypical moles (dysplastic nevi) and those with a personal history of melanoma. For these individuals, surveillance should be performed by the dermatologist and include total-body photography and dermoscopy where appropriate. Individuals with three or more primary melanomas and families with at least one invasive melanoma and two or more cases of melanoma and/or pancreatic cancer among first- or second-degree relatives on the same side of the family may benefit from genetic testing. Precancerous and in situ lesions should be treated early. Early detection of small tumors allows the use of simpler treatment modalities with higher cure rates and lower morbidity.

DIAGNOSIS

T e main goal is to identify a melanoma before tumor invasion and life-threatening metastases have occurred. Early detection may be facilitated by applying the ABCDEs: asymmetry (benign lesions are usually symmetric); border irregularity (most nevi have clear-cut borders); color variegation (benign lesions usually have uniform light or dark pigment); diameter >6 mm (the size of a pencil eraser); and evolving (any change in size, shape, color, or elevation or new symptoms such as bleeding, itching, and crusting). Benign nevi usually appear on sun-exposed skin above the waist, rarely involving the scalp, breasts, or buttocks; atypical moles usually appear on sun-exposed skin, most often on the back, but can involve the scalp, breasts, or buttocks. Benign nevi are present in 85% of adults, with 10–40 moles scattered over the body; atypical nevi can be present in the hundreds.

T e entire skin surface, including the scalp and mucous membranes, as well as the nails should be examined in each patient. Bright room illumination is important, and a hand lens is helpful for evaluating variation in pigment pattern. Any suspicious lesions should be

biopsied, evaluated by a specialist, or recorded by chart and/or photography for follow-up. A focused method for examining individual lesions, dermoscopy, employs low-level magnification of the epidermis and may allow a more precise visualization of patterns of pigmentation than is possible with the naked eye. Complete physical examination with attention to the regional lymph nodes is part of the initial evaluation in a patient with suspected melanoma. The patient should be advised to have other family members screened if either melanoma or clinically atypical moles (dysplastic nevi) are present. Patients who fit into high-risk groups should be instructed to perform monthly self-examinations.

Biopsy

Any pigmented cutaneous lesion that has changed in size or shape or has other features suggestive of malignant melanoma is a candidate for biopsy. An excisional biopsy with 1- to 3-mm margins is suggested. This facilitates pathologic assessment of the lesion, permits accurate measurement of thickness if the lesion is melanoma, and constitutes definitive treatment if the lesion is benign. For lesions that are large or on anatomic sites where excisional biopsy may not be feasible (such as the face, hands, and feet), an incisional biopsy through the most nodular or darkest area of the lesion is acceptable; this should include the vertical growth phase of the primary tumor, if present. Incisional biopsy does not appear to facilitate the spread of melanoma. For suspicious lesions, every attempt should be made to preserve the ability to assess the deep and peripheral margins and to perform immunohistochemistry. Shave biopsies are an acceptable alternative, particularly if the suspicion of malignancy is low, but they should be deep and include underlying fat; cauterization should be avoided. The biopsy should be read by a pathologist experienced in pigmented lesions, and the report should include Breslow thickness, mitoses per square millimeter for lesions ≤1 mm, presence or absence of ulceration, and peripheral and deep margin status. Breslow thickness is the greatest thickness of a primary cutaneous melanoma measured on the slide from the top of the epidermal granular layer, or from the ulcer base, to the bottom of the tumor. To distinguish melanomas from benign nevi in cases with challenging histology, fluorescence in situ hybridization (FISH) with multiple probes and comparative genome hybridization (CGH) can be helpful.

CLINICAL CLASSIFICATION

Four major types of cutaneous melanoma have been recognized **(Table 34-2)**. In three of these types—superficial spreading melanoma, lentigo maligna melanoma, and acral lentiginous melanoma—the lesion has a period of superficial (so-called radial) growth during which it increases in size but does not penetrate deeply. It is during this period that the melanoma is most capable of being cured by surgical excision. The fourth type—nodular melanoma—does not have a recognizable radial growth phase and usually presents as a deeply invasive

TABLE 34-2

HISTOLOGIC SUBTYPES OF MALIGNANT MELANOMA

TYPE	SITE	AVERAGE AGE AT DIAGNOSIS, YEARS	DURATION OF KNOWN EXISTENCE, YEARS	COLOR
Lentigo maligna melanoma	Sun-exposed surfaces, particularly malar region of cheek and temple	70	5–20 or longer[a]	In flat portions, shades of brown and tan predominate, but whitish gray occasionally present; in nodules, shades of reddish brown, bluish gray, bluish black
Superficial spreading melanoma	Any site (more common on upper back and, in women, lower legs)	40–50	1–7	Shades of brown mixed with bluish red (violaceous), bluish black, reddish brown, and often whitish pink, and the border of lesion is at least in part visibly and/or palpably elevated
Nodular melanoma	Any	40–50	Months–<5 years	Reddish blue (purple) or bluish black; either uniform in color or mixed with brown or black
Acral lentiginous melanoma	Palm, sole, nail bed, mucous membrane	60	1–10	In flat portions, dark brown predominantly; in raised lesions (plaques), brown-black or blue-black predominantly

[a]During much of this time, the precursor stage, lentigo maligna, is confined to the epidermis.
Source: Adapted from AJ Sober, in NA Soter, HP Baden (eds): Pathophysiology of Dermatologic Diseases. New York, McGraw-Hill, 1984.

lesion that is capable of early metastasis. When tumors begin to penetrate deeply into the skin, they are in the so-called vertical growth phase. Melanomas with a radial growth phase are characterized by irregular and sometimes notched borders, variation in pigment pattern, and variation in color. An increase in size or change in color is noted by the patient in 70% of early lesions. Bleeding, ulceration, and pain are late signs and are of little help in early recognition. Superficial spreading melanoma is the most common variant observed in the white population. T e back is the most common site for melanoma in men. In women, the back and the lower leg (from knee to ankle) are common sites. Nodular melanomas are dark brown-black to blue-black nodules. Lentigo maligna melanoma usually is confined to chronically sun-damaged sites in older individuals. Acral lentiginous melanoma occurs on the palms, soles, nail beds, and mucous membranes. Although this type occurs in whites, it occurs most frequently (along with nodular melanoma) in blacks and East Asians. A fifth type of melanoma, desmoplastic melanoma, is associated with a fibrotic response, neural invasion, and a greater tendency for local recurrence. Occasionally, melanomas appear clinically to be amelanotic, in which case the diagnosis is established microscopically after biopsy of a new or a changing skin nodule. Melanomas can also arise in the mucosa of the head and neck (nasal cavity, paranasal sinuses and oral cavity), the gastrointestinal tract, the CNS, the female genital tract (vulva, vagina), and the uveal tract of the eye.

Although cutaneous melanoma subtypes are clinically and histopathologically distinct, this classification does not have independent prognostic value. Histologic subtype is not part of American Joint Committee on Cancer (AJCC) staging, although the College of American Pathologists (CAP) recommends inclusion in the pathology report. Newer classifications will increasingly emphasize molecular features of each melanoma (see below). T e molecular analysis of individual melanomas will provide a basis for distinguishing benign nevi from melanomas, and determination of the mutational status of the tumor will help elucidate the molecular mechanisms of tumorigenesis and be used to identify targets that will guide therapy.

PATHOGENESIS AND MOLECULAR CLASSIFICATION

Considerable evidence from epidemiologic and molecular studies suggests that cutaneous melanomas arise via multiple causal pathways. T ere are both environmental and genetic components. UV solar radiation causes genetic changes in the skin, impairs cutaneous immune function, increases the production of growth factors, and induces the formation of DNA-damaging reactive oxygen species that affect keratinocytes and melanocytes. A comprehensive catalog of somatic mutations from a human melanoma revealed more than 33,000 base mutations with damage to almost 300 protein-coding segments compared with normal cells from the same patient. T e dominant mutational signature ref ected DNA damage due to UV light exposure. T e melanoma also contained previously described driver mutations (i.e., mutations that confer selective clonal growth advantage and are implicated in oncogenesis). T ese driver mutations affect pathways that promote cell proliferation and inhibit normal pathways of apoptosis in response to DNA repair (see below). T e altered melanocytes accumulate DNA damage, and selection occurs for all the attributes that constitute the malignant phenotype: invasion, metastasis, and angiogenesis.

An understanding of the molecular changes that occur during the transformation of normal melanocytes into malignant melanoma would not only help classify patients but also would contribute to the understanding of etiology and aid the development of new therapeutic options. A genome-wide assessment of melanomas classified into four groups based on their location and degree of exposure to the sun has confirmed that there are distinct genetic pathways in the development of melanoma. T e four groups were cutaneous melanomas on skin without chronic sun-induced damage, cutaneous melanomas with chronic sun-induced damage, mucosal melanomas, and acral melanomas. Distinct patterns of DNA alterations were noted that varied with the site of origin and were independent of the histologic subtype of the tumor. T us, although the genetic changes are diverse, the overall pattern of mutation, amplification, and loss of cancer genes indicates they have convergent effects on key biochemical pathways involved in proliferation, senescence, and apoptosis. T e p16 mutation that affects cell cycle arrest and the ARF mutation that results in defective apoptotic responses to genotoxic damage were described earlier. T e proliferative pathways affected were the mitogen-activated protein (MAP) kinase and phosphatidylinositol 3' kinase/AKT pathways **(Fig. 34-2)**.

RAS and BRAF, members of the MAP kinase pathway, which classically mediates the transcription of genes involved in cell proliferation and survival, undergo somatic mutation in melanoma and thereby generate potential therapeutic targets. N-RAS is mutated in approximately 20% of melanomas, and somatic activating BRAF mutations are found in most benign nevi and 40–60% of melanomas. Neither mutation by itself appears to be sufficient to cause melanoma; thus, they often are accompanied by other mutations. T e BRAF mutation is most commonly a point mutation (T→A nucleotide change) that results in a valine-to-glutamate amino acid substitution (V600E). V600E BRAF mutations do not have the standard UV

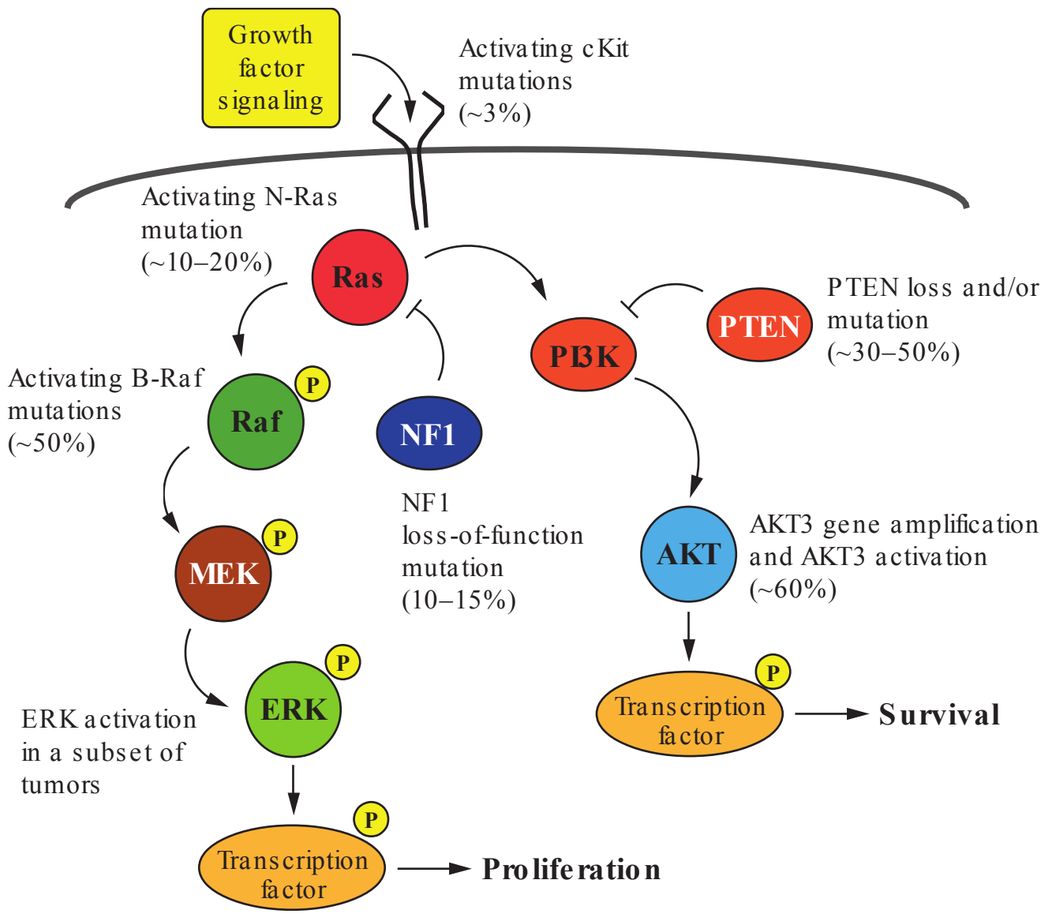

FIGURE 34-2

Major pathways involved in melanoma. The MAP kinase and PI3K/AKT pathways, which promote proliferation and inhibit apoptosis, respectively, are subject to mutations in melanoma. ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase kinase; NF-1; neurofibromatosis type 1 gene; PTEN, phosphatase and tensin homolog.

signature mutation (pyrimidine dimer); they are more common in younger patients and are present in most melanomas that arise on sites with intermittent sun exposure and are less common in melanomas from chronically sun-damaged skin.

Melanomas also harbor mutations in AKT (primarily in AKT3) and PTEN (phosphatase and tensin homolog). AKT can be amplified, and PTEN may be deleted or undergo epigenetic silencing that leads to constitutive activation of the PI3K/AKT pathway and enhanced cell survival by antagonizing the intrinsic pathway of apoptosis. Loss of PTEN, which dysregulates AKT activity, and mutation of AKT3 both prolong cell survival through inactivation of BAD, Bc12-antagonist of cell death, and activation of the forkhead transcription factor FOXO1, which leads to synthesis of prosurvival genes. A loss-of-function mutation in NF1, which can affect both MAP kinase and PI3K/AKT pathways, has been described in 10–15% of melanomas. In melanoma, these two signaling pathways (MAP kinase and PI3K/AKT) enhance tumorigenesis, chemoresistance, migration, and cell cycle dysregulation. Targeted agents that inhibit these pathways have been developed, and some are available for clinical use (see below). Optimal treatment of patients with melanoma may require simultaneous inhibition of both MAPK and PI3K pathways as well as promotion of immune eradication of malignancy.

PROGNOSTIC FACTORS

The prognostic factors of greatest importance to a newly diagnosed patient are included in the staging classification **(Table 34-3)**. The best predictor of metastatic risk is the lesion's Breslow thickness. The Clark level, which defines melanomas on the basis of the layer of skin to which a melanoma has invaded, does not add significant prognostic information and has minimal influence on treatment decisions. The anatomic site of the primary is also prognostic; favorable sites are the forearm and leg (excluding the feet), and unfavorable sites include the scalp, hands, feet, and mucous membranes. In general, women with stage I or II disease have better survival than men, perhaps in part because of earlier diagnosis; women frequently have melanomas on the lower leg, where self-recognition is more likely and the prognosis is better. The effect of age is not straightforward. Older individuals, especially men over 60, have worse prognoses, a finding that has been explained in part by a tendency toward later diagnosis (and thus thicker tumors) and in part by a higher proportion of acral melanomas in men. However, there is a greater risk of lymph node metastasis in young patients. Other important adverse factors recognized via the staging classification include high mitotic rate, presence of ulceration, microsatellite lesions and/or in-transit metastases, evidence of nodal involvement, elevated serum lactate dehydrogenase (LDH), and presence and site of distant metastases.

STAGING

Once the diagnosis of melanoma has been made, the tumor must be staged to determine the prognosis and treatment. Staging helps determine prognosis and aids in treatment selection. The current melanoma staging criteria and estimated 15-year survival by stage are depicted in Table 34-3. The clinical stage of the patient is determined after the pathologic evaluation of the melanoma skin lesion and clinical/radiologic assessment for metastatic disease. Pathologic staging also includes the microscopic evaluation of the regional lymph nodes obtained at sentinel lymph node biopsy or completion lymphadenectomy as indicated. All patients should have a complete history, with attention to symptoms that may represent metastatic disease such as malaise, weight loss, headaches, visual changes, and pain, and physical examination directed to the site of the primary melanoma, looking for persistent disease or for dermal or subcutaneous nodules that could represent satellite or in-transit metastases, and to the regional draining lymph nodes, CNS, liver, and lungs. A complete blood count (CBC), complete metabolic panel, and LDH should be performed. Although these are low-yield tests for uncovering occult metastatic

TABLE 34-3

STAGING CRITERIA FOR MELANOMA

PATHOLOGIC AND TNM STAGE	THICKNESS, mm	ULCERATION	NO. OF INVOLVED LYMPH NODES	NODAL INVOLVEMENT	15-YEAR SURVIVAL ESTIMATE (%)
0					98
Tis	In situ	No	0	None	
IA					92
T1a	<1	No, mitosis <1/mm	0	None	
IB					80
T1b	<1	Yes or mitosis > 1/mm	0	None	
T2a	1.01–2	No	0	None	
IIA					62
T2b	1.01–2	Yes	0	None	
T3a	2.01–4	No	0	None	
IIB					51
T3b	2.01–4	Yes	0	None	
T4a	>4	No	0	None	
IIC					37
T4b	>4	Yes	0	None	
IIIA					68
N1a	T1-4a	No	1	Microscopic	
N2a	T1-4a	No	2 or 3	Microscopic	
IIIB					38
N1a	Any	Yes	1	Microscopic	
N2a	Any	Yes	2 or 3	Microscopic	
N1b	Any	Yes or no	1	Macroscopic	
N2b	Any	Yes or no	2 or 3	Macroscopic	
N2c	Any	Yes or no	In-transit metastases/satellites, no nodal involvement		
IIIC					22
N1b	Any	Yes or no	1	Macroscopic	
N2b	Any	Yes or no	2 or 3	Macroscopic	
N2c	Any	Yes or no	In-transit metastases/satellites, no nodal involvement		
N3	Any	Yes or no	4+ metastatic nodes, matted nodes or in-transit metastases/satellites, with metastatic nodes		
IV		Distant metastasis			<10
M1a		Skin, subcutaneous			
M1b		Lung			
M1c		Other visceral site			
		Elevated lactate dehydrogenase			

disease, a microcytic anemia would raise the possibility of bowel metastases, particularly in the small bowel, and an unexplained elevated LDH should prompt a more extensive evaluation, including computed tomography (CT) scan or possibly a positron emission tomography (PET) (or CT/PET combined) scan. If signs or symptoms of metastatic disease are present, appropriate diagnostic imaging should be performed. At initial presentation, more than 80% of patients will have disease confined to the skin and a negative history and physical exam, in which case imaging is not indicated.

TREATMENT Melanoma

MANAGEMENT OF CLINICALLY LOCALIZED MELANOMA (STAGE I, II) For a newly diagnosed cutaneous melanoma, wide surgical excision of the lesion with a margin of normal skin is necessary to remove all malignant cells and minimize possible local recurrence. The following margins are recommended for a primary melanoma: in situ, 0.5–1.0 cm; invasive up to 1 mm thick, 1 cm; >1.01–2 mm, 1–2 cm; and >2 mm, 2 cm. For lesions on the face, hands, and feet, strict adherence to these margins must

give way to individual considerations about the constraints of surgery and minimization of morbidity. In all instances, however, inclusion of subcutaneous fat in the surgical specimen facilitates adequate thickness measurement and assessment of surgical margins by the pathologist. Topical imiquimod also has been used, particularly for lentigo maligna, in cosmetically sensitive locations.

Sentinel lymph node biopsy (SLNB) is a valuable staging tool that has replaced elective regional nodal dissection for the evaluation of regional nodal status. SLNB provides prognostic information and helps identify patients at high risk for relapse who may be candidates for adjuvant therapy. T e initial (sentinel) draining node(s) from the primary site is (are) identified by injecting a blue dye and a radioisotope around the primary site. T e sentinel node(s) then is (are) identified by inspection of the nodal basin for the blue-stained node and/or the node with high uptake of the radioisotope. T e identified nodes are removed and subjected to careful histopathologic analysis with serial section using hematoxylin and eosin stains as well as immunohistochemical stains (e.g., S100, HMB45, and MelanA) to identify melanocytes.

Not every patient requires a SLNB. Patients whose melanomas are ≤0.75 mm thick have <5% risk of sentinel lymph node (SLN) disease and do not require a SLNB. Patients with tumors >1 mm thick generally undergo SLNB. For melanomas 0.76–1.0 mm thick, SLNB may be considered for lesions with high-risk features such as ulceration, high mitotic index, or lymphovascular invasion, but wide excision alone is the usual definitive therapy. Most other patients with clinically negative lymph nodes should undergo a SLNB. Patients whose SLNB is negative are spared a complete node dissection and its attendant morbidities, and can simply be followed or, based on the features of the primary melanoma, be considered for adjuvant therapy or a clinical trial. T e current standard of care for all patients with a positive SLN is to perform a complete lymphadenectomy; however, ongoing clinical studies will determine whether patients with small-volume SLN metastases can be managed safely without additional surgery. Patients with microscopically positive lymph nodes should be considered for adjuvant therapy with interferon or enrollment in a clinical trial.

MANAGEMENT OF REGIONALLY METASTATIC MELANOMA (STAGE III)

Melanomas may recur at the edge of the scar or graft, as satellite metastases, which are separate from but within 2 cm of the scar; as in-transit metastases, which are recurrences >2 cm from the primary lesion but not beyond the regional nodal basin; or, most commonly, as metastasis to a draining lymph node basin. Each of these presentations is managed surgically, following which there is the possibility of long-term disease-free survival. Isolated limb perfusion or infusion with melphalan and hyperthermia are options for patients with extensive cutaneous regional recurrences in an extremity. High complete response rates have been reported and significant palliation of symptoms can be achieved, but there is no change in overall survival.

Patients rendered free of disease after surgery may be at high risk for a local or distant recurrence and should be considered for adjuvant therapy. Radiotherapy can reduce the risk of local recurrence after lymphadenectomy, but does not affect overall survival. Patients with large nodes (>3–4 cm), four or more involved lymph nodes, or extranodal spread on microscopic examination should be considered for radiation. Systemic adjuvant therapy is indicated primarily for patients with stage III disease, but high-risk, node-negative patients (>4 mm thick or ulcerated lesions) and patients with completely resected stage IV disease also may benefit. Either interferon α2b (IFN-α2b), which is given at 20 million units/m^2 IV 5 days a week for 4 weeks followed by 10 million units/m^2 SC three times a week for 11 months (1 year total), or subcutaneous peginterferon α2b (6 μg/kg per week for 8 weeks followed by 3 μg/kg per week for a total of 5 years) is acceptable adjuvant therapy. Treatment is accompanied by significant toxicity, including a f ulike illness, decline in performance status, and the development of depression. Side effects can be managed in most patients by appropriate treatment of symptoms, dose reduction, and treatment interruption. Sometimes IFN must be permanently discontinued before all of the planned doses are administered because of unacceptable toxicity. T e high-dose regimen is significantly more toxic than peginterferon, but the latter requires 4 additional years of therapy. Adjuvant treatment with IFN improves disease-free survival, but its impact on overall survival remains controversial. Enrollment in a clinical trial is appropriate for these patients, many of whom will otherwise be observed without treatment either because they are poor candidates for IFN or because the patient (or their oncologist) does not believe the beneficial effects of IFN outweigh the toxicity. T e recently approved immunotherapy and targeted agents are being evaluated in the adjuvant setting.

TREATMENT Metastatic Disease

At diagnosis, most patients with melanoma will have early-stage disease; however, some will present with metastases, and others will develop metastases after initial therapy. Patients with a history of melanoma who develop signs or symptoms suggesting recurrent disease should undergo restaging that includes physical examination, CBC, complete metabolic panel, LDH, and appropriate diagnostic imaging that may include a magnetic resonance image (MRI) of the brain and total-body PET/CT or CT scans of the chest, abdomen, and pelvis. Distant metastases (stage IV), which may involve any organ, commonly involve the skin and lymph nodes as well as viscera, bone, or the brain. Historically, metastatic melanoma was considered incurable; median survival ranges from 6 to 15 months, depending on the organs involved. T e prognosis is better for patients with skin and subcutaneous metastases (M1a) than for lung (M1b) and worst for those with metastases to liver, bone, and brain

TABLE 34-4

TREATMENT OPTIONS FOR METASTATIC MELANOMA

- Surgery: Metastasectomy for small number of lesions
- Immunotherapy:
  - Interleukin 2
  - Immune checkpoint blockade
    - - FDA approved
      - Anti-CTLA-4: ipilimumab
    - - Experimental
      - Anti-PD-1: nivolumab, lambrolizumab
      - Anti-PD-L1
  - Molecular targeted therapy:
    - BRAF inhibitor: vemurafenib, dabrafenib
    - MEK inhibitor: trametinib
  - Chemotherapy: dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel (Abraxane), carboplatin

(M1c). An elevated serum LDH is a poor prognostic factor and places the patient in stage M1c regardless of the site of the metastases (Table 34-3). Although historical data suggest that the 15-year survival of patients with M1a, M1b, and M1c disease is less than 10%, there is optimism that newer therapies will increase the number of melanoma patients with long-term survival, especially patients with M1a and M1b disease.

T e treatment for patients with stage IV melanoma has changed dramatically in the past 2 years. Two new classes of therapeutic agents for melanoma have been approved by the U.S. Food and Drug Administration (FDA). T e immune T cell checkpoint inhibitor, ipilimumab, and three new oral agents that target the MAP kinase pathway: the BRAF inhibitors, vemurafenib and dabrafenib, and the MEK inhibitor, trametinib, are now available, so patients with stage IV disease now have multiple therapeutic options (Table 34-4).

Patients with oligometastatic disease should be referred to a surgical oncologist for consideration of metastasectomy, because they may experience long-term disease-free survival after surgery. Patients with solitary metastases are the best candidates, but surgery increasingly is being used even for patients with metastases at more than one site. Patients rendered free of disease can be considered for IFN therapy or a clinical trial because their risk of developing additional metastases is very high. Surgery can also be used as an adjunct to immunotherapy when only a few of many metastatic lesions prove resistant to systemic therapy.

IMMUNOTHERAPY T e cytokine interleukin 2 (IL-2 or aldesleukin) has been approved to treat patients with melanoma since 1995. IL-2 is used to treat stage IV patients who have a good performance status and is administered at centers with experience managing IL-2-related toxicity. Patients require hospitalization in an intensive care unit–like setting to receive high-dose IL-2 600,000 or 720,000 IU every 8 h for up to 14 doses (one cycle). Patients continue treatment until they achieve maximal benefit, usually 4–6 cycles. Treatment is associated with long-term disease-free survival (probable cures) in 5% of treated patients. T e mechanism by which IL-2 causes tumor regression has not been identified, but it is presumed that IL-2 induces melanoma-specific T cells that eliminate tumor cells by recognizing specific antigens. Rosenberg and his colleagues at the National Cancer Institute (NCI) have combined adoptive transfer of in vitro–expanded tumor-infiltrating lymphocytes with high-dose IL-2 in patients who were preconditioned with nonmyeloablative chemotherapy (sometimes combined with total-body irradiation). Tumor regression was observed in more than 50% of patients with IL-2-refractory metastatic melanoma.

Immune checkpoint blockade with monoclonal antibodies to the inhibitory immune receptors CTLA-4 and PD-1 has shown promising clinical efficacy. An array of inhibitory receptors are upregulated during an immune response. An absolute requirement to ensure proper regulation of a normal immune response, the continued expression of inhibitory receptors during chronic infection (hepatitis, HIV) and in cancer patients denotes exhausted T cells with limited potential for proliferation, cytokine production, or cytotoxicity **(Fig. 34-3)**. Checkpoint blockade with a monoclonal antibody results in improved T cell function with eradication of tumor cells in preclinical animal models. Ipilimumab, a fully human IgG antibody that binds CTLA-4 and blocks inhibitory signals, was the first treatment of any kind to improve survival in patients with metastatic melanoma. A full course of therapy is four IV outpatient infusions of ipilimumab 3 mg/kg every 3 weeks. Although response rates were low (~10%) in randomized clinical trials, survival of both previously treated and untreated patients was improved, and ipilimumab was approved by the FDA in March 2011.

In addition to its antitumor effects, ipilimumab's interference with normal regulatory mechanisms produced a novel spectrum of side effects that resembled autoimmunity. T e most common immune-related adverse events were skin rash

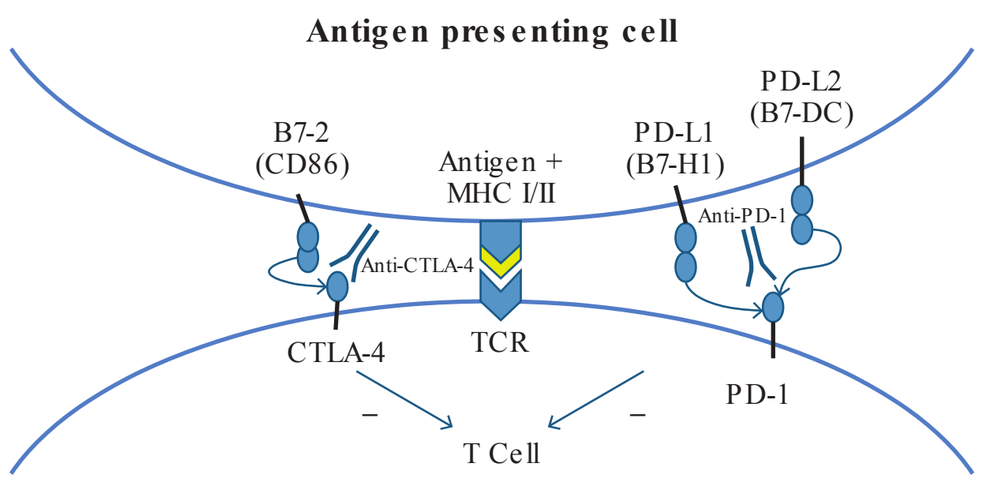

FIGURE 34-3

Inhibitory regulatory pathways that influence T cell function, memory, and lifespan after engagement of the T cell receptor by antigen presented by antigen-presenting cells in the context of MHC I/II. CTLA-4 and PD-1 are part of the CD28 family and have inhibitory effects that can be mitigated by antagonistic antibodies to the receptors or ligand, resulting in enhanced T cell function and antitumor effects. CTLA-4, cytotoxic T lymphocyte antigen-4; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; TCR, T cell receptor.

and diarrhea (sometimes severe, life-threatening colitis), but toxicity could involve most any organ (e.g., hypophysitis, hepatitis, nephritis, pneumonitis, myocarditis, neuritis). Vigilance and early treatment with steroids that do not appear to interfere with the antitumor effects are required to manage these patients safely. Widespread use of ipilimumab has not been completely embraced by the oncology community because of the low objective response rate, significant toxicity (including death), and high cost (drug cost alone for a course of therapy is approximately $120,000 in 2013). Despite these reservations, ipilimumab's overall survival benefit (17% of patients alive at 7 years) indicates that treatment should be strongly considered for all eligible patients.

Chronic T cell activation also leads to induction of PD-1 on the surface of T cells. Expression of one of its ligands, PD-L1, on tumor cells can protect them from immune destruction (Fig. 34-3). Early trials attempting to block the PD-1:PD-L1 axis by IV administration of anti-PD-1 or anti-PD-L1 have shown substantial clinical activity in patients with advanced melanoma (and lung cancer) with significantly less toxicity than ipilimumab. Anti-PD-1 therapy looks promising, but is not currently available except by participation in clinical trials. Intriguingly, preliminary results from a clinical trial indicate that blocking both inhibitory pathways with ipilimumab and anti-PD-1 leads to superior antitumor activity than treatment with either agent alone. T e main benefit to patients from immune-based therapy (IL-2, ipilimumab, and anti-PD-1) is the durability of the responses achieved. Although the percentage of patients whose tumors regress following immunotherapy is lower than the response rate after targeted therapy (see below), the durability of immunotherapy-induced responses (>10 years in some cases) appears to be superior to responses after targeted therapy and suggests that many of these patients have been cured.

TARGETED THERAPY RAF and MEK inhibitors of the MAP kinase pathway are a new and exciting approach for patients whose melanomas harbor a BRAF mutation. T e high frequency of oncogenic mutations in the RAS-RAF-MEK-ERK pathway, which delivers proliferation and survival signals from the cell surface to the cytoplasm and nucleus, has led to the development of inhibitors to BRAF and MEK. Two BRAF inhibitors, vemurafenib and dabrafenib, have been approved for the treatment of stage IV patients whose melanomas harbor a mutation at position 600 in the gene for BRAF. T e oral BRAF inhibitors cause tumor regression in approximately 50% of patients, and overall survival is improved compared to treatment with chemotherapy. Treatment is accompanied by manageable side effects that differ from those following immunotherapy or chemotherapy. A class-specific complication of BRAF inhibition is the development of numerous skin lesions, some of which are well-differentiated squamous cell skin cancers (seen in up to a quarter of patients). Patients should be comanaged with a dermatologist as these skin cancers will need excision. Metastases have not been reported, and treatment can be continued safely following simple excision. Long-term results following treatment with BRAF inhibitors are not yet available, but the current concern is that over time the vast majority of patients will relapse and eventually die from drug-resistant disease. T ere are a number of mechanisms by which resistance develops, usually via maintenance of MAP kinase signaling; however, mutations in the BRAF gene that affect binding of the inhibitor are not among them. T e MEK inhibitor trametinib has activity as a single agent, but appears to be less effective than either of the BRAF inhibitors. Combined therapy with the BRAF inhibitor and MEK inhibitor showed improved progression-free survival compared to BRAF inhibitor therapy alone; and, interestingly, the neoplastic skin lesions that were so troubling with BRAF inhibition alone did not occur. Although the durability of responses following combined therapy remains to be determined, its use in metastatic melanoma is FDA approved. Activating mutations in the c-kit receptor tyrosine kinase are found in a minority of cutaneous melanomas with chronic sun damage, but more commonly in mucosal and acral lentiginous subtypes. Overall, the number of patients with c-kit mutations is exceedingly small, but when present, they are largely identical to mutations found in gastrointestinal stromal tumors (GISTs); melanomas with activating c-kit mutations can have clinically meaningful responses to imatinib.

CHEMOTHERAPY No chemotherapy regimen has ever been shown to improve survival in metastatic melanoma, and the advances in immunotherapy and targeted therapy have relegated chemotherapy to the palliation of symptoms. Drugs with antitumor activity include dacarbazine (DTIC) or its orally administered analog temozolomide (TMZ), cisplatin and carboplatin, the taxanes (paclitaxel alone or albumin-bound and docetaxel), and carmustine (BCNU), which have reported response rates of 12–20%.

INITIAL APPROACH TO PATIENT WITH METASTATIC DISEASE Upon diagnosis of stage IV disease, whether by biopsy or diagnostic imaging, a sample of the patient's tumor needs to undergo molecular testing to determine whether a druggable mutation (e.g., BRAF) is present. Analysis of a metastatic lesion is preferred, but any biopsy will suffice because there is little discordance between primary and metastatic lesions. Treatment algorithms start with the tumor's BRAF status. For BRAF "wild-type" tumors, immunotherapy is recommended. For patients whose tumors harbor a BRAF mutation, initial therapy with either a BRAF inhibitor or immunotherapy is acceptable. Molecular testing may also include N-RAS and c-kit in appropriate tumors.

T e majority of patients still die from their melanoma, despite improvements in therapy. T erefore, enrollment in a clinical trial is always an important consideration, even for previously untreated patients. Most patients with stage IV disease will eventually progress despite advances in therapy, and many, because of disease burden, poor performance status, or concomitant illness, will be unsuitable for therapy. T erefore, a major focus of care should be the timely integration of palliative care and hospice.

FOLLOW-UP

Skin examination and surveillance at least once a year are recommended for all patients with melanoma. T e National Comprehensive Cancer Network (NCCN) guidelines for patients with stage IA–IIA melanoma recommend a comprehensive history and physical examination every 6–12 months for 5 years, and then annually as clinically indicated. Particular attention should be paid to the draining lymph nodes in stage I–III patients as resection of lymph node recurrences may still be curative. A CBC, LDH, and chest x-ray are recommended at the physician's discretion, but are ineffective tools for the detection of occult metastases. Routine imaging for metastatic disease is not recommended at this time. For patients with higher stage disease (IIB–IV), imaging (chest x-ray, CT, and/or PET/CT scans) every 4–12 months can be considered. Because no discernible survival benefit has been demonstrated for routine surveillance, it is reasonable to perform scans only if clinically indicated.

NONMELANOMA SKIN CANCER

Nonmelanoma skin cancer (NMSC) is the most common cancer in the United States. Although tumor registries do not routinely gather data on the incidence of basal cell and squamous cell skin cancers, it is estimated that the annual incidence is 1.5–2 million cases in the United States. Basal cell carcinomas (BCCs) account for 70–80% of NMSCs. Squamous cell carcinomas (SCCs), which comprise ~20% of NMSCs, are more significant because of their ability to metastasize and account for 2400 NMSC deaths annually. T ere has also been an increase in the incidence of nonepithelial skin cancer, especially Merkel cell carcinoma, with nearly 5000 new diagnoses and 3000 deaths annually.

PATHOPHYSIOLOGY AND ETIOLOGY

T e most significant cause of BCC and SCC is UV exposure, whether through direct exposure to sunlight or by artificial UV light sources (tanning beds). Both UVA and UVB can induce DNA damage through free radical formation (UVA) or induction of pyrimidine dimers (UVB). T e sun emits energy across the UV spectrum, whereas tanning bed equipment typically emits 97% UVA and 3% UVB. DNA damage induced by UV irradiation can result in cell death or repair of damaged DNA by nucleotide excision repair (NER). Inherited disorders of NER, such as xeroderma pigmentosum, are associated with a greatly increased incidence of skin cancer and help to establish the link between UV-induced DNA damage, inadequate DNA repair, and skin cancer. T e genes damaged most commonly by UV in BCC involve the Hedgehog pathway (Hh). In SCC, p53 and N-RAS are commonly affected. T ere is a dose-response relationship between tanning bed use and the incidence of skin cancer. As few as four tanning bed visits per year confers a 15% increase in BCC and an 11% increase in SCC and melanoma. Tanning bed use as a teenager or young adult confers greater risk than comparable exposure in older individuals. Other associations include blond or red hair, blue or green eyes, a tendency to sunburn easily, and an outdoor occupation. T e incidence of NMSC increases with decreasing latitude. Most tumors develop on sun-exposed areas of the head and neck. T e risk of lip or oral SCC is increased with cigarette smoking. Human papillomaviruses and UV radiation may act as cocarcinogens.

Solid organ transplant recipients on chronic immunosuppression have a 65-fold increase in SCC and a 10-fold increase in BCC. T e frequency of skin cancer is proportional to the level and duration of immunosuppression and the extent of sun exposure before and after transplantation. SCCs in this population also demonstrate higher rates of local recurrence, metastasis, and mortality. T ere is increasing use of tumor necrosis factor (TNF) antagonists to treat inf ammatory bowel disease and autoimmune disorders such as rheumatoid and psoriatic arthritis. TNF antagonists may also confer an increased risk of NMSC. BRAF-targeted therapy can induce SCCs including keratoacanthoma-type SCCs in keratinocytes, with preexisting H-RAS overexpression present in approximately 60% of patients.

Other risk factors include HIV infection, ionizing radiation, thermal burn scars, and chronic ulcerations. Albinism, xeroderma pigmentosum, Muir-Torre syndrome, Rombo's syndrome, Bazex-Dupré-Christol syndrome, dyskeratosis congenita, and basal cell nevus syndrome (Gorlin syndrome) also increase the incidence of NMSC. Mutations in Hh genes encoding the tumor-suppressor patched homolog 1 (PTCH1) and smoothened homolog (SMO) occur in BCC. Aberrant PTCH1 signaling is propagated by the nuclear transcription factors Gli1 and Gli2, which are salient in the development of BCC and have led to the FDA approval of an oral SMO inhibitor, vismodegib, to treat advanced inoperable or metastatic BCC **(Fig. 34-4)**. Vismodegib also reduces the incidence of BCC in patients with basal cell nevus syndrome who have PTCH1 mutations, affirming the importance of Hh in the onset of BCC.

CLINICAL PRESENTATION

Ba sa l cell ca rcino ma

BCC arises from epidermal basal cells. T e least invasive of BCC subtypes, superficial BCC, consists of often subtle, erythematous scaling plaques that slowly enlarge and are most commonly seen on the trunk and

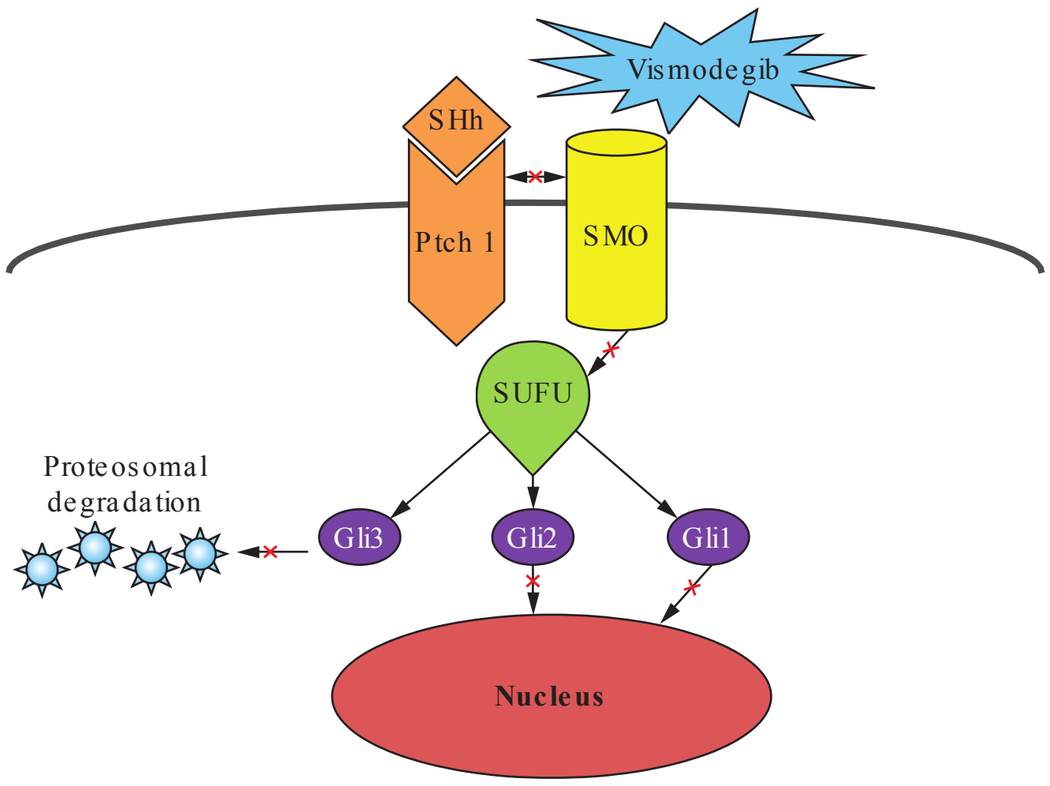

FIGURE 34-4
Influence of vismodegib on the hedgehog (Hh) pathway. Normally, one of three Hh ligands (sonic [SHh], Indian, or desert) binds to patched homolog 1 (PTCH1), causing its degradation and release of smoothened homolog (SMO). The downstream events of SMO release are the activation of Gli1, Gli2, and Gli3 through the transcriptional regulator known as SUFU. Gli1 and Gli2 translocate to the nucleus and promote gene transcription. Vismodegib is an SMO antagonist that decreases the interaction between SMO and PTCH1, resulting in decreased Hh pathway signaling, gene transcription, and cell division. The downstream Hh pathway events inhibited by vismodegib are indicated in red.

proximal extremities **(Fig. 34-5)**. This BCC subtype may be confused with benign inflammatory dermatoses, especially nummular eczema and psoriasis. BCC also can present as a small, slowly growing pearly nodule, often with tortuous telangiectatic vessels on its surface, rolled borders, and a central crust (nodular BCC). The occasional presence of melanin in this variant of nodular BCC (pigmented BCC) may lead to confusion with melanoma. Morpheaform (fibrosing), infiltrative, and micronodular BCC, the most invasive and potentially aggressive subtypes, manifest as solitary, flat or slightly depressed, indurated whitish, yellowish, or pink scar-like plaques. Borders are typically indistinct, and lesions can be subtle; thus, delay in treatment is common, and tumors can be more extensive than expected clinically.

Squamous cell carcinoma

Primary cutaneous SCC is a malignant neoplasm of keratinizing epidermal cells. SCC has a variable clinical course, ranging from indolent to rapid growth kinetics, with the potential for metastasis to regional and distant sites. Commonly, SCC appears as an ulcerated erythematous nodule or superficial erosion on sun-exposed skin of the head, neck, trunk, and extremities (Fig. 34-5). It may also appear as a banal, firm, dome-shaped papule or rough-textured plaque. It is commonly mistaken for a wart or callous when the inflammatory response to the lesion is minimal. Clinically visible overlying telangiectasias are uncommon, although dotted or coiled vessels are a hallmark of SCC when viewed through a dermatoscope. The margins of this tumor may be ill defined, and fixation to underlying structures may occur ("tethering").

A very rapidly growing but low-grade form of SCC, called keratoacanthoma (KA), typically appears as a large dome-shaped papule with a central keratotic crater. Some KAs regress spontaneously without therapy, but because progression to metastatic SCC has been documented, KAs should be treated in the same manner as other types of cutaneous SCC. KAs are also associated with medications that target BRAF mutations and occur in 15–25% of patients receiving these medications.

Actinic keratoses and cheilitis (actinic keratoses occurring on the lip), both premalignant forms of SCC, present as hyperkeratotic papules on sun-exposed areas. The potential for malignant degeneration in untreated lesions ranges from 0.25 to 20%. SCC in situ, also called Bowen's disease, is the intraepidermal form of SCC and usually presents as a scaling, erythematous plaque. As with invasive SCC, SCC in situ most commonly arises on sun-damaged skin, but can occur anywhere on the body. Bowen's disease forming secondary to infection with human papillomavirus (HPV) can arise on skin with minimal or no prior sun exposure, such as the buttock or posterior thigh. Treatment of premalignant and in situ lesions reduces the subsequent risk of invasive disease.

NATURAL HISTORY

Basal cell carcinoma

The natural history of BCC is that of a slowly enlarging, locally invasive neoplasm. The degree of local destruction and risk of recurrence vary with the size, duration, location, and histologic subtype of the tumor. Location on the central face, ears, or scalp may portend a higher risk. Small nodular, pigmented, cystic, or superficial BCCs respond well to most treatments. Large lesions and micronodular, infiltrative, and morpheaform subtypes may be more aggressive. The metastatic potential of BCC is low (0.0028–0.1% in immunocompetent patients), but the risk of recurrence or a new primary NMSC is about 40% over 5 years.

Squamous cell carcinoma

The natural history of SCC depends on tumor and host characteristics. Tumors arising on sun-damaged skin have a lower metastatic potential than do those on

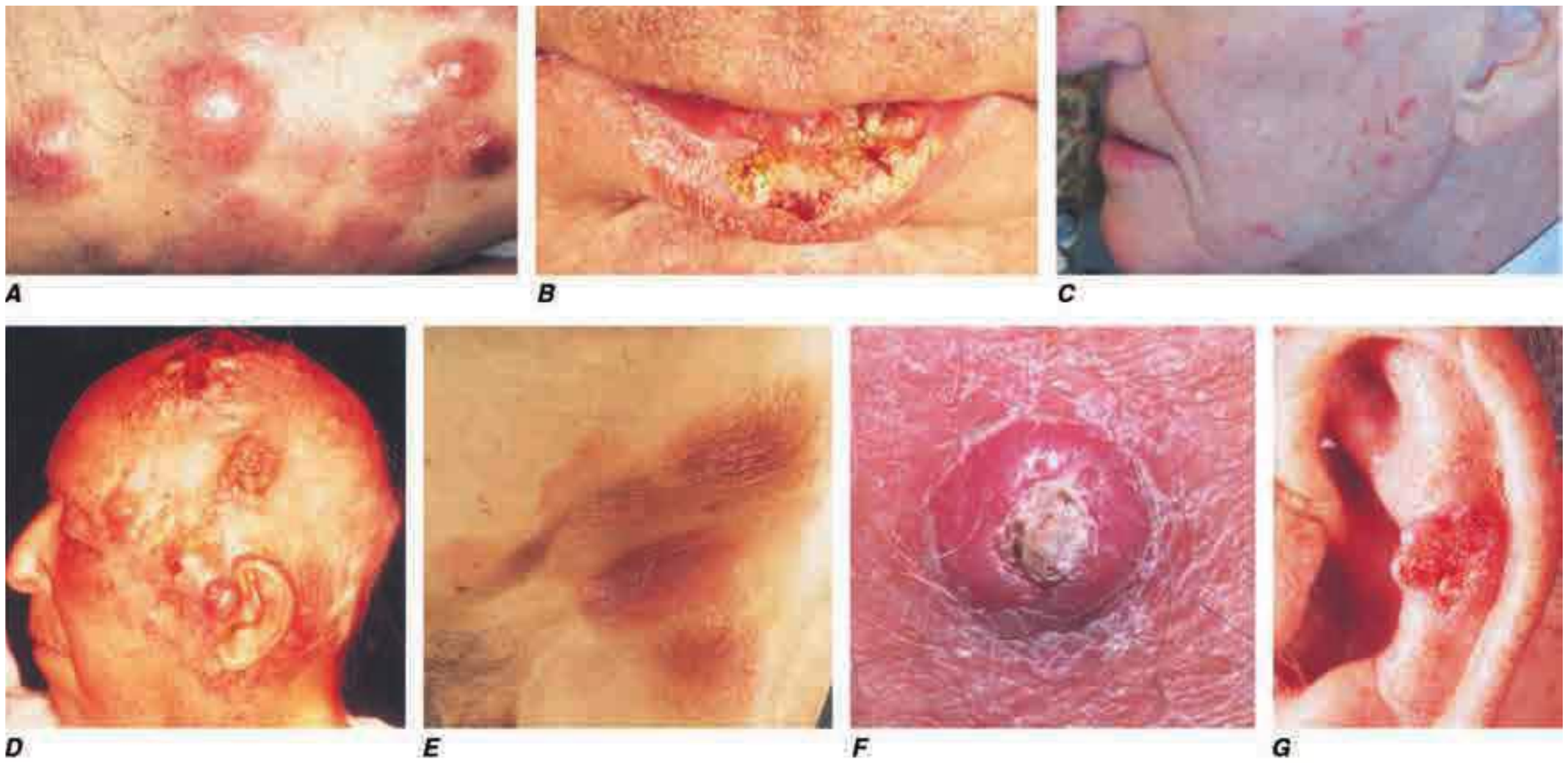

FIGURE 34-5

Cutaneous neoplasms. A. Non-Hodgkin's lymphoma involves the skin with typical violaceous, "plum-colored" nodules. B. Squamous cell carcinoma is seen here as a hyperkeratotic crusted and somewhat eroded plaque on the lower lip. Sun-exposed skin in areas such as the head, neck, hands, and arms represent other typical sites of involvement. C. Actinic keratoses consist of hyperkeratotic erythematous papules and patches on sun-exposed skin. They arise in middle-aged to older adults and have some potential for malignant transformation. D. Metastatic carcinoma to the skin is characterized by inflammatory, often ulcerated dermal nodules. E. Mycosis fungoides is a cutaneous T cell lymphoma, and plaque-stage lesions are seen in this patient. F. Keratoacanthoma is a low-grade squamous cell carcinoma that presents as an exophytic nodule with central keratinous debris. G. This basal cell carcinoma shows central ulceration and a pearly, rolled telangiectatic tumor border.

non-sun-exposed areas. Cutaneous SCC metastasizes in 0.3–5.2% of individuals, most frequently to regional lymph nodes. Tumors occurring on the lower lip and ear develop regional metastases in 13 and 11% of patients, respectively, whereas the metastatic potential of SCC arising in scars, chronic ulcerations, and genital or mucosal surfaces is higher. Recurrent SCC has a much higher potential for metastatic disease, approaching 30%. Large, poorly differentiated, deep tumors with perineural or lymphatic invasion, multifocal tumors, and those arising in immunosuppressed patients often behave aggressively.

TREATMENT Basal Cell Carcinoma

Treatments used for BCC include electrodesiccation and curettage (ED&C), excision, cryosurgery, radiation therapy (RT), laser therapy, Mohs micrographic surgery (MMS), topical 5-fluorouracil, photodynamic therapy (PDT), and topical immunomodulators such as imiquimod. The therapy chosen depends on tumor characteristics including depth and location, patient age, medical status, and patient preference. ED&C remains the most commonly employed method for superficial, minimally invasive nodular BCCs and low-risk tumors (e.g., a small tumor of a less aggressive subtype in a favorable location). Wide local excision with standard margins is usually selected for invasive, ill-defined, and more aggressive subtypes of tumors, or for cosmetic reasons. MMS, a specialized type of surgical excision that provides the best method for tumor removal while preserving uninvolved tissue, is associated with cure rates >98%. It is the preferred modality for lesions that are recurrent, in high-risk or cosmetically sensitive locations (including recurrent tumors in these locations), and in which maximal tissue conservation is critical (e.g., the eyelids, lips, ears, nose, and digits). RT can cure patients not considered surgical candidates and can be used as a surgical adjunct in high-risk tumors. Younger patients may not be good candidates for RT because of the risks of long-term carcinogenesis and radiodermatitis. Imiquimod can be used to treat superficial and smaller nodular BCCs, although it is not FDA-approved for nodular BCC. Topical 5-fluorouracil therapy should be limited to superficial BCC. PDT, which uses selective activation of a photoactive drug by visible light, has been used in patients with numerous tumors. Intralesional chemotherapy (5-fluorouracil and

IFN) for NMSC has existed since the mid-twentieth century, but is used so infrequently that recent consensus guidelines for the treatment of BCC and SCC do not include it. Like RT, it remains an option for well-selected patients who cannot or will not undergo surgery.

SQUAMOUS CELL CARCINOMA Therapy for cutaneous SCC should be based on the size, location, histologic differentiation, patient age, and functional status. Surgical excision and MMS are standard treatments. Cryosurgery and ED&C have been used for premalignant lesions and small, superficial, in situ primary tumors. Lymph node metastases are treated with surgical resection, RT, or both. Systemic chemotherapy combinations that include cisplatin can palliate patients with advanced disease. SCC and keratoacanthomas that develop in patients receiving BRAF-targeted therapy should be excised, but their development should not deter the continued use of BRAF therapy. Retinoid prophylaxis can also be considered for patients receiving BRAF-targeted therapy, although no prospective studies have been completed thus far.

PREVENTION

The general principles for prevention are those described for melanoma earlier. Unique strategies for NMSC include active surveillance for patients on immunosuppressive medications or BRAF-targeted therapy. Chemoprophylaxis using synthetic retinoids and immunosuppression reduction when possible may be useful in controlling new lesions and managing patients with multiple tumors.

OTHER NONMELANOMA CUTANEOUS MALIGNANCIES

Neoplasms of cutaneous adnexae and sarcomas of fibrous, mesenchymal, fatty, and vascular tissues make up the remaining 1–2% of NMSCs.

Merkel cell carcinoma (MCC) is a neural crest–derived highly aggressive malignancy with mortality rates approaching 33% at 3 years. An oncogenic Merkel cell polyomavirus is present in 80% of tumors. Many patients have detectable cellular or humoral immune responses to polyoma viral proteins, although this immune response is insufficient to eradicate the malignancy. Survival depends on extent of disease: 90% survive with local disease, 52% with nodal involvement, and only 10% with distant disease at 3 years. MCC incidence tripled over the last 20 years with an estimated 1600 cases per year in the United States. Immunosuppression can increase incidence and diminish prognosis. MCC lesions typically present as an asymptomatic rapidly expanding bluish-red/violaceous tumor on sun-exposed skin of older white patients. Treatment is surgical excision with sentinel lymph node biopsy for accurate staging in patients with localized disease, often followed by adjuvant RT. Patients with extensive disease can be offered systemic chemotherapy; however, there is no convincing survival benefit. Whenever possible a clinical trial should be considered for this rare but aggressive NMSC, especially in light of the potential for new treatments directed at the oncogenic virus that causes this malignancy.

Extramammary Paget's disease is an uncommon apocrine malignancy arising from stem cells of the epidermis that are characterized histologically by the presence of Paget cells. These tumors present as moist erythematous patches on anogenital or axillary skin of the elderly. Outcomes are generally good with site-directed surgery, and 5-year disease specific survival is approximately 95% with localized disease. Advanced age and extensive disease at presentation are factors that confer diminished prognosis. RT or topical imiquimod can be considered for more extensive disease. Local management may be challenging because these tumors often extend far beyond clinical margins; surgical excision with MMS has the highest cure rates. Similarly, MMS is the treatment of choice in other rare cutaneous tumors with extensive subclinical extension such as dermatofibromasarcoma protuberans.

Kaposi's sarcoma (KS) is a soft tissue sarcoma of vascular origin that is induced by the human herpesvirus 8. The incidence of KS increased dramatically during the AIDS epidemic, but has now decreased tenfold with the institution of highly active antiretroviral therapy.

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CHAPTER 35

HEAD AND NECK CANCER

Everett E. Vokes

Epithelial carcinomas of the head and neck arise from the mucosal surfaces in the head and neck and typically are squamous cell in origin. T is category includes tumors of the paranasal sinuses, the oral cavity, and the nasopharynx, oropharynx, hypopharynx, and larynx. Tumors of the salivary glands differ from the more common carcinomas of the head and neck in etiology, histopathology, clinical presentation, and therapy. T ey are rare and histologically highly heterogeneous. **T yroid malignancies are described in Chap. 50.**

INCIDENCE AND EPIDEMIOLOGY

T e number of new cases of head and neck cancers (oral cavity, pharynx, and larynx) in the United States was 53,640 in 2013, accounting for about 3% of adult malignancies; 11,520 people died from the disease. T e worldwide incidence exceeds half a million cases annually. In North America and Europe, the tumors usually arise from the oral cavity, oropharynx, or larynx. T e incidence of oropharyngeal cancers is increasing in recent years. Nasopharyngeal cancer is more commonly seen in the Mediterranean countries and in the Far East, where it is endemic in some areas.

ETIOLOGY AND GENETICS

Alcohol and tobacco use are the most significant risk factors for head and neck cancer, and when used together, they act synergistically. Smokeless tobacco is an etiologic agent for oral cancers. Other potential carcinogens include marijuana and occupational exposures such as nickel refining, exposure to textile fibers, and woodworking.

Some head and neck cancers have a viral etiology. Epstein-Barr virus (EBV) infection is frequently associated with nasopharyngeal cancer, especially in endemic areas of the Mediterranean and Far East. EBV antibody titers can be measured to screen high-risk populations. Nasopharyngeal cancer has also been associated with consumption of salted fish and in-door pollution.

In Western countries, the human papilloma virus (HPV) is associated with a rising incidence of tumors arising from the oropharynx, i.e., the tonsillar bed and base of tongue. Over 50% of oropharyngeal tumors are caused by HPV in the United States. HPV 16 is the dominant viral subtype, although HPV 18 and other oncogenic subtypes are seen as well. Alcohol- and tobacco-related cancers, on the other hand, have decreased in incidence. HPV-related oropharyngeal cancer occurs in a younger patient population and is associated with increased numbers of sexual partners and oral sexual practices. It is associated with a better prognosis, especially for nonsmokers.

Dietary factors may contribute. T e incidence of head and neck cancer is higher in people with the lowest consumption of fruits and vegetables. Certain vitamins, including carotenoids, may be protective if included in a balanced diet. Supplements of retinoids, such as cis-retinoic acid, have not been shown to prevent head and neck cancers (or lung cancer) and may increase the risk in active smokers. No specific risk factors or environmental carcinogens have been identified for salivary gland tumors.

HISTOPATHOLOGY, CARCINOGENESIS, AND MOLECULAR BIOLOGY

Squamous cell head and neck cancers are divided into well-differentiated, moderately well-differentiated, and poorly differentiated categories. Poorly differentiated tumors have a worse prognosis than well-differentiated tumors. For nasopharyngeal cancers, the less common differentiated squamous cell carcinoma is distinguished from nonker-atinizing and undifferentiated carcinoma (lymphoepithelioma) that contains infiltrating lymphocytes and is commonly associated with EBV.

Salivary gland tumors can arise from the major (parotid, submandibular, sublingual) or minor salivary glands (located in the submucosa of the upper aerodigestive tract). Most parotid tumors are benign, but half of submandibular and sublingual gland tumors and most minor salivary gland tumors are malignant. Malignant tumors include mucoepidermoid and adenoid cystic carcinomas and adenocarcinomas.

T e mucosal surface of the entire pharynx is exposed to alcohol- and tobacco-related carcinogens and is at risk for the development of a premalignant or malignant lesion. Erythroplakia (a red patch) or leukoplakia (a white patch) can be histopathologically classified as hyperplasia, dysplasia, carcinoma in situ, or carcinoma. However, most head and neck cancer patients do not present with a history of premalignant lesions. Multiple synchronous or metachronous cancers can also be observed. In fact, over time, patients with early-stage head and neck cancer are at greater risk of dying from a second malignancy than from a recurrence of the primary disease.

Second head and neck malignancies are usually not therapy-induced; they reflect the exposure of the upper aerodigestive mucosa to the same carcinogens that caused the first cancer. T ese second primaries develop in the head and neck area, the lung, or the esophagus. T us, computed tomography (CT) screening for lung cancer in heavy smokers who have already developed a head and neck cancer should be considered. Rarely, patients can develop a radiation therapy–induced sarcoma af er having undergone prior radiotherapy for a head and neck cancer.

Much progress has been made in describing the molecular features of head and neck cancer. These features have allowed investigators to describe the genetic and epigenetic alterations and the mutational spectrum of these tumors. Early reports demonstrated frequent overexpression of the epidermal growth factor receptor (EGFR). Overexpression was shown to correlate with poor prognosis. However, it has not proved to be a good predictor of tumor response to EGFR inhibitors, which are successful in only about 10–15% of patients. p53 mutations are also found frequently with other major affected oncogenic driver pathways including the mitotic signaling and Notch pathways and cell cycle regulation. The PI3K pathway is frequently altered, especially in HPV-positive tumors, where it is the only mutated cancer gene identified to date. Overall, these alterations affect mitogenic signaling, genetic stability, cellular proliferation, and differentiation. HPV is known to act through inhibition of the p53 and RB tumor-suppressor genes, thereby initiating the carcinogenic process, and has a mutational spectrum distinct from alcohol- and tobacco-related tumors.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Most tobacco-related head and neck cancers occur in patients older than age 60 years. HPV-related malignancies are frequently diagnosed in younger patients, usually in their forties or fif ies, whereas EBV-related nasopharyngeal cancer can occur in all ages, including teenagers. T e manifestations vary according to the stage and primary site of the tumor. Patients with nonspecific signs and symptoms in the head and neck area should be evaluated with a thorough otolaryngologic exam, particularly if symptoms persist longer than 2–4 weeks. Males are more frequently affected than women by head and neck cancers, including HPV-positive tumors.

Cancer of the nasopharynx typically does not cause early symptoms. However, it may cause unilateral serous otitis media due to obstruction of the eustachian tube, unilateral or bilateral nasal obstruction, or epistaxis. Advanced nasopharyngeal carcinoma causes neuropathies of the cranial nerves due to skull base involvement.

Carcinomas of the oral cavity present as nonhealing ulcers, changes in the fit of dentures, or painful lesions. Tumors of the tongue base or oropharynx can cause decreased tongue mobility and alterations in speech. Cancers of the oropharynx or hypopharynx rarely cause early symptoms, but they may cause sore throat and/or otalgia. HPV-related tumors frequently present with neck lymphadenopathy as the first sign.

Hoarseness may be an early symptom of laryngeal cancer, and persistent hoarseness requires referral to a specialist for indirect laryngoscopy and/or radiographic studies. If a head and neck lesion treated initially with antibiotics does not resolve in a short period, further workup is indicated; to simply continue the antibiotic treatment may be to lose the chance of early diagnosis of a malignancy.

Advanced head and neck cancers in any location can cause severe pain, otalgia, airway obstruction, cranial neuropathies, trismus, odynophagia, dysphagia, decreased tongue mobility, fistulas, skin involvement, and massive cervical lymphadenopathy, which may be unilateral or bilateral. Some patients have enlarged lymph nodes even though no primary lesion can be detected by endoscopy or biopsy; these patients are considered to have carcinoma of unknown primary **(Fig. 35-1)**. If the enlarged nodes are located in the upper neck and the tumor cells are of squamous cell histology, the malignancy probably arose from a mucosal surface in the head or neck. Tumor cells in supraclavicular lymph nodes may also arise from a primary site in the chest or abdomen.

T e physical examination should include inspection of all visible mucosal surfaces and palpation of the floor

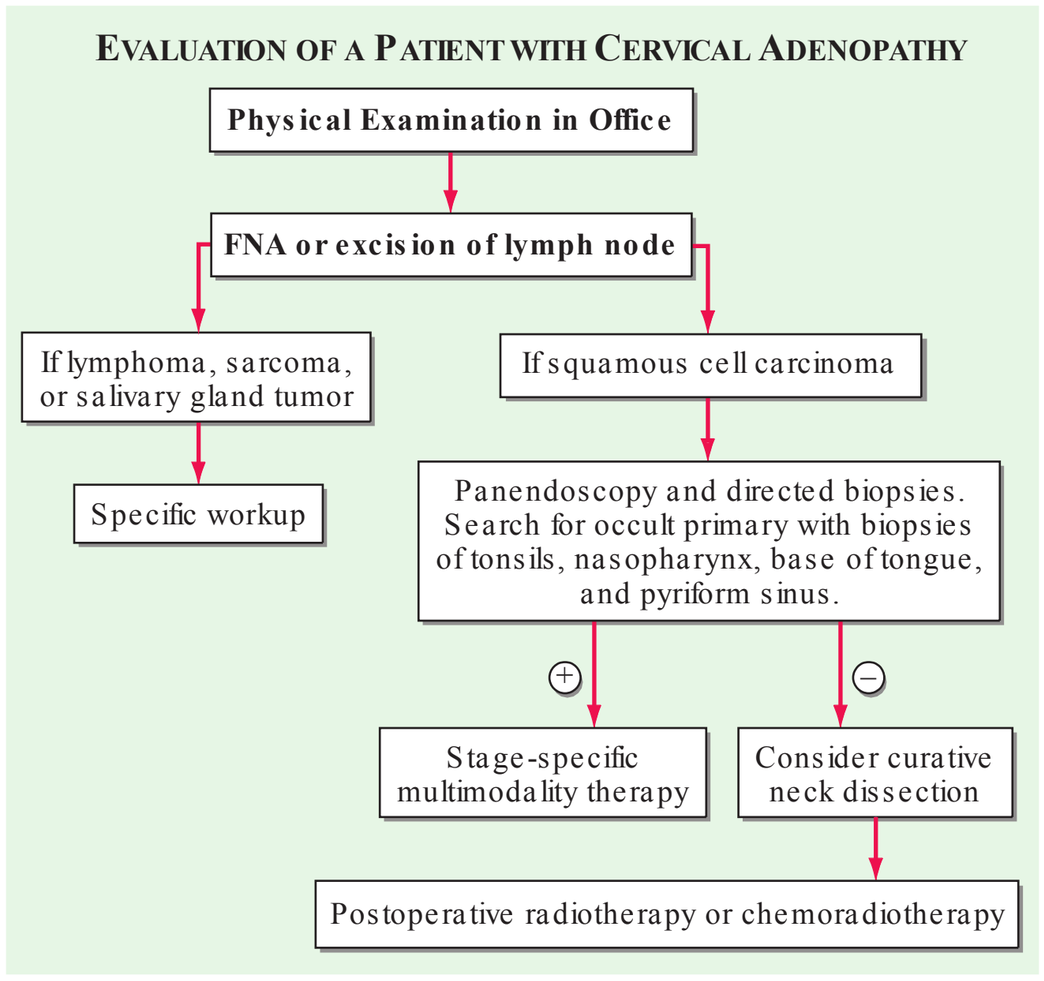


FIGURE 35-1
Evaluation of a patient with cervical adenopathy without a primary mucosal lesion; a diagnostic workup. FNA, fine-needle aspiration.

of the mouth and of the tongue and neck. In addition to tumors themselves, leukoplakia (a white mucosal patch) or erythroplakia (a red mucosal patch) may be observed; these "premalignant" lesions can represent hyperplasia, dysplasia, or carcinoma in situ and require biopsy. Further examination should be performed by a specialist. Additional staging procedures include CT of the head and neck to identify the extent of the disease. Patients with lymph node involvement should have CT scan of the chest and upper abdomen to screen for distant metastases. In heavy smokers, the CT scan of the chest can also serve as a screening tool to rule out a second lung primary tumor. A positron emission tomography (PET) scan may also be administered and can help to identify or exclude distant metastases. The definitive staging procedure is an endoscopic examination under anesthesia, which may include laryngoscopy, esophagoscopy, and bronchoscopy; during this procedure, multiple biopsy samples are obtained to establish a primary diagnosis, define the extent of primary disease, and identify any additional premalignant lesions or second primaries.

Head and neck tumors are classified according to the tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer **(Fig. 35-2)**. This classification varies according to the specific anatomic subsite. In general, primary tumors are classified as T1 to T3 by increasing size, whereas T4 usually represents invasion of another structure such as bone, muscle, or root of tongue. Lymph nodes are staged by size, number, and location (ipsilateral vs contralateral to the primary). Distant metastases are found in <10% of patients at initial diagnosis and are more common in patients with advanced lymph node stage; microscopic involvement of the lungs, bones, or liver is more common, particularly in patients with advanced neck lymph node disease. Modern imaging techniques may increase the number of patients with clinically detectable distant metastases in the future.

In patients with lymph node involvement and no visible primary, the diagnosis should be made by lymph node excision (Fig. 35-1). If the results indicate squamous cell carcinoma, a panendoscopy should be performed, with biopsy of all suspicious-appearing areas and directed biopsies of common primary sites, such as the nasopharynx, tonsil, tongue base, and pyriform sinus. HPV-positive tumors especially can have small primary tumors that spread early to locoregional lymph nodes.

TREATMENT Head and Neck Cancer

Patients with head and neck cancer can be grossly categorized into three clinical groups: those with localized disease, those with locally or regionally advanced disease (lymph node positive), and those with recurrent and/or metastatic disease. Comorbidities associated with tobacco and alcohol abuse can affect treatment outcome and define long-term risks for patients who are cured of their disease.

LOCALIZED DISEASE

Nearly one-third of patients have localized disease, that is, T1 or T2 (stage I or stage II) lesions without detectable lymph node involvement or distant metastases. These patients are treated with curative intent by either surgery or radiation therapy. The choice of modality differs according to anatomic location and institutional expertise. Radiation therapy is often preferred for laryngeal cancer to preserve voice function, and surgery is preferred for small lesions in the oral cavity to avoid the long-term complications of radiation, such as xerostomia and dental decay. Overall 5-year survival is 60–90%. Most recurrences occur within the first 2 years following diagnosis and are usually local.

LOCALLY OR REGIONALLY ADVANCED DISEASE

Locally or regionally advanced disease—disease with a large primary tumor and/or lymph node metastases—is the stage of presentation for >50% of patients. Such patients can also be treated with curative intent, but not with surgery or radiation therapy alone. Combined-modality therapy including surgery, radiation therapy, and chemotherapy is most successful. It can be administered as induction chemotherapy (chemotherapy before surgery and/or radiotherapy) or as concomitant (simultaneous) chemotherapy and radiation therapy. The latter is currently most commonly used and supported by the best evidence. Five-year survival rates exceed 50% in many trials, but part of this increased survival may be due to an increasing fraction of study populations with HPV-related tumors who carry

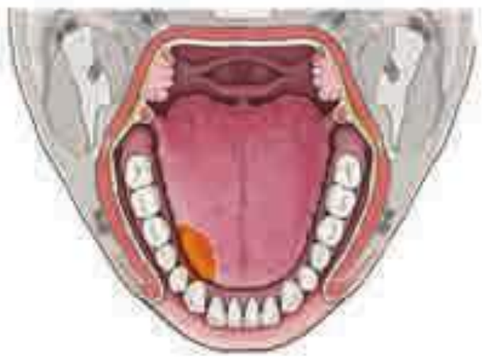
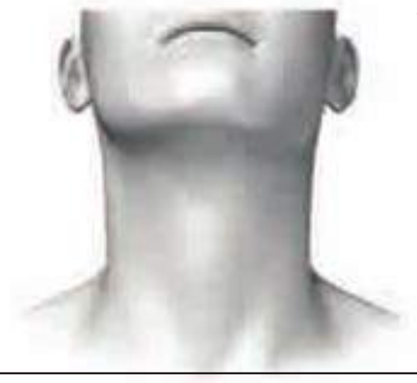
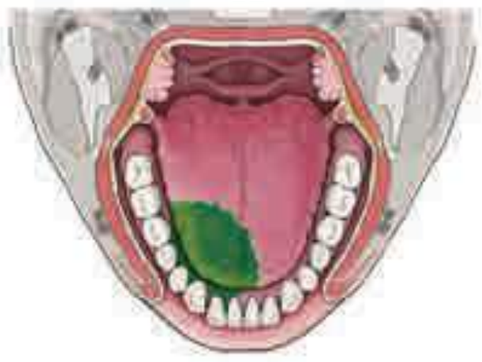
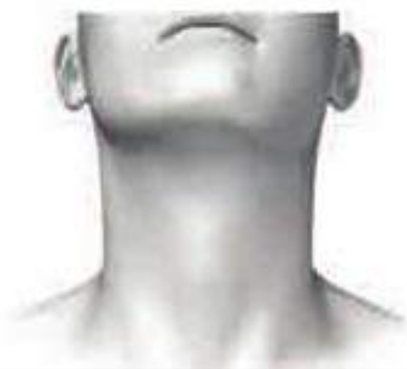
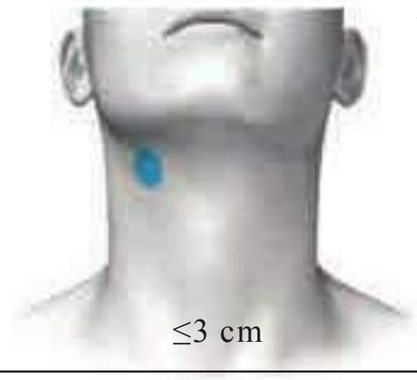
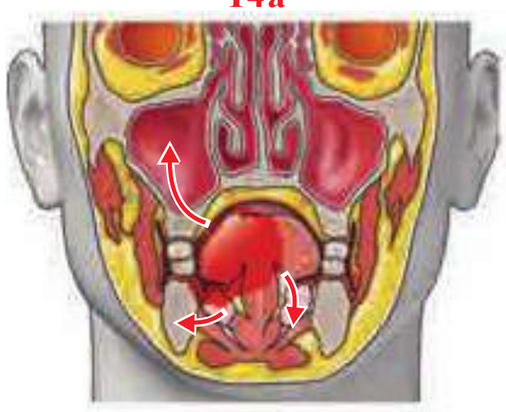
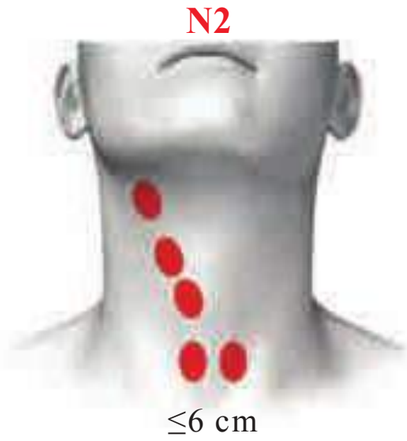
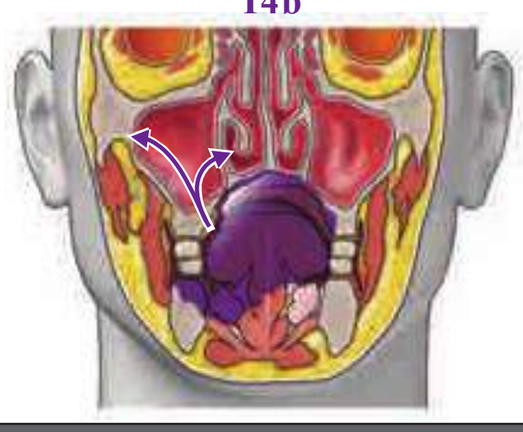
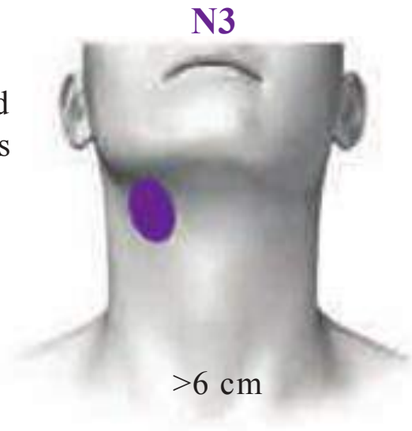
Definition of TNM			Stage groupings		
Stage I	**T1**  Tumor ≤ 2 cm in greatest dimension without extraparenchymal extension	**N0**  N0- No regional lymph node metastasis	**T1**	N0	M0
Stage II	**T2**  Tumor ≥ 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension	**N0**  N0- No regional lymph node metastasis	**T2**	N0	M0
Stage III	**T3**  Tumor ≥ 4 cm and/or tumor having extraparenchymal extension	**N1**  ≤3 cm N1- Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greateast dimension	**T3**	N0	M0
			T1	**N1**	M0
			T2	**N1**	M0
			T3	**N1**	M0
Stage IVA	**T4a**  Tumor invades skin, mandible, ear canal, and or fascial nerve	**N2**  ≤6 cm N2a- Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm N2b- Metastasis in a multiple ipsilateral lymph node, none >6 cm N2c- Metastasis in a bilateral or contralateral lymph nodes, none >6 cm	**T4a**	N0	M0
			T4a	**N1**	M0
			T1	**N2**	M0
			T2	**N2**	M0
			T3	**N2**	M0
			T4a	**N2**	M0
Stage IVB	**T4b**  Tumor invades skull base and/or pterygoid plates and/or encases carotid artery	**N3**  >6 cm N3- Metastasis in a lymph node >6 cm in greatest dimension	**T4b**	**Any N**	M0
			Any T	**N3**	M0
Stage IVC		**M1**	**Any T**	**Any N**	**M1**

FIGURE 35-2
Tumor-node-metastasis (TNM) staging system.

a better prognosis. HPV testing of newly diagnosed tumors is now performed for most patients at the time of diagnosis, and clinical trials for HPV-related tumors are focused on exploring reductions in treatment intensity, especially radiation dose, in order to ameliorate long-term toxicities (fibrosis, swallowing dysfunction).

In patients with intermediate-stage tumors (stage III and early stage IV), concomitant chemoradiotherapy can be administered either as a primary treatment for patients with unresectable disease, to pursue an organ-preserving approach, or in the postoperative setting for intermediate-stage resectable tumors.

Induction Chemotherapy In this strategy, patients receive chemotherapy (current standard is a three-drug regimen of docetaxel, cisplatin, and fluorouracil [5-FU]) before surgery and radiation therapy. Most patients who receive three cycles show tumor reduction, and the response is clinically "complete" in up to half of patients. T is "sequential" multimodality therapy allows for organ preservation (omission of surgery) in patients with laryngeal and hypopharyngeal cancer, and it has been shown to result in higher cure rates compared with radiotherapy alone.

Concomitant Chemoradiotherapy With the concomitant strategy, chemotherapy and radiation therapy are given simultaneously rather than in sequence. Tumor recurrences from head and neck cancer develop most commonly locoregionally (in the head and neck area of the primary and draining lymph nodes). T e concomitant approach is aimed at enhancing tumor cell killing by radiation therapy in the presence of chemotherapy (radiation enhancement) and is a conceptually attractive approach for bulky tumors. Toxicity (especially mucositis, grade 3 or 4 in 70–80%) is increased with concomitant chemoradiotherapy. However, meta-analyses of randomized trials document an improvement in 5-year survival of 8% with concomitant chemotherapy and radiation therapy. Results seem more favorable in recent trials as more active drugs or more intensive radiotherapy schedules are used. In addition, concomitant chemoradiotherapy produces better laryngectomy-free survival (organ preservation) than radiation therapy alone in patients with advanced larynx cancer. T e use of radiation therapy together with cisplatin has also produced improved survival in patients with advanced nasopharyngeal cancer. T e outcome of HPV-related cancers seems to be especially favorable following cisplatin-based chemoradiotherapy.

T e success of concomitant chemoradiotherapy in patients with unresectable disease has led to the testing of a similar approach in patients with resected intermediate-stage disease as a postoperative therapy. Concomitant chemoradiotherapy produces a significant improvement over postoperative radiation therapy alone for patients whose tumors demonstrate higher risk features, such as extracapsular spread beyond involved lymph nodes, involvement of multiple lymph nodes, or positive margins at the primary site following surgery.

A monoclonal antibody to EGFR (cetuximab) increases survival rates when administered during radiotherapy. EGFR blockade results in radiation sensitization and has milder systemic side effects than traditional chemotherapy agents, although an acneiform skin rash is commonly observed. Nevertheless, the integration of cetuximab into current standard chemoradiotherapy regimens has failed to show additional improvement in survival and is not recommended.

RECURRENT AND/OR METASTATIC DISEASE Five to ten percent of patients present with metastatic disease, and 30–50% of patients with locoregionally advanced disease experience recurrence, frequently outside the head and neck region. Patients with recurrent and/or metastatic disease are, with few exceptions, treated with palliative intent. Some patients may require local or regional radiation therapy for pain control, but most are given chemotherapy. Response rates to chemotherapy average only 30–50%; the durations of response are short, and the median survival time is 8–10 months. T erefore, chemotherapy provides transient symptomatic benefit. Drugs with single-agent activity in this setting include methotrexate, 5-FU, cisplatin, paclitaxel, and docetaxel. Combinations of cisplatin with 5-FU, carboplatin with 5-FU, and cisplatin or carboplatin with paclitaxel or docetaxel are frequently used.

EGFR-directed therapies, including monoclonal antibodies (e.g., cetuximab) and tyrosine kinase inhibitors (TKIs) of the EGFR signaling pathway (e.g., erlotinib or gefitinib), have single-agent activity of approximately 10%. Side effects are usually limited to an acneiform rash and diarrhea (for the TKIs). T e addition of cetuximab to standard combination chemotherapy with cisplatin or carboplatin and 5-FU was shown to result in a significant increase in median survival. Drugs targeting specific mutations are under investigation, but no such strategy has yet been shown to be feasible in head and neck cancer.

COMPLICATIONS Complications from treatment of head and neck cancer are usually correlated to the extent of surgery and exposure of normal tissue structures to radiation. Currently, the extent of surgery has been limited or completely replaced by chemotherapy and radiation therapy as the primary approach. Acute complications of radiation include mucositis and dysphagia. Long-term complications include xerostomia, loss of taste, decreased tongue mobility, second malignancies, dysphagia, and neck fibrosis. T e complications of chemotherapy vary with the regimen used but usually include myelosuppression, mucositis, nausea and vomiting, and nephrotoxicity (with cisplatin).

T e mucosal side effects of therapy can lead to malnutrition and dehydration. Many centers address issues of dentition before starting treatment, and some place feeding tubes to ensure control of hydration and nutrition intake. About 50% of patients develop hypothyroidism from the treatment; thus, thyroid function should be monitored.

SALIVARY GLAND TUMORS

Most benign salivary gland tumors are treated with surgical excision, and patients with invasive salivary gland tumors are treated with surgery and radiation therapy. T ese tumors may recur regionally; adenoid cystic carcinoma has a tendency to recur along the nerve tracks. Distant metastases may occur as late as 10–20 years af er the initial diagnosis. For metastatic disease, therapy is given with palliative intent, usually chemotherapy with doxorubicin and/or cisplatin. Identification of novel agents with activity in these tumors is a high priority.

CHAPTER 36

NEOPLASMS OF THE LUNG

Leora Horn ■ Christine M. Lovly ■ David H. Johnson

Lung cancer, which was rare prior to 1900 with fewer than 400 cases described in the medical literature, is considered a disease of modern man. By the mid-twentieth century, lung cancer had become epidemic and firmly established as the leading cause of cancer-related death in North America and Europe, killing over three times as many men as prostate cancer and nearly twice as many women as breast cancer. T is fact is particularly troubling because lung cancer is one of the most preventable of all of the major malignancies. Tobacco consumption is the primary cause of lung cancer, a reality firmly established in the mid-twentieth century and codified with the release of the U.S. Surgeon General's 1964 report on the health effects of tobacco smoking. Following the report, cigarette use started to decline in North America and parts of Europe, and with it, so did the incidence of lung cancer. To date, the decline in lung cancer is seen most clearly in men; only recently has the decline become apparent among women in the United States. Unfortunately, in many parts of the world, especially in countries with developing economies, cigarette use continues to increase, and along with it, the incidence of lung cancers is also rising. Although tobacco smoking remains the primary cause of lung cancer worldwide, approximately 60% of new lung cancers in the United States occur in former smokers (smoked ≥100 cigarettes per lifetime, quit ≥1 year), many of whom quit decades ago, or never smokers (smoked <100 cigarettes per lifetime). Moreover, one in five women and one in 12 men diagnosed with lung cancer have never smoked. Given the magnitude of the problem, it is incumbent that every internist has a general knowledge of lung cancer and its management.

EPIDEMIOLOGY

Lung cancer is the most common cause of cancer death among American men and women. More than 225,000 individuals will be diagnosed with lung cancer in the United States in 2013, and over 150,000 individuals will die from the disease. T e incidence of lung cancer peaked among men in the late 1980s and has plateaued in women. Lung cancer is rare below age 40, with rates increasing until age 80, after which the rate tapers off. T e projected lifetime probability of developing lung cancer is estimated to be approximately 8% among males and approximately 6% among females. T e incidence of lung cancer varies by racial and ethnic group, with the highest age-adjusted incidence rates among African Americans. T e excess in age-adjusted rates among African Americans occurs only among men, but examinations of age-specific rates show that below age 50, mortality from lung cancer is more than 25% higher among African American than Caucasian women. Incidence and mortality rates among Hispanics and Native and Asian Americans are approximately 40–50% those of whites.

RISK FACTORS

Cigarette smokers have a 10-fold or greater increased risk of developing lung cancer compared to those who have never smoked. A deep sequencing study suggested that one genetic mutation is induced for every 15 cigarettes smoked. T e risk of lung cancer is lower among persons who quit smoking than among those who continue smoking; former smokers have a ninefold increased risk of developing lung cancer compared to men who have never smoked versus the 20-fold excess in those who continue to smoke. T e size of the risk reduction increases with the length of time the person has quit smoking, although generally even long-term former smokers have higher risks of lung cancer than those who never smoked. Cigarette smoking has been shown to increase the risk of all the major lung cancer cell types. Environmental tobacco smoke (ETS) or second-hand smoke is also an established cause of

lung cancer. The risk from ETS is less than from active smoking, with about a 20–30% increase in lung cancer observed among never smokers married for many years to smokers, in comparison to the 2000% increase among continuing active smokers.

Although cigarette smoking is the cause of the majority of lung cancers, several other risk factors have been identified, including occupational exposures to asbestos, arsenic, bischloromethyl ether, hexavalent chromium, mustard gas, nickel (as in certain nickel-refining processes), and polycyclic aromatic hydrocarbons. Occupational observations also have provided insight into possible mechanisms of lung cancer induction. For example, the risk of lung cancer among asbestos-exposed workers is increased primarily among those with underlying asbestosis, raising the possibility that the scarring and inflammation produced by this fibrotic nonmalignant lung disease may in many cases (although likely not in all) be the trigger for asbestos-induced lung cancer. Several other occupational exposures have been associated with increased rates of lung cancer, but the causal nature of the association is not as clear.

The risk of lung cancer appears to be higher among individuals with low fruit and vegetable intake during adulthood. This observation led to hypotheses that specific nutrients, in particular retinoids and carotenoids, might have chemopreventative effects for lung cancer. However, randomized trials failed to validate this hypothesis. In fact, studies found the incidence of lung cancer was increased among smokers with supplementation. Ionizing radiation is also an established lung carcinogen, most convincingly demonstrated from studies showing increased rates of lung cancer among survivors of the atom bombs dropped on Hiroshima and Nagasaki and large excesses among workers exposed to alpha irradiation from radon in underground uranium mining. Prolonged exposure to low-level radon in homes might impart a risk of lung cancer equal or greater than that of ETS. Prior lung diseases such as chronic bronchitis, emphysema, and tuberculosis have been linked to increased risks of lung cancer as well.

Smoking cessation

Given the undeniable link between cigarette smoking and lung cancer (not even addressing other tobacco-related illnesses), physicians must promote tobacco abstinence. Physicians also must help their patients who smoke to stop smoking. Smoking cessation, even well into middle age, can minimize an individual's subsequent risk of lung cancer. Stopping tobacco use before middle age avoids more than 90% of the lung cancer risk attributable to tobacco. However, there is little health benefit derived from just "cutting back." Importantly, smoking cessation can even be beneficial in individuals with an established diagnosis of lung cancer, as it is associated with improved survival, fewer side effects from therapy, and an overall improvement in quality of life. Moreover, smoking can alter the metabolism of many chemotherapy drugs, potentially adversely altering the toxicities and therapeutic benefits of the agents. Consequently, it is important to promote smoking cessation even *after* the diagnosis of lung cancer is established.

Physicians need to understand the essential elements of smoking cessation therapy. The individual must want to stop smoking and must be willing to work hard to achieve the goal of smoking abstinence. Self-help strategies alone only marginally affect quit rates, whereas individual and combined pharmacotherapies in combination with counseling can significantly increase rates of cessation. Therapy with an antidepressant (e.g., bupropion) and nicotine replacement therapy (varenicline, a $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist) are approved by the U.S. Food and Drug Administration (FDA) as first-line treatments for nicotine dependence. However, both drugs have been reported to increase suicidal ideation and must be used with caution. In a randomized trial, varenicline was shown to be more efficacious than bupropion or placebo. Prolonged use of varenicline beyond the initial induction phase proved useful in maintaining smoking abstinence. Clonidine and nortriptyline are recommended as second-line treatments. Of note, reducing cigarettes smoked before quit day and quitting abruptly, with no prior reduction, yield comparable quit rates. Therefore, patients can be given the choice to quit in either of these ways.

Inherited predisposition to lung cancer

Exposure to environmental carcinogens, such as those found in tobacco smoke, induce or facilitate the transformation from bronchoepithelial cells to the malignant phenotype. The contribution of carcinogens on transformation is modulated by polymorphic variations in genes that affect aspects of carcinogen metabolism. Certain genetic polymorphisms of the P450 enzyme system, specifically CYP1A1, and chromosome fragility are associated with the development of lung cancer. These genetic variations occur at relatively high frequency in the population, but their contribution to an individual's lung cancer risk is generally low. However, because of their population frequency, the overall impact on lung cancer risk could be high. In addition, environmental factors, as modified by inherited modulators, likely affect specific genes by deregulating important pathways to enable the cancer phenotype.

First-degree relatives of lung cancer probands have a two- to threefold excess risk of lung cancer and other cancers, many of which are not smoking-related. These data suggest that specific genes and/or genetic variants

may contribute to susceptibility to lung cancer. However, very few such genes have yet been identified. Individuals with inherited mutations in RB (patients with retinoblastoma living to adulthood) and p53 (Li-Fraumeni syndrome) genes may develop lung cancer. Common gene variants involved in lung cancer have been recently identified through large, collaborative, genome-wide association studies. T ese studies identified three separate loci that are associated with lung cancer (5p15, 6p21, and 15q25) and include genes that regulate acetylcholine nicotinic receptors and telomerase production. A rare germline mutation (T790M) involving the epidermal growth factor receptor (EGFR) maybe be linked to lung cancer susceptibility in never smokers. Likewise, a susceptibility locus on chromosome 6q greatly increases risk lung cancer risk among light and never smokers.Although progress has been made, there is a significant amount of work that remains to be done in identifying heritable risk factors for lung cancer. Currently no molecular criteria are suitable to select patients for more intense screening programs or for specific chemopreventative strategies.

PATHOLOGY

T e World Health Organization (WHO) defines lung cancer as tumors arising from the respiratory epithelium (bronchi, bronchioles, and alveoli). T e WHO classification system divides epithelial lung cancers into four major cell types: small-cell lung cancer (SCLC), adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma; the latter three types are collectively known as non-small-cell carcinomas (NSCLCs) **(Fig. 36-1)**. Small-cell carcinomas consist of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, absent or inconspicuous nucleoli, and a high mitotic count. SCLC may be distinguished from NSCLC by the presence of neuroendocrine markers including CD56, neural cell adhesion molecule (NCAM), synaptophysin, and chromogranin.

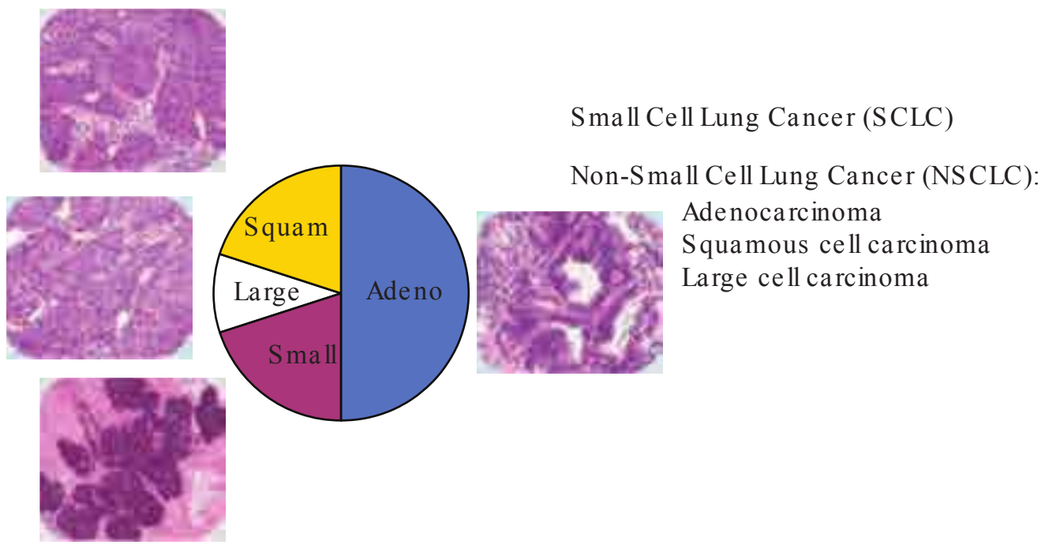


FIGURE 36-1
Traditional histologic view of lung cancer.

In North America, adenocarcinoma is the most common histologic type of lung cancer. Adenocarcinomas possess glandular differentiation or mucin production and may show acinar, papillary, lepidic, or solid features or a mixture of these patterns. Squamous cell carcinomas of the lung are morphologically identical to extrapulmonary squamous cell carcinomas and cannot be distinguished by immunohistochemistry alone. Squamous cell tumors show keratinization and/or intercellular bridges that arise from bronchial epithelium. T e tumor tends to consists of sheets of cells rather than the three-dimensional groups of cells characteristic of adenocarcinomas. Large-cell carcinomas comprise less than 10% of lung carcinomas. T ese tumors lack the cytologic and architectural features of small-cell carcinoma and glandular or squamous differentiation. Together these four histologic types account for approximately 90% of all epithelial lung cancers.

All histologic types of lung cancer can develop in current and former smokers, although squamous and small-cell carcinomas are most commonly associated with heavy tobacco use. T rough the first half of the twentieth century, squamous carcinoma was the most common subtype of NSCLC diagnosed in the United States. However, with the decline in cigarette consumption over the past four decades, adenocarcinoma has become the most frequent histologic subtype of lung cancer in the United States as both squamous carcinoma and small-cell carcinoma are on the decline. In lifetime never smokers or former light smokers (<10 pack-year history), women, and younger adults (<60 years), adenocarcinoma tends to be the most common form of lung cancer.

Historically, the major pathologic distinction was simply between SCLC and NSCLC, because these tumors have quite different natural histories and therapeutic approaches (see below). Likewise, until fairly recently, there was no apparent need to distinguish among the various subtypes of NSCLC because there were no clear differences in therapeutic outcome based on histology alone. However, this perspective radically changed in 2004 with the recognition that a small percentage of lung adenocarcinomas harbored mutation in EGFR that rendered those tumors exquisitely sensitive to inhibitors of the EGFR tyrosine kinases (e.g., gefitinib and erlotinib). T is observation, coupled with the subsequent identification of other "actionable" molecular alterations **(Table 36-1)** and the recognition that some active chemotherapy agents performed quite differently in squamous carcinomas versus adenocarcinomas, firmly established the need for modifications in the then-existing 2004 WHO lung cancer classification system. T e revised 2011 classification system, developed jointly by the International Association for the Study of Lung Cancer, the American T oracic Society,

TABLE 36-1

DRIVER MUTATIONS IN NON-SMALL-CELL LUNG CANCER (NSCLC)

GENE	ALTERATION	FREQUENCY IN NSCLC	TYPICAL HISTOLOGY
AKT1	Mutation	1%	Adenocarcinoma, squamous
ALK	Rearrangement	3–7%	Adenocarcinoma
BRAF	Mutation	1–3%	Adenocarcinoma
DDR2	Mutation	~4%	Squamous
EGFR	Mutation	10–35%	Adenocarcinoma
FGFR1	Amplification	~20%	Squamous
HER2	Mutation	2–4%	Adenocarcinoma
KRAS	Mutation	15–25%	Adenocarcinoma
MEK1	Mutation	1%	Adenocarcinoma
MET	Amplification	2–4%	Adenocarcinoma
NRAS	Mutation	1%	Adenocarcinoma
PIK3CA	Mutation	1–3%	Squamous
PTEN	Mutation	4–8%	Squamous

and the European Respiratory Society, provides an integrated approach to the classification of lung adenocarcinomas that includes clinical, molecular, radiographic, and pathologic information. It also recognizes that most lung cancers present in an advanced stage and are often diagnosed based on small biopsies or cytologic specimens, rendering clear histologic distinctions dif cult if not impossible.

Previously, in the 2004 classification system, tumors *f*ailing to show definite glandular or squamous morphology in a small biopsy or cytologic specimen were simply classified as non-small-cell carcinoma, not otherwise specif ed. However, because the distinction between adenocarcinoma and squamous carcinoma is now viewed as critical to optimal therapeutic decision making, the modified classification approach recommends these lesions be further characterized using a limited special stain workup. T is distinction can be achieved using a single marker for adenocarcinoma (thyroid transcription factor-1 or napsin-A) plus a squamous marker (p40 or p63) and/or mucin stains. T e modified classification system also recommends preservation of suf cient specimen material for appropriate molecular testing necessary to help guide therapeutic decision making (see below).

Another significant modification to the WHO classification system is the discontinuation of the terms bronchioloalveolar carcinoma and mixed-subtype adenocarcinoma. T e term bronchioloalveolar carcinoma was dropped due to its inconsistent use and because it caused confusion in routine clinical care and research. As formerly used, the term encompassed at least five different entities with diverse clinical and molecular properties. T e terms adenocarcinoma in situ and minimally invasive adenocarcinoma are now recommended for small solitary adenocarcinomas (≤3 cm) with either pure lepidic growth (term used to describe single-layered growth of atypical cuboidal cells coating the alveolar walls) or predominant lepidic growth with ≤5 mm invasion. Individuals with these entities experience 100% or near 100% 5-year disease-free survival with complete tumor resection. Invasive adenocarcinomas, representing more than 70–90% of surgically resected lung adenocarcinomas, are now classified by their predominant pattern: lepidic, acinar, papillary, and solid patterns. Lepidic-predominant subtype has a favorable prognosis, acinar and papillary have an intermediate prognosis, and solid-predominant has a poor prognosis. T e terms signet ring and clear cell adenocarcinoma have been eliminated from the variants of invasive lung adenocarcinoma, whereas the term micropapillary, a subtype with a particularly poor prognosis, has been added. Although EGFR mutations are encountered most frequently in nonmucinous adenocarcinomas with a lepidic- or papillary-predominant pattern, most adenocarcinoma subtypes can harbor EGFR or KRAS mutations. T e same is true of ALK, RET, and ROS1 rearrangements. What was previously termed mucinous bronchioloalveolar carcinoma is now called invasive mucinous adenocarcinoma. T ese tumors generally lack EGFR mutations and show a strong correlation with KRAS mutations. Overall, the revised WHO reclassification of lung cancer addresses important advances in diagnosis and treatment, most importantly, the critical advances in understanding the specific genes and molecular pathways that initiate and sustain lung tumorigenesis resulting in new "targeted" therapies with improved specificity and better antitumor ef cacy.

IMMUNOHISTOCHEMISTRY

T e diagnosis of lung cancer most often rests on the morphologic or cytologic features correlated with clinical and radiographic findings. Immunohistochemistry may be used to verify neuroendocrine differentiation within a tumor, with markers such as neuron-specific enolase (NSE), CD56 or NCAM, synaptophysin, chromogranin, and Leu7. Immunohistochemistry is also helpful in differentiating primary from metastatic adenocarcinomas; thyroid transcription factor-1 (TTF-1), identified in tumors of thyroid and pulmonary origin, is positive in over 70% of pulmonary adenocarcinomas and is a reliable indicator of primary lung cancer, provided a thyroid primary has been excluded. A negative TTF-1, however, does not exclude the possibility of a lung primary. TTF-1 is also positive in neuroendocrine

tumors of pulmonary and extrapulmonary origin. Napsin-A (Nap-A) is an aspartic protease that plays an important role in maturation of surfactant B7 and is expressed in cytoplasm of type II pneumocytes. In several studies, Nap-A has been reported in >90% of primary lung adenocarcinomas. Notably, a combination of Nap-A and TTF-1 is useful in distinguishing primary lung adenocarcinoma (Nap-A positive, TTF-1 positive) from primary lung squamous cell carcinoma (Nap-A negative, TTF-1 negative) and primary SCLC (Nap-A negative, TTF-1 positive). Cytokeratins 7 and 20 used in combination can help narrow the differential diagnosis; nonsquamous NSCLC, SCLC, and mesothelioma may stain positive for CK7 and negative for CK20, whereas squamous cell lung cancer often will be both CK7 and CK20 negative. p63 is a useful marker for the detection of NSCLCs with squamous differentiation when used in cytologic pulmonary samples. Mesothelioma can be easily identified ultrastructurally, but it has historically been dif cult to differentiate from adenocarcinoma through morphology and immunohistochemical staining. Several markers in the last few years have proven to be more helpful including CK5/6, calretinin, and Wilms tumor gene-1 (WT-1), all of which show positivity in mesothelioma.

MOLECULAR PATHOGENESIS

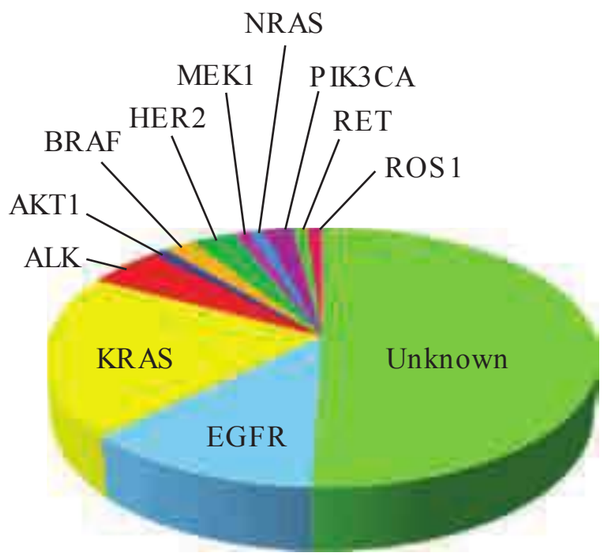
Cancer is a disease involving dynamic changes in the genome. As proposed by Hanahan and Weinberg, virtually all cancer cells acquire six hallmark capabilities: self-suf ciency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. T e order in which these hallmark capabilities are acquired appears quite variable and can differ from tumor to tumor. Events leading to acquisition of these hallmarks can vary widely, although broadly, cancers arise as a result from accumulations of gain-of-function mutations in oncogenes and loss-of-function mutations in tumor-suppressor genes. Further complicating the study of lung cancer, the sequence of events that lead to disease is clearly different for the various histopathologic entities.

T e exact cell of origin for lung cancers is not clearly defined. Whether one cell of origin leads to all histologic forms of lung cancer is unclear. However, for lung adenocarcinoma, evidence suggests that type II epithelial cells (or alveolar epithelial cells) have the capacity to give rise to tumors. For SCLC, cells of neuroendocrine origin have been implicated as precursors.

For cancers in general, one theory holds that a small subset of the cells within a tumor (i.e., "stem cells") are responsible for the full malignant behavior of the tumor. As part of this concept, the large bulk of the cells in a cancer are "offspring" of these cancer stem cells. While clonally related to the cancer stem cell subpopulation, most cells by themselves cannot regenerate the full malignant phenotype. T e stem cell concept may explain the failure of standard medical therapies to eradicate lung cancers, even when there is a clinical complete response. Disease recurs because therapies do not eliminate the stem cell component, which may be more resistant to chemotherapy. Precise human lung cancer stem cells have yet to be identified.

Lung cancer cells harbor multiple chromosomal abnormalities, including mutations, amplifications, insertions, deletions, and translocations. One of the earliest sets of oncogenes found to be aberrant was the MYC family of transcription factors (MYC, MYCN, and MYCL). MYC is most frequently activated via gene amplification or transcriptional dysregulation in both SCLC and NSCLC. Currently, there are no MYC-specific drugs.

Among lung cancer histologies, adenocarcinomas have been the most extensively catalogued for recurrent genomic gains and losses as well as for somatic mutations **(Fig. 36-2)**. While multiple different kinds of aberrations have been found, a major class involves "driver mutations," which are mutations that occur in genes encoding signaling proteins that when aberrant, drive initiation and maintenance of tumor cells. Importantly, driver mutations can serve as potential Achilles' heels for tumors, if their gene products can be targeted appropriately. For example, one set of mutations involves EGFR, which belongs to the ERBB (HER) family of protooncogenes, including EGFR (ERBB1), HER2/neu (ERBB2), HER3 (ERBB3), and HER4 (ERBB4). T ese genes encode cell-surface receptors consisting of an extracellular ligand-binding domain, a transmembrane structure, and an intracellular tyrosine kinase (TK) domain. T e binding of ligand to receptor activates receptor dimerization and TK autophosphorylation, initiating a cascade of intracellular events,



Frequency of driver mutations in NSCLC	
AKT1	1%
ALK	3–7%
BRAF	1–3%
EGFR	10–35%
HER2	2–4%
KRAS	15–25%
MEK1	1%
NRAS	1%
PIK3CA	1–3%
RET	1–2%
ROS1	1–2%

FIGURE 36-2
Driver mutations in adenocarcinomas.

and leading to increased cell proliferation, angiogenesis, metastasis, and a decrease in apoptosis. Lung adenocarcinomas can arise when tumors express mutant EGFR. T ese same tumors display high sensitivity to small-molecule EGFR TK inhibitors (TKIs). Additional examples of driver mutations in lung adenocarcinoma include the GTPase KRAS, the serine-threonine kinase BRAF, and the lipid kinase PIK3CA. More recently, more subsets of lung adenocarcinoma have been identifed as defined by the presence of specific chromsomal rearrangements resulting in the abberant activation of the TKs ALK, ROS1, and RET. Notably, most driver mutations in lung cancer appear to be mutually exclusive, suggesting that acquisition of one of these mutations is suf cient to drive tumorigenesis. Although driver mutations have mostly been found in adenocarinomas, three potential molecular targets recently have been identified in squamous cell lung carcinomas: FGFR1 amplification, DDR2 mutations, and PIK3CA mutations/PTEN loss (Table 36-1). Together, these potentially "actionable" defects occur in up to 50% of squamous carcinomas.

A large number of tumor-suppressor genes have also been identified that are inactivated during the pathogenesis of lung cancer. T ese include TP53, RB1, RASSF1A, CDKN2A/B, LKB1 (STK11), and FHIT. Nearly 90% of SCLCs harbor mutations in TP53 and RB1. Several tumor-suppressor genes on chromosome 3p appear to be involved in nearly all lung cancers. Allelic loss for this region occurs very early in lung cancer pathogenesis, including in histologically normal smoking-damaged lung epithelium.

EARLY DETECTION AND SCREENING

In lung cancer, clinical outcome is related to the stage at diagnosis, and hence, it is generally assumed that early detection of occult tumors will lead to improved survival. Early detection is a process that involves screening tests, surveillance, diagnosis, and early treatment. Screening refers to the use of simple tests across a healthy population in order to identify individuals who harbor asymptomatic disease. For a screening program to be successful, there must be a high burden of disease within the target population; the test must be sensitive, specific, accessible, and cost effective; and there must be effective treatment that can reduce mortality. With any screening procedure, it is important to consider the possible influence of lead-time bias (detecting the cancer earlier without an effect on survival), length-time bias (indolent cancers are detected on screening and may not affect survival, whereas aggressive cancers are likely to cause symptoms earlier in patients and are less likely to be detected), and overdiagnosis (diagnosing cancers so slow growing that they are unlikely to cause the death of the patient) **(Chap. 28)**.

Because a majority of lung cancer patients present with advanced disease beyond the scope of surgical resection, there is understandable skepticism about the value of screening in this condition. Indeed, randomized controlled trials conducted in the 1960s to 1980s using screening chest x-rays (CXR), with or without sputum cytology, reported no impact on lung cancer–specific mortality in patients characterized as high risk (males age ≥45 years with a smoking history). T ese studies have been criticized for their design, statistical analyses, and outdated imaging modalities. T e results of the more recently conducted Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) are consistent with these earlier reports. Initiated in 1993, participants in the PLCO lung cancer screening trial received annual CXR screening for 4 years, whereas participants in the usual care group received no interventions other than their customary medical care. T e diagnostic follow-up of positive screening results was determined by participants and their physicians. T e PLCO trial differed from previous lung cancer screening studies in that women and never smokers were eligible. T e study was designed to detect a 10% reduction in lung cancer mortality in the interventional group. A total of 154,901 individuals between 55 and 74 years of age were enrolled (77,445 assigned to annual CXR screenings; 77,456 assigned to usual care). Participant demographics and tumor characteristics were well balanced between the two groups. T rough 13 years of follow-up, cumulative lung cancer incidence rates (20.1 vs 19.2 per 10,000 person-years; rate ratio [RR], 1.05; 95% confidence interval [CI], 0.98–1.12) and lung cancer mortality (n = 1213 vs n = 1230) were identical between the two groups. T e stage and histology of detected cancers in the two groups also were similar. T ese data corroborate previous recommendations against CXR screening for lung cancer.

In contrast to CXR, low-dose, noncontrast, thin-slice spiral chest computed tomography (LDCT) has emerged as an effective tool to screen for lung cancer. In nonrandomized studies conducted in the 1990s, LDCT scans were shown to detect more lung nodules and cancers than standard CXR in selected high-risk populations (e.g., age ≥60 years and a smoking history of ≥10 pack-years). Notably, up to 85% of the lung cancers discovered in these trials were classified as stage I disease and therefore considered potentially curable with surgical resection.

T ese data prompted the National Cancer Institute (NCI) to initiate the National Lung Screening Trial (NLST), a randomized study designed to determine if LDCT screening could reduce mortality from lung

cancer in high-risk populations as compared with standard posterior anterior CXR. High-risk patients were defined as individuals between 55 and 74 years of age, with a ≥30 pack-year history of cigarette smoking; former smokers must have quit within the previous 15 years. Excluded from the trial were individuals with a previous lung cancer diagnosis, a history of hemoptysis, an unexplained weight loss of >15 lb in the preceding year, or a chest CT within 18 months of enrollment. A total of 53,454 persons were enrolled and randomized to annual screening yearly for three years (LDCT screening, n = 26,722; CXR screening, n = 26,732). Any noncalcified nodule measuring ≥4 mm in any diameter found on LDCT and CXR images with any noncalcified nodule or mass were classified as "positive." Participating radiologists had the option of not calling a final screen positive if a noncalcified nodule had been stable on the three screening exams. Overall, 39.1% of participants in the LDCT group and 16% in the CXR group had at least one positive screening result. Of those who screened positive, the false-positive rate was 96.4% in the LDCT group and 94.5% in the CXR group. T is was consistent across all three rounds. In the LDCT group, 1060 cancers were identified compared with 941 cancers in the CXR group (645 vs 572 per 100,000 person-years; RR, 1.13; 95% CI, 1.03 to 1.23). Nearly twice as many early-stage IA cancers were detected in the LDCT group compared with the CXR group (40% vs 21%). T e overall rates of lung cancer death were 247 and 309 deaths per 100,000 participants in the LDCT and CXR groups, respectively, representing a 20% reduction in lung cancer mortality in the LDCT-screened population (95% CI, 6.8–26.7%; p = .004). Compared with the CXR group, the rate of death in the LDCT group from any cause was reduced by 6.7% (95% CI, 1.2–13.6; p = .02) **(Table 36-2)**. T e number needed to screen (NNTS) to prevent one lung cancer death was calculated to be 320.

LDCT screening for lung cancer comes with known risks including a high rate of false-positive results, false-negative results, potential for unnecessary follow-up testing, radiation exposure, overdiagnosis, changes in anxiety and quality of life, and substantial financial costs. By far the biggest challenge confronting the use of CT screening is the high false-positive rate. False positives can have a substantial impact on patients through the expense and risk of unneeded further evaluation and emotional stress. T e management of these patients usually consists of serial CT scans over time to see if the nodules grow, attempted fine-needle aspirates, or surgical resection. At $300 per scan (NCI estimated cost), the outlay for initial LDCT alone could run into the billions of dollars annually, an expense that only further escalates when factoring in various downstream expenditures an individual might incur in the assessment of positive findings. A formal cost-effectiveness analysis of the NLST is expected soon that should help resolve this crucial concern.

Despite the aforementioned caveats, screening of individuals who meet the NLST criteria for lung cancer risk (or in some cases, modified versions of these criteria) seems warranted, provided comprehensive multidisciplinary coordinated care and follow-up similar to those provided to NLST participants are available. Algorithms to improve candidate selection are under development. When discussing the option of LDCT screening, use of absolute risks rather than relative risks is helpful because studies indicate the public can process absolute terminology more effectively than relative risk projections. A useful guide has been developed by the NCI to help patients and physicians assess the benefits and harms of LDCT screening for lung cancer **(Table 36-3)**. Finally, even a small negative effect of screening on smoking behavior (either lower quit rates or higher recidivism) could easily offset the potential gains in a population. Fortunately no such impact has been reported to date. Nonetheless, smoking cessation must be included as an indispensable component of any screening program.

TABLE 36-2

RESULTS OF NATIONAL LUNG SCREENING TRIAL

	EVENT NUMBER		RATES OF EVENTS PER 100,000 PERSON-YEARS		RELATIVE RISK (95% CI)	
	LDCT (N = 26,772)	CXR (N = 26,732)	LDCT	CXR	RR	P VALUE
Lung cancer mortality	356	443	247	309	0.80 (0.73–0.93)	.004
All-cause mortality	1877	2000	1303	1395	0.93 (0.86–0.99)	.02
Mortality not due to lung cancer	1521	1557	1056	1086	0.99 (0.95–1.02)	.51

Abbreviations: CI, confidence interval; CXR, chest x-ray; LDCT, low-dose computed tomography; RR, rate ratio.
Source: Modified from PB Bach et al: JAMA 307:2418, 2012.

TABLE 36-3

THE BENEFITS AND HARMS OF LDCT SCREENING FOR LUNG CANCER BASED ON NLST DATA

	LDCT	CXR
Benefits: How Did CT Scans Cause Help Compared to CXR?		
4 in 1000 fewer died from lung cancer	13 in 1000	17 in 1000
5 in 1000 fewer died from all causes	70 in 1000	75 in 1000
Harms: What Problems Did CT Scans Cause Compared to CXR?		
223 in 1000 had at least 1 false alarm	365 in 1000	142 in 1000
18 in 1000 had a false alarm leading to an invasive procedure	25 in 1000	7 in 1000
2 in 1000 had a major complication from an invasive procedure	3 in 1000	1 in 1000

Abbreviations: CXR, chest x-ray; LDCT, low-dose computed tomography; NLST, National Lung Screening Trial.
Source: Modified from S Woloshin et al: N Engl J Med 367:1677, 2012.

TABLE 36-4

PRESENTING SIGNS AND SYMPTOMS OF LUNG CANCER

SYMPTOM AND SIGNS	RANGE OF FREQUENCY
Cough	8–75%
Weight loss	0–68%
Dyspnea	3–60%
Chest pain	20–49%
Hemoptysis	6–35%
Bone pain	6–25%
Clubbing	0–20%
Fever	0–20%
Weakness	0–10%
Superior vena cava obstruction	0–4%
Dysphagia	0–2%
Wheezing and stridor	0–2%

Source: Reproduced with permission from MA Beckles: Chest 123:97-104, 2003.

TABLE 36-5

CLINICAL FINDINGS SUGGESTIVE OF METASTATIC DISEASE

Symptoms elicited in history	• Constitutional: weight loss >10 lb • Musculoskeletal: focal skeletal pain • Neurologic: headaches, syncope, seizures, extremity weakness, recent change in mental status
Signs found on physical examination	• Lymphadenopathy (>1 cm) • Hoarseness, superior vena cava syndrome • Bone tenderness • Hepatomegaly (>13 cm span) • Focal neurologic signs, papilledema • Soft-tissue mass
Routine laboratory tests	• Hematocrit, <40% in men; <35% in women • Elevated alkaline phosphatase, GGT, SGOT, and calcium levels

Abbreviations: GGT, gamma-glutamyltransferase; SGOT, serum glutamic-oxaloacetic transaminase.
Source: Reproduced with permission from GA Silvestri et al: Chest 123 (1 Suppl):147S, 2003.

CLINICAL MANIFESTATIONS

Over half of all patients diagnosed with lung cancer present with locally advanced or metastatic disease at the time of diagnosis. The majority of patients present with signs, symptoms, or laboratory abnormalities that can be attributed to the primary lesion, local tumor growth, invasion or obstruction of adjacent structures, growth at distant metastatic sites, or a paraneoplastic syndrome **(Tables 36-4 and 36-5)**. The prototypical lung cancer patient is a current or former smoker of either sex, usually in the seventh decade of life. A history of chronic cough with or without hemoptysis in a current or former smoker with chronic obstructive pulmonary disease (COPD) age 40 years or older should prompt a thorough investigation for lung cancer even in the face of a normal CXR. A persistent pneumonia without constitutional symptoms and unresponsive to repeated courses of antibiotics also should prompt an evaluation for the underlying cause. Lung cancer arising in a life-time never smoker is more common in women and East Asians. Such patients also tend to be younger than their smoking counterparts at the time of diagnosis. The clinical presentation of lung cancer in never smokers tends to mirror that of current and former smokers.

Patients with central or endobronchial growth of the primary tumor may present with cough, hemoptysis, wheeze, stridor, dyspnea, or postobstructive pneumonitis. Peripheral growth of the primary tumor may cause pain from pleural or chest wall involvement, dyspnea on a restrictive basis, and symptoms of a lung abscess resulting from tumor cavitation. Regional spread of tumor in the thorax (by contiguous growth or by metastasis to regional lymph nodes) may cause tracheal obstruction, esophageal compression with dysphagia, recurrent laryngeal paralysis with hoarseness, phrenic nerve palsy with elevation of the hemidiaphragm and

dyspnea, and sympathetic nerve paralysis with Horner's syndrome (enophthalmos, ptosis, miosis, and anhydrosis). Malignant pleural effusions can cause pain, dyspnea, or cough. Pancoast (or superior sulcus tumor) syndromes result from local extension of a tumor growing in the apex of the lung with involvement of the eighth cervical and first and second thoracic nerves, and present with shoulder pain that characteristically radiates in the ulnar distribution of the arm, often with radiologic destruction of the first and second ribs. Often Horner's syndrome and Pancoast syndrome coexist. Other problems of regional spread include superior vena cava syndrome from vascular obstruction; pericardial and cardiac extension with resultant tamponade, arrhythmia, or cardiac failure; lymphatic obstruction with resultant pleural effusion; and lymphangitic spread through the lungs with hypoxemia and dyspnea. In addition, lung cancer can spread transbronchially, producing tumor growth along multiple alveolar surfaces with impairment of gas exchange, respiratory insuf - ciency, dyspnea, hypoxemia, and sputum production. Constitutional symptoms may include anorexia, weight loss, weakness, fever, and night sweats. Apart from the brevity of symptom duration, these parameters fail to clearly distinguish SCLC from NSCLC or even from neoplasms metastatic to lungs.

Extrathoracic metastatic disease is found at autopsy in more than 50% of patients with squamous carcinoma, 80% of patients with adenocarcinoma and large-cell carcinoma, and greater than 95% of patients with SCLC. Approximately one-third of patients present with symptoms as a result of distant metastases. Lung cancer metastases may occur in virtually every organ system, and the site of metastatic involvement largely determines other symptoms. Patients with brain metastases may present with headache, nausea and vomiting, seizures, or neurologic deficits. Patients with bone metastases may present with pain, pathologic fractures, or cord compression. T e latter may also occur with epidural metastases. Individuals with bone marrow invasion may present with cytopenias or leukoerythroblastosis. T ose with liver metastases may present with hepatomegaly, right upper quadrant pain, fever, anorexia, and weight loss. Liver dysfunction and biliary obstructions are rare. Adrenal metastases are common but rarely cause pain or adrenal insuf ciency unless they are large.

Paraneoplastic syndromes are common in patients with lung cancer, especially those with SCLC, and may be the presenting finding or the first sign of recurrence. In addition, paraneoplastic syndromes may mimic metastatic disease and, unless detected, lead to inappropriate palliative rather than curative treatment. Often the paraneoplastic syndrome may be relieved with successful treatment of the tumor. In some cases, the pathophysiology of the paraneoplastic syndrome is known, particularly when a hormone with biological activity is secreted by a tumor. However, in many cases, the pathophysiology is unknown. Systemic symptoms of anorexia, cachexia, weight loss (seen in 30% of patients), fever, and suppressed immunity are paraneoplastic syndromes of unknown etiology or at least not well defined. Weight loss greater than 10% of total body weight is considered a bad prognostic sign. Endocrine syndromes are seen in 12% of patients; hypercalcemia resulting from ectopic production of parathyroid hormone (PTH), or more commonly, PTH-related peptide, is the most common life-threatening metabolic complication of malignancy, primarily occurring with squamous cell carcinomas of the lung. Clinical symptoms include nausea, vomiting, abdominal pain, constipation, polyuria, thirst, and altered mental status.

Hyponatremia may be caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or possibly atrial natriuretic peptide (ANP). SIADH resolves within 1-4 weeks of initiating chemotherapy in the vast majority of cases. During this period, serum sodium can usually be managed and maintained above 128 mEq/L via fluid restriction. Demeclocycline can be a useful adjunctive measure when fluid restriction alone is insuf cient. Vasopressin receptor antagonists like tolvaptan also have been used in the management of SIADH. However, there are significant limitations to the use of tolvaptan including liver injury and overly rapid correction of the hyponatremia, which can lead to irreversible neurologic injury. Likewise, the cost of tolvaptan may be prohibitive (as high as $300 per tablet in some areas). Of note, patients with ectopic ANP may have worsening hyponatremia if sodium intake is not concomitantly increased. Accordingly, if hyponatremia fails to improve or worsens after 3–4 days of adequate fluid restriction, plasma levels of ANP should be measured to determine the causative syndrome.

Ectopic secretion of ACTH by SCLC and pulmonary carcinoids usually results in additional electrolyte disturbances, especially hypokalemia, rather than the changes in body habitus that occur in Cushing's syndrome from a pituitary adenoma. Treatment with standard medications, such as metyrapone and ketoconazole, is largely ineffective due to extremely high cortisol levels. T e most effective strategy for management of the Cushing's syndrome is effective treatment of the underlying SCLC. Bilateral adrenalectomy may be considered in extreme cases.

Skeletal–connective tissue syndromes include clubbing in 30% of cases (usually NSCLCs) and hypertrophic primary osteoarthropathy in 1–10% of cases (usually adenocarcinomas). Patients may develop periostitis, causing pain, tenderness, and swelling over the

affected bones and a positive bone scan. Neurologic-myopathic syndromes are seen in only 1% of patients but are dramatic and include the myasthenic Eaton-Lambert syndrome and retinal blindness with SCLC, whereas peripheral neuropathies, subacute cerebellar degeneration, cortical degeneration, and polymyositis are seen with all lung cancer types. Many of these are caused by autoimmune responses such as the development of anti-voltage-gated calcium channel antibodies in Eaton-Lambert syndrome. Patients with this disorder present with proximal muscle weakness, usually in the lower extremities, occasional autonomic dysfunction, and rarely, cranial nerve symptoms or involvement of the bulbar or respiratory muscles. Depressed deep tendon reflexes are frequently present. In contrast to patients with myasthenia gravis, strength improves with serial effort. Some patients who respond to chemotherapy will have resolution of the neurologic abnormalities. T us, chemotherapy is the initial treatment of choice. Paraneoplastic encephalomyelitis and sensory neuropathies, cerebellar degeneration, limbic encephalitis, and brainstem encephalitis occur in SCLC in association with a variety of antineuronal antibodies such as anti-Hu, anti-CRMP5, and ANNA-3. Paraneoplastic cerebellar degeneration may be associated with anti-Hu, anti-Yo, or P/Q calcium channel autoantibodies. Coagulation or thrombotic or other hematologic manifestations occur in 1–8% of patients and include migratory venous thrombophlebitis (Trousseau's syndrome), nonbacterial thrombotic (marantic) endocarditis with arterial emboli, and disseminated intravascular coagulation with hemorrhage, anemia, granulocytosis, and leukoerythroblastosis. T rombotic disease complicating cancer is usually a poor prognostic sign. Cutaneous manifestations such as dermatomyositis and acanthosis nigricans are uncommon (1%), as are the renal manifestations of nephrotic syndrome and glomerulonephritis (≤1%).

DIAGNOSING LUNG CANCER

Tissue sampling is required to confirm a diagnosis in all patients with suspected lung cancer. In patients with suspected metastatic disease, a biopsy of the most distant site of disease is preferred for tissue confirmation. Given the greater emphasis placed on molecular testing for NSCLC patients, a core biopsy is preferred to ensure adequate tissue for analysis. Tumor tissue may be obtained via minimally invasive techniques such as bronchial or transbronchial biopsy during fiberoptic bronchoscopy, by fine-needle aspiration or percutaneous biopsy using image guidance, or via endobronchial ultrasound (EBUS) guided biopsy. Depending on the location, lymph node sampling may occur via transesophageal endoscopic ultrasound-guided biopsy (EUS), EBUS, or blind biopsy. In patients with clinically palpable disease such as a lymph node or skin metastasis, a biopsy may be obtained. In patients with suspected metastatic disease, a diagnosis may be confirmed by percutaneous biopsy of a soft tissue mass, lytic bone lesion, bone marrow, pleural or liver lesion, or an adequate cell block obtained from a malignant pleural effusion. In patients with a suspected malignant pleural effusion, if the initial thoracentesis is negative, a repeat thoracentesis is warranted. Although the majority of pleural effusions are due to malignant disease, particularly if they are exudative or bloody, some may be parapneumonic. In the absence of distant disease, such patients should be considered for possible curative treatment.

T e diagnostic yield of any biopsy depends on several factors including location (accessibility) of the tumor, tumor size, tumor type, and technical aspects of the diagnostic procedure including the experience level of the bronchoscopist and pathologist. In general, central lesions such as squamous cell carcinomas, small-cell carcinomas, or endobronchial lesions such as carcinoid tumors are more readily diagnosed by bronchoscopic examination, whereas peripheral lesions such as adenocarcinomas and large-cell carcinomas are more amenable to transthoracic biopsy. Diagnostic accuracy for SCLC versus NSCLC for most specimens is excellent, with lesser accuracy for subtypes of NSCLC.

Bronchoscopic specimens include bronchial brush, bronchial wash, bronchioloalveolar lavage, transbronchial fine-needle aspiration (FNA), and core biopsy. For more accurate histologic classification, mutation analysis, or investigational purposes, reasonable efforts (e.g., a core needle biopsy) should be made to obtain more tissue than what is contained in a routine cytology specimen obtained by FNA. Overall sensitivity for combined use of bronchoscopic methods is approximately 80%, and together with tissue biopsy, the yield increases to 85–90%. Like transbronchial core biopsy specimens, transthoracic core biopsy specimens are also preferred. Sensitivity is highest for larger lesions and peripheral tumors. In general, core biopsy specimens, whether transbronchial, transthoracic, or EUS-guided, are superior to other specimen types. T is is primarily due to the higher percentage of tumor cells with fewer confounding factors such as obscuring inflammation and reactive nonneoplastic cells.

Sputum cytology is inexpensive and noninvasive but has a lower yield than other specimen types due to poor preservation of the cells and more variability in acquiring a good-quality specimen. T e yield for sputum cytology is highest for larger and centrally located tumors such as squamous cell carcinoma and small-cell

carcinoma histology. The specificity for sputum cytology averages close to 100%, although sensitivity is generally <70%. The accuracy of sputum cytology improves with increased numbers of specimens analyzed. Consequently, analysis of at least three sputum specimens is recommended.

STAGING LUNG CANCER

Lung cancer staging consists of two parts: first, a determination of the location of the tumor and possible metastatic sites (anatomic staging), and second, an assessment of a patient's ability to withstand various antitumor treatments (physiologic staging). All patients with lung cancer should have a complete history and physical examination, with evaluation of all other medical problems, determination of performance status, and history of weight loss. The most significant dividing line is between those patients who are candidates for surgical resection and those who are inoperable but will benefit from chemotherapy, radiation therapy, or both. Staging with regard to a patient's potential for surgical resection is principally applicable to NSCLC.

ANATOMIC STAGING OF PATIENTS WITH LUNG CANCER

The accurate staging of patients with NSCLC is essential for determining the appropriate treatment in patients with resectable disease and avoiding unnecessary surgical procedures in patients with advanced disease **(Fig. 36-3)**. All patients with NSCLC should undergo initial radiographic imaging with CT scan, positron emission tomography (PET), or preferably CT-PET. PET scanning attempts to identify sites of malignancy based on glucose metabolism by measuring the uptake of ^{18}F-fluorodeoxyglucose (FDG). Rapidly dividing cells, presumably in the lung tumors, will preferentially take up ^{18}F-FDG and appear as a "hot spot." To date, PET has been mostly used for staging and detection of metastases in lung cancer and in the detection of nodules >15 mm in diameter. Combined ^{18}F-FDG PET-CT imaging has been shown to improve the accuracy of staging in NSCLC compared to visual correlation of PET and CT or either study alone. CT-PET has been found to be superior in identifying pathologically enlarged mediastinal lymph nodes and extrathoracic metastases. A standardized uptake value (SUV) of >2.5 on PET is highly suspicious for malignancy. False negatives can be seen in

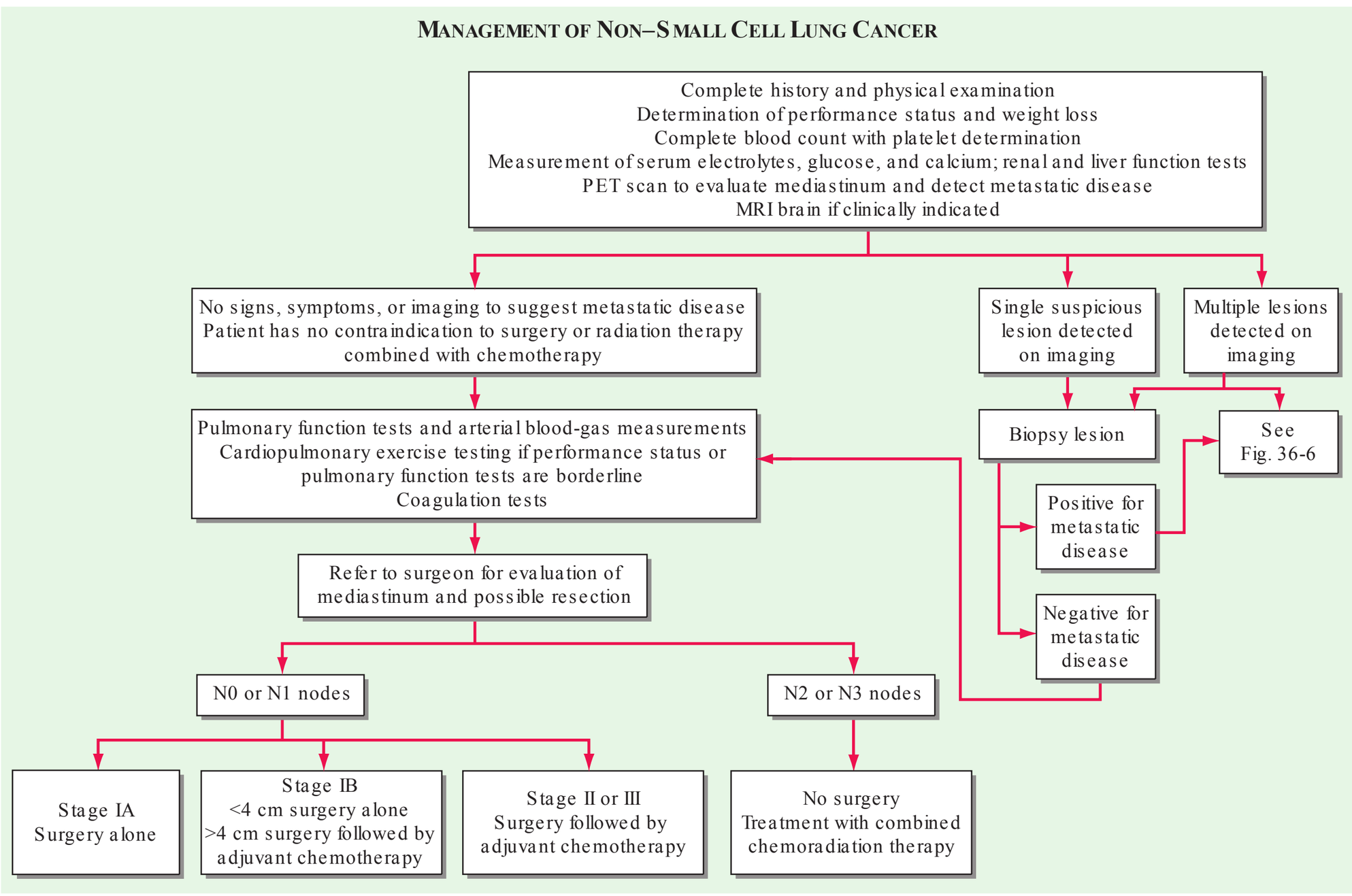


FIGURE 36-3

Algorithm for management of non-small-cell lung cancer. MRI, magnetic resonance imaging; PET, positron emission tomography.

diabetes, in lesions <8 mm, and in slow-growing tumors (e.g., carcinoid tumors or well-differentiated adenocarcinoma). False positives can be seen in certain infections and granulomatous disease (e.g., tuberculosis). T us, PET should never be used alone to diagnose lung cancer, mediastinal involvement, or metastases. Confirmation with tissue biopsy is required. For brain metastases, magnetic resonance imaging (MRI) is the most effective method. MRI can also be useful in selected circumstances, such as superior sulcus tumors to rule out brachial plexus involvement, but in general, MRI does not play a major role in NSCLC staging.

In patients with NSCLC, the following are contraindications to potential curative resection: extrathoracic metastases, superior vena cava syndrome, vocal cord and, in most cases, phrenic nerve paralysis, malignant pleural effusion, cardiac tamponade, tumor within 2 cm of the carina (potentially curable with combined chemoradiotherapy), metastasis to the contralateral lung, metastases to supraclavicular lymph nodes, contralateral mediastinal node metastases (potentially curable with combined chemoradiotherapy), and involvement of the main pulmonary artery. In situations where it will make a difference in treatment, abnormal scan findings require tissue confirmation of malignancy so that patients are not precluded from having potentially curative therapy.

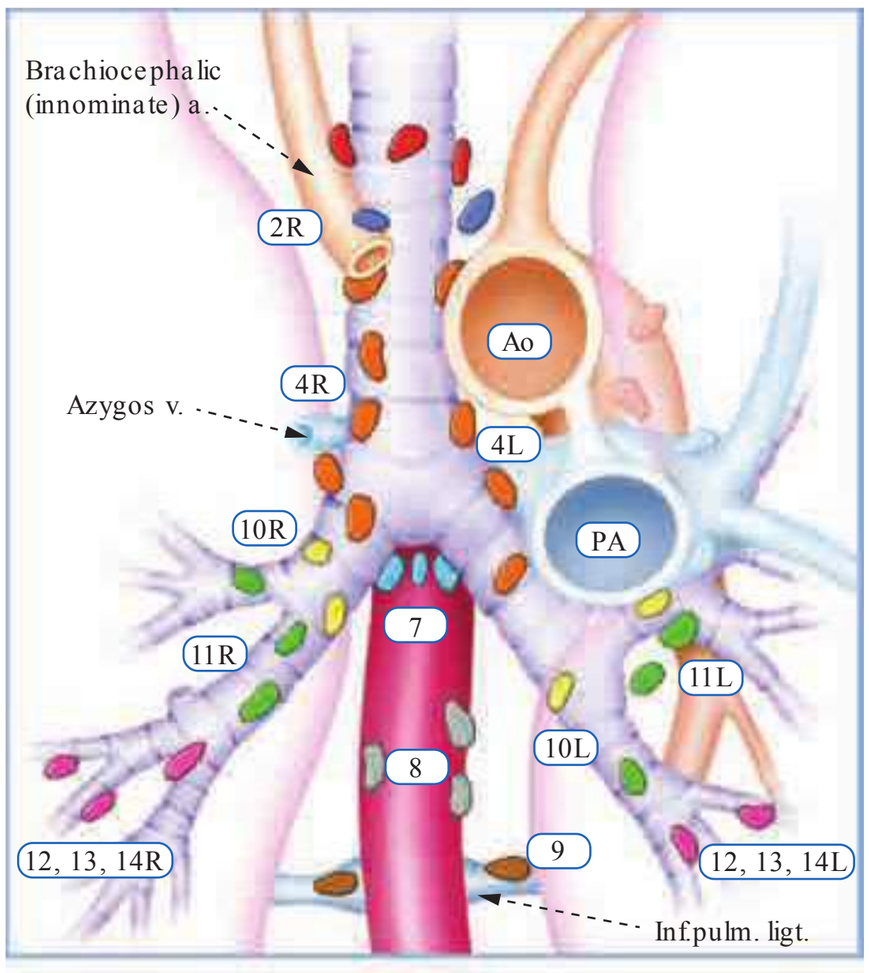
T e best predictor of metastatic disease remains a careful history and physical examination. If signs, symptoms, or findings from the physical examination suggest the presence of malignancy, then sequential imaging starting with the most appropriate study should be performed. If the findings from the clinical evaluation are negative, then imaging studies beyond CT-PET are unnecessary and the search for metastatic disease is complete. More controversial is how one should assess patients with known stage III disease. Because these patients are more likely to have asymptomatic occult metastatic disease, current guidelines recommend a more extensive imaging evaluation including imaging of the brain with either CT scan or MRI. In patients in whom distant metastatic disease has been ruled out, lymph node status needs to be assessed via a combination of radiographic imaging and/or minimally invasive techniques such as those mentioned above and/or invasive techniques such as mediastinoscopy, mediastinotomy, thoracoscopy, or thoracotomy. Approximately one-quarter to one-half of patients diagnosed with NSCLC will have mediastinal lymph node metastases at the time of diagnosis. Lymph node sampling is recommended in all patients with enlarged nodes detected by CT or PET scan and in patients with large tumors or tumors occupying the inner third of the lung. T e extent of mediastinal lymph node involvement is important in determining the appropriate treatment strategy: surgical resection followed by adjuvant chemotherapy versus combined chemoradiation alone (see below). A standard nomenclature for referring to the location of lymph nodes involved with lung cancer has evolved **(Fig. 36-4)**.

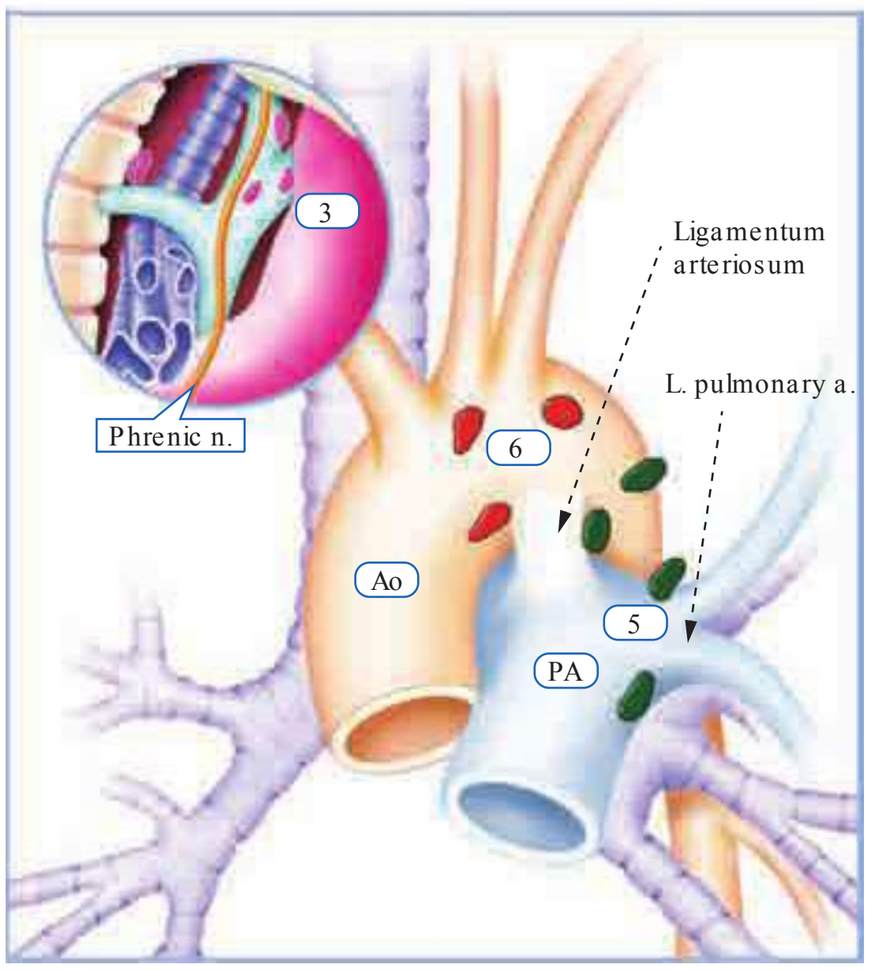
In SCLC patients, current staging recommendations include a CT scan of the chest and abdomen (because of the high frequency of hepatic and adrenal involvement), MRI of the brain (positive in 10% of asymptomatic patients), and radionuclide bone scan if symptoms or signs suggest disease involvement in these areas **(Fig. 36-5)**. Although there are less data on the use of CT-PET in SCLC, the most recent American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend PET scans in patients with clinical stage I SCLC who are being considered for curative intent surgical resection. In addition, invasive mediastinal staging and extrathoracic imaging (head MRI/CT and PET or abdominal CT plus bone scan) is also recommended for patients with clinical stage I SCLC if curative intent surgical resection is contemplated. Some practice guidelines also recommend the use of PET scanning in the staging of SCLC patients who are potential candidates for the addition of thoracic radiotherapy to chemotherapy. Bone marrow biopsies and aspirations are rarely performed now given the low incidence of isolated bone marrow metastases. Confirmation of metastatic disease, ipsilateral or contralateral lung nodules, or metastases beyond the mediastinum may be achieved by the same modalities recommended earlier for patients with NSCLC.

If a patient has signs or symptoms of spinal cord compression (pain, weakness, paralysis, urinary retention), a spinal CT or MRI scan and examination of the cerebrospinal fluid cytology should be performed. If metastases are evident on imaging, a neurosurgeon should be consulted for possible palliative surgical resection and/or a radiation oncologist should be consulted for palliative radiotherapy to the site of compression. If signs or symptoms of leptomeningitis develop at any time in a patient with lung cancer, an MRI of the brain and spinal cord should be performed, as well as a spinal tap, for detection of malignant cells. If the spinal tap is negative, a repeat spinal tap should be considered. T ere is currently no approved therapy for the treatment of leptomeningeal disease.

STAGING SYSTEM FOR NON-SMALL-CELL LUNG CANCER

T e tumor-node-metastasis (TNM) international staging system provides useful prognostic information and is used to stage all patients with NSCLC. T e various T (tumor size), N (regional node involvement), and M (presence or absence of distant metastasis) are combined





Superior mediastinal nodes

- **1 Highest mediastinal**
- **2 Upper paratracheal**
- **3 Prevascular and retrotracheal**
- **4 Lower paratracheal (including azygos nodes)**

N2 = single digit, ipsilateral
N3 = single digit, contralateral or supraclavicular

Aortic nodes

- **5 Subaortic (A-P window)**
- **6 Para-aortic (ascending aorta or phrenic)**

Inferior mediastinal nodes

- **7 Subcarinal**
- **8 Paraesophageal (below carina)**
- **9 Pulmonary ligament**

N1 nodes

- **10 Hilar**
- **11 Interlobar**
- **12 Lobar**
- **13 Segmental**
- **14 Subsegmental**

FIGURE 36-4
Lymph node stations in staging non-small-cell lung cancer. The International Association for the Study of Lung Cancer (IASLC) lymph node map, including the proposed grouping of lymph node stations into "zones" for the purposes of prognostic analyses. a., artery; Ao, aorta; Inf. pulm. ligt., inferior pulmonary ligament; n., nerve; PA, pulmonary artery; v. vein.

to form different stage groups **(Tables 36-6 and 36-7)**. The previous edition of the TNM staging system for lung cancer was developed based on a relatively small database of patients from a single institution. The latest seventh edition of the TNM staging system went into effect in 2010 and developed using a much more robust database of more than 100,000 patients with lung cancer who were treated in multiple countries between 1990 and 2000. Data from 67,725 patients with NSCLC were then used to reevaluate the prognostic value of the TNM descriptors **(Table 36-8)**. The major distinction between the sixth and seventh editions of the international staging systems is within the T classification; T1 tumors are divided into tumors ≤2 cm in size, as these patients were found to have a better prognosis compared to patients with tumors >2 cm but ≤3 cm. T2 tumors are divided into those that are >3 cm but ≤5 cm and those that are >5 cm but ≤7 cm. Tumors that are >7 cm are considered T3 tumors. T3 tumors also include tumors with invasion into local structures such as chest wall and diaphragm

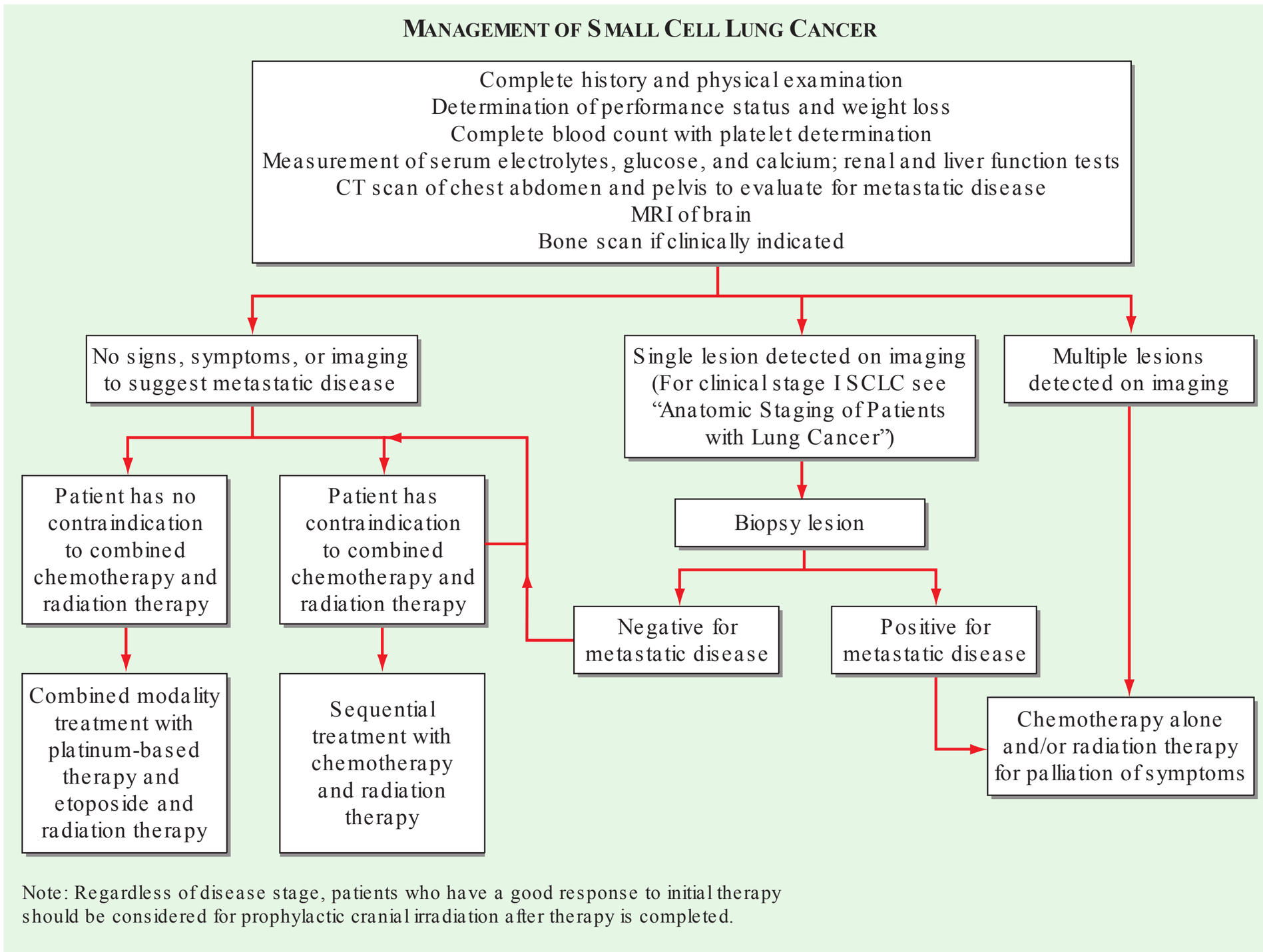


FIGURE 36-5
Algorithm for management of small-cell lung cancer. CT, computed tomography; MRI, magnetic resonance imaging.

and additional nodules in the same lobe. T4 tumors include tumors of any size with invasion into mediastinum, heart, great vessels, trachea, or esophagus or multiple nodules in the ipsilateral lung. No changes have been made to the current classification of lymph node involvement (N). Patients with metastasis may be classified as M1a (malignant pleural or pericardial effusion, pleural nodules, or nodules in the contralateral lung) or M1b (distant metastasis; e.g., bone, liver, adrenal, or brain metastasis). Based on these data, approximately one-third of patients have localized disease that can be treated with curative attempt (surgery or radiotherapy), one-third have local or regional disease that may or may not be amenable to a curative attempt, and one-third have metastatic disease at the time of diagnosis.

STAGING SYSTEM FOR SMALL-CELL LUNG CANCER

In patients with SCLC, it is now recommended that both the Veterans Administration system and the American Joint Committee on Cancer/International Union Against Cancer seventh edition system (TNM) be used to classify the tumor stage. The Veterans Administration system is a distinct two-stage system dividing patients into those with limited- or extensive-stage disease. Patients with limited-stage disease (LD) have cancer that is confined to the ipsilateral hemithorax and can be encompassed within a tolerable radiation port. Thus, contralateral supraclavicular nodes, recurrent laryngeal nerve involvement, and superior vena caval obstruction can all be part of LD. Patients with extensive-stage disease (ED) have overt metastatic disease by imaging or physical examination. Cardiac tamponade, malignant pleural effusion, and bilateral pulmonary parenchymal involvement generally qualify disease as ED, because the involved organs cannot be encompassed safely or effectively within a single radiation therapy port. Sixty to 70% of patients are diagnosed with ED at presentation. The TNM staging system is preferred in the rare SCLC patient presenting with what appears to be clinical stage I disease (see above).

PHYSIOLOGIC STAGING

Patients with lung cancer often have other comorbid conditions related to smoking including cardiovascular disease and COPD. To improve their preoperative

TABLE 36-6

SEVENTH EDITION TNM STAGING SYSTEMS FOR NON-SMALL-CELL LUNG CANCER

TNM STAGING SYSTEM FOR LUNG CANCER (7TH EDITION)	
Primary Tumor (T)	
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
T1a	Tumor ≤2 cm in diameter
T1b	Tumor >2 cm but ≤ 3 cm in diameter
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features: Involves main bronchus, ≥2 cm distal to carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor >3 cm but ≤5 cm
T2b	Tumor >5 cm but ≤7 cm
T3	Tumor >7 cm or any of the following: Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina) Atelectasis or obstructive pneumonitis of the entire lung Separate tumor nodules in the same lobe
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a dif erent ipsilateral lobe
Regional Lymph Nodes (N)	
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial ef usion
M1b	Distant metastasis (in extrathoracic organs)

Abbreviation: TNM, tumor-node-metastasis.
Source: Reproduced with permission from P Goldstraw et al: J Thorac Oncol 2:706, 2007.

condition, correctable problems (e.g., anemia, electrolyte and fluid disorders, infections, cardiac disease, and arrhythmias) should be addressed, appropriate chest physical therapy should be instituted, and patients should be encouraged to stop smoking. Because it is not always possible to predict whether a lobectomy or pneumonectomy will be required until the time of operation, a conservative approach is to restrict surgical resection to patients who could potentially tolerate a pneumonectomy. Patients with a forced expiratory volume in 1 s (FEV_1) of greater than 2 L or greater than 80% of predicted can tolerate a pneumonectomy, and those with an FEV_1 greater than 1.5 L have adequate reserve for a lobectomy. In patients with borderline lung function but a resectable tumor, cardiopulmonary exercise testing could be performed as part of the physiologic evaluation. T is test allows an estimate of the maximal oxygen consumption (Vo_{2max}). A Vo_{2max} <15 mL/(kg·min) predicts for a higher risk of postoperative complications. Patients deemed unable to tolerate lobectomy or pneumonectomy from a pulmonary functional standpoint may be candidates for more limited resections, such as wedge or anatomic segmental resection, although such procedures are associated with significantly higher rates of local recurrence and a trend toward decreased overall survival. All patients

TABLE 36-7

SEVENTH EDITION TNM STAGING SYSTEMS FOR NON-SMALL-CELL LUNG CANCER

STAGE GROUPINGS			
Stage IA	T1a-T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a,T1b,T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,T1b,T2a,T2b	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a or M1b

Abbreviation: TNM, tumor-node-metastasis.
Source: Reproduced with permission from P Goldstraw P et al: J Thorac Oncol 2:706, 2007.

TABLE 36-8

FIVE-YEAR SURVIVAL BY STAGE AND TNM CLASSIFICATION OF NON-SMALL-CELL LUNG CANCER (SEVENTH EDITION)

STAGE	TNM SEVENTH EDITION	5-YEAR SURVIVAL (%)
IA	T1a-T1bN0M0	73%
IB	T2aN0M0	58%
IIA	T1a-T2aN1M0 T2bN0M0	46%
IIB	T2bN1M0 T3N0M0	36%
IIIA	T1a-T3N2M0 T3N1M0 T4N0-1M0	24%
IIIB	T4N2M0 T1a-T4N3M0	9%
IV	Any T Any N plus M1a or M1b	13%

Abbreviation: TNM, tumor-node-metastasis.

should be assessed for cardiovascular risk using American College of Cardiology and American Heart Association guidelines. A myocardial infarction within the past 3 months is a contraindication to thoracic surgery because 20% of patients will die of reinfarction. An infarction in the past 6 months is a relative contraindication. Other major contraindications include uncontrolled arrhythmias, an FEV_1 of less than 1 L, Co_2 retention (resting Pco_2 >45 mmHg), DLco <40%, and severe pulmonary hypertension.

TREATMENT Non-Small-Cell Lung Cancer

The overall treatment approach to patients with NSCLC is shown in Fig. 36-3.

OCCULT AND STAGE 0 CARCINOMAS Patients with severe atypia on sputum cytology have an increased risk of developing lung cancer compared to those without atypia. In the uncommon circumstance where malignant cells are identified in a sputum or bronchial washing specimen but the chest imaging appears normal (TX tumor stage), the lesion must be localized. More than 90% of tumors can be localized by meticulous examination of the bronchial tree with a fiberoptic bronchoscope under general anesthesia and collection of a series of differential brushings and biopsies. Surgical resection following bronchoscopic localization has been shown to improve survival compared to no treatment. Close follow-up of these patients is indicated because of the high incidence of second primary lung cancers (5% per patient per year).

SOLITARY PULMONARY NODULE AND "GROUND-GLASS" OPACITIES A solitary pulmonary nodule is defined as an x-ray density completely surrounded by normal aerated lung with circumscribed margins, of any shape, usually 1–6 cm in greatest diameter. The approach to a patient with a solitary pulmonary nodule is based on an estimate of the probability of cancer, determined according to the patient's smoking history, age, and characteristics on imaging **(Table 36-9)**. Prior CXRs and CT scans should be obtained if available for comparison. A PET scan may be useful if the lesion is greater than 7–8 mm in diameter. If no diagnosis is apparent, Mayo investigators reported that clinical characteristics (age, cigarette smoking status, and prior cancer diagnosis) and three radiologic characteristics (nodule diameter, spiculation, and upper lobe location) were independent predictors of malignancy. At present, only two radiographic criteria are thought to predict the benign nature of a solitary pulmonary nodule: lack of growth over a period >2 years and certain characteristic patterns of calcification. Calcification alone, however, does not exclude malignancy; a dense central nidus, multiple punctuate foci, and "bulls eye" (granuloma) and "popcorn ball" (hamartoma) calcifications are highly suggestive of a benign lesion. In contrast, a relatively large lesion, lack of or asymmetric calcification, chest symptoms, associated atelectasis, pneumonitis, or growth of the lesion revealed by comparison with an old x-ray or CT scan or a positive PET scan may be suggestive of a malignant process and warrant further attempts to establish a histologic diagnosis. An algorithm for assessing these lesions is shown in **Fig. 36-6**.

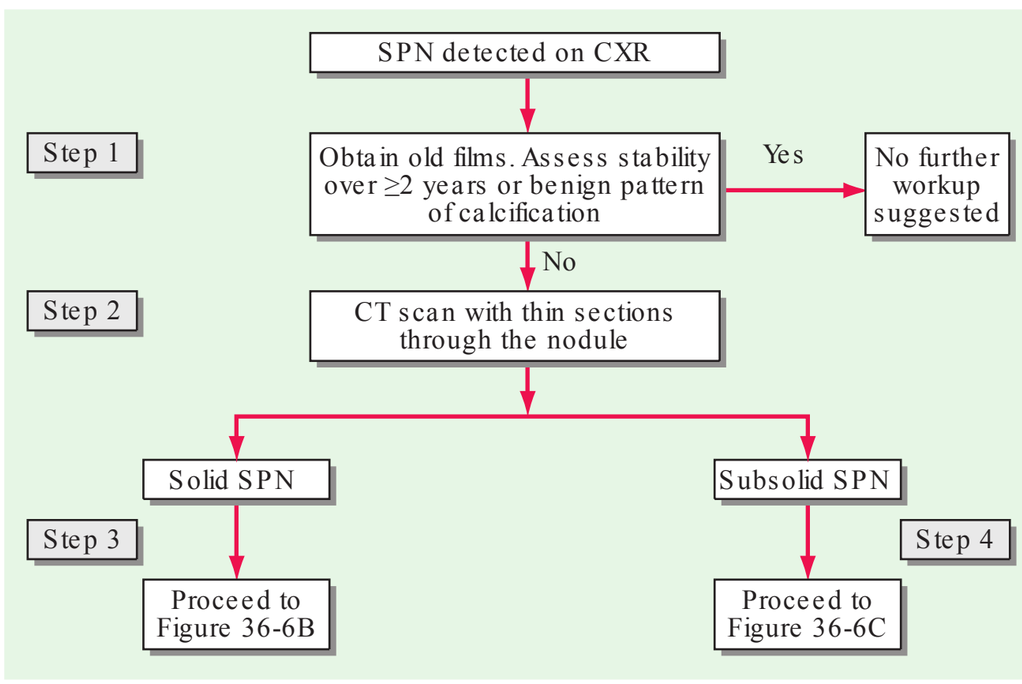
Since the advent of screening CTs, small "ground-glass" opacities (GGOs) have often been observed, particularly as the increased sensitivity of CTs enables detection of smaller lesions. Many of these GGOs, when biopsied, are found to be atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), or minimally invasive adenocarcinoma (MIA). AAH is usually a nodule of <5 mm and is minimally

TABLE 36-9

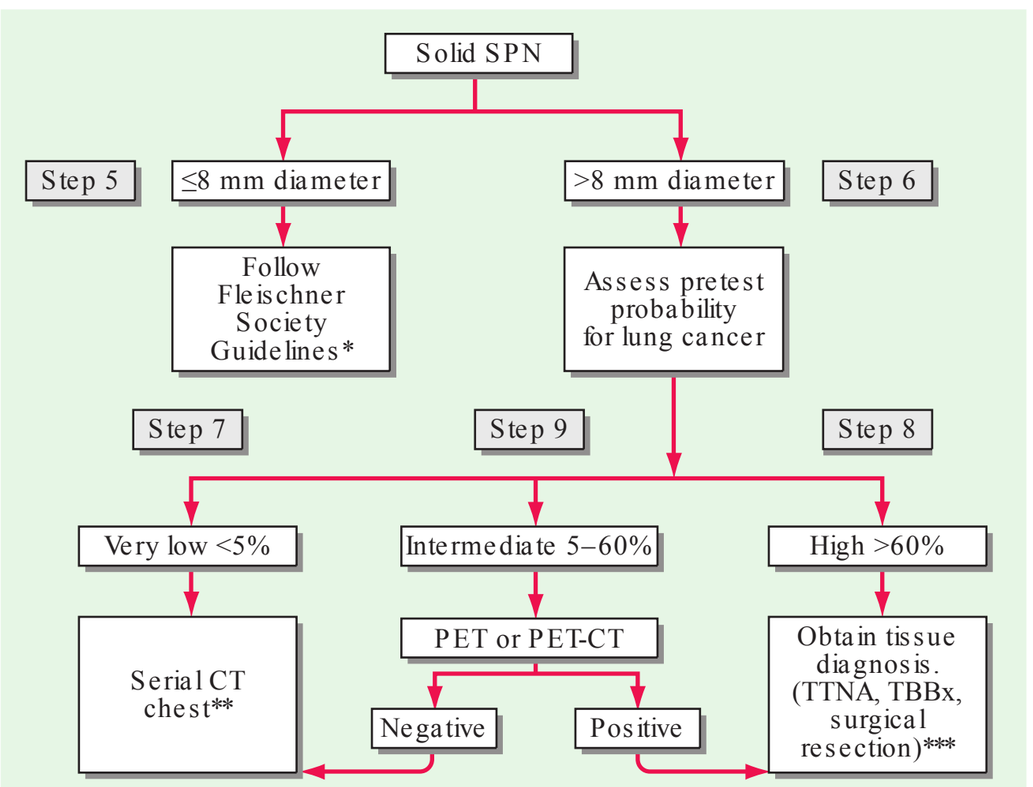
ASSESSMENT OF RISK OF CANCER IN PATIENTS WITH SOLITARY PULMONARY NODULES

	RISK		
VARIABLE	LOW	INTERMEDIATE	HIGH
Diameter (cm)	<1.5	1.5–2.2	≥2.3
Age (years)	<45	45–60	>60
Smoking status	Never smoker	Current smoker (<20 cigarettes/d)	Current smoker (>20 cigarettes/d)
Smoking cessation status	Quit ≥7 years ago or quit	Quit <7 years ago	Never quit
Characteristics of nodule margins	Smooth	Scalloped	Corona radiata or spiculated

Source: Reproduced with permission from D Ost et al: N Engl J Med 348:2535, 2003.



A



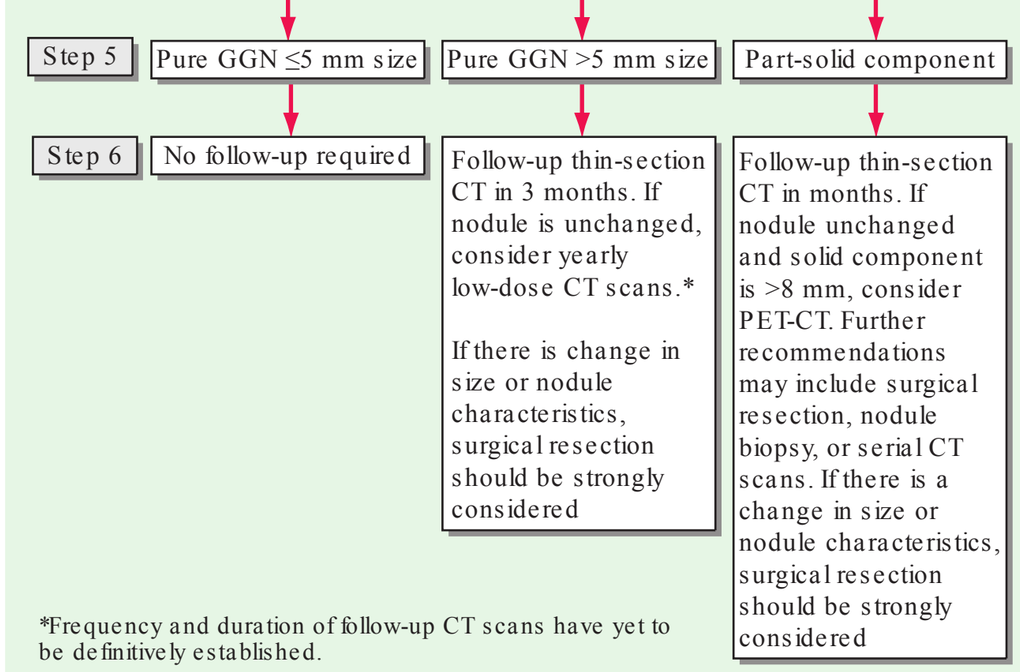
*Fleischner society guidelines; modified from: H. MacMahon, et al: Radiology 2005; 237;395–400

Nodule size (a):	Low-risk patient (b):	High-risk patient (c):
≤4 mm	No follow-up needed (d)	Follow-up at 12 months; if unchanged, no further follow-up
>4–6 mm	Follow-up CT at 12 months; if unchanged, no further follow-up	Follow-up CT at 6–12 months; then 18–24 months if no change
>6–8 mm	Follow-up CT at 6–12 months; then 18–24 months if no change	Follow-up CT at 3–6 months; then 9–12 and 24 months if no change
>8 mm	Follow-up CT at 3, 9, and 24 months; dynamic contrast-enhanced CT, PET, and/or biopsy	Same as low-risk patient

(a) Average of largest and smallest axial diameters of the nodule
(b) No smoking history and absence of other risk factors
(c) Previous or current smoking history or other risk factors
(d) Risk of malignancy (<0.1%) is substantially lower than for an asymptomatic smoker

**ACCP guidelines (see MK Gould et al: Chest 2007;132(suppl 3):108s-130S.
***Consider patient preference, severity of medical comorbidities, center specific expertise prior to tissue diagnosis.

B



C

FIGURE 36-6

A. Algorithm for evaluation of solitary pulmonary nodule (SPN). B. Algorithm for evaluation of solid SPN. C. Algorithm for evaluation of semisolid SPN. CT, computed tomography; CXR, chest radiograph; GGN, ground-glass nodule; PET, positron emission tomography; TTBx, transbronchial biopsy; TTNA, transthoracic needle biopsy. (Adapted from VK Patel et al: Chest 143:840, 2013.)

hazy, also called nonsolid or ground glass (i.e., hazy slightly increased attenuation, no solid component, and preservation of bronchial and vascular margins). On thin-section CT, AIS is usually a nonsolid nodule and tends to be slightly more opaque than AAH. MIA is mainly solid, usually with a small (<5 mm) central solid component. However, overlap exists among the imaging features of the preinvasive and minimally invasive lesions in the lung adenocarcinoma spectrum. Lepidic adenocarcinomas are usually solid but may be nonsolid. Likewise, the small invasive adenocarcinomas also are usually solid but may exhibit a small nonsolid component.

MANAGEMENT OF STAGES I AND II NSCLC **Surgical Resection of Stage I and II NSCLC** Surgical resection, ideally by an experienced thoracic surgeon, is the treatment of choice for patients with clinical stage I and II NSCLC who are able to tolerate the procedure. Operative mortality rates for patients resected by thoracic or cardiothoracic surgeons are lower compared to general surgeons. Moreover, survival rates are higher in patients who undergo resection in facilities with a high surgical volume compared to those performing fewer than 70 procedures per year, even though the higher-volume facilities often serve older and less socioeconomic advantaged populations. The improvement in survival is most evident in the immediate postoperative period. The extent of resection is a matter of surgical judgment based on findings at exploration. In patients with stage IA NSCLC, lobectomy is superior to wedge resection with respect to rates of local recurrence. There is also a trend toward improvement in overall survival. In patients with comorbidities, compromised pulmonary reserve, and small peripheral lesions, a limited resection, wedge resection, and segmentectomy (potentially by video-assisted thoracoscopic surgery) may be reasonable surgical option. Pneumonectomy is reserved for patients with central tumors and should be performed only in patients with excellent pulmonary reserve. The 5-year survival rates are 60–80% for patients with stage I NSCLC and 40–50% for patients with stage II NSCLC.

Accurate pathologic staging requires adequate segmental, hilar, and mediastinal lymph node sampling. Ideally this includes a mediastinal lymph node dissection. On the right side, mediastinal stations 2R, 4R, 7, 8R, and 9R should be dissected; on the left side, stations 5, 6, 7, 8L, and 9L should be dissected. Hilar lymph nodes are typically resected and sent for pathologic review, although it is helpful to specifically dissect and label level 10 lymph nodes when possible. On the left side, level 2 and sometimes level 4 lymph nodes are generally obscured by the aorta. Although the therapeutic benefit of nodal dissection versus nodal sampling is controversial, a pooled analysis of three trials involving patients with stages I to IIIA NSCLC demonstrated a superior 4-year survival in patients undergoing resection and a complete mediastinal lymph node dissection compared with lymph node sampling. Moreover, complete mediastinal lymphadenectomy added little morbidity to a pulmonary resection for lung cancer when carried out by an experienced thoracic surgeon.

Radiation Therapy in Stages I and II NSCLC There is currently no role for postoperative radiation therapy in patients following resection of stage I or II NSCLC. However, patients with stage I and II disease who either refuse or are not suitable candidates for surgery should be considered for radiation therapy with curative intent. Stereotactic body radiation therapy (SBRT) is a relatively new technique used to treat patients with isolated pulmonary nodules (≤5 cm) who are not candidates for or refuse surgical resection. Treatment is typically administered in three to five fractions delivered over 1–2 weeks. In uncontrolled studies, disease control rates are >90%, and 5-year survival rates of up to 60% have been reported with SBRT. By comparison, survival rates typically range from 13 to 39% in patients with stage I or II NSCLC treated with standard external-beam radiotherapy. Cryoablation is another technique occasionally used to treat small, isolated tumors (i.e., ≤3 cm). However, very little data exist on long-term outcomes with this technique.

Chemotherapy in Stages I and II NSCLC Although a landmark meta-analysis of cisplatin-based adjuvant chemotherapy trials in patients with resected stages I to IIIA NSCLC (the Lung Adjuvant Cisplatin Evaluation [LACE] Study) demonstrated a 5.4% improvement in 5-year survival for adjuvant chemotherapy compared to surgery alone, the survival benefit was seemingly confined to patients with stage II or III disease **(Table 36-10)**. By contrast, survival was actually worsened in stage IA patients with the application of adjuvant therapy. In stage IB, there was a modest improvement in survival of questionable clinical significance. Adjuvant chemotherapy was also detrimental in patients with poor performance status (Eastern Cooperative Oncology Group [ECOG] performance status = 2). These data suggest that adjuvant chemotherapy is best applied in patients with resected stage II or III NSCLC. There is no apparent role for adjuvant chemotherapy in patients with resected stage IA or IB NSCLC. A possible exception to the prohibition of adjuvant therapy in this setting is the stage IB patient with a resected lesion ≥4 cm.

As with any treatment recommendation, the risks and benefits of adjuvant chemotherapy should be considered on an individual patient basis. If a decision is made to proceed with adjuvant chemotherapy, in general, treatment should be initiated 6–12 weeks after surgery, assuming the patient has fully recovered, and should be administered for no more than four cycles. Although a cisplatin-based chemotherapy is the preferred treatment regimen, carboplatin can be substituted for cisplatin in patients who are unlikely to tolerate cisplatin for reasons such as reduced renal function, presence of neuropathy, or hearing impairment. No specific chemotherapy regimen is considered optimal in this setting, although platinum plus vinorelbine is most commonly used.

Neoadjuvant chemotherapy, which is the application of chemotherapy administered *before* an attempted surgical resection, has been advocated by some experts on the assumption that such an approach will more effectively extinguish occult micrometastases compared to postoperative chemotherapy. In addition, it is thought that preoperative

TABLE 36-10

ADJUVANT CHEMOTHERAPY TRIALS IN NON-SMALL-CELL LUNG CANCER

TRIAL	STAGE	TREATMENT	NO. OF PATIENTS	5-YEAR SURVIVAL (%)	P
IALT	I–III	Cisplatin-based Control	932 835	44.5 40.4	< .03
BR10	IB–II	Cisplatin + vinorelbine Control	242 240	69 54	.03
ANITA	IB–IIIA	Cisplatin + vinorelbine Control	407 433	60 58	.017
ALPI	I–III	MVP Control	548 540	50 45	.49
BLT	I–III	Cisplatin-based Control	192 189	60 58	.90
CALGB	IB	Carboplatin + paclitaxel	173 171	59 57	.10

Abbreviations: ALPI, Adjuvant Lung Cancer Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; BLT, Big Lung Trial; CALGB, Cancer and Lung Cancer Group B; IALT, International Adjuvant Lung Cancer Trial; MVP, mitomycin, vindesine, and cisplatin.

chemotherapy might render an inoperable lesion resectable. With the exception of superior sulcus tumors, however, the role of neoadjuvant chemotherapy in stage I to III disease is not well defined. However, a meta-analysis of 15 randomized controlled trials involving more than 2300 patients with stage I to III NSCLC suggested there may be a modest 5-year survival benefit (i.e., ~5%) that is virtually identical to the survival benefit achieved with postoperative chemotherapy. Accordingly, neoadjuvant therapy may prove useful in selected cases (see below). A decision to use neoadjuvant chemotherapy should always be made in consultation with an experienced surgeon.

In should be noted that all patients with resected NSCLC are at high risk of recurrence, most of which occurs within 18–24 months of surgery, or developing a second primary lung cancer. T us, it is reasonable to follow these patients with periodic imaging studies. Given the results of the NLST, periodic CT scans appear to be the most appropriate screening modality. Based on the timing of most recurrences, some guidelines recommend a contrasted chest CT scan every 6 months for the first 3 years after surgery, followed by yearly CT scans of the chest without contrast thereafter.

MANAGEMENT OF STAGE III NSCLC Management of patients with stage III NSCLC usually requires a combined-modality approach. Patients with stage IIIA disease commonly are stratified into those with "nonbulky" or "bulky" mediastinal lymph node (N2) disease. Although the definition of "bulky" N2 disease varies somewhat in the literature, the usual criteria include the size of a dominant lymph node (i.e., >2–3 cm in short-axis diameter as measured by CT), groupings of multiple smaller lymph nodes, evidence of extracapsular nodal involvement, or involvement of more than two lymph node stations. T e distinction between nonbulky and bulky stage IIIA disease is mainly used to select potential candidates for upfront surgical resection or for resection after neoadjuvant therapy. Many aspects of therapy of patients with stage III NSCLC remain controversial, and the optimal treatment strategy has not been clearly defined. Moreover, although there are many potential treatment options, none yields a very high probability of cure. Furthermore, because stage III disease is highly heterogeneous, no single treatment approach can be recommended for all patients. Key factors guiding treatment choices include the particular combination of tumor (T) and nodal (N) disease, the ability to achieve a complete surgical resection if indicated, and the patient's overall physical condition and preferences. For example, in carefully selected patients with limited stage IIIA disease where involved mediastinal lymph nodes can be completed resected, initial surgery followed by postoperative chemotherapy (with or without radiation therapy) may be indicated. By contrast, for patients with clinically evident bulky mediastinal lymph node involvement, the standard approach to treatment is concurrent chemoradiotherapy. Nevertheless, in some cases, the latter group of patients may be candidates for surgery following chemoradiotherapy.

Absent and Nonbulky Mediastinal (N2, N3) Lymph Node Disease For the subset of stage IIIA patients initially thought to have clinical stage I or II disease (i.e., pathologic involvement of mediastinal [N2] lymph nodes is not detected preoperatively), surgical resection is often the treatment of choice. T is is followed by adjuvant chemotherapy in patients with microscopic lymph node involvement in a resection specimen. Postoperative radiation therapy (PORT) may also have a role for those with close or positive surgical margins. Patients with tumors involving the chest wall or proximal airways within 2 cm of the carina with hilar lymph node involvement (but not N2 disease) are classified as having T3N1 stage IIIA disease. T ey too are best managed with surgical resection, if technically feasible, followed by adjuvant chemotherapy if completely resected.

Patients with tumors exceeding 7 cm in size also are now classified as T3 and are consider stage IIIA if tumor has spread to N1 nodes. T e appropriate initial management of these patients involves surgical resection when feasible, provided the mediastinal staging is negative, followed by adjuvant chemotherapy for those who achieve complete tumor resection. Patients with T3N0 or T3N1 disease due to the presence of satellite nodules within the same lobe as the primary tumor also are candidates for surgery, as are patients with ipsilateral nodules in another lobe and negative mediastinal nodes (IIIA, T4N0 or T4N1). Although data regarding adjuvant chemotherapy in the latter subsets of patients are limited, it is often recommended.

Patients with T4N0-1 were reclassified as having stage IIIA tumors in the seventh edition of the TNM system. T ese patients may have involvement of the carina, superior vena cava, or a vertebral body and yet still be candidates for surgical resection in selected circumstances. T e decision to proceed with an attempted resection must be made in consultation with an experienced thoracic surgeon often in association with a vascular or cardiac surgeon and an orthopedic surgeon depending on tumor location. However, if an incomplete resection is inevitable or if there is evidence of N2 involvement (stage IIIB), surgery for T4 disease is contraindicated. Most T4 lesions are best treated with chemoradiotherapy.

T e role of PORT in patients with completely resected stage III NSCLC is controversial. To a large extent, the use of PORT is dictated by the presence or absence of N2 involvement and, to a lesser degree, by the biases of the treating physician. Using the Surveillance, Epidemiology, and End Results (SEER) database, a recent meta-analysis of PORT identified a significant increase in survival in patients with N2 disease but not in patients with N0 or N1 disease. An earlier analysis by the PORT Meta-analysis Trialist Group using an older database produced similar results.

Known Mediastinal (N2, N3) Lymph Node Disease When pathologic involvement of mediastinal lymph nodes is documented preoperatively, a combined-modality approach is recommended assuming the patient is a candidate for treatment with curative intent. T ese patients are at high risk for both local and distant recurrence if managed with resection alone. For patients with stage III disease who are not candidates for initial surgical resection, concurrent chemoradiotherapy is most commonly used as the initial treatment. Concurrent chemoradiotherapy has been shown to produce superior survival compared to sequential chemoradiotherapy; however, it also is associated with greater host toxicities (including fatigue, esophagitis, and neutropenia). T erefore, for patients with a good performance status, concurrent chemoradiotherapy is the preferred treatment approach, whereas sequential chemoradiotherapy may be more appropriate for patients with a performance status that is not as good. For patients who are not candidates for a combined-modality treatment approach, typically due to a poor performance status or a comorbidity that makes chemotherapy untenable, radiotherapy alone may provide a modest survival benefit in addition to symptom palliation.

For patients with potentially resectable N2 disease, it remains uncertain whether surgery after neoadjuvant chemoradiotherapy improves survival. In an NCI-sponsored Intergroup randomized trial comparing concurrent chemoradiotherapy alone to concurrent chemoradiotherapy followed by attempted surgical resection, no survival benefit was observed in the trimodality arm compared to the bimodality therapy. In fact, patients subjected to a pneumonectomy had a worse survival outcome. By contrast, those treated with a lobectomy appeared to have a survival advantage based on a retrospective subset analysis. T us, in carefully selected, otherwise healthy patients with nonbulky mediastinal lymph node involvement, surgery may be a reasonable option if the primary tumor can be fully resected with a lobectomy. T is is not the case if a pneumonectomy is required to achieve complete resection.

Superior Sulcus Tumors (Pancoast Tumors) Superior sulcus tumors represent a distinctive subset of stage III disease. T ese tumors arise in the apex of the lung and may invade the second and third ribs, the brachial plexus, the subclavian vessels, the stellate ganglion, and adjacent vertebral bodies. T ey also may be associated with Pancoast syndrome, characterized by pain that may arise in the shoulder or chest wall or radiate to the neck. Pain characteristically radiates to the ulnar surface of the hand. Horner's syndrome (enophthalmos, ptosis, miosis, and anhydrosis) due to invasion of the paravertebral sympathetic chain may be present as well. Patients with these tumors should undergo the same staging procedures as all patients with stage II and III NSCLC. Neoadjuvant chemotherapy or combined chemoradiotherapy followed by surgery is reserved for those without N2 involvement. T is approach yields excellent survival outcomes (>50% 5-year survival in patients with an R0 resection). Patients with N2 disease are less likely to benefit from surgery and can be managed with chemoradiotherapy alone. Patients presenting with metastatic disease can be treated with radiation therapy (with or without chemotherapy) for symptom palliation.

MANAGEMENT OF METASTATIC NSCLC Approximately 40% of NSCLC patients present with advanced, stage IV disease at the time of diagnosis. T ese patients have a poor median survival (4–6 months) and a 1-year survival of 10% when managed with best supportive care alone. In addition, a significant number of patients who first presented with early-stage NSCLC will eventually relapse with distant disease. Patients who have recurrent disease have a better prognosis than those presenting with metastatic disease at the time of diagnosis. Standard medical management, the judicious use of pain medications, and the appropriate use of radiotherapy and chemotherapy form the cornerstone of management. Chemotherapy palliates symptoms, improves the quality of life, and improves survival in patients with stage IV NSCLC, particularly in patients with good performance status. In addition, economic analysis has

found chemotherapy to be cost-effective palliation for stage IV NSCLC. However, the use of chemotherapy for NSCLC requires clinical experience and careful judgment to balance potential benefits and toxicities. Of note, the early application of palliative care in conjunction with chemotherapy is associated with improved survival and a better quality of life.

First-Line Chemotherapy for Metastatic or Recurrent NSCLC A landmark meta-analysis published in 1995 provided the earliest meaningful indication that chemotherapy could provide a survival benefit in metastatic NSCLC as opposed to supportive care alone. However, the survival benefit was seemingly confined to cisplatin-based chemotherapy regimens (hazard ratio 0.73; 27% reduction in the risk of death; 10% improvement in survival at 1 year). These data launched two decades of clinical research aimed at detecting the optimal chemotherapy regimen for advanced NSCLC. For the most part, however, these efforts proved unsuccessful because the overwhelming majority of randomized trials showed no major survival improvement with any one regimen versus another **(Table 36-11)**. On the other hand, differences in progression-free survival, cost, side effects, and schedule were frequently observed. These first-line studies were later extended to elderly patients, where doublet chemotherapy was found to improve overall survival compared to single agents in the "fit" elderly (e.g., elderly patients with no major comorbidities) and in patients with an ECOG performance status of 2. An ongoing debate in the treatment of patients with advanced NSCLC is the appropriate duration of platinum-based chemotherapy. Several large phase III randomized trials have failed to show a meaningful benefit for increasing the duration of platinum-based doublet chemotherapy beyond four to six cycles. In fact, longer duration of chemotherapy has been associated with increased toxicities and impaired quality of life. Therefore, prolonged front-line therapy (beyond four to six cycles) with platinum-based regimens is not recommended. Maintenance therapy following initial platinum-based therapy is discussed below.

Although specific tumor histology was once considered irrelevant to treatment choice in NSCLC, with the recent recognition that selected chemotherapy agents perform quite differently in squamous versus adenocarcinomas, accurate

TABLE 36-11

FIRST-LINE CHEMOTHERAPY TRIALS FOR METASTATIC NON-SMALL-CELL LUNG CANCER

TRIAL	REGIMEN	NO. OF PATIENTS	RR (%)	MEDIAN SURVIVAL (MONTHS)
ECOG1594	Cisplatin + paclitaxel	288	21	7.8
	Cisplatin + gemcitabine	288	22	8.1
	Cisplatin + docetaxel	289	17	7.4
	Carboplatin + paclitaxel	290	17	8.1
TAX-326	Cisplatin + docetaxel	406	32	11.3
	Cisplatin + vinorelbine	394	25	10.1
	Carboplatin + docetaxel	404	24	9.4
EORTC	Cisplatin + paclitaxel	159	32	8.1
	Cisplatin + gemcitabine	160	37	8.9
	Paclitaxel + gemcitabine	161	28	6.7
ILCP	Cisplatin + gemcitabine	205	30	9.8
	Carboplatin + paclitaxel	204	32	9.9
	Cisplatin + vinorelbine	203	30	9.5
SWOG	Cisplatin + vinorelbine	202	28	8.0
	Carboplatin + paclitaxel	206	25	8.0
FACS	Cisplatin + irinotecan	145	31	13.9
	Carboplatin + paclitaxel	145	32	12.3
	Cisplatin + gemcitabine	146	30	14.0
	Cisplatin + vinorelbine	145	33	11.4
Scagliotti	Cisplatin + gemcitabine	863	28	10.3
	Cisplatin + pemetrexed	862	31	10.3
iPASS[a]	Carboplatin + paclitaxel	608	32	17.3
	Gefitinib	609	43	18.6

[a]Enrolled selected patients: 18 years of age or older, had histologic or cytologically confirmed stage IIIB or IV non-small-cell lung cancer with histologic features of adenocarcinoma (including bronchioloalveolar carcinoma), were nonsmokers (defined as patients who had smoked <100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of ≤10 pack-years of smoking), and had had no previous chemotherapy or biologic or immunologic therapy.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; ILCP, Italian Lung Cancer Project; SWOG, Southwest Oncology Group; FACS, Follow-up After Colorectal Surgery; iPASS, Iressa Pan-Asian Study.

determination of histology has become essential. Specifically, in a landmark randomized phase III trial, patients with nonsquamous NSCLC were found to have an improved survival when treated with cisplatin and pemetrexed compared to cisplatin and gemcitabine. By contrast, patients with squamous carcinoma had an improved survival when treated with cisplatin and gemcitabine. T is survival difference is thought to be related to the differential expression of thymidylate synthase (TS), one of the targets of pemetrexed, between tumor types. Squamous cancers have a much higher expression of TS compared to adenocarcinomas, accounting for their lower responsiveness to pemetrexed. By contrast, the activity of gemcitabine is not impacted by the levels of TS. Bevacizumab, a monoclonal antibody against VEGF, has been shown to improve response rate, progression-free survival, and overall survival in patients with advanced disease when combined with chemotherapy (see below). However, bevacizumab cannot be given to patients with squamous cell histology NSCLC because of their tendency to experience serious hemorrhagic effects.

Agents That Inhibit Angiogenesis Bevacizumab, a monoclonal antibody directed against VEGF, was the first antiangiogenic agent approved for the treatment of patients with advanced NSCLC in the United States. T is drug primarily acts by blocking the growth of new blood vessels, which are required for tumor viability. Two randomized phase III trials of chemotherapy with or without bevacizumab had conflicting results. T e first trial, conducted in North America, compared carboplatin plus paclitaxel with or without bevacizumab in patients with recurrent or advanced nonsquamous NSCLC and reported a significant improvement in response rate, progression-free survival, and overall survival in patients treated with chemotherapy plus bevacizumab versus chemotherapy alone. Bevacizumab-treated patients had a significantly higher incidence of toxicities. T e second trial, conducted in Europe, compared cisplatin/gemcitabine with or without bevacizumab in patients with recurrent or advanced nonsquamous NSCLC and reported a significant improvement in progression-free survival but no improvement in overall survival for bevacizumab-treated patients. A randomized phase III trial compared carboplatin/pemetrexed and bevacizumab to carboplatin/paclitaxel and bevacizumab as first-line therapy in patients with recurrent or advanced nonsquamous NSCLC and reported no significant difference in progression-free survival or overall survival between treatment groups. T erefore, currently carboplatin/paclitaxel and bevacizumab or carboplatin/pemetrexed and bevacizumab are appropriate regimens for first-line treatment for stage IV nonsquamous NSCLC patients. Of note, there are many small-molecule inhibitors of VEGFR; however, these VEGFR TKIs have not proven to be effective in the treatment of NSCLC.

Maintenance Therapy for Metastatic NSCLC Maintenance chemotherapy in nonprogressing patients (patients with a complete response, partial response, or stable disease) is a controversial topic in the treatment of NSCLC. Conceptually, there are two types of maintenance strategies: (1) switch maintenance therapy, where patients receive four to six cycles of platinum-based chemotherapy and are switched to an entirely different regimen; and (2) continuation maintenance therapy, where patients receive four to six cycles of platinum-based chemotherapy and then the platinum agent is discontinued but the agent it is paired with is continued **(Table 36-12)**. Two studies investigated switch maintenance single-agent chemotherapy with docetaxel or pemetrexed in nonprogressing patients following treatment with first-line platinum-based chemotherapy. Both trials randomized patients to immediate single-agent therapy versus observation and reported improvements in progression-free and overall survival. In both trials, a significant portion of patients in the observation arm did not receive therapy with the agent under investigation upon disease progression; 37% of study patients never received docetaxel in the docetaxel study and 81% of patients never received pemetrexed in the pemetrexed study. In the trial of maintenance docetaxel versus observation, survival was identical to the treatment group in the subset of patients who received docetaxel on progression, indicating this is an active agent in NSCLC. T ese data are not available for the pemetrexed study. Two additional trials evaluated switch maintenance therapy with erlotinib after platinum-based chemotherapy in patients with advanced NSCLC and reported an improvement in progression-free survival and overall survival in the erlotinib treatment group. Currently, maintenance pemetrexed or erlotinib following platinum-based chemotherapy in patients with advanced NSCLC are approved by the U.S. FDA. However, maintenance therapy is not without toxicity and, at this time, should be considered on an individual patient basis.

Targeted Therapies for Select Molecular Cohorts of NSCLC As the ef - cacy of traditional cytotoxic chemotherapeutic agents plateaued in NSCLC, there was a critical need to define novel therapeutic treatment strategies. T ese novel strategies have largely been based on the identification of somatic driver mutations within the tumor. T ese driver mutations occur in genes encoding signaling proteins that, when aberrant, drive initiation and maintenance of tumor cells. Importantly, driver mutations can serve as Achilles' heels for tumors, if their gene products can be targeted therapeutically with small-molecule inhibitors. For example, EGFR mutations have been detected in 10–15% of North American patients diagnosed with NSCLC. EGFR mutations are associated with younger age, light (<10 pack-year) and nonsmokers, and adenocarcinoma histology. Approximately 90% of these mutations are exon 19 deletions or exon 21 L858R point mutations within the EGFR TK domain, resulting in hyperactivation of both EGFR kinase activity and downstream signaling. Lung tumors that harbor activating mutations within the EGFR kinase domain display high sensitivity to small-molecule EGFR TKIs. Erlotinib and afatinib are FDA-approved oral small-molecule TKIs that inhibit EGFR. Outside the United States, gefitinib also is available. Several large, international, phase III studies have demonstrated improved response rates, progression-free survival,

TABLE 36-12

MAINTENANCE THERAPY TRIALS

GROUP	CT	SURVIVAL		
		NO. OF PATIENTS	OS (MONTHS)	PFS (MONTHS)
Switch Maintenance				
Fidias	Immediate docetaxel	153	12.3	5.7
	Delayed docetaxel	156	9.7	2.7
Ciuleanu	Pemetrexed	444	13.4	4.3
	BSC	222	10.6	2.6
Paramount	Pemetrexed	472	13.9	4.1
	BSC	297	11.0	2.8
ATLAS	Bev + erlotinib	384	15.9	4.8
	Bev + placebo	384	13.9	3.8
SATURN	Erlotinib	437	12.3	2.9
	Placebo	447	11.1	2.6
Continuation Maintenance				
ECOG4599	Bev 15 mg/kg	444	12.3	6.2
	BSC	434	10.3	4.5
AVAiL	Bev 15 mg/kg	351	13.4	6.5
	Bev 7.5 mg/kg	345	13.6	6.7
	Placebo	347	13.1	6.1
POINTBREAK	Pemetrexed + Bev 15 mg/kg			8.6
	Bev 15 mg/kg			6.9

Abbreviations: Bev, bevacizumab; BSC, best supportive care; CT, chemotherapy; OS, overall survival; PFS, progression-free survival.

and overall survival in patients with EGFR mutation–positive NSCLC patients treated with an EGFR TKI as compared with standard first-line chemotherapy regimens **(Table 36-13)**.

Although response rates with EGFR TKI therapy are clearly superior in patients with lung tumors harboring activating EGFR kinase domain mutations, the EGFR TKI erlotinib is also FDA approved for second- and third-line therapy in patients with advanced NSCLC irrespective of tumor genotype. The reason for this apparent discrepancy is that erlotinib was initially evaluated in lung cancer before the discovery of EGFR activating mutations. In fact, EGFR mutations were initially identified in lung cancer by studying the tumors of patients who had dramatic responses to this agent. With the rapid pace of scientific discovery, additional driver mutations in lung cancer have been identified and targeted therapeutically with impressive clinical results. For example, chromosomal rearrangements involving the anaplastic lymphoma kinase (ALK) gene on chromosome 2 have been found in ~3-7% of NSCLC. The result of these ALK rearrangements is hyperactivation of the ALK TK domain. Similar to EGFR, ALK rearrangements are typically (but not exclusively) associated with younger age, light (<10 pack-year) and nonsmokers, and adenocarcinoma histology. Remarkably, ALK rearrangements were initially described

TABLE 36-13

RESULTS OF PHASE III TRIALS COMPARING CHEMOTHERAPY AND FIRST-LINE EGFR TKI IN EGFR MUTATION–POSITIVE PATIENTS

STUDY	THERAPY	NO. OF PATIENTS	ORR (%)	PFS (MONTHS)
IPASS	CbP	129	47	6.3
	Gefitinib	132	71	9.3
EURTAC	CG	87	15	5.2
	Erlotinib	86	58	9.7
OPTIMAL	CG	72	36	4.6
	Erlotinib	82	83	13.1
NEJOO2	CG	114	31	5.4
	Gefitinib	114	74	10.8
WJTOG3405	CD	89	31	6.3
	Gefitinib	88	62	9.2
LUXLUNG 3	CP	115	23	6.9
	Afatinib	230	56	11.1

Abbreviations: CbP, carboplatin and paclitaxel; CD, cisplatin and docetaxel; CG, cisplatin and gemcitabine; CP, cisplatin and paclitaxel; ORR, overall response rate; PFS, progression-free survival.

in lung cancer in 2007, and by 2011, the first ALK inhibitor, crizotinib, received FDA approval for patients with lung tumors harboring ALK rearrangements.

In addition to EGFR and ALK, other driver mutations have been discovered with varying frequencies in NSCLC, including KRAS, BRAF, PIK3CA, NRAS, AKT1, MET, MEK1 (MAP2K1), ROS1, and RET. Mutations within the KRAS GTPase are found in approximately 20% of lung adenocarcinomas. To date, however, no small-molecule inhibitors are available to specifically target mutant KRAS. Each of the other driver mutations occurs in less than 1–3% of lung adenocarcinomas. T e great majority of the driver mutations are mutually exclusive, and there are ongoing clinical studies for their specific inhibitors. For example, the BRAF inhibitor vemurafenib and the RET inhibitor cabozantinib have already demonstrated ef cacy in patients with lung cancer harboring BRAF mutations or RET gene fusions, respectively. Most of these mutations are present in adenocarcinoma; however, mutations that may be linked to future targeted therapies in squamous cell carcinomas are emerging. In addition, there are active research efforts aimed at defining novel targetable mutations in lung cancer as well as defining mechanisms of acquired resistance to small-molecule inhibitors used in the treatment of patients with NSCLC.

Second-Line Chemotherapy and Beyond Second-line therapy for advanced NSCLC was almost never recommended until a seminal study in 2000 showed that docetaxel improved survival compared to supportive care alone. As first-line chemotherapy regimens improve, a substantial number of patients will maintain a good performance status and a desire for further therapy when they develop recurrent disease. Currently, several agents are FDA approved for second-line use in NSCLC including docetaxel, pemetrexed, erlotinib (approved for second-line therapy regardless of tumor genotype), and crizotinib (for patients with ALK-mutant lung cancer only). Most of the survival benefit for any of these agents is realized in patients who maintain a good performance status.

Immunotherapy For more than 30 years, the investigation of vaccines and immunotherapies in lung cancer has yielded little in the way of meaningful benefit. Recently, however, this perception has changed based on preliminary results of studies using monoclonal antibodies that activate antitumor immunity through blockade of immune checkpoints. For example, ipilimumab, a monoclonal antibody directed at cytotoxic T lymphocyte antigen-4 (CTLA-4), was studied in combination with paclitaxel plus carboplatin in patients with both SCLC and NSCLC. T ere appeared to be a small but not statistically significant advantage to the combination when ipilimumab was instituted after several cycles of chemotherapy. A randomized phase III trial in SCLC is under way to validate these data. Antibodies to the T cell programmed cell death receptor 1 (PD-1), nivolumab and pembrolizumab, have been shown to produce responses in lung cancer, renal cell cancer, and melanoma. Many of these responses have had very long duration (i.e., >1 year). Monoclonal antibodies to the PD-1 ligand (anti-PDL-1), which may be expressed on the tumor cell, have also been shown to produce responses in patients with melanoma and lung cancer. Preliminary studies in melanoma suggest that the combination of ipilimumab and nivolumab could produce higher response rates compared to either agent alone. A similar strategy is being investigated in SCLC patients. Further evaluation of these agents in both NSCLC and SCLC is ongoing in combination with already approved chemotherapy and targeted agents.

Supportive Care No discussion of the treatment strategies for patients with advanced lung cancer would be complete without a mention of supportive care. Coincident with advances in chemotherapy and targeted therapy was a pivotal study that demonstrated that the early integration of palliative care with standard treatment strategies improved both quality of life and mood for patients with advanced lung cancer. Aggressive pain and symptom control is an important component for optimal treatment of these patients.

TREATMENT Small-Cell Lung Cancer

SURGERY FOR LIMITED-DISEASE SMALL-CELL LUNG CANCER SCLC is a highly aggressive disease characterized by its rapid doubling time, high growth fraction, early development of disseminated disease, and dramatic response to first-line chemotherapy and radiation. In general, surgical resection is not routinely recommended for patients because even patients with LD-SCLC still have occult micrometastases. However, the most recent American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend surgical resection over non-surgical treatment in SCLC patients with clinical stage I disease after a thorough evaluation for distant metastases and invasive mediastinal stage evaluation (grade 2C). After resection, these patients should receive platinum-based adjuvant chemotherapy (grade 1C). If the histologic diagnosis of SCLC is made in patients on review of a resected surgical specimen, such patients should receive standard SCLC chemotherapy as well.

CHEMOTHERAPY Chemotherapy significantly prolongs survival in patients with SCLC. Four to six cycles of platinum-based chemotherapy with either cisplatin or carboplatin plus either etoposide or irinotecan has been the mainstay of treatment for nearly three decades and is recommended over other chemotherapy regimens irrespective of initial stage. Cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV) may be an alternative for patients who are unable to tolerate a platinum-based regimen. Despite response rates to first-line therapy as high as 80%, the median survival ranges from 12 to 20 months for patients with LD and from 7 to 11 months for patients with ED. Regardless of disease extent, the majority of patients relapse and develop chemotherapy-resistant disease. Only 6–12% of patients with LD-SCLC and 2% of patients

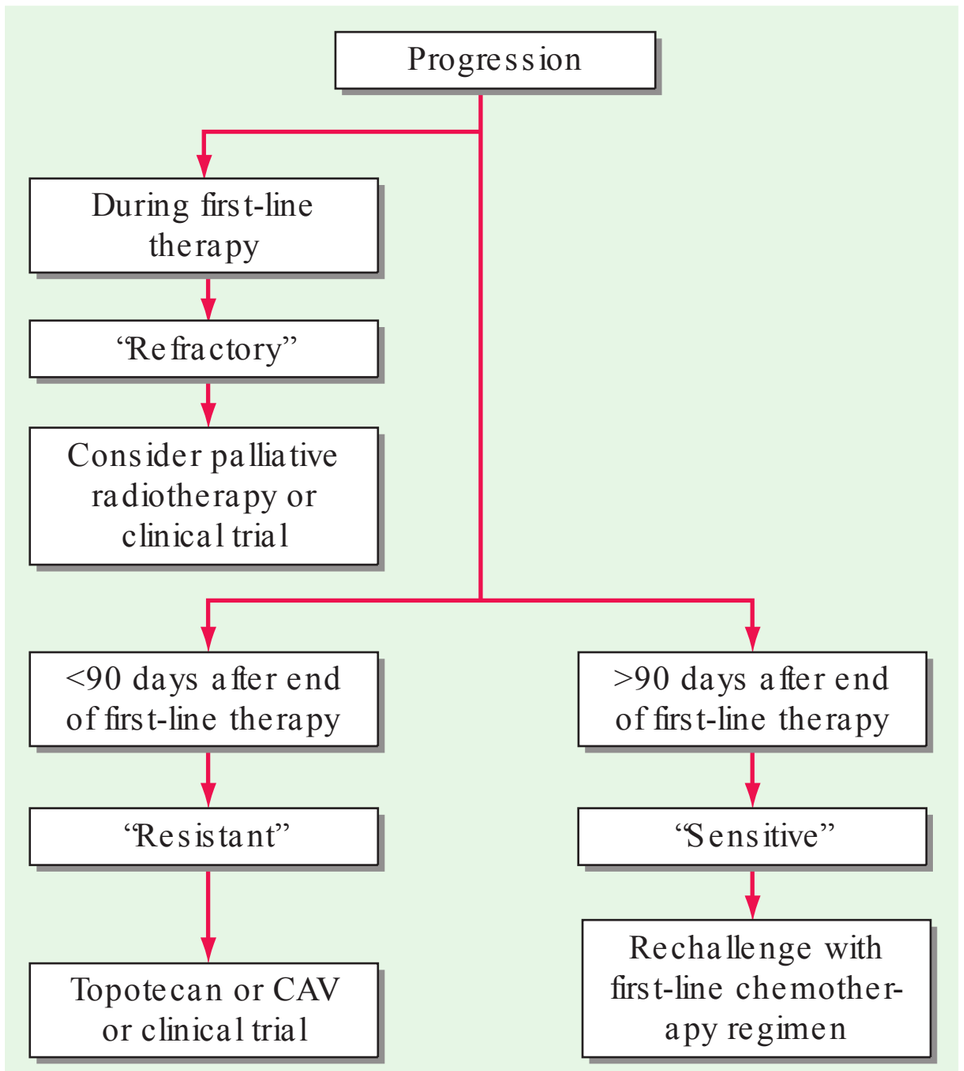


FIGURE 36-7
Management of recurrent small-cell lung cancer (SCLC). CAV, cyclophosphamide, doxorubicin, and vincristine. (Adapted with permission from JP van Meerbeeck et al: Lancet 378:1741, 2011.)

with ED-SCLC live beyond 5 years. The prognosis is especially poor for patients who relapse within the first 3 months of therapy; these patients are said to have chemotherapy-resistant disease. Patients are said to have sensitive disease if they relapse more than 3 months after their initial therapy and are thought to have a somewhat better overall survival. These patients also are thought to have the greatest potential benefit from second-line chemotherapy **(Fig. 36-7)**. Topotecan is the only FDA-approved agent for second-line therapy in patients with SCLC. Topotecan has only modest activity and can be given either intravenously or orally. In one randomized trial, 141 patients who were not considered candidates for further IV chemotherapy were randomized to receive either oral topotecan or best supportive care. Although the response rate to oral topotecan was only 7%, overall survival was significantly better in patients receiving chemotherapy (median survival time, 26 weeks vs 14 weeks; p = .01). Moreover, patients given topotecan had a slower decline in quality of life than did those not receiving chemotherapy. Other agents with similar low levels of activity in the second-line setting include irinotecan, paclitaxel, docetaxel, vinorelbine, oral etoposide, and gemcitabine. Clearly novel treatments for this all too common disease are desperately needed.

THORACIC RADIATION THERAPY Thoracic radiation therapy (TRT) is a standard component of induction therapy for good performance status and limited-stage SCLC patients. Meta-analyses indicate that chemotherapy combined with chest irradiation improves 3-year survival by approximately 5% as compared with chemotherapy alone. The 5-year survival rate, however, remains disappointingly low at ~10–15%. Most commonly, TRT is combined with cisplatin and etoposide chemotherapy due to a superior toxicity profile as compared to anthracycline-containing chemotherapy regimens. As observed in locally advanced NSCLC, concurrent chemoradiotherapy is more effective than sequential chemoradiation but is associated with significantly more esophagitis and hematologic toxicity. Ideally TRT should be administered with the first two cycles of chemotherapy because later application appears slightly less effective. If for reasons of fitness or availability, this regimen cannot be offered, TRT should follow induction chemotherapy. With respect to fractionation of TRT, twice-daily 1.5-Gy fractioned radiation therapy has been shown to improve survival in LD-SCLC patients but is associated with higher rates of grade 3 esophagitis and pulmonary toxicity. Although it is feasible to deliver once-daily radiation therapy doses up to 70 Gy concurrently with cisplatin-based chemotherapy, there are no data to support equivalency of this approach compared with the 45-Gy twice-daily radiotherapy dose. Therefore, the current standard regimen of a 45-Gy dose administered in 1.5-Gy fractions twice daily for 30 days is being compared with higher-dose regimens in two phase III trials, one in the United States and one in Europe. Patients should be carefully selected for concurrent chemoradiation therapy based on good performance status and adequate pulmonary reserve. The role of radiotherapy in ED-SCLC is largely restricted to palliation of tumor-related symptoms such as bone pain and bronchial obstruction.

PROPHYLACTIC CRANIAL IRRADIATION Prophylactic cranial irradiation (PCI) should be considered in all patients with either LD-SCLC or ED-SCLC who have responded well to initial therapy. A meta-analysis including seven trials and 987 patients with LD-SCLC who had achieved a complete remission after upfront chemotherapy yielded a 5.4% improvement in overall survival for patients treated with PCI. In patients with ED-SCLC who have responded to first-line chemotherapy, a prospective randomized phase III trial showed that PCI reduced the occurrence of symptomatic brain metastases and prolonged disease-free and overall survival compared to no radiation therapy. Long-term toxicities, including deficits in cognition, have been reported after PCI but are difficult to sort out from the effects of chemotherapy or normal aging.

SUMMARY

The management of NSCLC has undergone major change in the past decade. To a lesser extent, the same is true for SCLC. For patients with early-stage disease, advances in radiotherapy and surgical procedures as well as new systemic therapies have greatly improved prognosis in both diseases. For patients with advanced disease, major progress in understanding tumor genetics has led to the development of targeted inhibitors

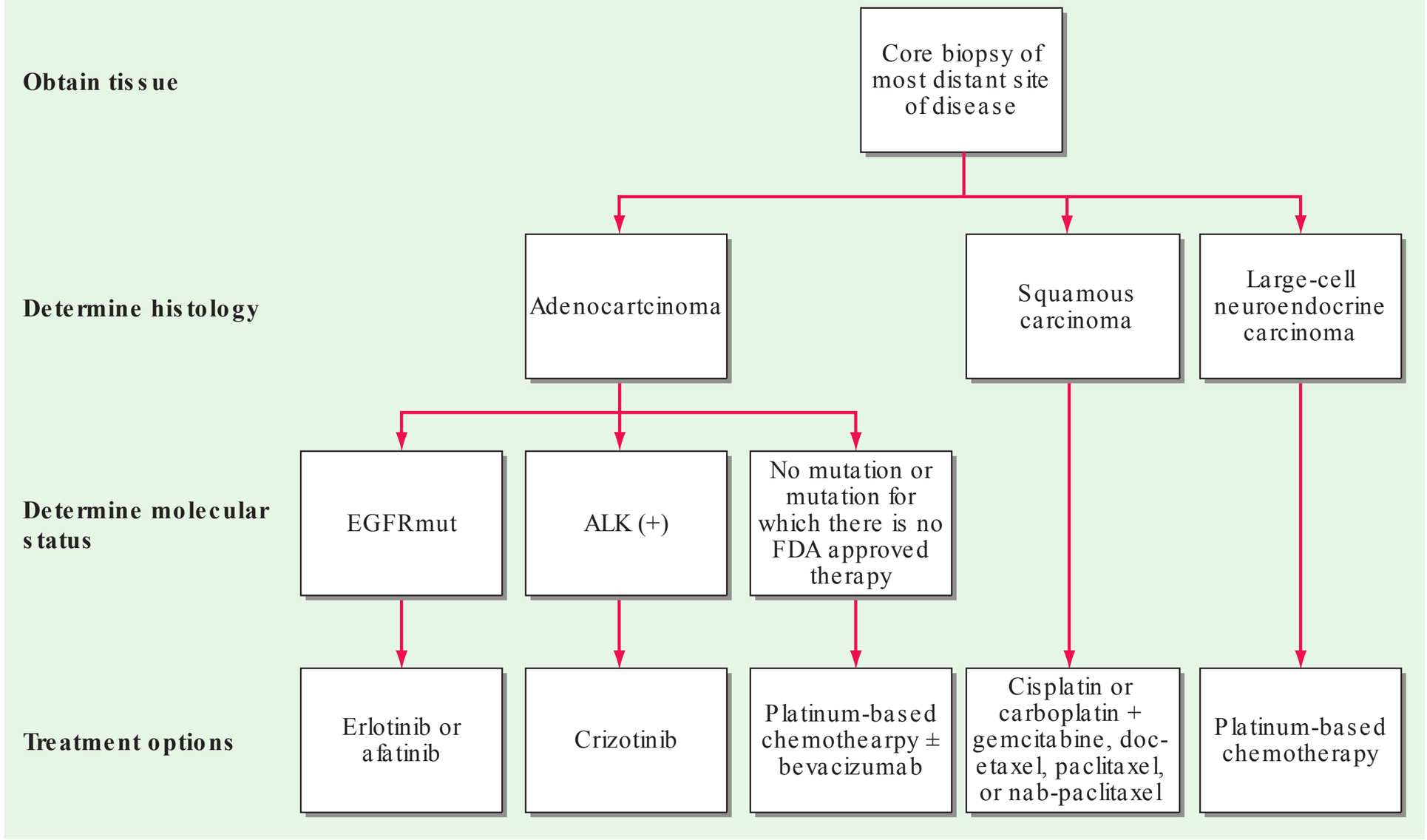


FIGURE 36-8
Approach to first-line therapy in a patient with stage IV non-small-cell lung cancer NSCLC. EGFRmut, EGFR mutation; FDA, Food and Drug Administration.

based specifically on the tumor's molecular profile. Furthermore, increased understanding of how to activate the immune system to drive antitumor immunity is proving to be a promising therapeutic strategy for some patients with advanced lung cancer. In **Fig. 36-8**, we propose an algorithm of the treatment approach for patient with stage IV NSCLC. However, the reality is that the majority of patients treated with targeted therapies or chemotherapy eventually develop resistance, which provides strong motivation for further research and enrollment of patients onto clinical trials in this rapidly evolving area.

CHAPTER 37

THYMOMA

Dan L. Longo

The thymus is derived from the third and fourth pharyngeal pouches and is located in the anterior mediastinum. It is composed of epithelial and stromal cells derived from the pharyngeal pouch and lymphoid precursors derived from mesodermal cells. It is the site to which bone marrow precursors that are committed to differentiate into T cells migrate to complete their differentiation. Like many organs, it is organized into functional regions, in this case the cortex and the medulla. The cortex of the thymus contains ~85% of the lymphoid cells, and the medulla contains ~15%. It appears that the primitive bone marrow progenitors enter the thymus at the corticomedullary junction and migrate first through the cortex toward the periphery of the gland and then toward the medulla as they mature. Medullary thymocytes have a phenotype that cannot be distinguished readily from that of mature peripheral blood and lymph node T cells.

Several things can go wrong with the thymus, but thymic abnormalities are very rare. If the thymus does not develop properly, serious deficiencies in T-cell development ensue and severe immunodeficiency is seen. If a lymphoid cell within the thymus becomes neoplastic, the disease that develops is a lymphoma. The majority of lymphoid tumors that develop in the thymus are derived from the precursor T cells, and the tumor is a precursor T-cell lymphoblastic lymphoma **(Chap. 16)**. Rare B cells exist in the thymus, and when they become neoplastic, the tumor is a mediastinal (thymic) B cell lymphoma **(Chap. 16)**. Hodgkin's disease, particularly the nodular sclerosing subtype, often involves the anterior mediastinum. Extranodal marginal zone (mucosa-associated lymphoid tissue [MALT]) lymphomas have been reported to involve the thymus in the setting of Sjögren's syndrome or other autoimmune disorders, and the lymphoma cells often express IgA instead of IgM on their surface. Castleman's disease can involve the thymus. Germ cell tumors and carcinoid tumors occasionally may arise in the thymus. If the epithelial cells of the thymus become neoplastic, the tumor that develops is a thymoma.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Thymoma, although rare (0.1–0.15 cases per 100,000 person-years), is the most common cause of an anterior mediastinal mass in adults, accounting for ~40% of all mediastinal masses. The other major causes of anterior mediastinal masses are lymphomas, germ cell tumors, and substernal thyroid tumors. Carcinoid tumors, lipomas, and thymic cysts also may produce radiographic masses. After combination chemotherapy for another malignancy, teenagers and young adults may develop a rebound thymic hyperplasia in the first few months after treatment. Granulomatous inflammatory diseases (tuberculosis, sarcoidosis) can produce thymic enlargement. Thymomas are most common in the fifth and sixth decades, are uncommon in children, and are distributed evenly between men and women.

About 40–50% of patients are asymptomatic; masses are detected incidentally on routine chest radiographs. When symptomatic, patients may have cough, chest pain, dyspnea, fever, wheezing, fatigue, weight loss, night sweats, or anorexia. Occasionally, thymomas may obstruct the superior vena cava. Pericardial effusion may be present. About 40% of patients with thymoma have another systemic autoimmune illness related to the thymoma. About 30% of patients with thymoma have myasthenia gravis, 5–8% have pure red cell aplasia, and ~5% have hypogammaglobulinemia. Thymoma with hypogammaglobulinemia also is called Good's syndrome. Among patients with myasthenia gravis, ~10–15% have a thymoma. Thymoma more rarely may

be associated with polymyositis, systemic lupus erythematosus, thyroiditis, Sjögren's syndrome, ulcerative colitis, pernicious anemia, Addison's disease, stiff person syndrome, scleroderma, and panhypopituitarism. In one series, 70% of patients with thymoma were found to have another systemic illness.

DIAGNOSIS AND STAGING

Once a mediastinal mass is detected, a surgical procedure is required for definitive diagnosis. An initial mediastinoscopy or limited thoracotomy can be undertaken to get suf cient tissue to make an accurate diagnosis. Fine-needle aspiration is poor at distinguishing between lymphomas and thymomas but is more reliable in diagnosing germ cell tumors and metastatic carcinoma. T ymomas and lymphomas require suf cient tissue to examine the tumor architecture to assure an accurate diagnosis and obtain prognostic information.

Once a diagnosis of thymoma is defined, subsequent staging generally occurs at surgery. However, chest computed tomography (CT) scans can assess local invasiveness in some instances. Magnetic resonance imaging (MRI) has a defined role in the staging of posterior mediastinal tumors, but it is not clear that it adds important information to the CT scan in anterior mediastinal tumors. Somatostatin receptor imaging with indium-labeled somatostatin analogues may be of value. If invasion is not distinguished by noninvasive testing, an effort to resect the entire tumor should be undertaken. If invasion is present, neoadjuvant chemotherapy may be warranted before surgery (see "Treatment" section below).

Some 90% of thymomas are in the anterior mediastinum, but some may be in other mediastinal sites or even the neck, based on aberrant migration of the developing thymic enlage.

T e staging system for thymoma was developed by Masaoka and colleagues **(Table 37-1)**. It is an anatomic system in which the stage is increased on the basis of the degree of invasiveness. T e 5-year survival of patients in the various stages is as follows: stage I, 96%; stage II, 86%; stage III, 69%; and stage IV, 50%. T e French Study Group on T ymic Tumors (GETT) has proposed modifications to the Masaoka scheme based on the degree of surgical removal because the extent of surgery has been noted to be a prognostic indicator. In their system, stage I tumors are divided into A and B on the basis of whether the surgeon suspects adhesions to adjacent structures; stage III tumors are divided into A and B based on whether disease was subtotally resected or only biopsied. T e concurrence between the two systems is high.

TABLE 37-1

MASAOKA STAGING SYSTEM FOR THYMOMAS

STAGE	DIAGNOSTIC CRITERIA
I	Macroscopically and microscopically completely encapsulated; no invasion through capsule
II	
IIA	Microscopic invasion outside the capsule
IIB	Macroscopic invasion into surrounding fat or grossly adherent to pleura or pericardium
III	
IIIA	Macroscopic invasion into neighboring organs, pericardium, or pleura but not great vessels
IIIB	Macroscopic invasion into neighboring organs that includes great vessels
IV	
IVA	Pleural or pericardial dissemination
IVB	Lymphatic or hematogenous metastases

	STAGE DISTRIBUTION, %	5-YEAR SURVIVAL, %	10-YEAR SURVIVAL, %
I	36	95–100	86–100
II	26	70–100	50–100
III	22	68–89	47–60
IV	10	47–69	0–11

Source: From A Masaoka et al: Cancer 48:2485, 1981. Updated from S Tomaszek et al: Ann Thorac Surg 87:1973, 2009, and CB Falkson et al: J Thorac Oncol 4:911, 2009.

PATHOLOGY AND ETIOLOGY

T ymomas are epithelial tumors, and all of them have malignant potential. It is not worthwhile to try to divide them into benign and malignant forms; the key prognostic feature is whether they are noninvasive or invasive. About 65% of thymomas are encapsulated and noninvasive, and about 35% are invasive. T ey may have a variable percentage of lymphocytes within the tumor, but genetic studies suggest that the lymphocytes are benign polyclonal cells. T e epithelial component of the tumor may consist primarily of round or oval cells derived mainly from the cortex or spindle-shaped cells derived mainly from the medulla or combinations of the two types (World Health Organization classification; **Table 37-2)**. Cytologic features are not reliable predictors of biologic behavior. In part, this unreliability may be related to the moderate reproducibility of the system. About 90% of A, AB, and B1 tumors are localized. A very small number of patients have aggressive histology features characteristic of carcinomas. T ymic carcinomas are invasive and have a poor prognosis.

Genetic lesions are common in thymomas. T e most common abnormalities affect chromosome 6p21.3 (the MHC locus) and 6p25.2-25.3 (usually loss of heterozygosity). Abnormalities affecting a number of other genes altered in other types of tumors are also seen,

TABLE 37-2

WORLD HEALTH ORGANIZATION (WHO) HISTOLOGIC CLASSIFICATION OF THYMUS TUMORS

TYPE	HISTOLOGIC DESCRIPTION
A	Medullary thymoma
AB	Mixed thymoma
B1	Predominantly cortical thymoma
B2	Cortical thymoma
B3	Well-differentiated thymic carcinoma
C	Thymic carcinoma

TYPE	DISTRIBUTION, %	PROGNOSIS (10-YEAR DISEASE-FREE SURVIVAL), %
A	8	100
AB	26	90–100
B1	15	78–94
B2	28	83
B3	15	36
C	8	0–35

Source: From S Tomaszek et al: Ann Thorac Surg 87:1973, 2009.

including p53, RB, FHIT, and APC. Thymic carcinomas may overexpress c-kit, HER2, or growth factor receptor genes (epidermal growth factor receptor and insulin-like growth factor receptor). Some data suggest that Epstein-Barr virus may be associated with thymomas. Some tumors overexpress the p21 ras gene product. However, molecular pathogenesis remains undefined. A thymoma susceptibility locus has been defined on rat chromosome 7, but the relationship between this gene locus, termed Tsr1, and human thymoma has not been examined.

INFLUENCE OF THYMECTOMY ON THE COURSE OF ACCOMPANYING DISEASES

Patients with myasthenia gravis have a high incidence of thymic abnormalities (~80%), but overt thymoma is present in only ~10–15% of patients with myasthenia gravis. It is thought that the thymus plays a role in breaking self-tolerance and generating T cells that recognize the acetylcholine receptor as a foreign antigen. Although patients with thymoma and myasthenia gravis are less likely to have a remission in the myasthenia as a consequence of thymectomy than are patients with thymic abnormalities other than thymoma, the course of myasthenia gravis is not significantly different in patients with or without thymoma. Thymectomy produces at least some symptomatic improvement in ~65% of patients with myasthenia gravis. In one large series, thymoma patients with myasthenia gravis had a better long-term survival from thymoma resection than did those without myasthenia gravis.

About 30–50% of patients with pure red cell aplasia have a thymoma. Thymectomy results in the resolution of pure red cell aplasia in ~30% of patients. About 10% of patients with hypogammaglobulinemia have a thymoma, but hypogammaglobulinemia rarely responds to thymectomy.

TREATMENT Thymoma

Treatment is determined by the stage of disease. For patients with encapsulated tumors and stage I disease, complete resection is sufficient to cure 96% of patients. For patients with stage II disease, complete resection may be followed by 30–60 Gy of postoperative radiation therapy to the site of the primary tumor. However, the value of radiation therapy in this setting has not been established. The main predictors of long-term survival are Masaoka stage and completeness of resection. For patients with stage III and IV disease, the use of neoadjuvant chemotherapy followed by radical surgery, with or without additional radiation therapy, and additional consolidation chemotherapy has been associated with excellent survival. Chemotherapy regimens that are most effective generally include a platinum compound (either cisplatin or carboplatin) and an anthracycline. Addition of cyclophosphamide, vincristine, and prednisone seems to improve response rates. Response rates of 50–93% have been reported in series of patients each of which involved fewer than 40 patients. A single most effective regimen has not been defined. No randomized controlled phase III studies have been reported. If surgery after neoadjuvant chemotherapy fails to produce a complete resection of residual disease, radiation therapy (50–60 Gy) may help reduce recurrence rates.

This multimodality approach appears to be superior to the use of surgery followed by radiation therapy alone, which produces a 5-year survival of ≤50% in patients with advanced-stage disease.

Some thymic carcinomas express c-kit, and one patient whose c-kit locus was mutated responded dramatically to imatinib. Many thymomas express epidermal growth factor receptors, but the antibodies to the receptor and the kinase inhibitors that block its action have not been evaluated systematically. Octreotide plus prednisone produces responses in about one-third of patients.

CHAPTER 38

BREAST CANCER

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Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast. In the year 2014, about 180,000 cases of invasive breast cancer and 40,000 deaths will occur in the United States. In addition, about 2000 men will be diagnosed with breast cancer. Epithelial malignancies of the breast are the most common cause of cancer in women (excluding skin cancer), accounting for about one-third of all cancer in women. As a result of improved treatment and earlier detection, the mortality rate from breast cancer has begun to decrease very substantially in the United States. T is Chapter will not consider rare malignancies presenting in the breast, such as sarcomas and lymphomas, but will focus on the epithelial cancers.

GENETIC CONSIDERATIONS

Human breast cancer is a clonal disease; a single transformed cell—the product of a series of somatic (acquired) or germline mutations—is eventually able to express full malignant potential. T us, breast cancer may exist for a long period as either a noninvasive disease or an invasive but nonmetastatic disease. T ese facts have significant clinical ramifications.

Not more than 10% of human breast cancers can be linked directly to germline mutations. Several genes have been implicated in familial cases. T e Li-Fraumeni syndrome is characterized by inherited mutations in the p53 tumor-suppressor gene, which lead to an increased incidence of breast cancer, osteogenic sarcomas, and other malignancies. Inherited mutations in P*T*EN have also been reported in breast cancer.

Another tumor-suppressor gene, BRCA1, has been identified at the chromosomal locus 17q21; this gene encodes a zinc finger protein, and the protein product functions as a transcription factor and is involved in gene repair. Women who inherit a mutated allele of this gene from either parent have at least a 60–80% lifetime chance of developing breast cancer and about a 33% chance of developing ovarian cancer. T e risk is higher among women born after 1940, presumably due to promotional effects of hormonal factors. Men who carry a mutant allele of the gene have an increased incidence of prostate cancer and breast cancer. A fourth gene, termed BRCA2, which has been localized to chromosome 13q12, is also associated with an increased incidence of breast cancer in men and women.

Germline mutations in BRCA1 and BRCA2 can be readily detected; patients with these mutations should be counseled appropriately. All women with strong family histories for breast cancer should be referred to genetic screening programs, particularly women of Ashkenazi Jewish descent who have a high likelihood of a specific founder BRCA1 mutation (substitution of adenine for guanine at position 185).

Even more important than the role these genes play in inherited forms of breast cancer may be their role in sporadic breast cancer. A p53 mutation is present in nearly 40% of human breast cancers as an acquired defect. Acquired mutations in P*T*EN occur in about 10% of the cases. BRCA1 mutation in sporadic primary breast cancer has not been reported. However, decreased expression of BRCA1 mRNA (possibly via gene methylation) and abnormal cellular location of the BRCA1 protein have been found in some breast cancers. Loss of heterozygosity of BRCA1 and BRCA2 suggests that tumor-suppressor activity may be inactivated in sporadic cases of human breast cancer. Finally, increased expression of a dominant oncogene plays a role in about a quarter of human breast cancer cases. T e product of this gene, a member of the epidermal growth factor receptor superfamily, is called erbB2 (HER/2 neu) and is overexpressed in these breast cancers due to gene amplification; this overexpression can contribute to transformation of human breast epithelium and is the target of effective systemic therapy in

adjuvant and metastatic disease settings. A series of acquired "driver" mutations have been identified in sporadic breast cancer by major sequencing consortia. Unfortunately, most occur in no more than 5% of cases and generally do not have effective agents to target them, so "personalized medicine" is for now more of a dream than a reality.

EPIDEMIOLOGY

Breast cancer is a hormone-dependent disease. Women without functioning ovaries who never receive estrogen replacement therapy do not develop breast cancer. The female-to-male ratio is about 150:1. For most epithelial malignancies, a log-log plot of incidence versus age shows a single-component straight-line increase with every year of life. A similar plot for breast cancer shows two components: a straight-line increase with age but with a decrease in slope beginning at the age of menopause. The three dates in a woman's life that have a major impact on breast cancer incidence are age at menarche, age at first full-term pregnancy, and age at menopause. Women who experience menarche at age 16 years have only 50–60% of the breast cancer risk of a woman having menarche at age 12 years; the lower risk persists throughout life. Similarly, menopause occurring 10 years before the median age of menopause (52 years), whether natural or surgically induced, reduces lifetime breast cancer risk by about 35%. Women who have a first full-term pregnancy by age 18 years have a 30–40% lower risk of breast cancer compared with nulliparous women. Thus, length of menstrual life—particularly the fraction occurring before first full-term pregnancy—is a substantial component of the total risk of breast cancer. These three factors (menarche, age of first full-term pregnancy, and menopause) can account for 70–80% of the variation in breast cancer frequency in different countries. Also, duration of maternal nursing correlates with substantial risk reduction independent of either parity or age at first full-term pregnancy.

International variation in incidence has provided some of the most important clues on hormonal carcinogenesis. A woman living to age 80 years in North America has one chance in nine of developing invasive breast cancer. Asian women have one-fifth to one-tenth the risk of breast cancer of women in North America or Western Europe. Asian women have substantially lower concentrations of estrogens and progesterone. These differences cannot be explained on a genetic basis because Asian women living in a Western environment have sex steroid hormone concentrations and risks identical to those of their Western counterparts. These migrant women, and more notably their daughters, also differ markedly in height and weight from Asian women in Asia; height and weight are critical regulators of age of menarche and have substantial effects on plasma concentrations of estrogens.

The role of diet in breast cancer etiology is controversial. While there are associative links between total caloric and fat intake and breast cancer risk, the exact role of fat in the diet is unproven. Increased caloric intake contributes to breast cancer risk in multiple ways: earlier menarche, later age at menopause, and increased postmenopausal estrogen concentrations reflecting enhanced aromatase activities in fatty tissues. On the other hand, central obesity is both a risk factor for occurrence and recurrence of breast cancer. Moderate alcohol intake also increases the risk by an unknown mechanism. Folic acid supplementation appears to modify risk in women who use alcohol but is not additionally protective in abstainers. Recommendations favoring abstinence from alcohol must be weighed against other social pressures and the possible cardioprotective effect of moderate alcohol intake. Chronic low-dose aspirin use is associated with a decreased incidence of breast cancer. Depression is also associated with both occurrence and recurrence of breast cancer.

Understanding the potential role of exogenous hormones in breast cancer is of extraordinary importance because millions of American women regularly use oral contraceptives and postmenopausal hormone replacement therapy. The most credible meta-analyses of oral contraceptive use suggest that these agents cause a small increased risk of breast cancer. By contrast, oral contraceptives offer a substantial protective effect against ovarian epithelial tumors and endometrial cancers. Hormone replacement therapy (HRT) has a powerful effect on breast cancer risk. Data from the Women's Health Initiative (WHI) trial showed that conjugated equine estrogens plus progestins increased the risk of breast cancer and adverse cardiovascular events but decreased the risk of bone fractures and colorectal cancer. On balance, there were more negative events with HRT; 6–7 years of HRT nearly doubled the risk of breast cancer. A parallel WHI trial with >12,000 women enrolled testing conjugated estrogens alone (estrogen replacement therapy in women who have had hysterectomies) showed no significant increase in breast cancer incidence. Thus, there are serious concerns about long-term HRT use in terms of cardiovascular disease and breast cancer. The WHI trial of conjugated equine estrogen alone demonstrated few adverse effects for women age <70; however, no comparable safety data are available for other more potent forms of estrogen replacement, and they should not be routinely used as substitutes. HRT in women previously diagnosed with breast cancer increases recurrence rates. Rapid decrease in the number of women on HRT has already led to a coincident decrease in breast cancer incidence.

In addition to the other factors, radiation is a risk factor in younger women. Women who have been exposed before age 30 years to radiation in the form of multiple fluoroscopies (200–300 cGy) or treatment for Hodgkin's disease (>3600 cGy) have a substantial increase in risk of breast cancer, whereas radiation exposure after age 30 years appears to have a minimal carcinogenic effect on the breast.

EVALUATION OF BREAST MASSES IN MEN AND WOMEN

Because the breasts are a common site of potentially fatal malignancy in women, examination of the breast is an essential part of the physical examination. Unfortunately, internists frequently do not examine breasts in men, and in women, they are apt to defer this evaluation to gynecologists. Because of the plausible association between early detection and improved outcome, it is the duty of every physician to identify breast abnormalities at the earliest possible stage and to institute a diagnostic workup. Women should be trained in breast self-examination (BSE). Although breast cancer in men is unusual, unilateral lesions should be evaluated in the same manner as in women, with the recognition that gynecomastia in men can sometimes begin unilaterally and is often asymmetric.

Virtually all breast cancer is diagnosed by biopsy of a nodule detected either on a mammogram or by palpation. Algorithms have been developed to enhance the likelihood of diagnosing breast cancer and reduce the frequency of unnecessary biopsy **(Fig. 38-1)**.

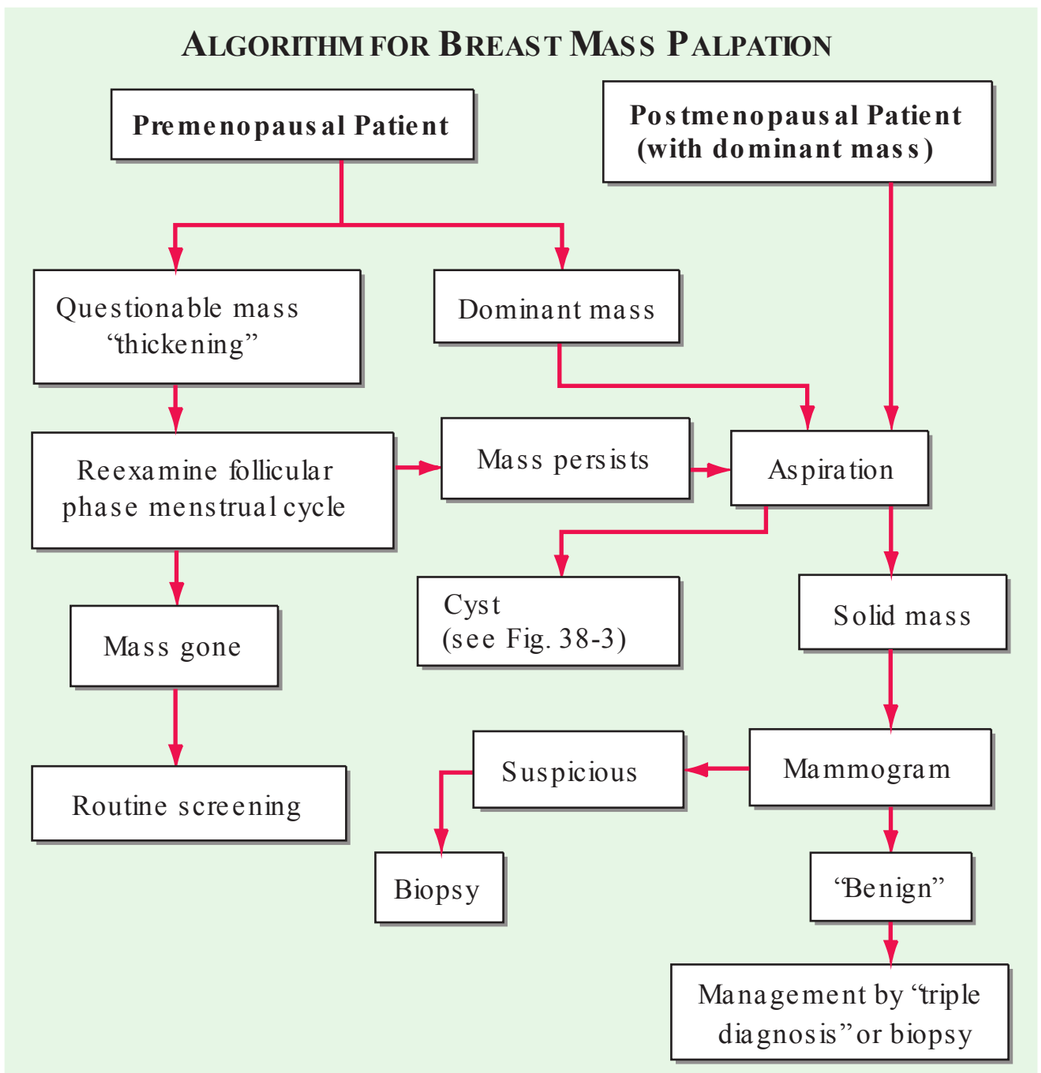


FIGURE 38-1
Approach to a palpable breast mass.

THE PALPABLE BREAST MASS

Women should be strongly encouraged to examine their breasts monthly. A potentially flawed study from China has suggested that BSE does not alter survival, but given its safety, the procedure should still be encouraged. At worst, this practice increases the likelihood of detecting a mass at a smaller size when it can be treated with more limited surgery. Breast examination by the physician should be performed in good light so as to see retractions and other skin changes. T e nipple and areolae should be inspected, and an attempt should be made to elicit nipple discharge. All regional lymph node groups should be examined, and any lesions should be measured. Physical examination alone cannot exclude malignancy. Lesions with certain features are more likely to be cancerous (hard, irregular, tethered or fixed, or painless lesions). A negative mammogram in the presence of a persistent lump in the breast does not exclude malignancy. Palpable lesions require additional diagnostic procedures, including biopsy.

In premenopausal women, lesions that are either equivocal or nonsuspicious on physical examination should be reexamined in 2–4 weeks, during the follicular phase of the menstrual cycle. Days 5–7 of the cycle are the best time for breast examination. A dominant mass in a postmenopausal woman or a dominant mass that persists through a menstrual cycle in a premenopausal woman should be aspirated by fine-needle biopsy or referred to a surgeon. If nonbloody fluid is aspirated, the diagnosis (cyst) and therapy have been accomplished together. Solid lesions that are persistent, recurrent, complex, or bloody cysts require mammography and biopsy, although in selected patients the so-called triple diagnostic technique (palpation, mammography, aspiration) can be used to avoid biopsy (Figs. 38-1, **38-2**, and **38-3**). Ultrasound can be used in

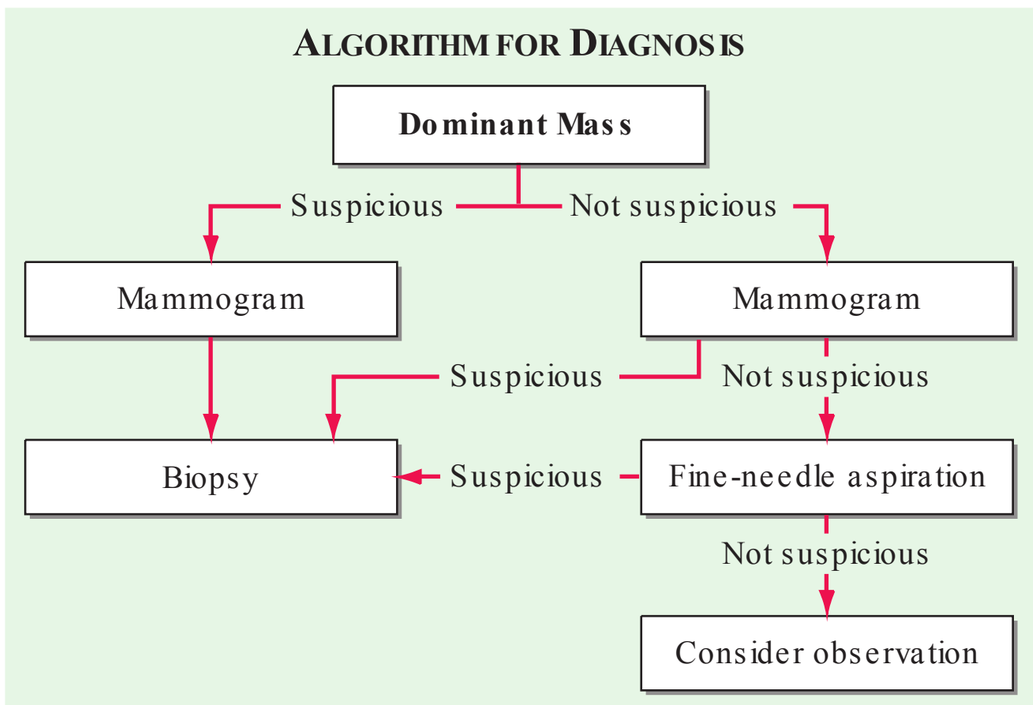


FIGURE 38-2
The "triple diagnosis" technique.

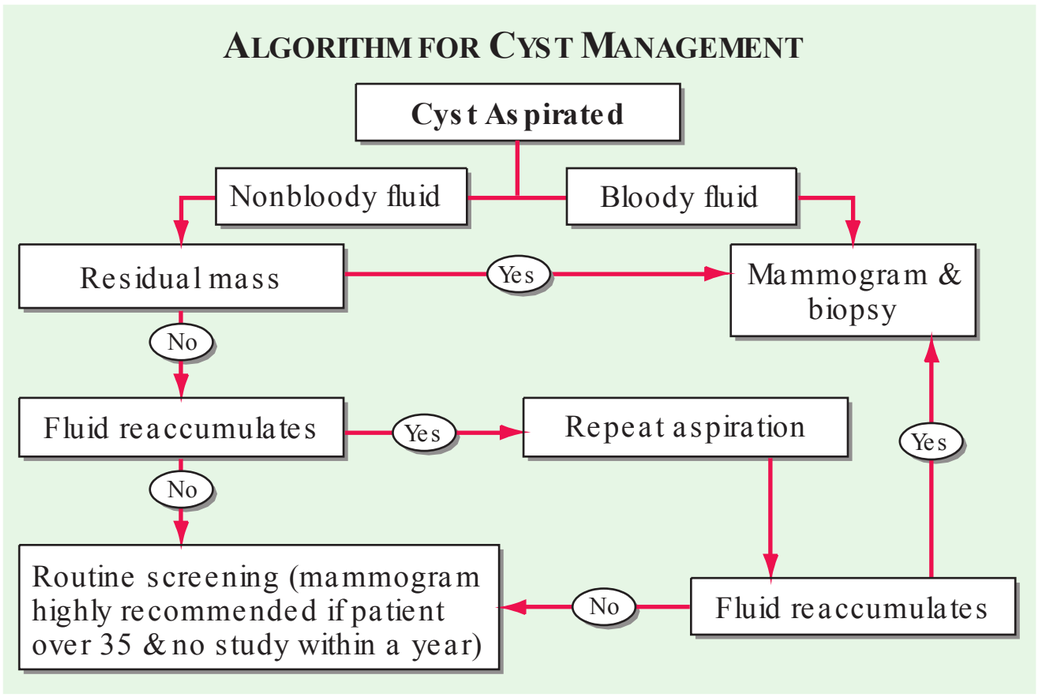


FIGURE 38-3
Management of a breast cyst.

place of fine-needle aspiration to distinguish cysts from solid lesions. Not all solid masses are detected by ultrasound; thus, a palpable mass that is not visualized on ultrasound must be presumed to be solid.

Several points are essential in pursuing these management decision trees. First, risk-factor analysis is not part of the decision structure. No constellation of risk factors, by their presence or absence, can be used to exclude biopsy. Second, fine-needle aspiration should be used only in centers that have proven skill in obtaining such specimens and analyzing them. The likelihood of cancer is low in the setting of a "triple negative" (benign-feeling lump, negative mammogram, and negative fine-needle aspiration), but it is not zero. The patient and physician must be aware of a 1% risk of false negatives. Third, additional technologies such as magnetic resonance imaging (MRI), ultrasound, and sestamibi imaging cannot be used to exclude the need for biopsy, although in unusual circumstances, they may provoke a biopsy.

THE ABNORMAL MAMMOGRAM

Diagnostic mammography should not be confused with screening mammography, which is performed after a palpable abnormality has been detected. Diagnostic mammography is aimed at evaluating the rest of the breast before biopsy is performed or occasionally is part of the triple-test strategy to exclude immediate biopsy.

Subtle abnormalities that are first detected by screening mammography should be evaluated carefully by compression or magnified views. These abnormalities include clustered microcalcifications, densities (especially if spiculated), and new or enlarging architectural distortion. For some nonpalpable lesions, ultrasound may be helpful either to identify cysts or to guide biopsy. If there is no palpable lesion and detailed mammographic studies are unequivocally benign, the patient should have routine follow-up appropriate to the patient's age. It cannot be stressed too strongly that in the presence of a breast lump a negative mammogram does not rule out cancer.

If a nonpalpable mammographic lesion has a low index of suspicion, mammographic follow-up in 3–6 months is reasonable. Workup of indeterminate and suspicious lesions has been rendered more complex by the advent of stereotactic biopsies. Morrow and colleagues have suggested that these procedures are indicated for lesions that require biopsy but are likely to be benign—that is, for cases in which the procedure probably will eliminate additional surgery. When a lesion is more probably malignant, open biopsy should be performed with a needle localization technique. Others have proposed more widespread use of stereotactic core biopsies for nonpalpable lesions on economic grounds and because diagnosis leads to earlier treatment planning. However, stereotactic diagnosis of a malignant lesion does not eliminate the need for definitive surgical procedures, particularly if breast conservation is attempted. For example, after a breast biopsy with needle localization (i.e., local excision) of a stereotactically diagnosed malignancy, reexcision may still be necessary to achieve negative margins. To some extent, these issues are decided on the basis of referral pattern and the availability of the resources for stereotactic core biopsies. A reasonable approach is shown in **Fig. 38-4**.

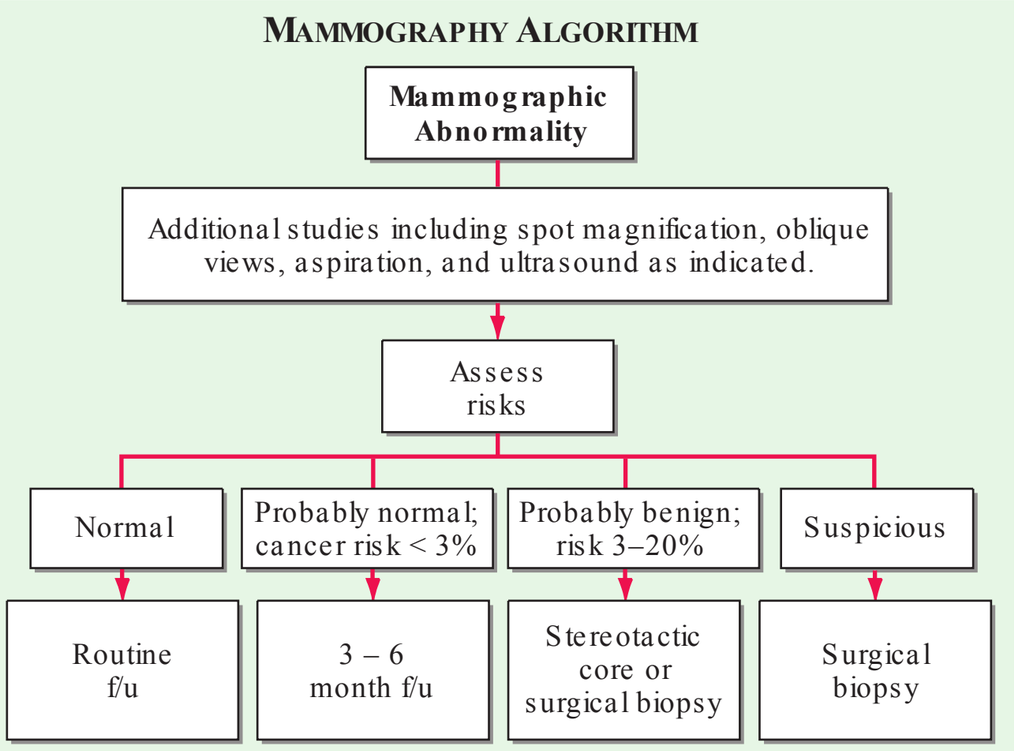


FIGURE 38-4
Approaches to abnormalities detected by mammogram.

BREAST MASSES IN THE PREGNANT OR LACTATING WOMAN

During pregnancy, the breast grows under the influence of estrogen, progesterone, prolactin, and human placental lactogen. Lactation is suppressed by progesterone, which blocks the effects of prolactin. After delivery, lactation is promoted by the fall in progesterone levels, which leaves the effects of prolactin unopposed. T e development of a dominant mass during pregnancy or lactation should never be attributed to hormonal changes. A dominant mass must be treated with the same concern in a pregnant woman as any other. Breast cancer develops in 1 in every 3000–4000 pregnancies. Stage for stage, breast cancer in pregnant patients is no different from premenopausal breast cancer in nonpregnant patients. However, pregnant women often have more advanced disease because the significance of a breast mass was not fully considered and/or because of endogenous hormone stimulation. Persistent lumps in the breast of pregnant or lactating women cannot be attributed to benign changes based on physical findings; such patients should be promptly referred for diagnostic evaluation.

BENIGN BREAST MASSES

Only about 1 in every 5–10 breast biopsies leads to a diagnosis of cancer, although the rate of positive biopsies varies in different countries and clinical settings. (T ese differences may be related to interpretation, medico-legal considerations, and availability of mammograms.) T e vast majority of benign breast masses are due to "fibrocystic" disease, a descriptive term for small fluid-filled cysts and modest epithelial cell and fibrous tissue hyperplasia. However, fibrocystic disease is a histologic, not a clinical, diagnosis, and women who have had a biopsy with benign findings are at greater risk of developing breast cancer than those who have not had a biopsy. T e subset of women with ductal or lobular cell proliferation (about 30% of patients), particularly the small fraction (3%) with atypical hyperplasia, have a fourfold greater risk of developing breast cancer than those women who have not had a biopsy, and the increase in the risk is about ninefold for women in this category who also have an affected first-degree relative. T us, careful follow-up of these patients is required. By contrast, patients with a benign biopsy without atypical hyperplasia are at little risk and may be followed routinely.

SCREENING

Breast cancer is virtually unique among the epithelial tumors in adults in that screening (in the form of annual mammography) improves survival. Meta-analysis examining outcomes from every randomized trial of mammography conclusively shows a 25–30% reduction in the chance of dying from breast cancer with annual screening after age 50 years; the data for women between ages 40 and 50 years are almost as positive; however, since the incidence is much lower in younger women, there are more false positives. While controversy continues to surround the assessment of screening mammography, the preponderance of data strongly supports the benefits of screening mammography. New analyses of older randomized studies have occasionally suggested that screening may not work. While the design defects in some older studies cannot be retrospectively corrected, most experts, including panels of the American Society of Clinical Oncology and the American Cancer Society (ACS), continue to believe that screening conveys substantial benefit. Furthermore, the profound drop in breast cancer mortality rate seen over the past decade is unlikely to be solely attributable to improvements in therapy. It seems prudent to recommend annual or biannual mammography for women past the age of 40 years. Although no randomized study of BSE has ever shown any improvement in survival, its major benefit is identification of tumors appropriate for conservative local therapy. Better mammographic technology, including digitized mammography, routine use of magnified views, and greater skill in mammographic interpretation, combined with newer diagnostic techniques (MRI, magnetic resonance spectroscopy, positron emission tomography, etc.) may make it possible to identify breast cancers even more reliably and earlier. Screening by any technique other than mammography is not indicated. However, the ACS suggests that younger women who are BRCA1 or BRCA2 carriers or untested first-degree relatives of women with cancer; women with a history of radiation therapy to the chest between ages 10 and 30 years; women with a lifetime risk of breast cancer of at least 20%; and women with a history of Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndromes may benefit from MRI screening, where the higher sensitivity may outweigh the loss of specificity.

STAGING

Correct staging of breast cancer patients is of extraordinary importance. Not only does it permit an accurate prognosis, but in many cases, therapeutic decision-making is based largely on the TNM (primary tumor, regional nodes, metastasis) classification **(Table 38-1)**. Comparison with historic series should be undertaken with caution, as the staging has changed several times in the past 20 years. T e current staging is complex and results in significant changes in outcome by stage as compared with prior staging systems.

TABLE 38-1

STAGING OF BREAST CANCER

Primary Tumor (T)	
T0	No evidence of primary tumor
TIS	Carcinoma in situ
T1	Tumor ≤2 cm
T1a	Tumor >0.1 cm but ≤0.5 cm
T1b	Tumor >0.5 but ≤1 cm
T1c	Tumor >1 cm but ≤2 cm
T2	Tumor >2 cm but ≤5 cm
T3	Tumor >5 cm
T4	Extension to chest wall, inflammation, satellite lesions, ulcerations
Regional Lymph Nodes (N)	
PN0(i–)	No regional lymph node metastasis histologically, negative IHC
PN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
PN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
PN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
PN1	Metastasis in one to three axillary lymph nodes, or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
PN1mi	Micrometastasis (>0.2 mm, none >2 mm)
PN1a	Metastasis in one to three axillary lymph nodes
PN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[a]
PN1c	Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.[a] (If associated with greater than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.)
pN2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[a] ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral subcarinal lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis (includes spread to ipsilateral supraclavicular nodes)

Stage Grouping

Stage 0	TIS	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

[a]Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Abbreviations: IHC, immunohistochemistry; RT-PCR, reverse transcriptase polymerase chain reaction.

Source: Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010; www.springeronline.com.

One of the most exciting aspects of breast cancer biology has been its subdivision into at least five subtypes based on gene expression profiling.

1. **Luminal A:** T e luminal tumors express cytokeratins 8 and 18, have the highest levels of estrogen receptor expression, tend to be low grade, are most likely to respond to endocrine therapy, and have a favorable prognosis. T ey tend to be less responsive to chemotherapy.
2. **Luminal B:** Tumor cells are also of luminal epithelial origin, but with a gene expression pattern distinct from luminal A. Prognosis is somewhat worse that luminal A.
3. **Normal breast–like:** T ese tumors have a gene expression profile reminiscent of nonmalignant "normal" breast epithelium. Prognosis is similar to the luminal B group. T is subtype is somewhat controversial and may represent contamination of the sample by normal mammary epithelium.
4. HER2 **amplif ed:** T ese tumors have amplification of the HER2 gene on chromosome 17q and frequently exhibit coamplification and overexpression of other genes adjacent to HER2. Historically the clinical prognosis of such tumors was poor. However, with the advent of trastuzumab and other targeted therapies, the clinical outcome of HER2-positive patients is markedly improving.
5. **Basal:** T ese estrogen receptor/progesterone receptor–negative and HER2-negative tumors (so-called triple negative) are characterized by markers of basal/myoepithelial cells. T ey tend to be high grade, and express cytokeratins 5/6 and 17 as well as vimentin, p63, CD10, α-smooth muscle actin, and epidermal growth factor receptor (EGFR). Patients with BRCA mutations also fall within this molecular subtype. T ey also have stem cell characteristics.

PRIMARY BREAST CANCER Breast-conserving treatments, consisting of the removal of the primary tumor by some form of lumpectomy with or without irradiating the breast, result in a survival that is as good as (or slightly superior to) that after extensive surgical procedures, such as mastectomy or modified radical mastectomy, with or without further irradiation. Postlumpectomy breast irradiation greatly reduces the risk of recurrence in the breast. While breast conservation is associated with a possibility of recurrence in the breast, 10-year survival is at least as good as that after more extensive surgery. Postoperative radiation to regional nodes following mastectomy is also associated with an improvement in survival. Because radiation therapy can also reduce the rate of local or regional recurrence, it should be strongly considered following mastectomy for women with high-risk primary tumors (i.e., T2 in size, positive margins, positive nodes). At present, nearly one-third of women in the United States are managed by lumpectomy. Breast-conserving surgery is not suitable for all patients: it is not generally suitable for tumors >5 cm (or for smaller tumors if the breast is small), for tumors involving the nipple-areola complex, for tumors with extensive intraductal disease involving multiple quadrants of the breast, for women with a history of collagen-vascular disease, and for women who either do not have the motivation for breast conservation or do not have convenient access to radiation therapy. However, these groups probably do not account for more than one-third of patients who are treated with mastectomy. T us, a great many women still undergo mastectomy who could safely avoid this procedure and probably would if appropriately counseled.

Sentinel lymph node biopsy (SLNB) is generally the standard of care for women with localized breast cancer and clinically negative axilla. If SLNB is negative, more extensive axillary surgery is not required, avoiding much of the risk of lymphedema following more extensive axillary dissections. In the presence of minimal involvement of a sentinel lymph node, further axillary surgery is not required.

An extensive intraductal component is a predictor of recurrence in the breast, and so are several clinical variables. Both axillary lymph node involvement and involvement of vascular or lymphatic channels by metastatic tumor in the breast are associated with a higher risk of relapse in the breast but are not contraindications to breast-conserving treatment. When these patients are excluded, and when lumpectomy with negative tumor margins is achieved, breast conservation is associated with a recurrence rate in the breast of 5% or less. T e survival of patients who have recurrence in the breast is somewhat worse than that of women who do not. T us, recurrence in the breast is a negative prognostic variable for long-term survival. However, recurrence in the breast is not the cause of distant metastasis. If recurrence in the breast caused metastatic disease, then women treated with lumpectomy, who have a higher rate of recurrence in the breast, should have poorer survival than women treated with mastectomy, and they do not. Most patients should consult with a radiation oncologist before making a final decision concerning local therapy. However, a multimodality clinic in which the surgeon, radiation oncologist, medical oncologist, and other caregivers cooperate to evaluate the patient and develop a treatment plan is usually considered a major advantage by patients.

Adjuvant Therapy T e use of systemic therapy after local management of breast cancer substantially improves survival. More than half of the women who would otherwise die of metastatic breast cancer remain disease-free when treated with the appropriate systemic regimen. T ese data have grown more and more impressive with longer follow-up and more effective regimens.

PROGNOSTIC VARIABLES T e most important prognostic variables are provided by tumor staging. T e size of the tumor and the status of the axillary lymph nodes provide reasonably accurate information on the likelihood of tumor relapse. T e relation of pathologic stage to 5-year survival is shown in **Table 38-2**. For most women, the need for adjuvant therapy can be readily defined on this basis alone. In the absence of lymph node

TABLE 38-2

5-YEAR SURVIVAL RATE FOR BREAST CANCER BY STAGE

STAGE	5-YEAR SURVIVAL, %
0	99
I	92
IIA	82
IIB	65
IIIA	47
IIIB	44
IV	14

Source: Modified from data of the National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER).

involvement, involvement of microvessels (either capillaries or lymphatic channels) in tumors is nearly equivalent to lymph node involvement. The greatest controversy concerns women with intermediate prognoses. There is rarely justification for adjuvant chemotherapy in most women with tumors <1 cm in size whose axillary lymph nodes are negative. HER2-positive tumors are a potential exception. Detection of breast cancer cells either in the circulation or bone marrow is associated with an increased relapse rate. The most exciting development in this area is the use of gene expression arrays to analyze patterns of tumor gene expression. Several groups have independently defined gene sets that reliably predict disease-free and overall survival far more accurately than any single prognostic variable including the Oncotype DX™ analysis of 21 genes. Also, the use of such standardized risk assessment tools such as Adjuvant! Online (www.adjuvantonline.com) is very helpful. These tools are highly recommended in otherwise ambiguous circumstances.

Estrogen receptor status and progesterone receptor status are of prognostic significance. Tumors that lack either or both of these receptors are more likely to recur than tumors that have them.

Several measures of tumor growth rate correlate with early relapse. S-phase analysis using flow cytometry is the most accurate measure. Indirect S-phase assessments using antigens associated with the cell cycle, such as PCNA (Ki67), are also valuable. Tumors with a high proportion (more than the median) of cells in S-phase pose a greater risk of relapse; chemotherapy offers the greatest survival benefit for these tumors. Assessment of DNA content in the form of ploidy is of modest value, with nondiploid tumors having a somewhat worse prognosis.

Histologic classification of the tumor has also been used as a prognostic factor. Tumors with a poor nuclear grade have a higher risk of recurrence than tumors with a good nuclear grade. Semiquantitative measures such as the Elston score improve the reproducibility of this measurement.

Molecular changes in the tumor are also useful. Tumors that overexpress erbB2 (HER2/neu) or have a mutated p53 gene have a worse prognosis. Particular interest has centered on erbB2 overexpression as measured by immunohistochemistry or fluorescence in situ hybridization. Tumors that overexpress erbB2 are more likely to respond to doxorubicin-containing regimens; erbB2 overexpression also predicts those tumors that will respond to HER2/neu antibodies (trastuzumab) (Herceptin) and HER2/neu kinase inhibitors.

Other variables that have also been used to evaluate prognosis include proteins associated with invasiveness, such as type IV collagenase, cathepsin D, plasminogen activator, plasminogen activator receptor, and the metastasis-suppressor gene nm23. None of these has been widely accepted as a prognostic variable for therapeutic decision-making. One problem in interpreting these prognostic variables is that most of them have not been examined in a study using a large cohort of patients.

ADJUVANT REGIMENS Adjuvant therapy is the use of systemic therapies in patients whose known disease has received local therapy but who are at risk of relapse. Selection of appropriate adjuvant chemotherapy or hormone therapy is highly controversial in some situations. Meta-analyses have helped to define broad limits for therapy but do not help in choosing optimal regimens or in choosing a regimen for certain subgroups of patients. A summary of recommendations is shown in **Table 38-3**. In general, premenopausal women for whom any form of adjuvant systemic therapy is indicated should receive multidrug chemotherapy. Antihormone therapy improves survival in premenopausal patients who are estrogen receptor positive and should be added following completion of chemotherapy. Prophylactic surgical or medically induced castration may also be associated with a substantial survival benefit (primarily in estrogen receptor–positive patients) but is not widely used in this country.

Data on postmenopausal women are also controversial. The impact of adjuvant chemotherapy is quantitatively less clear-cut than in premenopausal patients, particularly in estrogen receptor–positive cases, although survival advantages have been shown. The first decision is whether chemotherapy or endocrine therapy should be used. While adjuvant endocrine therapy (aromatase inhibitors and tamoxifen) improves survival regardless of axillary lymph node status, the improvement in survival is modest for patients in whom multiple lymph nodes are involved. For this reason, it has been usual to give chemotherapy to postmenopausal patients who have no medical contraindications and who have more than one positive lymph node; hormone therapy is commonly given subsequently. For postmenopausal women for whom systemic therapy is warranted but who have a more favorable prognosis (based more commonly on analysis such as the Oncotype DX methodology), hormone therapy may be used alone. Large clinical trials have shown superiority for aromatase inhibitors over tamoxifen alone in the adjuvant setting, although tamoxifen appears essentially equivalent in women who are obese and therefore presumably have higher endogenous concentrations of estrogen. Unfortunately the

TABLE 38-3

SUGGESTED APPROACHES TO ADJUVANT THERAPY

AGE GROUP	LYMPH NODE STATUS[a]	ESTROGEN RECEPTOR (ER) STATUS	TUMOR	RECOMMENDATION
Premenopausal	Positive	Any	Any	Multidrug chemotherapy + tamoxifen if ER-positive + trastuzumab in HER2/neu-positive tumors
Premenopausal	Negative	Any	>2 cm, or 1–2 cm with other poor prognostic variables	Multidrug chemotherapy + tamoxifen if ER-positive + trastuzumab in HER2/neu-positive tumors. Consider Oncotype or similar testing.
Postmenopausal	Positive	Negative	Any	Multidrug chemotherapy + trastuzumab in HER2/neu-positive tumors
Postmenopausal	Positive	Positive	Any	Aromatase inhibitors and tamoxifen with or without chemotherapy + trastuzumab in HER2/neu-positive tumors
Postmenopausal	Negative	Positive	>2 cm, or 1–2 cm with other poor prognostic variables	Aromatase inhibitors and tamoxifen + trastuzumab in HER2/neu-positive tumors
Postmenopausal	Negative	Negative	>2 cm, or 1–2 cm with other poor prognostic variables	Consider multidrug chemotherapy + trastuzumab in HER2/neu-positive tumors

[a]As determined by pathologic examination.

optimal plan is unclear. Tamoxifen for 5 years followed by an aromatase inhibitor, the reverse strategy, or even switching to an aromatase inhibitor after 2–3 years of tamoxifen has been shown to be better than tamoxifen alone. Continuation of tamoxifen for 10 years yields further benefit and is a reasonable decision for women with less favorable prognoses. Unfortunately, multiple studies have revealed very suboptimal adherence to long-term adjuvant endocrine regimens, and every effort should be made to encourage their continuous use. No valid information currently permits selection among the three clinically approved aromatase inhibitors. Concomitant use of bisphosphonates is almost always warranted; however, it is not finally settled as to whether their prophylactic use increases survival in addition to just decreasing recurrences in bone.

Most comparisons of adjuvant chemotherapy regimens show little difference among them, although small advantages for doxorubicin-containing regimens and "dose-dense" regimens are usually seen.

One approach—so-called neoadjuvant chemotherapy—involves the administration of adjuvant therapy before definitive surgery and radiation therapy. Because the objective response rates of patients with breast cancer to systemic therapy in this setting exceed 75%, many patients will be "downstaged" and may become candidates for breast-conserving therapy. However, overall survival has not been improved using this approach as compared with the same drugs given postoperatively. Patients who achieve a pathologic complete remission after neoadjuvant chemotherapy not unexpectedly have a substantially improved survival. The neoadjuvant setting also provides a wonderful opportunity for the evaluation of new agents. For example, a second HER2 targeting antibody, pertuzumab, has been shown to provide additional benefit when combined with trastuzumab in the neoadjuvant setting.

Other adjuvant treatments under investigation include the use of taxanes, such as paclitaxel and docetaxel, and therapy based on alternative kinetic and biologic models. In such approaches, high doses of single agents are used separately in relatively dose-intensive cycling regimens. Node-positive patients treated with doxorubicin-cyclophosphamide for four cycles followed by four cycles of a taxane have a substantial improvement in survival compared with women receiving doxorubicin-cyclophosphamide alone, particularly in women with estrogen receptor–negative tumors. In addition, administration of the same drug combinations at the same dose but at more frequent intervals (every 2 weeks with cytokine support as compared with the standard every 3 weeks) is even more effective. Among the 25% of women whose tumors overexpress HER2/neu, addition of trastuzumab given concurrently with a taxane and then for a year after chemotherapy produces significant improvement in survival. Although longer follow-up will be important, this is now the standard care for most women with HER2/neu-positive breast cancers. Cardiotoxicity, immediate and long-term, remains a concern, and further efforts to exploit non-anthracycline-containing

regimens are being pursued. Very-high-dose therapy with stem cell transplantation in the adjuvant setting has not proved superior to standard-dose therapy and should not be routinely used.

A variety of exciting approaches are close to adoption, and the literature needs to be followed attentively. Tyrosine kinase inhibitors such as lapatinib and additional HER2-targeting antibodies such as pertuzumab are very promising. Finally, as described in the next section, a novel class of agents targeting DNA repair—the so-called poly–ADP ribose polymerase (PARP) inhibitors—is likely to have a major effect on breast cancers either caused by BRCA1 or BRCA2 mutations or sharing similar defects in DNA repair in their etiology.

SYSTEMIC THERAPY OF METASTATIC DISEASE About one-third of patients treated for apparently localized breast cancer develop metastatic disease. Although a small number of these patients enjoy long remissions when treated with combinations of systemic and local therapy, most eventually succumb to metastatic disease. The median survival for all patients diagnosed with metastatic breast cancer is less than 3 years. Soft tissue, bony, and visceral (lung and liver) metastases each account for approximately one-third of sites of initial relapses. However, by the time of death, most patients will have bony involvement. Recurrences can appear at any time after primary therapy. A very cruel fact about breast cancer recurrences is that at least half of all breast cancer recurrences occur >5 years after initial therapy. It is now clear that a variety of host factors can influence recurrence rates, including depression and central obesity, and these diseases should be managed as aggressively as possible.

Because the diagnosis of metastatic disease alters the outlook for the patient so drastically, it should rarely be made without a confirmatory biopsy. Every oncologist has seen patients with tuberculosis, gallstones, sarcoidosis, or other nonmalignant diseases misdiagnosed and treated as though they had metastatic breast cancer or even second malignancies such as multiple myeloma thought to be recurrent breast cancer. This is a catastrophic mistake and justifies biopsy for virtually every patient at the time of initial suspicion of metastatic disease. Furthermore, there are well-documented changes in hormone receptor status that can occur and substantially alter treatment decisions.

The choice of therapy requires consideration of local therapy needs, the overall medical condition of the patient, and the hormone receptor status of the tumor, as well as clinical judgment. Because therapy of systemic disease is palliative, the potential toxicities of therapies should be balanced against the response rates. Several variables influence the response to systemic therapy. For example, the presence of estrogen and progesterone receptors is a strong indication for endocrine therapy. On the other hand, patients with short disease-free intervals, rapidly progressive visceral disease, lymphangitic pulmonary disease, or intracranial disease are unlikely to respond to endocrine therapy.

In many cases, systemic therapy can be withheld while the patient is managed with appropriate local therapy. Radiation therapy and occasionally surgery are effective at relieving the symptoms of metastatic disease, particularly when bony sites are involved. Many patients with bone-only or bone-dominant disease have a relatively indolent course. Under such circumstances, systemic chemotherapy has a modest effect, whereas radiation therapy may be effective for long periods. Other systemic treatments, such as strontium-89 and/or bisphosphonates, may provide a palliative benefit without inducing objective responses. Most patients with metastatic disease, and certainly all who have bone involvement, should receive concurrent bisphosphonates. Because the goal of therapy is to maintain well-being for as long as possible, emphasis should be placed on avoiding the most hazardous complications of metastatic disease, including pathologic fracture of the axial skeleton and spinal cord compression. New back pain in patients with cancer should be explored aggressively on an emergent basis; to wait for neurologic symptoms is a potentially catastrophic error. Metastatic involvement of endocrine organs can cause profound dysfunction, including adrenal insufficiency and hypopituitarism. Similarly, obstruction of the biliary tree or other impaired organ function may be better managed with a local therapy than with a systemic approach.

Many patients are inappropriately treated with toxic regimens into their last days of life. Often oncologists are unwilling to have the difficult conversations that are required with patients nearing the end of life, and not uncommonly, patients and families can pressure physicians into treatments with very little survival value. Palliative care consultation and realistic assessment of treatment expectations need to be reviewed with patients and families. We urge consideration of palliative care consultations for patients who have received at least two lines of therapy for metastatic disease.

Endocrine Therapy Normal breast tissue is estrogen dependent. Both primary and metastatic breast cancer may retain this phenotype. The best means of ascertaining whether a breast cancer is hormone dependent is through analysis of estrogen and progesterone receptor levels on the tumor. Tumors that are positive for the estrogen receptor and negative for the progesterone receptor have a response rate of ~30%. Tumors that are positive for both receptors have a response rate approaching 70%. If neither receptor is present, the objective response rates are <5%. Receptor analyses provide information as to the correct ordering of endocrine therapies as opposed to chemotherapy. Because of their lack of toxicity and because some patients whose receptor analyses are reported as negative respond to endocrine therapy, an endocrine treatment should be attempted in virtually every patient with metastatic breast cancer. Potential endocrine therapies are summarized in **Table 38-4**. The choice of endocrine therapy is usually determined by toxicity profile and availability. In most postmenopausal patients, the initial endocrine therapy should be an aromatase inhibitor rather than tamoxifen. For the subset of postmenopausal women who are estrogen receptor–positive but also HER2/neu-positive, response rates to aromatase

TABLE 38-4

ENDOCRINE THERAPIES FOR BREAST CANCER

THERAPY	COMMENTS
Castration	For premenopausal women
Surgical	
LHRH agonists	
Antiestrogens	
Tamoxifen	Useful in pre- and postmenopausal women[a]
"Pure" antiestrogens	Responses in tamoxifen-resistant and aromatase inhibitor–resistant patients[a]
Surgical adrenalectomy	Rarely used second-line choice
Aromatase inhibitors	Low toxicity; now first choice for metastatic disease[a]
High-dose progestogens	Common fourth-line choice after aromatase inhibitors, tamoxifen, and fulvestrant
Hypophysectomy	Rarely used
Additive androgens or estrogens	Plausible fourth-line therapies; potentially toxic

[a]Consider retreatment with Everolimus in combination for disease progression
Abbreviation: LHRH, luteinizing hormone–releasing hormone.

inhibitors are substantially higher than to tamoxifen. Aromatase inhibitors are not used in premenopausal women because their hypothalamus can respond to estrogen deprivation by producing gonadotropins that promote estrogen synthesis. Newer "pure" antiestrogens that are free of agonistic effects are also effective. Cases in which tumors shrink in response to tamoxifen withdrawal (as well as withdrawal of pharmacologic doses of estrogens) have been reported. A series of studies with aromatase inhibitors, tamoxifen, and fulvestrant have all shown that the addition of everolimus to the hormonal treatment can lead to significant benefit after progression on the endocrine agent alone. Everolimus (an mTOR inhibitor) in coordination with endocrine agents is now being explored as front-line therapy and in the adjuvant setting. Endogenous estrogen formation may be blocked by analogues of luteinizing hormone–releasing hormone in premenopausal women. Additive endocrine therapies, including treatment with progestogens, estrogens, and androgens, may also be tried in patients who respond to initial endocrine therapy; the mechanism of action of these latter therapies is unknown. Patients who respond to one endocrine therapy have at least a 50% chance of responding to a second endocrine therapy. It is not uncommon for patients to respond to two or three sequential endocrine therapies; however, combination endocrine therapies do not appear to be superior to individual agents, and combinations of chemotherapy with endocrine therapy are not useful. The median survival of patients with metastatic disease is approximately 2 years, although many patients, particularly older persons and those with hormone-dependent disease, may respond to endocrine therapy for 3–5 years or longer.

Chemotherapy Unlike many other epithelial malignancies, breast cancer responds to multiple chemotherapeutic agents, including anthracyclines, alkylating agents, taxanes, and antimetabolites. Multiple combinations of these agents have been found to improve response rates somewhat, but they have had little effect on duration of response or survival. The choice among multidrug combinations frequently depends on whether adjuvant chemotherapy was administered and, if so, what type. Although patients treated with adjuvant regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF regimens) may subsequently respond to the same combination in the metastatic disease setting, most oncologists use drugs to which the patients have not been previously exposed. Once patients have progressed after combination drug therapy, it is most common to treat them with single agents. Given the significant toxicity of most drugs, the use of a single effective agent will minimize toxicity by sparing the patient exposure to drugs that would be of little value. No method to select the drugs most efficacious for a given patient has been demonstrated to be useful.

Most oncologists use either an anthracycline or paclitaxel following failure with the initial regimen. However, the choice has to be balanced with individual needs. One randomized study has suggested that docetaxel may be superior to paclitaxel. A nanoparticle formulation of paclitaxel (Abraxane) is also effective.

The use of a humanized antibody to erbB2 (trastuzumab [Herceptin]) combined with paclitaxel can improve response rate and survival for women whose metastatic tumors overexpress erbB2. A novel antibody conjugate (ADC) that links trastuzumab to a cytotoxic agent has been approved for management of HER2-positive breast cancer. The magnitude of the survival extension is modest in patients with metastatic disease. Similarly, the use of bevacizumab (Avastin) has improved the response rate and response duration to paclitaxel. Objective responses in previously treated patients may also be seen with gemcitabine, vinca alkaloids, capecitabine, vinorelbine, and oral etoposide, as well as a new class of agents, epothilones. There are few comparative trials of one agent versus another in metastatic disease. It is a sad fact that choices are often influenced by aggressive marketing of new very expensive agents that have not been shown to be superior to other generic agents. Platinum-based agents have become far more widely used in both the adjuvant and advanced disease settings for some breast cancers, particularly those of the "triple-negative" subtype.

HIGH-DOSE CHEMOTHERAPY INCLUDING AUTOLOGOUS BONE MARROW TRANSPLANTATION Autologous bone marrow transplantation combined with high doses of single agents can produce objective responses even in heavily pretreated patients. However, such responses are rarely durable and do not alter the clinical course for most patients with advanced metastatic disease.

STAGE III BREAST CANCER Between 10 and 25% of patients present with so-called locally advanced, or stage III, breast cancer at diagnosis. Many of these cancers are technically operable, whereas others, particularly cancers with chest wall involvement, inflammatory breast cancers, or cancers with large matted axillary lymph nodes, cannot be managed with surgery initially. Although no randomized trials have shown any survival benefit for neoadjuvant regimens as compared to adjuvant therapy, this approach has gained widespread use. More than 90% of patients with locally advanced breast cancer show a partial or better response to multidrug chemotherapy regimens that include an anthracycline. Early administration of this treatment reduces the bulk of the disease and frequently makes the patient a suitable candidate for salvage surgery and/or radiation therapy. T ese patients should be managed in multimodality clinics to coordinate surgery, radiation therapy, and systemic chemotherapy. Such approaches produce long-term disease-free survival in about 30–50% of patients. T e neoadjuvant setting is also an ideal time to evaluate the ef cacy of novel treatments because the effect on the tumor can be directly assessed.

BREAST CANCER PREVENTION Women who have one breast cancer are at risk of developing a contralateral breast cancer at a rate of approximately 0.5% per year. When adjuvant tamoxifen or an aromatase inhibitor is administered to these patients, the rate of development of contralateral breast cancers is reduced. In other tissues of the body, tamoxifen has estrogen-like effects that are beneficial, including preservation of bone mineral density and long-term lowering of cholesterol. However, tamoxifen has estrogen-like effects on the uterus, leading to an increased risk of uterine cancer (0.75% incidence after 5 years on tamoxifen). Tamoxifen also increases the risk of cataract formation. T e Breast Cancer Prevention Trial (BCPT) revealed a >49% reduction in breast cancer among women with a risk of at least 1.66% taking the drug for 5 years. Raloxifene has shown similar breast cancer prevention potency but may have different effects on bone and heart. T e two agents have been compared in a prospective randomized prevention trial (the Study of Tamoxifen and Raloxifene [STAR] trial). T e agents are approximately equivalent in preventing breast cancer with fewer thromboembolic events and endometrial cancers with raloxifene; however, raloxifene did not reduce noninvasive cancers as effectively as tamoxifen, so no clear winner has emerged. A newer selective estrogen receptor modulator (SERM), lasofoxifene, has been shown to reduce cardiovascular events in addition to breast cancer and fractures, and further studies of this agent should be watched with interest. It should be recalled that prevention of contralateral breast cancers in women diagnosed with one cancer is a reasonable surrogate for breast cancer prevention because these are second primaries not recurrences. In this regard, the aromatase inhibitors are all considerably more effective than tamoxifen; however, they are not approved for primary breast cancer prevention. It remains puzzling that agents with the safety profile of raloxifene, which can reduce breast cancer risk by 50% with additional benefits in preventing osteoporotic fracture, are still so infrequently prescribed. T ey should be far more commonly offered to women than they are.

NONINVASIVE BREAST CANCER Breast cancer develops as a series of molecular changes in the epithelial cells that lead to ever more malignant behavior. Increased use of mammography has led to more frequent diagnoses of noninvasive breast cancer. T ese lesions fall into two groups: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (lobular neoplasia). T e management of both entities is controversial.

Ductal Carcinoma In Situ Proliferation of cytologically malignant breast epithelial cells within the ducts is termed DCIS. Atypical hyperplasia may be dif cult to differentiate from DCIS. At least one-third of patients with untreated DCIS develop invasive breast cancer within 5 years. However, many low-grade DCIS lesions do not appear to progress over many years; therefore, many patients are overtreated. Unfortunately there is no reliable means of distinguishing patients who require treatment from those who may be safely observed. For many years, the standard treatment for this disease was mastectomy. However, treatment of this condition by lumpectomy and radiation therapy gives survival that is as good as the survival for invasive breast cancer treated by mastectomy. In one randomized trial, the combination of wide excision plus irradiation for DCIS caused a substantial reduction in the local recurrence rate as compared with wide excision alone with negative margins, although survival was identical in the two arms. No studies have compared either of these regimens to mastectomy. Addition of tamoxifen to any DCIS surgical/radiation therapy regimen further improves local control. Data for aromatase inhibitors in this setting are not available.

Several prognostic features may help to identify patients at high risk for local recurrence after either lumpectomy alone or lumpectomy with radiation therapy. T ese include extensive disease; age <40; and cytologic features such as necrosis, poor nuclear grade, and comedo subtype with overexpression of erbB2. Some data suggest that adequate excision with careful determination of pathologically clear margins is associated with a low recurrence rate. When surgery is combined with radiation therapy, recurrence (which is usually in the same quadrant) occurs with a frequency of ≤10%. Given the fact that half of these recurrences will be invasive, about 5% of the initial cohort will eventually develop invasive breast cancer. A reasonable expectation of mortality for these patients is about 1%, a figure that approximates the mortality rate for DCIS managed by mastectomy. Although this train of reasoning has not formally been proved valid, it is reasonable to recommend that patients who desire breast preservation, and in whom DCIS appears to be reasonably localized, be managed by adequate surgery with meticulous pathologic evaluation, followed by breast irradiation and tamoxifen. For patients with localized DCIS, axillary lymph node dissection is unnecessary. More controversial is the question of what management is optimal when there is any degree of invasion. Because of a significant likelihood (10–15%) of axillary

lymph node involvement even when the primary lesion shows only microscopic invasion, it is prudent to do at least a sentinel lymph node sampling for all patients with any degree of invasion. Further management is dictated by the presence of nodal spread.

Lobular Neoplasia Proliferation of cytologically malignant cells within the lobules is termed lobular neoplasia. Nearly 30% of patients who have had adequate local excision of the lesion develop breast cancer (usually infiltrating ductal carcinoma) over the next 15–20 years. Ipsilateral and contralateral cancers are equally common. Therefore, lobular neoplasia may be a premalignant lesion that suggests an elevated risk of subsequent breast cancer, rather than a form of malignancy itself, and aggressive local management seems unreasonable. Most patients should be treated with an SERM or an aromatase inhibitor (for postmenopausal women) for 5 years and followed with careful annual mammography and semiannual physical examinations. Additional molecular analysis of these lesions may make it possible to discriminate between patients who are at risk of further progression and require additional therapy and those in whom simple follow-up is adequate.

MALE BREAST CANCER Breast cancer is about 1/150th as frequent in men as in women; 1720 men developed breast cancer in 2006. It usually presents as a unilateral lump in the breast and is frequently not diagnosed promptly. Given the small amount of soft tissue and the unexpected nature of the problem, locally advanced presentations are somewhat more common. When male breast cancer is matched to female breast cancer by age and stage, its overall prognosis is identical. Although gynecomastia may initially be unilateral or asymmetric, any unilateral mass in a man older than age 40 years should receive a careful workup including biopsy. On the other hand, bilateral symmetric breast development rarely represents breast cancer and is almost invariably due to endocrine disease or a drug effect. It should be kept in mind, nevertheless, that the risk of cancer is much greater in men with gynecomastia; in such men, gross asymmetry of the breasts should arouse suspicion of cancer. Male breast cancer is best managed by mastectomy and axillary lymph node dissection or SLNB. Patients with locally advanced disease or positive nodes should also be treated with irradiation. Approximately 90% of male breast cancers contain estrogen receptors, and approximately 60% of cases with metastatic disease respond to endocrine therapy. No randomized studies have evaluated adjuvant therapy for male breast cancer. Two historic experiences suggest that the disease responds well to adjuvant systemic therapy, and, if not medically contraindicated, the same criteria for the use of adjuvant therapy in women should be applied to men.

The sites of relapse and spectrum of response to chemotherapeutic drugs are virtually identical for breast cancers in either sex.

FOLLOW-UP OF BREAST CANCER PATIENTS Despite the availability of sophisticated and expensive imaging techniques and a wide range of serum tumor marker tests, survival is not influenced by early diagnosis of relapse. Surveillance guidelines are given in **Table 38-5**. Despite pressure from patients and their families, routine computed tomography scans (or other imaging) are not recommended.

TABLE 38-5 BREAST CANCER SURVEILLANCE GUIDELINES

TEST	FREQUENCY
Recommended	
History; eliciting symptoms; physical examination	q3–6 months × 3 years; q6–12 months × 2 years; then annually
Breast self-examination	Monthly
Mammography	Annually
Pelvic examination	Annually (particularly for patients on SERMs)
Patient education about symptoms of recurrence	Ongoing
Coordination of care	Ongoing
Not Recommended	
Complete blood count	
Serum chemistry studies	
Chest radiographs	
Bone scans	
Ultrasound examination of the liver	
Computed tomography of chest, abdomen, or pelvis	
Tumor markers CA 15-3, CA 27-29, CEA	

Abbreviations: CEA, carcinoembryonic antigen; SERM, selective estrogen receptor modulator.
Source: Recommended Breast Cancer Surveillance Guidelines, ASCO Education Book, Fall, 1997.

CHAPTER 39

UPPER GASTROINTESTINAL TRACT CANCERS

Robert J. Mayer

Upper gastrointestinal cancers include malignancies arising in the esophagus, stomach, and small intestine.

ESOPHAGEAL CANCER

INCIDENCE AND ETIOLOGY

Cancer of the esophagus is an increasingly common and extremely lethal malignancy. T e diagnosis was made in 18,170 Americans in 2014 and led to 15,450 deaths. Almost all esophageal cancers are either squamous cell carcinomas or adenocarcinomas; the two histologic subtypes have a similar clinical presentation but different causative factors.

Worldwide, squamous cell carcinoma is the more common cell type, having an incidence that rises strikingly in association with geographic location. It occurs frequently within a region extending from the southern shore of the Caspian Sea on the west to northern China on the east, encompassing parts of Iran, central Asia, Afghanistan, Siberia, and Mongolia. Familial increased risk has been observed in regions with high incidence, although gene associations are not yet defined. High-incidence "pockets" of the disease are also present in such disparate locations as Finland, Iceland, Curaçao, southeastern Africa, and northwestern France. In North America and western Europe, the disease is more common in blacks than whites and in males than females; it appears most often after age 50 and seems to be associated with a lower socioeconomic status. Such cancers generally arise in the cervical and thoracic portions of the esophagus.

A variety of causative factors have been implicated in the development of squamous cell cancers of the esophagus **(Table 39-1)**. In the United States, the etiology of such cancers is primarily related to excess alcohol consumption and/or cigarette smoking. T e relative risk increases with the amount of tobacco smoked or alcohol consumed, with these factors acting synergistically. T e consumption of whiskey is linked to a higher incidence than the consumption of wine or beer. Squamous cell esophageal carcinoma has also been associated with the ingestion of nitrates, smoked opiates, and fungal toxins in pickled vegetables, as well as mucosal damage caused by such physical insults as long-term exposure to extremely hot tea, the ingestion of lye, radiation-induced strictures, and chronic achalasia. T e presence of an esophageal web in association with glossitis and iron deficiency (i.e., Plummer-Vinson or Paterson-Kelly syndrome) and congenital hyperkeratosis and pitting of the palms and soles (i.e., tylosis palmaris et plantaris) have each been linked with squamous cell esophageal cancer, as have dietary deficiencies of molybdenum, zinc, selenium, and vitamin A. Patients with head and neck cancer are at increased risk of squamous cell cancer of the esophagus.

TABLE 39-1

SOME ETIOLOGIC FACTORS ASSOCIATED WITH SQUAMOUS CELL CANCER OF THE ESOPHAGUS
Excess alcohol consumption
Cigarette smoking
Other ingested carcinogens
Nitrates (converted to nitrites)
Smoked opiates
Fungal toxins in pickled vegetables
Mucosal damage from physical agents
Hot tea
Lye ingestion
Radiation-induced strictures
Chronic achalasia
Host susceptibility
Esophageal web with glossitis and iron deficiency (i.e., Plummer-Vinson or Paterson-Kelly syndrome)
Congenital hyperkeratosis and pitting of the palms and soles (i.e., tylosis palmaris et plantaris)
? Dietary deficiencies of selenium, molybdenum, zinc, and vitamin A

TABLE 39-2

SOME ETIOLOGIC FACTORS ASSOCIATED WITH ADENOCARCINOMA OF THE ESOPHAGUS
Chronic gastroesophageal reflux
Obesity
Barrett's esophagus
Male sex
Cigarette smoking

For unclear reasons, the incidence of squamous cell esophageal cancer has decreased somewhat in both the black and white populations in the United States over the past 40 years, whereas the rate of adenocarcinoma has risen sevenfold, particularly in white males (male-to-female ratio of 6:1). Whereas squamous cell cancers comprised the vast majority of esophageal cancers in the United States as recently as 40–50 years ago, more than 75% of esophageal tumors are now adenocarcinomas, with the incidence of this histologic subtype continuing to increase rapidly. Understanding the cause for this increase is the focus of current investigation.

Several strong etiologic associations have been observed to account for the development of adenocarcinoma of the esophagus **(Table 39-2)**. Such tumors arise in the distal esophagus in association with chronic gastric reflux, often in the presence of Barrett's esophagus (replacement of the normal squamous epithelium of the distal esophagus by columnar mucosa), which occurs more commonly in obese individuals. Adenocarcinomas arise within dysplastic columnar epithelium in the distal esophagus. Even before frank neoplasia is detectable, aneuploidy and p53 mutations are found in the dysplastic epithelium. These adenocarcinomas behave clinically like gastric adenocarcinomas, although they are not associated with Helicobacter pylori infections. Approximately 15% of esophageal adenocarcinomas overexpress the HER2/neu gene.

CLINICAL FEATURES

About 5% of esophageal cancers occur in the upper third of the esophagus (cervical esophagus), 20% in the middle third, and 75% in the lower third. Squamous cell carcinomas and adenocarcinomas cannot be distinguished radiographically or endoscopically.

Progressive dysphagia and weight loss of short duration are the initial symptoms in the vast majority of patients. Dysphagia initially occurs with solid foods and gradually progresses to include semisolids and liquids. By the time these symptoms develop, the disease is already very advanced, because difficulty in swallowing does not occur until >60% of the esophageal circumference is infiltrated with cancer. Dysphagia may be associated with pain on swallowing (odynophagia), pain radiating to the chest and/or back, regurgitation or vomiting, and aspiration pneumonia. The disease most commonly spreads to adjacent and supraclavicular lymph nodes, liver, lungs, pleura, and bone. Tracheoesophageal fistulas may develop, primarily in patients with upper and mid-esophageal tumors. As with other squamous cell carcinomas, hypercalcemia may occur in the absence of osseous metastases, probably from parathormone-related peptide secreted by tumor cells **(Chap. 54)**.

DIAGNOSIS

Attempts at endoscopic and cytologic screening for carcinoma in patients with Barrett's esophagus, while effective as a means of detecting high-grade dysplasia, have not yet been shown to reduce the likelihood of death from esophageal adenocarcinoma. Esophagoscopy should be performed in all patients suspected of having an esophageal abnormality, to both visualize and identify a tumor and also to obtain histopathologic confirmation of the diagnosis. Because the population of persons at risk for squamous cell carcinoma of the esophagus (i.e., smokers and drinkers) also has a high rate of cancers of the lung and the head and neck region, endoscopic inspection of the larynx, trachea, and bronchi should also be carried out. A thorough examination of the fundus of the stomach (by retroflexing the endoscope) is imperative as well. The extent of tumor spread to the mediastinum and para-aortic lymph nodes should be assessed by computed tomography (CT) scans of the chest and abdomen and by endoscopic ultrasound. Positron emission tomography scanning provides a useful assessment of the presence of distant metastatic disease, offering accurate information regarding spread to mediastinal lymph nodes, which can be helpful in defining radiation therapy fields. Such scans, when performed sequentially, appear to provide a means of making an early assessment of responsiveness to preoperative chemotherapy.

TREATMENT Esophageal Cancer

The prognosis for patients with esophageal carcinoma is poor. Approximately 10% of patients survive 5 years after the diagnosis; thus, management focuses on symptom control. Surgical resection of all gross tumor (i.e., total resection) is feasible in only 45% of cases, with residual tumor cells frequently present at the resection margins. Such esophagectomies have been associated with a postoperative mortality rate of approximately 5% due to anastomotic fistulas, subphrenic abscesses, and cardiopulmonary complications. Although debate regarding the comparative benefits of transthoracic versus transhiatal resections has continued, experienced thoracic surgeons are now favoring minimally invasive transthoracic esophagectomies. Endoscopic resections of superficial squamous cell

cancers or adenocarcinomas are being examined but have not yet been shown to result in a similar likelihood of survival as observed with conventional surgical procedures. Similarly, the value of endoscopic ablation of dysplastic lesions in an area of Barrett's esophagus on reducing subsequent mortality from esophageal carcinoma is uncertain. Some experts have advocated fundoplication surgery (i.e., the removal of the gastroesophageal junction) as a means of cancer prevention in patients with Barrett's esophagus; again, objective data are not yet available to fully assess the risks versus benefits of this invasive procedure. About 20% of patients who survive a total surgical resection live for 5 years. The evaluation of chemotherapeutic agents in patients with esophageal carcinoma has been hampered by ambiguity in the definition of "response" and the debilitated physical condition of many treated individuals, particularly those with squamous cell cancers. Nonetheless, significant reductions in the size of measurable tumor masses have been reported in 15–25% of patients given single-agent treatment and in 30–60% of patients treated with drug combinations that include cisplatin. In the small subset of patients whose tumors overexpress the HER2/neu gene, the addition of the monoclonal antibody trastuzumab (Herceptin) appears to further enhance the likelihood of benefit, particularly in patients with gastroesophageal lesions. The use of the antiangiogenic agent bevacizumab (Avastin) seems to be of limited value in the setting of esophageal cancer. Combination chemotherapy and radiation therapy as the initial therapeutic approach, either alone or followed by an attempt at operative resection, seems to be beneficial. When administered along with radiation therapy, chemotherapy produces a better survival outcome than radiation therapy alone. The use of preoperative chemotherapy and radiation therapy followed by esophageal resection appears to prolong survival compared with surgery alone according to several randomized trials and a meta-analysis; some reports suggest that no additional benefit accrues when surgery is added if significant shrinkage of tumor has been achieved by the chemoradiation combination.

For the incurable, surgically unresectable patient with esophageal cancer, dysphagia, malnutrition, and the management of tracheoesophageal fistulas are major issues. Approaches to palliation include repeated endoscopic dilatation, the surgical placement of a gastrostomy or jejunostomy for hydration and feeding, endoscopic placement of an expansive metal stent to bypass the tumor, and radiation therapy.

TUMORS OF THE STOMACH

GASTRIC ADENOCARCINOMA

Incidence and Epidemiology

For unclear reasons, the incidence and mortality rates for gastric cancer have decreased in the United States during the past 80 years, although the disease remains the second most frequent cause of worldwide cancer-related death. The mortality rate from gastric cancer in the United States has dropped in men from 28 to 5.8 per 100,000 persons, whereas in women, the rate has decreased from 27 to 2.8 per 100,000. Nonetheless, in 2014, 22,220 new cases of stomach cancer were diagnosed in the United States, and 10,990 Americans died of the disease. Although the incidence of gastric cancer has decreased worldwide, it remains high in such disparate geographic regions as Japan, China, Chile, and Ireland.

The risk of gastric cancer is greater among lower socioeconomic classes. Migrants from high- to low-incidence nations maintain their susceptibility to gastric cancer, whereas the risk for their offspring approximates that of the new homeland. These findings suggest that an environmental exposure, probably beginning early in life, is related to the development of gastric cancer, with dietary carcinogens considered the most likely factor(s).

Pathology

About 85% of stomach cancers are adenocarcinomas, with 15% due to lymphomas, gastrointestinal stromal tumors (GISTs), and leiomyosarcomas. Gastric adenocarcinomas may be subdivided into two categories: a diffuse type, in which cell cohesion is absent, so that individual cells infiltrate and thicken the stomach wall without forming a discrete mass; and an intestinal type, characterized by cohesive neoplastic cells that form glandlike tubular structures. The diffuse carcinomas occur more often in younger patients, develop throughout the stomach (including the cardia), result in a loss of distensibility of the gastric wall (so-called linitis plastica, or "leather bottle" appearance), and carry a poorer prognosis. Diffuse cancers have defective intercellular adhesion, mainly as a consequence of loss of expression of E-cadherin. Intestinal-type lesions are frequently ulcerative, more commonly appear in the antrum and lesser curvature of the stomach, and are often preceded by a prolonged precancerous process, often initiated by H. pylori infection. Although the incidence of diffuse carcinomas is similar in most populations, the intestinal type tends to predominate in the high-risk geographic regions and is less likely to be found in areas where the frequency of gastric cancer is declining. Thus, different etiologic factor(s) are likely involved in these two subtypes. In the United States, ~30% of gastric cancers originate in the distal stomach, ~20% arise in the midportion of the stomach, and ~40% originate in the proximal third of the stomach. The remaining 10% involve the entire stomach.

Etiology

The long-term ingestion of high concentrations of nitrates found in dried, smoked, and salted foods appears to be associated with a higher risk. The nitrates are thought to be converted to carcinogenic nitrites by

TABLE 39-3

NITRATE-CONVERTING BACTERIA AS A FACTOR IN THE CAUSATION OF GASTRIC CARCINOMA[a]

Exogenous sources of nitrate-converting bacteria:
Bacterially contaminated food (common in lower socioeconomic classes, who have a higher incidence of the disease; diminished by improved food preservation and refrigeration)
Helicobacter pylori infection
Endogenous factors favoring growth of nitrate-converting bacteria in the stomach:
Decreased gastric acidity
Prior gastric surgery (antrectomy) (15- to 20-year latency period)
Atrophic gastritis and/or pernicious anemia
? Prolonged exposure to histamine H_2-receptor antagonists

[a]Hypothesis: Dietary nitrates are converted to carcinogenic nitrites by bacteria.

bacteria **(Table 39-3)**. Such bacteria may be introduced exogenously through the ingestion of partially decayed foods, which are consumed in abundance worldwide by the lower socioeconomic classes. Bacteria such as H. pylori may also contribute to this effect by causing chronic inflammatory atrophic gastritis, loss of gastric acidity, and bacterial growth in the stomach. Although the risk for developing gastric cancer is thought to be sixfold higher in people infected with H. pylori, it remains uncertain whether eradicating the bacteria after infection has already occurred actually reduces this risk. Loss of acidity may occur when acid-producing cells of the gastric antrum have been removed surgically to control benign peptic ulcer disease or when achlorhydria, atrophic gastritis, and even pernicious anemia develop in the elderly. Serial endoscopic examinations of the stomach in patients with atrophic gastritis have documented replacement of the usual gastric mucosa by intestinal-type cells. T is process of intestinal metaplasia may lead to cellular atypia and eventual neoplasia. Because the declining incidence of gastric cancer in the United States primarily reflects a decline in distal, ulcerating, intestinal-type lesions, it is conceivable that better food preservation and the availability of refrigeration for all socioeconomic classes have decreased the dietary ingestion of exogenous bacteria. H. pylori has not been associated with the diffuse, more proximal form of gastric carcinoma or with cancers arising at the gastroesophageal junction or in the distal esophagus. Approximately 10–15% of adenocarcinomas appearing in the proximal stomach, the gastroesophageal junction, and the distal esophagus overexpress the HER2/neu gene; individuals whose tumors demonstrate this overexpression benefit from treatment directed against this target (i.e., trastuzumab [Herceptin]).

Several additional etiologic factors have been associated with gastric carcinoma. Gastric ulcers and adenomatous polyps have occasionally been linked, but data on a cause-and-effect relationship are unconvincing. T e inadequate clinical distinction between benign gastric ulcers and small ulcerating carcinomas may, in part, account for this presumed association. T e presence of extreme hypertrophy of gastric rugal folds (i.e., Ménétrier's disease), giving the impression of polypoid lesions, has been associated with a striking frequency of malignant transformation; such hypertrophy, however, does not represent the presence of true adenomatous polyps. Individuals with blood group A have a higher incidence of gastric cancer than persons with blood group O; this observation may be related to differences in the mucous secretion, leading to altered mucosal protection from carcinogens. A germline mutation in the E-cadherin gene (CDH1), inherited in an autosomal dominant pattern and coding for a cell adhesion protein, has been linked to a high incidence of occult diffuse-type gastric cancers in young asymptomatic carriers. Duodenal ulcers are not associated with gastric cancer.

Clinical features

Gastric cancers, when superficial and surgically curable, usually produce no symptoms. As the tumor becomes more extensive, patients may complain of an insidious upper abdominal discomfort varying in intensity from a vague, postprandial fullness to a severe, steady pain. Anorexia, often with slight nausea, is very common but is not the usual presenting complaint. Weight loss may eventually be observed, and nausea and vomiting are particularly prominent in patients whose tumors involve the pylorus; dysphagia and early satiety may be the major symptoms caused by diffuse lesions originating in the cardia. T ere may be no early physical signs. A palpable abdominal mass indicates long-standing growth and predicts regional extension.

Gastric carcinomas spread by direct extension through the gastric wall to the perigastric tissues, occasionally adhering to adjacent organs such as the pancreas, colon, or liver. T e disease also spreads via lymphatics or by seeding of peritoneal surfaces. Metastases to intraabdominal and supraclavicular lymph nodes occur frequently, as do metastatic nodules to the ovary (Krukenberg's tumor), periumbilical region ("Sister Mary Joseph node"), or peritoneal cul-de-sac (Blumer's shelf palpable on rectal or vaginal examination); malignant ascites may also develop. T e liver is the most common site for hematogenous spread of tumor.

T e presence of iron-deficiency anemia in men and of occult blood in the stool in both sexes mandates a search for an occult gastrointestinal tract lesion. A careful assessment is of particular importance in patients with atrophic gastritis or pernicious anemia. Unusual clinical features associated with gastric adenocarcinomas include migratory thrombophlebitis, microangiopathic

hemolytic anemia, diffuse seborrheic keratoses (so-called Leser-Trélat sign), and acanthosis nigricans.

Diagnosis

The use of double-contrast radiographic examinations has been supplanted by esophagogastroscopy and CT scanning for the evaluation of patients with epigastric complaints.

Gastric ulcers identified at the time of such endoscopic procedure may appear benign but merit biopsy in order to exclude a malignancy. Malignant gastric ulcers must be recognized before they penetrate into surrounding tissues, because the rate of cure of early lesions limited to the mucosa or submucosa is >80%. Because gastric carcinomas are difficult to distinguish clinically or endoscopically from gastric lymphomas, endoscopic biopsies should be made as deeply as possible, due to the submucosal location of lymphoid tumors.

The staging system for gastric carcinoma is shown in **Table 39-4**.

TREATMENT Adenocarcinoma

Complete surgical removal of the tumor with resection of adjacent lymph nodes offers the only chance for cure. However, this is possible in less than a third of patients. A subtotal gastrectomy is the treatment of choice for patients with distal carcinomas, whereas total or near-total gastrectomies are required for more proximal tumors. The inclusion of extended lymph node dissection in these procedures appears to confer an added risk for complications without providing a meaningful enhancement in survival. The prognosis following complete surgical resection depends on the degree of tumor penetration into the stomach wall and is adversely influenced by regional lymph node involvement and vascular invasion, characteristics found in the vast majority of American patients. As a result, the probability of survival after 5 years for the 25–30% of patients able to undergo complete resection is ~20% for distal tumors and <10% for proximal tumors, with recurrences continuing for at least 8 years after surgery. In the absence of ascites or extensive hepatic or peritoneal metastases, even patients whose disease is believed to be incurable by surgery should be offered resection of the primary lesion. Reduction of tumor bulk is the best form of palliation and may enhance the probability of benefit from subsequent therapy. In high-incidence regions such as Japan and Korea, where the use of endoscopic screening programs has identified patients with superficial tumors, the use of laparoscopic gastrectomy has gained popularity. In the United States and western Europe, the use of this less invasive surgical approach remains investigational.

Gastric adenocarcinoma is a relatively radioresistant tumor, and the adequate control of the primary tumor requires doses of external-beam irradiation that exceed the tolerance of surrounding structures, such as bowel mucosa and spinal cord. As a result, the major role of radiation

TABLE 39-4

STAGING SYSTEM FOR GASTRIC CARCINOMA

			DATA FROM ACS IN THE UNITED STATES	
STAGE	TNM	FEATURES	NO. OF CASES, %	5-YEAR SURVIVAL, %
0	$T_{is}N0M0$	Node negative; limited to mucosa	1	90
IA	T1N0M0	Node negative; invasion of lamina propria or submucosa	7	59
IB	T2N0M0 T1N1M0	Node negative; invasion of muscularis propria	10	44
II	T1N2M0 T2N1M0	Node positive; invasion beyond mucosa but within wall or	17	29
	T3N0M0	Node negative; extension through wall		
IIIA	T2N2M0 T3N1-2M0	Node positive; invasion of muscularis propria or through wall	21	15
IIIB	T4N0-1M0	Node negative; adherence to surrounding tissue	14	9
IIIC	T4N2-3M0	>3 nodes positive; invasion of serosa or adjacent structures		
	T3N3M0	7 or more positive nodes; penetrates wall without invading serosa or adjacent structures		
IV	T4N2M0	Node positive; adherence to surrounding tissue or	30	3
	T1-4N0-2-M1	Distant metastases		

Abbreviations: ACS, American Cancer Society; TNM, tumor, node, metastasis.

therapy in patients has been palliation of pain. Radiation therapy alone after a complete resection does not prolong survival. In the setting of surgically unresectable disease limited to the epigastrium, patients treated with 3500–4000 cGy did not live longer than similar patients not receiving radiotherapy; however, survival was prolonged slightly when 5-fluorouracil (5-FU) plus leucovorin was given in combination with radiation therapy (3-year survival 50% vs 41% for radiation therapy alone). In this clinical setting, the 5-FU likely functions as a radiosensitizer.

T e administration of combinations of cytotoxic drugs to patients with advanced gastric carcinoma has been associated with partial responses in 30–50% of cases; responders appear to benefit from treatment. Such drug combinations have generally included cisplatin combined with epirubicin or docetaxel and infusional 5-FU or capecitabine, or with irinotecan. Despite the encouraging response rates, complete remissions are uncommon, the partial responses are transient, and the overall impact of multidrug therapy on survival has been limited; the median survival time for patients treated in this manner remains less than 12 months. As with adenocarcinomas arising in the esophagus, the addition of bevacizumab (Avastin) to chemotherapy regimens in treating gastric cancer appears to provide limited benefit. However, preliminary results utilizing another antiangiogenic compound—ramucirumab (Cyranza)—in the treatment of gastric cancer are encouraging. T e use of adjuvant chemotherapy alone following the complete resection of a gastric cancer has only minimally improved survival. However, combination chemotherapy administered before and after surgery (perioperative treatment) as well as postoperative chemotherapy combined with radiation therapy reduces the recurrence rate and prolongs survival.

PRIMARY GASTRIC LYMPHOMA

Primary lymphoma of the stomach is relatively uncommon, accounting for <15% of gastric malignancies and ~2% of all lymphomas. T e stomach is, however, the most frequent extranodal site for lymphoma, and gastric lymphoma has increased in frequency during the past 35 years. T e disease is dif cult to distinguish clinically from gastric adenocarcinoma; both tumors are most often detected during the sixth decade of life; present with epigastric pain, early satiety, and generalized fatigue; and are usually characterized by ulcerations with a ragged, thickened mucosal pattern demonstrated by contrast radiographs or endoscopic appearance. T e diagnosis of lymphoma of the stomach may occasionally be made through cytologic brushings of the gastric mucosa but usually requires a biopsy at gastroscopy or laparotomy. Failure of gastroscopic biopsies to detect lymphoma in a given case should not be interpreted as being conclusive, because superficial biopsies may miss the deeper lymphoid infiltrate. T e macroscopic pathology of gastric lymphoma may also mimic adenocarcinoma, consisting of either a bulky ulcerated lesion localized in the corpus or antrum or a diffuse process spreading throughout the entire gastric submucosa and even extending into the duodenum. Microscopically, the vast majority of gastric lymphoid tumors are lymphomas of B-cell origin. Histologically, these tumors may range from well-differentiated, superficial processes (mucosa-associated lymphoid tissue [MALT]) to high-grade, large-cell lymphomas. Like gastric adenocarcinoma, infection with H. pylori increases the risk for gastric lymphoma in general and MALT lymphomas in particular. Large-cell lymphomas of the stomach spread initially to regional lymph nodes (often to Waldeyer's ring) and may then disseminate.

TREATMENT Primary Gastric Lymphoma

Primary gastric lymphoma is a far more treatable disease than adenocarcinoma of the stomach, a fact that underscores the need for making the correct diagnosis. Antibiotic treatment to eradicate H. pylori infection has led to regression of about 75% of gastric MALT lymphomas and should be considered before surgery, radiation therapy, or chemotherapy is undertaken in patients having such tumors. A lack of response to such antimicrobial treatment has been linked to a specific chromosomal abnormality, i.e., t(11;18). Responding patients should undergo periodic endoscopic surveillance because it remains unclear whether the neoplastic clone is eliminated or merely suppressed, although the response to antimicrobial treatment is quite durable. Subtotal gastrectomy, usually followed by combination chemotherapy, has led to 5-year survival rates of 40–60% in patients with localized high-grade lymphomas. T e need for a major surgical procedure has been questioned, particularly in patients with preoperative radiographic evidence of nodal involvement, for whom chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]) plus rituximab is highly effective therapy. A role for radiation therapy is not defined because most recurrences develop at distant sites.

GASTRIC (NONLYMPHOID) SARCOMA

Leiomyosarcomas and GISTs make up 1–3% of gastric neoplasms. T ey most frequently involve the anterior and posterior walls of the gastric fundus and often ulcerate and bleed. Even those lesions that appear benign on histologic examination may behave in a malignant fashion. T ese tumors rarely invade adjacent viscera and characteristically do not metastasize to lymph nodes, but they may spread to the liver

and lungs. The treatment of choice is surgical resection. Combination chemotherapy should be reserved for patients with metastatic disease. All such tumors should be analyzed for a mutation in the c-kit receptor. GISTs are unresponsive to conventional chemotherapy; yet ~50% of patients experience objective response and prolonged survival when treated with imatinib mesylate (Gleevec) (400–800 mg PO daily), a selective inhibitor of the c-kit tyrosine kinase. Many patients with GIST whose tumors have become refractory to imatinib subsequently benefit from sunitinib (Sutent) or regorafenib (Stivarga), other inhibitors of the c-kit tyrosine kinase.

TUMORS OF THE SMALL INTESTINE

Small-bowel tumors comprise <3% of gastrointestinal neoplasms. Because of their rarity and inaccessibility, a correct diagnosis is often delayed. Abdominal symptoms are usually vague and poorly defined, and conventional radiographic studies of the upper and lower intestinal tract often appear normal. Small-bowel tumors should be considered in the differential diagnosis in the following situations: (1) recurrent, unexplained episodes of crampy abdominal pain; (2) intermittent bouts of intestinal obstruction, especially in the absence of inflammatory bowel disease (IBD) or prior abdominal surgery; (3) intussusception in the adult; and (4) evidence of chronic intestinal bleeding in the presence of negative conventional and endoscopic examination. A careful small-bowel barium study should be considered in such a circumstance; the diagnostic accuracy may be improved by infusing barium through a nasogastric tube placed into the duodenum (enteroclysis). Alternatively, capsule endoscopic procedures have been used.

BENIGN TUMORS

The histology of benign small-bowel tumors is difficult to predict on clinical and radiologic grounds alone. The symptomatology of benign tumors is not distinctive, with pain, obstruction, and hemorrhage being the most frequent symptoms. These tumors are usually discovered during the fifth and sixth decades of life, more often in the distal rather than the proximal small intestine. The most common benign tumors are adenomas, leiomyomas, lipomas, and angiomas.

Adenomas

These tumors include those of the islet cells and Brunner's glands as well as polypoid adenomas. Islet cell adenomas are occasionally located outside the pancreas; the associated syndromes are discussed in **Chap. 51**. Brunner's gland adenomas are not truly neoplastic but represent a hypertrophy or hyperplasia of submucosal duodenal glands. These appear as small nodules in the duodenal mucosa that secrete a highly viscous alkaline mucus. Most often, this is an incidental radiographic finding not associated with any specific clinical disorder.

Polypoid adenomas

About 25% of benign small-bowel tumors are polypoid adenomas **(see Table 40-2)**. They may present as single polypoid lesions or, less commonly, as papillary villous adenomas. As in the colon, the sessile or papillary form of the tumor is sometimes associated with a coexisting carcinoma. Occasionally, patients with Gardner's syndrome develop premalignant adenomas in the small bowel; such lesions are generally in the duodenum. Multiple polypoid tumors may occur throughout the small bowel (and occasionally the stomach and colorectum) in the Peutz-Jeghers syndrome. The polyps are usually hamartomas (juvenile polyps) having a low potential for malignant degeneration. Mucocutaneous melanin deposits as well as tumors of the ovary, breast, pancreas, and endometrium are also associated with this autosomal dominant condition.

Leiomyomas

These neoplasms arise from smooth-muscle components of the intestine and are usually intramural, affecting the overlying mucosa. Ulceration of the mucosa may cause gastrointestinal hemorrhage of varying severity. Cramping or intermittent abdominal pain is frequently encountered.

Lipomas

These tumors occur with greatest frequency in the distal ileum and at the ileocecal valve. They have a characteristic radiolucent appearance and are usually intramural and asymptomatic, but on occasion cause bleeding.

Angiomas

While not true neoplasms, these lesions are important because they frequently cause intestinal bleeding. They may take the form of telangiectasia or hemangiomas. Multiple intestinal telangiectasias occur in a nonhereditary form confined to the gastrointestinal tract or as part of the hereditary Osler-Rendu-Weber syndrome. Vascular tumors may also take the form of isolated hemangiomas, most commonly in the jejunum. Angiography, especially during bleeding, is the best procedure for evaluating these lesions.

MALIGNANT TUMORS

While rare, small-bowel malignancies occur in patients with long-standing regional enteritis and celiac sprue as well as in individuals with AIDS. Malignant tumors of the small bowel are frequently associated with fever, weight loss, anorexia, bleeding, and a palpable abdominal mass. After ampullary carcinomas (many of which arise from biliary or pancreatic ducts), the most frequently occurring small-bowel malignancies are adenocarcinomas, lymphomas, carcinoid tumors, and leiomyosarcomas.

ADENOCARCINOMAS

T e most common primary cancers of the small bowel are adenocarcinomas, accounting for ~50% of malignant tumors. T ese cancers occur most often in the distal duodenum and proximal jejunum, where they tend to ulcerate and cause hemorrhage or obstruction. Radiologically, they may be confused with chronic duodenal ulcer disease or with Crohn's disease if the patient has long-standing regional enteritis. T e diagnosis is best made by endoscopy and biopsy under direct vision. Surgical resection is the treatment of choice with suggested postoperative adjuvant chemotherapy options generally following treatment patterns used in the management of colon cancer.

LYMPHOMAS

Lymphoma in the small bowel may be primary or secondary. A diagnosis of a primary intestinal lymphoma requires histologic confirmation in a clinical setting in which palpable adenopathy and hepatosplenomegaly are absent and no evidence of lymphoma is seen on chest radiograph, CT scan, or peripheral blood smear or on bone marrow aspiration and biopsy. Symptoms referable to the small bowel are present, usually accompanied by an anatomically discernible lesion. Secondary lymphoma of the small bowel consists of involvement of the intestine by a lymphoid malignancy extending from involved retroperitoneal or mesenteric lymph nodes **(Chap. 16)**.

Primary intestinal lymphoma accounts for ~20% of malignancies of the small bowel. T ese neoplasms are non-Hodgkin's lymphomas; they usually have a diffuse, large-cell histology and are of T cell origin. Intestinal lymphoma involves the ileum, jejunum, and duodenum, in decreasing frequency—a pattern that mirrors the relative amount of normal lymphoid cells in these anatomic areas. T e risk of small-bowel lymphoma is increased in patients with a prior history of malabsorptive conditions (e.g., celiac sprue), regional enteritis, and depressed immune function due to congenital immunodeficiency syndromes, prior organ transplantation, autoimmune disorders, or AIDS.

T e development of localized or nodular masses that narrow the lumen results in periumbilical pain (made worse by eating) as well as weight loss, vomiting, and occasional intestinal obstruction. T e diagnosis of small-bowel lymphoma may be suspected from the appearance on contrast radiographs of patterns such as infiltration and thickening of mucosal folds, mucosal nodules, areas of irregular ulceration, or stasis of contrast material. T e diagnosis can be confirmed by surgical exploration and resection of involved segments. Intestinal lymphoma can occasionally be diagnosed by peroral intestinal mucosal biopsy, but because the disease mainly involves the lamina propria, full-thickness surgical biopsies are usually required.

Resection of the tumor constitutes the initial treatment modality. While postoperative radiation therapy has been given to some patients following a total resection, most authorities favor short-term (three cycles) systemic treatment with combination chemotherapy. T e frequent presence of widespread intraabdominal disease at the time of diagnosis and the occasional multicentricity of the tumor often make a total resection impossible. T e probability of sustained remission or cure is ~75% in patients with localized disease but is ~25% in individuals with unresectable lymphoma. In patients whose tumors are not resected, chemotherapy may lead to bowel perforation.

A unique form of small-bowel lymphoma, diffusely involving the entire intestine, was first described in oriental Jews and Arabs and is referred to as immunoproli*f*erative small intestinal disease (IPSID), Mediterranean lymphoma, or α heavy chain disease. T is is a B cell tumor. T e typical presentation includes chronic diarrhea and steatorrhea associated with vomiting and abdominal cramps; clubbing of the digits may be observed. A curious feature in many patients with IPSID is the presence in the blood and intestinal secretions of an abnormal IgA that contains a shortened α heavy chain and is devoid of light chains. It is suspected that the abnormal α chains are produced by plasma cells infiltrating the small bowel. T e clinical course of patients with IPSID is generally one of exacerbations and remissions, with death frequently resulting from either progressive malnutrition and wasting or the development of an aggressive lymphoma. T e use of oral antibiotics such as tetracycline appears to be beneficial in the early phases of the disorder, suggesting a possible infectious etiology. Combination chemotherapy has been administered during later stages of the disease, with variable results. Results are better when antibiotics and chemotherapy are combined.

CARCINOID TUMORS

Carcinoid tumors arise from argentaf n cells of the crypts of Lieberkühn and are found from the distal duodenum to the ascending colon, areas embryologically derived from the midgut. More than 50% of intestinal carcinoids are found in the distal ileum, with most congregating close to the ileocecal valve. Most intestinal carcinoids are asymptomatic and of low malignant potential, but invasion and metastases may occur, leading to the carcinoid syndrome **(Chap. 51)**.

LEIOMYOSARCOMAS

Leiomyosarcomas often are >5 cm in diameter and may be palpable on abdominal examination. Bleeding, obstruction, and perforation are common. Such tumors should be analyzed for the expression of mutant c-kit receptor (defining GIST), and in the presence of metastatic disease, justifying treatment with imatinib mesylate (Gleevec) or, in imatinib-refractory patients, sunitinib (Sutent) or regorafenib (Stivarga).

CHAPTER 40

LOWER GASTROINTESTINAL CANCERS

Robert J. Mayer

Lower gastrointestinal cancers include malignant tumors of the colon, rectum, and anus.

COLORECTAL CANCER

INCIDENCE

Cancer of the large bowel is second only to lung cancer as a cause of cancer death in the United States: 136,830 new cases occurred in 2014, and 50,310 deaths were due to colorectal cancer. T e incidence rate has decreased significantly during the past 25 years, likely due to enhanced and more compliantly followed screening practices. Similarly, mortality rates in the United States have decreased by approximately 25%, resulting largely from earlier detection and improved treatment.

POLYPS AND MOLECULAR PATHOGENESIS

Most colorectal cancers, regardless of etiology, arise from adenomatous polyps. A polyp is a grossly visible protrusion from the mucosal surface and may be classified pathologically as a nonneoplastic hamartoma (e.g., juvenile polyp), a hyperplastic mucosal proliferation (hyperplastic polyp), or an adenomatous polyp. Only adenomas are clearly premalignant, and only a minority of adenomatous polyps evolve into cancer. Adenomatous polyps may be found in the colons of ~30% of middle-aged and ~50% of elderly people; however, <1% of polyps ever become malignant. Most polyps produce no symptoms and remain clinically undetected. Occult blood in the stool is found in <5% of patients with polyps.

A number of molecular changes are noted in adenomatous polyps and colorectal cancers that are thought to reflect a multistep process in the evolution of normal colonic mucosa to life-threatening invasive carcinoma. T ese developmental steps toward carcinogenesis include, but are not restricted to, point mutations in the K-ras protooncogene; hypomethylation of DNA, leading to gene activation; loss of DNA (allelic loss) at the site of a tumor-suppressor gene (the adenomatous polyposis coli [APC] gene) on the long arm of chromosome 5 (5q21); allelic loss at the site of a tumor-suppressor gene located on chromosome 18q (the deleted in colorectal cancer [DCC] gene); and allelic loss at chromosome 17p, associated with mutations in the p53 tumor-suppressor gene **(see Fig. 25-2)**. T us, the altered proliferative pattern of the colonic mucosa, which results in progression to a polyp and then to carcinoma, may involve the mutational activation of an oncogene followed by and coupled with the loss of genes that normally suppress tumorigenesis. It remains uncertain whether the genetic aberrations always occur in a defined order. Based on this model, however, cancer is believed to develop only in those polyps in which most (if not all) of these mutational events take place.

Clinically, the probability of an adenomatous polyp becoming a cancer depends on the gross appearance of the lesion, its histologic features, and its size. Adenomatous polyps may be pedunculated (stalked) or sessile (flat-based). Invasive cancers develop more frequently in sessile polyps. Histologically, adenomatous polyps may be tubular, villous (i.e., papillary), or tubulovillous. Villous adenomas, most of which are sessile, become malignant more than three times as often as tubular adenomas. T e likelihood that any polypoid lesion in the large bowel contains invasive cancer is related to the size of the polyp, being negligible (<2%) in lesions <1.5 cm, intermediate (2–10%) in lesions 1.5–2.5 cm, and substantial (10%) in lesions >2.5 cm in size.

Following the detection of an adenomatous polyp, the entire large bowel should be visualized endoscopically because synchronous lesions are noted in about one-third of cases. Colonoscopy should then be repeated periodically, even in the absence of a

previously documented malignancy, because such patients have a 30–50% probability of developing another adenoma and are at a higher-than-average risk for developing a colorectal carcinoma. Adenomatous polyps are thought to require >5 years of growth before becoming clinically significant; colonoscopy need not be carried out more frequently than every 3 years for the vast majority of patients.

ETIOLOGY AND RISK FACTORS

Risk factors for the development of colorectal cancer are listed in **Table 40-1**.

Diet

The etiology for most cases of large-bowel cancer appears to be related to environmental factors. The disease occurs more often in upper socioeconomic populations who live in urban areas. Mortality from colorectal cancer is directly correlated with per capita consumption of calories, meat protein, and dietary fat and oil as well as elevations in the serum cholesterol concentration and mortality from coronary artery disease. Geographic variations in incidence largely are unrelated to genetic differences, since migrant groups tend to assume the large-bowel cancer incidence rates of their adopted countries. Furthermore, population groups such as Mormons and Seventh Day Adventists, whose lifestyle and dietary habits differ somewhat from those of their neighbors, have significantly lower-than-expected incidence and mortality rates for colorectal cancer. The incidence of colorectal cancer has increased in Japan since that nation has adopted a more "Western" diet. At least three hypotheses have been proposed to explain the relationship to diet, none of which is fully satisfactory.

Animal fats

One hypothesis is that the ingestion of animal fats found in red meats and processed meat leads to an increased proportion of anaerobes in the gut microflora, resulting in the conversion of normal bile acids into carcinogens. This provocative hypothesis is supported by several reports of increased amounts of fecal anaerobes in the stools of patients with colorectal cancer. Diets high in animal (but not vegetable) fats are also associated with high serum cholesterol, which is also associated with enhanced risk for the development of colorectal adenomas and carcinomas.

Insulin resistance

The large number of calories in Western diets coupled with physical inactivity has been associated with a higher prevalence of obesity. Obese persons develop insulin resistance with increased circulating levels of insulin, leading to higher circulating concentrations of insulin-like growth factor type I (IGF-I). This growth factor appears to stimulate proliferation of the intestinal mucosa.

Fiber

Contrary to prior beliefs, the results of randomized trials and case-controlled studies have failed to show any value for dietary fiber or diets high in fruits and vegetables in preventing the recurrence of colorectal adenomas or the development of colorectal cancer.

The weight of epidemiologic evidence, however, implicates diet as being the major etiologic factor for colorectal cancer, particularly diets high in animal fat and in calories.

TABLE 40-1

RISK FACTORS FOR THE DEVELOPMENT OF COLORECTAL CANCER
Diet: Animal fat
Hereditary syndromes
Polyposis coli
MYH-associated polyposis
Nonpolyposis syndrome (Lynch's syndrome)
Inflammatory bowel disease
Streptococcus bovis bacteremia
? Tobacco use

HEREDITARY FACTORS AND SYNDROMES

Up to 25% of patients with colorectal cancer have a family history of the disease, suggesting a hereditary predisposition. Inherited large-bowel cancers can be divided into two main groups: the well-studied but uncommon polyposis syndromes and the more common nonpolyposis syndromes **(Table 40-2)**.

Polyposis coli

Polyposis coli (familial polyposis of the colon) is a rare condition characterized by the appearance of thousands of adenomatous polyps throughout the large bowel. It is transmitted as an autosomal dominant trait; the occasional patient with no family history probably developed the condition due to a spontaneous mutation. Polyposis coli is associated with a deletion in the long arm of chromosome 5 (including the APC gene) in both neoplastic (somatic mutation) and normal (germline mutation) cells. The loss of this genetic material (i.e., allelic loss) results in the absence of tumor-suppressor genes whose protein products would normally inhibit neoplastic growth. The presence of soft tissue and bony tumors, congenital hypertrophy of the retinal pigment epithelium, mesenteric desmoid tumors, and ampullary cancers in addition to the colonic polyps characterizes

TABLE 40-2

HEREDITABLE (AUTOSOMAL DOMINANT) GASTROINTESTINAL POLYPOSIS SYNDROMES

SYNDROME	DISTRIBUTION OF POLYPS	HISTOLOGIC TYPE	MALIGNANT POTENTIAL	ASSOCIATED LESIONS
Familial adenomatous polyposis	Large intestine	Adenoma	Common	None
Gardner's syndrome	Large and small intestines	Adenoma	Common	Osteomas, fibromas, lipomas, epidermoid cysts, ampullary cancers, congenital hypertrophy of retinal pigment epithelium
Turcot's syndrome	Large intestine	Adenoma	Common	Brain tumors
MYH-associated polyposis	Large intestine	Adenoma	Common	None
Nonpolyposis syndrome (Lynch's syndrome)	Large intestine (often proximal)	Adenoma	Common	Endometrial and ovarian tumors (most frequently) gastric, genitourinary, pancreatic, biliary cancers (less frequently)
Peutz-Jeghers syndrome	Small and large intestines, stomach	Hamartoma	Rare	Mucocutaneous pigmentation; tumors of the ovary, breast, pancreas, endometrium
Juvenile polyposis	Large and small intestines, stomach	Hamartoma, rarely progressing to adenoma	Rare	Various congenital abnormalities

a subset of polyposis coli known as Gardner's syndrome. The appearance of malignant tumors of the central nervous system accompanying polyposis coli defines Turcot's syndrome. The colonic polyps in all these conditions are rarely present before puberty but are generally evident in affected individuals by age 25. If the polyposis is not treated surgically, colorectal cancer will develop in almost all patients before age 40. Polyposis coli results from a defect in the colonic mucosa, leading to an abnormal proliferative pattern and impaired DNA repair mechanisms. Once the multiple polyps are detected, patients should undergo a total colectomy. Medical therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) such as sulindac and selective cyclooxygenase-2 inhibitors such as celecoxib can decrease the number and size of polyps in patients with polyposis coli; however, this effect on polyps is only temporary, and the use of NSAIDs has not been shown to reduce the risk of cancer. Colectomy remains the primary therapy/prevention. The offspring of patients with polyposis coli, who often are prepubertal when the diagnosis is made in the parent, have a 50% risk for developing this premalignant disorder and should be carefully screened by annual flexible sigmoidoscopy until age 35. Proctosigmoidoscopy is a sufficient screening procedure because polyps tend to be evenly distributed from cecum to anus, making more invasive and expensive techniques such as colonoscopy or barium enema unnecessary. Testing for occult blood in the stool is an inadequate screening maneuver. If a causative germline APC mutation has been identified in an affected family member, an alternative method for identifying carriers is testing DNA from peripheral blood mononuclear cells for the presence of the specific APC mutation. The detection of such a germline mutation can lead to a definitive diagnosis before the development of polyps.

MYH-Associated polyposis

MYH-associated polyposis (MAP) is a rare autosomal recessive syndrome caused by a biallelic mutation in the MUT4H gene. This hereditary condition may have a variable clinical presentation, resembling polyposis coli or colorectal cancer occurring in younger individuals without polyposis. Screening and colectomy guidelines for this syndrome are less clear than for polyposis coli, but annual to biennial colonoscopic surveillance is generally recommended starting at age 25–30.

Hereditary nonpolyposis colon cancer

Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch's syndrome, is another autosomal dominant trait. It is characterized by the presence of three or more relatives with histologically documented colorectal cancer, one of whom is a first-degree relative of the other two; one or more cases of colorectal cancer diagnosed before age 50 in the family; and colorectal cancer involving at least two generations. In contrast to polyposis coli, HNPCC is associated with an unusually high frequency of cancer arising in the proximal large bowel. The median age for the appearance of an

adenocarcinoma is <50 years, 10–15 years younger than the median age for the general population. Despite having a poorly differentiated, mucinous histologic appearance, the proximal colon tumors that characterize HNPCC have a better prognosis than sporadic tumors from patients of similar age. Families with HNPCC often include individuals with multiple primary cancers; the association of colorectal cancer with either ovarian or endometrial carcinomas is especially strong in women, and an increased appearance of gastric, small-bowel, genitourinary, pancreaticobiliary, and sebaceous skin tumors has been reported as well. It has been recommended that members of such families undergo annual or biennial colonoscopy beginning at age 25 years, with intermittent pelvic ultrasonography and endometrial biopsy for af icted women; such a screening strategy has not yet been validated. HNPCC is associated with germline mutations of several genes, particularly hMSH2 on chromosome 2 and hMLH1 on chromosome 3. T ese mutations lead to errors in DNA replication and are thought to result in DNA instability because of defective repair of DNA mismatches resulting in abnormal cell growth and tumor development. Testing tumor cells through molecular analysis of DNA or immunohistochemical staining of paraffin-fixed tissue for "microsatellite instability" (sequence changes reflecting defective mismatch repair) in patients with colorectal cancer and a positive family history for colorectal or endometrial cancer may identify probands with HNPCC.

INFLAMMATORY BOWEL DISEASE

Large-bowel cancer is increased in incidence in patients with long-standing inflammatory bowel disease (IBD). Cancers develop more commonly in patients with ulcerative colitis than in those with granulomatous (i.e., Crohn's) colitis, but this impression may result in part from the occasional difficulty of differentiating these two conditions. T e risk of colorectal cancer in a patient with IBD is relatively small during the initial 10 years of the disease, but then appears to increase at a rate of ~0.5–1% per year. Cancer may develop in 8–30% of patients after 25 years. T e risk is higher in younger patients with pancolitis.

Cancer surveillance strategies in patients with IBD are unsatisfactory. Symptoms such as bloody diarrhea, abdominal cramping, and obstruction, which may signal the appearance of a tumor, are similar to the complaints caused by a flare-up of the underlying disease. In patients with a history of IBD lasting ≥15 years who continue to experience exacerbations, the surgical removal of the colon can significantly reduce the risk for cancer and also eliminate the target organ for the underlying chronic gastrointestinal disorder. T e value of such surveillance techniques as colonoscopy with mucosal biopsies and brushings for less symptomatic individuals with chronic IBD is uncertain. T e lack of uniformity regarding the pathologic criteria that characterize dysplasia and the absence of data that such surveillance reduces the development of lethal cancers have made this costly practice an area of controversy.

OTHER HIGH-RISK CONDITIONS

Streptococcus bovis bacteremia

For unknown reasons, individuals who develop endocarditis or septicemia from this fecal bacterium have a high incidence of occult colorectal tumors and, possibly, upper gastrointestinal cancers as well. Endoscopic or radiographic screening appears advisable.

Tobacco use

Cigarette smoking is linked to the development of colorectal adenomas, particularly after >35 years of tobacco use. No biologic explanation for this association has yet been proposed.

PRIMARY PREVENTION

Several orally administered compounds have been assessed as possible inhibitors of colon cancer. T e most effective class of chemopreventive agents is aspirin and other NSAIDs, which are thought to suppress cell proliferation by inhibiting prostaglandin synthesis. Regular aspirin use reduces the risk of colon adenomas and carcinomas as well as death from large-bowel cancer; such use also appears to diminish the likelihood for developing additional premalignant adenomas following successful treatment for a prior colon carcinoma. T is effect of aspirin on colon carcinogenesis increases with the duration and dosage of drug use. Oral folic acid supplements and oral calcium supplements appear to reduce the risk of adenomatous polyps and colorectal cancers in case-controlled studies. T e value of vitamin D as a form of chemoprevention is under study. Antioxidant vitamins such as ascorbic acid, tocopherols, and β-carotene are ineffective at reducing the incidence of subsequent adenomas in patients who have undergone the removal of a colon adenoma. Estrogen replacement therapy has been associated with a reduction in the risk of colorectal cancer in women, conceivably by an effect on bile acid synthesis and composition or by decreasing synthesis of IGF-I.

SCREENING

T e rationale for colorectal cancer screening programs is that the removal of adenomatous polyps will prevent

colorectal cancer, and that earlier detection of localized, superficial cancers in asymptomatic individuals will increase the surgical cure rate. Such screening programs are particularly important for individuals with a family history of the disease in first-degree relatives. The relative risk for developing colorectal cancer increases to 1.75 in such individuals and may be even higher if the relative was afflicted before age 60. The prior use of proctosigmoidoscopy as a screening tool was based on the observation that 60% of early lesions are located in the rectosigmoid. For unexplained reasons, however, the proportion of large-bowel cancers arising in the rectum has been decreasing during the past several decades, with a corresponding increase in the proportion of cancers in the more proximal descending colon. As such, the potential for proctosigmoidoscopy to detect a sufficient number of occult neoplasms to make the procedure cost-effective has been questioned.

Screening strategies for colorectal cancer that have been examined during the past several decades are listed in **Table 40-3**.

Many programs directed at the early detection of colorectal cancers have focused on digital rectal examinations and fecal occult blood (i.e., stool guaiac) testing. The digital examination should be part of any routine physical evaluation in adults older than age 40 years, serving as a screening test for prostate cancer in men, a component of the pelvic examination in women, and an inexpensive maneuver for the detection of masses in the rectum. However, because of the proximal migration of colorectal tumors, its value as an overall screening modality for colorectal cancer has become limited. The development of the fecal occult blood test has greatly facilitated the detection of occult fecal blood. Unfortunately, even when performed optimally, the fecal occult blood test has major limitations as a screening technique. About 50% of patients with documented colorectal cancers have a negative fecal occult blood test, consistent with the intermittent bleeding pattern of these tumors. When random cohorts of asymptomatic persons have been tested, 2–4% have fecal occult blood-positive stools. Colorectal cancers have been found in <10% of these "test-positive" cases, with benign polyps being detected in an additional 20–30%. Thus, a colorectal neoplasm will not be found in most asymptomatic individuals with occult blood in their stool. Nonetheless, persons found to have fecal occult blood-positive stool routinely undergo further medical evaluation, including sigmoidoscopy and/or colonoscopy—procedures that are not only uncomfortable and expensive but also associated with a small risk for significant complications. The added cost of these studies would appear justifiable if the small number of patients found to have occult neoplasms because of fecal occult blood screening could be shown to have an improved prognosis and prolonged survival. Prospectively controlled trials have shown a statistically significant reduction in mortality rate from colorectal cancer for individuals undergoing annual stool guaiac screening. However, this benefit only emerged after >13 years of follow-up and was extremely expensive to achieve, because all positive tests (most of which were falsely positive) were followed by colonoscopy. Moreover, these colonoscopic examinations quite likely provided the opportunity for cancer prevention through the removal of potentially premalignant adenomatous polyps because the eventual development of cancer was reduced by 20% in the cohort undergoing annual screening.

With the appreciation that the carcinogenic process leading to the progression of the normal bowel mucosa to an adenomatous polyp and then to a cancer is the result of a series of molecular changes, investigators have examined fecal DNA for evidence of mutations associated with such molecular changes as evidence of the occult presence of precancerous lesions or actual malignancies. Such a strategy has been tested in more than 4000 asymptomatic individuals whose stool was assessed for occult blood and for 21 possible mutations in fecal DNA; these study subjects also underwent colonoscopy. Although the fecal DNA strategy suggested the presence of more advanced adenomas and cancers than did the fecal occult blood testing approach, the overall sensitivity, using colonoscopic findings as the standard, was less than 50%, diminishing enthusiasm for further pursuit of the fecal DNA screening strategy.

The use of imaging studies to screen for colorectal cancers has also been explored. Air contrast barium enemas had been used to identify sources of occult blood in the stool prior to the advent of fiberoptic endoscopy; the cumbersome nature of the procedure and inconvenience to patients limited its widespread adoption. The introduction of computed tomography (CT) scanning led to the development of virtual (i.e., CT) colonography as an alternative to the growing use of endoscopic screening techniques. Virtual colonography was proposed as being

TABLE 40-3

SCREENING STRATEGIES FOR COLORECTAL CANCER
Digital rectal examination
Stool testing
• Occult blood
• Fecal DNA
Imaging
• Contrast barium enema
• Virtual (i.e., computed tomography colonography)
Endoscopy
• Flexible sigmoidoscopy
• Colonoscopy

equivalent in sensitivity to colonoscopy and being available in a more widespread manner because it did not require the same degree of operator expertise as fiberoptic endoscopy. However, virtual colonography requires the same cathartic preparation that has limited widespread acceptance of endoscopic colonoscopy, is diagnostic but not therapeutic (i.e., patients with suspicious findings must undergo a subsequent endoscopic procedure for polypectomy or biopsy), and, in the setting of general radiology practices, appears to be less sensitive as a screening technique when compared with endoscopic procedures.

With the appreciation of the inadequacy of fecal occult blood testing alone, concerns about the practicality of imaging approaches, and the wider adoption of endoscopic examinations by the primary care community, screening strategies in asymptomatic persons have changed. At present, both the American Cancer Society and the National Comprehensive Cancer Network suggest either fecal occult blood testing annually coupled with flexible sigmoidoscopy every 5 years or colonoscopy every 10 years beginning at age 50 in asymptomatic individuals with no personal or family history of polyps or colorectal cancer. T e recommendation for the inclusion of flexible sigmoidoscopy is strongly supported by the recently published results of three randomized trials performed in the United States, the United Kingdom, and Italy, involving more than 350,000 individuals, which consistently showed that periodic (even single) sigmoidoscopic examinations, after more than a decade of median follow-up, lead to an approximate 21% reduction in the development of colorectal cancer and a more than 25% reduction in mortality from the malignant disease. Less than 20% of participants in these studies underwent a subsequent colonoscopy. In contrast to the cathartic preparation required before colonoscopic procedures, which is only performed by highly trained specialists, flexible sigmoidoscopy requires only an enema as preparation and can be accurately performed by nonspecialty physicians or physician-extenders. T e randomized screening studies using flexible sigmoidoscopy led to the estimate that approximately 650 individuals needed to be screened to prevent one colorectal cancer death; this contrasts with the data for mammography where the number of women needing to be screened to prevent one breast cancer death is 2500, reinforcing the efficacy of endoscopic surveillance for colorectal cancer screening. Presumably the benefit from the sigmoidoscopic screening is the result of the identification and removal of adenomatous polyps; it is intriguing that this benefit has been achieved using a technique that leaves the proximal half of the large bowel unvisualized.

It remains to be seen whether surveillance colonoscopy, which has gained increasing popularity in the United States for colorectal cancer screening, will prove to be more effective than flexible sigmoidoscopy. Ongoing randomized trials being conducted in Europe are addressing this issue. Although flexible sigmoidoscopy only visualizes the distal half of the large bowel, leading to the assumption that colonoscopy represents a more informative approach, colonoscopy has been reported as being less accurate for screening the proximal rather than the distal colon, perhaps due to technical considerations but also possibly because of a greater frequency of serrated (i.e., "flat") polyps in the right colon, which are more difficult to identify. At present, colonoscopy performed every 10 years has been offered as an alternative to annual fecal occult blood testing with periodic (every 5 years) flexible sigmoidoscopy. Colonoscopy has been shown to be superior to double-contract barium enema and also to have a higher sensitivity for detecting villous or dysplastic adenomas or cancers than the strategy using occult fecal blood testing and flexible sigmoidoscopy. Whether colonoscopy performed every 10 years beginning at age 50 is medically superior and economically equivalent to flexible sigmoidoscopy remains to be determined.

CLINICAL FEATURES

Presenting symptoms

Symptoms vary with the anatomic location of the tumor. Because stool is relatively liquid as it passes through the ileocecal valve into the right colon, cancers arising in the cecum and ascending colon may become quite large without resulting in any obstructive symptoms or noticeable alterations in bowel habits. Lesions of the right colon commonly ulcerate, leading to chronic, insidious blood loss without a change in the appearance of the stool. Consequently, patients with tumors of the ascending colon often present with symptoms such as fatigue, palpitations, and even angina pectoris and are found to have a hypochromic, microcytic anemia indicative of iron deficiency. Because the cancers may bleed intermittently, a random fecal occult blood test may be negative. As a result, the unexplained presence of iron-deficiency anemia in any adult (with the possible exception of a premenopausal, multiparous woman) mandates a thorough endoscopic and/or radiographic visualization of the entire large bowel **(Fig. 40-1)**.

Because stool becomes more formed as it passes into the transverse and descending colon, tumors arising there tend to impede the passage of stool, resulting in the development of abdominal cramping, occasional obstruction, and even perforation. Radiographs of the abdomen often reveal characteristic annular, constricting lesions ("apple-core" or "napkin-ring") **(Fig. 40-2)**.

Cancers arising in the rectosigmoid are often associated with hematochezia, tenesmus, and narrowing of the caliber of stool; anemia is an infrequent finding.

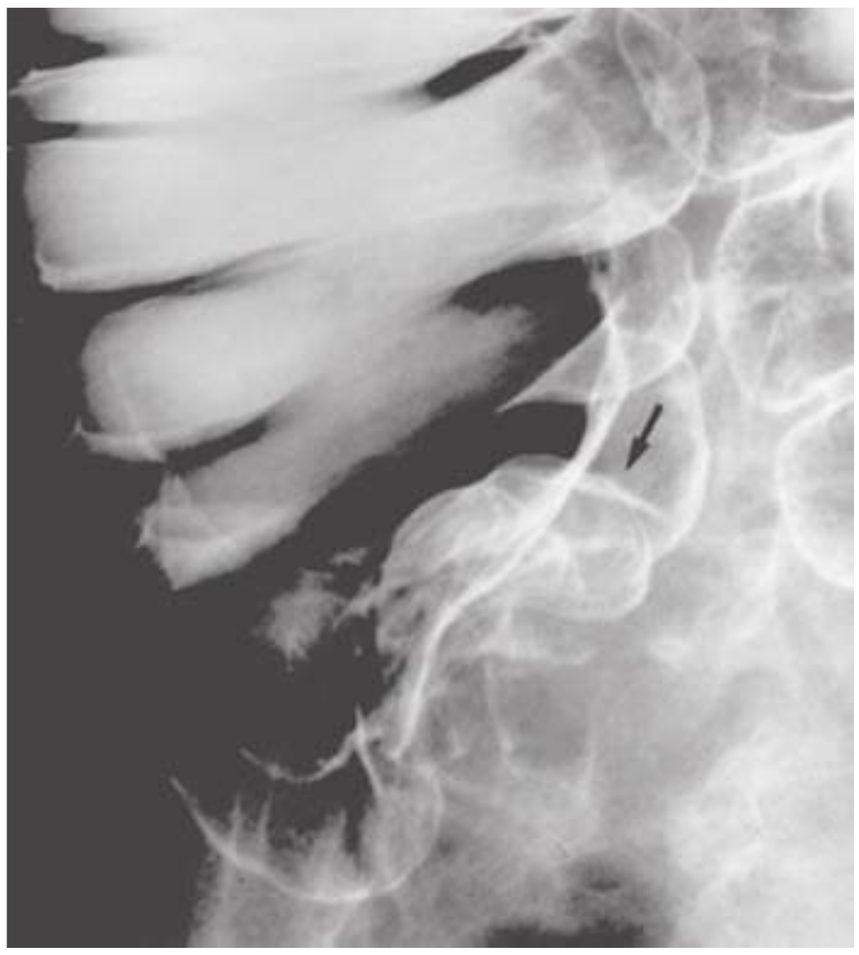


FIGURE 40-1
Double-contrast air-barium enema revealing a sessile tumor of the cecum in a patient with iron-deficiency anemia and guaiac-positive stool. The lesion at surgery was a stage II adenocarcinoma.

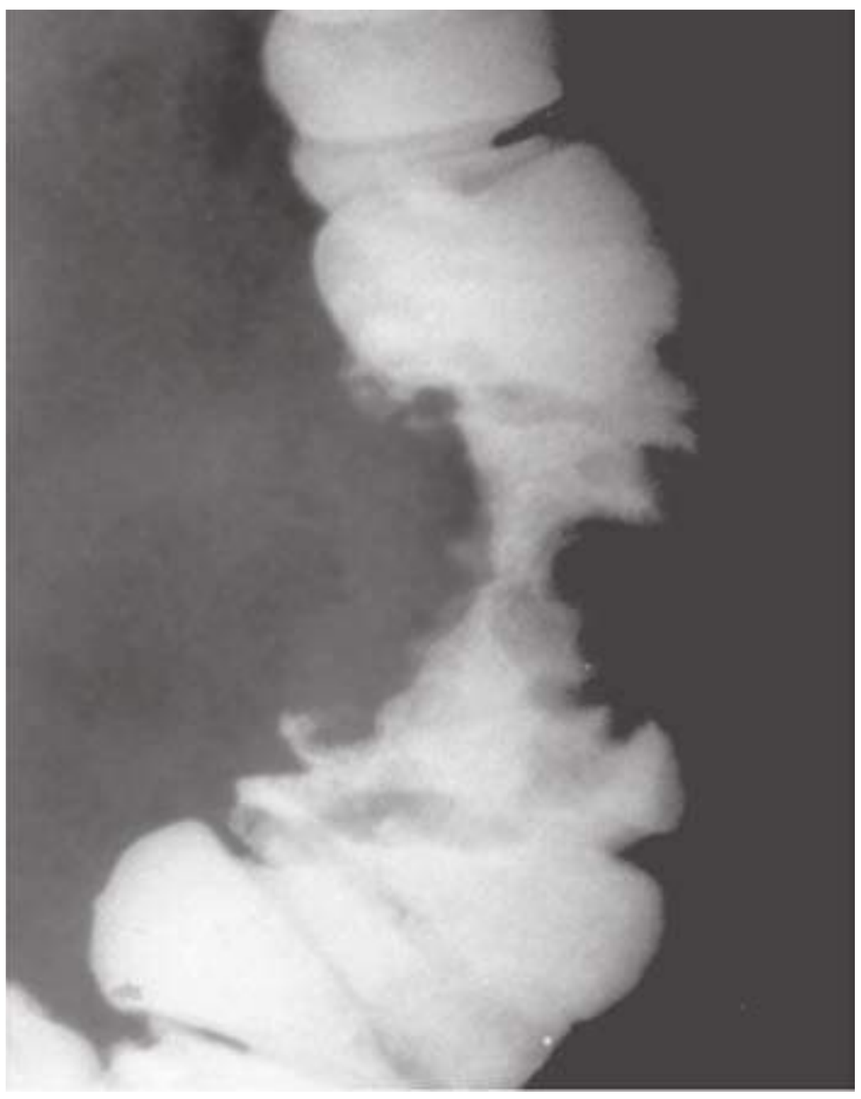


FIGURE 40-2
Annular, constricting adenocarcinoma of the descending colon. This radiographic appearance is referred to as an "apple-core" lesion and is always highly suggestive of malignancy.

While these symptoms may lead patients and their physicians to suspect the presence of hemorrhoids, the development of rectal bleeding and/or altered bowel habits demands a prompt digital rectal examination and proctosigmoidoscopy.

Staging, prognostic factors, and patterns of spread

The prognosis for individuals having colorectal cancer is related to the depth of tumor penetration into the bowel wall and the presence of both regional lymph node involvement and distant metastases. These variables are incorporated into the staging system introduced by Dukes and subsequently applied to a TNM classification method, in which T represents the depth of tumor penetration, N the presence of lymph node involvement, and M the presence or absence of distant metastases **(Fig. 40-3)**. Superficial lesions that do not involve regional lymph nodes and do not penetrate through the submucosa (T1) or the muscularis (T2) are designated as stage I (T1–2N0M0) disease; tumors that penetrate through the muscularis but have not spread to lymph nodes are stage II disease (T3-4N0M0); regional lymph node involvement defines stage III (TXN1-2M0) disease; and metastatic spread to sites such as liver, lung, or bone indicates stage IV (TXNXM1) disease. Unless gross evidence of metastatic disease is present, disease stage cannot be determined accurately before surgical resection and pathologic analysis of the operative specimens. It is not clear whether the detection of nodal metastases by special immunohistochemical molecular techniques has the same prognostic implications as disease detected by routine light microscopy.

Most recurrences after a surgical resection of a large-bowel cancer occur within the first 4 years, making 5-year survival a fairly reliable indicator of cure. The likelihood for 5-year survival in patients with colorectal cancer is stage-related (Fig. 40-3). That likelihood has improved during the past several decades when similar surgical stages have been compared. The most plausible explanation for this improvement is more thorough intraoperative and pathologic staging. In particular, more exacting attention to pathologic detail has revealed that the prognosis following the resection of a colorectal cancer is not related merely to the presence or absence of regional lymph node involvement; rather, prognosis may be more precisely gauged by the number of involved lymph nodes (one to three lymph nodes ["N1"] vs four or more lymph nodes ["N2"]) and the number of nodes examined. A minimum of 12 sampled lymph nodes is thought necessary to accurately define tumor stage, and the more nodes examined, the better. Other predictors of a poor prognosis after a total surgical resection include tumor penetration through the bowel wall into pericolic fat, poorly differentiated histology, perforation and/or tumor adherence to adjacent organs (increasing the risk for an anatomically adjacent recurrence), and venous invasion by tumor **(Table 40-4)**. Regardless of the clinicopathologic stage,

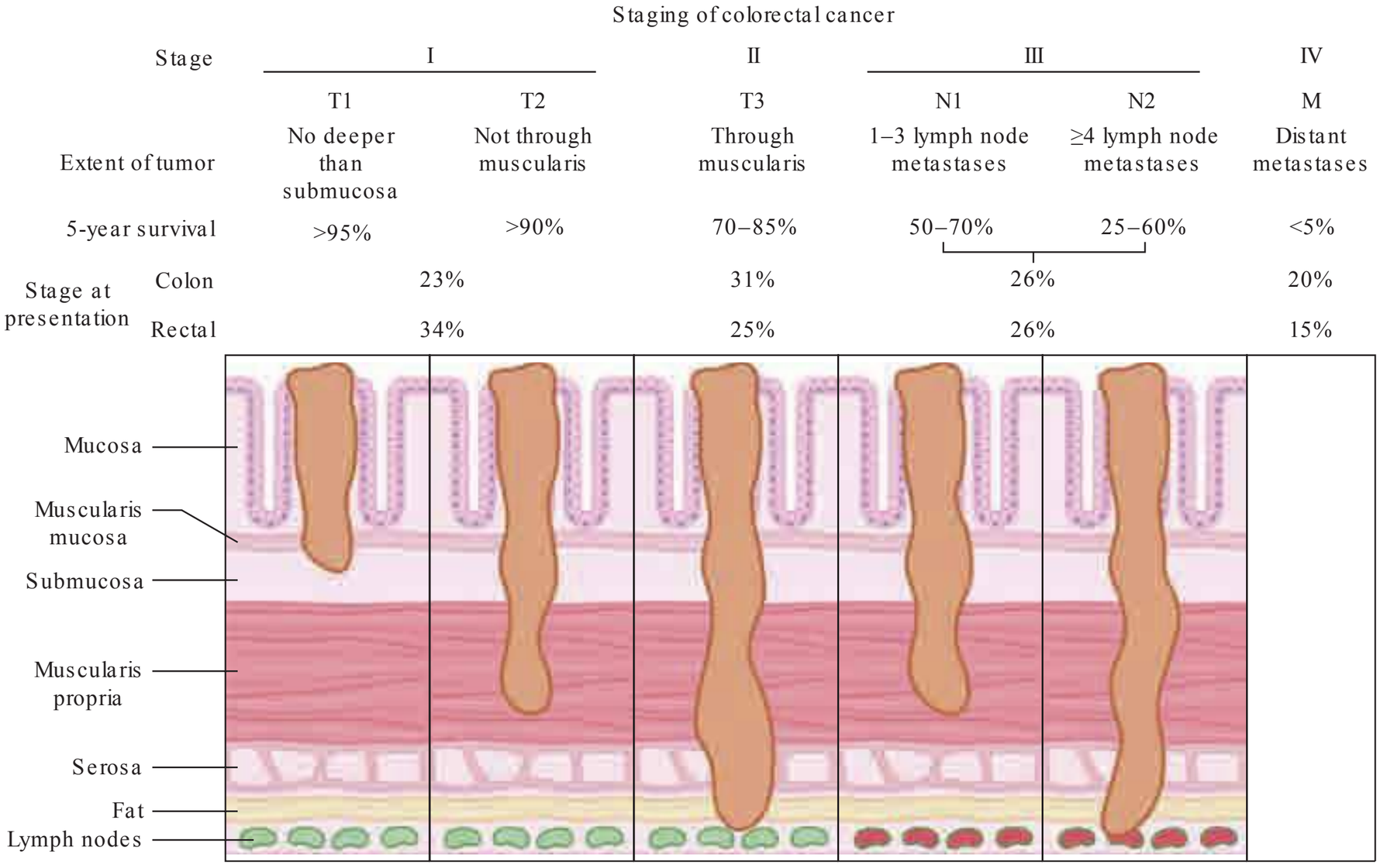


FIGURE 40-3
Staging and prognosis for patients with colorectal cancer.

a preoperative elevation of the plasma carcinoembryonic antigen (CEA) level predicts eventual tumor recurrence. The presence of aneuploidy and specific chromosomal deletions, such as a mutation in the b-raf gene in tumor cells, appears to predict for a higher risk for metastatic spread. Conversely, the detection of microsatellite instability in tumor tissue indicates a more favorable outcome. In contrast to most other cancers, the prognosis in colorectal cancer is not influenced by the size of the primary lesion when adjusted for nodal involvement and histologic differentiation.

TABLE 40-4

PREDICTORS OF POOR OUTCOME FOLLOWING TOTAL SURGICAL RESECTION OF COLORECTAL CANCER
Tumor spread to regional lymph nodes
Number of regional lymph nodes involved
Tumor penetration through the bowel wall
Poorly differentiated histology
Perforation
Tumor adherence to adjacent organs
Venous invasion
Preoperative elevation of CEA titer (>5 ng/mL)
Aneuploidy
Specific chromosomal deletion (e.g., mutation in the b-raf gene)

Abbreviation: CEA, carcinoembryonic antigen.

Cancers of the large bowel generally spread to regional lymph nodes or to the liver via the portal venous circulation. The liver represents the most frequent visceral site of metastasis; it is the initial site of distant spread in one-third of recurring colorectal cancers and is involved in more than two-thirds of such patients at the time of death. In general, colorectal cancer rarely spreads to the lungs, supraclavicular lymph nodes, bone, or brain without prior spread to the liver. A major exception to this rule occurs in patients having primary tumors in the distal rectum, from which tumor cells may spread through the paravertebral venous plexus, escaping the portal venous system and thereby reaching the lungs or supraclavicular lymph nodes without hepatic involvement. The median survival after the detection of distant metastases has ranged in the past from 6–9 months (hepatomegaly, abnormal liver chemistries) to 24–30 months (small liver nodule initially identified by elevated CEA level and subsequent CT scan), but effective systemic therapy is significantly improving this prognosis.

Efforts to use gene expression profiles to identify patients at risk of recurrence or those particularly likely to benefit from adjuvant therapy have not yet yielded practice-changing results. Despite a burgeoning literature examining a host of prognostic factors, pathologic stage at diagnosis remains the best predictor of long-term prognosis. Patients with lymphovascular invasion and high preoperative CEA levels are likely to have a more aggressive clinical course.

Total resection of tumor is the optimal treatment when a malignant lesion is detected in the large bowel. An evaluation for the presence of metastatic disease, including a thorough physical examination, biochemical assessment of liver function, measurement of the plasma CEA level, and a CT scan of the chest, abdomen, and pelvis, should be performed before surgery. When possible, a colonoscopy of the entire large bowel should be performed to identify synchronous neoplasms and/or polyps. T e detection of metastases should not preclude surgery in patients with tumor-related symptoms such as gastrointestinal bleeding or obstruction, but it often prompts the use of a less radical operative procedure. T e necessity for a primary tumor resection in asymptomatic individuals with metastatic disease is an area of controversy. At the time of laparotomy, the entire peritoneal cavity should be examined, with thorough inspection of the liver, pelvis, and hemidiaphragm and careful palpation of the full length of the large bowel. Following recovery from a complete resection, patients should be observed carefully for 5 years by semiannual physical examinations and blood chemistry measurements. If a complete colonoscopy was not performed preoperatively, it should be carried out within the first several postoperative months. Some authorities favor measuring plasma CEA levels at 3-month intervals because of the sensitivity of this test as a marker for otherwise undetectable tumor recurrence. Subsequent endoscopic surveillance of the large bowel, probably at triennial intervals, is indicated, because patients who have been cured of one colorectal cancer have a 3–5% probability of developing an additional bowel cancer during their lifetime and a >15% risk for the development of adenomatous polyps. Anastomotic ("suture-line") recurrences are infrequent in colorectal cancer patients, provided the surgical resection margins are adequate and free of tumor. T e value of periodic CT scans of the abdomen, assessing for an early, asymptomatic indication of tumor recurrence, is an area of uncertainty, with some experts recommending the test be performed annually for the first 3 postoperative years.

Radiation therapy to the pelvis is recommended for patients with rectal cancer because it reduces the 20–25% probability of regional recurrences following complete surgical resection of stage II or III tumors, especially if they have penetrated through the serosa. T is alarmingly high rate of local disease recurrence is believed to be due to the fact that the contained anatomic space within the pelvis limits the extent of the resection and because the rich lymphatic network of the pelvic side wall immediately adjacent to the rectum facilitates the early spread of malignant cells into surgically inaccessible tissue. T e use of sharp rather than blunt dissection of rectal cancers (total mesorectal excision) appears to reduce the likelihood of local disease recurrence to ~10%. Radiation therapy, either pre- or postoperatively, further reduces the likelihood of pelvic recurrences but does not appear to prolong survival. Combining radiation therapy with 5-fluorouracil (5-FU)-based chemotherapy, preferably prior to surgical resection, lowers local recurrence rates and improves overall survival. Preoperative radiotherapy is indicated for patients with large, potentially unresectable rectal cancers; such lesions may shrink enough to permit subsequent surgical removal. Radiation therapy is not effective as the primary treatment of colon cancer.

Systemic therapy for patients with colorectal cancer has become more effective. 5-FU remains the backbone of treatment for this disease. Partial responses are obtained in 15–20% of patients. T e probability of tumor response appears to be somewhat greater for patients with liver metastases when chemotherapy is infused directly into the hepatic artery, but intraarterial treatment is costly and toxic and does not appear to appreciably prolong survival. T e concomitant administration of folinic acid (leucovorin) improves the efficacy of 5-FU in patients with advanced colorectal cancer, presumably by enhancing the binding of 5-FU to its target enzyme, thymidylate synthase. A threefold improvement in the partial response rate is noted when folinic acid is combined with 5-FU; however, the effect on survival is marginal, and the optimal dose schedule remains to be defined. 5-FU is generally administered intravenously but may also be given orally in the form of capecitabine (Xeloda) with seemingly similar efficacy.

Irinotecan (CPT-11), a topoisomerase 1 inhibitor, prolongs survival when compared to supportive care in patients whose disease has progressed on 5-FU. Furthermore, the addition of irinotecan to 5-FU and leucovorin (LV) (e.g., FOLFIRI) improves response rates and survival of patients with metastatic disease. T e FOLFIRI regimen is as follows: irinotecan, 180 mg/m^2 as a 90-min infusion on day 1; LV, 400 mg/m^2 as a 2-h infusion during irinotecan administration; immediately followed by 5-FU bolus, 400 mg/m^2, and 46-h continuous infusion of 2.4–3 g/m^2 every 2 weeks. Diarrhea is the major side effect from irinotecan. Oxaliplatin, a platinum analogue, also improves the response rate when added to 5-FU and LV (FOLFOX) as initial treatment of patients with metastatic disease. T e FOLFOX regimen is as follows: 2-h infusion of LV (400 mg/m^2 per day) followed by a 5-FU bolus (400 mg/m^2 per day) and 22-h infusion (1200 mg/m^2) every 2 weeks, together with oxaliplatin, 85 mg/m^2 as a 2-h infusion on day 1. Oxaliplatin frequently causes a dose-dependent sensory neuropathy that often but not always resolves following the cessation of therapy. FOLFIRI and FOLFOX are equal in efficacy. In metastatic disease, these regimens may produce median survivals of 2 years.

Monoclonal antibodies are also effective in patients with advanced colorectal cancer. Cetuximab (Erbitux) and panitumumab (Vectibix) are directed against the epidermal growth factor receptor (EGFR), a transmembrane glycoprotein involved in signaling pathways affecting growth and proliferation of tumor cells. Both cetuximab and panitumumab, when given alone, have been shown to benefit a small proportion of previously treated patients, and cetuximab appears

to have therapeutic synergy with such chemotherapeutic agents as irinotecan, even in patients previously resistant to this drug; this suggests that cetuximab can reverse cellular resistance to cytotoxic chemotherapy. T e antibodies are not effective in the approximate 40% subset of colon tumors that contain mutated K-ras. T e use of both cetuximab and panitumumab can lead to an acne-like rash, with the development and severity of the rash being correlated with the likelihood of antitumor efficacy. Inhibitors of the EGFR tyrosine kinase such as erlotinib (Tarceva) or sunitinib (Sutent) do not appear to be effective in colorectal cancer.

Bevacizumab (Avastin) is a monoclonal antibody directed against the vascular endothelial growth factor (VEGF) and is thought to act as an antiangiogenesis agent. T e addition of bevacizumab to irinotecan-containing combinations and to FOLFOX initially appeared to significantly improve the outcome observed with chemotherapy alone, but subsequent studies have suggested a lesser degree of benefit. T e use of bevacizumab can lead to hypertension, proteinuria, and an increased likelihood of thromboembolic events.

Patients with solitary hepatic metastases without clinical or radiographic evidence of additional tumor involvement should be considered for partial liver resection, because such procedures are associated with 5-year survival rates of 25–30% when performed on selected individuals by experienced surgeons.

T e administration of 5-FU and LV for 6 months after resection of tumor in patients with stage III disease leads to a 40% decrease in recurrence rates and 30% improvement in survival. T e likelihood of recurrence has been further reduced when oxaliplatin has been combined with 5-FU and LV (e.g., FOLFOX); unexpectedly, the addition of irinotecan to 5-FU and LV as well as the addition of either bevacizumab or cetuximab to FOLFOX did not significantly enhance outcome. Patients with stage II tumors do not appear to benefit appreciably from adjuvant therapy, with the use of such treatment generally restricted to those patients having biologic characteristics (e.g., perforated tumors, T4 lesions, lymphovascular invasion) that place them at higher likelihood for recurrence. T e addition of oxaliplatin to adjuvant treatment for patients older than age 70 and those with stage II disease does not appear to provide any therapeutic benefit.

In rectal cancer, the delivery of preoperative or postoperative combined-modality therapy (5-FU plus radiation therapy) reduces the risk of recurrence and increases the chance of cure for patients with stage II and III tumors, with the preoperative approach being better tolerated. T e 5-FU acts as a radiosensitizer when delivered together with radiation therapy. Life-extending adjuvant therapy is used in only about half of patients older than age 65 years. T is age bias is unfortunate because the benefits and likely the tolerance of adjuvant therapy in patients age ≥65 years appear similar to those seen in younger individuals.

CANCERS OF THE ANUS

Cancers of the anus account for 1–2% of the malignant tumors of the large bowel. Most such lesions arise in the anal canal, the anatomic area extending from the anorectal ring to a zone approximately halfway between the pectinate (or dentate) line and the anal verge. Carcinomas arising proximal to the pectinate line (i.e., in the transitional zone between the glandular mucosa of the rectum and the squamous epithelium of the distal anus) are known as basaloid, cuboidal, or cloacogenic tumors; about one-third of anal cancers have this histologic pattern. Malignancies arising distal to the pectinate line have squamous histology, ulcerate more frequently, and constitute ~55% of anal cancers. T e prognosis for patients with basaloid and squamous cell cancers of the anus is identical when corrected for tumor size and the presence or absence of nodal spread.

T e development of anal cancer is associated with infection by human papillomavirus, the same organism etiologically linked to cervical cancer. T e virus is sexually transmitted. T e infection may lead to anal warts (condyloma acuminata), which may progress to anal intraepithelial neoplasia and on to squamous cell carcinoma. T e risk for anal cancer is increased among homosexual males, presumably related to anal intercourse. Anal cancer risk is increased in both men and women with AIDS, possibly because their immunosuppressed state permits more severe papillomavirus infection. Vaccination against human papilloma viruses may reduce the eventual risk for anal cancer. Anal cancers occur most commonly in middle-aged persons and are more frequent in women than men. At diagnosis, patients may experience bleeding, pain, sensation of a perianal mass, and pruritus.

Radical surgery (abdominal-perineal resection with lymph node sampling and a permanent colostomy) was once the treatment of choice for this tumor type. T e 5-year survival rate after such a procedure was 55–70% in the absence of spread to regional lymph nodes and <20% if nodal involvement was present. An alternative therapeutic approach combining external beam radiation therapy with concomitant chemotherapy (5-FU and mitomycin C) has resulted in biopsy-proven disappearance of all tumor in >80% of patients whose initial lesion was <3 cm in size. Tumor recurrences develop in <10% of these patients, meaning that ~70% of patients with anal cancers can be cured with nonoperative treatment and without the need for a colostomy. Surgery should be reserved for the minority of individuals who are found to have residual tumor after being managed initially with radiation therapy combined with chemotherapy.

CHAPTER 41

TUMORS OF THE LIVER AND BILIARY TREE

Brian I. Carr

HEPATOCELLULAR CARCINOMA

INCIDENCE

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. The annual global incidence is approximately 1 million cases, with a male-to-female ratio of approximately 4:1 (1:1 without cirrhosis to 9:1 in many high-incidence countries). The incidence rate equals the death rate. In the United States, approximately 22,000 new cases are diagnosed annually, with 18,000 deaths. The death rates in males in low-incidence countries such as the United States are 1.9 per 100,000 per year; in intermediate areas such as Austria and South Africa, they range from 5.1–20; and in high-incidence areas such as in the Orient (China and Korea), they are as high as 23.1–150 per 100,000 per year **(Table 41-1)**. The incidence of HCC in the United States is approximately 3 per 100,000 persons, with significant gender, ethnic, and geographic variations. These numbers are rapidly increasing and may be an underestimate. Approximately 4 million chronic hepatitis C virus (HCV) carriers are in the United States alone. Approximately 10% of them, or 400,000, are likely to develop cirrhosis. Approximately 5%, or 20,000, of these patients may develop HCC annually. Add to this the two other common predisposing factors—hepatitis B virus (HBV) and chronic alcohol consumption—and 60,000 new HCC cases annually seem possible. Future advances in HCC survival will likely depend in part on immunization strategies for HBV (and HCV) and earlier diagnosis by screening of patients at risk of HCC development.

Current directions

With the U.S. HCV epidemic, HCC is increasing in most states, and obesity-associated liver disease (nonalcoholic steatohepatitis [NASH]) is increasingly recognized as a cause.

TABLE 41-1

AGE-ADJUSTED INCIDENCE RATES FOR HEPATOCELLULAR CARCINOMA

	PERSONS PER 100,000 PER YEAR	
COUNTRY	MALE	FEMALE
Argentina	6.0	2.5
Brazil, Recife	9.2	8.3
Brazil, Sao Paulo	3.8	2.6
Mozambique	112.9	30.8
South Africa, Cape: Black	26.3	8.4
South Africa, Cape: White	1.2	0.6
Senegal	25.6	9.0
Nigeria	15.4	3.2
Gambia	33.1	12.6
Burma	25.5	8.8
Japan	7.2	2.2
Korea	13.8	3.2
China, Shanghai	34.4	11.6
India, Bombay	4.9	2.5
India, Madras	2.1	0.7
Great Britain	1.6	0.8
France	6.9	1.2
Italy, Varese	7.1	2.7
Norway	1.8	1.1
Spain, Navarra	7.9	4.7

EPIDEMIOLOGY

There are two general types of epidemiologic studies of HCC—those of country-based incidence rates (Table 41-1) and those of migrants. Endemic hot spots occur in areas of China and sub-Saharan Africa, which are associated both with high endemic hepatitis B carrier rates as well as mycotoxin contamination of foodstuffs (aflatoxin B_1), stored grains, drinking water, and soil. Environmental factors

are important, for example, Japanese in Japan have a higher incidence than Japanese living in Hawaii, who in turn have a higher incidence than those living in California.

ETIOLOGIC FACTORS

Chemical carcinogens

Causative agents for HCC have been studied along two general lines. First are agents identified as carcinogenic in experimental animals (particularly rodents) that are thought to be present in the human environment **(Table 41-2)**. Second is the association of HCC with various other clinical conditions. Probably the best-studied and most potent ubiquitous natural chemical carcinogen is a product of the Aspergillus fungus, called aflatoxin B_1. T is mold and aflatoxin product can be found in a variety of stored grains in hot, humid places, where peanuts and rice are stored in unrefrigerated conditions. Aflatoxin contamination of foodstuffs correlates well with incidence rates in Africa and to some extent in China. In endemic areas of China, even farm animals such as ducks have HCC. T e most potent carcinogens appear to be natural products of plants, fungi, and bacteria, such as bush trees containing pyrrolizidine alkaloids as well as tannic acid and safrole. Pollutants such as pesticides and insecticides are known rodent carcinogens.

Hepatitis

Both case-control and cohort studies have shown a strong association between chronic hepatitis B carrier rates and increased incidence of HCC. In Taiwanese male postal carriers who were hepatitis B surface antigen (HBsAg)-positive, a 98-fold greater risk for HCC was found compared to HBsAg-negative individuals. T e incidence of HCC in Alaskan natives is markedly increased related to a high prevalence of HBV infection. HBV-based HCC may involve rounds of hepatic destruction with subsequent proliferation and not necessarily frank cirrhosis. T e increase in Japanese HCC incidence rates in the last three decades is thought to be from hepatitis C. A large-scale World Health Organization (WHO)-sponsored intervention study is currently under way in Asia involving HBV vaccination of the newborn. HCC in African blacks is not associated with severe cirrhosis but is poorly differentiated and very aggressive. Despite uniform HBV carrier rates among the South African Bantu, there is a ninefold difference in HCC incidence between Mozambicans living along the coast and inland. T ese differences are attributed to the additional exposure to dietary aflatoxin B_1 and other carcinogenic mycotoxins. A typical interval between HCV-associated transfusion and subsequent HCC is approximately 30 years. HCV-associated HCC patients tend to have more frequent and advanced cirrhosis, but in HBV-associated HCC, only half the patients have cirrhosis, with the remainder having chronic active hepatitis.

TABLE 41-2

FACTORS ASSOCIATED WITH AN INCREASED RISK OF DEVELOPING HEPATOCELLULAR CARCINOMA

COMMON	UNUSUAL
Cirrhosis from any cause	Primary biliary cirrhosis
Hepatitis B or C chronic infection	Hemochromatosis
Ethanol chronic consumption	α_1 Antitrypsin deficiency
NASH/NAFL	Glycogen storage diseases
Af atoxin B_1 or other mycotoxins	Citrullinemia
	Porphyria cutanea tarda
	Hereditary tyrosinemia
	Wilson's disease

Abbreviations: NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis.

Other etiologic conditions

T e 75–85% association of HCC with underlying cirrhosis has long been recognized, more typically with macronodular cirrhosis in Southeast Asia, but also with micronodular cirrhosis (alcohol) in Europe and the United States. It is still not clear whether cirrhosis itself is a predisposing factor to the development of HCC or whether the underlying causes of the cirrhosis are actually the carcinogenic factors. However, ~20% of U.S. patients with HCC do not have underlying cirrhosis. Several underlying conditions are associated with an increased risk for cirrhosis-associated HCC (Table 41-2), including hepatitis, alcohol, autoimmune chronic active hepatitis, cryptogenic cirrhosis, and NASH. A less common association is with primary biliary cirrhosis and several metabolic diseases including hemochromatosis, Wilson's disease, α_1 antitrypsin deficiency, tyrosinemia, porphyria cutanea tarda, glycogenesis types 1 and 3, citrullinemia, and orotic aciduria. T e etiology of HCC in those 20% of patients who have no cirrhosis is currently unclear, and their HCC natural history is not well-defined.

Current directions

Many patients have multiple etiologies, and the interactions of HBV, HCV, alcohol, smoking, and aflatoxins are just beginning to be explored.

CLINICAL FEATURES

Symptoms

These include abdominal pain, weight loss, weakness, abdominal fullness and swelling, jaundice, and nausea **(Table 41-3)**. Presenting signs and symptoms differ somewhat between high- and low-incidence areas. In high-risk areas, especially in South African blacks, the most common symptom is abdominal pain; by contrast, only 40–50% of Chinese and Japanese patients present with abdominal pain. Abdominal swelling may occur as a consequence of ascites due to the underlying chronic liver disease or may be due to a rapidly expanding tumor. Occasionally, central necrosis or acute hemorrhage into the peritoneal cavity leads to death. In countries with an active surveillance program, HCC tends to be identified at an earlier stage, when symptoms may be due only to the underlying disease. Jaundice is usually due to obstruction of the intrahepatic ducts from underlying liver disease. Hematemesis may occur due to esophageal varices from the underlying portal hypertension. Bone pain is seen in 3–12% of patients, but necropsies show pathologic bone metastases in ~20% of patients. However, 25% of patients may be asymptomatic.

TABLE 41-3

HEPATOCELLULAR CARCINOMA CLINICAL PRESENTATION (N = 547)

SYMPTOM	NO. OF PATIENTS (%)
No symptom	129 (24)
Abdominal pain	219 (40)
Other (workup of anemia and various diseases)	64 (12)
Routine physical exam finding, elevated LFTs	129 (24)
Weight loss	112 (20)
Appetite loss	59 (11)
Weakness/malaise	83 (15)
Jaundice	30 (5)
Routine CT scan screening of known cirrhosis	92 (17)
Cirrhosis symptoms (ankle swelling, abdominal bloating, increased girth, pruritus, GI bleed)	98 (18)
Diarrhea	7 (1)
Tumor rupture	1
Patient Characteristics	
Mean age (yr)	56 ± 13
Male:Female	3:1
Ethnicity	
White	72%
Middle Eastern	10%
Asian	13%
African American	5%
Cirrhosis	81%
No cirrhosis	19%
Tumor Characteristics	
Hepatic tumor numbers	
1	20%
2	25%
3 or more	65%
Portal vein invasion	75%
Unilobar	25%
Bilobar	75%

Abbreviations: CT, computed tomography; GI, gastrointestinal; LFT, liver function test.

Physical signs

Hepatomegaly is the most common physical sign, occurring in 50–90% of the patients. Abdominal bruits are noted in 6–25%, and ascites occurs in 30–60% of patients. Ascites should be examined by cytology. Splenomegaly is mainly due to portal hypertension. Weight loss and muscle wasting are common, particularly with rapidly growing or large tumors. Fever is found in 10–50% of patients, from unclear cause. The signs of chronic liver disease may often be present, including jaundice, dilated abdominal veins, palmar erythema, gynecomastia, testicular atrophy, and peripheral edema. Budd-Chiari syndrome can occur due to HCC invasion of the hepatic veins, with tense ascites and a large tender liver.

Paraneoplastic syndromes

Most paraneoplastic syndromes in HCC are biochemical abnormalities without associated clinical consequences. They include hypoglycemia (also caused by end-stage liver failure), erythrocytosis, hypercalcemia, hypercholesterolemia, dysfibrinogenemia, carcinoid syndrome, increased thyroxin-binding globulin, changes in secondary sex characteristics (gynecomastia, testicular atrophy, and precocious puberty), and porphyria cutanea tarda. Mild hypoglycemia occurs in rapidly growing HCC as part of terminal illness, and profound hypoglycemia may occur, although the cause is unclear. Erythrocytosis occurs in 3–12% of patients and hypercholesterolemia in 10–40%. A high percentage of patients have thrombocytopenia associated with their fibrosis or leukopenia, resulting from portal hypertension, and not from cancer infiltration of bone marrow, as in other tumor types. Furthermore, large HCCs have normal or high platelet levels (thrombocytosis), as in ovarian and other gastrointestinal cancers, probably related to elevated interleukin 6 (IL-6) levels.

STAGING

Multiple clinical staging systems for HCC have been described. A widely used one has been the American

Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification. However, the Cancer of the Liver Italian Program (CLIP) system is now popular because it takes cirrhosis into account, based on the original Okuda system **(Table 41-4)**. Patients with Okuda stage III disease have a dire prognosis because they usually cannot be curatively resected, and the condition of their liver typically precludes chemotherapy. Other staging systems have been proposed, and a consensus is needed. T ey are all based on combining the prognostic features of liver damage with those of tumor aggressiveness and include the Barcelona Clinic Liver Cancer (BCLC) system from Spain **(Fig. 41-1)**, which is externally validated and incorporates baseline survival estimates; the Chinese University Prognostic Index (CUPI); the important and simple Japan Integrated Staging Score (JIS); and SLiDe, which stands for s tage, li ver damage, and de s-γ-carboxy prothrombin. CLIP and BCLC appear most popular in the West, whereas JIS is favored in Japan. Each system has its champions. T e best prognosis is for stage I, solitary tumors less than 2 cm in diameter without vascular invasion. Adverse prognostic features include ascites, jaundice, vascular invasion, and elevated α fetoprotein (AFP). Vascular invasion in particular has profound effects on prognosis and may be microscopic or macroscopic (visible on computed tomography [CT] scans). Most large tumors have microscopic vascular invasion, so full staging can usually be made only after surgical resection. Stage III disease contains a mixture of lymph node–positive and–negative tumors. Stage III patients with positive lymph node disease have a poor prognosis, and few patients survive 1 year. T e prognosis of stage IV is poor after either resection or transplantation, and 1-year survival is rare.

New directions

Consensus is needed on staging. T ese systems will soon be refined or upended by proteomics.

APPROACH TO THE PATIENT: Hepatocellular Carcinoma

HISTORY AND PHYSICAL T e history is important in evaluating putative predisposing factors, including a history of hepatitis or jaundice, blood transfusion, or use of intravenous drugs. A family history of HCC or hepatitis should be sought and a detailed social history taken to include job descriptions for industrial exposure to possible carcinogenic drugs as well as contraceptive hormones. Physical examination should include assessing stigmata of underlying liver disease such as jaundice, ascites, peripheral edema, spider nevi, palmar erythema, and weight loss. Evaluation of the abdomen for hepatic size, masses or ascites, hepatic nodularity and tenderness, and splenomegaly is needed, as is assessment of overall performance status and psychosocial evaluation.

SEROLOGIC ASSAYS AFP is a serum tumor marker for HCC; however, it is only increased in approximately one-half of U.S. patients. T e lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) assay is thought to be more specific. T e other widely used assay is that for des-γ-carboxy prothrombin (DCP), a protein induced by vitamin K absence (PIVKA-2). T is protein is increased in as many as 80% of HCC patients but may also be elevated in patients with vitamin K deficiency; it is always elevated after warfarin use. It may also predict for portal vein invasion. Both AFP-L3

TABLE 41-4

CLIP AND OKUDA STAGING SYSTEMS FOR HEPATOCELLULAR CARCINOMA

CLIP CLASSIFICATION

	POINTS		
VARIABLES	0	1	2
i. Tumor number	Single	Multiple	–
Hepatic replacement by tumor (%)	<50	<50	>50
ii. Child-Pugh score	A	B	C
iii. α Fetoprotein level (ng/mL)	<400	≥400	–
iv. Portal vein thrombosis (CT)	No	Yes	–

CLIP stages (score = sum of points): CLIP 0, 0 points; CLIP 1, 1 point; CLIP 2, 2 points; CLIP 3, 3 points.

Okuda Classif cation

Tumor Extent[a]		Ascites		Albumin (g/L)		Bilirubin (mg/dL)	
≥50%	<50	+	–	≤3	>3	≥ 3	<3
(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)

Okuda stages: stage 1, all (–); stage 2, 1 or 2 (+); stage 3, 3 or 4 (+).

[a]Extent of liver occupied by tumor.

Abbreviation: CLIP, Cancer of the Liver Italian Program.

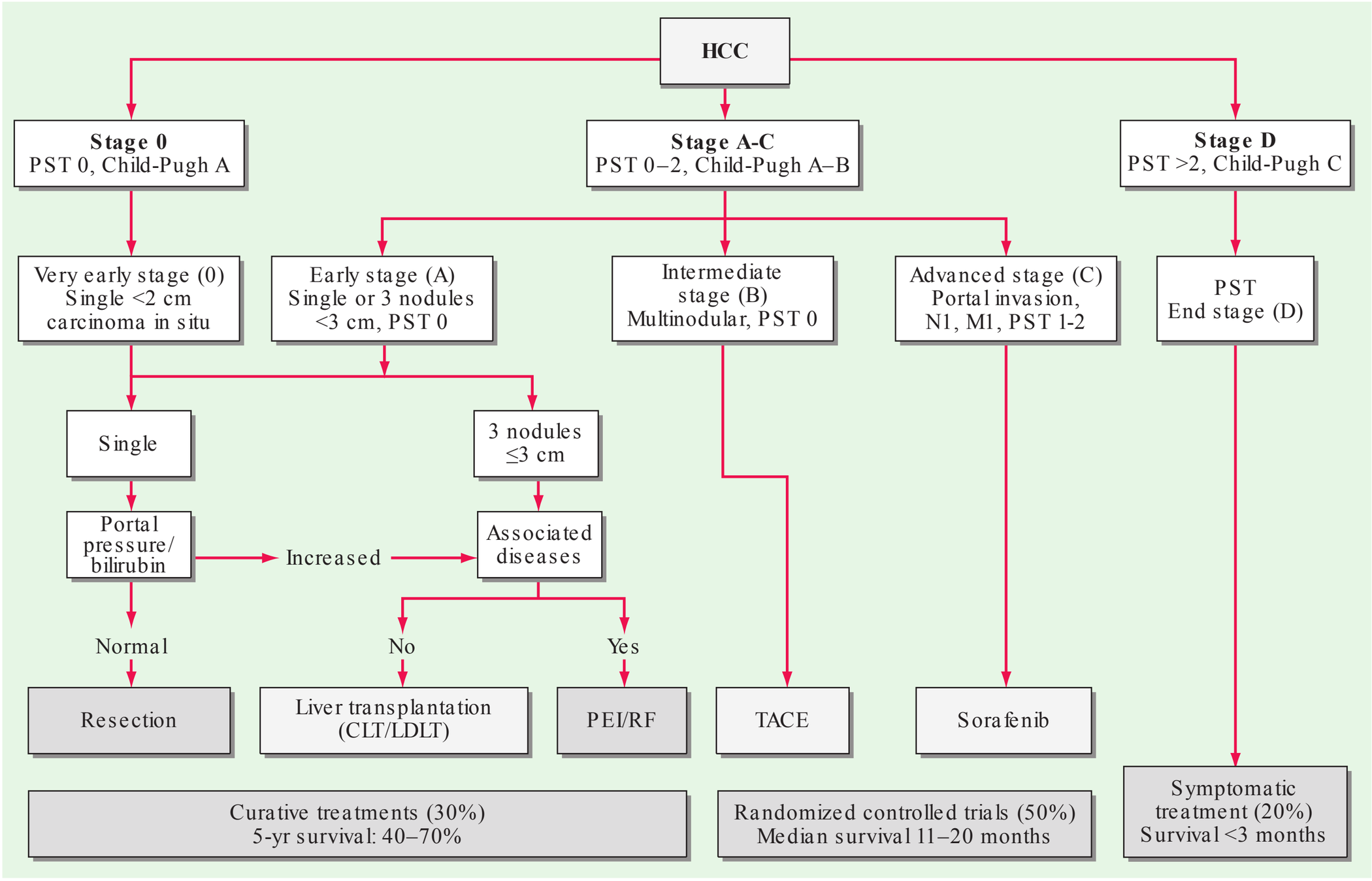


FIGURE 41-1
Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment schedule. Patients with very early hepatocellular carcinoma (HCC) (stage 0) are optimal candidates for resection. Patients with early HCC (stage A) are candidates for radical therapy (resection, liver transplantation [LT], or local ablation via percutaneous ethanol injection [PEI] or radiofrequency [RF] ablation). Patients with intermediate HCC (stage B) benefit from transcatheter arterial chemoembolization (TACE). Patients with advanced HCC, defined as presence of macroscopic vascular invasion, extrahepatic spread, or cancer-related symptoms (Eastern Cooperative Oncology Group performance status 1 or 2) (stage C), benefit from sorafenib. Patients with end-stage disease (stage D) will receive symptomatic treatment. Treatment strategy will transition from one stage to another on treatment failure or contraindications for the procedures. CLT, cadaveric liver transplantation; LDLT, living donor liver transplantation; PST, Performance Status Test. (Modified from JM Llovet et al: JNCI 100:698, 2008.)

and DCP are U.S. Food and Drug Administration (FDA) approved. Many other assays have been developed, such as glypican-3, but none have greater aggregate sensitivity and specificity. In a patient presenting with either a new hepatic mass or other indications of recent hepatic decompensation, carcinoembryonic antigen (CEA), vitamin B_{12}, AFP, ferritin, PIVKA-2, and antimitochondrial antibody should be measured, and standard liver function tests should be performed, including prothrombin time (PT), partial thromboplastin time (PTT), albumin, transaminases, γ-glutamyl transpeptidase, and alkaline phosphatase. γ-Glutamyl transpeptidase and alkaline phosphatase may be particularly important in the 50% of HCC patients who have low AFP levels. Decreases in platelet count and white blood cell count may reflect portal hypertension and associated hypersplenism. Hepatitis A, B, and C serology should be measured. If HBV or HCV serology is positive, quantitative measurements of HBV DNA or HCV RNA are needed.

New Directions Newer biomarkers are being evaluated, especially tissue- and serum-based genomics profiling. Newer plasma biomarkers include glypican-3, osteopontin, insulin-like growth factor I, and vascular endothelial growth factor. However, they are still in process of validation. Furthermore, the commercial availability of kits for isolating circulating tumor cells is permitting the molecular profiling of HCCs without the need for further tissue biopsy.

RADIOLOGY An ultrasound examination of the liver is an excellent screening tool. The two characteristic vascular abnormalities are hypervascularity of the tumor mass (neovascularization or abnormal tumor-feeding arterial vessels) and thrombosis by tumor invasion of otherwise

normal portal veins. To determine tumor size and extent and the presence of portal vein invasion accurately, a helical/triphasic CT scan of the abdomen and pelvis, with fast-contrast bolus technique, should be performed to detect the vascular lesions typical of HCC. Portal vein invasion is normally detected as an obstruction and expansion of the vessel. A chest CT is used to exclude metastases. Magnetic resonance imaging (MRI) can also provide detailed information, especially with the newer contrast agents. Ethiodol (Lipiodol) is an ethiodized oil emulsion retained by liver tumors that can be delivered by hepatic artery injection (5–15 mL) for CT imaging 1 week later. For small tumors, Ethiodol injection is very helpful before biopsy because the histologic presence of the dye constitutes proof that the needle biopsied the mass under suspicion. A prospective comparison of triphasic CT, gadolinium-enhanced MRI, ultrasound, and fluorodeoxyglucose positron emission tomography (FDG-PET) showed similar results for CT, MRI, and ultrasound; PET imaging appears to be positive in only a subset of HCC patients. Abdominal CT versus MRI/CT uses a faster single breath-hold, is less complex, and is less dependent on patient cooperation. MRI requires a longer examination, and ascites can cause artifacts, but MRI is better able to distinguish dysplastic or regenerative nodules from HCC. Imaging criteria have been developed for HCC that do not require biopsy proof, as they have >90% specificity. The criteria include nodules >1 cm with arterial enhancement and portal venous washout and, for small tumors, specified growth rates on two scans performed less than 6 months apart (Organ Procurement and Transplant Network). Nevertheless, explant pathology after liver transplant for HCC has shown that ~20% of patients diagnosed without biopsy did not actually have a tumor.

New Directions The altered tumor vascularity that is a consequence of molecularly targeted therapies is the basis for newer imaging techniques including contrast-enhanced ultrasound (CEUS) and dynamic MRI.

PATHOLOGIC DIAGNOSIS Histologic proof of the presence of HCC is obtained through a core liver biopsy of the liver mass under ultrasound guidance, as well as random biopsy of the underlying liver. Bleeding risk is increased compared to other cancers because (1) the tumors are hypervascular and (2) patients often have thrombocytopenia and decreased liver-dependent clotting factors. Bleeding risk is further increased in the presence of ascites. Tracking of tumor has an uncommon problem. Fine-needle aspirates can provide sufficient material for diagnosis of cancer, but core biopsies are preferred. Tissue architecture allows the distinction between HCC and adenocarcinoma. Laparoscopic approaches can also be used. For patients suspected of having portal vein involvement, a core biopsy of the portal vein may be performed safely. If positive, this is regarded as an exclusion criterion for transplantation for HCC.

New Directions Immunohistochemistry has become mainstream. Prognostic subgroupings are being defined based on growth signaling pathway proteins and genotyping strategies, including a prognostically significant five-gene profile score. Furthermore, molecular profiling of the underlying liver has provided evidence for a "field-effect" of cirrhosis in generating recurrent or new HCCs after primary resection. In addition, characteristics of HCC stem cells have been identified and include EpCAM, CD44, and CD90 expression, which may form the basis of stem cell therapeutic targeting strategies.

SCREENING HIGH-RISK POPULATIONS

There are two goals of screening, both in patients at increased risk for developing HCC, such as those with cirrhosis. The first goal is to detect smaller tumors that are potentially curable by ablation. The second goal is to enhance survival, compared with patients who were not diagnosed by surveillance. Evidence from Taiwan has shown a survival advantage to population screening in HBV-positive patients, and other evidence has shown its efficacy in diagnosis for HCV. Prospective studies in high-risk populations showed that ultrasound was more sensitive than AFP elevations alone, although most practitioners request both tests at 6-month intervals for HBV and HCV carriers, especially in the presence of cirrhosis or worsening of liver function tests. However, an Italian study in patients with cirrhosis identified a yearly HCC incidence of 3% but showed no increase in the rate of detection of potentially curable tumors with aggressive screening. Prevention strategies including universal vaccination against hepatitis are more likely to be effective than screening efforts. Despite absence of formal guidelines, most practitioners obtain 6-month AFP and ultrasound (cheap and ubiquitous, even in poor countries) or CT (more sensitive, especially in overweight patients, but more costly) studies when following high-risk patients (HBV carriers, HCV cirrhosis, family history of HCC).

Current directions

Cost-benefit analysis is not yet convincing, even though screening is intuitively sound. However, studies from areas with high HBV carrier rates have shown a survival benefit for screening as a result of earlier stage at diagnosis. A definitive clinical trial on screening is unlikely, due to difficulties in obtaining informed consent for patients who are not to be screened. γ-Glutamyl transpeptidase appears useful for detecting small tumors.

PREVENTION

Prevention strategies can only be planned when the causes of a cancer are known or strongly suspected. T is is true of few human cancers, with significant exceptions being smoking and lung cancer, papilloma virus and cancer of the cervix uteri, and cirrhosis of any cause or dietary contamination by aflatoxin B_1 for HCC. Aflatoxin B_1 is one of the most potent known chemical carcinogens and is a product of the Aspergillus mold that grows on peanuts and rice when stored in hot and humid climates. T e obvious strategy is to refrigerate these foodstuffs when stored and to conduct surveillance programs for elevated aflatoxin B_1 levels, as happens in the United States, but not usually in Asia. HBV is commonly transmitted from mother to fetus in Asia (except Japan), and neonatal HBV vaccination programs have resulted in a big decrease in adolescent HBV and, thus, in predicted HCC rates. T ere are millions of HBV and HCV carriers (4 million with HCV in the United States) who are already infected. Nucleoside analogue–based chemoprevention (entecavir) of HBV-mediated HCC in Japan resulted in a fivefold decrease in HCC incidence over 5 years in cirrhotic but not in noncirrhotic HBV patients. More powerful and effective HCV therapies promise the possibility of prevention of HCV-based HCC in the future.

TREATMENT Hepatocellular Carcinoma

Most HCC patients have two liver diseases, cirrhosis and HCC, each of which is an independent cause of death. T e presence of cirrhosis usually places constraints on resection surgery, ablative therapies, and chemotherapy. T us patient assessment and treatment planning have to take the severity of the nonmalignant liver disease into account. T e clinical management choices for HCC can be complex **(Fig. 41-2, Tables 41-5 and 41-6)**. T e natural history of HCC is highly variable. Patients presenting with advanced tumors (vascular invasion, symptoms, extrahepatic spread) have a median survival of ~4 months, with or without treatment. Treatment results from the literature are dif cult to interpret. Survival is not always a measure of the ef cacy of therapy because of the adverse effects on survival of the underlying liver disease. A multidisciplinary team, including a hepatologist, interventional radiologist, surgical oncologist, resection surgeon, transplant surgeon, and medical oncologist, is important for the comprehensive management of HCC patients.

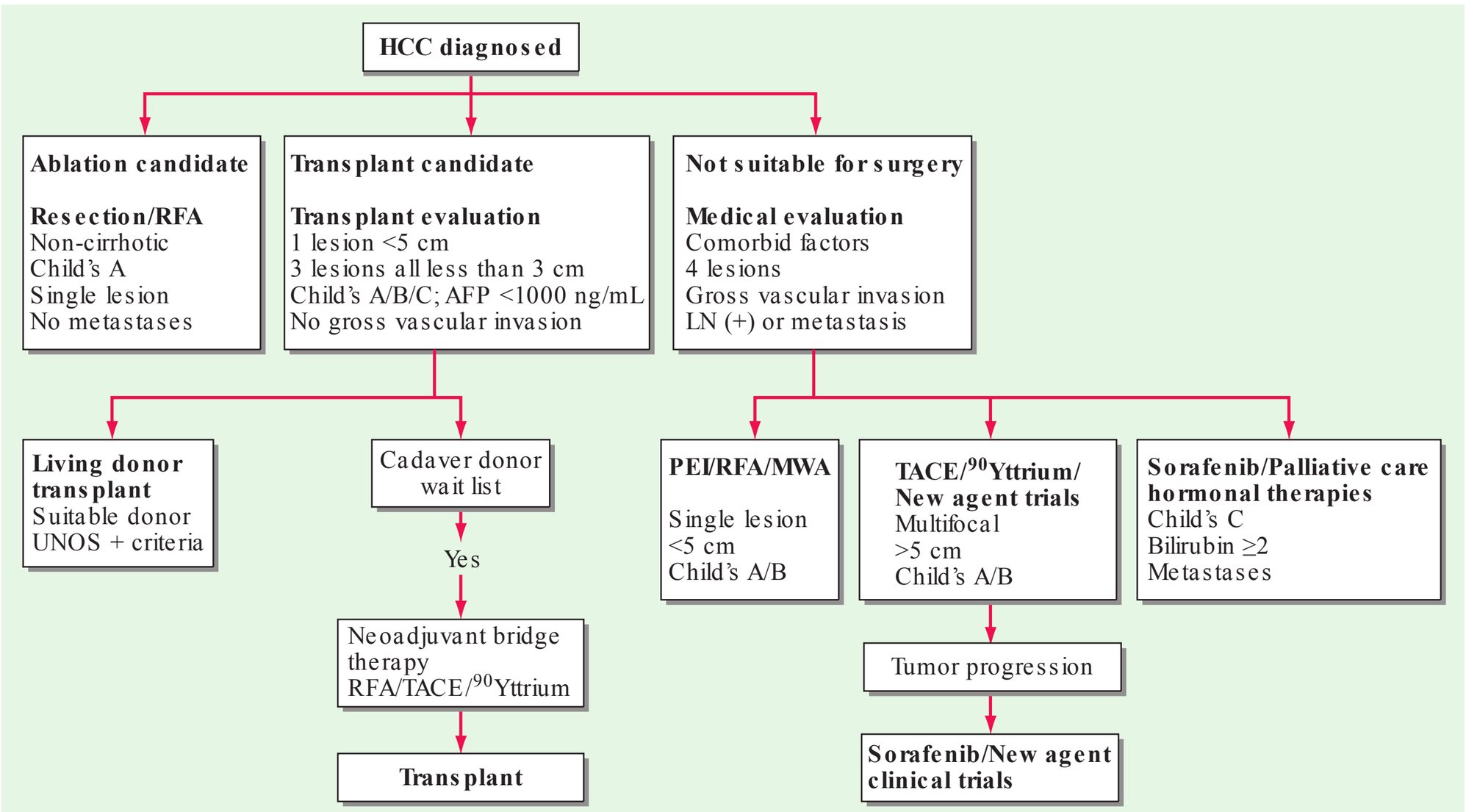


FIGURE 41-2

Hepatocellular carcinoma (HCC) treatment algorithm. The initial clinical evaluation is aimed at assessing the extent of the tumor and the underlying functional compromise of the liver by cirrhosis. Patients are classified as having resectable disease or unresectable disease or as being candidates for transplantation. AFP, α fetoprotein; LN, lymph node; MWA, microwave ablation; OLTX, orthotopic liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; UNOS, United Network for Organ Sharing. Child's A/B/C refers to the Child-Pugh classification of liver failure.

TABLE 41-5

TREATMENT OPTIONS FOR HEPATOCELLULAR CARCINOMA
Surgery
Resection Liver transplantation
Local Ablative Therapies
Radiofrequency ablation (RFA) Microwave ablation (MWA) Cryosurgery Percutaneous ethanol injection (PEI)
Regional Therapies: Hepatic Artery Transcatheter Treatments
Transarterial chemotherapy Transarterial embolization Transarterial chemoembolization Transarterial drug-eluting beads Transarterial radiotherapies: ^{90}Yttrium microspheres ^{131}Iodine–Ethiodol Proton beam radiation
Conformal External-Beam Radiation and Intensity-Modulated Radiation Therapy
Systemic therapies Molecularly targeted therapies (sorafenib, etc.) Chemotherapy Immunotherapy Hormonal therapy + growth control
Supportive Therapies

TNM STAGES I AND II HCC Early-stage tumors are successfully treated using various techniques, including surgical resection, local ablation (thermal, radiofrequency [RFA], or microwave ablation (MWA]), and local injection therapies (Table 41-6). Because the majority of patients with HCC suffer from a field defect in the cirrhotic liver, they are at risk for subsequent multiple primary liver tumors. Many will also have significant underlying liver disease and may not tolerate major surgical loss of hepatic parenchyma, and they may be eligible for orthotopic liver transplant (OLTX). Living related donor transplants have increased in popularity, resulting in absence of waiting for a transplant. An important principle in treating early-stage HCC in the nontransplant setting is to use liver-sparing treatments and to focus on treatment of both the tumor and the cirrhosis.

Surgical Excision The risk of major hepatectomy is high (5–10% mortality rate) due to the underlying liver disease and the potential for liver failure, but acceptable in selected cases and highly dependent on surgical experience. The risk is lower in high-volume centers. Preoperative portal vein occlusion can sometimes be performed to cause atrophy of the HCC-involved lobe and compensatory hypertrophy of the noninvolved liver, permitting safer resection. Intraoperative ultrasound is useful for planning the surgical approach. The ultrasound can image the proximity of major vascular structures that may be encountered during the dissection. In cirrhotic patients, any major liver surgery can result in liver failure. The Child-Pugh classification of liver failure is still a reliable prognosticator for tolerance of hepatic surgery, and only Child A patients should be considered for surgical resection. Child B and C patients with stages I and II HCC should be referred for OLTX if appropriate, as well as patients with ascites or a recent history of variceal bleeding. Although open surgical excision is the most reliable, the patient may be better served with a laparoscopic approach to resection, using RFA, MWA, or percutaneous ethanol injection (PEI). No adequate comparisons of these different techniques have been undertaken, and the choice of treatment is usually based on physician skill. However, RFA has been shown to be superior to PEI in necrosis induction for tumors <3 cm in diameter and is thought to be equivalent

TABLE 41-6

SOME RANDOMIZED CLINICAL TRIALS INVOLVING TRANSHEPATIC ARTERY CHEMOEMBOLIZATION (TACE) FOR HEPATOCELLULAR CARCINOMA				
AUTHOR	YEAR	AGENTS 1	AGENTS 2	SURVIVAL EFFECT
Kawaii	1992	Doxorubicin + Embo	Embo	No
Chang	1994	Cisplatin + Embo	Embo	No
Hatanaka	1995	Cisplatin, doxorubicin, + Embo	Same + Lipiodol	No
Uchino	1993	Cisplatin, doxorubicin, + oral FU	Same + Tamoxifen	No
Lin	1988	Embo	Embo + IVFU	No
Yoshikawa	1994	Epirubicin + Ethiodol	Epirubicin	No
Pelletier	1990	Doxorubicin + Gelfoam	None	No
Trinchet	1995	Cisplatin + Gelfoam	None	No
Bruix	1998	Coils + Gelfoam	None	No
Pelletier	1998	Cisplatin + Ethiodol	None	No
Trinchet	1995	Cisplatin + Gelfoam	None	No
Lo	2002	Cisplatin + Ethiodol	None	Yes
Llovet	2002	Doxorubicin + Ethiodol	None	Yes

Abbreviations: Embo, embolization; FU, 5-fuorouracil.

to open resection and, thus, is the treatment of first choice for these small tumors. As tumors get larger than 3 cm, especially ≥5 cm, the effectiveness of RFA-induced necrosis diminishes. T e combination of transcatheter arterial chemoembolization (TACE) with RFA has shown superior results to TACE alone in a prospective, randomized trial. Although vascular invasion is a preeminent negative prognostic factor, microvascular invasion in small tumors appears not to be a negative factor.

Local Ablation Strategies RFA uses heat to ablate tumors. T e maximum size of the probe arrays allows for a 7-cm zone of necrosis, which would be adequate for a 3- to 4-cm tumor. T e heat reliably kills cells within the zone of necrosis. Treatment of tumors close to the main portal pedicles can lead to bile duct injury and obstruction. T is limits the location of tumors that are anatomically suited for this technique. RFA can be performed percutaneously with CT or ultrasound guidance, or at the time of laparoscopy with ultrasound guidance.

Local Injection Therapy Numerous agents have been used for local injection into tumors, most commonly ethanol (PEI). T e relatively soft HCC within the hard background cirrhotic liver allows for injection of large volumes of ethanol into the tumor without diffusion into the hepatic parenchyma or leakage out of the liver. PEI causes direct destruction of cancer cells, but it is not selective for cancer and will destroy normal cells in the vicinity. However, it usually requires multiple injections (average three), in contrast to one for RFA. T e maximum size of tumor reliably treated is 3 cm, even with multiple injections.

CURRENT DIRECTIONS Resection and RFA each obtain similar results. However, a distinction has been made between the causes and prevention strategies needed to prevent early versus late tumor recurrences after resection. Early recurrence has been linked to tumor invasion factors, especially microvascular tumor invasion with elevated transaminases, whereas late recurrence has been associated with cirrhosis and virus hepatitis factors and, thus, the development of new tumors. See the section on virus-directed adjuvant therapy below.

Liver Transplantation (OLTX) A viable option for stages I and II tumors in the setting of cirrhosis is OLTX, with survival approaching that for noncancer cases. OLTX for patients with a single lesion ≤5 cm or three or fewer nodules, each ≤3 cm (Milan criteria), resulted in excellent tumor-free survival (≥70% at 5 years). For advanced HCC, OLTX has been abandoned due to high tumor recurrence rates. Priority scoring for OLTX previously led to HCC patients waiting too long for their OLTX, resulting in some tumors becoming too advanced during the patient's wait for a donated liver. A variety of therapies were used as a "bridge" to OLTX, including RFA, TACE, and hepatic arterial ^{90}Y-radioembolization. T ese pretransplant treatments allow patients to remain on the waiting list longer, giving them greater opportunities to be transplanted, because they can stabilize the tumor and prevent it from growing in the months until a donor liver becomes available. What remains unclear, however, is whether this translates into prolonged survival after transplant. Further, it is not known whether patients who have had their tumor(s) treated preoperatively follow the recurrence pattern predicted by their tumor status at the time of transplant (i.e., post–local ablative therapy), or if they follow the course set by their tumor parameters present before such treatment. T e United Network for Organ Sharing (UNOS) point system for priority scoring of OLTX recipients now includes additional points for patients with HCC. T e success of living related donor liver transplantation programs has also led to patients receiving transplantation earlier for HCC and often with greater than minimal tumors.

CURRENT DIRECTIONS Expanded criteria for larger HCCs beyond the Milan criteria (one lesion <5 cm or three lesions, each <3 cm), such as the University of California, San Francisco (UCSF) criteria (single lesion ≤6.5 cm or two lesions ≤4.5 cm with a total diameter ≤8 cm; 1- and 5-year survival rates of 90 and 75%, respectively), are being increasingly accepted by various UNOS areas for OLTX with satisfactory longer-term survival comparable to Milan criteria results. Furthermore, downstaging of HCCs that are too large for the Milan criteria by medical therapy (TACE) is increasingly recognized as acceptable treatment before OLTX with equivalent outcomes to patients who originally were within Milan criteria. Within-criteria patients with AFP levels >1000 ng/mL have exceptionally high post-OLTX recurrence rates. Also, the use of "salvage" OLTX after recurrent HCC after resection has produced conflicting outcomes. Shortages of organs combined with advances in resection safety have led to increasing use of resection for patients with good liver function.

Adjuvant Therapy T e role of adjuvant chemotherapy for patients after resection or OLTX remains unclear. Both adjuvant and neoadjuvant approaches have been studied, but no clear advantage in disease-free or overall survival has been found. However, a meta-analysis of several trials revealed a significant improvement in disease-free and overall survival. Although analysis of postoperative adjuvant systemic chemotherapy trials demonstrated no disease-free or overall survival advantage, single studies of TACE and neoadjuvant ^{131}I-Ethiodol showed enhanced survival after resection.

Antiviral therapy, instead of anticancer therapy, has been successful in decreasing postresection tumor recurrences in the postresection adjuvant setting. Nucleoside analogues in HBV-based HCC and peg-interferon plus ribavirin for HCV-based HCC have both been effective in reducing recurrence rates.

CURRENT DIRECTIONS A large adjuvant trial examining resection and transplantation, with or without sorafenib (see below) is in progress. T e success of viral therapies in decreasing HCC recurrence after resection is part of a broader focus on the tumor microenvironment (stroma, blood vessels, inflammatory cells, and cytokines) as mediators of HCC progression and as targets for new therapies.

TNM STAGES III AND IV HCC Fewer surgical options exist for stage III tumors involving major vascular structures. In patients without cirrhosis, a major hepatectomy is feasible, although prognosis is poor. Patients with Child A cirrhosis may be resected,

but a lobectomy is associated with significant morbidity and mortality rates, and long-term prognosis is poor. Nevertheless, a small percentage of patients will achieve long-term survival, justifying an attempt at resection when feasible. Because of the advanced nature of these tumors, even successful resection can be followed by rapid recurrence. T ese patients are not considered candidates for transplantation because of the high tumor recurrence rates, unless their tumors can first be down-staged with neoadjuvant therapy. Decreasing the size of the primary tumor allows for less surgery, and the delay in surgery allows for extrahepatic disease to manifest on imaging studies and avoid unhelpful OLTX. T e prognosis is poor for stage IV tumors, and no surgical treatment is recommended.

Systemic Chemotherapy A large number of controlled and uncontrolled clinical studies have been performed with most of the major classes of cancer chemotherapy. No single agent or combination of agents given systemically reproducibly leads to even a 25% response rate or has any effect on survival.

Regional Chemotherapy In contrast to the dismal results of systemic chemotherapy, a variety of agents given via the hepatic artery have activity for HCC confined to the liver (Table 41-6). Two randomized controlled trials have shown a survival advantage for TACE in a selected subset of patients. One used doxorubicin, and the other used cisplatin. Despite the fact that increased hepatic extraction of chemotherapy has been shown for very few drugs, some drugs such as cisplatin, doxorubicin, mitomycin C, and possibly neocarzinostatin, produce substantial objective responses when administered regionally. Few data are available on continuous hepatic arterial infusion for HCC, although pilot studies with cisplatin have shown encouraging responses. Because the reports have not usually stratified responses or survival based on TNM staging, it is dif cult to know long-term prognosis in relation to tumor extent. Most of the studies on regional hepatic arterial chemotherapy also use an embolizing agent such as Ethiodol, gelatin sponge particles (Gelfoam), starch (Spherex), or microspheres. Two products are composed of microspheres of defined size ranges—Embospheres (Biospheres) and Contour SE—using particles of 40–120, 100–300, 300–500, and 500–1000 μm in size. T e optimal diameter of the particles for TACE has yet to be defined. Consistently higher objective response rates are reported for arterial administration of drugs together with some form of hepatic artery occlusion compared with any form of systemic chemotherapy to date. T e widespread use of some form of embolization in addition to chemotherapy has added to its toxicities. T ese include a frequent but transient fever, abdominal pain, and anorexia (all in >60% of patients). In addition, >20% of patients have increased ascites or transient elevation of transaminases. Cystic artery spasm and cholecystitis are also not uncommon. However, higher responses have also been obtained. T e hepatic toxicities associated with embolization may be ameliorated by the use of degradable starch microspheres, with 50–60% response rates. Two randomized studies of TACE versus placebo showed a survival advantage for treatment (Table 41-6). In addition, it is not clear that formal oncologic CT response criteria are adequate for HCC. A loss of vascularity on CT without size change may be an index of loss of viability and thus of response to TACE. A major problem that TACE trials have had in showing a survival advantage is that many HCC patients die of their underlying cirrhosis, not the tumor. Nevertheless, two randomized controlled trials, one using doxorubicin and the other using cisplatin, showed a survival advantage for TACE versus placebo (Table 41-6). However, improving quality of life is a legitimate goal of regional therapy. Drug-eluting beads using doxorubicin (DEB-TACE) have been claimed to produce equivalent survival with less toxicity, but this strategy has not been tested in a randomized trial.

Kinase Inhibitors A survival advantage has been observed for the oral multikinase inhibitor, sorafenib (Nexavar), versus placebo in two randomized trials. It targets both the Raf mitogenic pathway and the vascular endothelial growth factor receptor (VEGFR) endothelial vasculogenesis pathway. However, tumor responses were negligible, and the survival in the treatment arm in Asians was less than the placebo arm in the Western trial **(Table 41-7)**. Sorafenib has considerable toxicity, with 30–40% of patients requiring "drug holidays," dose reductions, or cessation of therapy. T e most common toxicities include fatigue, hypertension, diarrhea, mucositis, and skin changes, such as the painful hand-foot syndrome, hair loss, and itching, each in 20–40% of patients. Several "look-alike" new agents that also target angiogenesis have either proved to be inferior or more toxic. T ese include sunitinib, brivanib, linifanib, everolimus, and bevacizumab **(Table 41-8)**. T e idea of angiogenesis alone as a major HCC therapeutic target may need revision.

TABLE 41-7

TARGETED THERAPIES IN HEPATOCELLULAR CARCINOMA: TRIALS

PHASE III	TARGET	SURVIVAL (MO)
Sorafenib vs placebo	Raf, VEGFR, PDGFR	10.7 vs 7.9
Sorafenib vs placebo (Asians)	Raf, VEGFR, PDGFR	6.5 vs 4.2

Abbreviations: PDGFR, platelet-derived growth factor receptor; Raf, rapidly accelerated fibrosarcoma; VEGFR vascular endothelial growth factor receptor.

TABLE 41-8

PROMISING TARGETED THERAPIES THAT FAILED THEIR CLINICAL TRIAL GOALS

Sunitinib
Brivanib
Linifanib
Everolimus
Erlotinib
ThermaDox
Oncolytic virus JX-594
Bevacizumab
Bevacizumab plus erlotinib vs sorafenib
Sorafenib plus erlotinib vs sorafenib

New Therapies Although prolonged survival has been reported in phase II trials using newer agents, such as bevacizumab plus erlotinib, the data from a phase III trial were disappointing. Several forms of radiation therapy have been used in the treatment of HCC, including external-beam radiation and conformal radiation therapy. Radiation hepatitis remains a dose-limiting problem. The pure beta emitter ^{90}Yttrium attached to either glass (TheraSphere) or resin (SIR-Spheres) microspheres injected into a major branch hepatic artery has been assessed in phase II trials of HCC and has encouraging tumor control and survival effects with minimal toxicities. Randomized phase III trials comparing it to TACE have yet to be completed. The main attractiveness of ^{90}Yttrium therapy is its safety in the presence of major branch portal vein thrombosis, where TACE is dangerous or contraindicated. Furthermore, external-beam radiation has been reported to be safe and useful in the control of major branch portal or hepatic vein invasion (thrombosis) by tumors. The studies have all been small. Vitamin K has been assessed in clinical trials at high dosage for its HCC-inhibitory actions. This idea is based on the characteristic biochemical defect in HCC of elevated plasma levels of immature prothrombin (DCP or PIVKA-2), due to a defect in the activity of prothrombin carboxylase, a vitamin K–dependent enzyme. Two vitamin K randomized controlled trials from Japan show decreased tumor occurrence, but a major phase III trial aimed at limiting postresection recurrence was not successful.

CURRENT DIRECTIONS A number of new kinase inhibitors are being evaluated for HCC **(Tables 41-9 and 41-10)**. These include the biologicals, such as Raf kinase and vascular endothelial growth factor (VEGF) inhibitors, and agents that target various steps of the cell growth pathway. Current hopes focus particularly on the Met pathway inhibitors such as tivantinib and several IGF receptor antagonists. ^{90}Yttrium looks promising and without chemotherapy toxicities. It is particularly attractive because, unlike TACE, it seems safe in the presence of portal vein thrombosis, a pathognomonic feature of HCC aggressiveness. The bottleneck of liver donors for OLTX is at last widening with increasing use of living donors, and criteria for OLTX for larger HCCs are slowly expanding. Patient participation in clinical trials assessing new therapies is encouraged (www.clinicaltrials.gov).

The main effort now is the evaluation of combinations of the compounds listed in Tables 41-7 to 41-9 that target different pathways, as well as the combination of any of these targeted therapies, but especially sorafenib, with TACE or ^{90}Yttrium radioembolization. Combining TACE with sorafenib appears to be safe in phase II studies with promising survival data, but randomized studies are still in progress. The same is true for intra-arterial ^{90}Yttrium plus sorafenib as therapy for HCC and as bridge to transplant therapy.

TABLE 41-9

NEW TARGETED AGENTS AND THEIR TARGETS IN CURRENT CLINICAL TRIALS

TARGETS	INHIBITORS
EGF receptor	Erlotinib Gefitinib Cetuximab Panitumumab
cMET	Tivantinib (ARQ197) EMD1204831 Cabozantinib
VEGF receptor	Bevacizumab Regorafenib Brivanib Cediranib Sunitinib
FGF1 receptor	AEW54 R1507 (MAb) Linsitinib (OSI-906) Brivanib
TRAIL-R1 (proapoptosis)	Mapatumumab
PDGF receptor	Sorafenib Dovitinib Linifanib
IGF-I receptor	IMC-A12 B11B022 Cixutumumab
Ubiquitin-proteasome	Bortezomib

Abbreviations: EGF, epidermal growth factor; FGF1, fibroblast growth factor 1; IGF-I, insulin-like growth factor I; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

TABLE 41-10

SOME NOVEL MEDICAL TREATMENTS FOR HEPATOCELLULAR CARCINOMA

EGF receptor antagonists: erlotinib, gefitinib, lapatinib, cetuximab, brivanib
Multikinase antagonists: sorafenib, sunitinib
VEGF antagonist: bevacizumab
VEGFR antagonist: ABT-869 (linifanib)
mTOR antagonists: sirolimus, temsirolimus, everolimus
Proteasome inhibitors: bortezomib
Vitamin K
^{131}I–Ethiodol (lipiodol)
^{131}I–Ferritin
^{90}Yttrium microspheres (TheraSphere, SIR-Spheres)
^{166}Holmium, ^{188}Rhenium
Three-dimensional conformal radiation
Proton beam high-dose radiotherapy
Gamma knife, CyberKnife
New targets: inhibitors of cyclin dependent kinases (Cdk), TRAIL induction caspases, and stem cells

Abbreviations: EGF, epidermal growth factor; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

SIGNIFICANCE AND EVALUATION OF RESPONSES TO NONSURGICAL THERAPIES

Tumor growth or spread is considered a poor prognostic sign and evidence of treatment failure. By contrast, patients receiving chemotherapy are judged to have a response if there is shrinkage of tumor size. Lack of response/size decrease has been thought of as treatment failure. T ree considerations in HCC management have completely changed the views concerning nonshrinkage after therapy. First, the correlation between response to chemotherapy and survival is poor in various tumors; in some tumors, such as ovarian cancer and small-cell lung cancer, substantial tumor shrinkage on chemotherapy is followed by rapid tumor regrowth. Second, the Sorafenib HCC Assessment Randomized Protocol (SHARP) phase III trial of sorafenib versus placebo for unresectable HCC showed that survival could be significantly enhanced in the treatment arm with only 2% of the patients having tumor response but 70% of patients having disease stabilization. T is observation has led to a reconsideration of the usefulness of response and the significance of disease stability. T ird, HCC is a typically highly vascular tumor, and the vascularity is considered to be a measure of tumor viability. As a result, the Response Evaluation Criteria in Solid Tumors (RECIST) have been modified to mRECIST, which requires measurement of vascular/viable tumor on the CT or MRI scan. A partial response is defined as a 30% decrease in the sum of diameters of viable (arterially enhancing) target tumors. T e need for semiquantitation of tumor vascularity on scans has led to the introduction of diffusion-weighted MRI imaging. Tissue-specific imaging agents such as gadoxetic acid (Primovist or Eovist) and the move to functional and genetic imaging mark a shift in approaches. Furthermore, plasma AFP response may be a biologic marker of radiologic response.

TREATMENT SUMMARY

Long-term survival is associated with resection or ablation or transplantation, all of which can yield >70% 5-year survival. Liver transplant is the only therapy that can treat the tumor and the underlying liver disease simultaneously and may be the most important advance in HCC therapy in 50 years. Unfortunately, it benefits only patients with limited size tumors without macrovascular portal vein invasion. Untreated patients with multinodular asymptomatic tumors without vascular invasion or extrahepatic spread have a median survival of approximately 16 months. Chemoembolization (TACE) improves their median survival to 19–20 months and is considered standard therapy for these patients, who represent the majority of HCC patients, although ^{90}Yttrium therapy may provide similar results with less toxicity. Patients with advanced-stage disease, vascular invasion, or metastases have a median survival of around 6 months. Among this group, outcomes may vary according to their underlying liver disease. It is this group at which kinase inhibitors are directed.

SUMMARY

The most common modes of patient presentation

1. A patient with known history of hepatitis, jaundice, or cirrhosis, with an abnormality on ultrasound or CT scan, or rising AFP or DCP (PIVKA-2) (Table 41-5)
2. A patient with an abnormal liver function test as part of a routine examination
3. Radiologic workup for liver transplant for cirrhosis
4. Symptoms of HCC including cachexia, abdominal pain, or fever

History and physical examination

1. Clinical jaundice, asthenia, itching (scratches), tremors, or disorientation
2. Hepatomegaly, splenomegaly, ascites, peripheral edema, skin signs of liver failure

Clinical evaluation

1. Blood tests: full blood count (splenomegaly), liver function tests, ammonia levels, electrolytes, AFP and DCP (PIVKA-2), Ca^{2+} and Mg^{2+}; hepatitis B, C, and D serology (and quantitative HBV DNA or HCV RNA, if either is positive); neurotensin (specific for fibrolamellar HCC)
2. Triphasic dynamic helical (spiral) CT scan of liver (if inadequate, then follow with an MRI); chest CT scan; upper and lower gastrointestinal endoscopy (for varices, bleeding, ulcers); and brain scan (only if symptoms suggest)
3. Core biopsy: of the tumor and separate biopsy of the underlying liver

Therapy

1. HCC <2 cm: RFA, PEI, or resection (Tables 41-5 and 41-6)
2. HCC >2 cm, no vascular invasion: liver resection, RFA, or OLTX
3. Multiple unilobar tumors or tumor with vascular invasion: TACE or sorafenib
4. Bilobar tumors, no vascular invasion: TACE with OLTX for patients with tumor response
5. Extrahepatic HCC or elevated bilirubin: sorafenib or bevacizumab plus erlotinib (combination agent trials are in progress)

OTHER PRIMARY LIVER TUMORS

FIBROLAMELLAR HCC (FL-HCC)

T is rarer variant of HCC has a quite different biology than adult-type HCC. None of the known HCC causative factors seem important here. It is typically a disease of younger adults, often teenagers and predominantly females. It is AFP-negative, but patients typically have elevated blood neurotensin levels, normal liver function tests, and no cirrhosis. Radiology is similar for HCC, except that characteristic adult-type portal vein invasion is less common. Although it is often multifocal in the liver, and therefore not resectable, metastases are common, especially to lungs and locoregional lymph nodes, but survival is often much better than with adult-type HCC. Resectable tumors are associated with 5-year survival ≥50%. Patients often present with a huge liver or unexplained weight loss, fever, or elevated liver function tests on routine evaluations. T ese huge masses suggest quite slow growth for many tumors. Surgical resection is the best management option, even for metastases, as these tumors respond much less well to chemotherapy than adult-type HCC. Although several series of OLTX for FL-HCC have been reported, the patients seem to die from tumor recurrences, with a 2- to 5-year lag compared with OLTX for adult-type HCC. Anecdotal responses to gemcitabine plus cisplatin-TACE are reported.

Epithelioid hemangioendothelioma (EHE)

T is rare vascular tumor of adults is also usually multifocal and can also be associated with prolonged survival, even in the presence of metastases, which are commonly in the lung. T ere is usually no underlying cirrhosis. Histologically, these tumors are usually of borderline malignancy and express factor VIII, confirming their endothelial origin. OLTX may produce prolonged survival.

Cholangiocarcinoma (CCC)

CCC typically refers to mucin-producing adenocarcinomas (different from HCC) that arise from the biliary tract and have features of cholangiocyte differentiation. T ey are grouped by their anatomic site of origin, as intrahepatic (IHC), perihilar (central, ~65% of CCCs), and peripheral (or distal, ~30% of CCCs). IHC is the second most common primary liver tumor. Depending on the site of origin, they have different features and require different treatments. T ey arise on the basis of cirrhosis less frequently than HCC, but may complicate primary biliary cirrhosis. However, cirrhosis and both primary biliary cirrhosis and HCV predispose to IHC. Nodular tumors arising at the bifurcation of the common bile duct are called Klatskin tumors and are often associated with a collapsed gallbladder, a finding that mandates visualization of the entire biliary tree. T e approach to management of central and peripheral CCC is quite different. Incidence is increasing. Although most CCCs have no obvious cause (etiology unknown), a number of predisposing factors have been identified. Predisposing diseases include primary sclerosing cholangitis (10–20% of primary sclerosing cholangitis [PSC] patients), an autoimmune disease, and liver fluke in Asians, especially Opisthorchis viverrini and Clonorchis sinensis. CCC seems also to be associated with any cause of chronic biliary inflammation and injury, with alcoholic liver disease, choledocholithiasis, choledochal cysts (10%), and Caroli's disease (a rare inherited form of bile duct ectasia). CCC most typically presents as painless jaundice, often with pruritus or weight loss. Diagnosis is made by biopsy, percutaneously for peripheral liver lesions, or more commonly via endoscopic retrograde cholangiopancreatography (ERCP) under direct vision for central lesions. T e tumors often stain positively for cytokeratins 7, 8, and 19 and negatively for cytokeratin 20. However, histology alone cannot usually distinguish CCC from metastases from colon or pancreas primary tumors. Serologic tumor markers appear to be nonspecific, but CEA, CA 19-9, and CA-125 are often elevated in CCC patients and are useful for following response to therapy. Radiologic evaluation typically starts with ultrasound, which is very useful in visualizing dilated bile ducts, and then proceeds with either MRI or magnetic resonance cholangiopancreatography (MRCP) or helical CT scans. Invasive cholangiopancreatography (ERCP) is then needed to define the biliary tree and obtain a biopsy or is needed therapeutically to decompress an obstructed biliary tree with internal stent placement. If that fails, then percutaneous biliary drainage will be needed, with the biliary drainage flowing into an external bag. Central tumors often invade the porta hepatis, and locoregional lymph node involvement by tumor is frequent. Incidence has been increasing in recent decades; few patients survive 5 years. T e usual treatment is surgical, but combination systemic chemotherapy may be effective. After complete surgical resection for IHC, 5-year survival is 25–30%. Combination radiation therapy with liver transplant has produced a 5-year recurrence-free survival rate of 65%.

TREATMENT Cholangiocarcinoma

Hilar CCC is resectable in ~30% of patients and usually involves bile duct resection and lymphadenectomy for prognostication. Typical survival is approximately 24 months, with recurrences being mainly in the operative bed but with

~30% in the lungs and liver. Distal CCC, which involves the main ducts, is normally treated by resection of the extrahepatic bile ducts, often with pancreaticoduodenectomy. Survival is similar. Due to the high rates of locoregional recurrences or positive surgical margins, many patients receive postoperative adjuvant radiotherapy. Its effect on survival has not been assessed. Intraluminal brachyradiotherapy has also shown some promise. However, photodynamic therapy enhanced survival in one study. In this technique, sodium porfimer is injected intravenously and then subjected to intraluminal red light laser photoactivation. OLTX has been assessed for treatment of unresectable CCC. Five-year survival was ~20%, so enthusiasm waned. However, neoadjuvant radiotherapy with sensitizing chemotherapy has shown better survival rates for CCC treated by OLTX and is currently used by UNOS for perihilar CCC <3 cm with neither intrahepatic or extrahepatic metastases. A 12-center data collection study of 287 patients with perihilar CCC confirmed the benefit of this approach in a subset of patients, with a 53% 5-year survival rate but with 10% patient dropout before transplantation. T e patients had neoadjuvant external radiation with radiosensitizing therapy. Patients with tumors >3 cm had significantly shorter survival. Multiple chemotherapeutic agents have been assessed for activity and survival in unresectable CCC. Most have been inactive. However, both systemic and hepatic arterial gemcitabine have shown promising results. T e combination of cisplatin plus gemcitabine has produced a survival advantage compared with gemcitabine alone in a 410-patient randomized controlled phase III trial for patients with locally advanced or metastatic CCC and is now considered standard therapy for unresectable CCC. Median overall survival in the combination arm was 11.7 months versus 8.1 months for gemcitabine alone. Significant responses were seen mainly in patients with IHC and gallbladder cancer. However, neither surgery for lymph node–positive disease nor regional chemotherapy in nonsurgical patients has shown any survival advantage thus far. Several case series have shown safety and some responses for hepatic arterial chemotherapy with gemcitabine, drug-eluting beads, and ^{90}Yttrium microspheres, but no convincing clinical trials are available. Clinical trials are under way with targeted therapies. Bevacizumab plus erlotinib gave a 10% partial response rate with median overall survival of 9.9 months. A sorafenib trial yielded an overall survival of 4.4 months, but 50% of the patients had received previous chemotherapy. Patients with unresectable tumors should be treated in clinical trials.

GALLBLADDER CANCER

Gallbladder (GB) cancer has an even worse prognosis than CCC, with a typical survival of ~6 months or less. Women are affected much more commonly than men (4:1), unlike HCC or CCC, and GB cancer occurs more frequently than CCC. Most patients have a history of antecedent gallstones, but very few patients with gallstones develop GB cancer (~0.2%). GB cancer presents similarly to CCC and is often diagnosed unexpectedly during gallstone or cholecystitis surgery. Presentation is typically that of chronic cholecystitis, chronic right upper quadrant pain, and weight loss. Useful but nonspecific serum markers include CEA and CA 19-9. CT scans or MRCP typically reveal a GB mass. T e mainstay of treatment is surgical, either simple or radical cholecystectomy for stage I or II disease, respectively. Survival rates are near 100% at 5 years for stage I, and range from 60–90% at 5 years for stage II. More advanced GB cancer has worse survival, and many patients are unresectable. Adjuvant radiotherapy, used in the presence of local lymph node disease, has not been shown to enhance survival. Chemotherapy is not useful in advanced or metastatic GB cancer.

CARCINOMA OF THE AMPULLA OF VATER

T is tumor arises within 2 cm of the distal end of the common bile duct and is mainly (90%) an adenocarcinoma. Locoregional lymph nodes are commonly involved (50%), and the liver is the most frequent site for metastases. T e most common clinical presentation is jaundice, and many patients also have pruritus, weight loss, and epigastric pain. Initial evaluation is performed with an abdominal ultrasound to assess vascular involvement, biliary dilation, and liver lesions. T is is followed by a CT scan or MRI and especially MRCP. T e most effective therapy is resection by pylorus-sparing pancreaticoduodenectomy, an aggressive procedure resulting in better survival rates than with local resection. Survival rates are ~25% at 5 years in operable patients with involved lymph nodes and ~50% in patients without involved nodes. Unlike CCC, approximately 80% of patients are thought to be resectable at diagnosis. Adjuvant chemotherapy or radiotherapy has not been shown to enhance survival. For metastatic tumors, chemotherapy is currently experimental.

TUMORS METASTATIC TO THE LIVER

T ese are predominantly from colon, pancreas, and breast primary tumors but can originate from any organ primary. Ocular melanomas are prone to liver metastasis. Tumor spread to the liver normally carries a poor prognosis for that tumor type. Colorectal and breast hepatic metastases were previously treated with continuous hepatic arterial infusion chemotherapy. However, more effective systemic drugs for each of these two cancers, especially the addition of oxaliplatin to colorectal cancer regimens, have reduced the use of hepatic artery infusion therapy. In a large randomized study of systemic versus infusional plus systemic chemotherapy for

resected colorectal metastases to the liver, the patients receiving infusional therapy had no survival advantage, mainly due to extrahepatic tumor spread. ^{90}Yttrium resin beads are approved in the United States for treatment of colorectal hepatic metastases. T e role of this modality, either alone or in combination with chemotherapy, is being evaluated in many centers. Palliation may be obtained from chemoembolization, PEI, or RFA.

BENIGN LIVER TUMORS

T ree common benign tumors occur and all are found predominantly in women. T ey are hemangiomas, adenomas, and focal nodular hyperplasia (FNH). FNH is typically benign, and usually no treatment is needed. Hemangiomas are the most common and are entirely benign. Treatment is unnecessary unless their expansion causes symptoms. Adenomas are associated with contraceptive hormone use. T ey can cause pain and can bleed or rupture, causing acute problems. T eir main interest for the physician is a low potential for malignant change and a 30% risk of bleeding. For this reason, considerable effort has gone into differentiating these three entities radiologically. On discovery of a liver mass, patients are usually advised to stop taking sex steroids, because adenoma regression may then occasionally occur. Adenomas can often be large masses ranging from 8–15 cm. Due to their size and definite, but low, malignant potential and potential for bleeding, adenomas are typically resected. T e most useful diagnostic differentiating tool is a triphasic CT scan performed with HCC fast bolus protocol for arterial-phase imaging, together with subsequent delayed venous-phase imaging. Adenomas usually do not appear on the basis of cirrhosis, although both adenomas and HCCs are intensely vascular on the CT arterial phase and both can exhibit hemorrhage (40% of adenomas). However, adenomas have smooth, well-defined edges, and enhance homogeneously, especially in the portal venous phase on delayed images, when HCCs no longer enhance. FNHs exhibit a characteristic central scar that is hypovascular on the arterial-phase and hypervascular on the delayed-phase CT images. MRI is even more sensitive in depicting the characteristic central scar of FNH.

CHAPTER 42

PANCREATIC CANCER

Elizabeth Smyth ■ David Cunningham

Pancreatic cancer is the fourth leading cause of cancer death in the United States and is associated with a poor prognosis. Endocrine tumors affecting the pancreas are discussed in **Chap. 51**. Infiltrating ductal adenocarcinomas, the subject of this Chapter, account for the vast majority of cases and arise most frequently in the head of pancreas. At the time of diagnosis, 85–90% of patients have inoperable or metastatic disease, which is reflected in the 5-year survival rate of only 6% for all stages combined. An improved 5-year survival of up to 24% may be achieved when the tumor is detected at an early stage and when complete surgical resection is accomplished.

EPIDEMIOLOGY

Pancreatic cancer represents 3% of all newly diagnosed malignancies in the United States. T e most common age group at diagnosis is 65–84 years for both sexes. Pancreatic cancer was estimated to have been diagnosed in approximately 45,220 patients and accounted for approximately 38,460 deaths in 2013. Although survival rates have almost doubled over the past 35 years for this disease, overall survival remains low.

GLOBAL CONSIDERATIONS

An estimated 278,684 cases of pancreatic cancer occur annually worldwide (the thirteenth most common cancer globally), with up to 60% of these cases diagnosed in more developed countries. It remains the eighth most common cause of cancer death in men and the ninth most common in women. T e incidence is highest in the United States and western Europe and lowest in parts of Africa and South Central Asia. However, increasing rates of obesity, diabetes, and tobacco use in addition to access to diagnostic radiology in the developing world are likely to increase incidence rates in these countries. In this situation, consideration of the cost implications of adoption of current treatment paradigms in resource-constrained environments will be necessary. Primary prevention such as limiting tobacco use and avoiding obesity may be more cost effective than improvements in treatment of preexisting disease.

RISK FACTORS

Cigarette smoking may be the cause of up to 20–25% of all pancreatic cancers and is the most common environmental risk factor for this disease. A longstanding history of type 1 or type 2 diabetes also appears to be a risk factor; however, diabetes may also occur in association with pancreatic cancer, possibly confounding this interpretation. Other risk factors may include obesity, chronic pancreatitis, and ABO blood group status. Alcohol does not appear to be a risk factor unless excess consumption gives rise to chronic pancreatitis.

GENETIC AND MOLECULAR CONSIDERATIONS

Pancreatic cancer is associated with a number of well-defined molecular hallmarks. T e four genes most commonly mutated or inactivated in pancreatic cancer are KRAS (predominantly codon 12, in 60–75% of pancreatic cancers), the tumor-suppressor genes p16 (deleted in 95% of tumors), p53 (inactivated or mutated in 50–70% of tumors), and SMAD4 (deleted in 55% of tumors). T e pancreatic cancer precursor lesion pancreatic intraepithelial neoplasia (PanIN) acquires these genetic abnormalities in a progressive manner associated with increasing dysplasia; initial KRAS mutations are followed by p16 loss and finally p53 and SMAD4 alterations. SMAD4 gene inactivation is associated with a pattern of widespread metastatic disease in advanced-stage patients and poorer survival in patients with surgically resected pancreatic adenocarcinoma.

Up to 16% of pancreatic cancers may be inherited. Germline mutations in the following genes are associated with a significantly increased risk of pancreatic cancer and other cancers: (1) STK11 gene (Peutz-Jeghers syndrome), which carries a 132-fold increased lifetime risk of pancreatic cancer above the general population; (2) BRCA2 (increased risk of breast, ovarian, and pancreatic cancer); (3) p16/CDKN2A (familial atypical multiple mole melanoma), which carries an increased risk of melanoma and pancreatic cancer; (4) PALB2, which confers an increased risk of breast and pancreatic cancer; (5) hMLH1 and MSH2 (Lynch syndrome), which carries an increased risk of colon and pancreatic cancer; and (6) ATM (ataxia-telangiectasia), which carries an increased risk of breast cancer, lymphoma, and pancreatic cancer. Familial pancreatitis and an increased risk of pancreatic cancer are associated with mutations of the PRSS1 (serine protease 1) gene. However, for most familial pancreatic syndromes, the underlying genetic cause remains unexplained. T e absolute number of affected first-degree relatives is also correlated with increased cancer risk, and patients with at least two first-degree relatives with pancreatic cancer should be considered to have familial pancreatic cancer until proven otherwise.

T e desmoplastic stroma surrounding pancreatic adenocarcinoma functions as a mechanical barrier to chemotherapy and secretes compounds essential for tumor progression and metastasis. Key mediators of these functions include the activated pancreatic stellate cell and the glycoprotein SPARC (secreted protein acidic and rich in cysteine), which is expressed in 80% of pancreatic ductal adenocarcinomas. Targeting this extracellular environment has become increasingly important in the treatment of advanced disease.

SCREENING AND PRECURSOR LESIONS

Screening is not routinely recommended because the incidence of pancreatic cancer in the general population is low (lifetime risk 1.3%), putative tumor markers such as carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) have insufficient sensitivity, and computed tomography (CT) has inadequate resolution to detect pancreatic dysplasia. Endoscopic ultrasound (EUS) is a more promising screening tool, and preclinical efforts are focused on identifying biomarkers that may detect pancreatic cancer at an early stage. Consensus practice recommendations based largely on expert opinion have chosen a threshold of greater than fivefold increased risk for developing pancreatic cancer to select individuals who may benefit from screening. T is includes people with two or more first-degree relatives with pancreatic cancer, patients with Peutz-Jeghers syndrome, and BRCA 2, p16, and hereditary nonpolyposis colorectal cancer (HNPCC) mutation carriers with one or more affected first-degree relatives.

PanIN represents a spectrum of small (<5 mm) neoplastic but noninvasive precursor lesions of the pancreatic ductal epithelium demonstrating mild, moderate, or severe dysplasia (PanIN 1–3, respectively); however, not all PanIN lesions will progress to frank invasive malignancy. Cystic pancreatic tumors such as intraductal mucinous papillary neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are increasingly detected radiologically and are frequently asymptomatic. Main duct IPMNs are more likely to occur in older persons and have higher malignant potential than branched duct IPMNs (invasive cancer in 45% vs 18% of resected lesions, respectively). In contrast, MCNs are solitary lesions of the distal pancreas that do not communicate with the duct system. MCNs have an almost exclusive female distribution (95%). T e rate of invasive cancer in resected MCNs is lower (<18%) with increased rates associated with larger tumors or the presence of nodules.

CLINICAL FEATURES

Clinical presentation

Obstructive jaundice occurs frequently when the cancer is located in the head of the pancreas. T is may be accompanied by symptoms of abdominal discomfort, pruritus, lethargy, and weight loss. Less common presenting features include epigastric pain, backache, new-onset diabetes mellitus, and acute pancreatitis caused by pressure effects on the pancreatic duct. Nausea and vomiting, resulting from gastroduodenal obstruction, may also be a symptom of this disease.

Physical signs

Patients can present with jaundice and cachexia, and scratch marks may be present. Of patients with operable tumors, 25% have a palpable gallbladder (Courvoisier's sign). Physical signs related to the development of distant metastases include hepatomegaly, ascites, lef supraclavicular lymphadenopathy (Virchow's node), and periumbilical nodules (Sister Mary Joseph's nodes).

DIAGNOSIS

Diagnostic imaging

Patients who present with clinical features suggestive of pancreatic cancer undergo imaging to confirm the presence of a tumor and to establish whether the mass is likely to be inflammatory or malignant in nature. Other imaging objectives include the local and distant staging of the tumor, which will determine resectability and provide prognostic information. Dual-phase,

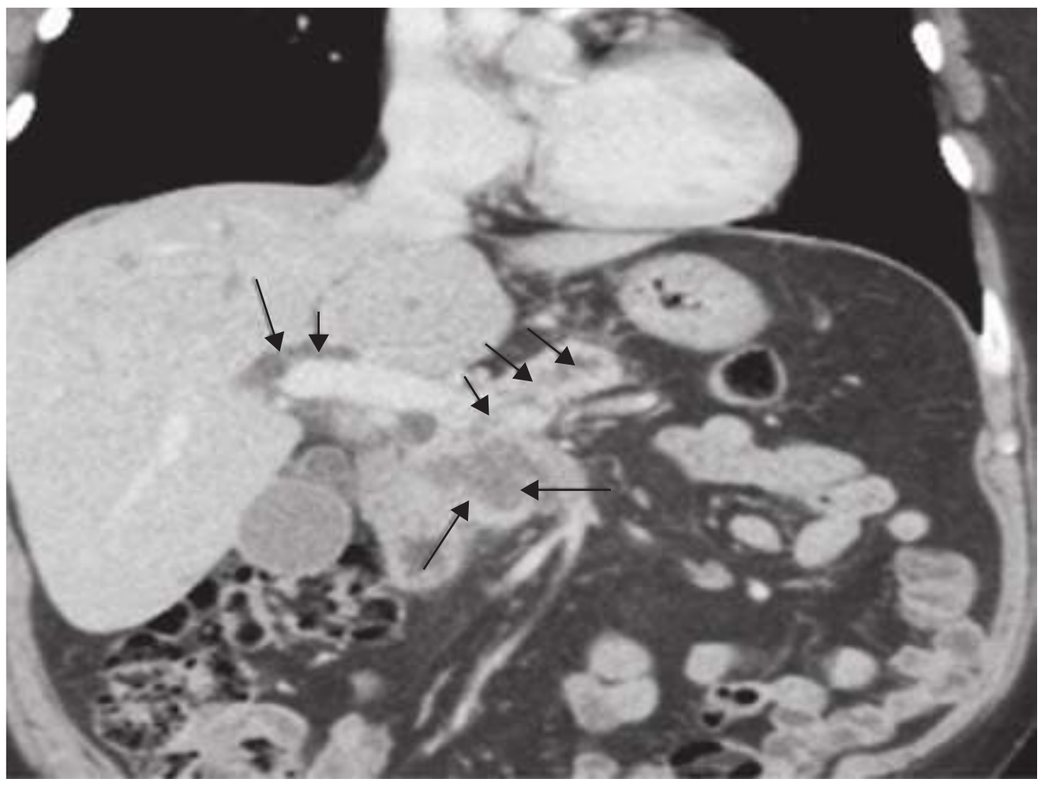


FIGURE 42-1
Coronal computed tomography showing pancreatic cancer and dilated intrahepatic and pancreatic ducts (arrows).

contrast-enhanced spiral CT is the imaging modality of choice **(Fig. 42-1)**. It provides accurate visualization of surrounding viscera, vessels, and lymph nodes, thus determining tumor resectability. Intestinal infiltration and liver and lung metastases are also reliably depicted on CT. T ere is no advantage of magnetic resonance imaging (MRI) over CT in predicting tumor resectability, but selected cases may benefit from MRI to characterize the nature of small indeterminate liver lesions and to evaluate the cause of biliary dilatation when no obvious mass is seen on CT. Endoscopic retrograde cholangiopancreatography (ERCP) is useful for revealing small pancreatic lesions, identifying stricture or obstruction in pancreatic or common bile ducts, and facilitating stent placement; however, it is associated with a risk of pancreatitis **(Fig. 42-2)**. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive method for accurately depicting the level and degree of bile and pancreatic duct dilatation. EUS is highly sensitive in detecting lesions less than 3 cm in size (more sensitive than CT for lesions <2 cm) and is useful as a local staging tool for assessing vascular invasion and lymph node involvement. Fluorodeoxyglucose positron emission tomography (FDG-PET) should be considered before surgery or radical chemoradiotherapy (CRT), because it is superior to conventional imaging in detecting distant metastases.

Tissue diagnosis and cytology

Preoperative confirmation of malignancy is not always necessary in patients with radiologic appearances consistent with operable pancreatic cancer. However, EUS-guided fine-needle aspiration is the technique of choice when there is any doubt, and also for use in patients who require neoadjuvant treatment. It has an accuracy of approximately 90% and has a smaller risk of intraperitoneal dissemination compared with the percutaneous route. Percutaneous biopsy of the pancreatic primary or liver metastases is only acceptable in patients with inoperable or metastatic disease. ERCP is a useful method for obtaining ductal brushings, but the sensitivity of ERCP for diagnosis ranges from 35 to 70%.

Serum markers

Tumor-associated CA19-9 is elevated in approximately 70–80% of patients with pancreatic carcinoma but is not recommended as a routine diagnostic or screening test because its sensitivity and specificity are inadequate for accurate diagnosis. Preoperative CA19-9 levels correlate with tumor stage, and postresection CA19-9 level has prognostic value. It is an indicator of asymptomatic recurrence in patients with completely resected tumors and is used as a biomarker of response in patients with advanced disease undergoing chemotherapy. A number of studies have established a high pretreatment CA19-9 level as an independent prognostic factor.

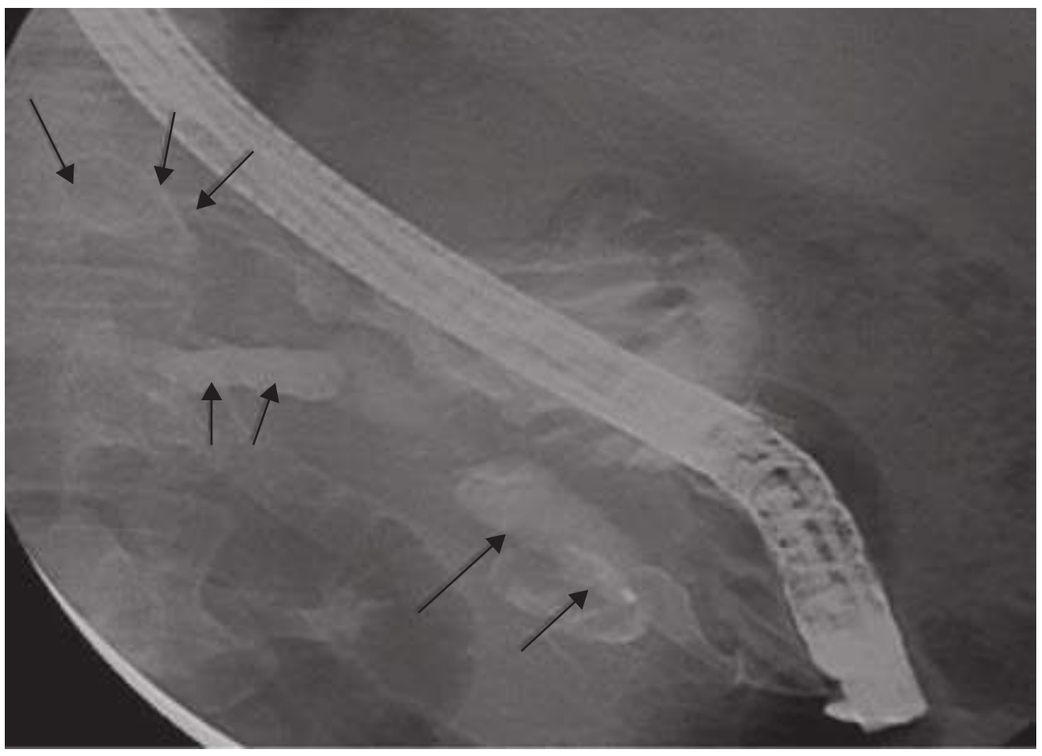


FIGURE 42-2
Endoscopic retrograde cholangiopancreatography showing contrast in dilated pancreatic duct (arrows).

STAGING

T e American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging of pancreatic cancer takes into account the location and size of the tumor, the involvement of lymph nodes, and distant metastasis. T is information is then combined to assign a stage **(Fig. 42-3)**. From a practical standpoint, patients are grouped according to whether the cancer is resectable, locally advanced (unresectable, but without distant spread), or metastatic.

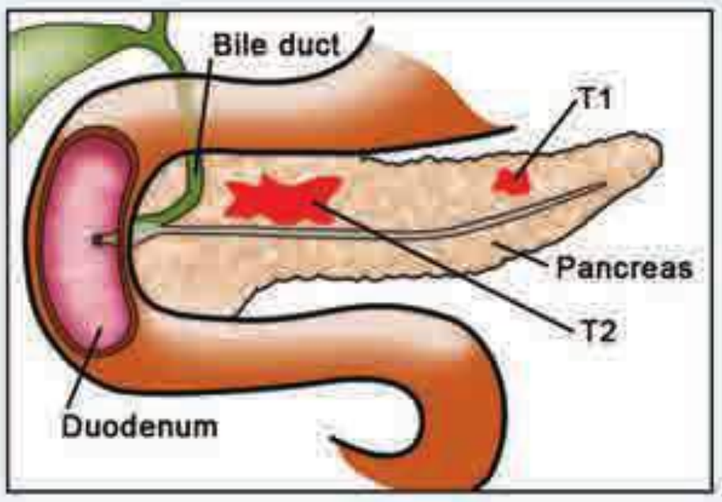
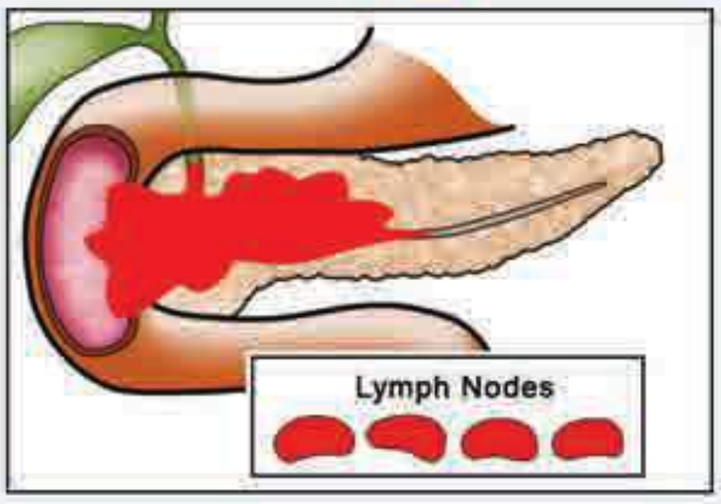
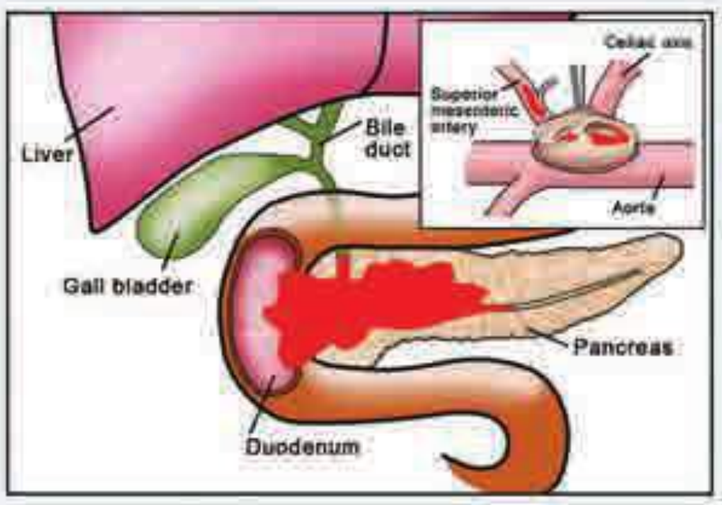
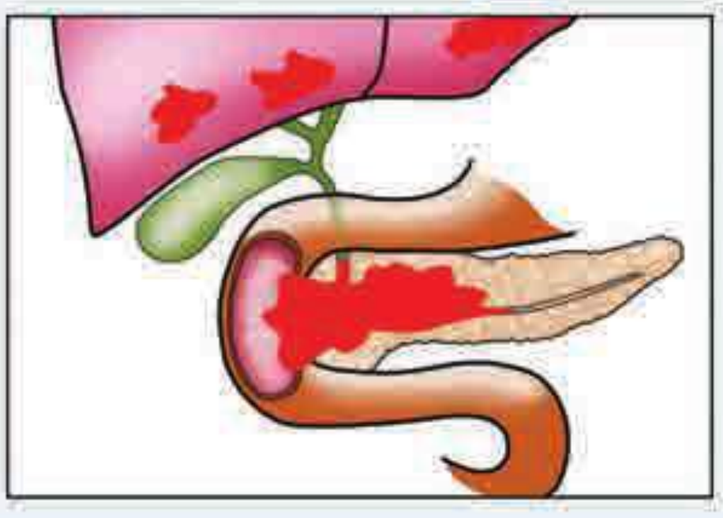
	AJCC Stage	TNM Stage	Extent of Tumor	5 year Survival	Stage at Presentation (14% Unknown)
	I	T1/N0	Limited to pancreas ≤ 2cm	20%	7%
		T2/N0	Limited to pancreas > 2cm		
	II	T3 or N1	Beyond pancreas or regional lymph node metastases	8%	26%
	III	T4 any N	Involves celiac axis or superior mesenteric artery		
	IV	M1	Distant metastases	2%	53%

FIGURE 42-3
Staging of pancreatic cancer, and survival according to stage. AJCC, American Joint Committee on Cancer. (Illustration by Stephen Millward.)

RESECTABLE DISEASE Approximately 10% of patients present with localized nonmetastatic disease that is potentially suitable for surgical resection. Approximately 30% of patients have R1 resection (microscopic residual disease) following surgery. Those who undergo R0 resection (no microscopic or macroscopic residual tumor) and who receive adjuvant treatment have the best chance of cure, with an estimated median survival of 20–23 months and a 5-year survival of approximately 20%. Outcomes are more favorable in patients with small (<3 cm), well-differentiated tumors and lymph node–negative disease.

Patients should have surgery in dedicated pancreatic centers that have lower postoperative morbidity and mortality rates. The standard surgical procedure for patients with tumors of the pancreatic head or uncinate process is a pylorus-preserving pancreaticoduodenectomy (modified Whipple's procedure). The procedure of choice for tumors of the pancreatic body and tail is a distal pancreatectomy, which routinely includes splenectomy.

Postoperative treatment improves long-term outcomes in this group of patients. Adjuvant chemotherapy comprising six cycles of gemcitabine is common practice worldwide based on data from three randomized controlled trials **(Table 42-1)**. The Charité Onkologie trial (CONKO 001) found that the use of gemcitabine after complete resection significantly delayed the development of recurrent disease compared with surgery alone. The European Study Group for Pancreatic Cancer 3 (ESPAC-3) trial, which investigated the benefit of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine, revealed no survival difference between the two drugs. However, the toxicity profile of adjuvant gemcitabine was superior to 5-FU/FA by virtue of its lower incidence of stomatitis and diarrhea. Adjuvant radiotherapy is not commonly used in Europe based on the negative results of the ESPAC-1 study. Adjuvant 5-FU-based CRT with gemcitabine before and after radiotherapy as used in the Radiation Therapy Oncology Group (RTOG) 97-04 trial is preferred in the United States. This approach may be most beneficial in patients with bulky tumors involving the pancreatic head.

INOPERABLE LOCALLY ADVANCED DISEASE Approximately 30% of patients present with locally advanced, unresectable, but nonmetastatic pancreatic carcinoma. The median survival with gemcitabine is 9 months. Patients who respond to chemotherapy or who achieve stable disease after 3–6 months of gemcitabine have frequently been offered consolidation radiotherapy. However, a large, phase III, randomized controlled trial, LAP-07, did not demonstrate any improvement in survival for patients treated with CRT after 4 months of disease control on either gemcitabine or a gemcitabine/erlotinib combination.

METASTATIC DISEASE Approximately 60% of patients with pancreatic cancer present with metastatic disease. Patients with poor performance status do not usually benefit from chemotherapy. Gemcitabine was the standard treatment with a median survival of 6 months and a 1-year survival rate of only 20%. The addition of nab-paclitaxel (an albumin bound nanoparticle formulation of paclitaxel) to gemcitabine results in significantly improved 1-year survival compared to gemcitabine alone (35% vs 22%, p <.001). Capecitabine, an oral fluoropyrimidine, has also been combined with gemcitabine (GEM-CAP) in a phase III trial that showed an improvement in response rate and progression-free survival over single-agent gemcitabine, but no overall survival benefit. However, pooling of two other randomized controlled trials with this trial in a meta-analysis resulted in a survival advantage with GEM-CAP. Addition of erlotinib, a small-molecule epidermal growth factor receptor inhibitor, produced a statistically significant but clinically marginal benefit when added to gemcitabine in the advanced disease setting. A phase III trial limited to good performance status patients with metastatic pancreatic cancer

TABLE 42-1

PHASE III STUDIES OF ADJUVANT CHEMOTHERAPY IN RESECTED PANCREATIC CANCER

			SURVIVAL	
STUDY	COMPARATOR ARM	NO. OF PATIENTS	PFS/DFS (MONTHS)	MEDIAN SURVIVAL (MONTHS)
ESPAC-1, Neoptolemos et al: N Engl J Med 350:1200, 2004	Chemotherapy (folinic acid + bolus 5-FU) vs no chemotherapy	289	PFS 15.3 vs 9.4. (p = .02)	20.1 vs 15.5 (HR 0.71; 95% CI 0.55–0.92; p = .009)
CONKO 001, Oettle et al: JAMA 297:267, 2007	Gemcitabine vs observation	368	Median DFS 13.4 vs 6.9 (p <.001)	22.1 vs 20.2 (p = .06)
ESPAC-3, Neoptolemos et al: JAMA 304:1073, 2010	5-FU/LV vs gemcitabine	1088		23 vs 23.6 (HR 0.94; 95% CI 0.81–1.08, p = .39)

Abbreviations: CI, confidence interval; CONKO, Charité Onkologie; DFS, disease-free survival; ESPAC, European Study Group for Pancreatic Cancer; 5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; PFS, progression-free survival.

TABLE 42-2

SELECTED PHASE III STUDIES EVALUATING CHEMOTHERAPY TREATMENT IN ADVANCED PANCREATIC CANCER

STUDY	COMPARATOR ARM	NO. OF PATIENTS	SURVIVAL	
			PFS (MONTHS)	MEDIAN SURVIVAL (MONTHS)
Moore et al: J Clin Oncol 26:1960, 2007	Gemcitabine vs gemcitabine + erlotinib	569	3.55 vs 3.75 (HR 0.77; 95% CI 0.64–0.92; p = .004)	5.91 vs 6.24 (HR 0.82; 95% CI 0.69–0.99; p = .038)
Cunningham et al: J Clin Oncol 27:5513, 2009	Gemcitabine vs gemcitabine + capecitabine (GEM-CAP)	533	3.8 vs 5.3 (HR 0.78; 95% CI 0.66–0.93; p = .004)	6.2 vs 7.1 (HR 0.86; 95% CI 0.72–1.02; p = .08)
Von Hof et al: N Engl J Med 369:1691, 2013	Gemcitabine vs gemcitabine + nab-paclitaxel	861	3.7 vs 5.5 (HR 0.69; 95% CI 0.58–0.82; p <.001)	6.7 vs 8.5 (HR 0.72; 95% CI 0.62–0.83; p <.001)
Conroy et al: N Engl J Med 364:1817, 2011	Gemcitabine vs FOLFIRINOX	342	3.3 vs 6.4 (HR 0.47; 95% CI 0.37–0.59; p <.001)	6.8 vs 11.1 (HR 0.57; 95% CI 0.45–0.73; p <.001)

showed improved survival with the combination of 5-FU/FA, irinotecan, and oxaliplatin (FOLFIRINOX) compared with gemcitabine, but with increased toxicity **(Table 42-2)**.

FUTURE DIRECTIONS

The early detection and future treatment of pancreatic cancer relies on an improved understanding of molecular pathways involved in the development of this disease. This will ultimately lead to the discovery of novel agents and the identification of patient groups who are likely to benefit most from targeted therapy.

Acknowledgment

Dr. Irene Chong is acknowledged for her work on this chapter in the HPIM 18th edition of Harrison's Principles of Internal Medicine.

CHAPTER 43

BLADDER AND RENAL CELL CARCINOMAS

Howard I. Scher ■ Jonathan E. Rosenberg ■ Robert J. Motzer

BLADDER CANCER

Transitional cell epithelium lines the urinary tract from the renal pelvis to the ureter, urinary bladder, and the proximal two-thirds of the urethra. Cancers can occur at any point: 90% of malignancies develop in the bladder, 8% in the renal pelvis, and 2% in the ureter or urethra. Bladder cancer is the fourth most common cancer in men and the thirteenth in women, with an estimated 72,570 new cases and 15,210 deaths in the United States predicted for the year 2013. T e almost 5:1 ratio of incidence to mortality reflects the higher frequency of the less lethal superficial variants compared to the more lethal invasive and metastatic variants. T e incidence is roughly four times higher in men than in women and twofold higher in white men than in black men, with a median age of 65 years.

Once diagnosed, urothelial tumors exhibit polychronotropism, which is the tendency to recur over time in new locations in the urothelial tract. As long as urothelium is present, continuous monitoring is required.

EPIDEMIOLOGY

Cigarette smoking is believed to contribute to up to 50% of urothelial cancers in men and nearly 40% in women. The risk of developing a urothelial cancer in male smokers is increased two- to fourfold relative to nonsmokers and continues for 10 years or longer after cessation. Other implicated agents include aniline dyes, the drugs phenacetin and chlornaphazine, and external beam radiation. Chronic cyclophosphamide exposure also increases risk, whereas vitamin A supplements appear to be protective. Exposure to Schistosoma haematobium, a parasite found in many developing countries, is associated with an increase in both squamous and transitional cell carcinomas of the bladder.

PATHOLOGY

Clinical subtypes are grouped into three categories: 75% are superficial, 20% invade muscle, and 5% are metastatic at presentation. Staging of the tumor within the bladder is based on the pattern of growth and depth of invasion. T e revised tumor, node, metastasis (TNM) staging system is illustrated in **Fig. 43-1**. About half of invasive tumors presented originally as superficial lesions that later progressed. Tumors are also rated by grade. Low-grade (highly differentiated) tumors rarely progress to a higher stage, whereas high-grade tumors do.

More than 95% of urothelial tumors in the United States are transitional cell in origin. Pure squamous cancers with keratinization constitute 3%, adenocarcinomas 2%, and small cell tumors (often with paraneoplastic syndromes) <1%. Adenocarcinomas develop primarily in the urachal remnant in the dome of the bladder or in the periurethral tissues. Paragangliomas, lymphomas, and melanomas are rare. Of the transitional cell tumors, low-grade papillary lesions that grow on a central stalk are most common. T ese tumors are very friable, have a tendency to bleed, and have a high risk for recurrence, yet they rarely progress to the more lethal invasive variety. In contrast, carcinoma in situ (CIS) is a high-grade tumor that is considered a precursor of the more lethal muscle-invasive disease.

PATHOGENESIS

T e multicentric nature of the disease and high recurrence suggests a field effect in the urothelium that results in a predisposition to develop cancer. Molecular genetic analyses suggest that the superficial and invasive lesions develop along distinct molecular pathways. Low-grade noninvasive papillary tumors harbor constitutive activation of the receptor tyrosine kinase-Ras signal transduction pathway and high frequencies of fibroblast growth factor receptor 3 and

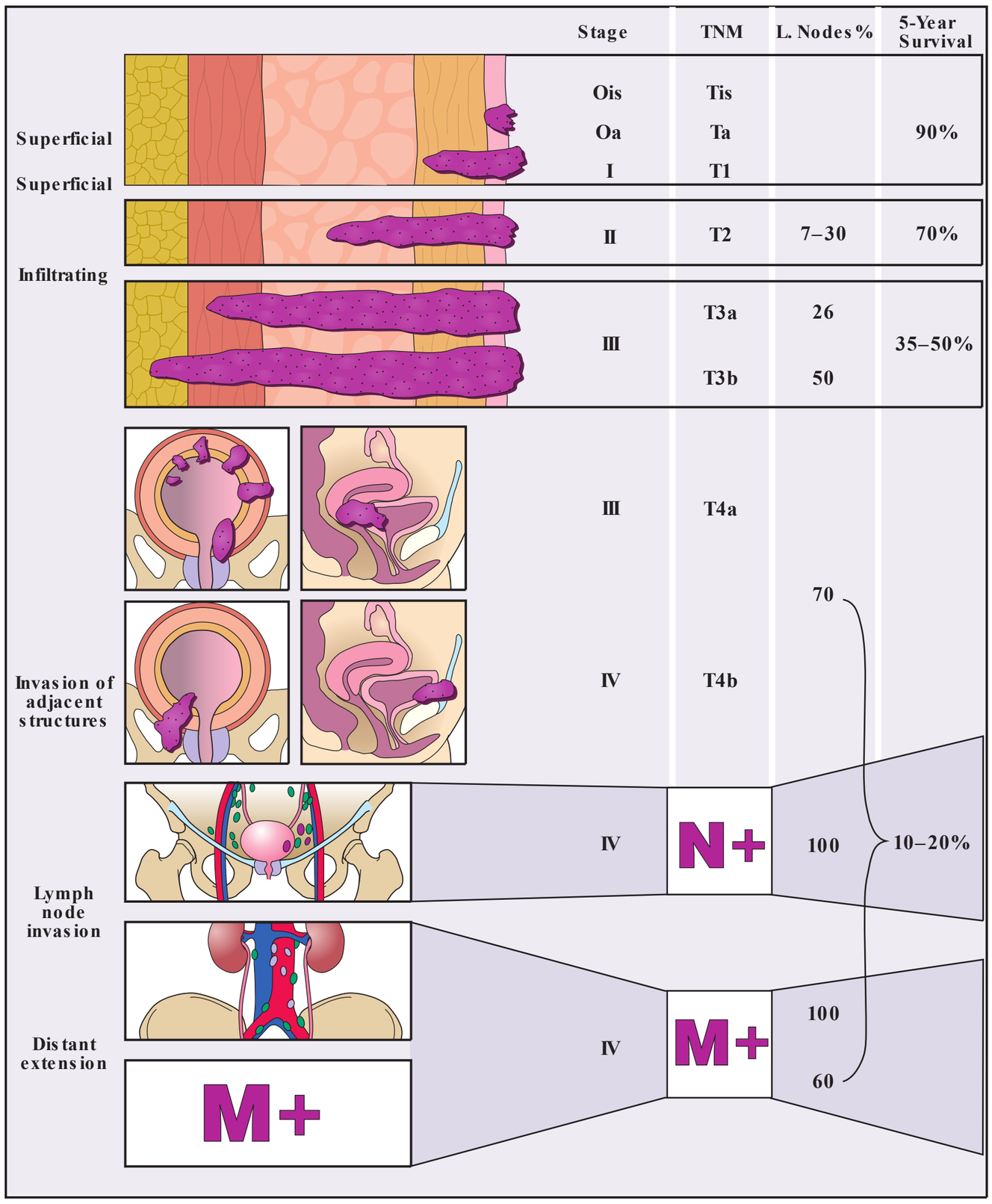


FIGURE 43-1
Bladder staging. TNM, tumor, node, metastasis.

phosphoinositide-3 kinase α subunit mutations. In contrast, CIS and invasive tumors have a higher frequency of TP53 and RB gene alterations. Within all clinical stages, including Tis, T1, and T2 or greater lesions, tumors with alterations in p53, p21, and/or RB have a higher probability of recurrence, metastasis, and death from disease.

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

Hematuria occurs in 80–90% of patients and often reflects exophytic tumors. T e bladder is the most common source of gross hematuria (40%), but benign cystitis (22%) is a more common cause than bladder cancer (15%). Microscopic hematuria is more commonly of prostate origin (25%); only 2% of bladder cancers produce microscopic hematuria. Once hematuria is documented, a urinary cytology, visualization of the urothelial tract by computed tomography (CT) or magnetic resonance urogram or intravenous pyelogram, and cystoscopy are recommended if no other etiology is found. Screening asymptomatic individuals for hematuria increases the diagnosis of tumors at an early stage but has not been shown to prolong life. After hematuria, irritative symptoms are the next most common presentation. Ureteral obstruction may cause flank pain. Symptoms of metastatic disease are rarely the first presenting sign.

T e endoscopic evaluation includes an examination under anesthesia to determine whether a palpable mass is present. A flexible endoscope is inserted into the bladder, and bladder barbotage for cytology is performed. Visual inspection includes mapping the location, size, and number of lesions, as well as a description of the growth pattern (solid vs papillary). All visible tumors should be resected, and a sample of the muscle underlying the tumor should be obtained to assess the depth of invasion. Normal-appearing areas are biopsied at random to ensure no CIS is present. A notation is made as to whether a tumor was completely or incompletely resected. Selective catheterization and

visualization of the upper tracts should be performed if the cytology is positive and no disease is visible in the bladder. Ultrasonography, CT, and/or magnetic resonance imaging (MRI) are used to determine whether a tumor extends to perivesical fat (T3) and to document nodal spread. Distant metastases are assessed by CT of the chest and abdomen, MRI, or radionuclide imaging of the skeleton.

TREATMENT Bladder Cancer

Management depends on whether the tumor invades muscle and whether it has spread to the regional lymph nodes and beyond. T e probability of spread increases with increasing T stage.

NON–MUSCLE-INVASIVE DISEASE At a minimum, the management is complete endoscopic resection with or without intravesical therapy. T e decision to recommend intravesical therapy depends on the histologic subtype, number of lesions, depth of invasion, presence or absence of CIS, and antecedent history. Recurrences develop in upward of 50% of cases, of which 5-20% progress to a more advanced stage. In general, solitary papillary lesions are managed by transurethral surgery alone. CIS and recurrent disease are treated by transurethral surgery followed by intravesical therapy.

Intravesical therapies are used in two general contexts: as an adjuvant to a complete endoscopic resection to prevent recurrence or to eliminate disease that cannot be controlled by endoscopic resection alone. Intravesical treatments are advised for patients with diffuse CIS, recurrent disease, >40% involvement of the bladder surface by tumor, or T1 disease. T e standard therapy, based on randomized comparisons, is Bacillus Calmette-Guérin (BCG) in six weekly instillations, often followed by maintenance administrations for ≥1 year. Other agents with activity include mitomycin C, interferon, and gemcitabine. T e side effects of intravesical therapies include dysuria, urinary frequency, and, depending on the drug, myelosuppression or contact dermatitis. Rarely, intravesical BCG may produce a systemic illness associated with granulomatous infections in multiple sites requiring antituberculin therapy.

Following the endoscopic resection, patients are monitored for recurrence at 3-month intervals during the first year. Recurrence may develop anywhere along the urothelial tract, including the renal pelvis, ureter, or urethra. Persistent disease in the bladder and new tumors are treated with a second course of BCG or intravesical chemotherapy with valrubicin or gemcitabine. In some cases, cystectomy is recommended. Tumors in the ureter or renal pelvis are typically managed by resection during retrograde examination or, in some cases, by instillation through the renal pelvis. Prostatic urethral tumors may require cystoprostatectomy if the tumor cannot be resected completely.

MUSCLE-INVASIVE DISEASE T e treatment of a tumor that has invaded muscle can be separated into control of the primary tumor and systemic chemotherapy to treat micrometastatic disease. Radical cystectomy is the standard treatment in the United States, although in selected cases, a bladder-sparing approach is used. T is approach includes complete endoscopic resection; partial cystectomy; or a combination of resection, systemic chemotherapy, and external beam radiation therapy. In some countries, external beam radiation therapy is considered standard. In the United States, it is generally limited to those patients deemed unfit for cystectomy, those with unresectable local disease, or as part of an experimental bladder-sparing approach.

Indications for cystectomy include muscle-invading tumors not suitable for segmental resection; non–muscle-invasive tumors unsuitable for conservative management (e.g., due to multicentric and frequent recurrences resistant to intravesical instillations); high-grade T1 tumors especially if associated with CIS; and bladder symptoms (e.g., frequency or hemorrhage) that impair quality of life.

Radical cystectomy is major surgery that requires appropriate preoperative evaluation and management. It involves removal of the bladder and pelvic lymph nodes and creation of a conduit or reservoir for urinary flow. Grossly abnormal lymph nodes are evaluated by frozen section. If metastases are confirmed, the procedure is often aborted. In males, radical cystectomy includes the removal of the prostate, seminal vesicles, and proximal urethra. Impotence is universal unless the nerves responsible for erectile function are preserved. In females, the procedure includes removal of the bladder, urethra, uterus, fallopian tubes, ovaries, anterior vaginal wall, and surrounding fascia.

Several options are frequently used for urinary diversion. Ileal conduits bring urine directly from the ureter to the abdominal wall. Some patients receive either a continent cutaneous reservoir constructed from detubularized bowel or an orthotopic neobladder. Approximately 25% of men receive a neobladder, leading to 85–90% continence during the day. Cutaneous reservoirs are drained by intermittent catheterization. Contraindications to a neobladder include renal insuf - ciency, an inability to self-catheterize, or CIS or an exophytic tumor in the urethra. Diffuse CIS in the bladder is a relative contraindication based on the risk of a urethral recurrence. Concurrent ulcerative colitis or Crohn's disease may hinder the use of bowel.

A partial cystectomy may be considered when the disease is limited to the dome of the bladder, a ≥2 cm margin can be achieved, there is no associated CIS, and the bladder capacity is adequate after resection. T is occurs in 5–10% of cases. Carcinomas in the ureter or in the renal pelvis are treated with nephroureterectomy with a bladder cuff to remove the tumor.

T e probability of recurrence following surgery is based on pathologic stage, presence or absence of lymphatic or vascular invasion, and nodal spread. Among those

TABLE 43-1

SURVIVAL FOLLOWING SURGERY FOR BLADDER CANCER		
PATHOLOGIC STAGE	5-YEAR SURVIVAL, %	10-YEAR SURVIVAL, %
T2,N0	89	87
T3a,N0	78	76
T3b,N0	62	61
T4,N0	50	45
Any T,N1	35	34

whose cancers recur, the recurrence develops in a median of 1 year. Long-term outcomes vary by pathologic stage and histology **(Table 43-1)**. The number of lymph nodes removed is also prognostic, whether or not the nodes contained tumor.

Chemotherapy (described below) has been shown to prolong the survival of patients with muscle-invasive disease when combined with definitive treatment of the bladder by radical cystectomy or radiation therapy. Presurgical (or neoadjuvant) chemotherapy has been the most thoroughly explored, and increases the cure rate by 5–15%, whereas postsurgical (adjuvant) chemotherapy has not been proven definitively beneficial. For the majority of patients, chemotherapy alone is inadequate to eradicate the disease. Use of neoadjuvant chemotherapy is increasing, although it still remains underused. Experimental studies are evaluating bladder preservation strategies by combining chemotherapy and radiation therapy in patients whose tumors were endoscopically removed.

METASTATIC DISEASE The primary goal of metastatic disease treatment is to achieve complete remission with chemotherapy alone or with a combined-modality approach of chemotherapy followed by surgical resection of residual disease. One can define a goal in terms of cure or palliation on the basis of the probability of achieving a complete response to chemotherapy using prognostic factors, such as Karnofsky performance status (KPS) (<80%) and whether the pattern of spread is nodal or visceral (liver, lung, or bone). For those with zero, one, or two risk factors, the probability of complete remission is 38, 25, and 5%, respectively, and median survival is 33, 13.4, and 9.3 months, respectively. Patients who have low KPS or who have visceral disease or bone metastases rarely achieve long-term survival. The toxicities also vary as a function of risk, and treatment-related mortality rates are as high as 3–4% using some combinations in these poor-risk patient groups. For most patients, treatment is palliative, aimed at delaying or relieving cancer-related symptoms, because few patients experience durable complete remissions.

CHEMOTHERAPY A number of chemotherapeutic drugs have activity as single agents; cisplatin, paclitaxel, and gemcitabine are considered most active. Standard therapy consists of two-, three-, or four-drug combinations. Overall response rates of >50% have been reported using combinations such as methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); gemcitabine and cisplatin (GC); or gemcitabine, paclitaxel, and cisplatin (GPC). MVAC was considered standard, but the toxicities of neutropenia and fever, mucositis, diminished renal and auditory function, and peripheral neuropathy led to the development of alternative regimens. At present, GC is used more commonly than MVAC based on the results of a comparative trial of MVAC versus GC that showed less neutropenia and fever and less mucositis for the GC regimen with similar response rates and median overall survival. Anemia and thrombocytopenia were more common with GC. GPC is not more effective than GC.

Chemotherapy has also been tested in the neoadjuvant and adjuvant settings. In a randomized trial, patients receiving three cycles of neoadjuvant MVAC followed by cystectomy had a significantly better median (6.2 years) and 5-year survival (57%) compared to cystectomy alone (median survival 3.8 years; 5-year survival 42%). Similar results were obtained in an international study of three cycles of cisplatin, methotrexate, and vinblastine (CMV) followed by either radical cystectomy or radiation therapy. The decision to administer adjuvant therapy is based on recurrence risk after cystectomy. Studies of adjuvant chemotherapy have been underpowered, and most closed for lack of accrual. One underpowered study using the GPC regimen suggested that adjuvant treatment improved survival, although many patients never received chemotherapy for metastases. Another underpowered study did not show a benefit for GC chemotherapy. Therefore, preoperative chemotherapy is preferred when medically appropriate. Indications for adjuvant chemotherapy in patients who did not receive neoadjuvant treatment include nodal disease, extravesical tumor extension, or vascular invasion in the resected specimen.

The management of bladder cancer is summarized in **Table 43-2**.

TABLE 43-2

MANAGEMENT OF BLADDER CANCER	
NATURE OF LESION	MANAGEMENT APPROACH
Non–muscle-invasive disease	Endoscopic removal, usually with intravesical therapy
Muscle-invasive disease	Cystectomy ± systemic chemotherapy (before or after surgery)
Metastatic disease	Curative or palliative chemotherapy (based on prognostic factors) ± surgery

CARCINOMA OF THE RENAL PELVIS AND URETER

About 5000 cases of renal pelvis and ureter cancer occur each year; nearly all are transitional cell carcinomas similar to bladder cancer in biology and appearance. T is tumor is associated with chronic phenacetin abuse and aristolochic acid consumption in Chinese herbal preparations; aristolochic acid also seems to be associated with Balkan nephropathy, a chronic interstitial nephritis endemic in Bulgaria, Greece, Bosnia-Herzegovina, and Romania. In addition, upper tract urothelial carcinoma is linked to hereditary nonpolyposis colorectal cancer.

T e most common symptom is painless gross hematuria, and the disease is usually detected on imaging during the workup for hematuria. Patterns of spread are like bladder cancer. For low-grade disease localized to the renal pelvis and ureter, nephroureterectomy (including excision of the distal ureter with a portion of the bladder) is associated with 5-year survival of 80–90%. More invasive or poorly differentiated tumors are more likely to recur locally and to metastasize. Metastatic disease is treated with the chemotherapy used in bladder cancer, and the outcome is similar to that of metastatic bladder cancer.

RENAL CELL CARCINOMA

Renal cell carcinomas account for 90–95% of malignant neoplasms arising from the kidney. Notable features include resistance to cytotoxic agents, infrequent responses to biologic response modifiers such as interleukin (IL) 2, robust activity to antiangiogenesis targeted agents, and a variable clinical course for patients with metastatic disease, including anecdotal reports of spontaneous regression.

EPIDEMIOLOGY

T e incidence of renal cell carcinoma continues to rise and is now nearly 65,000 cases annually in the United States, resulting in 13,700 deaths. T e male-to-female ratio is 2:1. Incidence peaks between the ages of 50 and 70 years, although this malignancy may be diagnosed at any age. Many environmental factors have been investigated as possible contributing causes; the strongest association is with cigarette smoking. Risk is also increased for patients who have acquired cystic disease of the kidney associated with end-stage renal disease and for those with tuberous sclerosis. Most cases are sporadic, although familial forms have been reported. One is associated with von Hippel-Lindau (VHL) syndrome. VHL syndrome is an autosomal dominant disorder. Genetic studies identified the VHL gene on the short arm of chromosome 3. Approximately 35% of individuals with VHL disease develop clear cell renal cell carcinoma. Other associated neoplasms include retinal hemangioma, hemangioblastoma of the spinal cord and cerebellum, pheochromocytoma, neuroendocrine tumors and cysts, and cysts in the epididymis of the testis in men and the broad ligament in women.

PATHOLOGY AND GENETICS

Renal cell neoplasia represents a heterogeneous group of tumors with distinct histopathologic, genetic, and clinical features ranging from benign to high-grade malignant **(Table 43-3)**. T ey are classified on the basis of morphology and histology. Categories include clear cell carcinoma (60% of cases), papillary tumors (5–15%), chromophobe tumors (5–10%), oncocytomas (5–10%), and collecting or Bellini duct tumors (<1%). Papillary tumors tend to be bilateral and multifocal. Chromophobe tumors have a more indolent clinical course, and oncocytomas are considered benign neoplasms. In contrast, Bellini duct carcinomas, which are thought to arise from the collecting ducts within the renal medulla, are rare but often very aggressive. Clear cell tumors, the predominant histology, are found in >80% of patients who develop metastases. Clear cell tumors arise from the epithelial cells of the proximal tubules and usually show chromosome 3p deletions.

TABLE 43-3

CLASSIFICATION OF EPITHELIAL NEOPLASMS ARISING FROM THE KIDNEY

CARCINOMA TYPE	GROWTH PATTERN	CELL OF ORIGIN	CYTOGENETICS
Clear cell	Acinar or sarcomatoid	Proximal tubule	3p-, 5q+, 14q-
Papillary	Papillary or sarcomatoid	Proximal tubule	+7, +17, -Y
Chromophobe	Solid, tubular, or sarcomatoid	Distal tubules/cortical collecting duct	Whole arm losses (1, 2, 6, 10, 13, 17, and 21)
Oncocytic	Tumor nests	Cortical collecting duct	Undetermined
Collecting duct	Papillary or sarcomatoid	Medullary collecting duct	Undetermined

Deletions of 3p21–26 (where the VHL gene maps) are identified in patients with familial as well as sporadic tumors. VHL encodes a tumor suppressor protein that is involved in regulating the transcription of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and a number of other hypoxia-inducible proteins. Inactivation of VHL leads to overexpression of these agonists of the VEGF and PDGF receptors, which promote tumor angiogenesis and tumor growth. Agents that inhibit proangiogenic growth factor activity show antitumor effects. Enormous genetic variability has been documented in tumors from individual patients. Although the tumors have a clear clonal origin and often contain VHL mutations in common, different portions of the primary tumor and different metastatic sites may have wide variation in genetic lesions they contain. T is tumor heterogeneity may underlie the emergence of treatment resistance.

CLINICAL PRESENTATION

T e presenting signs and symptoms include hematuria, abdominal pain, and a flank or abdominal mass. Other symptoms are fever, weight loss, anemia, and a varicocele. T e tumor is most commonly detected as an incidental finding on a radiograph. Widespread use of radiologic cross-sectional imaging procedures (CT, ultrasound, MRI) contributes to earlier detection, including incidental renal masses detected during evaluation for other medical conditions. T e increasing number of incidentally discovered low-stage tumors has contributed to an improved 5-year survival for patients with renal cell carcinoma and increased use of nephron-sparing surgery (partial nephrectomy). A spectrum of paraneoplastic syndromes has been associated with these malignancies, including erythrocytosis, hypercalcemia, nonmetastatic hepatic dysfunction (Stauffer's syndrome), and acquired dysfibrinogenemia. Erythrocytosis is noted at presentation in only about 3% of patients. Anemia, a sign of advanced disease, is more common.

T e standard evaluation of patients with suspected renal cell tumors includes a CT scan of the abdomen and pelvis, chest radiograph, urine analysis, and urine cytology. If metastatic disease is suspected from the chest radiograph, a CT of the chest is warranted. MRI is useful in evaluating the inferior vena cava in cases of suspected tumor involvement or invasion by thrombus. In clinical practice, any solid renal masses should be considered malignant until proven otherwise; a definitive diagnosis is required. If no metastases are demonstrated, surgery is indicated, even if the renal vein is invaded. T e differential diagnosis of a renal mass includes cysts, benign neoplasms (adenoma, angiomyolipoma, oncocytoma), inflammatory lesions (pyelonephritis or abscesses), and other primary or metastatic cancers. Other malignancies that may involve the kidney include transitional cell carcinoma of the renal pelvis, sarcoma, lymphoma, and Wilms' tumor. All of these are less common causes of renal masses than is renal cell cancer.

STAGING AND PROGNOSIS

Staging is based on the American Joint Committee on Cancer (AJCC) staging system **(Fig. 43-2)**. Stage I tumors are <7 cm in greatest diameter and confined to

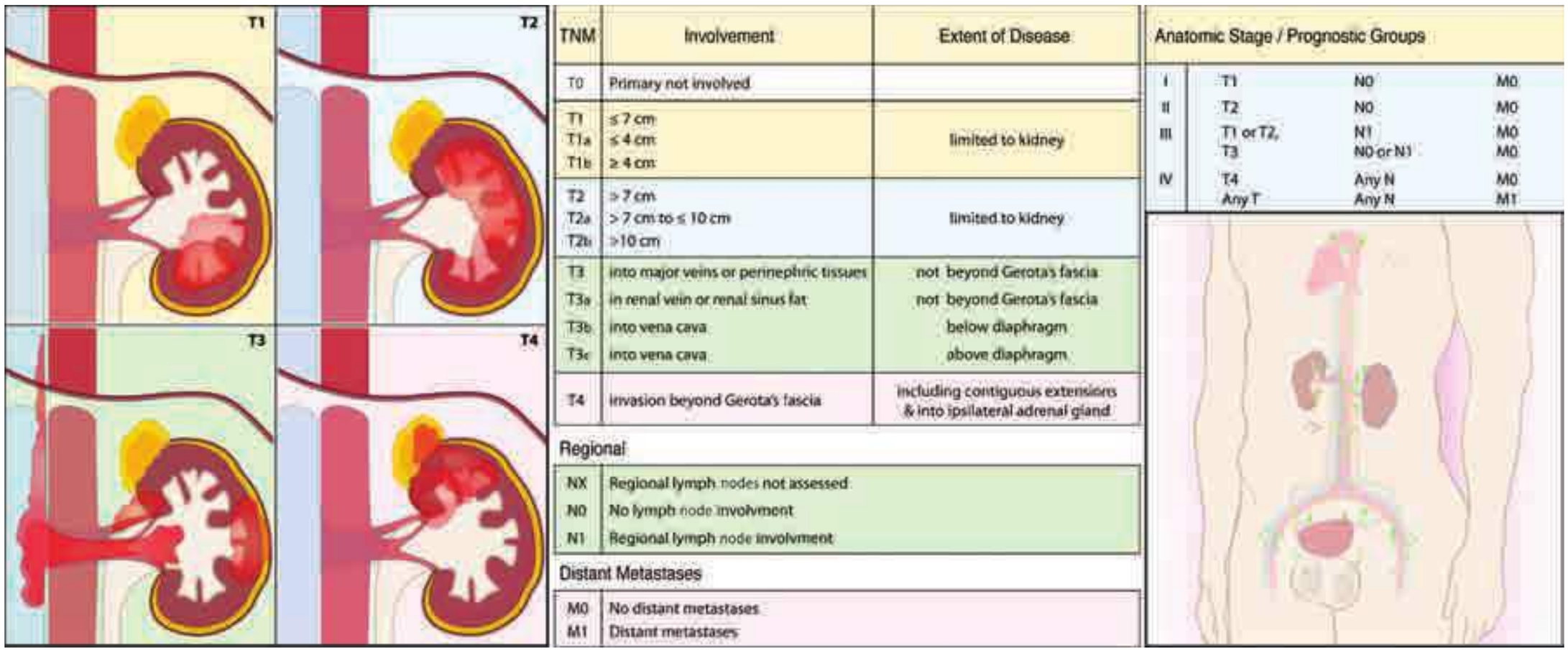


FIGURE 43-2
Renal cell carcinoma staging. TNM, tumor, node, metastasis.

the kidney, stage II tumors are ≥7 cm and confined to the kidney, stage III tumors extend through the renal capsule but are confined to Gerota's fascia (IIIa) or involve a single hilar lymph node (N1), and stage IV disease includes tumors that have invaded adjacent organs (excluding the adrenal gland) or involve multiple lymph nodes or distant metastases. The 5-year survival rate varies by stage: >90% for stage I, 85% for stage II, 60% for stage III, and 10% for stage IV.

TREATMENT Renal Cell Carcinoma

LOCALIZED TUMOR

The standard management for stage I or II tumors and selected cases of stage III disease is radical or partial nephrectomy. A radical nephrectomy involves en bloc removal of Gerota's fascia and its contents, including the kidney, the ipsilateral adrenal gland in some cases, and adjacent hilar lymph nodes. The role of a regional lymphadenectomy is controversial. Extension into the renal vein or inferior vena cava (stage III disease) does not preclude resection even if cardiopulmonary bypass is required. If the tumor is resected, half of these patients have prolonged survival.

Nephron-sparing approaches via open or laparoscopic surgery may be appropriate for patients who have only one kidney, depending on the size and location of the lesion. A nephron-sparing approach can also be used for patients with bilateral tumors. Partial nephrectomy techniques are applied electively to resect small masses for patients with a normal contralateral kidney. Adjuvant therapy following this surgery does not improve outcome, even in cases with a poor prognosis.

ADVANCED DISEASE Surgery has a limited role for patients with metastatic disease. Long-term survival may occur in patients who relapse after nephrectomy in a solitary site that is removed. One indication for nephrectomy with metastases at initial presentation is to alleviate pain or hemorrhage of a primary tumor. Also, a cytoreductive nephrectomy before systemic treatment improves survival for carefully selected patients with stage IV tumors.

Metastatic renal cell carcinoma is refractory to chemotherapy. Cytokine therapy with IL-2 or interferon α (IFN-α) produces regression in 10–20% of patients. IL-2 produces durable complete remission in a small proportion of cases. In general, cytokine therapy is considered unsatisfactory for most patients.

The situation changed dramatically when two large-scale randomized trials established a role for antiangiogenic therapy, as predicted by the genetic studies. These trials separately evaluated two orally administered antiangiogenic agents, sorafenib and sunitinib, that inhibited receptor tyrosine kinase signaling through the VEGF and PDGF receptors. Both showed efficacy as second-line treatment following progression during cytokine treatment, resulting in approval by regulatory authorities for the treatment of advanced renal cell carcinoma. A randomized phase III trial comparing sunitinib to IFN-α showed superior efficacy for sunitinib with an acceptable safety profile. The trial resulted in a change in the standard first-line treatment from IFN to sunitinib. Sunitinib is usually given orally at a dose of 50 mg/d for 4 out of 6 weeks. Pazopanib and axitinib are newer agents of the same class. Pazopanib was compared to sunitinib in a randomized first-line phase III trial. Efficacy was similar, and there was less fatigue and skin toxicity, resulting in better quality of life scores for pazopanib compared with sunitinib. Temsirolimus and everolimus, inhibitors of the mammalian target of rapamycin (mTOR), show activity in patients with untreated poor-prognosis tumors and in sunitinib/sorafenib-refractory tumors. Patients benefit from the sequential use of axitinib and everolimus following progression to sunitinib or pazopanib first-line therapy.

The prognosis of metastatic renal cell carcinoma is variable. In one analysis, no prior nephrectomy, a KPS <80, low hemoglobin, high corrected calcium, and abnormal lactate dehydrogenase were poor prognostic factors. Patients with zero, one or two, and three or more factors had a median survival of 24, 12, and 5 months, respectively. These tumors may follow an unpredictable and protracted clinical course. It may be best to document progression before considering systemic treatment.

CHAPTER 44

BENIGN AND MALIGNANT DISEASES OF THE PROSTATE

Howard I. Scher ■ James A. Eastham

Benign and malignant changes in the prostate increase with age. Autopsies of men in the eighth decade of life show hyperplastic changes in >90% and malignant changes in >70% of individuals. T e high prevalence of these diseases among the elderly, who often have competing causes of morbidity and mortality, mandates a risk-adapted approach to diagnosis and treatment. T is can be achieved by considering these diseases as a series of states. Each state represents a distinct clinical milestone for which therapy(ies) may be recommended based on current symptoms, the risk of developing symptoms, or death from disease in relation to death from other causes within a given time frame. For benign proliferative disorders, symptoms of urinary frequency, infection, and potential for obstruction are weighed against the side effects and complications of medical or surgical intervention. For prostate malignancies, the risks of developing the disease, symptoms, or death from cancer are balanced against the morbidities of the recommended treatments and preexisting comorbidities.

ANATOMY

T e prostate is located in the pelvis and is surrounded by the rectum, the bladder, the periprostatic and dorsal vein complexes and neurovascular bundles that are responsible for erectile function, and the urinary sphincter that is responsible for passive urinary control. T e prostate is composed of branching tubuloalveolar glands arranged in lobules surrounded by fibromuscular stroma. T e acinar unit includes an epithelial compartment made up of epithelial, basal, and neuroendocrine cells and separated by a basement membrane, and a stromal compartment that includes fibroblasts and smooth-muscle cells. Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) are produced in the epithelial cells. Both prostate epithelial cells and stromal cells express androgen receptors (ARs) and depend on androgens for growth. Testosterone, the major circulating androgen, is converted by the enzyme 5α-reductase to dihydrotestosterone in the gland.

T e periurethral portion of the gland increases in size during puberty and after the age of 55 years due to the growth of nonmalignant cells in the transition zone of the prostate that surrounds the urethra. Most cancers develop in the peripheral zone, and cancers in this location may be palpated during a digital rectal examination (DRE).

PROSTATE CANCER

In 2013, approximately 238,590 prostate cancer cases were diagnosed, and 29,720 men died from prostate cancer in the United States. T e absolute number of prostate cancer deaths has decreased in the past 5 years, which has been attributed by some to the widespread use of PSA-based detection strategies. However, the benefit of screening on survival is unclear. T e paradox of management is that although 1 in 6 men will eventually be diagnosed with the disease, and the disease remains the second leading cause of cancer deaths in men, only 1 man in 30 with prostate cancer will die of his disease.

EPIDEMIOLOGY

Epidemiologic studies show that the risk of being diagnosed with prostate cancer increases by a factor of two if one first-degree relative is affected and by four if two

or more are affected. Current estimates are that 40% of early-onset and 5–10% of all prostate cancers are hereditary. Prostate cancer affects ethnic groups differently. Matched for age, African-American males have both a higher incidence of prostate cancer and larger tumors and more worrisome histologic features than white males. Polymorphic variants of the AR, the cytochrome P450 C17, and the steroid 5α-reductase type II (SRD5A2) genes have been implicated in the variations in incidence.

T e prevalence of autopsy-detected cancers is similar around the world, while the incidence of clinical disease varies. T us, environmental and dietary factors may play a role in prostate cancer growth and progression. High consumption of dietary fats, such as α-linoleic acid or the polycyclic aromatic hydrocarbons that form when red meats are cooked, is believed to increase risk. Similar to breast cancer in Asian women, the risk of prostate cancer in Asian men increases when they move to Western environments. Protective factors include consumption of the isoflavonoid genistein (which inhibits 5α-reductase) found in many legumes, cruciferous vegetables that contain the isothiocyanate sulforaphane, retinoids such as lycopene found in tomatoes, and inhibitors of cholesterol biosynthesis (e.g., statin drugs). T e development of prostate cancer is a multistep process. One early change is hypermethylation of the GSTP1 gene promoter, which leads to loss of function of a gene that detoxifies carcinogens. T e finding that many prostate cancers develop adjacent to a lesion termed proliferative inflammatory atrophy (PIA) suggests a role for inflammation.

PREVENTION

Currently no drugs or dietary supplements are approved by the U.S. Food and Drug Administration (FDA) for prevention of prostate cancer, nor are any recommended by the major clinical guidelines. Although statins may have some protective effect, the potential risks outweigh the benefits given the small number of men who die of prostate cancer. T e results from several large, double-blind, randomized chemoprevention trials established 5α-reductase inhibitors (5ARI) as the most likely therapy to reduce the future risk of a prostate cancer diagnosis. T e Prostate Cancer Prevention Trial (PCPT), in which men older than age 55 years received placebo or the 5ARI finasteride, which inhibits the type 1 isoform, showed a 25% (95% confidence interval 19–31%) reduction in the period prevalence of prostate cancer across all age groups in favor of finasteride (18.4%) over placebo (24.4%). In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, a similar 23% reduction in the 4-year period prevalence was observed in favor of dutasteride ($p = .001$). Dutasteride inhibits both the type 1 and type 2 5ARI isoforms. While both studies met their endpoint, there was concern that most of the cancers that were prevented were low risk and that there was a slightly higher rate of clinically significant cancers (those with higher Gleason score) in the treatment arm. Neither drug was FDA-approved for prostate cancer prevention. In comparison, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which enrolled African-American men age ≥50 years and others age ≥55 years, showed no difference in cancer incidence in patients receiving vitamin E (4.6%) or selenium (4.9%) alone or in combination (4.6%) relative to placebo (4.4%). A similar lack of benefit for vitamin E, vitamin C, and selenium was seen in the Physicians Health Study II.

THE CLINICAL STATES MODEL

T e prostate cancer continuum—from the appearance of a preneoplastic and invasive lesion localized to the prostate, to a metastatic lesion that results in symptoms and, ultimately, mortality—can span decades. To facilitate disease management, competing risks are considered in the context of a series of clinical states **(Fig. 44-1)**. T e states are defined operationally on the basis of whether or not a cancer diagnosis has been established and, for those with a diagnosis, whether or not metastases are detectable on imaging studies and the measured level of testosterone in the blood. With this approach, an individual resides in only one state and remains in that state until he has progressed. At each assessment, the decision to offer treatment and the specific form of treatment are based on the risk posed by the cancer relative to competing causes of mortality that may be present in that individual. It follows that the more advanced the disease, the greater is the need for treatment.

For those without a cancer diagnosis, the decision to undergo testing to detect a cancer is based on the individual's estimated life expectancy and, separately, the probability that a clinically significant cancer may be present. For those with a prostate cancer diagnosis, the clinical states model considers the probability of developing symptoms or dying from prostate cancer. T us, a patient with localized prostate cancer who has had all cancer removed surgically remains in the state of localized disease as long as the PSA remains undetectable. T e time within a state becomes a measure of the ef - cacy of an intervention, although the effect may not be assessable for years. Because many men with active cancer are not at risk for metastases, symptoms, or death, the clinical states model allows a distinction between cure—the elimination of all cancer cells, the primary therapeutic objective when treating most cancers—and

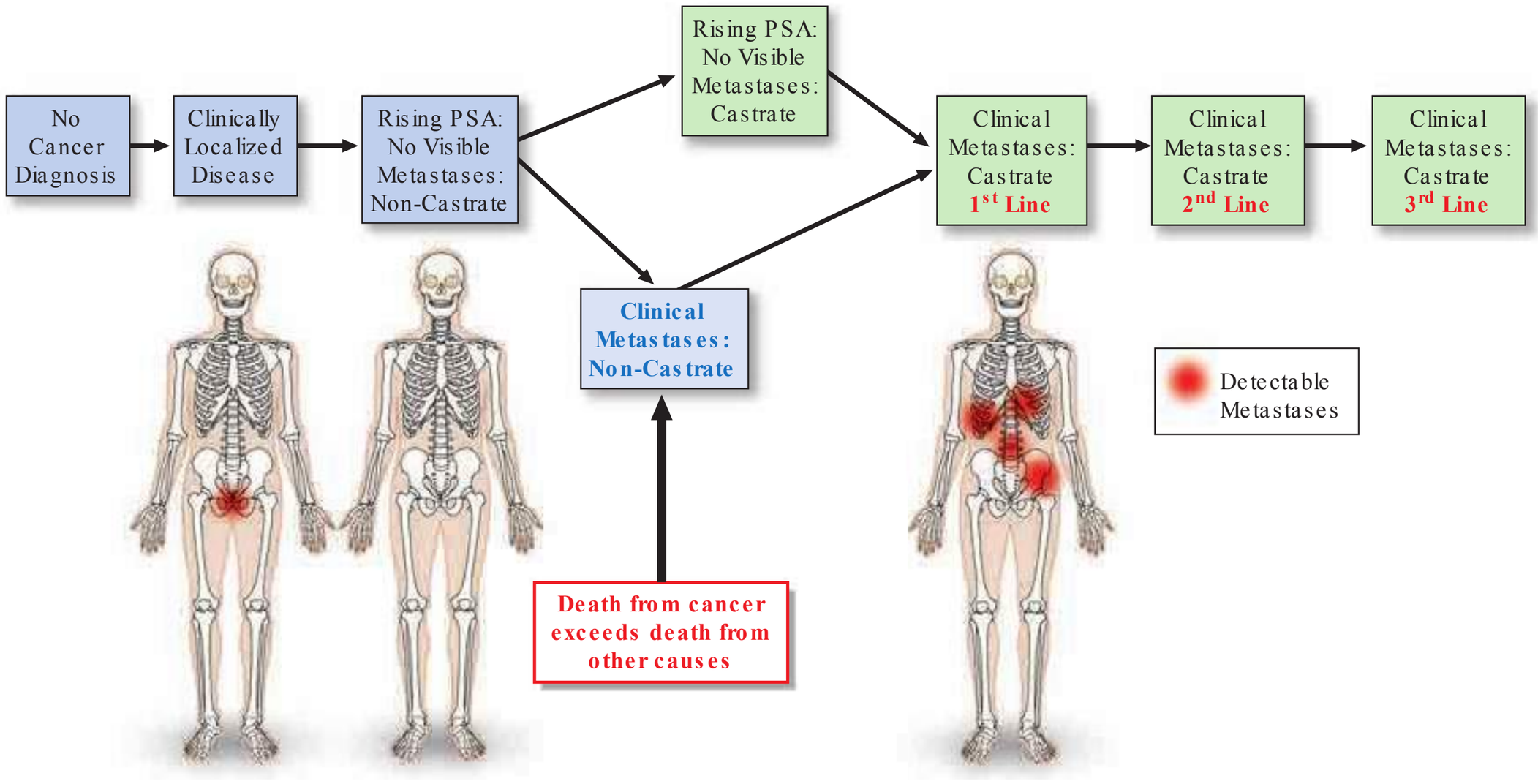


FIGURE 44-1
Clinical states of prostate cancer. PSA, prostate-specific antigen.

cancer control, in which the tempo of the illness is altered and symptoms are controlled until the patient dies of other causes. These can be equivalent therapeutically from a patient standpoint if the patient has not experienced symptoms of the disease or the treatment needed to control it. Even when a recurrence is documented, immediate therapy is not always necessary. Rather, as at the time of diagnosis, the need for intervention is based on the tempo of the illness as it unfolds in the individual, relative to the risk-to-benefit ratio of the therapy being considered.

SCREENING AND DIAGNOSIS

Physical examination

The need to pursue a diagnosis of prostate cancer is based on symptoms, an abnormal DRE, or, more typically, a change in or an elevated serum PSA. The urologic history should focus on symptoms of outlet obstruction, continence, potency, or change in ejaculatory pattern.

The DRE focuses on prostate size and consistency and abnormalities within or beyond the gland. Many cancers occur in the peripheral zone and may be palpated on DRE. Carcinomas are characteristically hard, nodular, and irregular, while induration may also be due to benign prostatic hypertrophy (BPH) or calculi. Overall, 20–25% of men with an abnormal DRE have cancer.

Prostate-specific antigen

PSA (kallikrein-related peptidase 3; KLK3) is a kallikrein-related serine protease that causes liquefaction of seminal coagulum. It is produced by both nonmalignant and malignant epithelial cells and, as such, is prostate-specific, not prostate cancer–specific. Serum levels may also increase from prostatitis and BPH. Serum levels are not significantly affected by DRE, but the performance of a prostate biopsy can increase PSA levels up to tenfold for 8–10 weeks. PSA circulating in the blood is inactive and mainly occurs as a complex with the protease inhibitor α_1-antichymotrypsin and as free (unbound) PSA forms. The formation of complexes between PSA, α_2-macroglobulin, or other protease inhibitors is less significant. Free PSA is rapidly eliminated from the blood by glomerular filtration with an estimated half-life of 12–18 h. Elimination of PSA bound to α_1-antichymotrypsin is slow (estimated half-life of 1–2 weeks) because it too is largely cleared by the kidneys. Levels should be undetectable after about 6 weeks if the prostate has been removed. Immunohistochemical staining for PSA can be used to establish a prostate cancer diagnosis.

PSA-based screening and early detection

PSA testing was approved by the U.S. FDA in 1994 for early detection of prostate cancer, and the widespread use of the test has played a significant role in the proportion of men diagnosed with early-stage cancers:

more than 70–80% of newly diagnosed cancers are clinically organ-confined. The level of PSA in blood is strongly associated with the risk and outcome of prostate cancer. A single PSA measured at age 60 is associated (area under the curve [AUC] of 0.90) with lifetime risk of death from prostate cancer. Most prostate cancer deaths (90%) occur among men with PSA levels in the top quartile (>2 ng/mL), although only a minority of men with PSA >2 ng/mL will develop lethal prostate cancer. Despite this and mortality rate reductions reported from large randomized prostate cancer screening trials, routine use of the test remains controversial.

The U.S. Preventive Services Task Force (USPSTF) reviewed the evidence for screening for prostate cancer and made a clear recommendation against screening. By giving a grade of "D" in the recommendation statement that was based on this review, the USPSTF concluded that "there is moderate or high certainty that this service has no net benefit or that the harms outweigh the benefits." Whether the harms of screening, overdiagnosis, and overtreatment are justified by the benefits in terms of reduced prostate cancer mortality is open to reasonable doubt. In response to the USPSTF, the American Urological Association (AUA) updated their consensus statement regarding prostate cancer screening. They concluded that the quality of evidence for the benefits of screening was moderate, and evidence for harm was high for men age 55–69 years. For men outside this age range, evidence was lacking for benefit, but the harms of screening, including overdiagnosis and overtreatment, remained. The AUA recommends shared decision making considering PSA-based screening for men age 55–69, a target age group for whom benefits may outweigh harms. Outside this age range, PSA-based screening as a routine test was not recommended based on the available evidence. The entire guideline is available at www.AUAnet.org/education/guidelines/prostate-cancer-detection.cfm.

The PSA criteria used to recommend a diagnostic prostate biopsy have evolved over time. However, based on the commonly used cut point for prostate biopsy (a total PSA ≥4 ng/mL), most men with a PSA elevation do not have histologic evidence of prostate cancer at biopsy. In addition, many men with PSA levels below this cut point harbor cancer cells in their prostate. Information from the PCPT demonstrates that there is no PSA below which the risk of prostate cancer is zero. Thus, the PSA level establishes the likelihood that a man will harbor cancer if he undergoes a prostate biopsy. The goal is to increase the sensitivity of the test for younger men more likely to die of the disease and to reduce the frequency of detecting cancers of low malignant potential in elderly men more likely to die of other causes. Patients with symptomatic prostatitis should have a course of antibiotics before biopsy. However, the routine use of antibiotics in an asymptomatic man with an elevated PSA level is strongly discouraged.

Prostate biopsy

A diagnosis of cancer is established by an image-guided needle biopsy. Direct visualization by transrectal ultrasound (TRUS) or magnetic resonance imaging (MRI) assures that all areas of the gland are sampled. Contemporary schemas advise an extended-pattern 12-core biopsy that includes sampling from the peripheral zone as well as a lesion-directed palpable nodule or suspicious image-guided sampling. Men with an abnormal PSA and negative biopsy are advised to undergo a repeat biopsy.

Biopsy pathology

Each core of the biopsy is examined for the presence of cancer, and the amount of cancer is quantified based on the length of the cancer within the core and the percentage of the core involved. Of the cancers identified, >95% are adenocarcinomas; the rest are squamous or transitional cell tumors or, rarely, carcinosarcomas. Metastases to the prostate are rare, but in some cases colon cancers or transitional cell tumors of the bladder invade the gland by direct extension.

When prostate cancer is diagnosed, a measure of histologic aggressiveness is assigned using the Gleason grading system, in which the dominant and secondary glandular histologic patterns are scored from 1 (well-differentiated) to 5 (undifferentiated) and summed to give a total score of 2–10 for each tumor. The most poorly differentiated area of tumor (i.e., the area with the highest histologic grade) often determines biologic behavior. The presence or absence of perineural invasion and extracapsular spread is also recorded.

Prostate cancer staging

The tumor, node, metastasis (TNM) staging system includes categories for cancers identified solely on the basis of an abnormal PSA (T1c), those that are palpable but clinically confined to the gland (T2), and those that have extended outside the gland (T3 and T4) **(Table 44-1, Fig. 44-2)**. DRE alone is inaccurate in determining the extent of disease within the gland, the presence or absence of capsular invasion, involvement of seminal vesicles, and extension of disease to lymph nodes. Because of the inadequacy of DRE for staging, the TNM staging system was modified to include the results of imaging. Unfortunately, no single test has proven to accurately indicate the stage or the presence of organ-confined disease, seminal vesicle involvement, or lymph node spread.

TRUS is the imaging technique most frequently used to assess the primary tumor, but its chief use is directing

TABLE 44-1

TNM CLASSIFICATION	
TNM Staging System for Prostate Cancer[a]	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Localized Disease	
T1	Clinically inapparent tumor, neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in ≤5% of resected tissue; not palpable
T1b	Tumor incidental histologic finding in >5% of resected tissue
T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within prostate[b]
T2a	Tumor involves half of one lobe or less
T2b	Tumor involves more than one half of one lobe, not both lobes
T2c	Tumor involves both lobes
Local Extension	
T3	Tumor extends through the prostate capsule[c]
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.
Metastatic Disease	
N1	Positive regional lymph nodes
M1	Distant metastases

[a]Revised from SB Edge et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.
[b]Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.
[c]Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.
Abbreviations: PSA, prostate-specific antigen; TNM, tumor, node, metastasis.

prostate biopsies, not staging. No TRUS finding consistently indicates cancer with certainty. Computed tomography (CT) lacks sensitivity and specificity to detect extraprostatic extension and is inferior to MRI in visualization of lymph nodes. In general, MRI performed with an endorectal coil is superior to CT to detect cancer in the prostate and to assess local disease extent. T1-weighted MRI produces a high signal in the periprostatic fat, periprostatic venous plexus, perivesicular tissues, lymph nodes, and bone marrow. T2-weighted MRI demonstrates the internal architecture of the prostate and seminal vesicles. Most cancers have a low signal, while the normal peripheral zone has a high signal, although the technique lacks sensitivity and specificity. MRI is also useful for the planning of surgery and radiation therapy.

Radionuclide bone scans (bone scintigraphy) are used to evaluate spread to osseous sites. T is test is sensitive but relatively nonspecific because areas of increased uptake are not always related to metastatic disease. Healing fractures, arthritis, Paget's disease, and other conditions will also cause abnormal uptake. True-positive bone scans are uncommon when the PSA is <10 ng/mL unless the tumor is high grade.

TREATMENT Treatment of Prostate Cancer by Clinical State

CLINICALLY LOCALIZED PROSTATE CANCER Clinically localized prostate cancers are those that appear to be nonmetastatic after staging studies are performed. Patients with clinically localized disease are managed by radical prostatectomy, radiation therapy, or active surveillance. Choice of therapy requires the consideration of several factors: the presence of symptoms, the probability that the untreated tumor will adversely affect the

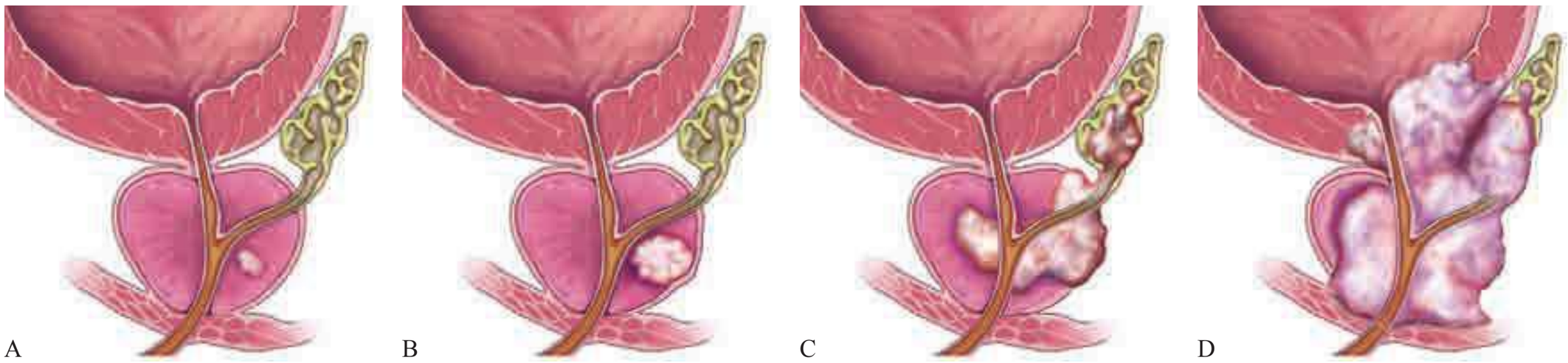


FIGURE 44-2
T stages of prostate cancer. A. T1—Clinically inapparent tumor, neither palpable nor visible by imaging; B. T2—Tumor confined within prostate; C. T3—Tumor extends through prostate capsule and may invade the seminal vesicles; D. T4—Tumor is fixed or invades adjacent structures. Eighty-one percent of patients present with local disease (T1 and T2), which is associated with a 5-year survival rate of 100%. An additional 12% of patients present with regional disease (T3 and T4 without metastases), which is also associated with a 100% survival rate after 5 years. Four percent of patients present with distant disease (T4 with metastases), which is associated with a 28% 5-year survival rate. (Three percent of patients are ungraded, and this group is associated with a 73% 5-year survival rate.) (Data from AJCC, http://seer.cancer.gov/statfacts/html/prost.html. Figure © 2014 Memorial Sloan-Kettering Cancer Center; used with permission.)

quality or duration of survival and thus require treatment, and the probability that the tumor can be cured by single-modality therapy directed at the prostate or that it will require both local and systemic therapy to achieve cure.

Data from the literature do not provide clear evidence for the superiority of any one treatment relative to another. Comparison of outcomes of various forms of therapy is limited by the lack of prospective trials, referral bias, the experience of the treating teams, and differences in endpoints and cancer control definitions. Often, PSA relapse–free survival is used because an effect on metastatic progression or survival may not be apparent for years. After radical surgery to remove all prostate tissue, PSA should become undetectable in the blood within 6 weeks. If PSA remains or becomes detectable after radical prostatectomy, the patient is considered to have persistent disease. After radiation therapy, in contrast, PSA does not become undetectable because the remaining nonmalignant elements of the gland continue to produce PSA even if all cancer cells have been eliminated. Similarly, cancer control is not well defined for a patient managed by active surveillance because PSA levels will continue to rise in the absence of therapy. Other outcomes are time to objective progression (local or systemic), cancer-specific survival, and overall survival; however, these outcomes may take years to assess.

The more advanced the disease, the lower the probability of local control and the higher the probability of systemic relapse. More important is that within the categories of T1, T2, and T3 disease are cancers with a range of prognoses. Some T3 tumors are curable with therapy directed solely at the prostate, and some T1 lesions have a high probability of systemic relapse that requires the integration of local and systemic therapy to achieve cure. For T1c cancers in particular, stage alone is inadequate to predict outcome and select treatment; other factors must be considered.

Nomograms To better assess risk and guide treatment selection, many groups have developed prognostic models or nomograms that use a combination of the initial clinical T stage, biopsy Gleason score, and baseline PSA. Some use discrete cut points (PSA <10 or ≥10 ng/mL; Gleason score of ≤6, 7, or ≥8); others employ nomograms that use PSA and Gleason score as continuous variables. More than 100 nomograms have been reported to predict the probability that a clinically significant prostate cancer is present, disease extent (organ-confined vs non–organ-confined, node-negative or -positive), or the probability of success of treatment for specific local therapies using pretreatment variables. Considerable controversy exists over what constitutes "high risk" based on a predicted probability of success or failure. In these situations, nomograms and predictive models can only go so far. Exactly what probability of success or failure would lead a physician to recommend and a patient to seek alternative approaches is controversial. As an example, it may be appropriate to recommend radical surgery for a younger patient with a low probability of cure. Nomograms are being refined continually to incorporate additional clinical parameters, biologic determinants, and year of treatment, which can also affect outcomes, making treatment decisions a dynamic process.

Treatment-Related Adverse Events The frequency of adverse events varies by treatment modality and the experience of the treating team. For example, following radical prostatectomy, incontinence rates range from 2–47% and impotence rates range from 25–89%. Part of the variability relates to how the complication is defined and whether the patient or physician is reporting the event. The time of the assessment is also important. After surgery, impotence is immediate but may reverse over time, while with radiation therapy impotence is not immediate but may develop over time. Of greatest concern to patients are the effects on continence, sexual potency, and bowel function.

Radical Prostatectomy The goal of radical prostatectomy is to excise the cancer completely with a clear margin, to maintain continence by preserving the external sphincter, and to preserve potency by sparing the autonomic nerves in the neurovascular bundle. The procedure is advised for patients with a life expectancy of 10 years or more and is performed via a retropubic or perineal approach or via a minimally invasive robotic-assisted or hand-held laparoscopic approach. Outcomes can be predicted using postoperative nomograms that consider pretreatment factors and the pathologic findings at surgery. PSA failure is usually defined as a value greater than 0.1 or 0.2 ng/mL. Specific criteria to guide the choice of one approach over another are lacking. Minimally invasive approaches offer the advantage of a shorter hospital stay and reduced blood loss. Rates of cancer control, recovery of continence, and recovery of erectile function are comparable between open and minimally invasive approaches. The individual surgeon rather than the surgical approach used is most important in determining outcomes after surgery.

Neoadjuvant hormonal therapy has also been explored in an attempt to improve the outcomes of surgery for high-risk patients, using a variety of definitions. The results of several large trials testing 3 or 8 months of androgen depletion before surgery showed that serum PSA levels decreased by 96%, prostate volumes decreased by 34%, and margin positivity rates decreased from 41% to 17%. Unfortunately, hormones did not produce an improvement in PSA relapse–free survival. Thus, neoadjuvant hormonal therapy is not recommended.

Factors associated with incontinence following radical prostatectomy include older age and urethral length, which impacts the ability to preserve the urethra beyond the apex and the distal sphincter. The skill and experience of the surgeon are also factors. Recovery of erectile function is associated with younger age, quality of erections before surgery, and the absence of damage to the neurovascular bundles. In general, erectile function begins to return about 6 months after surgery if both neurovascular bundles are preserved. Potency is reduced by half if at least one neurovascular bundle is sacrificed. Overall, with the availability of drugs such as

phosphodiesterase-5 (PDE5) inhibitors, intraurethral inserts of alprostadil, and intracavernosal injections of vasodilators, many patients recover satisfactory sexual function.

Radiation Therapy Radiation therapy is given by external beam, by radioactive sources implanted into the gland, or by a combination of the two techniques.

EXTERNAL-BEAM RADIATION THERAPY Contemporary external-beam radiation therapy requires three-dimensional conformal treatment plans to maximize the dose to the prostate and to minimize the exposure of the surrounding normal tissue. Intensity-modulated radiation therapy (IMRT) permits shaping of the dose and allows the delivery of higher doses to the prostate and a further reduction in normal tissue exposure than three-dimensional conformal treatment alone. These advances have enabled the safe administration of doses >80 Gy and resulted in higher local control rates and fewer side effects.

Cancer control after radiation therapy has been defined by various criteria, including a decline in PSA to <0.5 or 1 ng/mL, "nonrising" PSA values, and a negative biopsy of the prostate 2 years after completion of treatment. The current standard definition of biochemical failure (the Phoenix definition) is a rise in PSA by ≥2 ng/mL higher than the lowest PSA achieved. The date of failure is "at call" and not backdated.

Radiation dose is critical to the eradication of prostate cancer. In a representative study, a PSA nadir of <1.0 ng/mL was achieved in 90% of patients receiving 75.6 or 81.0 Gy versus 76% and 56% of those receiving 70.2 and 64.8 Gy, respectively. Positive biopsy rates at 2.5 years were 4% for those treated with 81 Gy versus 27% and 36% for those receiving 75.6 and 70.2 Gy, respectively.

Overall, radiation therapy is associated with a higher frequency of bowel complications (mainly diarrhea and proctitis) than surgery. The frequency relates directly to the volume of the anterior rectal wall receiving full-dose treatment. In one series, grade 3 rectal or urinary toxicities were seen in 2.1% of patients who received a median dose of 75.6 Gy, whereas grade 3 urethral strictures requiring dilatation developed in 1% of cases, all of whom had undergone a transurethral resection of the prostate (TURP). Pooled data show that the frequency of grade 3 and 4 toxicities is 6.9% and 3.5%, respectively, for patients who received >70 Gy. The frequency of erectile dysfunction is related to the age of the patient, the quality of erections pretreatment, the dose administered, and the time of assessment. Postradiation erectile dysfunction is related to a disruption of the vascular supply and not the nerve fibers.

Neoadjuvant hormone therapy before radiation therapy has the aim of decreasing the size of the prostate and, consequently, reducing the exposure of normal tissues to full-dose radiation, increasing local control rates, and decreasing the rate of systemic failure. Short-term hormone therapy can reduce toxicities and improve local control rates, but long-term treatment (2–3 years) is needed to prolong the time to PSA failure and lower the risk of metastatic disease in men with high-risk cancers. The impact on survival has been less clear.

BRACHYTHERAPY Brachytherapy is the direct implantation of radioactive sources (seeds) into the prostate. It is based on the principle that the deposition of radiation energy in tissues decreases as a function of the square of the distance from the source **(Chap. 29)**. The goal is to deliver intensive irradiation to the prostate, minimizing the exposure of the surrounding tissues. The current standard technique achieves a more homogeneous dose distribution by placing seeds according to a customized template based on imaging assessment of the cancer and computer-optimized dosimetry. The implantation is performed transperineally as an outpatient procedure with real-time imaging.

Improvements in brachytherapy techniques have resulted in fewer complications and a marked reduction in local failure rates. In a series of 197 patients followed for a median of 3 years, 5-year actuarial PSA relapse–free survival for patients with pretherapy PSA levels of 0–4, 4–10, and >10 ng/mL were 98%, 90%, and 89%, respectively. In a separate report of 201 patients who underwent posttreatment biopsies, 80% were negative, 17% were indeterminate, and 3% were positive. The results did not change with longer follow-up. Nevertheless, many physicians feel that implantation is best reserved for patients with good or intermediate prognostic features.

Brachytherapy is well tolerated, although most patients experience urinary frequency and urgency that can persist for several months. Incontinence has been seen in 2–4% of cases. Higher complication rates are observed in patients who have undergone a prior TURP, whereas those with obstructive symptoms at baseline are at a higher risk for retention and persistent voiding symptoms. Proctitis has been reported in <2% of patients.

Active Surveillance Although prostate cancer is the most common form of cancer affecting men in the United States, patients are being diagnosed earlier and more frequently present with early-stage disease. Active surveillance, described previously as watchful waiting or deferred therapy, is the policy of monitoring the illness at fixed intervals with DREs, PSA measurements, and repeat prostate biopsies as indicated until histopathologic or serologic changes correlative of progression warrant treatment with curative intent. It evolved from studies that evaluated predominantly elderly men with well-differentiated tumors who demonstrated no clinically significant progression for protracted periods, recognition of the contrast between incidence and disease-specific mortality, the high prevalence of autopsy cancers, and an effort to reduce overtreatment. A recent screening study estimated that between 50–100 men with low-risk disease would need to be treated to prevent one prostate cancer–specific death.

Arguing against active surveillance are the results of a Swedish randomized trial of radical prostatectomy versus active surveillance. With a median follow-up of 6.2 years, men treated by radical surgery had a lower risk of prostate cancer death relative to active surveillance patients (4.6% vs 8.9%)

and a lower risk of metastatic progression (hazard ratio 0.63). Case selection is critical, and determining clinical parameters predictive of cancer aggressiveness that can be used to reliably select men most likely to benefit from active surveillance is an area of intense study. In one prostatectomy series, it was estimated that 10–15% of those treated had "insignificant" disease. One set of criteria includes men with clinical T1c tumors that are biopsy Gleason grade 6 or less involving three or fewer cores, each of them having less than 50% involvement by tumor and a PSA density of less than 0.15.

Concerns about active surveillance include the limited ability to predict pathologic findings by needle biopsy even when multiple cores are obtained, the recognized multifocality of the disease, and the possibility of a missed opportunity to cure the disease. Nomograms to help predict which patients can safely be managed by active surveillance continue to be refined, and as their predictive accuracy improves, it can be anticipated that more patients will be candidates.

RISING PSA AFTER DEFINITIVE LOCAL THERAPY T is term is applied to a group of patients in whom the sole manifestation of disease is a rising PSA after surgery and/or radiation therapy. By definition, there is no evidence of disease on an imaging study. For these patients, the central issue is whether the rise in PSA results from persistent disease in the primary site, systemic disease, or both. In theory, disease in the primary site may still be curable by additional local treatment.

T e decision to recommend radiation therapy after prostatectomy is guided by the pathologic findings at surgery, because imaging studies such as CT and bone scan are typically uninformative. Some recommend a choline-11 positron emission tomography (PET) scan, but availability in the United States is limited. Others recommend that a biopsy of the urethrovesical anastomosis be obtained before considering radiation, whereas others treat empirically based on risk. Factors that predict for response to salvage radiation therapy are a positive surgical margin, lower Gleason score in the radical prostatectomy specimen, long interval from surgery to PSA failure, slow PSA doubling time, absence of disease in the lymph nodes, and a low (<0.5–1 ng/mL) PSA value at the time of radiation treatment. Radiation therapy is generally not recommended if the PSA was persistently elevated after surgery, which usually indicates that the disease has spread outside of the area of the prostate bed and is unlikely to be controlled with radiation therapy. As is the case for other disease states, nomograms to predict the likelihood of success are available.

For patients with a rising PSA after radiation therapy, salvage local therapy can be considered if the disease was "curable" at the time of diagnosis, if persistent disease has been documented by a biopsy of the prostate, and if no metastatic disease is seen on imaging studies. Unfortunately, case selection is poorly defined in most series, and morbidities are significant. Options include salvage radical prostatectomy, salvage cryotherapy, salvage radiation therapy, and salvage irreversible electroporation.

T e rise in PSA after surgery or radiation therapy may indicate subclinical or micrometastatic disease with or without local recurrence. In these cases, the need for treatment depends, in part, on the estimated probability that the patient will develop clinically detectable metastatic disease on a scan and in what time frame. T at immediate therapy is not always required was shown in a series where patients who developed a biochemical recurrence after radical prostatectomy received no systemic therapy until metastatic disease was documented. Overall, the median time to metastatic progression by imaging was 8 years, and 63% of the patients with rising PSA values remained free of metastases at 5 years. Factors associated with progression included the Gleason score of the radical prostatectomy specimen, time to recurrence, and PSA doubling time. For those with Gleason grade ≥8, the probability of metastatic progression was 37%, 51%, and 71% at 3, 5, and 7 years, respectively. If the time to recurrence was <2 years and PSA doubling time was long (>10 months), the proportions with metastatic disease at the same time intervals were 23%, 32%, and 53%, versus 47%, 69%, and 79% if the doubling time was short (<10 months). PSA doubling times are also prognostic for survival. In one series, all patients who succumbed to disease had PSA doubling times of 3 months or less.

Most physicians advise treatment if the PSA doubling time is 12 months or less. A dif culty with predicting the risk of metastatic spread, symptoms, or death from disease in the rising PSA state is that most patients receive some form of therapy before the development of metastases. Nevertheless, predictive models continue to be refined.

METASTATIC DISEASE: NONCASTRATE T e state of noncastrate metastatic prostate cancer includes men with metastases visible on an imaging study and noncastrate levels of testosterone (>150 ng/dL). T e patient may be newly diagnosed or have a recurrence after treatment for localized disease. Symptoms of metastatic disease include pain from osseous spread, although many patients are asymptomatic despite extensive spread. Less common are symptoms related to marrow compromise (myelophthisis), spinal cord compression, or a coagulopathy.

Standard treatment is to deplete/lower androgens by medical or surgical means and/or to block androgen binding to the AR with antiandrogens. More than 90% of male hormones originate in the testes; <10% are synthesized in the adrenal gland. Surgical orchiectomy is the "gold standard" but is rarely used due to the availability of effective medical therapies and the more widespread use of hormones on an intermittent basis by which patients are treated for defined periods of time, following which the treatments are intentionally discontinued (discussed further below) **(Fig. 44-3)**.

Testosterone-Lowering Agents Medical therapies that lower testosterone levels include the gonadotropin-releasing hormone (GnRH) agonists/antagonists, 17,20-lyase inhibitors, CYP17 inhibitors, estrogens, and progestational agents. Of these, GnRH analogues such as leuprolide acetate and goserelin

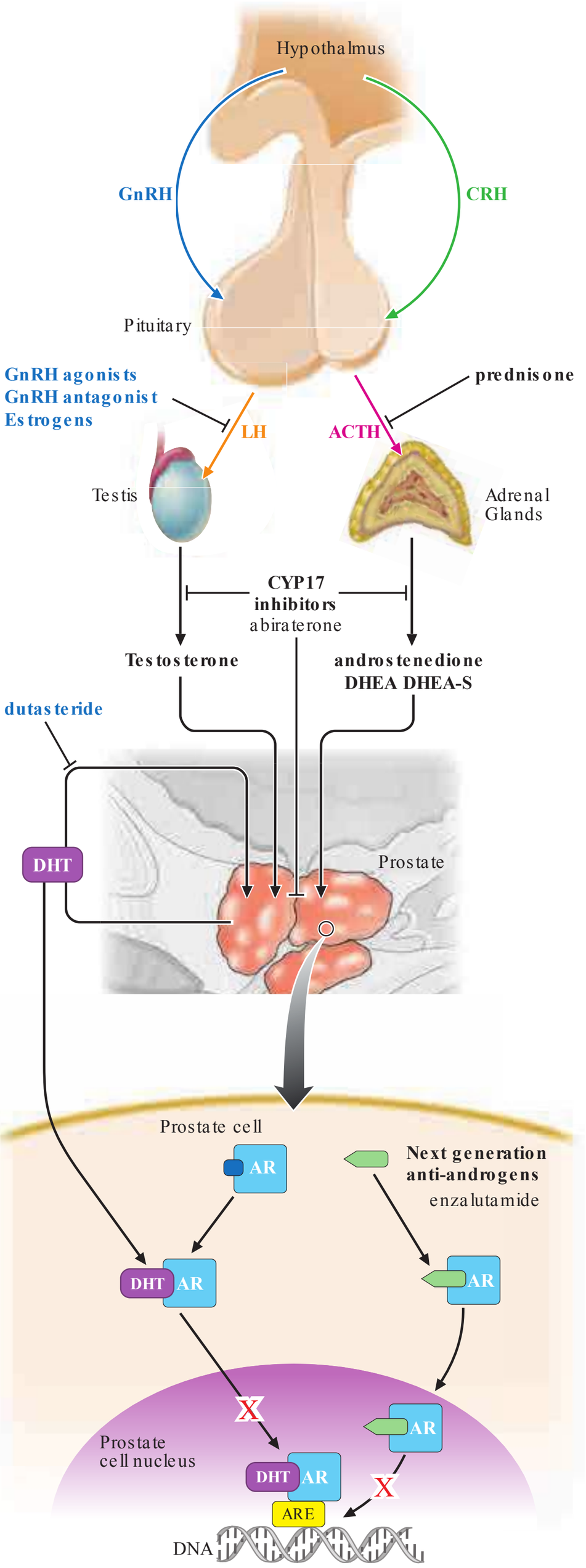


FIGURE 44-3
Sites of action of different hormone therapies. ACTH, adrenocorticotropic hormone; AR, androgen receptor; ARE, androgen-response element; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulphate; DHT, dihydrotestosterone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

acetate initially produce a rise in luteinizing hormone and follicle-stimulating hormone, followed by a downregulation of receptors in the pituitary gland, which effects a chemical castration. They were approved on the basis of randomized comparisons showing an improved safety profile (specifically, reduced cardiovascular toxicities) relative to diethylstilbestrol (DES), with equivalent potency. The initial rise in testosterone may result in a clinical flare of the disease. As such, these agents are relatively contraindicated in men with significant obstructive symptoms, cancer-related pain, or spinal cord compromise. GnRH antagonists such as degarelix achieve castrate levels of testosterone within 48 h without the initial rise in serum testosterone and do not cause a flare in the disease. Estrogens such as DES are rarely used due to the risk of vascular complications such as fluid retention, phlebitis, embolic events, and stroke. Progestational agents alone are less efficacious.

Agents that lower testosterone are associated with an androgen-depletion syndrome that includes hot flushes, weakness, fatigue, loss of libido, impotence, sarcopenia, anemia, change in personality, and depression. Changes in lipids, obesity, and insulin resistance, along with an increased risk of diabetes and cardiovascular disease, can also occur, mimicking the metabolic syndrome. A decrease in bone density may also result that worsens over time and results in an increased risk of clinical fractures. This is a particular concern, often underappreciated, for men with preexisting osteopenia secondary to hypogonadism or glucocorticoid or alcohol use. Baseline fracture risk can be assessed using the Fracture Risk Assessment Scale (FRAX), and to minimize fracture risk, patients are advised to take calcium and vitamin D supplementation, along with a bisphosphonate or the RANK ligand inhibitor, denosumab.

Antiandrogens First-generation nonsteroidal antiandrogens such as flutamide, bicalutamide, and nilutamide block ligand binding to the AR and were initially approved to block the disease flare that may occur with the rise in serum testosterone associated with GnRH agonist therapy. When antiandrogens are given alone, testosterone levels typically increase above baseline, but relative to testosterone-lowering therapies, they cause fewer hot flushes, less of an effect on libido, less muscle wasting, fewer personality changes, and less bone loss. Gynecomastia remains a significant problem but can be alleviated in part by tamoxifen.

Most reported randomized trials suggest that the cancer-specific outcomes are inferior when antiandrogens are used alone. Bicalutamide, even at 150 mg (three times the recommended dose), was associated with a shorter time to progression and inferior survival compared to surgical castration for patients with established metastatic disease. Nevertheless, some men may accept the trade-off of a potentially inferior cancer outcome for an improved quality of life.

Combined androgen blockade, the administration of an antiandrogen plus a GnRH analogue or surgical orchiectomy, and triple androgen blockade, which includes the addition

of a 5ARI, have not been shown to be superior to androgen depletion monotherapies and are no longer recommended. In practice, most patients who are treated with a GnRH agonist receive an antiandrogen for the first 2–4 weeks of treatment to protect against the flare.

Intermittent Androgen Deprivation Therapy (IADT) The use of hormones in an "on-and-off" approach was initially proposed as a way to prevent the selection of cells that are resistant to androgen depletion and to reduce side effects. The hypothesis is that by allowing endogenous testosterone levels to rise, the cells that survive androgen depletion will induce a normal differentiation pathway. It is postulated that by allowing the surviving cells to proliferate in the presence of androgen, sensitivity to subsequent androgen depletion will be retained and the chance of developing a castration-resistant state will be reduced. Applied in the clinic, androgen depletion is continued for 2–6 months beyond the point of maximal response. Once treatment is stopped, endogenous testosterone levels increase, and the symptoms associated with hormone treatment abate. PSA levels also begin to rise, and at some level, treatment is restarted. With this approach, multiple cycles of regression and proliferation have been documented in individual patients. It is unknown whether the intermittent approach increases, decreases, or does not change the overall duration of sensitivity to androgen depletion. The approach is safe, but long-term data are needed to assess the course in men with low PSA levels. A randomized trial showed similar survival time between patients treated with intermittent versus continuous treatment, with a slightly higher risk of prostate cancer–specific mortality in the intermittent group, and higher cardiovascular mortality in patients on continuous therapy. The intermittent therapy was better tolerated.

Outcomes of Androgen Depletion The anti–prostate cancer effects of the various androgen depletion/blockade strategies are similar, and the outcomes predictable: an initial response, then a period of stability in which tumor cells are dormant and nonproliferative, followed after a variable period of time by a rise in PSA and tumor regrowth as a castration-resistant lesion that for most men is invariably lethal. Androgen depletion is not curative because cells that survive castration are present when the disease is first diagnosed. Considered by disease manifestation, PSA levels return to normal in 60–70% of cases, and measurable lesions regress in about 50%; improvements in bone scan occur in 25% of cases, but the majority of cases remain stable. The duration of response and survival is inversely proportional to disease extent at the time androgen depletion is first started, whereas the degree of PSA decline at 6 months has been shown to be prognostic. In a large-scale trial, PSA nadir proved prognostic.

An active question is whether hormones should be given in the adjuvant setting after surgery or radiation treatment of the primary tumor or whether to wait until PSA recurrence, metastatic disease, or symptoms are documented. Trials in support of early therapy have often been underpowered relative to the reported benefit or have been criticized on methodologic grounds. One trial showing a survival benefit for patients treated with radiation therapy and 3 years of androgen depletion, relative to radiation alone, was criticized for the poor outcomes of the control group. Another showing a survival benefit for patients with positive lymph nodes who were randomized to immediate medical or surgical castration compared to observation ($p = .02$) was criticized because the confidence intervals around the 5- and 8-year survival distributions for the two groups overlapped. A large randomized study comparing early to late hormone treatment (orchiectomy or GnRH analogue) in patients with locally advanced or asymptomatic metastatic disease showed that patients treated early were less likely to progress from M0 to M1 disease, to develop pain, and to die of prostate cancer. This trial was criticized because therapy was delayed "too long" in the late-treatment group. Noteworthy is that the American Society of Clinical Oncology Guidelines recommend deferring treatment until the disease has recurred and the prognosis has been reassessed. These guidelines do not support immediate therapy.

METASTATIC DISEASE: CASTRATE Castration-resistant prostate cancer (CRPC) is defined as disease that progresses despite androgen suppression by medical or surgical therapies where the measured levels of testosterone are 50 ng/mL or lower. The rise in PSA indicates continued signaling through the AR signaling axis, the result of a series of oncogenic changes that include overexpression of androgen biosynthetic enzymes that can lead to increased intratumoral androgens, and overexpression of the receptor itself that enables signaling to occur even in the setting of low levels of androgen. The majority of CRPC cases are not "hormone-refractory," and considering them as such can deny patients safe and effective treatment. CRPC can manifest in many ways. For some, it is a rise in PSA with no change in radiographs and no new symptoms. In others, it is a rising PSA and progression in bone with or without symptoms of disease. Still others will show soft tissue disease with or without osseous metastases, and others have visceral spread.

For the individual patient, it is first essential to ensure that a castrate status be documented. Patients receiving an antiandrogen alone, whose serum testosterone levels are elevated, should be treated first with a GnRH analogue or orchiectomy and observed for response. Patients on an antiandrogen in combination with a GnRH analogue should have the antiandrogen discontinued, because approximately 20% will respond to the selective discontinuation of the antiandrogen.

Chemotherapy and New Agents Through 2009, docetaxel was the only systemic therapy proven to prolong life. As a single agent, the drug produced PSA declines in 50% of patients, measurable disease regression in 25%, and improvement in both preexisting pain and prevention of future cancer-related pain. Since then, six agents with diverse mechanisms of action that target the tumor itself or other aspects of the metastatic process have been proven to prolong life and were FDA approved. The first was sipuleucel-T, the first biologic approach shown to prolong life in which antigen-presenting cells are activated ex

vivo, pulsed with antigen, and reinfused. T e second, cabazitaxel, a non–cross-resistant taxane, was shown to be superior to mitoxantrone in the post-docetaxel setting. T is was followed by the CYP17 inhibitor abiraterone acetate, which lowers androgen levels in the tumor, adrenal glands, and testis, and the next-generation antiandrogen enzalutamide, which not only has a higher binding af nity to the AR relative to first-generation compounds, but uniquely inhibits nuclear location and DNA binding of the receptor complex. Both abiraterone acetate and enzalutamide were first approved for postchemotherapy treated patients on the basis of placebo-controlled phase III trials—a further indication that these tumors are not uniformly hormone-refractory. T e indication for abiraterone acetate was later expanded to the prechemotherapy setting, based on a second trial using a co-primary endpoint of radiographic progression–free survival and overall survival. Similar results were seen with enzalutamide, for which an expanded indication is also anticipated. Alpharadin (radium-223 chloride), an alpha-emitting bone-seeking radioisotope, has been shown to prolong life in patients with symptoms related to osseous disease. T e alpharadin result validated the bone microenvironment as a therapeutic target independent of direct effects on the tumor itself, as no declines in PSA were observed in the trial. Notable is that in addition to a survival benefit, the drug also reduced the development of significant skeletal events.

Other bone-targeted agents, such as the bisphosphonates and the RANK ligand inhibitor denosumab, protect against bone loss associated with androgen depletion and also reduce skeletal-related events by targeting bone osteoclasts. In one trial, denosumab was shown to be superior to zoledronic acid with respect to skeletal-related events, but had a slightly higher frequency of osteonecrosis of the jaw.

In clinical practice, most men seek to avoid chemotherapy and are first treated with a biologic agent and/or newer hormonal agent approved for this indication. It is crucial to the management of the individual patient to define therapeutic objectives before initiating treatment, as there are defined standards of care for different disease manifestations. For example, sipuleucel-T is not indicated for patients with symptoms or visceral disease because the effects on the disease occur late. Similarly, alpharadin is not indicated for patients with disease that is predominantly in soft tissue or who have osseous disease that is not causing symptoms.

Pain Management Management of pain secondary to osseous metastatic disease is a critical part of therapy. Optimal palliation requires assessing whether the symptoms are from metastases that threaten or that are already affecting the spinal cord, the cauda equina, or the base of the skull, which are best treated with external-beam radiation, as are single sites of pain. Neurologic symptoms require emergency evaluation because loss of function may be permanent if not addressed quickly. Because the disease is often diffuse, palliation at one site is often followed by the emergence of symptoms in a separate site that had not received radiation. In these cases, bone-seeking radioisotopes such as alpharadin or the beta emitter ^{153}Sm-EDTMP (Quadramet) can be considered in addition to abiraterone acetate, docetaxel, and mitoxantrone, each of which is formally approved for the palliation of pain due to prostate cancer metastases.

BENIGN DISEASE

BENIGN PROSTATIC HYPERTROPHY

BPH is a pathologic process that contributes to the development of lower urinary tract symptoms in men. Such symptoms, arising from lower urinary tract dysfunction, are further subdivided into obstructive symptoms (urinary hesitancy, straining, weak stream, terminal dribbling, prolonged voiding, incomplete emptying) and irritative symptoms (urinary frequency, urgency, nocturia, urge incontinence, small voided volumes). Lower urinary tract symptoms and other sequelae of BPH are not just due to a mass effect, but are also likely due to a combination of the prostatic enlargement and age-related detrusor dysfunction.

TREATMENT Benign Prostatic Hypertrophy

T e symptoms are generally measured using a validated, reproducible index that is designed to determine disease severity and response to therapy—the AUA's Symptom Index (AUASI), also adopted as the International Prostate Symptom Score (IPSS) **(Table 44–2)**. Serial AUASI is particularly useful in following patients as they are treated with various forms of therapy. Asymptomatic patients do not require treatment regardless of the size of the gland, whereas patients with an inability to urinate, gross hematuria, recurrent infection, or bladder stones may require surgery. In patients with symptoms, uroflowmetry can identify those with normal flow rates who are unlikely to benefit from treatment, and bladder ultrasound can identify those with high postvoid residuals who may need intervention. Pressure-flow (urodynamic) studies detect primary bladder dysfunction. Cystoscopy is recommended if hematuria is documented and to assess the urinary outflow tract before surgery. Imaging of the upper tracts is advised for patients with hematuria, a history of calculi, or prior urinary tract problems.

Symptomatic relief is the most common reason men seek treatment for BPH, and therefore the goal of therapy for BPH is usually relief of these symptoms. Alpha-adrenergic receptor antagonists are thought to treat the dynamic aspect of BPH by reducing sympathetic tone of the bladder outlet, thereby decreasing resistance and improving urinary flow. 5ARIs are thought to treat the static aspect of BPH by reducing prostate volume and having a similar, albeit delayed effect. T ey have also proven to be beneficial in the prevention of BPH progression, as measured by prostate volume, the risk of developing

TABLE 44-2

AUA SYMPTOM INDEX

QUESTIONS TO BE ANSWERED	AUA SYMPTOM SCORE (CIRCLE 1 NUMBER ON EACH LINE)					
	NOT AT ALL	LESS THAN 1 TIME IN 5	LESS THAN HALF THE TIME	ABOUT HALF THE TIME	MORE THAN HALF THE TIME	ALMOST ALWAYS
Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
Over the past month, how often have you had to urinate again less than 2 h after you finished urinating?	0	1	2	3	4	5
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Over the past month, how often have you found it dif cult to postpone urination?	0	1	2	3	4	5
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	(None)	(1 time)	(2 times)	(3 times)	(4 times)	(5 times)
Sum of 7 circled numbers (AUA Symptom Score): ____						

Abbreviations: AUA, American Urological Association.
Source: MJ Barry et al: J Urol 148:1549, 1992. Used with permission.

acute urinary retention, and the risk of having BPH-related surgery. T e use of an alpha-adrenergic receptor antagonist and a 5ARI as combination therapy seeks to provide symptomatic relief while preventing progression of BPH.

Another class of medications that has shown improvement in lower urinary tract symptoms secondary to BPH is PDE5 inhibitors, used currently in the treatment of erectile dysfunction. All three of the PDE5 inhibitors available in the United States, sildenafil, vardenafil, and tadalafil, appear to be effective in the treatment of symptoms secondary to BPH. T e use of PDE5 inhibitors is not without controversy, however, given the fact that short-acting phosphodiesterase inhibitors such as sildenafil need to be dosed separately from alpha blockers such as tamsulosin because of potential hypotensive effects. Newer classes of pharmacologic agents have been used to treat symptoms secondary to BPH. Symptoms due to BPH often coexist with symptoms due to overactive bladder, and the most common pharmacologic agents for the treatment of overactive bladder symptoms are anticholinergics. T is has led to multiple studies evaluating the ef cacy of anticholinergics for the treatment of lower urinary tract symptoms secondary to BPH. Surgical therapy is now considered second-line therapy and is usually reserved for patients after a trial of medical therapy. T e goal of surgical therapy is to reduce the size of the prostate, effectively reducing resistance to urine flow.

Surgical approaches include TURP, transurethral incision, or removal of the gland via a retropubic, suprapubic, or perineal approach. Also used are transurethral ultrasound-guided laser-induced prostatectomy (TULIP), stents, and hyperthermia.

CHAPTER 45

TESTICULAR CANCER

Robert J. Motzer ■ Darren R. Feldman ■ George J. Bosl

Primary germ cell tumors (GCTs) of the testis arising by the malignant transformation of primordial germ cells constitute 95% of all testicular neoplasms. Infrequently, GCTs arise from an extragonadal site, including the mediastinum, retroperitoneum, and, very rarely, the pineal gland. T is disease is notable for the young age of the afflicted patients, the totipotent capacity for differentiation of the tumor cells, and its curability; approximately 95% of newly diagnosed patients are cured. Experience in the management of GCTs leads to improved outcome.

INCIDENCE AND EPIDEMIOLOGY

T e incidence of testicular GCT is now approximately 8000 cases annually in the United States, resulting in nearly 400 deaths. T e tumor occurs most frequently in men between the ages of 20 and 40 years. A testicular mass in a male ≥50 years should be regarded as a lymphoma until proved otherwise. GCT is at least four to five times more common in white than in African-American males, and a higher incidence has been observed in Scandinavia and New Zealand than in the United States.

ETIOLOGY AND GENETICS

Cryptorchidism is associated with a several-fold higher risk of GCT. Abdominal cryptorchid testes are at a higher risk than inguinal cryptorchid testes. Orchiopexy should be performed before puberty, if possible. Early orchiopexy reduces the risk of GCT and improves the ability to save the testis. An abdominal cryptorchid testis that cannot be brought into the scrotum should be removed. Approximately 2% of men with GCTs of one testis will develop a primary tumor in the other testis. Testicular feminization syndromes and family history increase the risk of testicular GCT, and Klinefelter's syndrome is associated with mediastinal GCT.

An isochromosome of the short arm of chromosome 12 [i(12p)] is pathognomonic for GCT. Excess 12p copy number, either in the form of i(12p) or as increased 12p on aberrantly banded marker chromosomes, occurs in nearly all GCTs, but the gene(s) on 12p involved in the pathogenesis are not yet defined.

CLINICAL PRESENTATION

A painless testicular mass is pathognomonic for a testicular malignancy. More commonly, patients present with testicular discomfort or swelling suggestive of epididymitis and/or orchitis. In this circumstance, a trial of antibiotics is reasonable. However, if symptoms persist or a residual abnormality remains, then testicular ultrasound examination is indicated.

Ultrasound of the testis is indicated whenever a testicular malignancy is considered and for persistent or painful testicular swelling. If a testicular mass is detected, a radical inguinal orchiectomy should be performed. Because the testis develops from the gonadal ridge, its blood supply and lymphatic drainage originate in the abdomen and descend with the testis into the scrotum. An inguinal approach is taken to avoid breaching anatomic barriers and permitting additional pathways of spread.

Back pain from retroperitoneal metastases is common and must be distinguished from musculoskeletal pain. Dyspnea from pulmonary metastases occurs infrequently. Patients with increased serum levels of human chorionic gonadotropin (hCG) may present with gynecomastia. A delay in diagnosis is associated with a more advanced stage and possibly worse survival.

T e staging evaluation for GCT includes a determination of serum levels of α fetoprotein (AFP), hCG, and lactate dehydrogenase (LDH). After orchiectomy, a computed tomography (CT) scan of the chest, abdomen, and pelvis is generally performed. Stage I disease is limited to the testis, epididymis, or spermatic cord.

Stage II disease is limited to retroperitoneal (regional) lymph nodes. Stage III disease is disease outside the retroperitoneum, involving supradiaphragmatic nodal sites or viscera. T e staging may be "clinical"—defined solely by physical examination, blood marker evaluation, and radiographs—or "pathologic"—defined by an operative procedure.

T e regional draining lymph nodes for the testis are in the retroperitoneum, and the vascular supply originates from the great vessels (for the right testis) or the renal vessels (for the left testis). As a result, the lymph nodes that are involved first by a right testicular tumor are the interaortocaval lymph nodes just below the renal vessels. For a left testicular tumor, the first involved lymph nodes are lateral to the aorta (paraaortic) and below the left renal vessels. In both cases, further retroperitoneal nodal spread is inferior, contralateral, and, less commonly, above the renal hilum. Lymphatic involvement can extend cephalad to the retrocrural, posterior mediastinal, and supraclavicular lymph nodes. Treatment is determined by tumor histology (seminoma versus nonseminoma) and clinical stage **(Fig. 45–1)**.

PATHOLOGY

GCTs are divided into nonseminoma and seminoma subtypes. Nonseminomatous GCTs are most frequent in the third decade of life and can display the full spectrum of embryonic and adult cellular differentiation. T is entity comprises four histologies: embryonal carcinoma, teratoma, choriocarcinoma, and endodermal sinus (yolk sac) tumor. Choriocarcinoma, consisting of both cytotrophoblasts and syncytiotrophoblasts, represents malignant trophoblastic differentiation and is invariably associated with secretion of hCG. Endodermal sinus tumor is the malignant counterpart of the fetal yolk sac and is associated with secretion of AFP. Pure embryonal carcinoma may secrete AFP or hCG, or both; this pattern is biochemical evidence of differentiation. Teratoma is composed of somatic cell types derived from two or more germ layers (ectoderm, mesoderm, or endoderm). Each of these histologies may be present alone or in combination with others. Nonseminomatous GCTs tend to metastasize early to sites such as the retroperitoneal lymph nodes and lung parenchyma. Sixty percent of patients present with disease limited to the testis (stage I), 20% with retroperitoneal metastases (stage II), and 20% with more extensive supradiaphragmatic nodal or visceral metastases (stage III).

Seminoma represents approximately 50% of all GCTs, has a median age in the fourth decade, and generally follows a more indolent clinical course. Eighty percent of patients present with stage I disease, approximately 10% with stage II disease, and 10% with stage III disease; lung or other visceral metastases are rare. When a tumor contains both seminoma and nonseminoma components, patient management is directed by the more aggressive nonseminoma component.

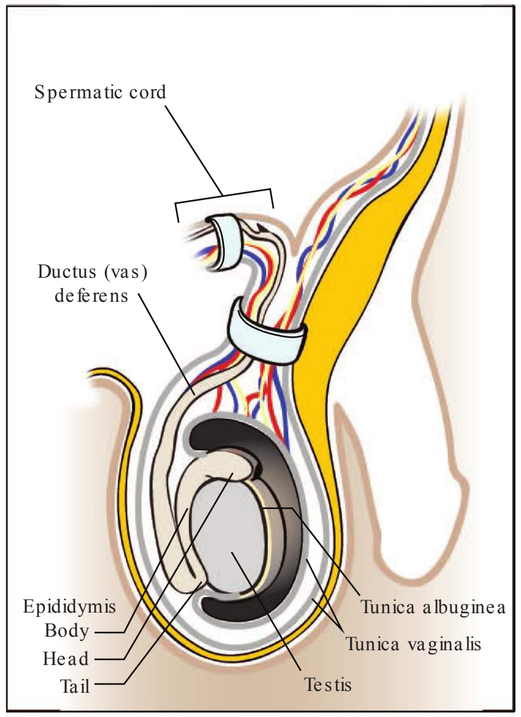
TUMOR MARKERS

Careful monitoring of the serum tumor markers AFP and hCG is essential in the management of patients with GCT, because these markers are important for diagnosis, as prognostic indicators, in monitoring treatment response, and in the early detection of relapse. Approximately 70% of patients presenting with disseminated nonseminomatous GCT have increased serum concentrations of AFP and/or hCG. Although hCG concentrations may be increased in patients with either nonseminoma or seminoma histology, the AFP concentration is increased only in patients with nonseminoma. T e presence of an increased AFP level in a patient whose tumor shows only seminoma indicates that an occult nonseminomatous component exists, and the patient should be treated for nonseminomatous GCT. LDH levels are less specific than AFP or hCG but are increased in 50–60% patients with metastatic nonseminoma and in up to 80% of patients with advanced seminoma.

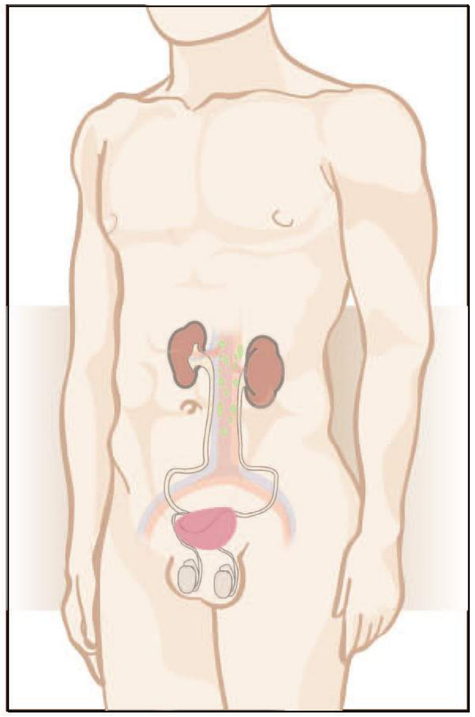
AFP, hCG, and LDH levels should be determined before and after orchiectomy. Increased serum AFP and hCG concentrations decay according to first-order kinetics; the half-life is 24–36 h for hCG and 5–7 days for AFP. AFP and hCG should be assayed serially during and after treatment. T e reappearance of hCG and/or AFP or the failure of these markers to decline according to the predicted half-life is an indicator of persistent or recurrent tumor.

TREATMENT Testicular Cancer

STAGE I NONSEMINOMA Patients with radiographs and physical examination showing no evidence of disease and serum AFP and hCG concentrations that are either normal or declining to normal according to the known half-life have clinical stage I disease. Approximately 20–50% of such patients will have retroperitoneal lymph node metastases (pathologic stage II) but will still be cured in over 95% of cases. Depending on risk of relapse, which is determined by the pathology (see below), surveillance, a nerve-sparing retroperitoneal lymph node dissection (RPLND), or adjuvant chemotherapy (one to two cycles of bleomycin, etoposide, and cisplatin [BEP]) may be appropriate choices depending on the availability of surgical expertise and patient and physician preference. If the primary tumor shows no evidence for lymphatic or vascular invasion and is limited to the testis (T1, clinical stage IA), then the risk of relapse is only 10–20%. Because over 80% of patients



Stage	Extent of Disease
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion; tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion



		Treatment Option	
Stage	Extent of Disease	Seminoma	Nonseminoma
IA	Testis only, no vascular/lymphatic invasion (T1)	Observation Chemotherapy or RT	Observation
IB	Testis only, with vascular/lymphatic invasion (T2), or extension through tunica albuginea (T2), or involvement of spermatic cord (T3) or scrotum (T4)	Observation Chemotherapy or RT	RPLND or Chemotherapy
IIA	Retroperitoneal Nodes < 2 cm	RT	RPLND +/– adjuvant Chemotherapy or Chemotherapy, often followed by RPLND
IIB	Retroperitoneal Nodes 2-5 cm	RT or Chemotherapy	Chemotherapy, often followed by RPLND
IIC	Retroperitoneal Nodes > 5 cm	Chemotherapy	Chemotherapy, often followed by RPLND
Distant Metastases			
III	Common sites include distant (or extra-abdominal) lymph nodes, lung, liver, bone, and brain	Chemotherapy	Chemotherapy, often followed by surgery (biopsy or resection)

FIGURE 45-1
Germ cell tumor staging and treatment. RPLND, retroperitoneal lymph node dissection; RT, radiotherapy.

with clinical stage IA nonseminoma are cured with orchiectomy alone and there is no survival advantage to RPLND (or adjuvant chemotherapy), surveillance is the preferred treatment option. T is avoids overtreatment with the potential for both acute and long-term toxicities (see below). Surveillance requires patients to be carefully followed with periodic chest radiography, physical examination, CT scan of the abdomen, and serum tumor marker determinations. T e median time to relapse is approximately 7 months, and late relapses (>2 years) are rare. Noncompliant patients can be considered for RPLND or adjuvant BEP.

If lymphatic or vascular invasion is present or the tumor extends through the tunica, spermatic cord, or scrotum (T2 through T4, clinical stage IB), then the risk of relapse is approximately 50%, and RPLND and adjuvant chemotherapy can be considered. Relapse rates are reduced to 3–5% after one to two cycles of adjuvant BEP. All three approaches (surveillance, RPLND, and adjuvant BEP) should cure >95% of patients with clinical stage IB disease.

RPLND is the standard operation for removal of the regional lymph nodes of the testis (retroperitoneal nodes). T e operation removes the lymph nodes draining the primary site and the nodal groups adjacent to the primary landing zone. T e standard (modified bilateral) RPLND removes all node-bearing tissue down to the bifurcation of the great vessels, including the ipsilateral iliac nodes. T e major long-term effect of this operation is retrograde ejaculation with resultant infertility. Nerve-sparing RPLND can preserve anterograde ejaculation in ~90% of patients. Patients with pathologic stage I disease are observed, and only the <10% who relapse require additional therapy. If nodes are found to be involved at RPLND, then a decision regarding adjuvant chemotherapy is made on the basis of the extent of retroperitoneal disease (see "Stage II Nonseminoma" below). Hence, because less than 20% of patients require chemotherapy, of the three approaches, RPLND results in the lowest number of patients at risk for the late toxicities of chemotherapy.

STAGE II NONSEMINOMA Patients with limited, ipsilateral retroperitoneal adenopathy ≤2 cm in largest diameter and normal levels of AFP and hCG can be treated with either a modified bilateral nerve-sparing RPLND or chemotherapy. T e local recurrence rate after a properly performed RPLND is very low. Depending on the extent of disease, the postoperative management options include either surveillance or two cycles of adjuvant chemotherapy. Surveillance is the preferred approach for patients with resected "low-volume" metastases (tumor nodes ≤2 cm in diameter and <6 nodes involved) because the probability of relapse is one-third or less. For those who relapse, risk-directed chemotherapy is indicated (see section on advanced GCT below). Because relapse occurs in ≥50% of patients with "high-volume" metastases (>6 nodes involved, or any involved node >2 cm in largest diameter, or extranodal tumor extension), two cycles of adjuvant chemotherapy should be considered, as it results in a cure in ≥98% of patients. Regimens consisting of etoposide plus cisplatin (EP) with or without bleomycin every 3 weeks are effective and well tolerated.

Increased levels of either AFP or hCG imply metastatic disease outside the retroperitoneum; full-dose (not adjuvant) chemotherapy is used in this setting. Primary management with chemotherapy is also favored for patients with larger (>2 cm) or bilateral retroperitoneal nodes (see section on advanced GCT below).

STAGES I AND II SEMINOMA Inguinal orchiectomy followed by immediate retroperitoneal radiation therapy or surveillance with treatment at relapse both result in cure in nearly 100% of patients with stage I seminoma. Historically, radiation was the mainstay of treatment, but the reported association between radiation and secondary malignancies and the absence of a survival advantage of radiation over surveillance has led many to favor surveillance for compliant patients. Approximately 15% of patients relapse, which is usually treated with chemotherapy. Longterm follow-up is essential, because approximately 30% of relapses occur after 2 years and 5% occur after 5 years. A single dose of carboplatin has also been investigated as an alternative to radiation therapy; the outcome was similar, but long-term safety data are lacking, and the retroperitoneum remained the most frequent site of relapse.

Generally, nonbulky retroperitoneal disease (stage IIA and small IIB) is treated with retroperitoneal radiation therapy. Approximately 90% of patients achieve relapse-free survival with retroperitoneal masses <3 cm in diameter. Due to higher relapse rates after radiation for bulkier disease, initial chemotherapy is preferred for all stage IIC and some stage IIB patients. Chemotherapy has been studied as an alternative to radiation for stage IIA and small stage IIB seminoma with lower recurrence rates compared with historical controls. T ese results, combined with studies demonstrating a threefold increase in the incidence of secondary malignancies and cardiovascular disease among patients who receive both radiation and chemotherapy (patients relapsing after radiation fall into this category), have led some experts to prefer chemotherapy for all stage II seminomas.

CHEMOTHERAPY FOR ADVANCED GCT Regardless of histology, all patients with stage IIC and stage III and most with stage IIB GCT are treated with chemotherapy. Combination chemotherapy programs based on cisplatin at doses of 100 mg/m^2 plus etoposide at doses of 500 mg/m^2 per cycle cure 70–80% of such patients, with or without bleomycin, depending on risk stratification (see below). A complete response (the complete disappearance of all clinical evidence of tumor on physical examination and radiography plus normal serum levels of AFP and hCG for ≥1 month) occurs after chemotherapy alone in ~60% of patients, and another 10–20% become disease free with surgical resection of residual masses containing viable GCT. Lower doses of cisplatin result in inferior survival rates.

T e toxicity of four cycles of the BEP is substantial. Nausea, vomiting, and hair loss occur in most patients, although nausea and vomiting have been markedly ameliorated by modern antiemetic regimens. Myelosuppression is frequent, and

symptomatic bleomycin pulmonary toxicity occurs in ~5% of patients. Treatment-induced mortality due to neutropenia with septicemia or bleomycin-induced pulmonary failure occurs in 1–3% of patients. Dose reductions for myelosuppression are rarely indicated. Long-term permanent toxicities include nephrotoxicity (reduced glomerular filtration and persistent magnesium wasting), ototoxicity, peripheral neuropathy, and infertility. When bleomycin is administered by weekly bolus injection, Raynaud's phenomenon appears in 5–10% of patients. Other evidence of small blood vessel damage, such as transient ischemic attacks and myocardial infarction, is seen less often.

RISK-DIRECTED CHEMOTHERAPY Because not all patients are cured and treatment may cause significant toxicities, patients are stratified into "good-risk," "intermediate-risk," and "poor-risk" groups according to pretreatment clinical features established by the International Germ Cell Cancer Consensus Group (Table 45-1). For good-risk patients, the goal is to achieve maximum ef cacy with minimal toxicity. For intermediate- and poor-risk patients, the goal is to identify more effective therapy with tolerable toxicity.

T e marker cut offs are included in the TNM (primary tumor, regional nodes, metastasis) staging of GCT. Hence, TNM stage groupings are based on both anatomy (site and extent of disease) and biology (marker status and histology). Seminoma is either good- or intermediate-risk, based on the absence or presence of nonpulmonary visceral metastases. No poor-risk category exists for seminoma. Marker levels and primary site play no role in defining risk for seminoma. Nonseminomas have good-, intermediate-, and poor-risk categories based on the primary site of the tumor, the presence or absence of nonpulmonary visceral metastases, and marker levels.

For ~90% of patients with good-risk GCTs, four cycles of EP or three cycles of BEP produce durable complete responses, with minimal acute and chronic toxicity, and a low relapse rate. Pulmonary toxicity is absent when bleomycin is not used and is rare when therapy is limited to 9 weeks; myelosuppression with neutropenic fever is less frequent; and the treatment mortality rate is negligible. Approximately 75% of intermediate-risk patients and 50% of poor-risk patients achieve durable complete remission with four cycles of BEP, and no regimen has proved superior.

POSTCHEMOTHERAPY SURGERY Resection of residual metastases after the completion of chemotherapy is an integral part of therapy. If the initial histology is nonseminoma and the marker values have normalized, all sites of residual disease should be resected. In general, residual retroperitoneal disease requires a modified bilateral RPLND. T oracotomy (unilateral or bilateral) and neck dissection are less frequently required to remove residual mediastinal, pulmonary parenchymal, or cervical nodal disease. Viable tumor (seminoma, embryonal carcinoma, yolk sac tumor, or choriocarcinoma) will be present in 15%, mature teratoma in 40%, and necrotic debris and fibrosis in 45% of resected specimens. T e frequency of teratoma or viable disease is highest in residual mediastinal tumors. If necrotic debris or mature teratoma is present, no further chemotherapy is necessary. If viable tumor is present but is completely excised, two additional cycles of chemotherapy are given.

TABLE 45-1

INTERNATIONAL GERM CELL CANCER CONSENSUS GROUP RISK CLASSIFICATION FOR ADVANCED GERM CELL TUMORS

RISK	NONSEMINOMA	SEMINOMA
Good	Gonadal or retroperitoneal primary site Absent nonpulmonary visceral metastases AFP <1000 ng/mL β-hCG <5000 mIU/mL LDH <1.5 × upper limit or normal (ULN)	Any primary site Absent nonpulmonary visceral metastases Any LDH, hCG
Intermediate	Gonadal or retroperitoneal primary site Absent nonpulmonary visceral metastases AFP 1000–10,000 ng/mL β-hCG 5000–50,000 mIU/mL LDH 1.5–10 × ULN	Any primary site Presence of nonpulmonary visceral metastases Any LDH, hCG
Poor	Mediastinal primary site Presence of nonpulmonary visceral metastases AFP >10,000 ng/mL β-hCG >50,000 mIU/mL LDH >10 × ULN	No patients classif ed as poor prognosis

Abbreviations: AFP, α fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.
Source: From International Germ Cell Cancer Consensus Group.

If the initial histology is pure seminoma, mature teratoma is rarely present, and the most frequent finding is necrotic debris. For residual retroperitoneal disease, a complete RPLND is technically dif cult due to extensive postchemotherapy fibrosis. Observation is recommended when no radiographic abnormality exists on CT scan. Positive findings on a positron emission tomography (PET) scan correlate with viable seminoma in residua and mandate surgical excision or biopsy.

SALVAGE CHEMOTHERAPY Of patients with advanced GCT, 20–30% fail to achieve a durable complete response to first-line chemotherapy. A combination of vinblastine, ifosfamide, and cisplatin (VeIP) will cure approximately 25% of patients as a second-line therapy. Patients are more likely to achieve a durable complete response if they had a testicular primary tumor and relapsed from a prior complete remission to first-line cisplatin-containing chemotherapy. Substitution of paclitaxel for vinblastine (TIP) in this setting was associated with durable remission in nearly two-thirds of patients. In contrast, for patients with a primary mediastinal nonseminoma or who did not achieve a complete response with first-line chemotherapy, then VeIP standard-dose salvage therapy is rarely beneficial. Such patients are usually managed with high-dose chemotherapy and/or surgical resection.

Chemotherapy consisting of dose-intensive, high-dose carboplatin plus high-dose etoposide, with peripheral blood stem cell support, induces a complete response in 25–40% of patients who have progressed after ifosfamide-containing salvage chemotherapy. Approximately one-half of the complete responses will be durable. High-dose therapy is standard of care for this patient population and has been suggested as the treatment of choice for all patients with relapsed or refractory disease. Paclitaxel is active when incorporated into high-dose combination programs. Cure is still possible in some relapsed patients.

EXTRAGONADAL GCT

T e prognosis and management of patients with extragonadal GCT depends on the tumor histology and site of origin. All patients with a diagnosis of extragonadal GCT should have a testicular ultrasound examination. Nearly all patients with retroperitoneal or mediastinal seminoma achieve a durable complete response to BEP or EP. T e clinical features of patients with primary retroperitoneal nonseminoma GCT are similar to those of patients with a primary tumor of testis origin, and careful evaluation will find evidence of a primary testicular GCT in about two-thirds of cases. In contrast, a primary mediastinal nonseminomatous GCT is associated with a poor prognosis; one-third of patients are cured with standard therapy (four cycles of BEP). Patients with newly diagnosed mediastinal nonseminoma are considered to have poor-risk disease and should be considered for clinical trials testing regimens of possibly greater ef cacy. In addition, mediastinal nonseminoma is associated with hematologic disorders, including acute myelogenous leukemia, myelodysplastic syndrome, and essential thrombocytosis unrelated to previous chemotherapy. T ese hematologic disorders are very refractory to treatment. Nonseminoma of any primary site may change into other malignant histologies such as embryonal rhabdomyosarcoma or adenocarcinoma. T is is called malignant transformation. i(12p) has been identified in the transformed cell type, indicating GCT clonal origin.

A group of patients with poorly differentiated tumors of unknown histogenesis, midline in distribution, and not associated with secretion of AFP or hCG has been described; a few (10–20%) are cured by standard cisplatin-containing chemotherapy. An i(12p) is present in ~25% of such tumors (the fraction that are cisplatin-responsive), confirming their origin from primitive germ cells. T is finding is also predictive of the response to cisplatin-based chemotherapy and resulting long-term survival. T ese tumors are heterogeneous; neuroepithelial tumors and lymphoma may also present in this fashion.

FERTILITY

Infertility is an important consequence of the treatment of GCTs. Preexisting infertility or impaired fertility is often present. Azoospermia and/or oligospermia are present at diagnosis in at least 50% of patients with testicular GCTs. Ejaculatory dysfunction is associated with RPLND, and germ cell damage may result from cisplatin-containing chemotherapy. Nerve-sparing techniques to preserve the retroperitoneal sympathetic nerves have made retrograde ejaculation less likely in the subgroups of patients who are candidates for this operation. Spermatogenesis does recur in some patients after chemotherapy. However, because of the significant risk of impaired reproductive capacity, semen analysis and cryopreservation of sperm in a sperm bank should be recommended to all patients before treatment.

CHAPTER 46

GYNECOLOGIC MALIGNANCIES

Michael V. Seiden

OVARIAN CANCER

INCIDENCE AND PATHOLOGY

Cancer arising in or near the ovary is actually a collection of diverse malignancies. T is collection of malignancies, often referred to as "ovary cancer," is the most lethal gynecologic malignancy in the United States and other countries that routinely screen women for cervical neoplasia. In 2014, it was estimated that there were 21,980 cases of ovarian cancer with 14,270 deaths in the United States. T e ovary is a complex and dynamic organ and, between the ages of approximately 11 and 50 years, is responsible for follicle maturation associated with egg maturation, ovulation, and cyclical sex steroid hormone production. T ese complex and linked biologic functions are coordinated through a variety of cells within the ovary, each of which possesses neoplastic potential. By far the most common and most lethal of the ovarian neoplasms arise from the ovarian epithelium or, alternatively, the neighboring specialized epithelium of the fallopian tube, uterine corpus, or cervix. Epithelial tumors may be benign (50%), malignant (33%), or of borderline malignancy (16%). Age influences risk of malignancy; tumors in younger women are more likely benign. T e most common of the ovarian epithelial malignancies are serous tumors (50%); tumors of mucinous (25%), endometrioid (15%), clear cell (5%), and transitional cell histology or Brenner tumor (1%) represent smaller proportions of epithelial ovarian tumors. In contrast, stromal tumors arise from the steroid hormone–producing cells and likewise have different phenotypes and clinical presentations largely dependent on the type and quantity of hormone production. Tumors arising in the germ cell are most similar in biology and behavior to testicular tumors in males **(Chap. 45)**.

Tumors may also metastasize to the ovary from breast, colon, appendiceal, gastric, and pancreatic primaries. Bilateral ovarian masses from metastatic mucin-secreting gastrointestinal cancers are termed Krukenberg tumors.

OVARIAN CANCER OF EPITHELIAL ORIGIN

Epidemiology and pathogenesis

A female has approximately a 1 in 72 lifetime risk (1.6%) of developing ovarian cancer, with the majority of affected women developing epithelial tumors. Each of the histologic variants of epithelial tumors is distinct with unique molecular features. As a group of malignancies, epithelial tumors of the ovary have a peak incidence in women in their sixties, although age at presentation can range across the extremes of adult life, with cases being reported in women in their twenties to nineties. Each histologic subtype of ovarian cancer likely has its own associated risk factors. Serous cancer, the most common type of epithelial ovarian cancer, is seen with increased frequency in women who are nulliparous or have a history of use of talc agents applied to the perineum; other risk factors include obesity and probably hormone replacement therapy. Protective factors include the use of oral contraceptives, multiparity, and breast-feeding. T ese protective factors are thought to work through suppression of ovulation and perhaps the associated reduction of ovulation associated inflammation of the ovarian epithelium or, alternatively, the serous epithelium located within the fimbriae of the fallopian tube. Other protective factors, such as fallopian tube ligation, are thought to protect the ovarian epithelium (or perhaps the distal fallopian tube fimbriae) from carcinogens that migrate from the vagina to the tubes and ovarian surface epithelium. Mucinous tumors are more frequent in women with a history of cigarette smoking, whereas endometrioid and clear cell tumors are more frequent in women with a history of endometriosis.

Considerable evidence now suggests that the precursor cell to serous carcinoma of the ovary might actually arise in the fimbria of the fallopian tube with extension or metastasis to the ovarian surface or capture of preneoplastic or neoplastic exfoliating tubal cells into an involuting ovarian follicle around the time of

ovulation. Careful histologic and molecular analysis of tubal epithelium demonstrates molecular and histologic abnormalities, termed serous tubular intraepithelial carcinoma (STIC) lesions, in a high proportion of women undergoing risk-reducing salpingo-oophorectomies in the context of high-risk germline mutations in BRCA1 and BRCA2, as well as a modest proportion of women with ovarian cancer in the absence of such mutations.

Genetic risk factors

A variety of genetic syndromes substantially increase a woman's risk of developing ovarian cancer. Approximately 10% of women with ovarian cancer have a germline mutation in one of two DNA repair genes: BRCA1 (chromosome 17q12-21) or BRCA2 (chromosome 13q12-13). Individuals inheriting a single copy of a mutant allele have a very high incidence of breast and ovarian cancer. Most of these women have a family history that is notable for multiple cases of breast and/or ovarian cancer, although inheritance through male members of the family can camouflage this genotype through several generations. T e most common malignancy in these women is breast carcinoma, although women harboring germline BRCA1 mutations have a marked increased risk of developing ovarian malignancies in their forties and fifties with a 30–50% lifetime risk of developing ovarian cancer. Women harboring a mutation in BRCA2 have a lower penetrance of ovarian cancer with perhaps a 20–40% chance of developing this malignancy, with onset typically in their fifties or sixties. Women with a BRCA2 mutation also are at slightly increased risk of pancreatic cancer. Likewise women with mutations in the DNA mismatch repair genes associated with Lynch syndrome, type 2 (MSH2, MLH1, MLH6, PMS1, PMS2) may have a risk of ovarian cancer as high as 1% per year in their forties and fifties. Finally, a small group of women with familial ovarian cancer may have mutations in other BRCA-associated genes such as RAD51, CHK2, and others. Screening studies in this select population suggest that current screening techniques, including serial evaluation of the CA-125 tumor marker and ultrasound, are insuf cient at detecting early-stage and curable disease, so women with these germline mutations are advised to undergo prophylactic removal of ovaries and fallopian tubes typically after completing childbearing and ideally before age 35–40 years. Early prophylactic oophorectomy also protects these women from subsequent breast cancer with a reduction of breast cancer risk of approximately 50%.

Presentation

Neoplasms of the ovary tend to be painless unless they undergo torsion. Symptoms are therefore typically related to compression of local organs or due to symptoms from metastatic disease. Women with tumors localized to the ovary do have an increased incidence of symptoms including pelvic discomfort, bloating, and perhaps changes in a woman's typical urinary or bowel pattern. Unfortunately, these symptoms are frequently dismissed by either the woman or her health care team. It is believed that high-grade tumors metastasize early in the neoplastic process. Unlike other epithelial malignancies, these tumors tend to exfoliate throughout the peritoneal cavity and thus present with symptoms associated with disseminated intraperitoneal tumors. T e most common symptoms at presentation include a multimonth period of progressive complaints that typically include some combination of heartburn, nausea, early satiety, indigestion, constipation, and abdominal pain. Signs include the rapid increase in abdominal girth due to the accumulation of ascites that typically alerts the patient and her physician that the concurrent gastrointestinal symptoms are likely associated with serious pathology. Radiologic evaluation typically demonstrates a complex adnexal mass and ascites. Laboratory evaluation usually demonstrates a markedly elevated CA-125, a shed mucin (Muc 16) associated with, but not specific for, ovarian cancer. Hematogenous and lymphatic spread are seen but are not the typical presentation. Ovarian cancers are divided into four stages, with stage I tumors confined to the ovary, stage II malignancies confined to the pelvis, and stage III tumors confined to the peritoneal cavity **(Table 46-1)**. T ese three stages are subdivided, with the most common presentation, stage IIIC, defined as tumors with bulky intraperitoneal disease. About 60% of women present with stage IIIC disease. Stage IV disease includes women with parenchymal metastases (liver, lung, spleen) or, alternatively, abdominal wall or pleural disease. T e 40% not presenting with stage IIIC disease are roughly evenly distributed among the other stages, although mucinous and clear cell tumors are overrepresented in stage I tumors.

Screening

Ovarian cancer is the fifth most lethal malignancy in women in the United States. It is curable in early stages, but seldom curable in advanced stages; hence, the development of effective screening strategies is of considerable interest. Furthermore, the ovary is well visualized with a variety of imaging techniques, most notably transvaginal ultrasound. Early-stage tumors often produce proteins that can be measured in the blood such as CA-125 and HE-4. Nevertheless, the incidence of ovarian cancer in the middle-aged female population is low, with only approximately 1 in 2000 women between the ages of 50 and 60 carrying an asymptomatic and undetected tumor. T us effective screening techniques must be sensitive but, more importantly, highly specific

TABLE 46-1

STAGING AND SURVIVAL IN GYNECOLOGIC MALIGNANCIES

STAGE	OVARIAN	5-YEAR SURVIVAL, %	ENDOMETRIAL	5-YEAR SURVIVAL, %	CERVIX	5-YEAR SURVIVAL, %
0	—		—		Carcinoma in situ	100
I	Confned to ovary	90–95	Confned to corpus	89	Confned to uterus	85
II	Confned to pelvis	70–80	Involves corpus and cervix	73	Invades beyond uterus but not to pelvic wall	65
III	Intraabdominal spread	20–50	Extends outside the uterus but not outside the true pelvis or to lymph nodes	52	Extends to pelvic wall and/or lower third of vagina, or hydronephrosis	35
IV	Spread outside abdomen	1–5	Extends outside the true pelvis or involves the bladder or rectum	17	Invades mucosa of bladder or rectum or extends beyond the true pelvis	7

to minimize the number of false-positive results. Even a screening test with 98% specificity and 50% sensitivity would have a positive predictive value of only about 1%. A large randomized study of active screening versus usual standard care demonstrated that a screening program consisting of six annual CA-125 measurements and four annual transvaginal ultrasounds in a population of women age 55–74 was not effective at reducing death from ovarian cancer and was associated with significant morbidity in the screened arm due to complications associated with diagnostic testing in the screened group. Although ongoing studies are evaluating the utility of alternative screening strategies, currently screening of normal-risk women is not recommended outside of a clinical trial.

TREATMENT Ovarian Cancer

In women presenting with a localized ovarian mass, the principal diagnostic and therapeutic maneuver is to determine if the tumor is benign or malignant and, in the event that the tumor is malignant, whether the tumor arises in the ovary or is a site of metastatic disease. Metastatic disease to the ovary can be seen from primary tumors of the colon, appendix, stomach (Krukenberg tumors), and breast. Typically women undergo a unilateral salpingo-oophorectomy, and if pathology reveals a primary ovarian malignancy, then the procedure is followed by a hysterectomy, removal of the remaining tube and ovary, omentectomy, and pelvic node sampling along with some random biopsies of the peritoneal cavity. T is extensive surgical procedure is performed because approximately 30% of tumors that by visual inspection appear to be confined to the ovary have already disseminated to the peritoneal cavity and/or surrounding lymph nodes.

If there is evidence of bulky intraabdominal disease, a comprehensive attempt at maximal tumor cytoreduction is attempted even if it involves partial bowel resection, splenectomy, and in certain cases more extensive upper abdominal surgery. T e ability to debulk metastatic ovarian cancer to minimal visible disease is associated with an improved prognosis compared with women left with visible disease. Patients without gross residual disease after resection have a median survival of 39 months, compared with 17 months for those left with macroscopic tumor. Once tumors have been surgically debulked, women receive therapy with a platinum agent, typically a taxane. Debate continues as to whether this therapy should be delivered intravenously or, alternatively, whether some of the therapy should be delivered directly into the peritoneal cavity via a catheter. T ree randomized studies have demonstrated improved survival with intraperitoneal therapy, but this approach is still not widely accepted due to technical challenges associated with this delivery route and increased toxicity. In women who present with bulky intraabdominal disease, an alternative approach is to treat with platinum plus a taxane for several cycles before attempting a surgical debulking procedure (neoadjuvant therapy). Subsequent surgical procedures are more effective at leaving the patient without gross residual tumor and appear to be less morbid. Two studies have demonstrated that the neoadjuvant approach is associated with an overall survival that is comparable to the traditional approach of primary surgery followed by chemotherapy.

With optimal debulking surgery and platinum-based chemotherapy (usually carboplatin dosed to an area under the curve [AUC] of 6 plus paclitaxel 175 mg/m^2 by 3-h infusion in 21-day cycles), 70% of women who present with advanced-stage tumors respond, and 40–50% experience a complete remission with normalization of their CA-125, computed tomography (CT) scans, and physical examination. Unfortunately, a small proportion of women who obtain a complete response to therapy will remain in remission. Disease recurs

within 1–4 years from the completion of their primary therapy in 75% of the complete responders. CA-125 levels often increase as a first sign of relapse; however, data are not clear that early intervention in relapsing patients influences survival. Recurrent disease is effectively managed, but not cured, with a variety of chemotherapeutic agents. Eventually all women with recurrent disease develop chemotherapy-refractory disease at which point refractory ascites, poor bowel motility, and obstruction or pseudoobstruction due to a tumor-infiltrated aperistaltic bowel are common. Limited surgery to relieve intestinal obstruction, localized radiation therapy to relieve pressure or pain from masses, or palliative chemotherapy may be helpful. Agents with >15% response rates include gemcitabine, topotecan, liposomal doxorubicin, pemetrexed, and bevacizumab. Approximately 10% of ovarian cancers are HER2/neu positive, and trastuzumab may induce responses in this subset.

Five-year survival correlates with the stage of disease: stage I, 85–90%; stage II, 70–80%; stage III, 20–50%; and stage IV, 1–5% (Table 46-1). Low-grade serous tumors are molecularly distinct from high-grade serous tumors and are, in general, poorly responsive to chemotherapy. Targeted therapies focused on inhibiting kinases downstream of RAS and BRAF are being tested. Patients with tumors of low malignant potential are managed by surgery; chemotherapy and radiation therapy do not improve survival.

OVARIAN SEX CORD AND STROMAL TUMORS

Epidemiology, presentation, and predisposing syndromes

Approximately 7% of ovarian neoplasms are stromal or sex cord tumors, with approximately 1800 cases expected each year in the United States. Ovarian stromal tumors or sex cord tumors are most common in women in their fifties or sixties, but tumors can present in the extremes of age, including the pediatric population. T ese tumors arise from the mesenchymal components of the ovary, including steroid-producing cells as well as fibroblasts. Essentially all of these tumors are of low malignant potential and present as unilateral solid masses. T ree clinical presentations are common: the detection of an abdominal mass; abdominal pain due to ovarian torsion, intratumoral hemorrhage, or rupture; or signs and symptoms due to hormonal production by these tumors.

T e most common hormone-producing tumors include thecomas, granulosa cell tumor, or juvenile granulosa tumors in children. T ese estrogen-producing tumors often present with breast tenderness as well as isosexual precocious pseudopuberty in children, menometrorrhagia, oligomenorrhea, or amenorrhea in premenopausal women, or alternatively as postmenopausal bleeding in older women. In some women, estrogen-associated secondary malignancies, such as endometrial or breast cancer, may present as synchronous malignancies. Alternatively, endometrial cancer may serve as the presenting malignancy with evaluation subsequently identifying a unilateral solid ovarian neoplasm that proves to be an occult granulosa cell tumor. Sertoli-Leydig tumors often present with hirsutism, virilization, and occasionally Cushing's syndrome due to increased production of testosterone, androstenedione, or other 17-ketosteroids. Hormonally inert tumors include fibroma that presents as a solitary mass often in association with ascites and occasionally hydrothorax also known as Meigs' syndrome. A subset of these tumors present in individuals with a variety of inherited disorders that predispose them to mesenchymal neoplasia. Associations include juvenile granulosa cell tumors and perhaps Sertoli-Leydig tumors with Ollier's disease (multiple enchondromatosis) or Maffucci's syndrome, ovarian sex cord tumors with annular tubules with Peutz-Jeghers syndrome, and fibromas with Gorlin's disease. Essentially all granulosa tumors and a minority of juvenile granulosa cell tumors and thecomas have a defined somatic point mutation in the FOXL2 gene at C134W generated by replacement of cysteine with a guanine at position 402. About 30% of Sertoli-Leydig tumors harbor a mutation in the RNA-processing gene DICER in the RNAIIIb domain.

TREATMENT Sex Cord Tumors

T e mainstay of treatment for sex cord tumors is surgical resection. Most women present with tumors confined to the ovary. For the small subset of women who present with metastatic disease or develop evidence of tumor recurrence after primary resection, survival is still typically long, often in excess of a decade. Because these tumors are slow growing and relatively refractory to chemotherapy, women with metastatic disease are often debulked because disease is usually peritoneal-based (as with epithelial ovarian cancer). Definitive data that surgical debulking of metastatic or recurrent disease prolongs survival are lacking, but ample data document women who have survived years or, in some cases, decades after resection of recurrent disease. In addition, large peritoneal-based metastases also have a proclivity for hemorrhage, sometimes with catastrophic complications. Chemotherapy is occasionally effective, and women tend to receive regimens designed to treat epithelial or germ cell tumors. Bevacizumab has some activity in clinical trials but is not approved for this specific indication. T ese tumors often produce high levels of müllerian inhibiting substance (MIS), inhibin, and, in the case of Sertoli-Leydig tumors, α fetoprotein (AFP). T ese proteins are detectable in serum and can be used as tumor markers to monitor women for recurrent disease because the increase or decrease of these proteins in the serum tends to reflect the changing bulk of systemic tumor.

GERM CELL TUMORS OF THE OVARY

Germ cell tumors, like their counterparts in the testis, are cancers of germ cells. T ese totipotent cells contain the programming for differentiation to essentially all tissue types, and hence the germ cell tumors include a histologic menagerie of bizarre tumors, including benign teratomas and a variety of malignant tumors, such as immature teratomas, dysgerminomas, yolk sac malignancies, and choriocarcinomas. Benign teratoma (or dermoid cyst) is the most common germ cell neoplasm of the ovary and often presents in young woman. T ese tumors include a complex mixture of differentiated tissue including tissues from all three germ layers. In older women, these differentiated tumors can develop malignant transformation, most commonly squamous cell carcinomas. Malignant germ cell tumors include dysgerminomas, yolk sac tumors, immature teratomas, and embryonal carcinoma and choriocarcinomas. T ere are no known genetic abnormalities that unify these tumors. A subset of dysgerminomas harbor mutations in c-kit oncogenes (as seen in gastrointestinal stromal tumors [GIST]), whereas a subset of germ cell tumors have isochromosome 12 abnormalities, as seen in testicular malignancies. In addition, a subset of dysgerminomas is associated with dysgenetic ovaries. Identification of a dysgerminoma arising in genotypic XY gonads is important in that it highlights the need to identify and remove the contralateral gonad due to risk of gonadoblastoma.

Presentation

Germ cell tumors can present at all ages, but the peak age of presentation tends to be in females in their late teens or early twenties. Typically these tumors will become large ovarian masses, which eventually present as palpable low abdominal or pelvic masses. Like sex cord tumors, torsion or hemorrhage may present urgently or emergently as acute abdominal pain. Some of these tumors produce elevated levels of human chorionic gonadotropin (hCG), which can lead to isosexual precocious puberty when tumors present in younger girls. Unlike epithelial ovarian cancer, these tumors have a higher proclivity for nodal or hematogenous metastases. As with testicular tumors, some of these tumors tend to produce AFP (yolk sac tumors) or hCG (embryonal carcinoma, choriocarcinomas, and some dysgerminomas) that are reliable tumor markers.

TREATMENT Germ Cell Tumors

Germ cell tumors typically present in women who are still of childbearing age, and because bilateral tumors are uncommon (except in dysgerminoma, 10–15%), the typical treatment is unilateral oophorectomy or salpingo-oophorectomy. Because nodal metastases to pelvic and para-aortic nodes are common and may affect treatment choices, these nodes should be carefully inspected and, if enlarged, should be resected if possible. Women with malignant germ cell tumors typically receive bleomycin, etoposide, and cisplatin (BEP) chemotherapy. In the majority of women, even those with advanced-stage disease, cure is expected. Close follow-up without adjuvant therapy of women with stage I tumors is reasonable if there is high confidence that the patient and health care team are committed to compulsive and careful follow-up, as chemotherapy at the time of tumor recurrence is likely to be curative.

Dysgerminoma is the ovarian counterpart of testicular seminoma. T e 5-year disease-free survival is 100% in early-stage patients and 61% in stage III disease. Although the tumor is highly radiation-sensitive, radiation produces infertility in many patients. BEP chemotherapy is as effective or more so without causing infertility. T e use of BEP following incomplete resection is associated with a 2-year disease-free survival rate of 95%. T is chemotherapy is now the treatment of choice for dysgerminoma.

FALLOPIAN TUBE CANCER

Transport of the egg to the uterus occurs via transit through the fallopian tube, with the distal ends of these tubes composed of fimbriae that drape about the ovarian surface and capture the egg as it erupts from the ovarian cortex. Fallopian tube malignancies are typically serous tumors. Previous teaching was that these malignancies were rare, but more careful histologic examination suggests that many "ovarian malignancies" might actually arise in the distal fimbria of the fallopian tube (see above). T ese women often present with adnexal masses, and like ovarian cancer, these tumors spread relatively early throughout the peritoneal cavity and respond to platinum and taxane therapy and have a natural history that is essentially identical to ovarian cancer (Table 46-1).

CERVICAL CANCER

GLOBAL CONSIDERATIONS

Cervical cancer is the second most common and most lethal malignancy in women worldwide likely due to the widespread infection with high-risk strains of human papillomavirus (HPV) and limited utilization of or access to Pap smear screening in many nations throughout the world. Nearly 500,000 cases of cervical cancer are expected worldwide, with approximately 240,000 deaths annually. Cancer incidence is particularly high in women residing in Central

and South America, the Caribbean, and southern and eastern Africa. Mortality rate is disproportionately high in Africa. In the United States, 12,360 women were diagnosed with cervical cancer and 4020 women died in 2014. Developed countries have looked at high-technology screening techniques for HPV involving automated polymerase chain reaction in thin preps that identify dysplastic cytology as well as high-risk HPV genetic material. Visual inspection of the cervix coated with acetic acid has demonstrated the ability to reduce mortality from cervical cancer with potential broad applicability in low-resource environments. T e development of effective vaccines for high-risk HPV types makes it imperative to determine economical, socially acceptable, and logistically feasible strategies to deliver and distribute this vaccine to girls and boys before their engagement in sexual activity.

HPV INFECTION AND PREVENTIVE VACCINATION

HPV is the primary neoplastic-initiating event in the vast majority of women with invasive cervical cancer. T is double-strand DNA virus infects epithelium near the transformation zone of the cervix. More than 60 types of HPV are known, with approximately 20 types having the ability to generate high-grade dysplasia and malignancy. HPV-16 and -18 are the types most frequently associated with high-grade dysplasia and targeted by both U.S. Food and Drug Administration–approved vaccines. T e large majority of sexually active adults are exposed to HPV, and most women clear the infection without specific intervention. T e 8-kilobase HPV genome encodes seven early genes, most notably E6 and E7, which can bind to RB and p53, respectively. High-risk types of HPV encode E6 and E7 molecules that are particularly effective at inhibiting the normal cell cycle checkpoint functions of these regulatory proteins, leading to immortalization but not full transformation of cervical epithelium. A minority of woman will fail to clear the infection with subsequent HPV integration into the host genome. Over the course of as short as months but more typically years, some of these women develop high-grade dysplasia. T e time from dysplasia to carcinoma is likely years to more than a decade and almost certainly requires the acquisition of other poorly defined genetic mutations within the infected and immortalized epithelium.

Risk factors for HPV infection and, in particular, dysplasia include a high number of sexual partners, early age of first intercourse, and history of venereal disease. Smoking is a cofactor; heavy smokers have a higher risk of dysplasia with HPV infection. HIV infection, especially when associated with low CD4+ T cell counts, is associated with a higher rate of high-grade dysplasia and likely a shorter latency period between infection and invasive disease. T e administration of highly active antiretroviral therapy reduces the risk of high-grade dysplasia associated with HPV infection.

Currently approved vaccines include the recombinant proteins to the late proteins, L1 and L2, of HPV-16 and -18. Vaccination of women before the initiation of sexual activity dramatically reduces the rate of HPV-16 and -18 infection and subsequent dysplasia. There is also partial protection against other HPV types, although vaccinated women are still at risk for HPV infection and still require standard Pap smear screening. Although no randomized trial data demonstrate the utility of Pap smears, the dramatic drop in cervical cancer incidence and death in developed countries employing wide-scale screening provides strong evidence for its effectiveness. In addition, even visual inspection of the cervix with preapplication of acetic acid using a “see and treat” strategy has demonstrated a 30% reduction in cervical cancer death. The incorporation of HPV testing by polymerase chain reaction or other molecular techniques increases the sensitivity of detecting cervical pathology but at the cost of identifying many women with transient infections who require no specific medical intervention.

CLINICAL PRESENTATIONS

T e majority of cervical malignancies are squamous cell carcinomas associated with HPV. Adenocarcinomas are also HPV-related and arise deep in the endocervical canal; they are typically not seen by visual inspection of the cervix and thus are often missed by Pap smear screening. A variety of rarer malignancies including atypical epithelial tumors, carcinoids, small cell carcinomas, sarcomas, and lymphomas have also been reported.

T e principal role of Pap smear testing is the detection of asymptomatic preinvasive cervical dysplasia of squamous epithelial lining. Invasive carcinomas often have symptoms or signs including postcoital spotting or intermenstrual cycle bleeding or menometrorrhagia. Foul-smelling or persistent yellow discharge may also be seen. Presentations that include pelvic or sacral pain suggest lateral extension of the tumor into pelvic nerve plexus by either the primary tumor or a pelvic node and are signs of advanced-stage disease. Likewise, flank pain from hydronephrosis from ureteral compression or deep venous thrombosis from iliac vessel compression suggests either extensive nodal disease or direct extension of the primary tumor to the pelvic sidewall. T e most common finding of physical exam is a visible tumor on the cervix.

Scans are not part of the formal clinical staging of cervical cancer yet are very useful in planning appropriate therapy. CT can detect hydronephrosis indicative of pelvic sidewall disease but is not accurate at evaluating other pelvic structures. Magnetic resonance imaging (MRI) is more accurate at estimating uterine extension and paracervical extension of disease into soft tissues typically bordered by broad and cardinal ligaments that support the uterus in the central pelvis. Positron emission tomography (PET) scan is the most accurate technique for evaluating the pelvis and more importantly nodal (pelvic, para-aortic, and scalene) sites for disease. T is technique seems more prognostic and accurate than CT, MRI, or lymphangiogram, especially in the para-aortic region.

Stage I cervical tumors are confined to the cervix, whereas stage II tumors extend into the upper vagina or paracervical soft tissue **(Fig. 46-1)**. Stage III tumors extend to the lower vagina or the pelvic sidewalls, whereas stage IV tumors invade the bladder or rectum or have spread to distant sites. Very small stage I cervical tumors can be treated with a variety of surgical procedures. In young women desiring to maintain fertility, radical trachelectomy removes the cervix with subsequent anastomosis of the upper vagina to the uterine corpus. Larger cervical tumors confined to the cervix can be treated with either surgical resection or radiation therapy in combination with cisplatin-based chemotherapy with a high chance of cure. Larger tumors that extend regionally down the vagina or into the paracervical soft tissues or the pelvic sidewalls are treated with combination chemotherapy and radiation therapy. T e treatment of recurrent or metastatic disease is unsatisfactory due to the relative resistance of these tumors to chemotherapy and currently available biological agents, although bevacizumab, a monoclonal antibody that is said to inhibit tumor-associated angiogenesis, has demonstrated clinically meaningful activity in the management of metastatic disease.

UTERINE CANCER

EPIDEMIOLOGY

Several different tumor types arise in uterine corpus. Most tumors arise in the glandular lining and are endometrial adenocarcinomas. Tumors can also arise in the smooth muscle; most are benign (uterine leiomyoma), with a small minority of tumors being sarcomas. T e endometrioid histologic subtype of endometrial cancer is the most common gynecologic malignancy in the United States. In 2014, an estimated 52,630 women were diagnosed with cancer of the uterine corpus, with 8590 deaths from the disease. Development of these tumors is a multistep process, with estrogen playing an important early role in driving endometrial gland proliferation. Relative overexposure to this class of hormones is a risk factor for the subsequent development of endometrioid tumors. In contrast, progestins drive glandular maturation and are protective. Hence, women with high endogenous or pharmacologic exposure to estrogens, especially if unopposed by progesterone, are at high risk for endometrial cancer. Obese women, women treated with unopposed estrogens, or women with estrogen-producing tumors (such as granulosa cell tumors of the ovary) are at higher risk for endometrial cancer. In addition, treatment with tamoxifen, which

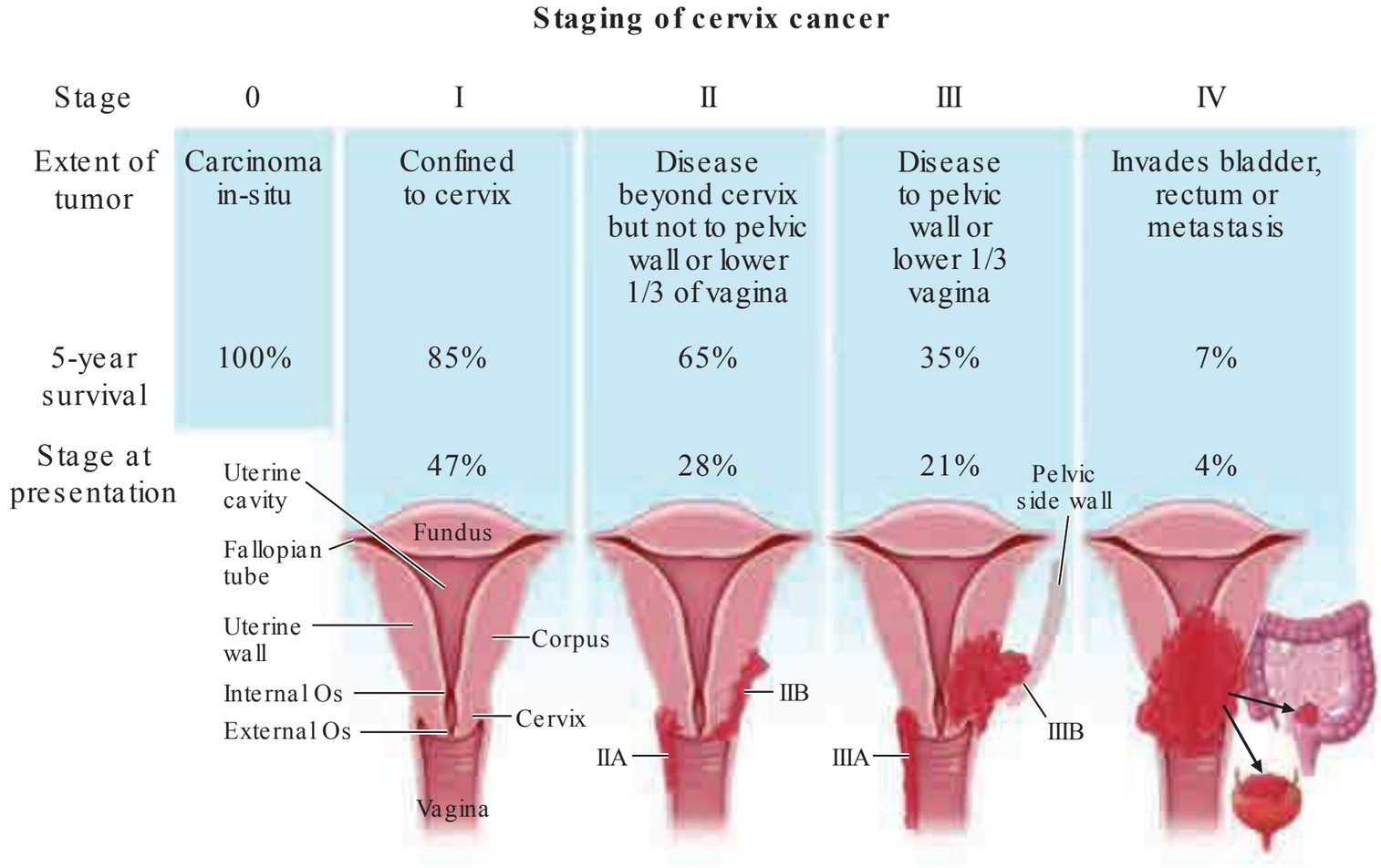


FIGURE 46-1
Anatomic display of the stages of cervix cancer defned by location, extent of tumor, frequency of presentation, and 5-year survival.

has antiestrogenic effects in breast tissue but estrogenic effects in uterine epithelium, is associated with an increased risk of endometrial cancer. Events such as the loss of the PTEN tumor suppressor gene with activation and often additional mutations in the PIK-3CA/AKT pathways likely serve as secondary events in carcinogenesis. T e Cancer Genome Atlas Research Network has demonstrated that endometrioid tumors can be divided into four subgroups: ultramutated, microsatellite instability hypermutated, copy number low, and copy number high subgroups. T ese groups have different natural histories; therapy for these subgroups may eventually be individualized. Serous tumors of the uterine corpus represent approximately 5–10% of epithelial tumors of the uterine corpus and possess distinct molecular characteristics that are most similar to those seen in serous tumors arising in the ovary or fallopian tube.

Women with a mutation in one of a series of DNA mismatch repair genes associated with the Lynch syndrome, also known as hereditary nonpolyposis colon cancer (HNPCC), are at increased risk for endometrioid endometrial carcinoma. T ese individuals have germline mutations in MSH2, MLH1, and in rare cases PMS1 and PMS2, with resulting microsatellite instability and hypermutation. Individuals who carry these mutations typically have a family history of cancer and are at markedly increased risk for colon cancer and modestly increased risk for ovarian cancer and a variety of other tumors. Middle-aged women with HNPCC carry a 4% annual risk of endometrial cancer and a relative overall risk of approximately 200-fold as compared to age-matched women without HNPCC.

PRESENTATIONS

T e majority of women with tumors of the uterine corpus present with postmenopausal vaginal bleeding due to shedding of the malignant endometrial lining. Premenopausal women often will present with atypical bleeding between typical menstrual cycles. T ese signs typically bring a woman to the attention of a health care professional, and hence the majority of women present with early-stage disease with the tumor confined to the uterine corpus. Diagnosis is typically established by endometrial biopsy. Epithelial tumors may spread to pelvic or para-aortic lymph nodes. Pulmonary metastases can appear later in the natural history of this disease but are very uncommon at initial presentation. Serous tumors tend to have patterns of spread much more reminiscent of ovarian cancer with many patients presenting with disseminated peritoneal disease and sometimes ascites. Some women presenting with uterine sarcomas will present with pelvic pain. Nodal metastases are uncommon with sarcomas, which are more likely to present with either intraabdominal disease or pulmonary metastases.

TREATMENT Uterine Cancer

Most women with endometrial cancer have disease that is localized to the uterus (75% are stage I, Table 46-1), and definitive treatment typically involves a hysterectomy with removal of the ovaries and fallopian tubes. T e resection of lymph nodes does not improve outcome but does provide prognostic information. Node involvement defines stage III disease, which is present in 13% of patients. Tumor grade and depth of invasion are the two key prognostic variables in early-stage tumors, and women with low-grade and/or minimally invasive tumors are typically observed after definitive surgical therapy. Patients with high-grade tumors or tumors that are deeply invasive (stage IB, 13%) are at higher risk for pelvic recurrence or recurrence at the vaginal cuff, which is typically prevented by vaginal vault brachytherapy.

Women with regional metastases or metastatic disease (3% of patients) with low-grade tumors can be treated with progesterone. Poorly differentiated tumors are typically resistant to hormonal manipulation and thus are treated with chemotherapy. T e role of chemotherapy in the adjuvant setting is currently under investigation. Chemotherapy for metastatic disease is delivered with palliative intent. Drugs that effectively target and inhibit signaling of the AKT-mTOR pathway are currently under investigation.

Five-year survival is 89% for stage I, 73% for stage II, 52% for stage III, and 17% for stage IV disease (Table 46-1).

GESTATIONAL TROPHOBLASTIC TUMORS

GLOBAL CONSIDERATIONS

Gestational trophoblastic diseases represent a spectrum of neoplasia from benign hydatidiform mole to choriocarcinoma due to persistent trophoblastic disease associated most commonly with molar pregnancy but occasionally seen after normal gestation. T e most common presentations of trophoblastic tumors are partial and complete molar pregnancies. T ese represent approximately 1 in 1500 conceptions in developed Western countries. T e incidence widely varies globally, with areas in Southeast Asia having a much higher incidence of molar pregnancy. Regions with high molar pregnancy rates are often associated with diets low in carotene and animal fats.

RISK FACTORS

Trophoblastic tumors result from the outgrowth or persistence of placental tissue. T ey arise most commonly in the uterus but can also arise in other sites such as the fallopian tubes due to ectopic pregnancy. Risk factors include poorly defined dietary and environmental

factors as well as conceptions at the extremes of reproductive age, with the incidence particularly high in females conceiving younger than age 16 or older than age 50. In older women, the incidence of molar pregnancy might be as high as one in three, likely due to increased risk of abnormal fertilization of the aged ova. Most trophoblastic neoplasms are associated with complete moles, diploid tumors with all genetic material from the paternal donor (known as parental disomy). T is is thought to occur when a single sperm fertilizes an enucleate egg that subsequently duplicates the paternal DNA. Trophoblastic proliferation occurs with exuberant villous stroma. If pseudopregnancy extends out past the 12th week, fluid progressively accumulates within the stroma, leading to "hydropic changes." T ere is no fetal development in complete moles.

Partial moles arise from the fertilization of an egg with two sperm; hence two-thirds of genetic material is paternal in these triploid tumors. Hydropic changes are less dramatic, and fetal development can often occur through late first trimester or early second trimester at which point spontaneous abortion is common. Laboratory findings will include excessively high hCG and high AFP. T e risk of persistent gestational trophoblastic disease after partial mole is approximately 5%. Complete and partial moles can be noninvasive or invasive. Myometrial invasion occurs in no more than one in six complete moles and a lower portion of partial moles.

PRESENTATION OF INVASIVE TROPHOBLASTIC DISEASE

T e clinical presentation of molar pregnancy is changing in developed countries due to the early detection of pregnancy with home pregnancy kits and the very early use of Doppler and ultrasound to evaluate the early fetus and uterine cavity for evidence of a viable fetus. T us, in these countries, the majority of women presenting with trophoblastic disease have their moles detected early and have typical symptoms of early pregnancy including nausea, amenorrhea, and breast tenderness. With uterine evacuation of early complete and partial moles, most women experience spontaneous remission of their disease as monitored by serial hCG levels. T ese women require no chemotherapy. Patients with persistent elevation of hCG or rising hCG after evacuation have persistent or actively growing gestational trophoblastic disease and require therapy. Most series suggest that between 15 and 25% of women will have evidence of persistent gestational trophoblastic disease after molar evacuation.

In women who lack access to prenatal care, presenting symptoms can be life threatening including the development of preeclampsia or even eclampsia. Hyperthyroidism can also be seen. Evacuation of large moles can be associated with life-threatening complications including uterine perforation, volume loss, high-output cardiac failure, and adult respiratory distress syndrome (ARDS).

For women with evidence of rising hCG or radiologic confirmation of metastatic or persistent regional disease, prognosis can be estimated through a variety of scoring algorithms that identify those women at low, intermediate, and high risk for requiring multiagent chemotherapy. In general, women with widely metastatic nonpulmonary disease, very elevated hCG, and prior normal antecedent term pregnancy are considered at high risk and typically require multiagent chemotherapy for cure.

TREATMENT Invasive Trophoblastic Disease

T e management for a persistent and rising hCG after evacuation of a molar conception is typically chemotherapy, although surgery can play an important role for disease that is persistently isolated in the uterus (especially if childbearing is complete) or to control hemorrhage. For women wishing to maintain fertility or with metastatic disease, the preferred treatment is chemotherapy. Chemotherapy is guided by the hCG level, which typically drops to undetectable levels with effective therapy. Single-agent treatment with methotrexate or dactinomycin cures 90% of women with low-risk disease. Patients with high-risk disease (high hCG levels, presentation 4 or more months after pregnancy, brain or liver metastases, failure of methotrexate therapy) are typically treated with multiagent chemotherapy (e.g., etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine [EMA-CO]), which is typically curative even in women with extensive metastatic disease. Cisplatin, bleomycin, and either etoposide or vinblastine are also active combinations. Survival in high-risk disease exceeds 80%. Cured women may get pregnant again without evidence of increased fetal or maternal complications.

CHAPTER 47

SOFT TISSUE AND BONE SARCOMAS AND BONE METASTASES

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Sarcomas are rare (<1% of all malignancies) mesenchymal neoplasms that arise in bone and soft tissues. These tumors are usually of mesodermal origin, although a few are derived from neuroectoderm, and they are biologically distinct from the more common epithelial malignancies. Sarcomas affect all age groups; 15% are found in children <15 years of age, and 40% occur after age 55 years. Sarcomas are one of the most common solid tumors of childhood and are the fifth most common cause of cancer deaths in children. Sarcomas may be divided into two groups, those derived from bone and those derived from soft tissues.

SOFT TISSUE SARCOMAS

Soft tissues include muscles, tendons, fat, fibrous tissue, synovial tissue, vessels, and nerves. Approximately 60% of soft tissue sarcomas arise in the extremities, with the lower extremities involved three times as often as the upper extremities. Thirty percent arise in the trunk, the retroperitoneum accounting for 40% of all trunk lesions. The remaining 10% arise in the head and neck.

INCIDENCE

Approximately 11,410 new cases of soft tissue sarcomas occurred in the United States in 2013. The annual age-adjusted incidence is 3 per 100,000 population, but the incidence varies with age. Soft tissue sarcomas constitute 0.7% of all cancers in the general population and 6.5% of all cancers in children.

EPIDEMIOLOGY

Malignant transformation of a benign soft tissue tumor is extremely rare, with the exception that malignant peripheral nerve sheath tumors (neurofibrosarcoma, malignant schwannoma) can arise from neurofibromas in patients with neurofibromatosis. Several etiologic factors have been implicated in soft tissue sarcomas.

Environmental factors

Trauma or previous injury is rarely involved, but sarcomas can arise in scar tissue resulting from a prior operation, burn, fracture, or foreign body implantation. Chemical carcinogens such as polycyclic hydrocarbons, asbestos, and dioxin may be involved in the pathogenesis.

Iatrogenic factors

Sarcomas in bone or soft tissues occur in patients who are treated with radiation therapy. The tumor nearly always arises in the irradiated field. The risk increases with time.

Viruses

Kaposi's sarcoma (KS) in patients with HIV type 1, classic KS, and KS in HIV-negative homosexual men is caused by human herpesvirus (HHV) 8. No other sarcomas are associated with viruses.

Immunologic factors

Congenital or acquired immunodeficiency, including therapeutic immunosuppression, increases the risk of sarcoma.

GENETIC CONSIDERATIONS

Li-Fraumeni syndrome is a familial cancer syndrome in which affected individuals have germline abnormalities of the tumor-suppressor gene p53

and an increased incidence of soft tissue sarcomas and other malignancies, including breast cancer, osteosarcoma, brain tumor, leukemia, and adrenal carcinoma **(Chap. 25)**. Neurofibromatosis 1 (NF-1, peripheral form, von Recklinghausen's disease) is characterized by multiple neurofibromas and café-au-lait spots. Neurofibromas occasionally undergo malignant degeneration to become malignant peripheral nerve sheath tumors. T e gene for NF-1 is located in the pericentromeric region of chromosome 17 and encodes neurofibromin, a tumor-suppressor protein with guanosine 5′-triphosphate (GTP) ase-activating activity that inhibits Ras function **(Chap. 48)**. Germline mutation of the Rb-1 locus (chromosome 13q14) in patients with inherited retinoblastoma is associated with the development of osteosarcoma in those who survive the retinoblastoma and of soft tissue sarcomas unrelated to radiation therapy. Other soft tissue tumors, including desmoid tumors, lipomas, leiomyomas, neuroblastomas, and paragangliomas, occasionally show a familial predisposition.

Ninety percent of synovial sarcomas contain a characteristic chromosomal translocation t(X;18)(p11;q11) involving a nuclear transcription factor on chromosome 18 called SYT and two breakpoints on X. Patients with translocations to the second X breakpoint (SSX2) may have longer survival than those with translocations involving SSX1.

Insulin-like growth factor (IGF) type II is produced by some sarcomas and may act as an autocrine growth factor and as a motility factor that promotes metastatic spread. IGF-II stimulates growth through IGF-I receptors, but its effects on motility are through different receptors. If secreted in large amounts, IGF-II may produce hypoglycemia **(Chap. 54)**.

CLASSIFICATION

Approximately 20 different groups of sarcomas are recognized on the basis of the pattern of differentiation toward normal tissue. For example, rhabdomyosarcoma shows evidence of skeletal muscle fibers with cross-striations; leiomyosarcomas contain interlacing fascicles of spindle cells resembling smooth muscle; and liposarcomas contain adipocytes. When precise characterization of the group is not possible, the tumors are called unclassi*fi*ed sarcomas. All of the primary bone sarcomas can also arise from soft tissues (e.g., extraskeletal osteosarcoma). T e entity malignant *fi*brous histiocytoma (MFH) includes many tumors previously classified as fibrosarcomas or as pleomorphic variants of other sarcomas and is characterized by a mixture of spindle (fibrous) cells and round (histiocytic) cells arranged in a storiform pattern with frequent giant cells and areas of pleomorphism. As immunohistochemical suggestion of differentiation, particularly myogenic differentiation, may be found in a significant fraction of these patients, many are now characterized as poorly differentiated leiomyosarcomas, and the terms undi*ff*erentiated pleomorphic sarcoma (UPS) and myxo*fi*brosarcoma are replacing MFH and myxoid MFH.

For purposes of treatment, most soft tissue sarcomas can be considered together. However, some specific tumors have distinct features. For example, liposarcoma can have a spectrum of behaviors. Pleomorphic liposarcomas and dedifferentiated liposarcomas behave like other high-grade sarcomas; in contrast, well-differentiated liposarcomas (better termed atypical lipomatous tumors) lack metastatic potential, and myxoid liposarcomas metastasize infrequently, but, when they do, they have a predilection for unusual metastatic sites containing fat, such as the retroperitoneum, mediastinum, and subcutaneous tissue. Rhabdomyosarcomas, Ewing's sarcoma, and other small-cell sarcomas tend to be more aggressive and are more responsive to chemotherapy than other soft tissue sarcomas.

Gastrointestinal stromal cell tumors (GISTs), previously classified as gastrointestinal leiomyosarcomas, are now recognized as a distinct entity within soft tissue sarcomas. Its cell of origin resembles the interstitial cell of Cajal, which controls peristalsis. T e majority of malignant GISTs have activating mutations of the c-kit gene that result in ligand-independent phosphorylation and activation of the KIT receptor tyrosine kinase, leading to tumorigenesis. Approximately 5–10% of tumors will have a mutation in the platelet-derived growth factor receptor α (PDGFRA). GISTs that are wild type for both KIT and PDGFRA mutations may show mutations in SDH B, C, or D and may be driven by the IGF-I pathway.

DIAGNOSIS

T e most common presentation is an asymptomatic mass. Mechanical symptoms referable to pressure, traction, or entrapment of nerves or muscles may be present. All new and persistent or growing masses should be biopsied, either by a cutting needle (core-needle biopsy) or by a small incision, placed so that it can be encompassed in the subsequent excision without compromising a definitive resection. Lymph node metastases occur in 5%, except in synovial and epithelioid sarcomas, clear-cell sarcoma (melanoma of the soft parts), angiosarcoma, and rhabdomyosarcoma, where nodal spread may be seen in 17%. T e pulmonary parenchyma is the most common site of metastases. Exceptions are GISTs, which metastasize to the liver; myxoid liposarcomas, which seek fatty tissue; and clear-cell sarcomas, which may metastasize to bones. Central nervous system metastases are rare, except in alveolar soft part sarcoma.

Radiographic evaluation

Imaging of the primary tumor is best with plain radiographs and magnetic resonance imaging (MRI) for tumors of the extremities or head and neck and by computed tomography (CT) for tumors of the chest, abdomen, or retroperitoneal cavity. A radiograph and CT scan of the chest are important for the detection of lung metastases. Other imaging studies may be indicated, depending on the symptoms, signs, or histology.

STAGING AND PROGNOSIS

The histologic grade, relationship to fascial planes, and size of the primary tumor are the most important prognostic factors. The current American Joint Committee on Cancer (AJCC) staging system is shown in **Table 47-1**. Prognosis is related to the stage. Cure is common in the absence of metastatic disease, but a small number of patients with metastases can also be cured. Most patients with stage IV disease die within 12 months, but some patients may live with slowly progressive disease for many years.

TREATMENT Soft Tissue Sarcomas

AJCC stage I patients are adequately treated with surgery alone. Stage II patients are considered for adjuvant radiation therapy. Stage III patients may benefit from adjuvant chemotherapy. Stage IV patients are managed primarily with chemotherapy, with or without other modalities.

SURGERY Soft tissue sarcomas tend to grow along fascial planes, with the surrounding soft tissues compressed to form a pseudocapsule that gives the sarcoma the appearance of a well-encapsulated lesion. This is invariably deceptive because "shelling out," or marginal excision, of such lesions results in a 50–90% probability of local recurrence. Wide excision with a negative margin, incorporating the biopsy site, is the standard surgical procedure for local disease. The adjuvant use of radiation therapy and/or chemotherapy improves the local control rate and permits the use of limb-sparing surgery with a local control rate (85–90%) comparable to that achieved by radical excisions and amputations. Limb-sparing approaches are indicated except when negative margins are not obtainable, when the risks of radiation are prohibitive, or when neurovascular structures are involved so that resection will result in serious functional consequences to the limb.

RADIATION THERAPY External-beam radiation therapy is an adjuvant to limb-sparing surgery for improved local control. Preoperative radiation therapy allows the use of smaller fields and smaller doses but results in a higher rate of wound complications. Postoperative radiation therapy must be given to larger fields, because the entire surgical bed must be encompassed, and in higher doses to compensate for hypoxia in the operated field. This results in a higher rate of late complications. Brachytherapy or interstitial therapy, in which the radiation source is inserted into the tumor bed, is comparable in efficacy (except in low-grade lesions), less time-consuming, and less expensive.

ADJUVANT CHEMOTHERAPY Chemotherapy is the mainstay of treatment for Ewing's primitive neuroectodermal tumors (PNET) and rhabdomyosarcomas. Meta-analysis of 14 randomized trials revealed a significant improvement in local control and disease-free survival in favor of doxorubicin-based chemotherapy. Overall survival improvement was 4% for all sites and 7% for the extremity site. An updated meta-analysis including four additional trials with doxorubicin and ifosfamide combination has reported a statistically significant 6% survival advantage in favor of chemotherapy. A chemotherapy regimen including an anthracycline and ifosfamide with growth factor support improved overall survival by 19% for high-risk (high-grade, ≥5 cm primary, or locally recurrent) extremity soft tissue sarcomas.

ADVANCED DISEASE Metastatic soft tissue sarcomas are largely incurable, but up to 20% of patients who achieve a complete response become long-term survivors. The therapeutic intent, therefore, is to produce a complete remission with chemotherapy (<10%) and/or surgery (30–40%). Surgical resection of metastases, whenever possible, is an integral part of the management. Some patients benefit from repeated surgical excision of metastases. The two most active chemotherapeutic agents are doxorubicin and ifosfamide. These drugs show a steep dose-response relationship in sarcomas. Gemcitabine with or without docetaxel has become an established second-line regimen and is particularly active in patients with undifferentiated pleomorphic sarcoma (UPS) and leiomyosarcomas. Dacarbazine also has some modest activity. Taxanes have selective activity in angiosarcomas, and vincristine, etoposide, and irinotecan are effective in rhabdomyosarcomas and Ewing's sarcomas. Pazopanib, an inhibitor of the vascular endothelial growth factor, platelet-derived growth factor (PDGF), and c-kit is now approved for patients with advanced soft tissue sarcomas excluding liposarcomas after failure of chemotherapy. Imatinib targets the KIT and PDGF tyrosine kinase activity and is standard therapy for advanced/metastatic GISTs and dermatofibrosarcoma protuberans. Imatinib is now also indicated as adjuvant therapy for completely resected primary GISTs. Three years of adjuvant imatinib appears to be superior to 1 year of therapy for high-risk GISTs, although the optimal treatment duration remains unknown.

BONE SARCOMAS

INCIDENCE AND EPIDEMIOLOGY

Bone sarcomas are rarer than soft tissue sarcomas; they accounted for only 0.2% of all new malignancies and 2890 new cases in the United States in 2013. Several

TABLE 47-1

AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM FOR SARCOMAS

HISTOLOGIC GRADE (G)	TUMOR SIZE (T)	NODE STATUS (N)	METASTASES (M)
Well differentiated (G1) Moderately differentiated (G2) Poorly differentiated (G3) Undifferentiated (G4)	≤5 cm (T1) >5 cm (T2) Superficial fascial involvement (Ta) Deep fascial involvement (Tb)	Not involved (N0) Involved (N1)	Absent (M0) Present (M1)

DISEASE STAGE	5-YEAR SURVIVAL, %
Stage I	98.8
A: G1,2; T1a,b; N0; M0 B: G1,2; T2a; N0; M0	
Stage II	81.8
A: G1,2; T2b; N0; M0 B: G3,4; T1; N0; M0 C: G3,4; T2a; N0; M0	
Stage III: G3,4; T2b; N0; M0	51.7
Stage IV	<20
A: any G; any T; N1; M0 B: any G; any T; any N; M1	

benign bone lesions have the potential for malignant transformation. Enchondromas and osteochondromas can transform into chondrosarcoma; fibrous dysplasia, bone infarcts, and Paget's disease of bone can transform into either UPS or osteosarcoma.

CLASSIFICATION

Benign tumors

The common benign bone tumors include enchondroma, osteochondroma, chondroblastoma, and chondromyxoid fibroma, of cartilage origin; osteoid osteoma and osteoblastoma, of bone origin; fibroma and desmoplastic fibroma, of fibrous tissue origin; hemangioma, of vascular origin; and giant-cell tumor, of unknown origin.

Malignant tumors

The most common malignant tumors of bone are plasma cell tumors **(Chap. 18)**. The four most common malignant nonhematopoietic bone tumors are osteosarcoma, chondrosarcoma, Ewing's sarcoma, and UPS. Rare malignant tumors include chordoma (of notochordal origin), malignant giant-cell tumor and adamantinoma (of unknown origin), and hemangioendothelioma (of vascular origin).

Musculoskeletal tumor society staging system

Sarcomas of bone are staged according to the Musculoskeletal Tumor Society staging system based on grade and compartmental localization. A Roman numeral reflects the tumor grade: stage I is low grade, stage II is high grade, and stage III includes tumors of any grade that have lymph node or distant metastases. In addition, the tumor is given a letter reflecting its compartmental localization. Tumors designated A are intracompartmental (i.e., confined to the same soft tissue compartment as the initial tumor), and tumors designated B are extracompartmental (i.e., extending into the adjacent soft tissue compartment or into bone). The tumor-node-metastasis (TNM) staging system is shown in **Table 47-2**.

OSTEOSARCOMA

Osteosarcoma, accounting for almost 45% of all bone sarcomas, is a spindle cell neoplasm that produces osteoid (unmineralized bone) or bone. Approximately 60% of all osteosarcomas occur in children and adolescents in the second decade of life, and approximately 10% occur in the third decade of life. Osteosarcomas in the fifth and sixth decades of life are frequently secondary to either radiation therapy or transformation in a preexisting benign condition, such as Paget's disease. Males are affected 1.5–2 times as often as females. Osteosarcoma has a predilection for metaphyses of long bones; the most common sites of involvement are the distal femur, proximal tibia, and proximal humerus. The classification of osteosarcoma is complex, but 75% of osteosarcomas fall into the "classic" category, which include osteoblastic, chondroblastic, and fibroblastic osteosarcomas. The remaining 25% are classified as "variants" on the basis of (1) clinical characteristics, as

TABLE 47-2

STAGING SYSTEM FOR BONE SARCOMAS		
Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	T1	Tumor ≤8 cm in greatest dimension
	T2	Tumor >8 cm in greatest dimension
	T3	Discontinuous tumors in the primary bone site
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
Distant metastasis (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Lung
	M1b	Other distant sites
Histologic grade (G)	GX	Grade cannot be assessed
	G1	Well differentiated—low grade
	G2	Moderately differentiated—low grade
	G3	Poorly differentiated—high grade
	G4	Undifferentiated—high grade (Ewing's is always classed G4)

Stage Grouping				
Stage IA	T1	N0	M0	G1,2 low grade
Stage IB	T2	N0	M0	G1,2 low grade
Stage IIA	T1	N0	M0	G3,4 high grade
Stage IIB	T2	N0	M0	G3,4 high grade
Stage III	T3	N0	M0	Any G
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

in the case of osteosarcoma of the jaw, postradiation osteosarcoma, or Paget's osteosarcoma; (2) morphologic characteristics, as in the case of telangiectatic osteosarcoma, small-cell osteosarcoma, or epithelioid osteosarcoma; or (3) location, as in parosteal or periosteal osteosarcoma. Diagnosis usually requires a synthesis of clinical, radiologic, and pathologic features. Patients typically present with pain and swelling of the affected area. A plain radiograph reveals a destructive lesion with a moth-eaten appearance, a spiculated periosteal reaction (sunburst appearance), and a cuff of periosteal new bone formation at the margin of the soft tissue mass (Codman's triangle). A CT scan of the primary tumor is best for defining bone destruction and the pattern of calcification, whereas MRI is better for defining intramedullary and soft tissue extension. A chest radiograph and CT scan are used to detect lung metastases. Metastases to the bony skeleton should be imaged by a bone scan or by fluorodeoxyglucose positron emission tomography (FDG-PET). Almost all osteosarcomas are hypervascular. Angiography is not helpful for diagnosis, but it is the most sensitive test for assessing the response to preoperative chemotherapy. Pathologic diagnosis is established either with a core-needle biopsy, where feasible, or with an open biopsy with an appropriately placed incision that does not compromise future limb-sparing resection. Most osteosarcomas are high-grade. The most important prognostic factor for long-term survival is response to chemotherapy. Preoperative chemotherapy followed by limb-sparing surgery (which can be accomplished in >80% of patients) followed by postoperative chemotherapy is standard management. The effective drugs are doxorubicin, ifosfamide, cisplatin, and high-dose methotrexate with leucovorin rescue. The various combinations of these agents that have been used have all been about equally successful. Long-term survival rates in extremity osteosarcoma range from 60 to 80%. Osteosarcoma is radioresistant; radiation therapy has no role in the routine management. UPS is considered a part of the spectrum of osteosarcoma and is managed similarly.

CHONDROSARCOMA

Chondrosarcoma, which constitutes ~20–25% of all bone sarcomas, is a tumor of adulthood and old age with a peak incidence in the fourth to sixth decades of life. It has a predilection for the fat bones, especially the shoulder and pelvic girdles, but can also affect the diaphyseal portions of long bones. Chondrosarcomas can arise de novo or as a malignant transformation of an enchondroma or, rarely, of the cartilaginous cap of an osteochondroma. Chondrosarcomas have an indolent natural history and typically present as pain and swelling. Radiographically, the lesion may have a lobular appearance with mottled or punctate or annular calcification of the cartilaginous matrix. It is difficult to distinguish low-grade chondrosarcoma from benign lesions by x-ray or histologic examination. The diagnosis is therefore influenced by clinical history and physical examination. A new onset of pain, signs of inflammation, and progressive increase in the size of the mass suggest malignancy. The histologic classification is complex, but most tumors fall within the classic category. Like other bone sarcomas, high-grade chondrosarcomas spread to the lungs. Most chondrosarcomas are resistant to chemotherapy, and surgical resection of primary or recurrent tumors, including pulmonary metastases, is the mainstay of therapy.

T is rule does not hold for two histologic variants. Dedifferentiated chondrosarcoma has a high-grade osteosarcoma or a malignant fibrous histiocytoma component that responds to chemotherapy. Mesenchymal chondrosarcoma, a rare variant composed of a small-cell element, also is responsive to systemic chemotherapy and is treated like Ewing's sarcoma.

EWING'S SARCOMA

Ewing's sarcoma, which constitutes ~10–15% of all bone sarcomas, is common in adolescence and has a peak incidence in the second decade of life. It typically involves the diaphyseal region of long bones and also has an affinity for f at bones. T e plain radiograph may show a characteristic "onion peel" periosteal reaction with a generous soft tissue mass, which is better demonstrated by CT or MRI. T is mass is composed of sheets of monotonous, small, round, blue cells and can be confused with lymphoma, embryonal rhabdomyosarcoma, and small-cell carcinoma. T e presence of p30/32, the product of the mic-2 gene (which maps to the pseudoautosomal region of the X and Y chromosomes), is a cell-surface marker for Ewing's sarcoma (and other members of the Ewing's family of tumors, sometimes called PNETs). Most PNETs arise in soft tissues; they include peripheral neuroepithelioma, Askin's tumor (chest wall), and esthesioneuroblastoma. Glycogen-filled cytoplasm detected by staining with periodic acid–Schiff is also characteristic of Ewing's sarcoma cells. T e classic cytogenetic abnormality associated with this disease (and other PNETs) is a reciprocal translocation of the long arms of chromosomes 11 and 22, t(11;22), which creates a chimeric gene product of unknown function with components from the f i-1 gene on chromosome 11 and ews on 22. T is disease is very aggressive, and it is therefore considered a systemic disease. Common sites of metastases are lung, bones, and bone marrow. Systemic chemotherapy is the mainstay of therapy, often being used before surgery. Doxorubicin, cyclophosphamide or ifosfamide, etoposide, vincristine, and dactinomycin are active drugs. Topotecan or irinotecan in combination with an alkylating agent is often used in relapsed patients. Targeted therapy with an anti-IGF-I receptor antibody in combination with an inhibitor of mammalian target of rapamycin (mTOR) appears to have promising activity in refractory cases. Local treatment for the primary tumor includes surgical resection, usually with limb salvage or radiation therapy. Patients with lesions below the elbow and below the mid-calf have a 5-year survival rate of 80% with effective treatment. Ewing's sarcoma at first presentation is a curable tumor, even in the presence of obvious metastatic disease, especially in children <11 years old.

TUMORS METASTATIC TO BONE

Bone is a common site of metastasis for carcinomas of the prostate, breast, lung, kidney, bladder, and thyroid and for lymphomas and sarcomas. Prostate, breast, and lung primaries account for 80% of all bone metastases. Metastatic tumors of bone are more common than primary bone tumors. Tumors usually spread to bone hematogenously, but local invasion from soft tissue masses also occurs. In descending order of frequency, the sites most often involved are the vertebrae, proximal femur, pelvis, ribs, sternum, proximal humerus, and skull. Bone metastases may be asymptomatic or may produce pain, swelling, nerve root or spinal cord compression, pathologic fracture, or myelophthisis (replacement of the marrow). Symptoms of hypercalcemia may be noted in cases of bony destruction.

Pain is the most frequent symptom. It usually develops gradually over weeks, is usually localized, and often is more severe at night. When patients with back pain develop neurologic signs or symptoms, emergency evaluation for spinal cord compression is indicated **(Chap. 56)**. Bone metastases exert a major adverse effect on quality of life in cancer patients.

Cancer in the bone may produce osteolysis, osteogenesis, or both. Osteolytic lesions result when the tumor produces substances that can directly elicit bone resorption (vitamin D–like steroids, prostaglandins, or parathyroid hormone–related peptide) or cytokines that can induce the formation of osteoclasts (interleukin 1 and tumor necrosis factor). Osteoblastic lesions result when the tumor produces cytokines that activate osteoblasts. In general, purely osteolytic lesions are best detected by plain radiography, but they may not be apparent until they are >1 cm. T ese lesions are more commonly associated with hypercalcemia and with the excretion of hydroxyproline-containing peptides indicative of matrix destruction. When osteoblastic activity is prominent, the lesions may be readily detected using radionuclide bone scanning (which is sensitive to new bone formation), and the radiographic appearance may show increased bone density or sclerosis. Osteoblastic lesions are associated with higher serum levels of alkaline phosphatase and, if extensive, may produce hypocalcemia. Although some tumors may produce mainly osteolytic lesions (e.g., kidney cancer) and others mainly osteoblastic lesions (e.g., prostate cancer), most metastatic lesions produce both types of lesion and may go through stages where one or the other predominates.

In older patients, particularly women, it may be necessary to distinguish metastatic disease of the spine from osteoporosis. In osteoporosis, the cortical bone may be preserved, whereas cortical bone destruction is usually noted with metastatic cancer.

TREATMENT Metastatic Bone Disease

Treatment of metastatic bone disease depends on the underlying malignancy and the symptoms. Some metastatic bone tumors are curable (lymphoma, Hodgkin's disease), and others are treated with palliative intent. Pain may be relieved by local radiation therapy. Hormonally responsive tumors are responsive to hormone inhibition (antiandrogens for prostate cancer, antiestrogens for breast cancer). Strontium-89, samarium-153, and radium-223 are bone-seeking radionuclides that can exert antitumor effects and relieve symptoms. Denosumab, a monoclonal antibody that binds to RANK ligand, inhibits osteoclastic activity and increases bone mineral density. Bisphosphonates such as pamidronate may relieve pain and inhibit bone resorption, thereby maintaining bone mineral density and reducing risk of fractures in patients with osteolytic metastases from breast cancer and multiple myeloma. Careful monitoring of serum electrolytes and creatinine is recommended. Monthly administration prevents bone-related clinical events and may reduce the incidence of bone metastases in women with breast cancer. When the integrity of a weight-bearing bone is threatened by an expanding metastatic lesion that is refractory to radiation therapy, prophylactic internal fixation is indicated. Overall survival is related to the prognosis of the underlying tumor. Bone pain at the end of life is particularly common; an adequate pain relief regimen including sufficient amounts of narcotic analgesics is required.

CHAPTER 48

PRIMARY AND METASTATIC TUMORS OF THE NERVOUS SYSTEM

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Primary brain tumors are diagnosed in approximately 52,000 people each year in the United States. At least one-half of these tumors are malignant and associated with a high mortality. Glial tumors account for about 30% of all primary brain tumors, and 80% of those are malignant. Meningiomas account for 35%, vestibular schwannomas 10%, and central nervous system (CNS) lymphomas about 2%. Brain metastases are three times more common than all primary brain tumors combined and are diagnosed in approximately 150,000 people each year. Metastases to the leptomeninges and epidural space of the spinal cord each occur in approximately 3–5% of patients with systemic cancer and are also a major cause of neurologic disability.

APPROACH TO THE PATIENT: Primary and Metastatic Tumors of the Nervous System

CLINICAL FEATURES Brain tumors of any type can present with a variety of symptoms and signs that fall into two categories: general and focal; patients often have a combination of the two **(Table 48-1)**. General or nonspecific symptoms include headache, with or without nausea or vomiting, cognitive difficulties, personality change, and gait disorder. Generalized symptoms arise when the enlarging tumor and its surrounding edema cause an increase in intracranial pressure or direct compression of cerebrospinal fluid (CSF) circulation leading to hydrocephalus. The classic headache associated with a brain tumor is most evident in the morning and improves during the day, but this particular pattern is actually seen in a minority of patients. Headaches are often holocephalic but can be ipsilateral to the side of a tumor. Occasionally, headaches have features of a typical migraine with unilateral throbbing pain associated with visual scotoma. Personality changes may include apathy and withdrawal from social circumstances, mimicking depression. Focal or lateralizing findings include hemiparesis, aphasia, or visual field defect. Lateralizing symptoms are typically subacute and progressive. A visual field defect is often unnoticed by the patient; its presence may only be revealed after it leads to an injury such as an automobile accident occurring in the blind visual field. Language difficulties may be mistaken for confusion. Seizures are a common presentation of brain tumors, occurring in about 25% of patients with brain metastases or malignant gliomas but can be the presenting symptom in up to 90% of patients with a low-grade glioma. All seizures that arise from a brain tumor will have a focal onset whether or not it is apparent clinically.

NEUROIMAGING Cranial MRI is the preferred diagnostic test for any patient suspected of having a brain tumor and should be performed with gadolinium contrast administration. Computed tomography (CT) scan should be reserved for those patients unable to undergo magnetic resonance imaging (MRI; e.g., pacemaker). Malignant brain tumors—whether primary or metastatic—typically enhance with gadolinium and may have central areas of necrosis; they are characteristically surrounded by edema of the neighboring white matter. Low-grade gliomas usually do not enhance with gadolinium and are best appreciated on fluid-attenuated inversion recovery (FLAIR) MRIs. Meningiomas have a characteristic appearance on MRI because they are dural-based with a dural tail and compress but do not invade the brain. Dural metastases or a dural lymphoma can have a similar appearance. Imaging is characteristic for many primary and metastatic tumors and sometimes will suffice to establish a diagnosis when the location precludes surgical

TABLE 48-1

SYMPTOMS AND SIGNS AT PRESENTATION OF BRAIN TUMORS

	HIGH-GRADE GLIOMA (%)	LOW-GRADE GLIOMA (%)	MENINGIOMA (%)	METASTASES (%)
Generalized				
Impaired cognitive function	50	10	30	60
Hemiparesis	40	10	36	60
Headache	50	40	37	50
Lateralizing				
Seizures	20	70+	17	18
Aphasia	20	<5	—	18
Visual field deficit	—	—	—	7

intervention (e.g., brainstem glioma). Functional MRI is useful in presurgical planning to define eloquent sensory, motor, or language cortex. Positron emission tomography (PET) is useful in determining the metabolic activity of the lesions seen on MRI; MR perfusion and spectroscopy can provide information on blood flow or tissue composition. These techniques may help distinguish tumor progression from necrotic tissue as a consequence of treatment with radiation and chemotherapy or identify foci of high-grade tumor in an otherwise low-grade-appearing glioma.

Neuroimaging is the only test necessary to diagnose a brain tumor. Laboratory tests are rarely useful, although patients with metastatic disease may have elevation of a tumor marker in their serum that reflects the presence of brain metastases (e.g., β human chorionic gonadotropin [β-hCG] from testicular cancer). Additional testing such as cerebral angiogram, electroencephalogram (EEG), or lumbar puncture is rarely indicated or helpful.

TREATMENT Brain Tumors

Therapy of any intracranial malignancy requires both symptomatic and definitive treatments. Definitive treatment is based on the specific tumor type and includes surgery, radiotherapy, and chemotherapy. However, symptomatic treatments apply to brain tumors of any type. Most high-grade malignancies are accompanied by substantial surrounding edema, which contributes to neurologic disability and raised intracranial pressure. Glucocorticoids are highly effective at reducing perilesional edema and improving neurologic function, often within hours of administration. Dexamethasone has been the glucocorticoid of choice because of its relatively low mineralocorticoid activity. Initial doses are typically 12–16 mg/d in divided doses given orally or IV (both are equivalent). Although glucocorticoids rapidly ameliorate symptoms and signs, their long-term use causes substantial toxicity including insomnia, weight gain, diabetes mellitus, steroid myopathy, and personality changes. Consequently, a taper is indicated as definitive treatment is administered and the patient improves.

Patients with brain tumors who present with seizures require antiepileptic drug therapy. There is no role for prophylactic antiepileptic drugs in patients who have not had a seizure. The agents of choice are those drugs that do not induce the hepatic microsomal enzyme system. These include levetiracetam, topiramate, lamotrigine, valproic acid, and lacosamide. Other drugs, such as phenytoin and carbamazepine, are used less frequently because they are potent enzyme inducers that can interfere with both glucocorticoid metabolism and the metabolism of chemotherapeutic agents needed to treat the underlying systemic malignancy or the primary brain tumor. Venous thromboembolic disease occurs in 20–30% of patients with high-grade gliomas and brain metastases. Therefore, prophylactic anticoagulants should be used during hospitalization and in nonambulatory patients. Those who have had either a deep vein thrombosis or pulmonary embolus can receive therapeutic doses of anticoagulation safely and without increasing the risk for hemorrhage into the tumor. Inferior vena cava filters are reserved for patients with absolute contraindications to anticoagulation such as recent craniotomy.

PRIMARY BRAIN TUMORS

PATHOGENESIS

No underlying cause has been identified for the majority of primary brain tumors. The only established risk factors are exposure to ionizing radiation (meningiomas, gliomas, and schwannomas) and immunosuppression (primary CNS lymphoma). Evidence for an association with exposure to electromagnetic fields including cellular telephones, head injury, foods containing N-nitroso compounds, or occupational risk factors are unproven. A small minority of patients have a family history of brain tumors. Some of these familial cases are associated with genetic syndromes **(Table 48-2)**.

TABLE 48-2

GENETIC SYNDROMES ASSOCIATED WITH PRIMARY BRAIN TUMORS

SYNDROME	INHERITANCE	GENE/PROTEIN	ASSOCIATED TUMORS
Cowden's syndrome	AD	Mutations of PTEN (ch10p23)	Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), meningioma, astrocytoma Breast, endometrial, thyroid cancer, trichilemmomas
Familial schwannomatosis	Sporadic Hereditary	Mutations in INI1/SNF5 (ch22q11)	Schwannomas, gliomas
Gardner's syndrome	AD	Mutations in APC (ch5q21)	Medulloblastoma, glioblastoma, craniopharyngioma Familial polyposis, multiple osteomas, skin and soft tissue tumors
Gorlin syndrome (basal cell nevus syndrome)	AD	Mutations in Patched 1 gene (ch9q22.3)	Medulloblastomas Basal cell carcinoma
Li-Fraumeni syndrome	AD	Mutations in p53 (ch17p13.1)	Gliomas, medulloblastomas Sarcomas, breast cancer, leukemias, others
Multiple endocrine neoplasia 1 (Werner's syndrome)	AD	Mutations in Menin (ch11q13)	Pituitary adenoma, malignant schwannomas Parathyroid and pancreatic islet cell tumors
Neurofibromatosis type 1 (NF1)	AD	Mutations in NF1/neurofibromin (ch17q12-22)	Schwannomas, astrocytomas, optic nerve gliomas, meningiomas Neurofibromas, neurofibrosarcomas, others
Neurofibromatosis type 2 (NF2)	AD	Mutations in NF2/merlin (ch22q12)	Bilateral vestibular schwannomas, astrocytomas, multiple meningiomas, ependymomas
Tuberous sclerosis (TSC) (Bourneville disease)	AD	Mutations in TSC1/TSC2 (ch9q34/16)	Subependymal giant-cell astrocytoma, ependymomas, glioma, ganglioneuroma, hamartoma
Turcot syndrome	AD AR	Mutations in APC[a] (ch5) hMLH1 (ch3p21)	Gliomas, medulloblastomas Adenomatous colon polyps, adenocarcinoma
von Hippel–Lindau (VHL)	AD	Mutations in VHL gene (ch3p25)	Hemangioblastomas Retinal angiomas, renal cell carcinoma, pheochromocytoma, pancreatic tumors and cysts, endolymphatic sac tumors of the middle ear

[a]Various DNA mismatch repair gene mutations may cause a similar clinical phenotype, also referred to as Turcot syndrome, in which there is a predisposition to nonpolyposis colon cancer and brain tumors.

Abbreviations: AD, autosomal dominant; APC, adenomatous polyposis coli; AR, autosomal recessive; ch, chromosome; PTEN, phosphatase and tensin homologue; TSC, tuberous sclerosis complex.

As with other neoplasms, brain tumors arise as a result of a multistep process driven by the sequential acquisition of genetic alterations. These include loss of tumor-suppressor genes (e.g., p53 and phosphatase and tensin homolog on chromosome 10 [PTEN]) and amplification and overexpression of protooncogenes such as the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptors (PDGFR). The accumulation of these genetic abnormalities results in uncontrolled cell growth and tumor formation.

Important progress has been made in understanding the molecular pathogenesis of several types of brain tumors, including glioblastoma and medulloblastoma. Morphologically indistinguishable glioblastomas can be separated into four subtypes defined by molecular profiling: (1) classical, characterized by overactivation of the EGFR pathway; (2) proneural, characterized by overexpression of PDGFRA, mutations of the isocitrate dehydrogenase (IDH) 1 and 2 genes, and expression of neural markers; (3) mesenchymal, defined by expression of mesenchymal markers and loss of NF1; and (4) neural, characterized by overactivity of EGFR and expression of neural markers. The clinical implications of these subtypes are under study. Medulloblastoma is the other primary brain tumor that has been highly analyzed, and four molecular subtypes have also been identified: (1) the Wnt subtype is defined by a mutation in β-catenin and has an excellent prognosis; (2) the SHH subtype has mutations in PTCH1, SMO, GLI2, or SUFU and has an intermediate prognosis; (3) group 3 has elevated MYC expression and has the worst prognosis; and (4) group 4 is characterized by isochromosome 17q. Targeted therapeutics are under development for some of the medulloblastoma subtypes, especially the SHH group.

INTRINSIC "MALIGNANT" TUMORS

ASTROCYTOMAS

T ese are infiltrative tumors with a presumptive glial cell of origin. T e World Health Organization (WHO) classifies astrocytomas into four prognostic grades based on histologic features: grade I (pilocytic astrocytoma, subependymal giant cell astrocytoma); grade II (diffuse astrocytoma); grade III (anaplastic astrocytoma); and grade IV (glioblastoma). Grades I and II are considered low-grade astrocytomas, and grades III and IV are considered high-grade astrocytomas.

Low-grade astrocytoma

T ese tumors occur predominantly in children and young adults.

Grade I astrocytomas

Pilocytic astrocytomas (WHO grade I) are the most common tumor of childhood. T ey occur typically in the cerebellum but may also be found elsewhere in the neuraxis, including the optic nerves and brainstem. Frequently they appear as cystic lesions with an enhancing mural nodule. T ese are well-demarcated lesions that are potentially curable if they can be resected completely. Giant-cell subependymal astrocytomas are usually found in the ventricular wall of patients with tuberous sclerosis. T ey of en do not require intervention but can be treated surgically or with inhibitors of the mammalian target of rapamycin (mTOR).

Grade II astrocytomas

T ese are infiltrative tumors that usually present with seizures in young adults. T ey appear as nonenhancing tumors with increased T2/FLAIR signal **(Fig. 48-1)**. If feasible, patients should undergo maximal surgical resection, although complete resection is rarely possible because of the invasive nature of the tumor. Radiation therapy (RT) is helpful, but there is no difference in overall survival between RT administered postoperatively or delayed until the time of tumor progression. T ere is increasing evidence that chemotherapeutic agents such as temozolomide, an oral alkylating agent, can be helpful in some patients. T e tumor transforms to a malignant astrocytoma in the majority of patients, leading to variable survival with a median of about 5 years.

High-grade astrocytoma

Grade III (anaplastic) astrocytoma

T ese account for approximately 15–20% of high-grade astrocytomas. T ey generally present in the fourth and fif h decades of life as variably enhancing tumors. Treatment is the same as for glioblastoma, consisting of maximal safe surgical resection followed by RT with concurrent and adjuvant temozolomide or by RT and adjuvant temozolomide alone.

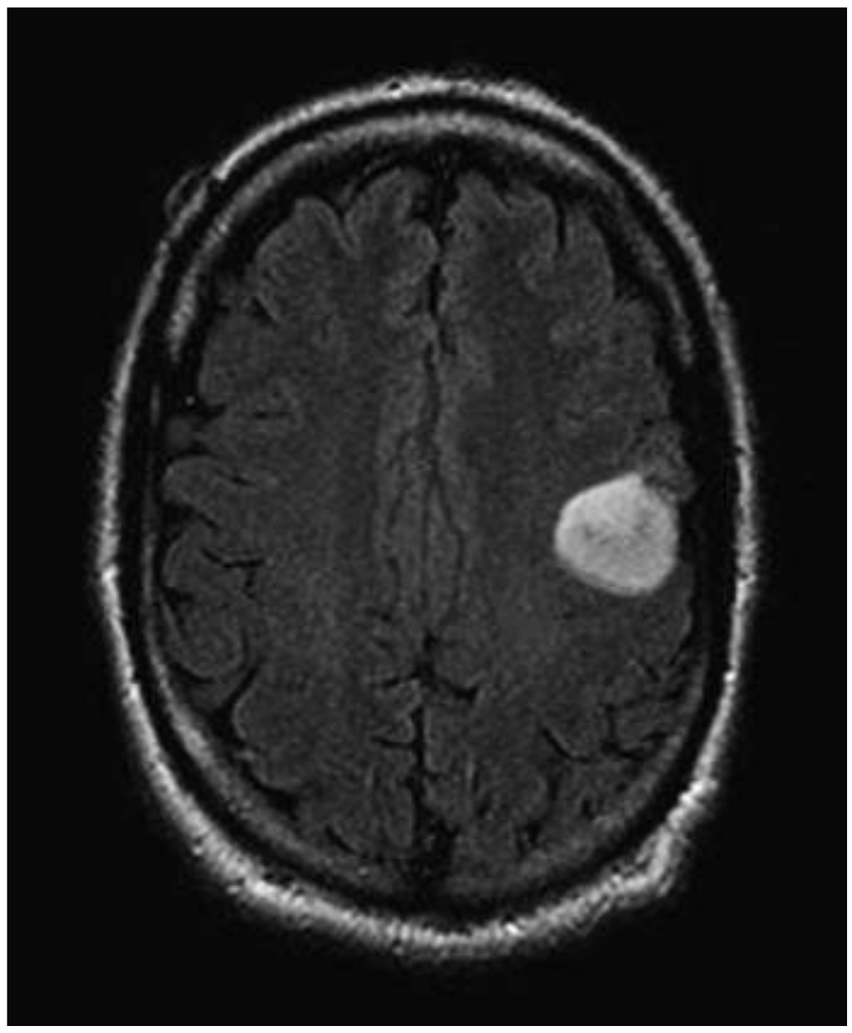


FIGURE 48-1
Fluid-attenuated inversion recovery (FLAIR) MRI of a left frontal low-grade astrocytoma. This lesion did not enhance.

Grade iv astrocytoma (glioblastoma)

Glioblastoma accounts for the majority of high-grade astrocytomas. T ey are the most common malignant primary brain tumor, with over 10,000 cases diagnosed each year in the United States. Patients usually present in the sixth and seventh decades of life with headache, seizures, or focal neurologic deficits. T e tumors appear as ring-enhancing masses with central necrosis and surrounding edema **(Fig. 48-2)**. T ese are highly infiltrative tumors, and the areas of increased T2/FLAIR signal surrounding the main tumor mass contain invading tumor cells. Treatment involves maximal surgical resection followed by partial-field external-beam RT (6000 cGy in thirty 200-cGy fractions) with concomitant temozolomide, followed by 6–12 months of adjuvant temozolomide. With this regimen, median survival is increased to 14.6 months compared to only 12 months with RT alone, and 2-year survival is increased to 27%, compared to 10% with RT alone. Patients whose tumor contains the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) are relatively resistant to temozolomide and have a worse prognosis compared to those whose tumors contain low levels of MGMT as a result of silencing of the MGMT gene by promoter hypermethylation. Implantation of biodegradable polymers containing the chemotherapeutic agent carmustine into the tumor bed af er resection of the tumor also produces a modest improvement in survival.

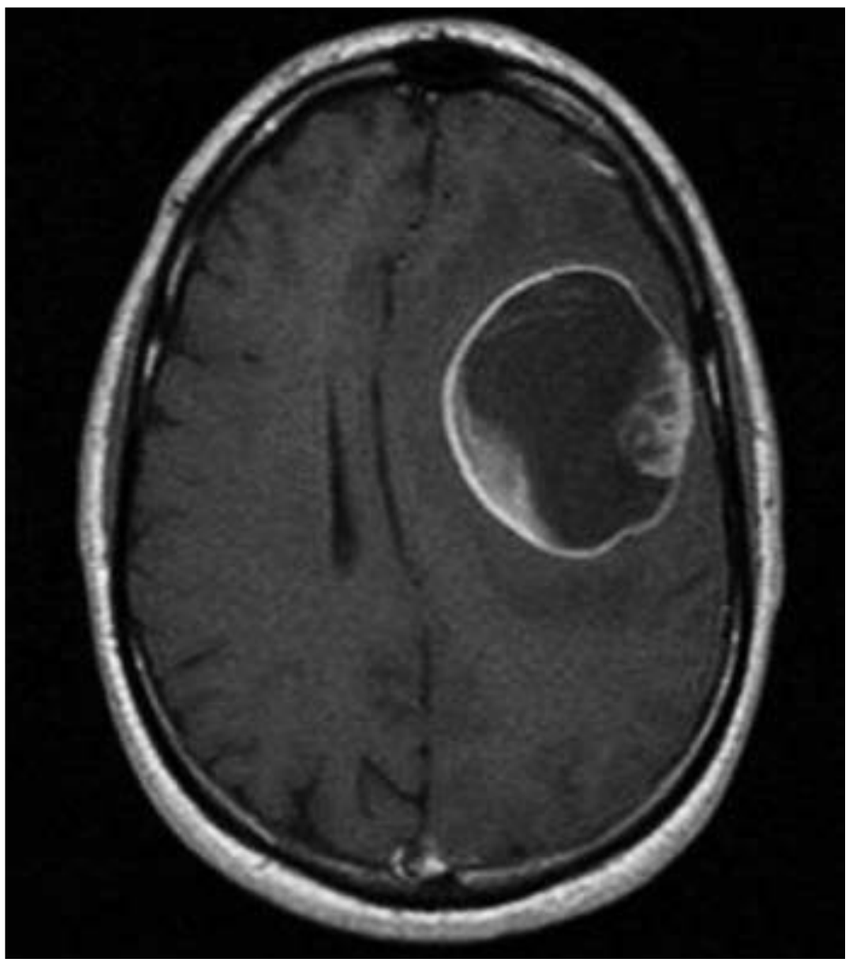
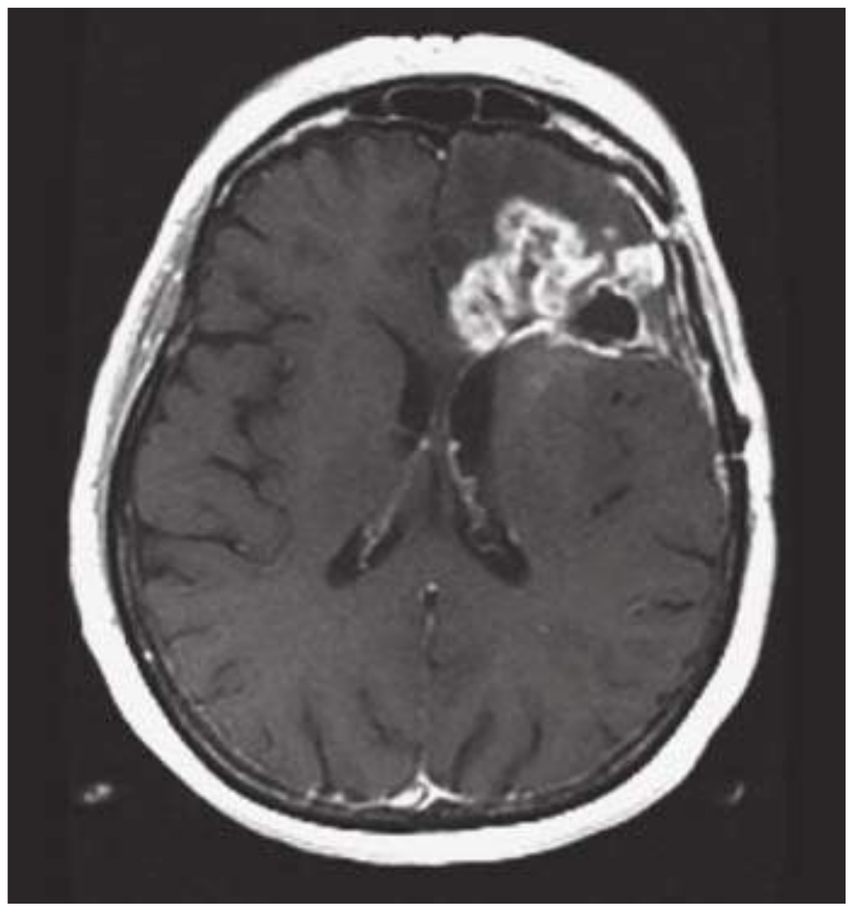


FIGURE 48-2
Postgadolinium T1 MRI of a large cystic left frontal glioblastoma.

Despite optimal therapy, glioblastomas invariably recur. Treatment options for recurrent disease may include reoperation, carmustine wafers, and alternate chemotherapeutic regimens. Reirradiation is rarely helpful. Bevacizumab, a humanized vascular endothelial growth factor (VEGF) monoclonal antibody, has activity in recurrent glioblastoma, increasing progression-free survival and reducing peritumoral edema and glucocorticoid use **(Fig. 48-3)**. Treatment decisions for patients with recurrent glioblastoma must be made on an individual basis, taking into consideration such factors as previous therapy, time to relapse, performance status, and quality of life. Whenever feasible, patients with recurrent disease should be enrolled in clinical trials. Novel therapies undergoing evaluation in patients with glioblastoma include targeted molecular agents directed at receptor tyrosine kinases and signal transduction pathways; antiangiogenic agents, especially those directed at the VEGF receptors; chemotherapeutic agents that cross the blood-brain barrier more effectively than currently available drugs; gene therapy; immunotherapy; and infusion of radiolabeled drugs and targeted toxins into the tumor and surrounding brain by means of convection-enhanced delivery.

The most important adverse prognostic factors in patients with high-grade astrocytomas are older age, histologic features of glioblastoma, poor Karnofsky performance status, and unresectable tumor. Patients whose tumor contains an unmethylated MGMT promoter resulting in the presence of the repair enzyme in tumor cells and resistance to temozolomide also have a worse prognosis.



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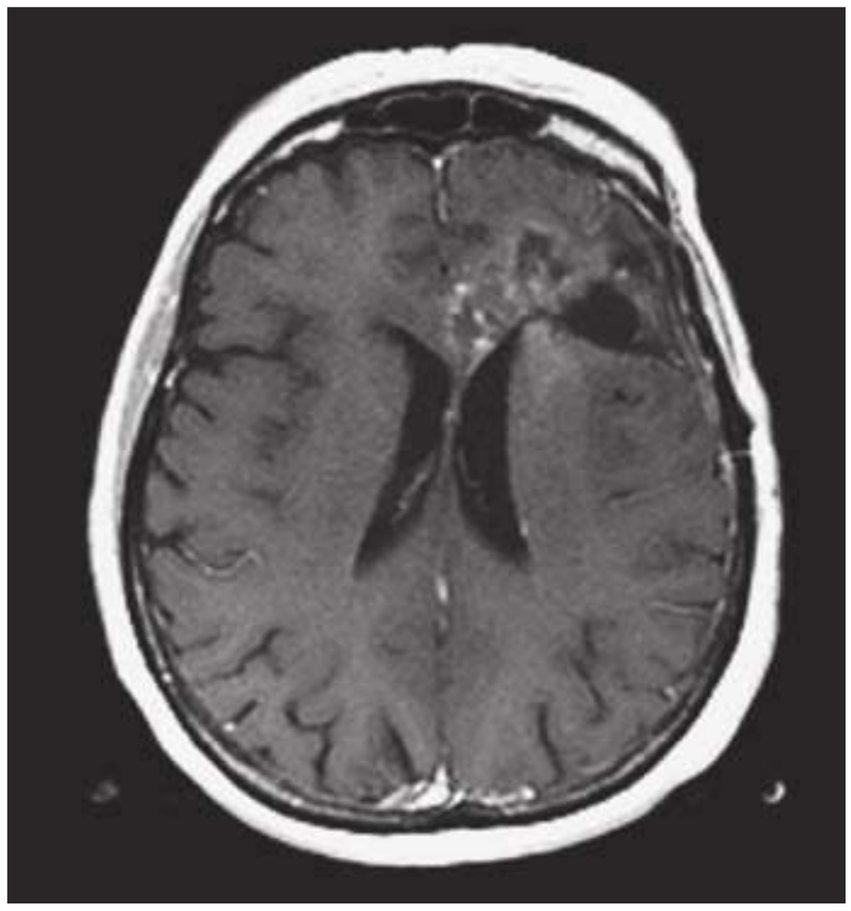


B

FIGURE 48-3
Postgadolinium T1 MRI of a recurrent glioblastoma before A and after B administration of bevacizumab. Note the decreased enhancement and mass effect.

Gliomatosis cerebri

Rarely, patients may present with a highly infiltrating, nonenhancing tumor of variable histologic grade involving more than two lobes of the brain. These tumors may be indolent initially, but will eventually behave aggressively and have a poor outcome. Treatment involves RT and temozolomide chemotherapy.

OLIGODENDROGLIOMA

Oligodendrogliomas account for approximately 15–20% of gliomas. They are classified by the WHO into well-differentiated oligodendrogliomas (grade II) or anaplastic

oligodendrogliomas (AOs) (grade III). Tumors with oligodendroglial components have distinctive pathologic features such as perinuclear clearing—giving rise to a "fried-egg" appearance—and a reticular pattern of blood vessel growth. Some tumors have both an oligodendroglial as well as an astrocytic component. T ese mixed tumors, or oligoastrocytomas (OAs), are also classified into well-differentiated OA (grade II) or anaplastic oligoastrocytomas (AOAs) (grade III).

Grade II oligodendrogliomas and OAs are generally more responsive to therapy and have a better prognosis than pure astrocytic tumors. T ese tumors present similarly to grade II astrocytomas in young adults. T e tumors are nonenhancing and of en partially calcified. T ey should be treated with surgery and, if necessary, RT and chemotherapy. Patients with oligodendrogliomas have a median survival in excess of 10 years.

AOs and AOAs present in the fourth and fif h decades as variably enhancing tumors. T ey are more responsive to therapy than grade III astrocytomas. Co-deletion of chromosomes 1p and 19q, mediated by an unbalanced translocation of 19p to 1q, occurs in 61–89% of patients with AO and 14–20% of patients with AOA. Tumors with the 1p and 19q co-deletion are particularly sensitive to chemotherapy with procarbazine, lomustine (cyclohexylchloroethylnitrosourea [CCNU]), and vincristine (PCV) or temozolomide, as well as to RT. Median survival of patients with AO or AOA is approximately 3–6 years, but those with co-deleted tumors can have a median survival of 10–14 years if treated with RT and chemotherapy.

EPENDYMOMAS

Ependymomas are tumors derived from ependymal cells that line the ventricular surface. T ey account for approximately 5% of childhood tumors and frequently arise from the wall of the fourth ventricle in the posterior fossa. Although adults can have intracranial ependymomas, they occur more commonly in the spine, especially in the filum terminale of the spinal cord where they have a myxopapillary histology. Ependymomas that can be completely resected are potentially curable. Partially resected ependymomas will recur and require irradiation. T e less common anaplastic ependymoma is more aggressive and is treated with resection and RT; chemotherapy has limited efficacy. Subependymomas are slow-growing benign lesions arising in the wall of ventricles that of en do not require treatment.

OTHER LESS COMMON GLIOMAS

Gangliogliomas and pleomorphic xanthoastrocytomas occur in young adults. T ey behave as more indolent forms of grade II gliomas and are treated in the same way. Brainstem gliomas usually occur in children or young adults. Despite treatment with RT and chemotherapy, the prognosis is poor, with a median survival of only 1 year. Gliosarcomas contain both an astrocytic as well as a sarcomatous component and are treated in the same way as glioblastomas.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma accounting for less than 3% of primary brain tumors. For unclear reasons, its incidence is increasing, particularly in immunocompetent individuals.

PCNSL in immunocompetent patients usually consists of a diffuse large B cell lymphoma. PCNSL may also occur in immunocompromised patients, usually those infected with the human immunodeficiency virus (HIV) or organ transplant recipients on immunosuppressive therapy. PCNSL in immunocompromised patients is typically large cell with immunoblastic and more aggressive features. T ese patients are usually severely immunocompromised, with CD4 counts of less than 50/mL. T e Epstein-Barr virus (EBV) frequently plays an important role in the pathogenesis of HIV-related PCNSL.

Immunocompetent patients with PCNSL are older (median 60 years) compared to patients with HIV-related PCNSL (median 31 years). PCNSL usually presents as a mass lesion, with neuropsychiatric symptoms, symptoms of increased intracranial pressure, lateralizing signs, or seizures.

On contrast-enhanced MRI, PCNSL usually appears as a densely enhancing tumor **(Fig. 48-4)**. Immunocompetent patients have solitary lesions more of en than immunosuppressed patients. Frequently there is involvement of the basal ganglia, corpus callosum, or periventricular region. Although the imaging features are of en characteristic, PCNSL can sometimes be difficult to differentiate from high-grade gliomas, infections, or demyelination. Stereotactic biopsy is necessary to obtain a histologic diagnosis. Whenever possible, glucocorticoids should be withheld until af er the biopsy has been obtained because they have a cytolytic effect on lymphoma cells and may lead to nondiagnostic tissue. In addition, patients should be tested for HIV and the extent of disease should be assessed by performing PET or CT of the body, MRI of the spine, CSF analysis, and slit-lamp examination of the eye. Bone marrow biopsy and testicular ultrasound are occasionally performed.

TREATMENT Primary Central Nervous System Lymphoma

PCNSL is more sensitive to glucocorticoids, chemotherapy, and RT than other primary brain tumors. Durable complete responses and long-term survival are possible with

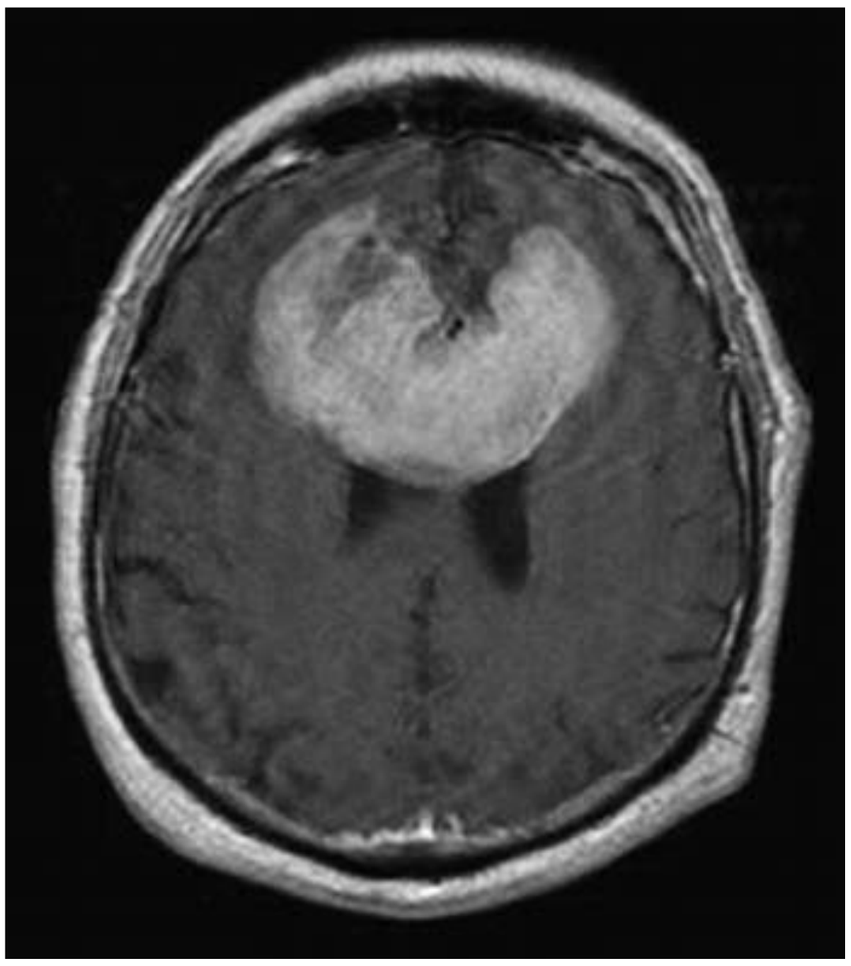


FIGURE 48-4
Postgadolinium T1 MRI demonstrating a large bifrontal primary central nervous system lymphoma (PCNSL). The periventricular location and dif use enhancement pattern are characteristic of lymphoma.

these treatments. High-dose methotrexate, a folate antagonist that interrupts DNA synthesis, produces response rates ranging from 35–80% and median survival of up to 50 months. T e combination of methotrexate with other chemotherapeutic agents such as cytarabine increases the response rate to 70–100%. T e addition of whole-brain RT to methotrexate-based chemotherapy prolongs progression-free survival but not overall survival. Furthermore, RT is associated with delayed neurotoxicity, especially in patients over the age of 60 years. As a result, full-dose RT is frequently omitted, but there may be a role for reduced-dose RT. T e anti-CD20 monoclonal antibody rituximab has activity in PCNSL and is of en incorporated into the chemotherapy regimen. For some patients, high-dose chemotherapy with autologous stem cell rescue may offer the best chance of preventing relapse. At least 50% of patients will eventually develop recurrent disease. Treatment options include RT for patients who have not had prior irradiation, re-treatment with methotrexate, as well as other agents such as temozolomide, rituximab, procarbazine, topotecan, and pemetrexed. High-dose chemotherapy with autologous stem cell rescue may have a role in selected patients with relapsed disease.

PCNSL IN IMMUNOCOMPROMISED PATIENTS PCNSL in immunocompromised patients of en produces multiple ring-enhancing lesions that can be difficult to differentiate from metastases and infections such as toxoplasmosis. T e diagnosis is usually established by examination of the CSF for cytology and EBV DNA, toxoplasmosis serologic testing, brain PET imaging for hypermetabolism of the lesions consistent with tumor instead of infection, and, if necessary, brain biopsy. Since the advent of highly active antiretroviral drugs, the incidence of HIV-related PCNSL has declined. T ese patients may be treated with whole-brain RT, high-dose methotrexate, and initiation of highly active antiretroviral therapy. In organ transplant recipients, reduction of immunosuppression may improve outcome.

MEDULLOBLASTOMAS

Medulloblastomas are the most common malignant brain tumor of childhood, accounting for approximately 20% of all primary CNS tumors among children. T ey arise from granule cell progenitors or from multipotent progenitors from the ventricular zone. Approximately 5% of children have inherited disorders with germline mutations of genes that predispose to the development of medulloblastoma. Gorlin syndrome, the most common of these inherited disorders, is due to mutations in the patched-1 (PTCH-1) gene, a key component in the sonic hedgehog pathway. Turcot syndrome, caused by mutations in the adenomatous polyposis coli (APC) gene and familial adenomatous polyposis, has also been associated with an increased incidence of medulloblastoma. Histologically, medulloblastomas are highly cellular tumors with abundant dark staining, round nuclei, and rosette formation (Homer-Wright rosettes). T ey present with headache, ataxia, and signs of brainstem involvement. On MRI they appear as densely enhancing tumors in the posterior fossa, sometimes associated with hydrocephalus. Seeding of the CSF is common. Treatment involves maximal surgical resection, craniospinal irradiation, and chemotherapy with agents such as cisplatin, lomustine, cyclophosphamide, and vincristine. Approximately 70% of patients have long-term survival but usually at the cost of significant neurocognitive impairment. A major goal of current research is to improve survival while minimizing long-term complications.

PINEAL REGION TUMORS

A large number of tumors can arise in the region of the pineal gland. T ese typically present with headache, visual symptoms, and hydrocephalus. Patients may have Parinaud syndrome characterized by impaired upgaze and accommodation. Some pineal tumors such as pineocytomas and benign teratomas can be treated simply by surgical resection. Germinomas respond to irradiation, whereas pineoblastomas and malignant germ cell tumors require craniospinal radiation and chemotherapy.

EXTRINSIC "BENIGN" TUMORS

MENINGIOMAS

Meningiomas are diagnosed with increasing frequency as more people undergo neuroimaging for various indications. T ey are now the most common primary brain tumor, accounting for approximately 35% of the total. T eir incidence increases with age. T ey tend to be more common in women and in patients with neurofibromatosis type 2. T ey also occur more commonly in patients with a past history of cranial irradiation.

Meningiomas arise from the dura mater and are composed of neoplastic meningothelial (arachnoidal cap) cells. T ey are most commonly located over the cerebral convexities, especially adjacent to the sagittal sinus, but can also occur in the skull base and along the dorsum of the spinal cord. Meningiomas are classified by the WHO into three histologic grades of increasing aggressiveness: grade I (benign), grade II (atypical), and grade III (malignant).

Many meningiomas are found incidentally following neuroimaging for unrelated reasons. T ey can also present with headaches, seizures, or focal neurologic deficits. On imaging studies they have a characteristic appearance usually consisting of a partially calcified, densely enhancing extraaxial tumor arising from the dura **(Fig. 48-5)**. Occasionally they may have a dural tail, consisting of thickened, enhanced dura extending like a tail from the mass. T e main differential diagnosis of meningioma is a dural metastasis.

If the meningioma is small and asymptomatic, no intervention is necessary and the lesion can be observed with serial MRI studies. Larger, symptomatic lesions should be resected. If complete resection is achieved, the patient is cured. Incompletely resected tumors tend to recur, although the rate of recurrence can be very slow with grade I tumors. Tumors that cannot be resected, or can only be partially removed, may benefit from treatment with external-beam RT or stereotactic radiosurgery (SRS). T ese treatments may also be helpful in patients whose tumor has recurred af er surgery. Hormonal therapy and chemotherapy are currently unproven.

Rarer tumors that resemble meningiomas include hemangiopericytomas and solitary fibrous tumors. T ese are treated with surgery and RT but have a higher propensity to recur locally or metastasize systemically.

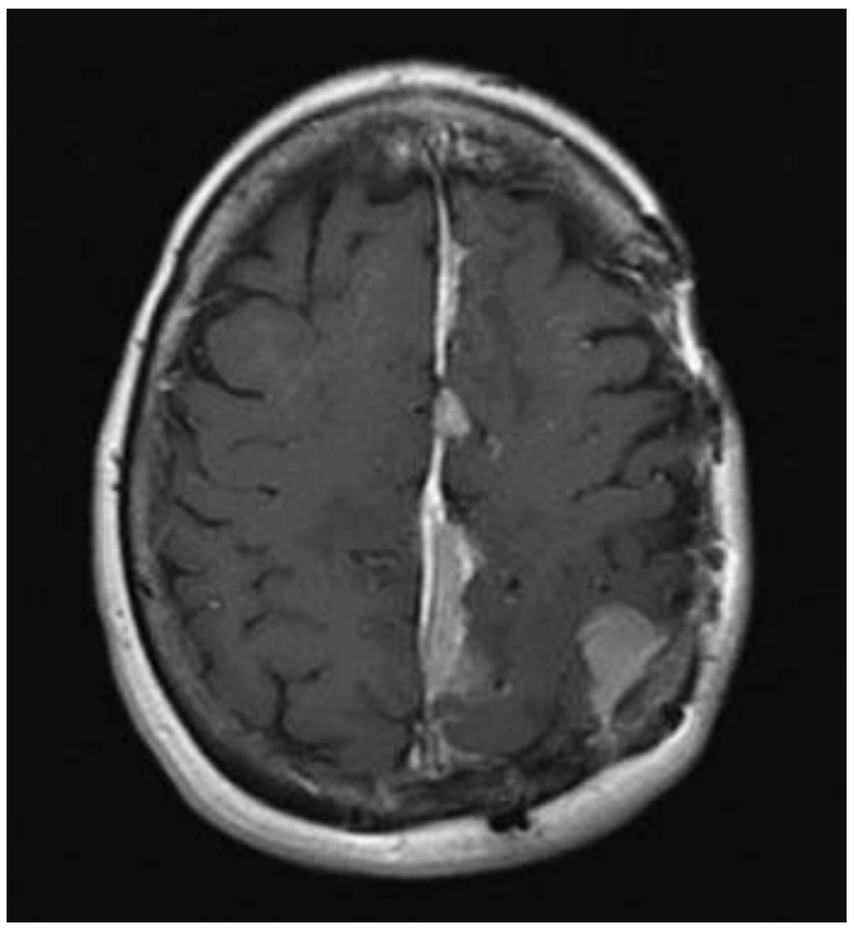


FIGURE 48-5
Postgadolinium T1 MRI demonstrating multiple meningiomas along the falx and left parietal cortex.

SCHWANNOMAS

T ese are generally benign tumors arising from the Schwann cells of cranial and spinal nerve roots. T e most common schwannomas, termed vestibular schwannomas or acoustic neuromas, arise from the vestibular portion of the eighth cranial nerve and account for approximately 9% of primary brain tumors. Patients with neurofibromatosis type 2 have a high incidence of vestibular schwannomas that are frequently bilateral. Schwannomas arising from other cranial nerves, such as the trigeminal nerve (cranial nerve V), occur with much lower frequency. Neurofibromatosis type 1 is associated with an increased incidence of schwannomas of the spinal nerve roots.

Vestibular schwannomas may be found incidentally on neuroimaging or present with progressive unilateral hearing loss, dizziness, tinnitus, or less commonly, symptoms resulting from compression of the brainstem and cerebellum. On MRI they appear as densely enhancing lesions, enlarging the internal auditory canal and of en extending into the cerebellopontine angle **(Fig. 48-6)**. T e differential diagnosis includes meningioma. Very small, asymptomatic lesions can be observed with serial MRIs. Larger lesions should be treated with surgery or SRS. T e optimal treatment will depend on the size of the tumor, symptoms, and the patient's preference. In patients with small vestibular schwannomas and relatively intact hearing, early surgical intervention increases the chance of preserving hearing.

PITUITARY TUMORS

T ese account for approximately 9% of primary brain tumors. T ey can be divided into functioning and nonfunctioning tumors. Functioning tumors are usually microadenomas (<1 cm in diameter) that secrete hormones and produce specific endocrine syndromes (e.g., acromegaly for growth hormone–secreting tumors,

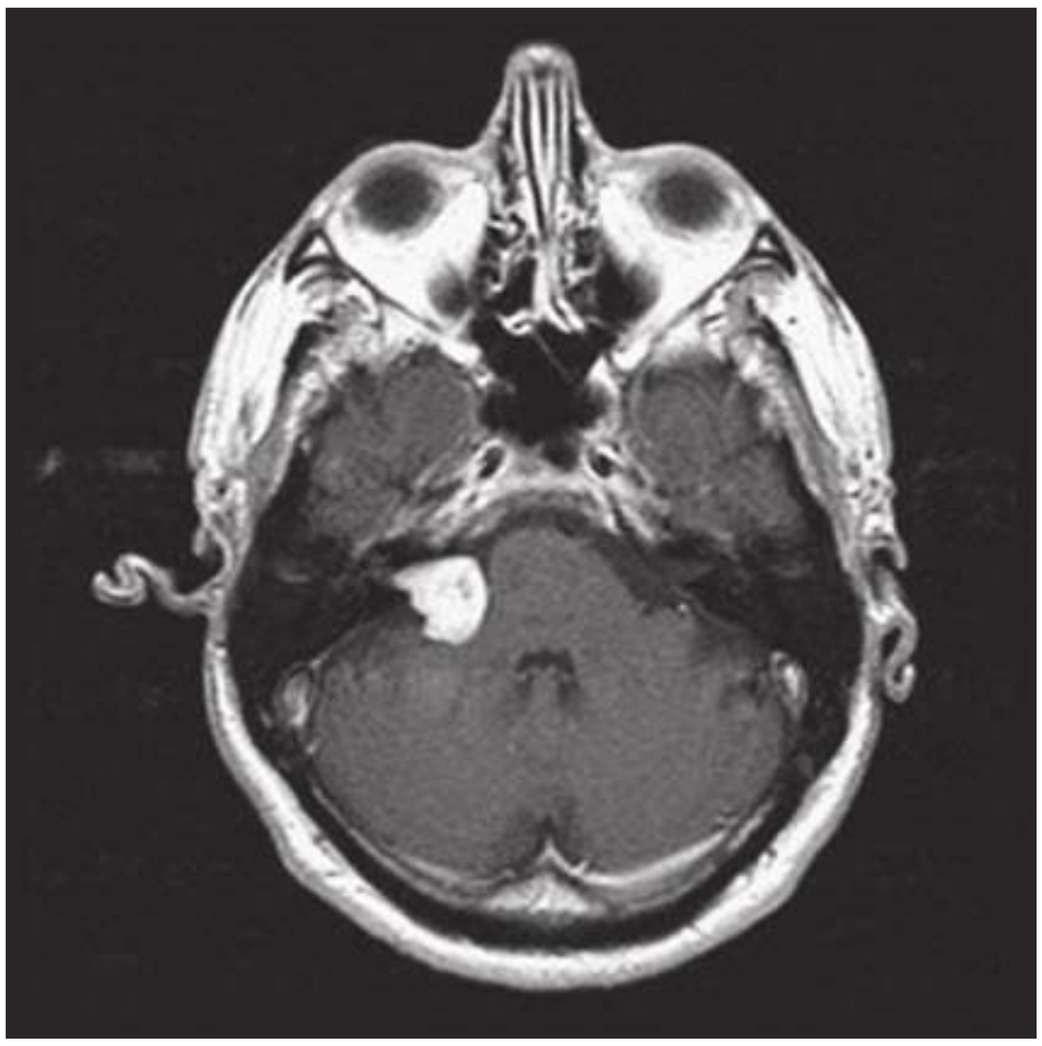


FIGURE 48-6
Postgadolinium MRI of a right vestibular schwannoma. The tumor can be seen to involve the internal auditory canal.

Cushing syndrome for adrenocorticotropic hormone [ACTH]-secreting tumors, and galactorrhea, amenorrhea, and infertility for prolactin-secreting tumors). Nonfunctioning pituitary tumors tend to be macroadenomas (>1 cm) that produce symptoms by mass effect, giving rise to headaches, visual impairment (such as bitemporal hemianopia), and hypopituitarism. Prolactin-secreting tumors respond well to dopamine agonists such as bromocriptine and cabergoline. Other pituitary tumors usually require treatment with surgery and sometimes RT or radiosurgery and hormonal therapy.

CRANIOPHARYNGIOMAS

Craniopharyngiomas are rare, usually suprasellar, partially calcified, solid, or mixed solid-cystic benign tumors that arise from remnants of Rathke's pouch. They have a bimodal distribution, occurring predominantly in children but also between the ages of 55 and 65 years. They present with headaches, visual impairment, and impaired growth in children and hypopituitarism in adults. Treatment involves surgery, RT, or a combination of the two.

OTHER BENIGN TUMORS

Dysembryoplastic neuroepithelial tumors (DNTs)

These are benign, supratentorial tumors, usually in the temporal lobe. They typically occur in children and young adults with a long-standing history of seizures. Surgical resection is curative.

Epidermoid cysts

These consist of squamous epithelium surrounding a keratin-filled cyst. They are usually found in the cerebellopontine angle and the intrasellar and suprasellar regions. They may present with headaches, cranial nerve abnormalities, seizures, or hydrocephalus. Imaging studies demonstrate extraaxial lesions with characteristics that are similar to CSF but have restricted diffusion. Treatment involves surgical resection.

Dermoid cysts

Like epidermoid cysts, dermoid cysts arise from epithelial cells that are retained during closure of the neural tube. They contain both epidermal and dermal structures such as hair follicles, sweat glands, and sebaceous glands. Unlike epidermoid cysts, these tumors usually have a midline location. They occur most frequently in the posterior fossa, especially the vermis, fourth ventricle, and suprasellar cistern. Radiographically, dermoid cysts resemble lipomas, demonstrating T1 hyperintensity and variable signal on T2. Symptomatic dermoid cysts can be treated with surgery.

Colloid cysts

These usually arise in the anterior third ventricle and may present with headaches, hydrocephalus, and, very rarely, sudden death. Surgical resection is curative, or a third ventriculostomy may relieve the obstructive hydrocephalus and be sufficient therapy.

NEUROCUTANEOUS SYNDROMES (PHAKOMATOSES)

A number of genetic disorders are characterized by cutaneous lesions and an increased risk of brain tumors. Most of these disorders have an autosomal dominant inheritance with variable penetrance.

NEUROFIBROMATOSIS TYPE 1 (NF1) (von RECKLINGHAUSEN'S DISEASE)

NF1 is an autosomal dominant disorder with an incidence of approximately 1 in 2600–3000. Approximately one-half the cases are familial; the remainder are caused by new mutations arising in patients with un-affected parents. The NF1 gene on chromosome 17q11.2 encodes a protein, neurofibromin, a guanosine triphosphatase (GTPase)-activating protein (GAP)

that modulates signaling through the ras pathway. Mutations of NF1 result in a large number of nervous system tumors including neurofibromas, plexiform neurofibromas, optic nerve gliomas, astrocytomas, and meningiomas. In addition to neurofibromas, which appear as multiple, sof , rubbery cutaneous tumors, other cutaneous manifestations of NF1 include café-au-lait spots and axillary freckling. NF1 is also associated with hamartomas of the iris termed Lisch nodules, pheochromocytomas, pseudoarthrosis of the tibia, scoliosis, epilepsy, and mental retardation.

NEUROFIBROMATOSIS TYPE 2 (NF2)

NF2 is less common than NF1, with an incidence of 1 in 25,000–40,000. It is an autosomal dominant disorder with full penetrance. As with NF1, approximately one-half the cases arise from new mutations. T e NF2 gene on 22q encodes a cytoskeletal protein, merlin (moesin, ezrin, radixin-like protein) that functions as a tumor suppressor. NF2 is characterized by bilateral vestibular schwannomas in over 90% of patients, multiple meningiomas, and spinal ependymomas and astrocytomas. Treatment of bilateral vestibular schwannomas can be challenging because the goal is to preserve hearing for as long as possible. T ese patients may also have diffuse schwannomatosis that may affect the cranial, spinal, or peripheral nerves; posterior subcapsular lens opacities; and retinal hamartomas.

TUBEROUS SCLEROSIS (BOURNEVILLE DISEASE)

T is is an autosomal dominant disorder with an incidence of approximately 1 in 5000–10,000 live births. It is caused by mutations in either the TSC1 gene, which maps to chromosome 9q34 and encodes a protein termed hamartin, or the TSC2 gene, which maps to chromosome 16p13.3 and encodes the protein tuberin. Hamartin forms a complex with tuberin, which inhibits cellular signaling through the mTOR, and acts as a negative regulator of the cell cycle. Patients with tuberous sclerosis may have seizures, mental retardation, adenoma sebaceum (facial angiofibromas), shagreen patch, hypomelanotic macules, periungual fibromas, renal angiomyolipomas, and cardiac rhabdomyomas. T ese patients have an increased incidence of subependymal nodules, cortical tubers, and subependymal giant-cell astrocytomas (SEGA). Patients frequently require anticonvulsants for seizures. SEGAs do not always require therapeutic intervention, but the most effective therapy is with the mTOR inhibitors sirolimus or everolimus, which of en decrease seizures as well as SEGA size.

TUMORS METASTATIC TO THE BRAIN

Brain metastases arise from hematogenous spread and frequently either arise from a lung primary or are associated with pulmonary metastases. Most metastases develop at the gray matter–white matter junction in the watershed distribution of the brain where intravascular tumor cells lodge in terminal arterioles. T e distribution of metastases in the brain approximates the proportion of blood flow such that about 85% of all metastases are supratentorial and 15% occur in the posterior fossa. T e most common sources of brain metastases are lung and breast carcinomas; melanoma has the greatest propensity to metastasize to the brain, being found in 80% of patients at autopsy **(Table 48-3)**. Other tumor types such as ovarian and esophageal carcinoma rarely metastasize to the brain. Prostate and breast cancer also have a propensity to metastasize to the dura and can mimic meningioma. Leptomeningeal metastases are common from hematologic malignancies and also breast and lung cancers. Spinal cord compression primarily arises in patients with prostate and breast cancer, tumors with a strong propensity to metastasize to the axial skeleton.

DIAGNOSIS OF METASTASES

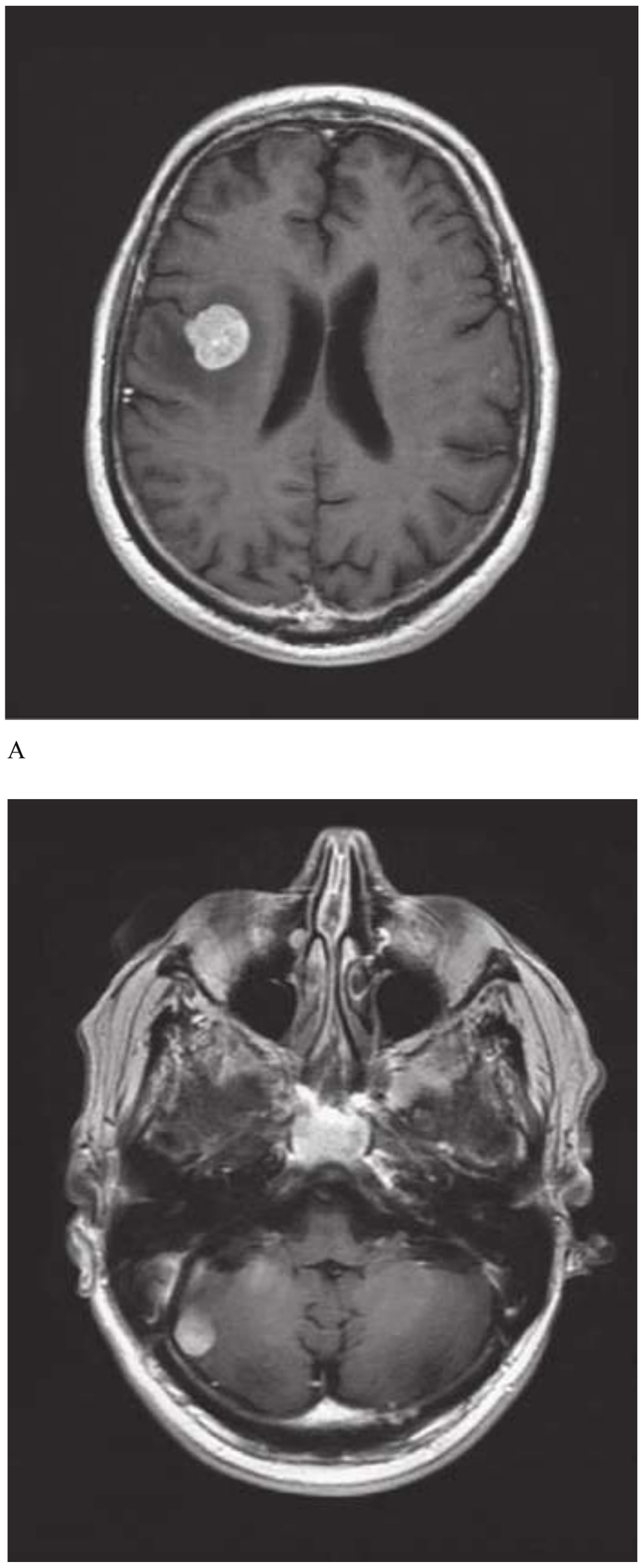
Brain metastases are best visualized on MRI, where they usually appear as well-circumscribed lesions **(Fig. 48-7)**. T e amount of perilesional edema can be highly variable, with large lesions causing minimal edema and sometimes very small lesions causing extensive edema. Enhancement may be in a ring pattern or diffuse. Occasionally, intracranial metastases will hemorrhage; although melanoma, thyroid, and kidney cancer have

TABLE 48-3

FREQUENCY OF NERVOUS SYSTEM METASTASES BY COMMON PRIMARY TUMORS

	BRAIN %	LM %	ESCC %
Lung	41	17	15
Breast	19	57	22
Melanoma	10	12	4
Prostate	1	1	10
GIT	7	—	5
Renal	3	2	7
Lymphoma	<1	10	10
Sarcoma	7	1	9
Other	11	—	18

Abbreviations: ESCC, epidural spinal cord compression; GIT, gastrointestinal tract; LM, leptomeningeal metastases.



A

B

FIGURE 48-7
Postgadolinium T1 MRI of multiple brain metastases from non-small-cell lung cancer involving the right frontal A and right cerebellar B hemispheres. Note the diffuse enhancement pattern and absence of central necrosis.

the greatest propensity to hemorrhage, the most common cause of a hemorrhagic metastasis is lung cancer because it accounts for the majority of brain metastases. The radiographic appearance of brain metastasis is nonspecific, and similar-appearing lesions can occur with infection including brain abscesses and also with demyelinating lesions, sarcoidosis, radiation necrosis in a previously treated patient, or a primary brain tumor that may be a second malignancy in a patient with systemic cancer. However, biopsy is rarely necessary for diagnosis in most patients because imaging alone in the appropriate clinical situation usually suffices. This is straightforward for the majority of patients with brain metastases because they have a known systemic cancer. However, in approximately 10% of patients, a systemic cancer may present with a brain metastasis, and if there is not an easily accessible systemic site to biopsy, then a brain lesion must be removed for diagnostic purposes.

TREATMENT Tumors Metastatic to the Brain

DEFINITIVE TREATMENT The number and location of brain metastases often determine the therapeutic options. The patient's overall condition and the current or potential control of the systemic disease are also major determinants. Brain metastases are single in approximately one-half of patients and multiple in the other half.

RADIATION THERAPY The standard treatment for brain metastases has been whole-brain radiotherapy (WBRT) usually administered to a total dose of 3000 cGy in 10 fractions. This affords rapid palliation, and approximately 80% of patients improve with glucocorticoids and RT. However, it is not curative. Median survival is only 4–6 months. More recently, SRS delivered through a variety of techniques including the gamma knife, linear accelerator, proton beam, and CyberKnife all can deliver highly focused doses of RT, usually in a single fraction. SRS can effectively sterilize the visible lesions and afford local disease control in 80–90% of patients. In addition, there are some patients who have clearly been cured of their brain metastases using SRS, whereas this is distinctly rare with WBRT. However, SRS can be used only for lesions 3 cm or less in diameter and should be confined to patients with only one to three metastases. The addition of WBRT to SRS improves disease control in the nervous system but does not prolong survival.

SURGERY Randomized controlled trials have demonstrated that surgical extirpation of a single brain metastasis followed by WBRT is superior to WBRT alone. Removal of two lesions or a single symptomatic mass, particularly if compressing the ventricular system, can also be useful. This is particularly useful in patients who have highly radioresistant lesions such as renal carcinoma. Surgical resection can afford rapid symptomatic improvement and prolonged survival. WBRT administered after complete resection of a brain metastasis improves disease control but does not prolong survival.

CHEMOTHERAPY Chemotherapy is rarely useful for brain metastases. Metastases from certain tumor types that are highly chemosensitive, such as germ cell tumors or small-cell lung cancer, may respond to chemotherapeutic regimens chosen according to the underlying malignancy. Increasingly, there are data demonstrating responsiveness of brain metastases to chemotherapy including small molecule–targeted therapy

when the lesion possesses the target. T is has been best illustrated in patients with lung cancer harboring EGFR mutations that sensitize them to EGFR inhibitors. Antiangiogenic agents such as bevacizumab may also prove efficacious in the treatment of CNS metastases.

LEPTOMENINGEAL METASTASES

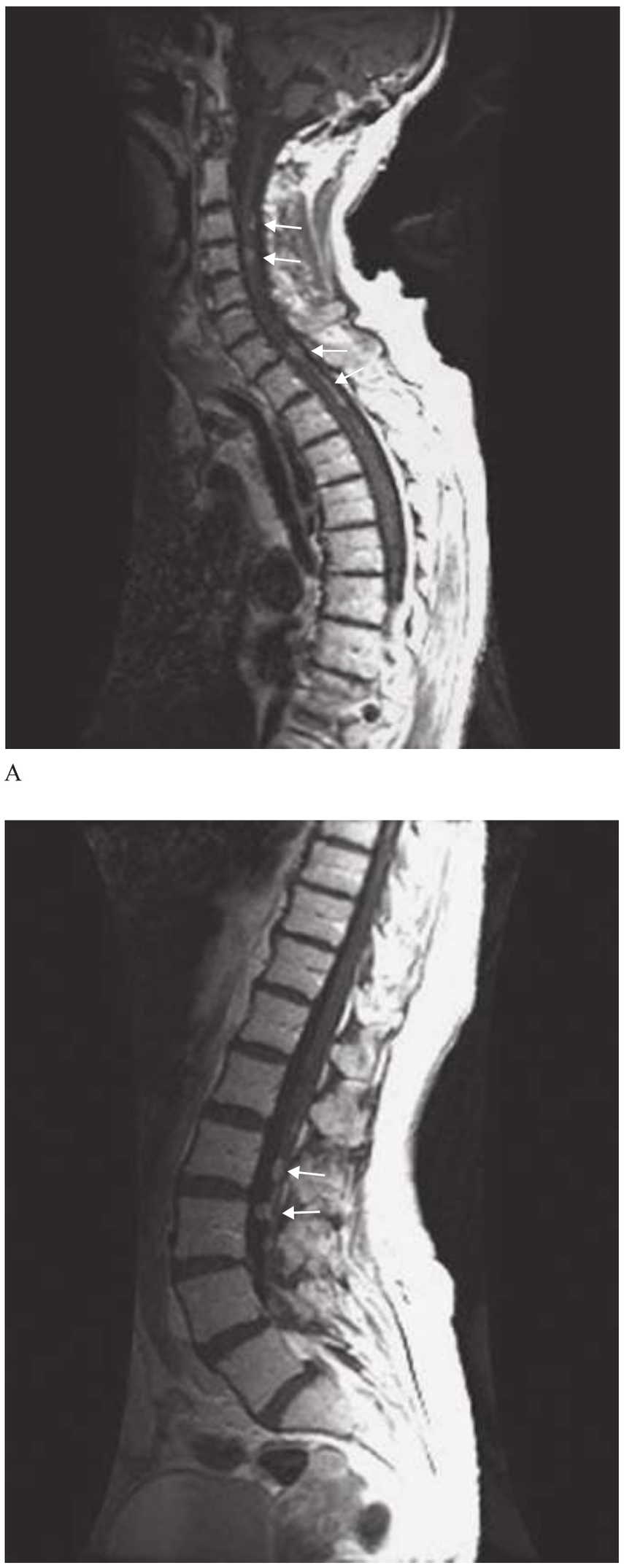
Leptomeningeal metastases are also identified as carcinomatous meningitis, meningeal carcinomatosis, or in the case of specific tumors, leukemic or lymphomatous meningitis. Among the hematologic malignancies, acute leukemia is the most common to metastasize to the subarachnoid space, and in lymphomas the aggressive diffuse lymphomas can metastasize to the subarachnoid space frequently as well. Among solid tumors, breast and lung carcinomas and melanoma most frequently spread in this fashion. Tumor cells reach the subarachnoid space via the arterial circulation or occasionally through retrograde flow in venous systems that drain metastases along the bony spine or cranium. In addition, leptomeningeal metastases may develop as a direct consequence of prior brain metastases and can develop in almost 40% of patients who have a metastasis resected from the cerebellum.

CLINICAL FEATURES

Leptomeningeal metastases are characterized clinically by multilevel symptoms and signs along the neuraxis. Combinations of lumbar and cervical radiculopathies, cranial neuropathies, seizures, confusion, and encephalopathy from hydrocephalus or raised intracranial pressure can be present. Focal deficits such as hemiparesis or aphasia are rarely due to leptomeningeal metastases unless there is direct brain infiltration, and they are more of en associated with coexisting brain lesions. New-onset limb pain in patients with breast cancer, lung cancer, or melanoma should prompt consideration of leptomeningeal spread.

LABORATORY AND IMAGING DIAGNOSIS

Leptomeningeal metastases are particularly challenging to diagnose because identification of tumor cells in the subarachnoid compartment may be elusive. MRI can be definitive in patients when there are clear tumor nodules adherent to the cauda equina or spinal cord, enhancing cranial nerves, or subarachnoid enhancement on brain imaging **(Fig. 48-8)**. Imaging is diagnostic in approximately 75% of patients and is more of en positive in patients with solid tumors. Demonstration of tumor cells in the CSF is definitive and of en considered the gold standard. However, CSF cytologic examination is positive in only 50% of patients on the first lumbar puncture and still misses 10% af er three CSF samples. CSF cytologic examination is most useful in hematologic malignancies. Accompanying CSF abnormalities include an elevated protein concentration and an elevated white count. Hypoglycorrhachia is noted in less



A

B

FIGURE 48-8

Postgadolinium MRI images of extensive leptomeningeal metastases from breast cancer. Nodules along the dorsal surface of the spinal cord A and cauda equina B are seen.

than 25% of patients but is useful when present. Identification of tumor markers or molecular confirmation of clonal proliferation with techniques such as flow cytometry within the CSF can also be definitive when present. Tumor markers are usually specific to solid tumors, and chromosomal or molecular markers are most useful in patients with hematologic malignancies. New technologies, such as rare cell capture, may enhance identification of tumor cells in the CSF.

TREATMENT Leptomeningeal Metastases

The treatment of leptomeningeal metastasis is palliative because there is no curative therapy. RT to the symptomatically involved areas, such as skull base for cranial neuropathy, can relieve pain and sometimes improve function. Whole-neuraxis RT has extensive toxicity with myelosuppression and gastrointestinal irritation as well as limited effectiveness. Systemic chemotherapy with agents that can penetrate the blood-CSF barrier may be helpful. Alternatively, intrathecal chemotherapy can be effective, particularly in hematologic malignancies. This is optimally delivered through an intraventricular cannula (Ommaya reservoir) rather than by lumbar puncture. Few drugs can be delivered safely into the subarachnoid space, and they have a limited spectrum of antitumor activity, perhaps accounting for the relatively poor response to this approach. In addition, impaired CSF flow dynamics can compromise intrathecal drug delivery. Surgery has a limited role in the treatment of leptomeningeal metastasis, but placement of a ventriculoperitoneal shunt can relieve raised intracranial pressure. However, it compromises delivery of chemotherapy into the CSF.

EPIDURAL METASTASIS

Epidural metastasis occurs in 3–5% of patients with a systemic malignancy and causes neurologic compromise by compressing the spinal cord or cauda equina. The most common cancers that metastasize to the epidural space are those malignancies that spread to bone, such as breast and prostate. Lymphoma can cause bone involvement and compression, but it can also invade the intervertebral foramens and cause spinal cord compression without bone destruction. The thoracic spine is affected most commonly, followed by the lumbar and then cervical spine.

CLINICAL FEATURES

Back pain is the presenting symptom of epidural metastasis in virtually all patients; the pain may precede neurologic findings by weeks or months. The pain is usually exacerbated by lying down; by contrast, arthritic pain

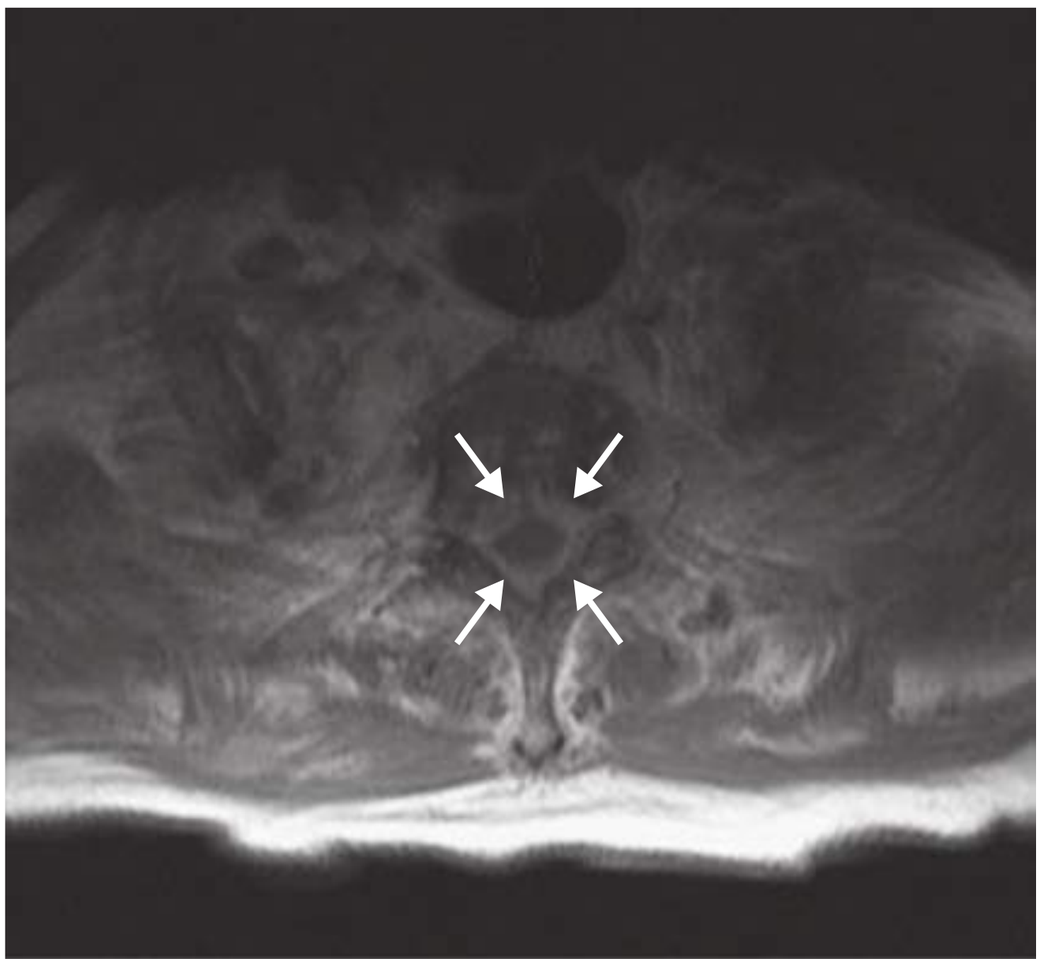


FIGURE 48-9
Postgadolinium T1 MRI showing circumferential epidural tumor around the thoracic spinal cord from esophageal cancer.

is often relieved by recumbency. Leg weakness is seen in about 50% of patients, as is sensory dysfunction. Sphincter problems are present in about 25% of patients at diagnosis.

DIAGNOSIS

Diagnosis is established by imaging, with MRI of the complete spine being the best test **(Fig. 48-9)**. Contrast is not needed to identify spinal or epidural lesions. Any patient with cancer who has severe back pain should undergo an MRI. Plain films, bone scans, or even CT scans may show bone metastases, but only MRI can reliably delineate epidural tumor. For patients unable to have an MRI, CT myelography should be performed to outline the epidural space. The differential diagnosis of epidural tumor includes epidural abscess, acute or chronic hematomas, and rarely, extramedullary hematopoiesis.

TREATMENT Epidural Metastasis

Epidural metastasis requires immediate treatment. A randomized controlled trial demonstrated the superiority of surgical resection followed by RT compared to RT alone. However, patients must be able to tolerate surgery, and the surgical procedure of choice is a complete removal of the mass, which is typically anterior to the spinal canal, necessitating an extensive approach and resection. Otherwise, RT is the mainstay of treatment and can be used for patients with radiosensitive tumors, such as lymphoma, or for those unable to undergo surgery. Chemotherapy is rarely used for epidural

metastasis unless the patient has minimal to no neurologic deficit and a highly chemosensitive tumor such as lymphoma or germinoma. Patients generally fare well if treated before there is severe neurologic deficit. Recovery af er paraparesis is better af er surgery than with RT alone, but survival is of en short due to widespread metastatic tumor.

NEUROLOGIC TOXICITY OF THERAPY

TOXICITY FROM RADIOTHERAPY

RT can cause a variety of toxicities in the CNS. T ese are usually described based on their relationship in time to the administration of RT: acute (occurring within days of RT), early delayed (months), or late delayed (years). In general, the acute and early delayed syndromes resolve and do not result in persistent deficits, whereas the late delayed toxicities are usually permanent and sometimes progressive.

Acute toxicity

Acute cerebral toxicity usually occurs during RT to the brain. RT can cause a transient disruption of the blood-brain barrier, resulting in increased edema and elevated intracranial pressure. T is is usually manifest as headache, lethargy, nausea, and vomiting and can be both prevented and treated with the administration of glucocorticoids. T ere is no acute RT toxicity that affects the spinal cord.

Early delayed toxicity

Early delayed toxicity is usually apparent weeks to months af er completion of cranial irradiation and is likely due to focal demyelination. Clinically it may be asymptomatic or take the form of worsening or reappearance of a preexisting neurologic deficit. At times a contrast-enhancing lesion can be seen on MRI/CT that can mimic the tumor for which the patient received the RT. For patients with a malignant glioma, this has been described as "pseudoprogression" because it mimics tumor recurrence on MRI but actually represents inflammation and necrotic debris engendered by effective therapy. T is is seen with increased frequency when chemotherapy, particularly temozolomide, is given concurrently with RT. Pseudoprogression can resolve on its own or, if very symptomatic, may require resection. A rare form of early delayed toxicity is the somnolence syndrome that occurs primarily in children and is characterized by marked sleepiness.

In the spinal cord, early delayed RT toxicity is manifest as a Lhermitte symptom with paresthesias of the limbs or along the spine when the patient flexes the neck. Although frightening, it is benign, resolves on its own, and does not portend more serious problems.

Late delayed toxicity

Late delayed toxicities are the most serious because they are of en irreversible and cause severe neurologic deficits. In the brain, late toxicities can take several forms, the most common of which include radiation necrosis and leukoencephalopathy. Radiation necrosis is a focal mass of necrotic tissue that is contrast enhancing on CT/MRI and may be associated with significant edema. T is may appear identical to pseudoprogression but is seen months to years af er RT and is always symptomatic. Clinical symptoms and signs include seizure and lateralizing findings referable to the location of the necrotic mass. T e necrosis is caused by the effect of RT on cerebral vasculature with resultant fibrinoid necrosis and occlusion of the blood vessels. It can mimic tumor radiographically, but unlike tumor, it is typically hypometabolic on a PET scan and has reduced perfusion on perfusion MR sequences. It may require resection for diagnosis and treatment unless it can be managed with glucocorticoids. T ere are rare reports of improvement with hyperbaric oxygen or anticoagulation, but the usefulness of these approaches is questionable.

Leukoencephalopathy is seen most commonly af er WBRT as opposed to focal RT. On T2 or FLAIR MR sequences, there is diffuse increased signal seen throughout the hemispheric white matter, of en bilaterally and symmetrically. T ere tends to be a periventricular predominance that may be associated with atrophy and ventricular enlargement. Clinically, patients develop cognitive impairment, gait disorder, and later urinary incontinence, all of which can progress over time. T ese symptoms mimic those of normal pressure hydrocephalus, and placement of a ventriculoperitoneal shunt can improve function in some patients but does not reverse the deficits completely. Increased age is a risk factor for leukoencephalopathy but not for radiation necrosis. Necrosis appears to depend on an as yet unidentified predisposition.

Other late neurologic toxicities include endocrine dysfunction if the pituitary or hypothalamus was included in the RT port. An RT-induced neoplasm can occur many years af er therapeutic RT for either a prior CNS tumor or a head and neck cancer; accurate diagnosis requires surgical resection or biopsy. In addition, RT causes accelerated atherosclerosis, which can cause stroke either from intracranial vascular disease or carotid plaque from neck irradiation.

T e peripheral nervous system is relatively resistant to RT toxicities. Peripheral nerves are rarely affected by RT, but the plexus is more vulnerable. Plexopathy develops more commonly in the brachial distribution than in the lumbosacral distribution. It must be differentiated from tumor progression in the plexus, which is usually accomplished with CT/MR imaging of the area or PET scan demonstrating tumor infiltrating the region. Clinically, tumor progression is usually painful, whereas

TABLE 48-4

NEUROLOGIC SIGNS CAUSED BY AGENTS COMMONLY USED IN PATIENTS WITH CANCER	
Acute encephalopathy (delirium)	Seizures
Methotrexate (high-dose IV, IT)	Methotrexate
Cisplatin	Etoposide (high-dose)
Vincristine	Cisplatin
Asparaginase	Vincristine
Procarbazine	Asparaginase
5-Fluorouracil (± levamisole)	Nitrogen mustard
Cytarabine (high-dose)	Carmustine
Nitrosoureas (high-dose or arterial)	Dacarbazine (intraarterial or high-dose)
Ifosfamide	Busulfan (high-dose)
Etoposide (high-dose)	Myelopathy (intrathecal drugs)
Bevacizumab (PRES)	Methotrexate
Chronic encephalopathy (dementia)	Cytarabine
Methotrexate	Thiotepa
Carmustine	Peripheral neuropathy
Cytarabine	Vinca alkaloids
Fludarabine	Cisplatin
Visual loss	Procarbazine
Tamoxifen	Etoposide
Gallium nitrate	Teniposide
Cisplatin	Cytarabine
Fludarabine	Taxanes
Cerebellar dysfunction/ataxia	Suramin
5-Fluorouracil (± levamisole)	Bortezomib
Cytarabine	
Procarbazine	

Abbreviations: IT, intrathecal; IV, intravenous; PRES, posterior reversible encephalopathy syndrome.

RT-induced plexopathy is painless. Radiation plexopathy is also more commonly associated with lymphedema of the affected limb. Sensory loss and weakness are seen in both.

TOXICITY FROM CHEMOTHERAPY

Neurotoxicity is second to myelosuppression as the dose-limiting toxicity of chemotherapeutic agents **(Table 48-4)**. Chemotherapy causes peripheral neuropathy from a number of commonly used agents, and the type of neuropathy can differ, depending on the drug. Vincristine causes paresthesias but little sensory loss and is associated with motor dysfunction, autonomic impairment (frequently ileus), and rarely cranial nerve compromise. Cisplatin causes large fiber sensory loss resulting in sensory ataxia but little cutaneous sensory loss and no weakness. The taxanes also cause a predominately sensory neuropathy. Agents such as bortezomib and thalidomide also cause neuropathy.

Encephalopathy and seizures are common toxicities from chemotherapeutic drugs. Ifosfamide can cause a severe encephalopathy, which is reversible with discontinuation of the drug and the use of methylene blue for severely affected patients. Fludarabine also causes a severe global encephalopathy that may be permanent. Bevacizumab and other anti-VEGF agents can cause posterior reversible encephalopathy syndrome. Cisplatin can cause hearing loss and less frequently vestibular dysfunction. Immunotherapy with anti-CTLA-4 monoclonal antibodies, such as ipilimumab, can cause an autoimmune hypophysitis.

CHAPTER 49

CARCINOMA OF UNKNOWN PRIMARY

Gauri R. Varadhachary ■ James L. Abbruzzese

Carcinoma of unknown primary (CUP) is a biopsy-proven malignancy for which the anatomic site of origin remains unidentified after an intensive search. CUP is one of the 10 most frequently diagnosed cancers worldwide, accounting for 3–5% of all cancers. Most investigators limit CUP to epithelial cancers and do not include lymphomas, metastatic melanomas, and metastatic sarcomas because these cancers have specific histology- and stage-based treatments that guide management.

The emergence of sophisticated imaging, robust immunohistochemistry (IHC), and genomic and proteomic tools has challenged the "unknown" designation. Additionally, effective targeted therapies in several cancers have moved the paradigm from empiricism to considering a personalized approach to CUP management. The reasons cancers present as CUP remain unclear. One hypothesis is that the primary tumor either regresses after seeding the metastasis or remains so small that it is not detected. It is possible that CUP falls on the continuum of cancer presentation where the primary has been contained or eliminated by the natural body defenses. Alternatively, CUP may represent a specific malignant event that results in an increase in metastatic spread or survival relative to the primary. Whether the CUP metastases truly define a clone that is genetically and phenotypically unique to this diagnosis remains to be determined.

CUP BIOLOGY

Studies looking for unique signature abnormalities in CUP tumors have not been positive. Abnormalities in chromosomes 1 and 12 and other complex cytogenetic abnormalities have been reported. Aneuploidy has been described in 70% of CUP patients with metastatic adenocarcinoma or undifferentiated carcinoma. The overexpression of various genes, including Ras, bcl-2 (40%), her-2 (11%), and p53 (26–53%), has been studied in CUP samples, but they have no effect on response to therapy or survival. The extent of angiogenesis in CUP relative to that in metastases from known primaries has also been evaluated, but no consistent findings have emerged. Using the Sequenom (SQM) Massarray platform, a study in consecutive CUP patients showed that the overall mutational rate was surprisingly low (18%). No "new" low-frequency mutations were found using a panel of mutations involving the P13K/AKT pathway, MEK pathway, receptors, and downstream effectors. Nevertheless, it is possible that newer "deep sequencing" techniques in select patients may yield consistent abnormalities.

CLINICAL EVALUATION

Initial CUP evaluation has two goals: search for the primary tumor based on pathologic evaluation of the metastases and determine the extent of disease. Obtaining a thorough medical history from CUP patients is essential, including paying particular attention to previous surgeries, removed lesions, and family medical history to assess potential hereditary cancers. Adequate physical examination, including a digital rectal examination in men and breast and pelvic examinations in women, should be performed based on clinical presentation.

Role of serum tumor markers and cytogenetics

Most tumor markers, including CEA, CA-125, CA 19-9, and CA 15-3, when elevated, are nonspecific and not helpful in determining the primary tumor site. Men who present with adenocarcinoma and osteoblastic metastasis should undergo a prostate-specific antigen (PSA) test. In patients with undifferentiated or poorly

differentiated carcinoma (especially with a midline tumor), elevated β-human chorionic gonadotropin (β-hCG) and α fetoprotein (AFP) levels suggest the possibility of an extragonadal germ cell (testicular) tumor. With the availability of IHC, cytogenetic studies are rarely needed.

Role of imaging studies

In the absence of contraindications, a baseline IV contrast computed tomography (CT) scan of the chest, abdomen, and pelvis is the standard of care. T is helps to search for the primary tumor, evaluate the extent of disease, and select the most accessible biopsy site. Older studies suggested that the primary tumor site is detected in 20–35% of patients who undergo a CT scan of the abdomen and pelvis, although by current definition, these patients do not have CUP. T ese studies also suggest a latent primary tumor prevalence of 20%; with more sophisticated imaging, this has decreased to ≤5% today.

Mammography should be performed in all women who present with metastatic adenocarcinoma, especially in those with adenocarcinoma and isolated axillary lymphadenopathy. Magnetic resonance imaging (MRI) of the breast is a follow-up modality in patients with axillary adenopathy and suspected occult primary breast carcinoma following a negative mammography and ultrasound. T e results of these imaging modalities can inf uence surgical management; a negative breast MRI result predicts a low tumor yield at mastectomy.

A conventional workup for a squamous cell carcinoma and cervical CUP (neck lymphadenopathy with no known primary tumor) includes a CT scan or MRI and invasive studies, including indirect and direct laryngoscopy, bronchoscopy, and upper endoscopy. Ipsilateral (or bilateral) staging tonsillectomy has been recommended for these patients. 18-Fluorodeoxyglucose positron emission tomography (18-FDG-PET) scans are useful in this patient population and may help guide the biopsy; determine the extent of disease; facilitate the appropriate treatment, including planning radiation fields; and help with disease surveillance. A smaller radiation field encompassing the primary (when found) and metastatic adenopathy decreases the risk of chronic xerostomia. Several studies have evaluated the utility of PET in patients with squamous cervical CUP, and head and neck primary tumors were identified in ~21–30%.

T e diagnostic contribution of PET to the evaluation of other CUP (outside of the neck adenopathy indication) remains controversial and is not routinely recommended. PET-CT can be helpful for patients who are candidates for surgical intervention for solitary metastatic disease because the presence of disease outside the primary site may affect surgical planning.

Invasive studies, including upper endoscopy, colonoscopy, and bronchoscopy, should be limited to symptomatic patients or those with laboratory, imaging, or pathologic abnormalities that suggest that these techniques will result in a high yield in finding a primary cancer.

Role of pathologic studies

A detailed pathologic examination of the most accessible biopsied tissue specimen is mandatory in CUP patients. Pathologic evaluation typically consists of hematoxylin and eosin stains and immunohistochemical tests.

Light microscopy evaluation

Adequate tissue obtained preferably by excisional biopsy or core-needle biopsy (instead of only a fine-needle aspiration) is stained with hematoxylin and eosin and subjected to light microscopic examination. On light microscopy, 60–65% of CUP is adenocarcinoma, and 5% is squamous cell carcinoma. T e remaining 30–35% is poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or poorly differentiated neoplasm. A small percentage of lesions are diagnosed as neuroendocrine cancers (2%), mixed tumors (adenosquamous or sarcomatoid carcinomas), or undifferentiated neoplasms **(Table 49-1)**.

Role of immunohistochemical analysis

Immunohistochemical stains are peroxidase-labeled antibodies against specific tumor antigens that are used to define tumor lineage. T e number of available immunohistochemical stains is ever-increasing. However, in CUP cases, more is not necessarily better, and immunohistochemical stains should be used in conjunction with the patient's clinical presentation and imaging studies to select the best therapy. Communication between the clinician and pathologist is essential. No stain is 100% specific, and overinterpretation should be avoided. PSA and thyroglobulin tissue markers, which are positive in

TABLE 49-1

MAJOR HISTOLOGIES IN CARCINOMA OF UNKNOWN PRIMARY

HISTOLOGY	PROPORTION, %
Well to moderately differentiated adenocarcinoma	60
Squamous cell cancer	5
Poorly differentiated adenocarcinoma, poorly differentiated carcinoma	30
Neuroendocrine	2
Undifferentiated malignancy	3

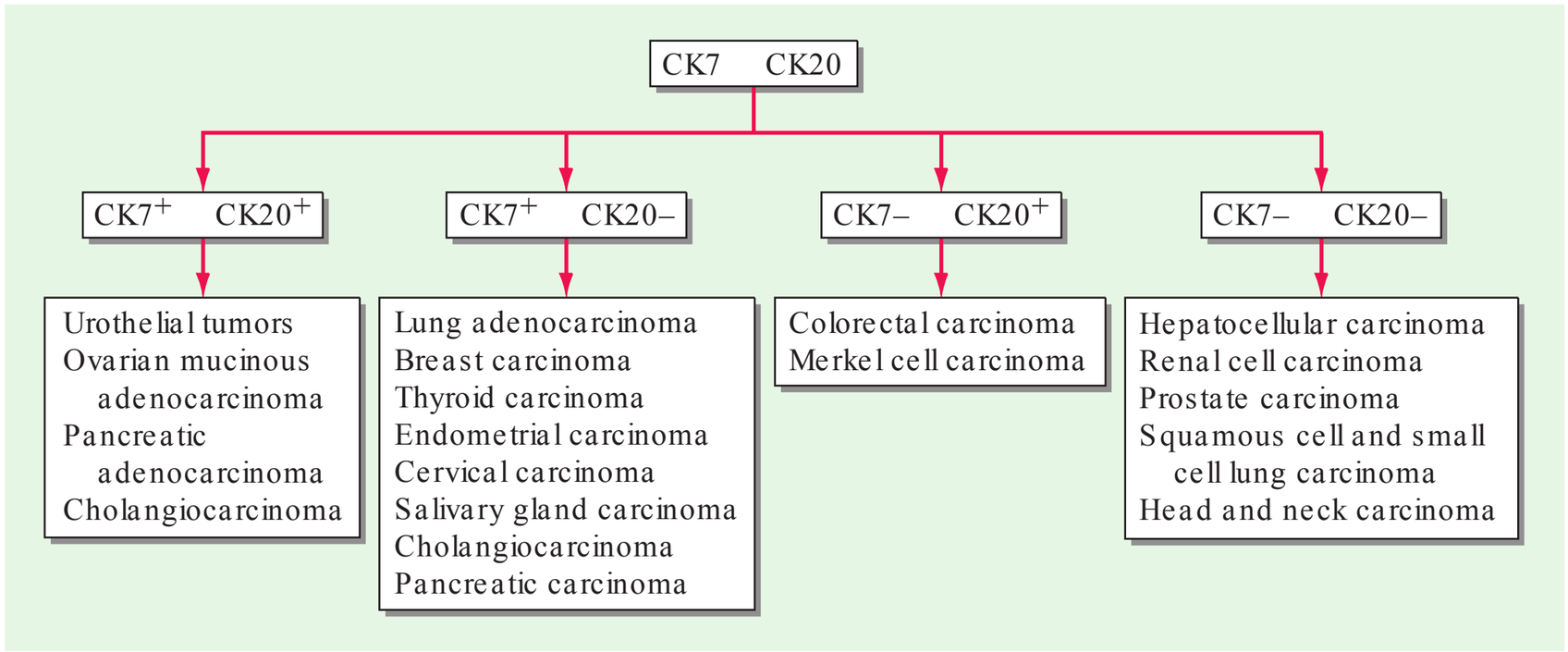


FIGURE 49-1
Approach to cytokeratin (CK7 and CK20) markers used in adenocarcinoma of unknown primary.

prostate and thyroid cancer, respectively, are the most specific of the current marker panel. However, these cancers rarely present as CUP, so the yield of these tests may be low. **Fig. 49-1** delineates a simple algorithm for immunohistochemical staining in CUP cases. **Table 49-2** lists additional tests that may be useful to further define the tumor lineage. A more comprehensive algorithm may improve the diagnostic accuracy but can make the process complex. With the use of immunohistochemical markers, electron microscopic analysis, which is time-consuming and expensive, is rarely needed.

There are >20 subtypes of cytokeratin (CK) intermediate filaments with different molecular weights and differential expression in various cell types and cancers. Monoclonal antibodies to specific CK subtypes have been used to help classify tumors according to their site of origin; commonly used CK stains in adenocarcinoma CUP are CK7 and CK20. CK7 is found in tumors of the lung, ovary, endometrium, breast, and upper gastrointestinal tract including pancreaticobiliary cancers, whereas CK20 is normally expressed in the gastrointestinal epithelium, urothelium, and Merkel cells.

TABLE 49-2

SELECT IMMUNOHISTOCHEMICAL STAINS USEFUL IN THE DIAGNOSIS OF CARCINOMA OF UNKNOWN PRIMARY (CUP)

LIKELY PRIMARY PROFILE	COMMONLY CONSIDERED IHC TO ASSIST IN DIFFERENTIAL DIAGNOSIS OF CUP[a]
Breast	Estrogen receptor (ER), gross cystic disease fibrous protein-15 (GCDFP-15), mammaglobin, Her-2/neu
Ovarian/mullerian	Estrogen receptor (ER), Wilms' tumor gene (WT-1), CK7, PAX8, PAX2
Lung adenocarcinoma	Thyroid transcription factor (TTF-1; nuclear staining), napsin A, surfactant protein A precursor (SP-A1)
Germ cell	β-hCG, AFP, OCT3/4, CKIT, CD30 (embryonal), SALL4
Prostate	PSA, α-methylacyl CoA racemase/P504S (AMACR/P504S), P501S (prostein), and prostate-specific membrane antigen (PSMA)
Intestinal	CK7, CK20, CDX-2, carcinoembryonic antigen (CEA)
Neuroendocrine	Chromogranin, synaptophysin, CD56
Sarcoma	Desmin (desmoid tumors), factor VIII (angiosarcomas), CD31, smooth muscle actin (leiomyosarcoma), MyoD1 (rhabdomyosarcoma)
Renal	RCC, CD10, PAX8
Hepatocellular carcinoma	Hep par-1, arginase-1 (Arg-1), TTF-1 (granular cytoplasmic staining)
Melanoma	S100, vimentin, HMB-45, tyrosinase and melan-A
Urothelial	CK7, CK20, thrombomodulin
Mesothelioma	Calretinin, WT-1
Lymphoma	Leukocyte common antigen (LCA), CD3, CD4, CD5, CD20, CD45
Squamous cell carcinoma (SCC)	p63, p40 (lung SCC), CK5/6

[a]Patterns emerging from coexpression of stains are better than individual stains to suggest putative primary site. Even with optimization, no IHC panel is 100% sensitive or specific (e.g., ovarian mucinous carcinoma can exhibit positivity with intestinal markers).
Abbreviations: AFP, α fetoprotein; β-hCG, β human chorionic gonadotropin; CUP, carcinoma of unknown primary; IHC, immunohistochemistry; PSA, prostate-specific antigen.

The nuclear CDX-2 transcription factor, which is the product of a homeobox gene necessary for intestinal organogenesis, is often used to aid in the diagnosis of gastrointestinal adenocarcinomas.

Thyroid transcription factor 1 (TTF-1) nuclear staining is typically positive in lung and thyroid cancers. Approximately 68% of adenocarcinomas and 25% of squamous cell lung cancers stain positive for TTF-1, which helps differentiate a lung primary tumor from metastatic adenocarcinoma in a pleural effusion, the mediastinum, or the lung parenchyma.

Gross cystic disease fibrous protein-15, a 15-kDa monomer protein, is a marker of apocrine differentiation that is detected in 62–72% of breast carcinomas. UROIII, high-molecular-weight cytokeratin, thrombomodulin, and CK20 are the markers used to diagnose lesions of urothelial origin.

IHC performs the best when used in groups that give rise to patterns that are strongly indicative of certain profiles. For example, the TTF-1/CK7+ and CK20+/CDX-2+/CK7– phenotypes have been reported as very suggestive of lung and lower gastrointestinal cancer profiles, respectively, although these patterns have not been validated prospectively in the absence of a primary cancer. IHC is not without its limitations; several factors affect tissue antigenicity (antigen retrieval, specimen processing, and fixation), interpretation of stains in tumor (nuclear, cytoplasmic, membrane) versus normal tissue, inter- and intraobserver variability, and tissue heterogeneity and inadequacy (given small biopsy sizes). Communication with the pathologist is critical to determine if additional tissue will be beneficial in the pathologic evaluation.

Role of tissue of origin molecular profiling

In the absence of a known primary, developing therapeutic strategies for CUP is challenging. The current diagnostic yield with imaging and immunochemistry is ~20–30% for CUP patients. The use of gene expression studies holds the promise of substantially increasing this yield. Gene expression profiles are most commonly generated using quantitative reverse transcriptase polymerase chain reaction (RT-PCR) or DNA microarray.

Neural network programs have been used to develop predictive algorithms from the gene expression profiles. Typically, a training set of gene profiles from known cancers (preferably from metastatic sites) is used to train the software. The program can then be used to predict the putative origin of a test tumor and presumably of true CUP. Comprehensive gene expression databases that have become available for common malignancies may also be useful in CUP. These approaches have been effective in testing against known primary cancers and their metastases.

mRNA- or microRNA-based tissue of origin molecular profiling assays have been studied in prospective and retrospective CUP trials. Most of the CUP studies have evaluated assay performance, although the challenge with validating the accuracy of an assay for CUP is that, by definition, the primary cancer diagnosis cannot be verified. Thus, current estimates of tissue of origin test accuracy have relied on indirect metrics including comparison with IHC, clinical presentation, and appearance of latent primaries. Using these measures, the assays suggest a plausible primary in ~70% of patients studied. The only outcomes-based study is a single-arm study reporting a median survival of 12.5 months for patients who received assay-directed site-specific therapy. Firm conclusions of therapeutic impact cannot be drawn from this study given the nonrandomized design, statistical biases, confounding variables including use of subsequent lines of (empiric) therapy, and the heterogeneity of the CUP cancers. Additional studies are needed to better understand the clinical influence of tissue of origin profiling tools and how these assays complement IHC and help guide therapy.

TREATMENT Carcinoma of Unknown Primary

GENERAL CONSIDERATIONS The treatment of CUP continues to evolve, albeit slowly. The median survival duration of most patients with disseminated CUP is ~6–10 months. Systemic chemotherapy is the primary treatment modality in most patients with disseminated disease, but the careful integration of surgery, radiation therapy, and even periods of observation is important in the overall management of this condition **(Figs. 49-2 and 49-3)**. Prognostic factors include performance status, site and number of metastases, response to chemotherapy, and serum lactate dehydrogenase (LDH) levels. Culine and colleagues developed a prognostic model using performance status and serum LDH levels, which allowed the assignment of patients into two subgroups with divergent outcomes. Future prospective trials using this prognostic model are warranted. Clinically, some CUP diagnoses fall into a favorable prognostic subset. Others, including those with disseminated CUP, do not and have a more unfavorable prognosis.

TREATMENT OF FAVORABLE CUP SUBSETS

Women with Isolated Axillary Adenopathy Women with isolated axillary adenopathy with adenocarcinoma or carcinoma are usually treated for stage II or III breast cancer based on pathologic findings. These patients should undergo a breast MRI if mammogram and ultrasound are negative. Radiation therapy to the ipsilateral breast is indicated if the breast MRI is positive. Chemotherapy and/or hormonal therapy are indicated based on patient's age (premenopausal or postmenopausal), nodal disease bulk, and hormone receptor status **(Chap. 38)**. It is important to verify that the pathology suggests a breast cancer profile (morphology, immunohistochemical breast markers including estrogen receptor, mammoglobin, GCDFP-15, HER-2 gene expression) before embarking on a breast cancer therapeutic program.

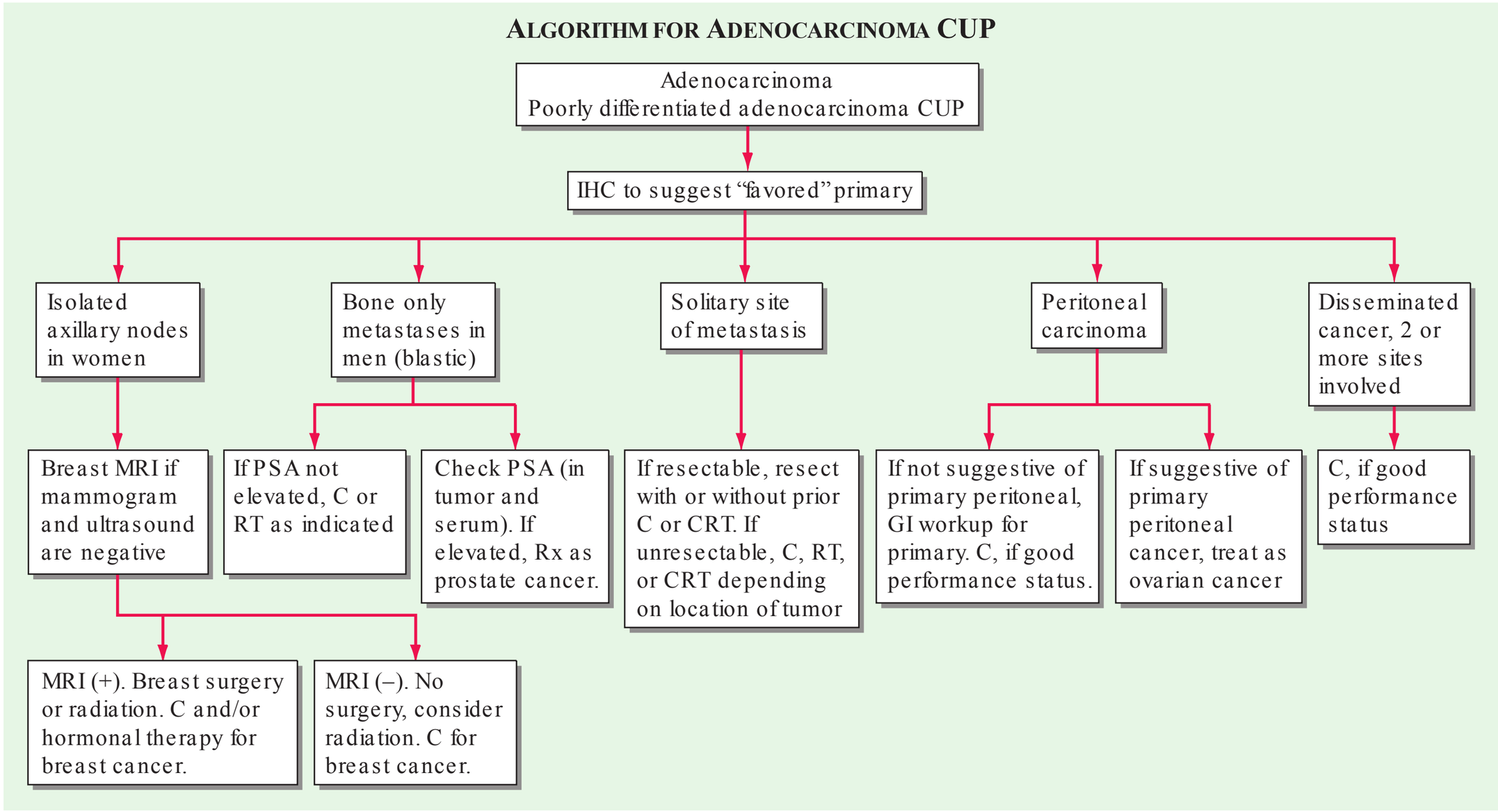


FIGURE 49-2

Treatment algorithm for adenocarcinoma and poorly differentiated adenocarcinoma of unknown primary (CUP). C, chemotherapy; CRT, chemoradiation; GI, gastrointestinal; IHC, immunohistochemistry; MRI, magnetic resonance imaging; PSA, prostate-specif c antigen; RT, radiation.

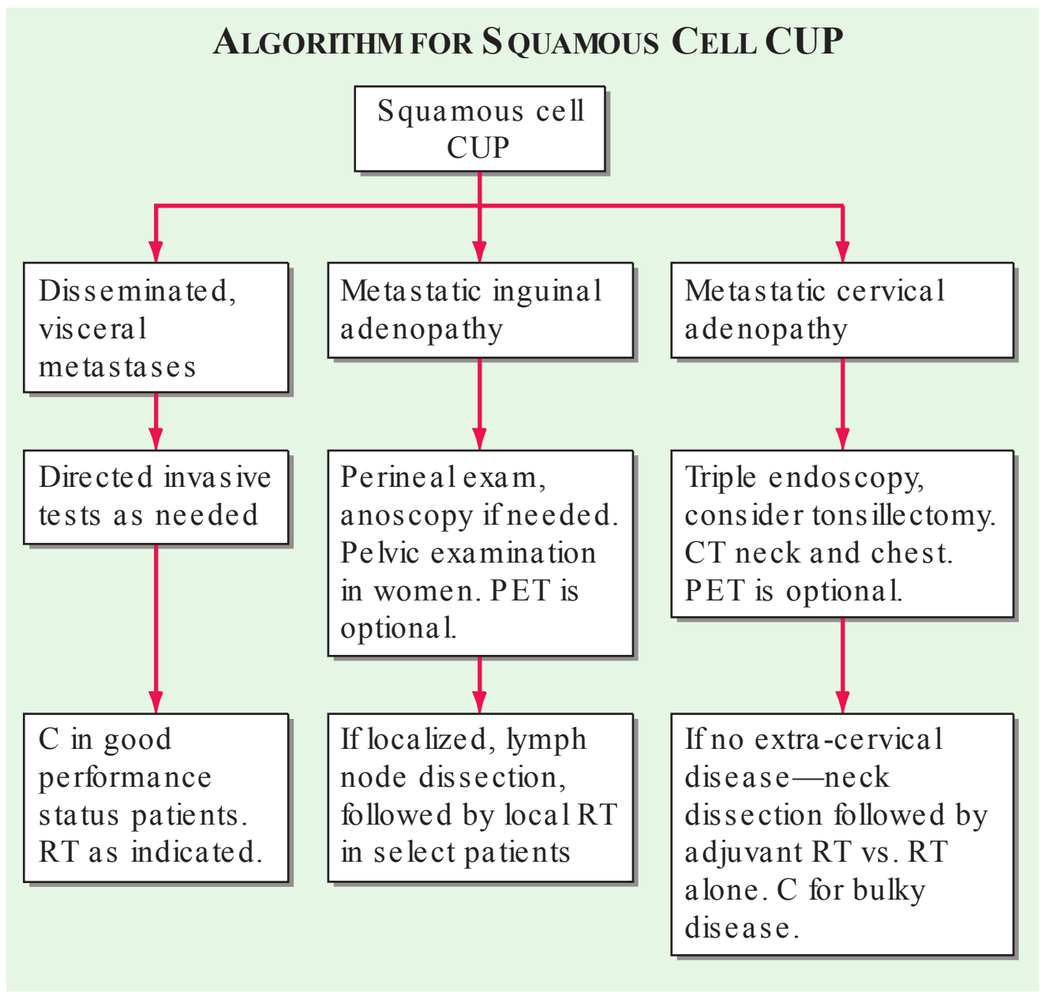


FIGURE 49-3

Treatment algorithm for squamous cell carcinoma of unknown primary (CUP). C, chemotherapy; CT, computed tomography; PET, positron emission tomography; RT, radiation.

WOMEN WITH PERITONEAL CARCINOMATOSIS The term primary peritoneal papillary serous carcinoma (PPSC) has been used to describe CUP with carcinomatosis with the pathologic and laboratory (elevated CA-125 antigen) characteristics of ovarian cancer but no ovarian primary tumor identified on transvaginal sonography or laparotomy. Studies suggest that ovarian cancer and PPSC, which are both of müllerian origin, have similar gene expression profiles. Similar to patients with ovarian cancer, patients with PPSC are candidates for cytoreductive surgery, followed by adjuvant taxane- and platinum-based chemotherapy. In one retrospective study of 258 women with peritoneal carcinomatosis who had undergone cytoreductive surgery and chemotherapy, 22% of patients had a complete response to chemotherapy; the median survival duration was 18 months (range 11–24 months). However, not all peritoneal carcinomatosis in women is PPSC. Careful pathologic evaluation can help diagnose a colon cancer profile (CDX-2+, CK-20+, CK7−) or a pancreaticobiliary cancer or even a mislabeled peritoneal mesothelioma (calretinin positive).

POORLY DIFFERENTIATED CARCINOMA WITH MIDLINE ADENOPATHY Men with poorly differentiated or undifferentiated carcinoma that presents as a midline adenopathy should be evaluated for extragonadal germ cell malignancy. If diagnosed and treated as such, they often experience a good response to treatment with platinum-based combination chemotherapy. Response

rates of >50% have been noted, and long-term survival rates of 10–15% long have been reported. Older patients (especially smokers) who present with mediastinal adenopathy are more likely to have a lung or head-and-neck cancer profile.

NEUROENDOCRINE CARCINOMA Low-grade neuroendocrine carcinoma often has an indolent course, and treatment decisions are based on symptoms and tumor bulk. Urine 5-HIAA and serum chromogranin may be elevated and can be followed as markers. Often the patient is treated with somatostatin analogues alone for hormone-related symptoms (diarrhea, flushing, nausea). Specific local therapies or systemic therapy would only be indicated if the patient is symptomatic with local pain secondary to significant growth of the metastasis or the hormone-related symptoms are not controlled with endocrine therapy. Patients with high-grade neuroendocrine carcinoma are treated as having small-cell lung cancer and are responsive to chemotherapy; 20–25% show a complete response, and up to 10% patients survive more than 5 years.

SQUAMOUS CELL CARCINOMA PRESENTING AS NECK ADENOPATHY Patients with early-stage squamous cell carcinoma involving the cervical lymph nodes are candidates for node dissection and radiation therapy, which can result in long-term survival. The role of chemotherapy in these patients is undefined, although chemoradiation therapy or induction chemotherapy is often used and is beneficial in bulky N2/N3 lymph node disease.

SOLITARY METASTATIC SITE Patients with solitary metastases can also experience good treatment outcomes. Some patients who present with locoregional disease are candidates for aggressive trimodality management; both prolonged disease-free interval and occasionally cure are possible.

MEN WITH BLASTIC SKELETAL METASTASES AND ELEVATED PSA Blastic bone-only metastasis is a rare presentation, and elevated serum PSA or tumor staining with PSA may provide confirmatory evidence of prostate cancer in these patients. Those with elevated levels are candidates for hormonal therapy for prostate cancer, although it is important to rule out other primary tumors (lung most common).

MANAGEMENT OF DISSEMINATED CUP Patients who present with liver, brain, and adrenal metastatic disease usually have a poor prognosis. Patients with nonserous papillary primary peritoneal carcinomatosis can have a large differential diagnosis, which is mainly of gastrointestinal profile and includes gastric, appendiceal, colon, and pancreaticobiliary profiles.

Traditionally, platinum-based combination chemotherapy regimens have been used to treat CUP. Several broadly used regimens have been studied in the last two decades; these include paclitaxel-carboplatin, gemcitabine-cisplatin, gemcitabine-oxaliplatin, and irinotecan and fluoropyrimidine-based therapies. These chemotherapeutic agents used as empiric regimens have shown a response rate of 25–40%, and their use obtains median survival times of 6–13 months.

Outside of favorable subsets, there is a small group of patients with a "definitive" IHC. These patients usually have a single diagnosis based on their clinicopathologic presentation and are often treated for the putative primary tumor. This does not guarantee a response, although it increases the probability of response when select drugs are chosen from a class of drugs known to work in that cancer type. Patients who do not fall into those categories are candidates for broad-spectrum platinum-based regimens, clinical trials, and additional trial-based genomic and proteomic tests. Today, we do not have effective drugs for several CUP cancer profiles, and treatments overlap for some cancers. However, as novel therapies are developed for additional known cancers, tissue of origin and assessment of molecular features of the tumor will be important and might direct more selective treatment.

SUMMARY

Patients with CUP should undergo a directed diagnostic search for the primary tumor on the basis of clinical and pathologic data. Subsets of patients have prognostically favorable disease, as defined by clinical or histologic criteria, and may substantially benefit from aggressive treatment and expect prolonged survival. However, for most patients who present with advanced CUP, the prognosis remains poor with early resistance to available cytotoxic therapy. The current focus has shifted away from empirical chemotherapeutic trials to understanding the metastatic phenotype, tissue of origin profiling, and evaluating molecular targets in CUP patients.

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SECTION X

ENDOCRINE NEOPLASIA

CHAPTER 50

THYROID CANCER

J. Larry Jameson ■ Susan J. Mandel ■ Anthony P. Weetman

PHYSICAL EXAMINATION

In addition to the examination of the thyroid itself, the physical examination should include a search for signs of abnormal thyroid function and the extrathyroidal features of ophthalmopathy and dermopathy (see below). Examination of the neck begins by inspecting the seated patient from the front and side and noting any surgical scars, obvious masses, or distended veins. The thyroid can be palpated with both hands from behind or while facing the patient, using the thumbs to palpate each lobe. It is best to use a combination of these methods, especially when nodules are small. The patient's neck should be slightly flexed to relax the neck muscles. After locating the cricoid cartilage, the isthmus, which is attached to the lower one-third of the thyroid lobes, can be identified and then followed laterally to locate either lobe (normally, the right lobe is slightly larger than the left). By asking the patient to swallow sips of water, thyroid consistency can be better appreciated as the gland moves beneath the examiner's fingers.

Features to be noted include thyroid size, consistency, nodularity, and any tenderness or fixation. An estimate of thyroid size (normally 12–20 g) should be made, and a drawing is often the best way to record findings. However, ultrasound is the method of choice when it is important to determine thyroid size accurately. The size, location, and consistency of any nodules should also be defined. A bruit or thrill over the gland, located over the insertion of the superior and inferior thyroid arteries (supero- or inferolaterally), indicates increased vascularity, as occurs in hyperthyroidism. If the lower borders of the thyroid lobes are not clearly felt, a goiter may be retrosternal. Large retrosternal goiters can cause venous distention over the neck and difficulty breathing, especially when the arms are raised (Pemberton's sign). With any central mass above the thyroid, the tongue should be extended, as thyroglossal cysts then move upward. The thyroid examination is not complete without assessment for lymphadenopathy in the supraclavicular and cervical regions of the neck.

Radioiodine uptake and thyroid scanning

The thyroid gland selectively transports radioisotopes of iodine (^{123}I, ^{125}I, ^{131}I) and ^{99m}Tc pertechnetate, allowing thyroid imaging and quantitation of radioactive tracer fractional uptake.

Nuclear imaging of Graves' disease is characterized by an enlarged gland and increased tracer uptake that is distributed homogeneously. Toxic adenomas appear as focal areas of increased uptake, with suppressed tracer uptake in the remainder of the gland. In toxic MNG, the gland is enlarged—often with distorted architecture—and there are multiple areas of relatively increased (functioning nodules) or decreased tracer uptake (suppressed thyroid parenchyma or nonfunctioning nodules). Subacute, viral, and postpartum thyroiditis are associated with very low uptake because of follicular cell damage and TSH suppression. Thyrotoxicosis factitia is also associated with low uptake. In addition, if there is excessive circulating exogenous iodine (e.g., from dietary sources of iodinated contrast dye), the radionuclide uptake is low even in the presence of increased thyroid hormone production.

Thyroid scintigraphy is not used in the routine evaluation of patients with thyroid nodules, but should be performed if the serum TSH level is subnormal to determine if functioning thyroid nodules are present. Functioning or "hot" nodules are almost never malignant, and fine-needle aspiration (FNA) biopsy is not indicated. The vast majority of thyroid nodules do not produce thyroid hormone ("cold" nodules), and these are more likely to be malignant (~5–10%). Whole-body and thyroid scanning is also used in the treatment and

TABLE 50-1

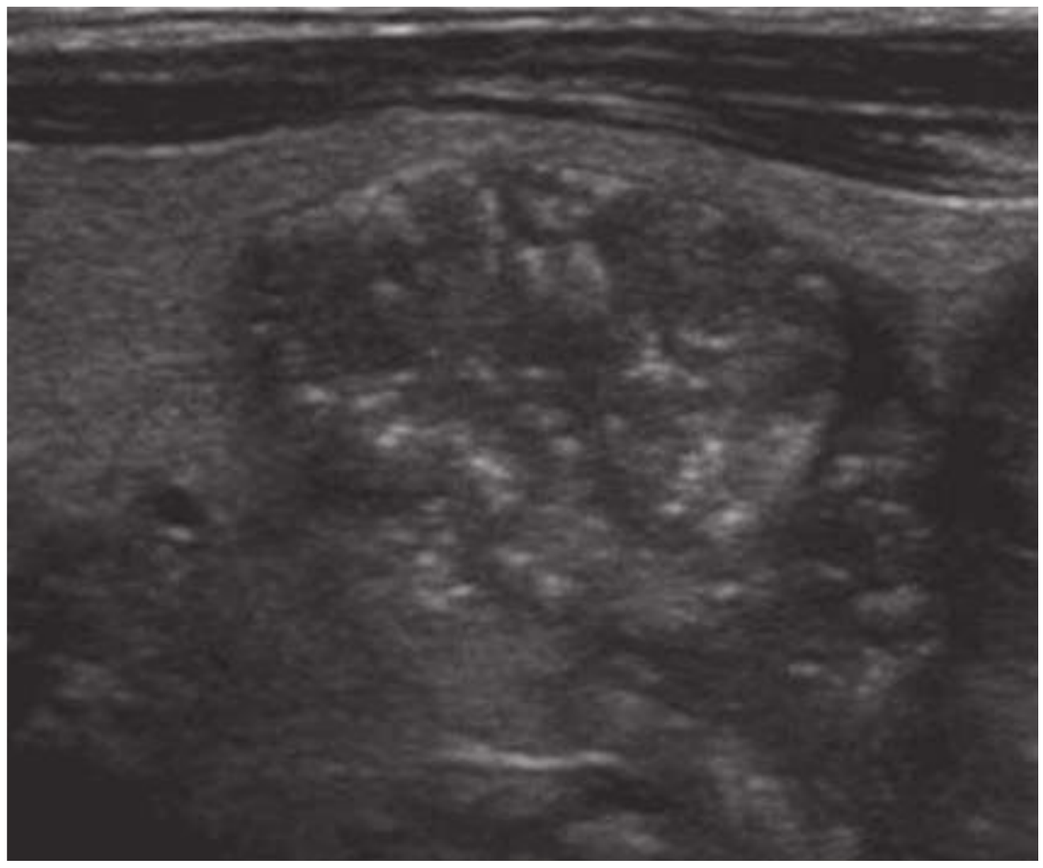
GRAYSCALE SONOGRAPHIC FEATURES ASSOCIATED WITH THYROID CANCER

	MEDIAN SENSITIVITY [RANGE]	MEDIAN SPECIFICITY [RANGE]
Hypoechoic compared with surrounding thyroid	81% [48–90%]	53% [36–92%]
Marked hypoechogenicity	41% [27–59%]	94% [92–94%]
Microcalcifications	44% [26–73%]	89% [69–98%]
Irregular, microlobulated margins	55% [17–84%]	79% [62–85%]
Solid consistency	86% [78–91%]	48% [30–58%]
Taller than wide shape on transverse view	48% [33–84%]	92% [82–93%]

surveillance of thyroid cancer. After thyroidectomy for thyroid cancer, the TSH level is raised by either using a thyroid hormone withdrawal protocol or recombinant human TSH injection (see below). Administration of ^{131}I allows whole-body scanning (WBS) to confirm remnant ablation and to detect any functioning metastases. In addition, WBS may be helpful in surveillance of patients at risk for recurrence.

Thyroid ultrasound

Ultrasonography is valuable for the diagnosis and evaluation of patients with nodular thyroid disease **(Table 50-1)**. Evidence-based guidelines recommend thyroid ultrasonography for all patients suspected of having thyroid nodules by either physical examination or another imaging study. Using 10- to 12-MHz linear transducers, resolution and image quality are excellent, allowing the characterization of nodules and cysts >3 mm. Certain sonographic patterns are highly suggestive of malignancy (e.g., hypoechoic solid nodules with infiltrative borders and microcalcifications), whereas other features correlate with benignity (e.g., spongiform nodules defined as those with multiple small internal cystic areas) **(Fig. 50-1)**. In addition to evaluating thyroid nodules, ultrasound is useful for monitoring nodule size and for the aspiration of nodules or cystic lesions. Ultrasound-guided FNA biopsy of thyroid lesions lowers the rate of inadequate sampling and decreases sample error, thereby reducing the false-negative rate of FNA cytology. Ultrasonography of the central and lateral cervical lymph node compartments is indispensable in the evaluation thyroid cancer patients, preoperatively and during follow-up.



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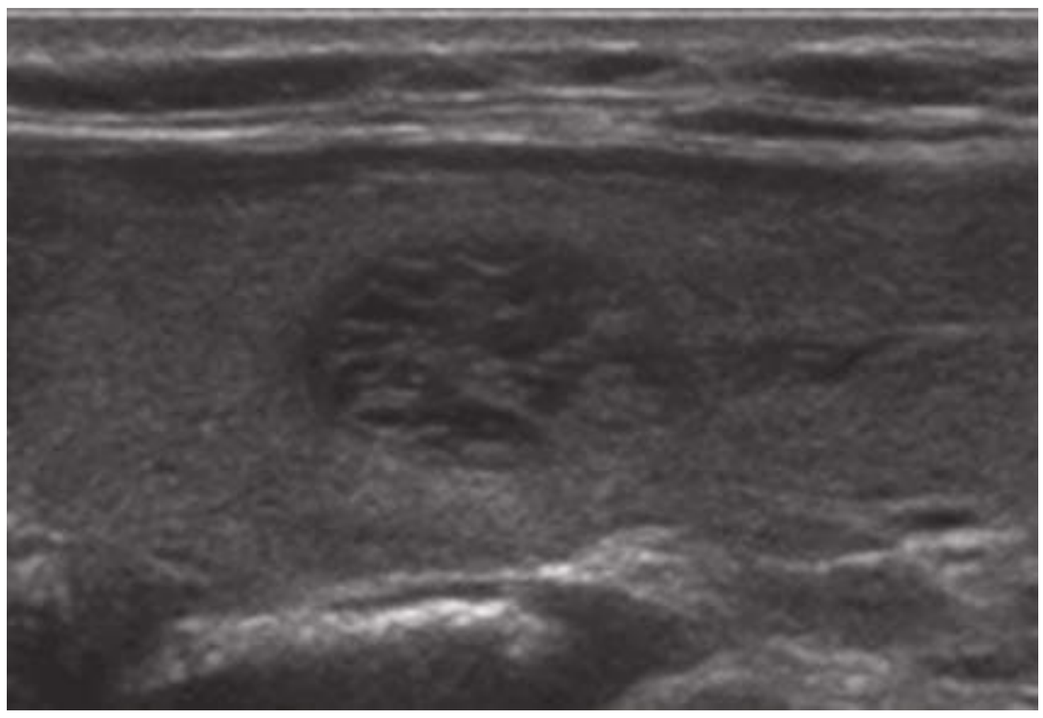

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FIGURE 50-1

Sonographic patterns of thyroid nodules. A. High suspicion ultrasound pattern for thyroid malignancy (hypoechoic solid nodule with irregular borders and microcalcifications). B. Very low suspicion ultrasound pattern for thyroid malignancy (spongiform nodule with microcystic areas comprises over >50% of nodule volume).

BENIGN NEOPLASMS

The various types of benign thyroid nodules are listed in **Table 50-2**. These lesions are common (5–10% adults), particularly when assessed by sensitive techniques such as ultrasound. The risk of malignancy is very low for macrofollicular adenomas and normofollicular adenomas. Microfollicular, trabecular, and Hürthle cell variants raise greater concern, and the histology is more difficult to interpret. Many are mixed cystic/solid lesions on ultrasound and may appear spongiform reflecting the pathology of macrofollicular structure.

TABLE 50-2

CLASSIFICATION OF THYROID NEOPLASMS

BENIGN	
Follicular epithelial cell adenomas	
Macrofollicular (colloid)	
Normofollicular (simple)	
Microfollicular (fetal)	
Trabecular (embryonal)	
Hürthle cell variant (oncocytic)	
MALIGNANT	**APPROXIMATE PREVALENCE, %**
Follicular epithelial cell	
Well-differentiated carcinomas	
Papillary carcinomas	80–90
Pure papillary	
Follicular variant	
Diffuse sclerosing variant	
Tall cell, columnar cell variants	
Follicular carcinomas	5–10
Minimally invasive	
Widely invasive	
Hürthle cell carcinoma (oncocytic)	
Insular carcinoma	
Undifferentiated (anaplastic) carcinomas	
C cell (calcitonin-producing)	
Medullary thyroid cancer	<10
Sporadic	
Familial	
MEN 2	
Other malignancies	
Lymphomas	1–2
Sarcomas	
Metastases	
Others	

Abbreviation: MEN, multiple endocrine neoplasia.

However, the majority of solid nodules (whether hypo-, iso-, or hyperechoic) are also benign. FNA, usually performed with ultrasound guidance, is the diagnostic procedure of choice to evaluate thyroid nodules (see the "Approach to the Patient" section on thyroid nodules). Pure thyroid cysts, <2% of all thyroid growths, consist of colloid and are benign as well. Cysts frequently recur, even after repeated aspiration, and may require surgical excision if they are large. Ethanol ablation to sclerose the cyst has been used successfully for patients who are symptomatic.

TSH suppression with levothyroxine therapy does not decrease thyroid nodule size in iodine-sufficient populations. However, if there is relative iodine deficiency, both iodine and levothyroxine therapy may decrease nodule volume. If levothyroxine is administered in this situation and the nodule has not decreased in size after 6–12 months of suppressive therapy, treatment should be discontinued because little benefit is likely to accrue from long-term treatment; the risk of iatrogenic subclinical thyrotoxicosis should also be considered.

THYROID CANCER

Thyroid carcinoma is the most common malignancy of the endocrine system. Malignant tumors derived from the follicular epithelium are classified according to histologic features. Differentiated tumors, such as papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC), are often curable, and the prognosis is good for patients identified with early-stage disease. In contrast, anaplastic thyroid cancer (ATC) is aggressive, responds poorly to treatment, and is associated with a bleak prognosis.

The incidence of thyroid cancer is ~12/100,000 per year in the United States and increases with age. Prognosis is worse in older persons (>65 years). Thyroid cancer is twice as common in women as men, but male gender is associated with a worse prognosis. Additional important risk factors include a history of childhood head or neck irradiation, large nodule size (≥4 cm), evidence for local tumor fixation or invasion into lymph nodes, and the presence of metastases **(Table 50-3)**. Several unique features of thyroid cancer facilitate its management: (1) thyroid nodules are amenable to biopsy by FNA; (2) iodine radioisotopes can be used to diagnose (^{123}I) and treat (^{131}I) differentiated thyroid cancer, reflecting the unique uptake of this anion by the thyroid gland; and (3) serum markers allow the detection of residual or recurrent disease, including the use of Tg levels for PTC and FTC, and calcitonin for medullary thyroid cancer (MTC).

TABLE 50-3

RISK FACTORS FOR THYROID CARCINOMA IN PATIENTS WITH THYROID NODULE

History of head and neck irradiation, including total-body irradiation for bone marrow transplant and brain radiation for childhood leukemia	Family history of thyroid cancer, MEN 2, or other genetic syndromes associated with thyroid malignancy (e.g., Cowden's syndrome, familial polyposis, Carney complex)
Exposure to ionizing radiation from fallout in childhood or adolescence	Vocal cord paralysis, hoarse voice
Age <20 or >65 years	Nodule fixed to adjacent structures
Increased nodule size (>4 cm)	Extrathyroidal extension
New or enlarging neck mass	Lateral cervical lymphadenopathy
Male gender	

Abbreviation: MEN, multiple endocrine neoplasia.

CLASSIFICATION

Thyroid neoplasms can arise in each of the cell types that populate the gland, including thyroid follicular cells, calcitonin-producing C cells, lymphocytes, and stromal and vascular elements, as well as metastases from other sites (Table 50-2). The American Joint Committee on Cancer (AJCC) has designated a staging system using the tumor, node, metastasis (TNM) classification **(Table 50-4)**. Several other classification and staging systems are also widely used, some of which place greater emphasis on histologic features or risk factors such as age or gender.

PATHOGENESIS AND GENETIC BASIS

Radiation

Early studies of the pathogenesis of thyroid cancer focused on the role of external radiation, which predisposes to chromosomal breaks, leading to genetic rearrangements and loss of tumor-suppressor genes. External radiation of the mediastinum, face, head, and neck region was administered in the past to treat an array of conditions, including acne and enlargement of the thymus, tonsils, and adenoids. Radiation exposure increases the risk of benign and malignant thyroid nodules, is associated with multicentric cancers, and shifts the incidence of thyroid cancer to an earlier age group. Radiation from nuclear fallout also increases the risk of thyroid cancer. Children seem more predisposed to the effects of radiation than adults. Of note, radiation derived from ^{131}I therapy appears to contribute minimal increased risk of thyroid cancer.

TABLE 50-4

THYROID CANCER CLASSIFICATION[a]		
Papillary or Follicular Thyroid Cancers		
	<45 Years	>45 Years
Stage I	Any T, any N, M0	T1, N0, M0
Stage II	Any T, any N, M1	T2, N0, M0
Stage III	—	T3, N0, M0
		T1–T3, N1a, M0
Stage IVA	—	T4a, any N, M0 T1–T3, N1b, M0
Stage IVB		T4b, any N, M0
Stage IVC		Any T, any N, M1
Anaplastic Thyroid Cancer		
Stage IV	All cases are stage IV	
Medullary Thyroid Cancer		
Stage I	T1, N0, M0	
Stage II	T2 or T3, N0, M0	
Stage III	T1–T3, N1a, M0	
Stage IVA	T4a, any N, M0 T1–T3, N1b, M0	
Stage IVB	T4b, any N, M0	
Stage IVC	Any T, any N, M1	

[a]Criteria include: T, the size and extent of the primary tumor (T1a ≤1 cm; T1b >1 cm but ≤2 cm; T2 >2 cm but ≤4 cm; T3 >4 cm or any tumor with extension into perithyroidal soft tissue or sternothyroid muscle; T4a invasion into subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve; T4b invasion into prevertebral fascia or encasement of carotid artery or mediastinal vessels); N, the absence (N0) or presence (N1a level IV central compartment; N1b levels II–V lateral compartment, upper mediastinal or retro/parapharyngeal) of regional node involvement; M, the absence (M0) or presence (M1) of distant metastases.
Source: American Joint Committee on Cancer staging system for thyroid cancers using the TNM classification, 7th edition.

TSH and growth factors

Many differentiated thyroid cancers express TSH receptors and, therefore, remain responsive to TSH. Higher serum TSH levels, even within normal range, are associated with increased thyroid cancer risk in patients with thyroid nodules. These observations provide the rationale for T_4 suppression of TSH in patients with thyroid cancer. Residual expression of TSH receptors also allows TSH-stimulated uptake of ^{131}I therapy (see below).

Oncogenes and tumor-suppressor genes

Thyroid cancers are monoclonal in origin, consistent with the idea that they originate as a consequence of mutations that confer a growth advantage to a single cell. In addition to increased rates of proliferation, some thyroid cancers exhibit impaired apoptosis and features that enhance invasion, angiogenesis, and metastasis. Thyroid neoplasms have been analyzed for a variety of genetic alterations, but without clear evidence of an ordered acquisition of somatic mutations as they progress from the benign to the malignant state. On the other hand, certain mutations are relatively specific for thyroid neoplasia, some of which correlate with histologic classification **(Table 50-5)**.

As described above, activating mutations of the TSH-R and the $G_{S\alpha}$ subunit are associated with autonomously functioning nodules. Although these mutations induce thyroid cell growth, this type of nodule is almost always benign.

Activation of the RET-RAS-BRAF signaling pathway is seen in up to 70% of PTCs, although the types of mutations are heterogeneous. A variety of rearrangements involving the RET gene on chromosome 10 bring this receptor tyrosine kinase under the control of other promoters, leading to receptor overexpression. RET rearrangements occur in 20–40% of PTCs in different series and were observed with increased frequency in tumors developing after the

TABLE 50-5

GENETIC ALTERATIONS IN THYROID NEOPLASIA

GENE/PROTEIN	TYPE OF GENE	CHROMOSOMAL LOCATION	GENETIC ABNORMALITY	TUMOR
TSH receptor	GPCR receptor	14q31	Point mutations	Toxic adenoma, dif erentiated carcinomas
$G_{S\alpha}$	G protein	20q13.2	Point mutations	Toxic adenoma, dif erentiated carcinomas
RET/PTC	Receptor tyrosine kinase	10q11.2	Rearrangements PTC1: inv(10)(q11.2q21) PTC2: t(10;17)(q11.2;q23) PTC3: ELE1/TK	PTC (more common in radiation-induced tumors)
RET	Receptor tyrosine kinase	10q11.2	Point mutations	MEN 2, medullary thyroid cancer
BRAF	MEK kinase	7q24	Point mutations, rearrangements	PTC, ATC
TRK	Receptor tyrosine kinase	1q23-24	Rearrangements	Multinodular goiter, papillary thyroid cancer
RAS	Signal transducing p21	NRAS 1p13.2 (most common); HRAS 11p15.5; KRAS 12p12.1	Point mutations	Follicular thyroid cancer, PTC follicular variant, adenomas
p53	Tumor suppressor, cell cycle control, apoptosis	17p13	Point mutations Deletion, insertion	Anaplastic cancer
APC	Tumor suppressor, adenomatous polyposis coli gene	5q21-q22	Point mutations	Anaplastic cancer, also associated with familial polyposis coli
p16 (MTS1, CDKN2A)	Tumor suppressor, cell cycle control	9p21	Deletions	Dif erentiated carcinomas
p21/WAF	Tumor suppressor, cell cycle control	6p21.2	Overexpression	Anaplastic cancer
MET	Receptor tyrosine kinase	7q31	Overexpression	Follicular thyroid cancer
c-MYC	Receptor tyrosine kinase	8q24.12-13	Overexpression	Dif erentiated carcinoma
PTEN	Phosphatase	10q23	Point mutations	PTC in Cowden's syndrome (multiple hamartomas, breast tumors, gastrointestinal polyps, thyroid tumors)
CTNNB1	β-Catenin	3p22	Point mutations	Anaplastic cancer
Loss of heterozygosity (LOH)	? Tumor suppressors	3p; 11q13, other loci	Deletions	Dif erentiated thyroid carcinomas, anaplastic cancer
PAX8-PPARγ1	Transcription factor-nuclear receptor fusion	t(2;3)(q13;p25)	Translocation	Follicular adenoma or carcinoma, rare PTC follicular variant

Abbreviations: APC, adenomatous polyposis coli; ATC, anaplastic thyroid cancer; BRAF, v-raf homologue, B1; CDKN2A, cyclin-dependent kinase inhibitor 2A; c-MYC, cellular homologue of myelocytomatosis virus protooncogene; ELE1/TK, RET-activating gene ele1/tyrosine kinase; GPCR, G protein–coupled receptor; $G_{S\alpha}$, G-protein stimulating α-subunit; MEK, mitogen extracellular signal-regulated kinase; MEN 2, multiple endocrine neoplasia-2; MET, met protooncogene (hepatocyte growth factor receptor); MTS, multiple tumor suppressor; p53, p53 tumor suppressor gene; PTC, papillary thyroid cancer; PTEN, phosphatase and tensin homologue; RAS, rat sarcoma protooncogene; RET, rearranged during transfection protooncogene; p21, p21 tumor suppressor; PAX8, paired domain transcription factor; PPARγ1, peroxisome-proliferator activated receptor γ1; TRK, tyrosine kinase receptor; TSH, thyroid-stimulating hormone; WAF, wild-type p53 activated fragment.

Source: Adapted with permission from P Kopp, JL Jameson, in JL Jameson (ed): Principles of Molecular Medicine. Totowa, NJ, Humana Press, 1998.

Chernobyl radiation accident. Rearrangements in PTC have also been observed for another tyrosine kinase gene, TRK1, which is located on chromosome 1. To date, the identification of PTC with RET or TRK1 rearrangements has not proven useful for predicting prognosis or treatment responses. BRAF V600E mutations appear to be the most common genetic alteration in PTC. T ese mutations activate the kinase, which stimulates the mitogen-activated protein MAP kinase (MAPK) cascade. RAS mutations, which also stimulate the MAPK cascade, are found in about 20–30% of thyroid neoplasms (NRAS > HRAS > KRAS), including both PTC and FTC. Of note, simultaneous RET, BRAF, and RAS mutations rarely occur in the same tumor, suggesting that activation of the MAPK cascade is critical for tumor development, independent of the step that initiates the cascade.

RAS mutations also occur in FTCs. In addition, a rearrangement of the thyroid developmental transcription factor PAX8 with the nuclear receptor PPARγ is identified in a significant fraction of FTCs. Overall, about 70% of follicular cancers have mutations or genetic rearrangements. Loss of heterozygosity of 3p or 11q, consistent with deletions of tumor-suppressor genes, is also common in FTCs.

Most of the mutations seen in dif erentiated thyroid cancers have also been detected in ATCs. BRAF mutations are seen in up to 50% of ATCs. Mutations in CTNNB1, which encodes β-catenin, occur in about two-thirds of ATCs, but not in PTC or FTC. Mutations of the tumor-suppressor P53 also play an important role in the development of ATC. Because P53 plays a role in cell cycle surveillance, DNA repair, and apoptosis, its loss may contribute to the rapid acquisition of genetic instability as well as poor treatment responses **(Chap. 26)** (Table 50-5).

T e role of molecular diagnostics in the clinical management of thyroid cancer is under investigation. In principle, analyses of specific mutations might aid in classification, prognosis, or choice of treatment. Although BRAF V600E mutations are associated with loss of iodine uptake by tumor cells, there is no clear evidence to date that this information alters clinical decision making. Higher recurrence rates have been variably reported in patients with BRAF-positive PTC, but the impact on survival rates is unclear. Sequencing of thyroid cancers as part of the Cancer Genome Atlas (TCGA) is likely to lead to new classification schemes based on molecular abnormalities in tumors.

MTC, when associated with multiple endocrine neoplasia (MEN) type 2, harbors an inherited mutation of the RET gene. Unlike the rearrangements of RET seen in PTC, the mutations in MEN 2 are point mutations that induce constitutive activity of the tyrosine kinase **(Chap. 52)**. MTC is preceded by hyperplasia of the C cells, raising the likelihood that as-yet-unidentified "second hits" lead to cellular transformation. A subset of sporadic MTC contains somatic mutations that activate RET.

WELL-DIFFERENTIATED THYROID CANCER

Papillary

PTC is the most common type of thyroid cancer, accounting for 70–90% of well-dif erentiated thyroid malignancies. Microscopic PTC is present in up to 25% of thyroid glands at autopsy, but most of these lesions are very small (several millimeters) and are not clinically significant. Characteristic cytologic features of PTC help make the diagnosis by FNA or after surgical resection; these include psammoma bodies, cleaved nuclei with an "orphan-Annie" appearance caused by large nucleoli, and the formation of papillary structures.

PTC tends to be multifocal and to invade locally within the thyroid gland as well as through the thyroid capsule and into adjacent structures in the neck. It has a propensity to spread via the lymphatic system but can metastasize hematogenously as well, particularly to bone and lung. Because of the relatively slow growth of the tumor, a significant burden of pulmonary metastases may accumulate, sometimes with remarkably few symptoms. T e prognostic implication of lymph node spread is debated. Lymph node involvement by thyroid cancer can be well tolerated but appears to increase the risk of recurrence and mortality, particularly in older patients. T e staging of PTC by the TNM system is outlined in Table 50-4. Most papillary cancers are identified in the early stages (>80% stages I or II) and have an excellent prognosis, with survival curves similar to expected survival **(Fig. 50-2)**. Mortality is markedly increased in stage IV disease, especially in the presence of distant metastases (stage IVC), but this group comprises only about 1% of patients. T e treatment of PTC is described below.

Follicular

T e incidence of FTC varies widely in dif erent parts of the world; it is more common in iodine-deficient regions. Currently, FTC accounts for only about 5% of all thyroid cancers diagnosed in the United States. FTC is difficult to diagnose by FNA because the distinction between benign and malignant follicular neoplasms rests largely on evidence of invasion into vessels, nerves, or adjacent structures. FTC tends to spread by hematogenous routes leading to bone, lung, and central nervous system metastases. Mortality rates associated with FTC are less favorable than for PTC, in part because a larger proportion of patients present with stage IV

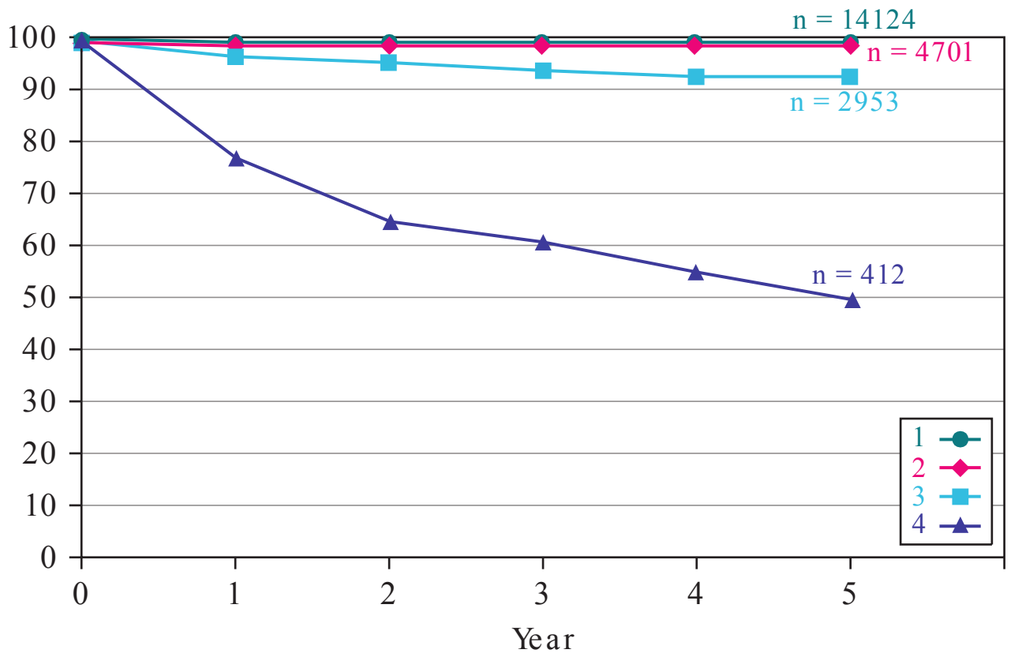


FIGURE 50-2
Survival rates of patients with different stages of papillary cancer. (Adapted with permission from Edge SB, Byrd DR: Thyroid, in Compton CC, Fritz AB, Greene FL, Trotti A [eds]: AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010, pp 87–92.)

disease. Poor prognostic features include distant metastases, age >50 years, primary tumor size >4 cm, Hürthle cell histology, and the presence of marked vascular invasion.

TREATMENT Well-Differentiated Thyroid Cancer Surgery

All well-differentiated thyroid cancers should be surgically excised. In addition to removing the primary lesion, surgery allows accurate histologic diagnosis and staging, and multicentric disease is commonly found in the contralateral thyroid lobe. Preoperative sonography should be performed in all patients to assess the central and lateral cervical lymph node compartments for suspicious adenopathy, which if present, can undergo FNA and then be removed at surgery. Bilateral, near-total thyroidectomy has been shown to reduce recurrence rates in all patients except those with T1a tumors (≤1 cm). If cytology is diagnostic for thyroid cancer, bilateral surgery should be done. If malignancy is identified pathologically after lobectomy, completion surgery is recommended unless the tumor is T1a or is a minimally invasive follicular cancer. Bilateral surgery for patients at higher risk allows monitoring of serum Tg levels and administration of radioiodine for remnant ablation and potential treatment of iodine-avid metastases, if indicated. Therefore, near-total thyroidectomy is preferable in almost all patients; complication rates are acceptably low if the surgeon is highly experienced in the procedure.

TSH Suppression Therapy Because most tumors are still TSH-responsive, levothyroxine suppression of TSH is a mainstay of thyroid cancer treatment. Although TSH suppression clearly provides therapeutic benefit, there are no prospective studies that define the optimal level of TSH suppression. The degree of TSH suppression should be individualized based on a patient's risk of recurrence. It should be adjusted over time as surveillance blood tests and imaging confirm absence of disease or, alternatively, indicate possible residual/recurrent cancer. For patients at low risk of recurrence, TSH should be suppressed into the low but detectable range (0.1–0.5 mIU/L). If subsequent surveillance testing indicates no evidence of disease, the TSH target may rise to the lower half of the normal range. For patients at high risk of recurrence or with known metastatic disease, TSH levels should be kept to <0.1 mIU/L if there are no strong contraindications to mild thyrotoxicosis. In this instance, unbound T_4 must also be monitored to avoid excessive treatment.

Radioiodine Treatment After near-total thyroidectomy, substantial thyroid tissue often remains, particularly in the thyroid bed and surrounding the parathyroid glands. Postsurgical radioablation of the remnant thyroid eliminates residual normal thyroid, facilitating the use of Tg determinations and radioiodine scanning for long-term follow-up. In addition, well-differentiated thyroid cancer often incorporates radioiodine, although less efficiently than normal thyroid follicular cells. Radioiodine uptake is determined primarily by expression of the NIS and is stimulated by TSH, requiring expression of the TSH-R. The retention time for radioactivity is influenced by the extent to which the tumor retains differentiated functions such as iodide trapping and organification. Consequently, for patients at risk of recurrence and for those with known distant metastatic disease, ^{131}I ablation may also potentially treat residual tumor cells.

INDICATIONS Not all patients benefit from radioiodine therapy. Neither recurrence nor survival rates are improved in stage I patients with T1 tumors (≤2 cm) confined to the thyroid. However, in higher risk patients (larger tumors, more aggressive variants of papillary cancer, tumor vascular invasion, presence of large-volume lymph node metastases), radioiodine reduces recurrence and may increase survival.

^{131}I THYROID ABLATION AND TREATMENT As noted above, the decision to use ^{131}I for thyroid ablation should be coordinated with the surgical approach, because radioablation is much more effective when there is minimal remaining normal thyroid tissue. Radioiodine is administered after iodine depletion (patient follows a low-iodine diet for 1≤2 weeks) and in the presence of elevated serum TSH levels to stimulate uptake of the isotope into both the remnant and potentially any residual tumor. To achieve high serum TSH levels, there are two approaches. A patient may be withdrawn from thyroid hormone so that endogenous TSH is secreted and, ideally, the serum TSH level is >25 mIU/L at the time of ^{131}I therapy. A typical strategy is to treat the patient for several weeks postoperatively with liothyronine (25 μg qd or bid), followed by thyroid hormone withdrawal for

2 weeks. Alternatively, recombinant human TSH (rhTSH) is administered as two daily consecutive injections (0.9 mg) with administration of ^{131}I 24 h after the second injection. The patient can continue to take levothyroxine and remains euthyroid. Both approaches have equal success in achieving remnant ablation.

A pretreatment scanning dose of ^{131}I (usually 111–185 MBq [3–5 mCi]) or ^{123}I (74 MBq [2 mCi]) can reveal the amount of residual tissue and provides guidance about the dose needed to accomplish ablation. However, because of concerns about radioactive "stunning" that impairs subsequent treatment, there is a trend to avoid pretreatment scanning with ^{131}I and use either ^{123}I or proceed directly to ablation, unless there is suspicion that the amount of residual tissue will alter therapy or that there is distant metastatic disease. In the United States, outpatient doses of up to 6475 MBq (175 mCi) can be given at most centers. T e administered dose depends on the indication for therapy with lower doses of 1850–2775 MBq (50–75 mCi) given for remnant ablation but higher doses of 3700–5500 MBq (100–150 mCi) used as adjuvant therapy when residual disease may be present. A WBS following radioiodine treatment is used to confirm the ^{131}I uptake in the remnant and to identify possible metastatic disease.

FOLLOW-UP WHOLE-BODY THYROID SCANNING AND THYROGLOBULIN DETERMINATIONS Serum thyroglobulin is a sensitive marker of residual/recurrent thyroid cancer after ablation of the residual postsurgical thyroid tissue. However, newer Tg assays have functional sensitivities as low as 0.1 ng/mL, as opposed to older assays with functional sensitivities of 1 ng/mL, reducing the number of patients with truly undetectable serum Tg levels. Because the vast majority of papillary thyroid cancer recurrences are in cervical lymph nodes, a neck ultrasound should be performed about 6 months after thyroid ablation; ultrasound has been shown to be more sensitive than WBS in this scenario.

In low-risk patients who have no clinical evidence of residual disease after ablation and a basal Tg <1 ng/mL on levothyroxine, an rhTSH-stimulated Tg level should be obtained 6–12 months after ablation, without WBS. If stimulated Tg levels are low (<1 ng/mL) and, ideally, undetectable, the risk of recurrence is <5% at 5 years. Newer data indicate that rhTSH stimulation may not be required for patients with undetectable basal Tg levels in sensitive assays, if there is documented absence of Tg antibodies. T ese patients can be followed with unstimulated Tg every 6–12 months and neck ultrasound as indicated. Levothyroxine dosing may then be titrated to a higher TSH level of 0.5–1.5 mIU/L.

T e use of WBS is reserved for patients with known iodine-avid metastases or those with elevated serum thyroglobulin levels and negative imaging with ultrasound, chest CT, and neck cross-sectional imaging who may require additional ^{131}I therapy.

In addition, most authorities advocate radioiodine treatment for scan-negative, Tg-positive (Tg >5–10 ng/mL) patients, as many derive therapeutic benefit from a large dose of ^{131}I. For such patients, rhTSH preparation is not FDA approved for the treatment of metastatic disease, and the traditional approach of thyroid hormone withdrawal should be followed. T is involves switching patients from levothyroxine (T_4) to the more rapidly cleared hormone liothyronine (T_3), thereby allowing TSH to increase more quickly. Whenever ^{131}I is administered, posttherapy WBS is the gold standard to assess iodine-avid metastases.

In addition to radioiodine, external beam radiotherapy is also used to treat specific metastatic lesions, particularly when they cause bone pain or threaten neurologic injury (e.g., vertebral metastases).

NEW POTENTIAL THERAPIES Kinase inhibitors are being explored as a means to target pathways known to be active in thyroid cancer, including the RAS, BRAF, EGFR, VEGFR, and angiogenesis pathways. A multicenter randomized controlled trial of the multikinase inhibitor sorafenib in 417 patients with progressive metastatic thyroid cancer reported a doubling of progression-free survival to 10.8 months in the treatment group compared with the placebo group. Ongoing trials are exploring whether dif erentiation protocols with kinase inhibitors or other approaches might enhance radioiodine uptake and efficacy.

ANAPLASTIC AND OTHER FORMS OF THYROID CANCER

Anaplastic thyroid cancer

As noted above, ATC is a poorly dif erentiated and aggressive cancer. T e prognosis is poor, and most patients die within 6 months of diagnosis. Because of the undif erentiated state of these tumors, the uptake of radioiodine is usually negligible, but it can be used therapeutically if there is residual uptake. Chemotherapy has been attempted with multiple agents, including anthracyclines and paclitaxel, but it is usually inef ective. External beam radiation therapy can be attempted and continued if tumors are responsive.

Thyroid lymphoma

Lymphoma in the thyroid gland often arises in the background of Hashimoto's thyroiditis. A rapidly expanding thyroid mass suggests the possibility of this diagnosis. Dif use large-cell lymphoma is the most common type in the thyroid. Biopsies reveal sheets of lymphoid cells that can be difficult to distinguish from small-cell lung cancer or ATC. T ese tumors are often highly sensitive to external radiation. Surgical resection should be avoided as initial therapy because it may

spread disease that is otherwise localized to the thyroid. If staging indicates disease outside of the thyroid, treatment should follow guidelines used for other forms of lymphoma **(Chap. 16)**.

MEDULLARY THYROID CARCINOMA

MTC can be sporadic or familial and accounts for about 5% of thyroid cancers. T ere are three familial forms of MTC: MEN 2A, MEN 2B, and familial MTC without other features of MEN **(Chap. 52)**. In general, MTC is more aggressive in MEN 2B than in MEN 2A, and familial MTC is more aggressive than sporadic MTC. Elevated serum calcitonin provides a marker of residual or recurrent disease. All patients with MTC should be tested for RET mutations, because genetic counseling and testing of family members can be of ered to those individuals who test positive for mutations.

T e management of MTC is primarily surgical. Unlike tumors derived from thyroid follicular cells, these tumors do not take up radioiodine. External radiation treatment and chemotherapy may provide palliation in patients with advanced disease **(Chap. 52)**.

APPROACH TO THE PATIENT: Thyroid Nodules

Palpable thyroid nodules are found in about 5% of adults, but the prevalence varies considerably worldwide. Given this high prevalence rate, practitioners commonly identify thyroid nodules either on physical examination or as incidental findings on imaging performed for another indication (e.g., carotid ultrasound, cervical spine MRI). T e main goal of this evaluation is to identify, in a cost-ef ective manner, the small subgroup of individuals with malignant lesions.

Nodules are more common in iodine-deficient areas, in women, and with aging. Most palpable nodules are >1 cm in diameter, but the ability to feel a nodule is influenced by its location within the gland (superficial versus deeply embedded), the anatomy of the patient's neck, and the experience of the examiner. More sensitive methods of detection, such as CT, thyroid ultrasound, and pathologic studies, reveal thyroid nodules in up to 50% of glands in individuals over the age of 50. T e presence of these thyroid incidentalomas has led to much debate about how to detect nodules and which nodules to investigate further.

An approach to the evaluation of a solitary nodule is outlined in **Fig. 50-3**. Most patients with thyroid nodules have normal thyroid function tests. Nonetheless, thyroid function should be assessed by measuring a TSH level, which may be suppressed by one or more autonomously functioning nodules. If the TSH is suppressed, a radionuclide scan is indicated to determine if the identified nodule is "hot," as lesions with increased uptake are almost never malignant and FNA is unnecessary. Otherwise, the next step in evaluation is performance of a thyroid ultrasound for three reasons: (1) Ultrasound will confirm if the palpable nodule is indeed a nodule. About 15% of "palpable" nodules are not confirmed on imaging, and therefore, no further evaluation is required. (2) Ultrasound will assess if there are additional nonpalpable nodules for which FNA may be recommended based on imaging features and size. (3) Ultrasound will characterize the imaging features of the nodule, which, combined with the nodule's size, facilitate decision making about FNA. Evidence-based guidelines from both the American T yroid Association and the American Association of Clinical Endocrinologists provide recommendations for nodule FNA based on sonographic imaging features and size cut of s, with lower size cut of s for nodules with more suspicious ultrasound characteristics. FNA biopsy, ideally performed with ultrasound guidance, has good sensitivity and specificity when performed by physicians familiar with the procedure and when the results are interpreted by experienced cytopathologists. T e technique is particularly useful for detecting PTC. However, the distinction between benign and malignant follicular lesions is often not possible using cytology alone. In several large studies, FNA biopsies yielded the following findings: 65% benign, 5% malignant or suspicious for malignancy, 10% nondiagnostic or yielding insufficient material for diagnosis, and 20% indeterminate. T e Bethesda System is now widely used to provide more uniform terminology for reporting thyroid nodule FNA cytology results. T is six-tiered classification system with the respective estimated malignancy rates is shown in **Table 50-6**. Specifically, the Bethesda System subcategorized cytology specimens previously labeled as indeterminate into three categories: atypia or follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm, and suspicious for malignancy.

Cytology results indicative of malignancy mandate surgery, after performing preoperative sonography to evaluate the cervical lymph nodes. Nondiagnostic cytology specimens generally result from cystic lesions but may also occur in fibrous long-standing nodules. Ultrasound-guided FNA is indicated when a repeat FNA is necessary. Repeat FNA will yield a diagnostic cytology in about 50% of cases. Benign nodules should be monitored by ultrasound for growth, and repeat FNA should be considered if the nodule enlarges. T e use of levothyroxine to suppress serum TSH is not

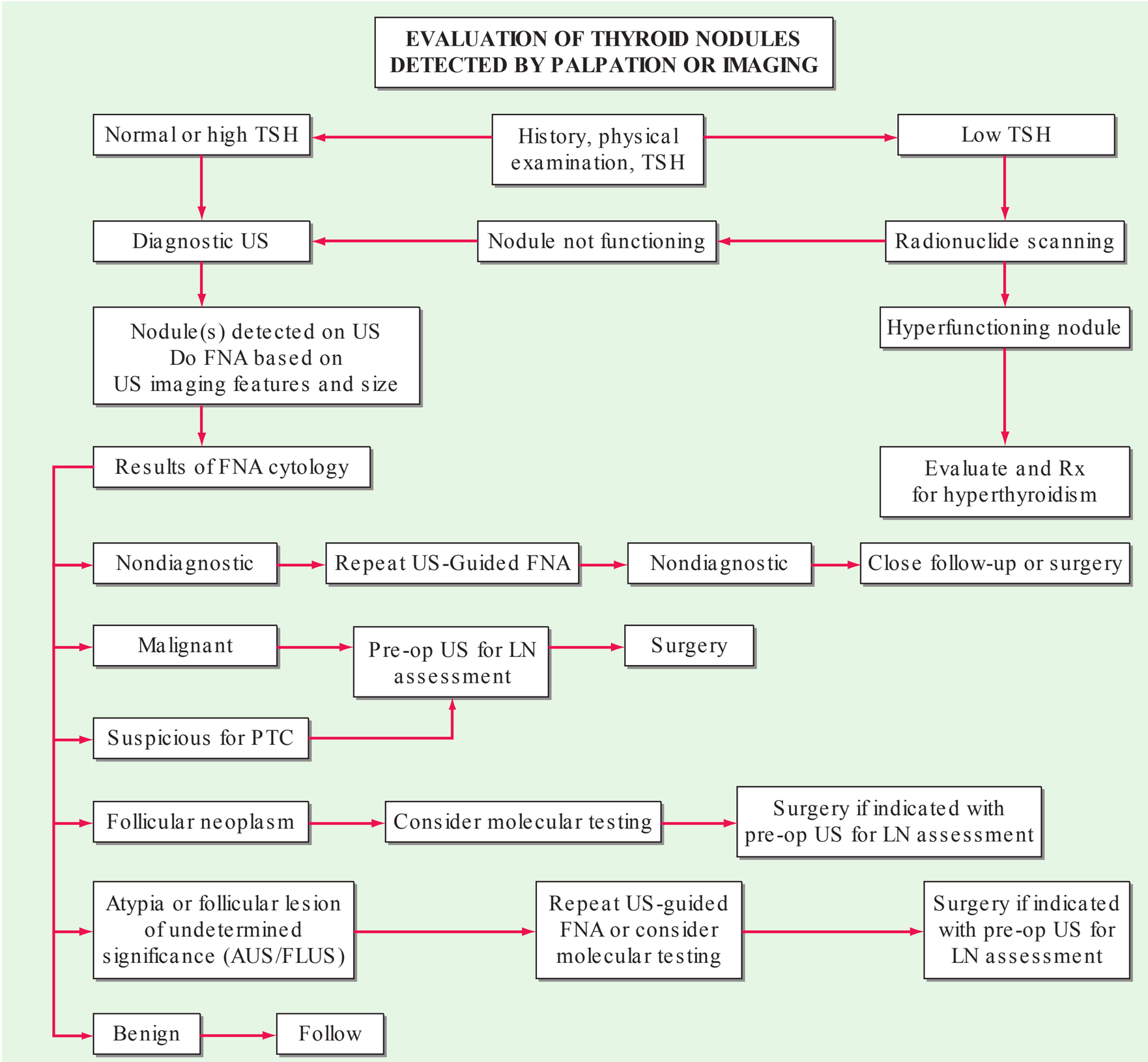


FIGURE 50-3

Approach to the patient with a thyroid nodule. See text and references for details. FNA, fine-needle aspiration; LN, lymph node; PTC, papillary thyroid cancer; TSH, thyroid-stimulating hormone; US, ultrasound.

ef ective in shrinking nodules in iodine-replete populations, and therefore, levothyroxine should not be used. T e three new cytology classifications introduced by the Bethesda System are associated with dif erent risks of malignancy (Table 50-6). For nodules with suspicious for malignancy cytology, surgery is recommended after ultrasound assessment of cervical lymph nodes. Options to be discussed with the patient include: (1) lobectomy with intraoperative frozen section; (2) near-total thyroidectomy; and (3) mutational analysis mainly for BRAF V600E, which is virtually diagnostic of PTC, and bilateral rather than unilateral thyroid surgery is required.

On the other hand, the majority of nodules with AUS/FLUS and follicular neoplasm cytology results are benign; only 10–30% are malignant. T e traditional approach for these patients is diagnostic lobectomy for histopathologic diagnosis. T erefore, up to 85% of patients undergo surgery for benign nodules. A high-sensitivity (~90%) novel molecular test using gene expression profiling technology may reduce the need for unnecessary surgery in these two groups. In

TABLE 50-6

BETHESDA CLASSIFICATION FOR THYROID CYTOLOGY

DIAGNOSTIC CATEGORY	RISK OF MALIGNANCY
Nondiagnostic or unsatisfactory	1–5%
Benign	2–4%
Atypia or follicular lesion of unknown significance (AUS/FLUS)	15–20%
Follicular neoplasm	20–30%
Suspicious for malignancy	60–75%
Malignant	97–100%

a multicenter trial of over 265 such nodules, a negative gene expression classifier test reduced the risk of malignancy to about 6%, leading to clinical recommendations for follow-up rather than surgery.

T e evaluation of a thyroid nodule is stressful for most patients. T ey are concerned about the possibility of thyroid cancer, whether verbalized or not. It is constructive, therefore, to review the diagnostic approach and to reassure patients when no malignancy is found. When a suspicious lesion or thyroid cancer is identified, the generally favorable prognosis and available treatment options can be reassuring.

CHAPTER 51

ENDOCRINE TUMORS OF THE GASTROINTESTINAL TRACT AND PANCREAS

Robert T. Jensen

GENERAL FEATURES OF GASTROINTESTINAL NEUROENDOCRINE TUMORS

Gastrointestinal (GI) neuroendocrine tumors (NETs) are tumors derived from the diffuse neuroendocrine system of the GI tract; that system is composed of amine- and acid-producing cells with different hormonal profiles, depending on the site of origin. T e tumors historically are divided into GI-NETs (in the GI tract) (also frequently called carcinoid tumors) and pancreatic neuroendocrine tumors (pNETs), although newer pathologic classifications have proposed that they all be classified as GI-NETs. T e term GI-NET has been proposed to replace the term carcinoid; however, the term carcinoid is widely used, and many are not familiar with this change. Accordingly, this chapter will use the term GI-NETs (carcinoids). T ese tumors originally were classified as APUDomas (for amine precursor uptake and decarboxylation), as were pheochromocytomas, melanomas, and medullary thyroid carcinomas, because they share certain cytochemical features as well as various pathologic, biologic, and molecular features **(Table 51-1)**. It was originally proposed that APUDomas had a similar embryonic origin from neural crest cells, but it is now known the peptide-secreting cells are not of neuroectodermal origin. Nevertheless, the concept of APUDomas is useful because these tumors have important similarities as well as some differences (Table 51-1). In this section, the areas of similarity between pNETs and GI-NETs (carcinoids) will be discussed together, and areas in which there are important differences will be discussed separately.

CLASSIFICATION/PATHOLOGY/TUMOR BIOLOGY OF NETS

NETs generally are composed of monotonous sheets of small round cells with uniform nuclei, and mitoses are uncommon. T ey can be identified tentatively on routine histology; however, these tumors are now recognized principally by their histologic staining patterns due to shared cellular proteins. Historically, silver staining was used, and tumors were classified as showing an argentaffin reaction if they took up and reduced silver or as being argyrophilic if they did not reduce it. Currently, immunocytochemical localization of chromogranins (A, B, C), neuron-specific enolase, and synaptophysin, which are all neuroendocrine cell markers, is used (Table 51-1). Chromogranin A is the most widely used.

Ultrastructurally, these tumors possess electron-dense neurosecretory granules and frequently contain small clear vesicles that correspond to synaptic vesicles of neurons. NETs synthesize numerous peptides, growth factors, and bioactive amines that may be ectopically secreted, giving rise to a specific clinical syndrome **(Table 51-2)**. T e diagnosis of the specific syndrome requires the clinical features of the disease (Table 51-2) and cannot be made from the immunocytochemistry results alone. T e presence or absence of a specific clinical syndrome also cannot be predicted from the immunocytochemistry alone (Table 51-1). Furthermore, pathologists cannot distinguish between benign and malignant NETs unless metastasis or invasion is present.

GI-NETs (carcinoids) frequently are classified according to their anatomic area of origin (i.e., foregut, midgut, hindgut) because tumors with similar areas of origin share functional manifestations, histochemistry, and secretory products **(Table 51-3)**. Foregut tumors generally have a low serotonin (5-HT) content; are argentaffin-negative but argyrophilic; occasionally secrete adrenocorticotropic hormone (ACTH) or 5-hydroxytryptophan (5-HTP), causing an atypical carcinoid syndrome **(Fig. 51-1)**; are often multihormonal; and may metastasize to bone. T ey uncommonly produce a clinical syndrome due to the secreted products.

TABLE 51-1

GENERAL CHARACTERISTICS OF GASTROINTESTINAL NEUROENDOCRINE TUMORS (GI-NETS [CARCINOIDS], PANCREATIC NEUROENDOCRINE TUMORS [PNETS])

A. Share general neuroendocrine cell markers (identification used for diagnosis)
   1. Chromogranins (A, B, C) are acidic monomeric soluble proteins found in the large secretory granules. Chromogranin A is the most widely used.
   2. Neuron-specific enolase (NSE) is the γ-γ dimer of the enzyme enolase and is a cytosolic marker of neuroendocrine dif erentiation.
   3. Synaptophysin is an integral membrane glycoprotein of 38,000 molecular weight found in small vesicles of neurons and neuroendocrine tumors.

B. Pathologic similarities
   1. All are APUDomas showing amine precursor uptake and decarboxylation.
   2. Ultrastructurally, they have dense-core secretory granules (>80 nm).
   3. Histologically, they generally appear similar with few mitoses and uniform nuclei.
   4. Frequently synthesize multiple peptides/amines, which can be detected immunocytochemically but may not be secreted.
   5. Presence or absence of clinical syndrome or type cannot be predicted by immunocytochemical studies.
   6. Histologic classifications (grading, TNM classification) have prognostic significance. Only invasion or metastases establish malignancy.

C. Similarities of biologic behavior
   1. Generally slow growing, but some are aggressive.
   2. Most are well-dif erentiated tumors having low proliferative indices.
   3. Secrete biologically active peptides/amines, which can cause clinical symptoms.
   4. Generally have high densities of somatostatin receptors, which are used for both localization and treatment.
   5. Most (>70%) secrete chromogranin A, which is frequently used as a tumor marker.

D. Similarities/dif erences in molecular abnormalities
   1. Similarities
      a. Uncommon—mutations in common oncogenes (ras, jun, fos, etc).
      b. Uncommon—mutations in common tumor-suppressor genes (p53, retinoblastoma).
      c. Alterations at MEN 1 locus (11q13) (frequently foregut, less commonly mid/hindgut NETs) and $p16^{INK4a}$ (9p21) occur in a proportion (10–45%).
      d. Methylation of various genes occurs in 40–87% (ras-associated domain family I, p14, p16, O^6-methylguanine methyltransferases, retinoic acid receptor β).
   2. Dif erences
      a. pNETs—loss of 1p (21%), 3p (8–47%), 3q (8–41%), 11q (21–62%), 6q (18–68%), Y (45%). Gains at 17q (10–55%), 7q (16–68%), 4q (33%), 18 (up to 45%).
      b. GI-NETs (carcinoids)—loss of 18q (38–88%), >18p (33–43%), >9p, 16q21 (21–23%). Gains at 17q, 19p (57%), 4q (33%), 14q (20%), 5 (up to 36%).
      c. pNETs: ATRX/DAXX mutations in 43%, MEN 1 mutations in 44%, mTor mutations (14%); uncommon in midgut GI-NETs (0–2%).

Abbreviations: ATRX, alpha-thalassemia X-lined mental retardation protein; DAXX, death domain associated protein; MEN 1, multiple endocrine neoplasia type 1; TNM, tumor, node, metastasis.

Midgut carcinoids are argentaffin-positive, have a high serotonin content, most frequently cause the typical carcinoid syndrome when they metastasize (Table 51-3, Fig. 51-1), release serotonin and tachykinins (substance P, neuropeptide K, substance K), rarely secrete 5-HTP or ACTH, and less commonly metastasize to bone. Hindgut carcinoids (rectum, transverse and descending colon) are argentaffin-negative, are often argyrophilic, rarely contain serotonin or cause the carcinoid syndrome (Fig. 51-1, Table 51-3), rarely secrete 5-HTP or ACTH, contain numerous peptides, and may metastasize to bone.

pNETs can be classified into nine well-established specific functional syndromes (Table 51-2), six additional very rare specific functional syndromes (less than five cases described), five possible specific functional syndromes (pNETs secreting calcitonin, neurotensin, pancreatic polypeptide, ghrelin) (Table 51-2), and nonfunctional pNETs. Other functional hormonal syndromes due to nonpancreatic tumors (usually intraabdominal in location) have been described only rarely and are not included in (Table 51-2). T ese include secretion by intestinal and ovarian tumors of peptide tyrosine tyrosine (PYY), which results in altered motility and constipation, and ovarian tumors secreting renin or aldosterone causing alterations in blood pressure or somatostatin causing diabetes or reactive hypoglycemia. Each of the functional syndromes listed in Table 51-2 is associated with symptoms due to the specific hormone released. In contrast, nonfunctional pNETs release no products that cause a specific clinical syndrome.

TABLE 51-2

GASTROINTESTINAL NEUROENDOCRINE TUMOR SYNDROMES

NAME	BIOLOGICALLY ACTIVE PEPTIDE(S) SECRETED	INCIDENCE (NEW CASES/10^6 POPULATION/ YEAR)	TUMOR LOCATION	MALIGNANT, %	ASSOCIATED WITH MEN 1, %	MAIN SYMPTOMS/ SIGNS
I. Established Specific Functional Syndromes						
A. Carcinoid syndrome due to GI-NET						
Carcinoid syndrome	Serotonin, possibly tachykinins, motilin, prostaglandins	0.5–2	Midgut (75–87%) Foregut (2–33%) Hindgut (1–8%) Unknown (2–15%)	95–100	Rare	Diarrhea (32–84%) Flushing (63–75%) Pain (10–34%) Asthma (4–18%) Heart disease (11–41%)
B. Well-established functional pNET syndromes						
Zollinger-Ellison syndrome	Gastrin	0.5–1.5	Duodenum (70%) Pancreas (25%) Other sites (5%)	60–90	20–25	Pain (79–100%) Diarrhea (30–75%) Esophageal symptoms (31–56%)
Insulinoma	Insulin	1–2	Pancreas (>99%)	<10	4–5	Hypoglycemic symptoms (100%)
VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA)	Vasoactive intestinal peptide	0.05–0.2	Pancreas (90%, adult) Other (10%, neural, adrenal, periganglionic)	40–70	6	Diarrhea (90–100%) Hypokalemia (80–100%) Dehydration (83%)
Glucagonoma	Glucagon	0.01–0.1	Pancreas (100%)	50–80	1–20	Rash (67–90%) Glucose intolerance (38–87%) Weight loss (66–96%)
Somatostatinoma	Somatostatin	Rare	Pancreas (55%) Duodenum/jejunum (44%)	>70	45	Diabetes mellitus (63–90%) Cholelithiasis (65–90%) Diarrhea (35–90%)
GRFoma	Growth hormone–releasing hormone	Unknown	Pancreas (30%) Lung (54%) Jejunum (7%) Other (13%)	>60	16	Acromegaly (100%)
ACTHoma	ACTH	Rare	Pancreas (4–16% all ectopic Cushing's)	>95	Rare	Cushing's syndrome (100%)
pNET causing carcinoid syndrome	Serotonin, ?tachykinins	Rare (43 cases)	Pancreas (<1% all carcinoids)	60–88	Rare	Same as carcinoid syndrome above
pNET causing hypercalcemia	PTHrP Others unknown	Rare	Pancreas (rare cause of hypercalcemia)	84	Rare	Abdominal pain due to hepatic metastases
II. Rare Specific Functional Syndromes						
pNET secreting renin	Renin	Rare	Pancreas	Unknown	No	Hypertension
pNET secreting luteinizing hormone	Luteinizing hormone	Rare	Pancreas	Unknown	No	Anovulation, virilization (female); reduced libido (male)

(continued)

TABLE 51-2

GASTROINTESTINAL NEUROENDOCRINE TUMOR SYNDROMES (CONTINUED)

NAME	BIOLOGICALLY ACTIVE PEPTIDE(S) SECRETED	INCIDENCE (NEW CASES/10^6 POPULATION/ YEAR)	TUMOR LOCATION	MALIGNANT, %	ASSOCIATED WITH MEN 1, %	MAIN SYMPTOMS/ SIGNS
pNET secreting erythropoietin	Erythropoietin	Rare	Pancreas	100	No	Polycythemia
pNET secreting IGF-II	Insulin-like growth factor II	Rare	Pancreas	Unknown	No	Hypoglycemia
pNET secreting GLP-1	Glucagon-like peptide-1	Rare	Pancreas	Unknown	No	Hypoglycemia, diabetes
pNET secreting enteroglucagon	Enteroglucagon	Rare	Pancreas, small intestine	Unknown	Rare	Small intestinal hypertrophy, intestinal stasis, malabsorption
III. Possible Specific Functional pNET Syndromes						
pNET secreting calcitonin	Calcitonin	Rare	Pancreas (rare cause of hyper-calcitonemia)	>80	16	Diarrhea (50%)
pNET secreting neurotensin	Neurotensin	Rare	Pancreas (100%)	Unknown	No	Motility disturbances, vascular symptoms
pNET secreting pancreatic polypeptide (PPoma)	Pancreatic polypeptide	1–2	Pancreas	>60	18–44	Watery diarrhea
pNET secreting ghrelin	Ghrelin	Rare	Pancreas	Unknown	No	Effects on appetite, body weight
IV. Non Functional Syndrome pNET						
PPoma/ nonfunctional[a]	None	1–2	Pancreas (100%)	>60	18–44	Weight loss (30–90%) Abdominal mass (10–30%) Pain (30–95%)

Abbreviations: ACTH, adrenocorticotropic hormone; GRFoma, growth hormone–releasing factor secreting pancreatic endocrine tumor; IGF-II, insulin-like growth factor II; MEN, multiple endocrine neoplasia; pNET, pancreatic neuroendocrine tumor; PPoma, tumor secreting pancreatic polypeptide; PTHrP, parathyroid hormone–related peptide; VIPoma, tumor secreting vasoactive intestinal peptide; WDHA, watery diarrhea, hypokalemia, and achlorhydria syndrome.

[a]Pancreatic polypeptide–secreting tumors (PPomas) are listed in two places because most authorities classify these as not associated with a specific hormonal syndrome (nonfunctional); however, rare cases of watery diarrhea proposed to be due to PPomas have been reported.

"Nonfunctional" is a misnomer in the strict sense because those tumors frequently ectopically secrete a number of peptides (pancreatic polypeptide [PP], chromogranin A, ghrelin, neurotensin, α subunits of human chorionic gonadotropin, and neuron-specific enolase); however, they cause no specific clinical syndrome. The symptoms caused by nonfunctional pNETs are entirely due to the tumor per se. pNETs frequently ectopically secrete PP (60–85%), neurotensin (30–67%), calcitonin (30–42%), and to a lesser degree, ghrelin (5–65%). Whereas a few studies have proposed their secretion can cause a specific functional syndrome, most studies support the conclusion that their ectopic secretion is not associated with a specific clinical syndrome, and thus they are listed in Table 51-2 as possible clinical syndromes. Because a large proportion of nonfunctional pNETs (60–90%) secrete PP, these tumors are often referred to as PPomas (Table 51-2).

GI-NETs (carcinoids) can occur in almost any GI tissue (Table 51-3); however, at present, most (70%) have their origin in one of three sites: bronchus, jejunoileum, or colon/rectum. In the past, GI-NET (carcinoids) most frequently were reported in the appendix (i.e., 40%); however, the bronchus/lung, rectum, and small intestine are now the most common sites. Overall, the GI tract is the most common site for these tumors, accounting for 64%, with the respiratory

TABLE 51-3

GI-NET (CARCINOID) LOCATION, FREQUENCY OF METASTASES, AND ASSOCIATION WITH THE CARCINOID SYNDROME

	LOCATION (% OF TOTAL)	INCIDENCE OF METASTASES	INCIDENCE OF CARCINOID SYNDROME
Foregut			
Esophagus	<0.1	—	—
Stomach	4.6	10	9.5
Duodenum	2.0	—	3.4
Pancreas	0.7	71.9	20
Gallbladder	0.3	17.8	5
Bronchus, lung, trachea	27.9	5.7	13
Midgut			
Jejunum	1.8	58.4	9
Ileum	14.9		9
Meckel's diverticulum	0.5	—	13
Appendix	4.8	38.8	<1
Colon	8.6	51	5
Liver	0.4	32.	—
Ovary	1.0	2 32	50
Testis	<0.1	—	50
Hindgut			
Rectum	13.6	3.9	—

Abbreviation: GI-NET, gastrointestinal neuroendocrine tumor.
Source: Location is from the PAN-SEER data (1973–1999), and incidence of metastases is from the SEER data (1992–1999), reported by IM Modlin et al: Cancer 97:934, 2003. Incidence of carcinoid syndrome is from 4349 cases studied from 1950–1971, reported by JD Godwin: Cancer 36:560, 1975.

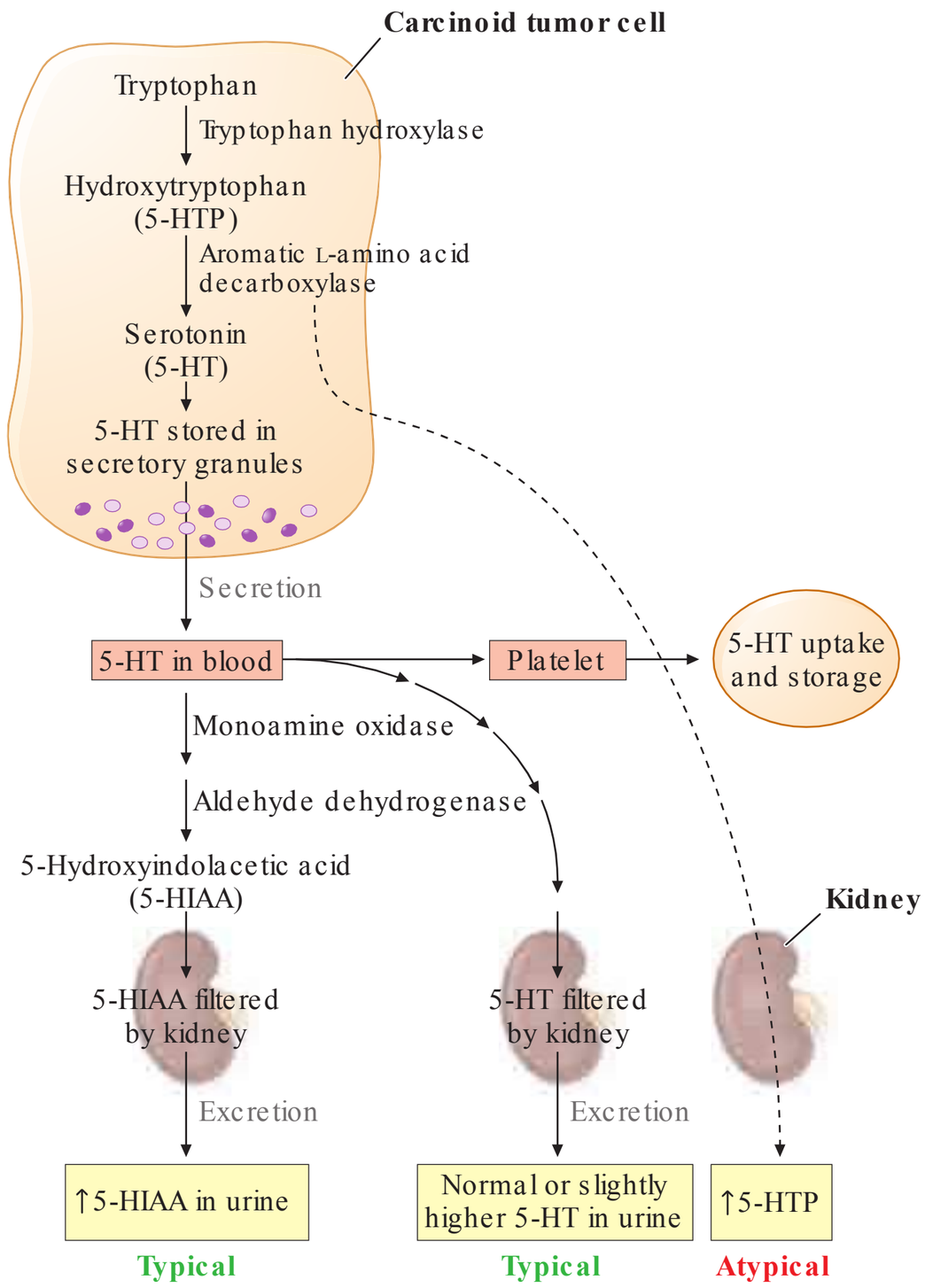


FIGURE 51-1
Synthesis, secretion, and metabolism of serotonin (5-HT) in patients with typical and atypical carcinoid syndromes. 5-HIAA, 5-hydroxyindolacetic acid.

tract a distant second at 28%. Both race and sex can affect the frequency as well as the distribution of GI-NETs (carcinoids). African Americans have a higher incidence of carcinoids. Race is particularly important for rectal carcinoids, which are found in 41% of Asians/Pacific Islanders with NETs compared to 32% of American Indians/Alaskan natives, 26% of African Americans, and 12% of white Americans. Females have a lower incidence of small intestinal and pancreatic carcinoids.

The term pancreatic neuroendocrine or endocrine tumor, although widely used and therefore retained here, is also a misnomer, strictly speaking, because these tumors can occur either almost entirely in the pancreas (insulinomas, glucagonomas, nonfunctional pNETs, pNETs causing hypercalcemia) or at both pancreatic and extrapancreatic sites (gastrinomas, VIPomas [vasoactive intestinal peptide], somatostatinomas, GRFomas [growth hormone–releasing factor]). pNETs are also called islet cell tumors; however, the use of this term is discouraged because it is not established that they originate from the islets, and many can occur at extrapancreatic sites.

Whereas the classification of GI neuroendocrine tumors into foregut, midgut, or hindgut is widely used and generally useful because the NETs within these areas have many similarities, they also have marked differences, particularly in biologic behavior, and it has not proved useful for prognostic purposes. More general classifications have been developed that allow NETs with similar features in different locations to be compared, have proven prognostic value, and are widely used. New classification systems have been developed for both GI-NETs (carcinoids) and pNETs by the World Health Organization (WHO), European Neuroendocrine Tumor Society (ENETS), and the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC). Although there are some differences between these different classification systems,

each uses similar information, and it is now recommended that the basic data underlying the classification be included in all standard pathology reports. T ese classification systems divide NETs from all sites into those that are well differentiated (low grade [G1] or intermediate grade [G2]) and those that are poorly differentiated (high grade [G3] divided into either small-cell carcinoma or large-cell neuroendocrine carcinoma). In these classification systems, both pNETs and GI-NETs (carcinoids) are classified as neuroendocrine tumors, and the old term of carcinoid is equivalent to well-differentiated neuroendocrine tumors of the GI tract. T ese classification systems are based on not only the differentiation of the NET, but also a grading system assessing proliferative indices (Ki-67 and the mitotic count). NETs are considered low grade (ENETS G1) if the Ki-67 is <3% and the mitotic count is <2 mitoses/high-power field (HPF), intermediate grade (ENETS G2) if the Ki-67 is 3–20% and the mitotic count is 2–20 mitoses/HPF, and high grade (ENETS G3) if the Ki-67 is >20% and the mitotic count is >20 mitoses/HPF. In addition to the grading system, a TNM classification has been proposed that is based on the level of tumor invasion, tumor size, and tumor extent (see **Table 51-4** for an example with pNETs and appendiceal GI-NETs [carcinoids]). Because of the proven prognostic value of these classification and grading systems, as well as the fact that NETs with different classifications/grades respond differently to treatments, the systems are now essential for the management of all NETs.

In addition to these classification/grading systems, a number of other factors have been identified that provide important prognostic information that can guide treatment **(Table 51-5)**.

T e exact incidence of GI-NETs (carcinoids) or pNETs varies according to whether only symptomatic tumors or all tumors are considered. T e incidence of clinically significant carcinoids is 7–13 cases/million population per year, whereas any malignant carcinoids at autopsy are reported in 21–84 cases/million population per year. T e incidence of GI-NETs (carcinoids) is approximately 25–50 cases per million in the United States, which makes them less common than adenocarcinomas of the GI tract. However, their incidence has increased sixfold in the last 30 years. In an analysis of 35,825 GI-NETs (carcinoids) (2004) from the U.S. Surveillance, Epidemiology, and End Results (SEER) database, their incidence was 5.25/100,000 per year, and the 29-year prevalence was 35/100,000. Clinically significant pNETs have a prevalence of 10 cases/million population, with insulinomas, gastrinomas, and nonfunctional pNETs having an incidence of 0.5–2 cases/million population per year (Table 51-2). pNETs account for 1–10% of all tumors arising in the pancreas and 1.3% of tumors in the SEER database, which consists primarily of malignant tumors. VIPomas are 2–8 times less common, glucagonomas are 17–30 times less common, and somatostatinomas are the least common. In autopsy studies, 0.5–1.5% of all cases have a pNET; however, in less than 1 in 1000 cases was a functional tumor thought to occur.

Both GI-NETs (carcinoids) and pNETs commonly show malignant behavior (Tables 51-2 and 51-3). With pNETs, except for insulinomas in which <10% are malignant, 50–100% in different series are malignant. With GI-NETs (carcinoids), the percentage showing malignant behavior varies in different locations (Table 51-3). For the three most common sites of occurrence, the incidence of metastases varies greatly from the jejunoileum (58%), lung/bronchus (6%), and rectum (4%) (Table 51-3). With both GI-NETs (carcinoids) and pNETs, a number of factors (Table 51-5)

TABLE 51-4

COMPARISON OF THE CRITERIA FOR THE TUMOR CATEGORY IN THE ENETS AND SEVENTH EDITION AJCC TNM CLASSIFICATIONS OF PANCREATIC AND APPENDICEAL NETS

	ENETS TNM	AJCC/UICC TNM
pNETs		
T1	Confined to pancreas, <2 cm	Confined to pancreas, <2 cm
T2	Confined to pancreas, 2–4 cm	Confined to pancreas, >2 cm
T3	Confined to pancreas, >4 cm, or invasion of duodenum or bile duct	Peripancreatic spread, but without major vascular invasion (truncus coeliacus, superior mesenteric artery)
T4	Invasion of adjacent organs or major vessels	Major vascular invasion
Appendiceal NETs		
T1	≤1 cm; invasion of muscularis propria	T1a, ≤1 cm; T1b, > 1–2 cm
T2	≤2 cm and <3 mm invasion of subserosa/ mesoappendix	>2–4 cm or invasion of cecum
T3	>2 cm or >3 mm invasion of subserosa/ mesoappendix	>4 cm or invasion of ileum
T4	Invasion of peritoneum/ other organs	Invasion of peritoneum/other organs

Abbreviations: AJCC, American Joint Committee on Cancer; ENETS, European Neuroendocrine Tumor Society; NET, neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; TNM, tumor, node, metastasis; UICC, International Union Against Cancer.

Source: Modified from DS Klimstra: Semin Oncol 40:23, 2013 and G Klöppel et al: Virchow Arch 456:595, 2010.

TABLE 51-5

PROGNOSTIC FACTORS IN NEUROENDOCRINE TUMORS

I. Both GI-NETs (carcinoids) and pNETs
Symptomatic presentation (p <.05)
Presence of liver metastases (p <.001)
Extent of liver metastases (p <.001)
Presence of lymph node metastases (p <.001)
Development of bone or extrahepatic metastases (p <.01)
Depth of invasion (p <.001)
Rapid rate of tumor growth
Elevated serum alkaline phosphatase levels (p = .003)
Primary tumor site (p <.001)
Primary tumor size (p <.005)
High serum chromogranin A level (p <.01)
Presence of one or more circulating tumor cells (p <.001)
Various histologic features
Tumor differentiation (p <.001)
High growth indices (high Ki-67 index, PCNA expression)
High mitotic counts (p <.001)
Necrosis present
Presence of cytokeratin 19 (p <.02)
Vascular or perineural invasion
Vessel density (low microvessel density, increased lymphatic density)
High CD10 metalloproteinase expression (in series with all grades of NETs)
Flow cytometric features (i.e., aneuploidy)
High VEGF expression (in low-grade or well-differentiated NETs only)
WHO, ENETS, AJCC/UICC, and grading classification
Presence of a pNET rather than GI-NET associated with poorer prognosis (p = .0001)
Older age (p <.01)
II. GI-NETs (Carcinoids)
Location of primary: appendix < lung, rectum < small intestine < pancreas
Presence of carcinoid syndrome
Laboratory results (urinary 5-HIAA levels [p <.01], plasma neuropeptide K [p <.05], serum chromogranin A [p <.01])
Presence of a second malignancy
Male sex (p <.001)
Molecular findings (TGF-α expression [p <.05], chr 16q LOH or gain chr 4p [p <.05])
WHO, ENETS, AJCC/UICC, and grading classification
Molecular findings (gain in chr 14, loss of 3p13 [ileal carcinoid], upregulation of Hoxc6)
III. pNETs
Location of primary: duodenal (gastrinoma) better than pancreatic
Ha-ras oncogene or p53 overexpression
Female gender
MEN 1 syndrome absent
Presence of nonfunctional tumor (some studies, not all)
WHO, ENETS, AJCC/UICC, and grading classification
Various histologic features: IHC positivity for c-KIT, low cyclin B1 expression (p <.01), loss of PTEN or of tuberous sclerosis-2 IHC, expression of fibroblast growth factor-13
Laboratory findings (increased chromogranin A in some studies; gastrinomas—increased gastrin level)
Molecular findings (increased HER2/neu expression [p = .032], chr 1q, 3p, 3q, or 6q LOH [p = .0004], EGF receptor overexpression [p = .034], gains in chr 7q, 17q, 17p, 20q; alterations in the VHL gene [deletion, methylation]; presence of FGFR4-G388R single-nucleotide polymorphism)

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; AJCC, American Joint Committee on Cancer; chr, chromosome; EGF, epidermal growth factor; FGFR, fibroblast growth factor receptor; GI-NET, gastrointestinal neuroendocrine tumor; IHC, immunohistochemistry; Ki-67, proliferation-associated nuclear antigen recognized by Ki-67 monoclonal antibody; LOH, loss of heterozygosity; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumors; PCNA, proliferating cell nuclear antigen; pNET, pancreatic neuroendocrine tumor; PTEN, phosphatase and tensin homologue deleted from chromosome 10; TGF-α, transforming growth factor α; TNM, tumor, node, metastasis; UICC, International Union Against Cancer; VEGF, vascular endothelial growth factor; WHO, World Health Organization.

are important prognostic factors in determining survival and the aggressiveness of the tumor. Patients with pNETs (excluding insulinomas) generally have a poorer prognosis than do patients with GI-NETs (carcinoids). The presence of liver metastases is the single most important prognostic factor in single and multivariate analyses for both GI-NETs (carcinoids) and pNETs. Particularly important in the development of liver metastases is the size of the primary tumor. For example, with small intestinal carcinoids, which are the most common cause of the carcinoid syndrome due to metastatic disease in the liver (Table 51-2), metastases occur in 15–25% if the tumor is <1 cm in diameter, 58–80% if it is 1–2 cm in diameter, and >75% if it is >2 cm in diameter. Similar data exist for gastrinomas and other pNETs; the size of the primary tumor is an independent predictor of the development of liver metastases. The presence of lymph node metastases or extrahepatic metastases; the depth of invasion; the rapid rate of growth; various histologic features (differentiation, mitotic rates, growth indices, vessel density, vascular endothelial growth factor [VEGF], and CD10 metalloproteinase expression); necrosis; presence of cytokeratin; elevated serum alkaline phosphatase levels; older age; presence of circulating tumor cells; and flow cytometric results, such as the presence of aneuploidy, are all important prognostic factors for the development of metastatic disease (Table 51-5). For patients with GI-NETs (carcinoids), additional associations with a worse prognosis include the development of the carcinoid syndrome (especially the development of carcinoid heart disease), male sex, the presence of a symptomatic tumor or greater increases in a number of tumor markers (5-hydroxyindolacetic acid [5-HIAA], neuropeptide K, chromogranin A), and the presence of various molecular features. With pNETs or gastrinomas, a worse prognosis is associated with female sex, overexpression of the Ha-ras oncogene or p53, the absence of multiple endocrine neoplasia type 1 (MEN 1), higher levels of various tumor markers (i.e., chromogranin A, gastrin), and presence of various histologic features (immunohistochemistry for c-KIT, low cyclin B1, loss of PTEN/TSC-2, expression of fibroblast growth factor-13) and various molecular features (Table 51-5). The TNM classification systems and the grading systems (G1–G3) have important prognostic value.

A number of diseases due to various genetic disorders are associated with an increased incidence of NETs **(Table 51-6)**. Each one is caused by a loss of a possible tumor-suppressor gene. The most important is MEN 1, which is an autosomal dominant disorder due to a defect in a 10-exon gene on 11q13, which encodes for a 610-amino-acid nuclear protein, menin **(Chap. 52)**. Patients with MEN 1 develop hyperparathyroidism due to parathyroid hyperplasia in 95–100% of cases, pNETs in 80–100%, pituitary adenomas in 54–80%, adrenal adenomas in 27–36%, bronchial carcinoids in 8%, thymic carcinoids in 8%, gastric carcinoids in 13–30% of patients with Zollinger-Ellison syndrome, skin tumors (angiofibromas [88%], collagenomas [72%]), central nervous system (CNS) tumors (meningiomas [<8%]), and smooth-muscle tumors (leiomyomas, leiomyosarcomas [1–7%]). Among patients with MEN 1, 80–100% develop nonfunctional pNETs (most are microscopic with 0–13% large/symptomatic), and functional pNETs occur in 20–80% in different series, with a mean of 54% developing Zollinger-Ellison syndrome, 18% insulinomas, 3% glucagonomas, 3% VIPomas, and <1%

TABLE 51-6

GENETIC SYNDROMES ASSOCIATED WITH AN INCREASED INCIDENCE OF NEUROENDOCRINE TUMORS (NETS) (GI-NETS [CARCINOIDS] OR PNETS)

SYNDROME	LOCATION OF GENE MUTATION AND GENE PRODUCT	NETS SEEN/ FREQUENCY
Multiple endocrine neoplasia type 1 (MEN 1)	11q13 (encodes 610-amino-acid protein, menin)	80–100% develop pNETS (microscopic), 20–80% (clinical): (nonfunctional > gastrinoma > insulinoma) GI-NETs (Carcinoids): gastric (13–30%), bronchial/thymic (8%)
von Hippel–Lindau disease	3q25 (encodes 213-amino-acid protein)	12–17% develop pNETS (almost always nonfunctional)
von Recklinghausen's disease (neurofibromatosis 1 [NF-1])	17q11.2 (encodes 2485-amino-acid protein, neurofibromin)	0–10% develop pNETs, primarily duodenal somatostatinomas (usually nonfunctional) Rarely insulinoma, gastrinoma
Tuberous sclerosis	9q34 (TSCI) (encodes 1164-amino-acid protein, hamartin), 16p13 (TSC2) (encodes 1807-amino-acid protein, tuberin)	Uncommonly develop pNETS (nonfunctional and functional [insulinoma, gastrinoma])

Abbreviations: GI, gastrointestinal; PNETs, pancreatic neuroendocrine tumors.

GRFomas or somatostatinomas. MEN 1 is present in 20–25% of all patients with Zollinger-Ellison syndrome, 4% of patients with insulinomas, and a low percentage (<5%) of patients with other pNETs.

T ree phacomatoses associated with NETs are von Hippel–Lindau disease (VHL), von Recklinghausen's disease (neurofibromatosis type 1 [NF-1]), and tuberous sclerosis (Bourneville's disease) (**Table 51-6**). VHL is an autosomal dominant disorder due to defects on chromosome 3p25, which encodes for a 213-amino-acid protein that interacts with the elongin family of proteins as a transcriptional regulator **(Chaps. 48, 52, and 53)**. In addition to cerebellar hemangioblastomas, renal cancer, and pheochromocytomas, 10–17% develop a pNET. Most are nonfunctional, although insulinomas and VIPomas have been reported. Patients with NF-1 (von Recklinghausen's disease) have defects in a gene on chromosome 17q11.2 that encodes for a 2845-amino-acid protein, neurofibromin, which functions in normal cells as a suppressor of the ras signaling cascade **(Chap. 48)**. Up to 10% of these patients develop an upper GI-NET (carcinoid), characteristically in the periampullary region (54%). Many are classified as somatostatinomas because they contain somatostatin immunocytochemically; however, they uncommonly secrete somatostatin and rarely produce a clinical somatostatinoma syndrome. NF-1 has rarely been associated with insulinomas and Zollinger-Ellison syndrome. NF-1 accounts for 48% of all duodenal somatostastinomas and 23% of all ampullary GI-NETs (carcinoids). Tuberous sclerosis is caused by mutations that alter either the 1164-amino-acid protein hamartin (TSC1) or the 1807-amino-acid protein tuberin (TSC2) **(Chap. 48)**. Both hamartin and tuberin interact in a pathway related to phosphatidylinositol 3-kinases and mammalian target of rapamycin (mTOR) signaling cascades. A few cases including nonfunctional and functional pNETs (insulinomas and gastrinomas) have been reported in these patients (Table 51-6). Mahvash disease is associated with the development of α-cell hyperplasia, hyperglucagonemia, and the development of NF pNETs and is due to a homozygous P86S mutation of the human glucagon receptor.

Mutations in common oncogenes (ras, myc, fos, src, jun) or common tumor-suppressor genes (p53, retinoblastoma susceptibility gene) are not commonly found in either pNETs or GI-NETs (carcinoids) (Table 51-1). However, frequent (70%) gene amplifications in MDM2, MDM4, and WIPI inactivating the p53 pathway are noted in well-differentiated pNETs, and the retinoblastoma pathway is altered in the majority of pNETs. In addition to these genes, additional alterations that may be important in their pathogenesis include changes in the MEN1 gene, p16/MTS1 tumor-suppressor gene, and DPC4/Smad4 gene; amplification of the HER-2/neu protooncogene; alterations in transcription factors (Hoxc6 [GI carcinoids]), growth factors, and their receptors; methylation of a number of genes that probably results in their inactivation; and deletions of unknown tumor-suppressor genes as well as gains in other unknown genes (Table 51-1). T e clinical antitumor activity of everolimus, an mTOR inhibitor, and sunitinib, a tyrosine kinase inhibitor (PDGFR, VEGFR1, VEGFR2, c-KIT, FLT-3), support the importance of the mTOR-AKT pathway and tyrosine kinase receptors in mediating growth of malignant NETs (especially pNETs). T e importance of the mTOR pathway in pNET growth is further supported by the finding that a single-nucleotide polymorphism (FGFR4-G388R, in fibroblast growth factor receptor 4) affects selectivity to the mTOR inhibitor and can result in significantly higher risk of advanced pNET stage and liver metastases (Table 51-5). Comparative genomic hybridization, genome-wide allelotyping studies, and genome-wide single-nucleotide polymorphism analyses have shown that chromosomal losses and gains are common in pNETs and GI-NETs (carcinoids), but they differ between these two NETs, and some have prognostic significance (Table 51-5). Mutations in the MEN1 gene are probably particularly important. Loss of heterozygosity at the MEN 1 locus on chromosome 11q13 is noted in 93% of sporadic pNETs (i.e., in patients without MEN 1) and in 26–75% of sporadic GI-NETs (carcinoids). Mutations in the MEN1 gene are reported in 31–34% of sporadic gastrinomas. Exomic sequencing of sporadic pNETs found that the most frequently altered gene was MEN1, occurring in 44% of patients, followed by mutations in 43% of patients in genes encoding for two subunits of a transcription/chromatin remodeling complex consisting of DAXX (death-domain-associated protein) and ATRX (α-thalassemia/mental retardation syndrome X-linked) and in 15% of patients in the mTOR pathway. T e presence of a number of these molecular alterations in pNETs or GI-NETs (carcinoids) correlates with tumor growth, tumor size, and disease extent or invasiveness and may have prognostic significance (Table 51-5).

GI-NETS (CARCINOIDS) AND CARCINOID SYNDROME

CHARACTERISTICS OF THE MOST COMMON GI-NETS (CARCINOIDS)

Appendiceal NETs (carcinoids)

Appendiceal NETs (carcinoids) occur in 1 in every 200–300 appendectomies, usually in the appendiceal tip, have an incidence of 0.15/100,000 per year, comprise 2–5% of all GI-NETs (carcinoids), and comprise

32–80% of all appendiceal tumors. Most (i.e., >90%) are <1 cm in diameter without metastases in older studies, but more recently, 2–35% have had metastases (Table 51-3). In the SEER data of 1570 appendiceal carcinoids, 62% were localized, 27% had regional metastases, and 8% had distant metastases. The risk of metastases increases with size, with those <1 cm having a 0 to <10% risk of metastases and those >2 cm having a 25–44% risk. Besides tumor size, other important prognostic factors for metastases include basal location, invasion of mesoappendix, poor differentiation, advanced stage or WHO/ENETS classification, older age, and positive resection margins. The 5-year survival is 88–100% for patients with localized disease, 78–100% for patients with regional involvement, and 12–28% for patients with distal metastases. In patients with tumors <1 cm in diameter, the 5-year survival is 95–100%, whereas it is 29% if tumors are >2 cm in diameter. Most tumors are well-differentiated G1 tumors (87%) (Table 51-4), with the remainder primarily well-differentiated G2 tumors (13%); poorly differentiated G3 tumors are uncommon (<1%). Their percentage of the total number of carcinoids decreased from 43.9% (1950–1969) to 2.4% (1992–1999). Appendiceal goblet cell (GC) NETs (carcinoids)/carcinomas are a rare subtype (<5%) that are mixed adeno-neuroendocrine carcinomas. They are malignant and are thought to comprise a distinct entity; they frequently present with advanced disease and are recommended to be treated as adenocarcinomas, not carcinoid tumors.

SMALL INTESTINAL NETS (CARCINOIDS)

Small intestinal (SI) NETs (carcinoids) have a reported incidence of 0.67/100,000 in the United States, 0.32/100,000 in England, and 1.12/100,000 in Sweden and comprise >50% of all SI tumors. There is a male predominance (1.5:1), and race affects frequency, with a lower frequency in Asians and greater frequency in African Americans. The mean age of presentation is 52–63 years, with a wide range (1–93 years). Familial SI carcinoid families exist but are very uncommon. These are frequently multiple; 9–18% occur in the jeunum, 70–80% are present in the ileum, and 70% occur within 6 cm (2.4 in.) of the ileocecal valve. Forty percent are <1 cm in diameter, 32% are 1–2 cm, and 29% are >2 cm. They are characteristically well differentiated; however, they are generally invasive, with 1.2% being intramucosal in location, 27% penetrating the submucosa, and 20% invading the muscularis propria. Metastases occur in a mean of 47–58% (range 20–100%). Liver metastases occur in 38%, to lymph nodes in 37% and more distant in 20–25%. They characteristically cause a marked fibrotic reaction, which can lead to intestinal obstruction. Tumor size is an important variable in the frequency of metastases. However, even small NETs (carcinoids) of the small intestine (<1 cm) have metastases in 15–25% of cases, whereas the proportion increases to 58–100% for tumors 1–2 cm in diameter. Carcinoids also occur in the duodenum, with 31% having metastases. Duodenal tumors <1 cm virtually never metastasize, whereas 33% of those >2 cm had metastases. SI NETs (carcinoids) are the most common cause (60–87%) of the carcinoid syndrome and are discussed in a later section **(Table 51-7)**. Important prognostic factors are listed in (Table 51-5), and particularly important are the tumor extent, proliferative index by grading, and stage (Table 51-4). The overall survival at 5 years is 55–75%; however, it varies markedly with disease extent, being 65–90% with localized disease, 66–72% with regional involvement, and 36–43% with distant disease.

Rectal NETs (carcinoids)

Rectal NETs (carcinoids) comprise 27% of all GI-NETs (carcinoids) and 16% of all NETs and are increasing in frequency. In the U.S. SEER data, they currently have an incidence of 0.86/100,000 per year (up from 0.2/100,000 per year in 1973) and represent 1–2% of all rectal tumors. They are found in approximately 1 in every 1500/2500 proctoscopies/colonoscopies or 0.05–0.07% of individuals undergoing these procedures. Nearly

TABLE 51-7

CLINICAL CHARACTERISTICS IN PATIENTS WITH CARCINOID SYNDROME

	PERCENTAGE (RANGE)	
	AT PRESENTATION	DURING COURSE OF DISEASE
Symptoms/signs		
Diarrhea	32–93%	68–100%
Flushing	23–100%	45–96%
Pain	10%	34%
Asthma/ wheezing	4–14%	3–18%
Pellagra	0–7%	0–5%
None	12%	22%
Carcinoid heart disease present	11–40%	14–41%
Demographics		
Male	46–59%	46–61%
Age		
Mean	57 yrs	59.2 yrs
Range	25–79 yrs	18–91 yrs
Tumor location		
Foregut	5–14%	0–33%
Midgut	57–87%	60–100%
Hindgut	1–7%	0–8%
Unknown	2–21%	0–26%

all occur between 4 and 13 cm above the dentate line. Most are small, with 66–80% being <1 cm in diameter, and rarely metastasize (5%). Tumors between 1 and 2 cm can metastasize in 5–30%, and those >2 cm, which are uncommon, in >70%. Most invade only to the submucosa (75%), with 2.1% confined to the mucosa, 10% to the muscular layer, and 5% to adjacent structures. Histologically, most are well differentiated (98%) with 72% ENETS/WHO grade G1 and 28% grade G2 (Table 51-4). Overall survival is 88%; however, it is very much dependent of the stage, with 5-year survival of 91% for localized disease, 36–49% for regional disease, and 20–32% for distant disease. Risk factors are listed in Table 51-5 and particularly include tumor size, depth of invasion, presence of metastases, differentiation, and recent TNM classification and grade.

Bronchial NETs (carcinoids)

Bronchial NETs (carcinoids) comprise 25–33% of all well-differentiated NETs and 90% of all the poorly differentiated NETs found, likely due to a strong association with smoking. T eir incidence ranges from 0.2 to 2/100,000 per year in the United States and European countries and is increasing at a rate of 6% per year. T ey are slightly more frequent in females and in whites compared with those of Hispanic/Asian/African descent, and are most commonly seen in the sixth decade of life, with a younger age of presentation for typical carcinoids (45 years) compared to atypical carcinoids (55 years).

A number of different classifications of bronchial GI-NETs (carcinoids) have been proposed. In some studies, they are classified into four categories: typical carcinoid (also called bronchial carcinoid tumor, Kulchitsky cell carcinoma I [KCC-I]), atypical carcinoid (also called well-differentiated neuroendocrine carcinoma [KC-II]), intermediate small-cell neuroendocrine carcinoma, and small-cell neuroendocarcinoma (KC-III). Another proposed classification includes three categories of lung NETs: benign or low-grade malignant (typical carcinoid), low-grade malignant (atypical carcinoid), and high-grade malignant (poorly differentiated carcinoma of the large-cell or small-cell type). T e WHO classification includes four general categories: typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma, and small-cell carcinoma. T e ratio of typical to atypical carcinoids is 8–10:1, with the typical carcinoids comprising 1–2% of lung tumors, atypical 0.1–0.2%, large-cell neuroendocrine tumors 0.3%, and small-cell lung cancer 9.8% of all lung tumors. T ese different categories of lung NETs have different prognoses, varying from excellent for typical carcinoid to poor for small-cell neuroendocrine carcinomas. T e occurrence of large-cell and small-cell lung carcinoids, but not typical or atypical lung carcinoids, is related to tobacco use. T e 5-year survival is very much influenced by the classification of the tumor, with survival of 92–100% for patients with a typical carcinoid, 61–88% with an atypical carcinoid, 13–57% with a large-cell neuroendocrine tumor, and 5% with a small-cell lung cancer.

Gastric NET (carcinoids)

Gastric NETs (carcinoids) account for 3 of every 1000 gastric neoplasms and 1.3–2% of all carcinoids, and their relative frequency has increased three- to four-fold over the last five decades (2.2% in 1950 to 9.6% in 2000–2007, SEER data). At present, it is unclear whether this increase is due to better detection with the increased use of upper GI endoscopy or to a true increase in incidence. Gastric NETs (carcinoids) are classified into three different categories, and this has important implications for pathogenesis, prognosis, and treatment. Each originates from gastric enterochromaffin-like (ECL) cells, one of the six types of gastric neuroendocrine cells, in the gastric mucosa. Two subtypes are associated with hypergastrinemic states, either chronic atrophic gastritis (type I) (80% of all gastric NETs [carcinoids]) or Zollinger-Ellison syndrome, which is almost always a part of the MEN 1 syndrome (type II) (6% of all cases). T ese tumors generally pursue a benign course, with type I uncommonly (<10%) associated with metastases, whereas type II tumors are slightly more aggressive, with 10–30% associated with metastases. T ey are usually multiple, small, and infiltrate only to the submucosa. T e third subtype of gastric NETs (carcinoids) (type III) (sporadic) occurs without hypergastrinemia (14–25% of all gastric carcinoids) and has an aggressive course, with 54–66% developing metastases. Sporadic carcinoids are usually single, large tumors; 50% have atypical histology, and they can be a cause of the carcinoid syndrome. Five-year survival is 99–100% in patients with type I, 60–90% in patients with type II, and 50% in patients with type III gastric NETs (carcinoids).

CLINICAL PRESENTATION OF NETS (CARCINOIDS)

GI/Lung NET (carcinoid) without the carcinoid syndrome

T e age of patients at diagnosis ranges from 10 to 93 years, with a mean age of 63 years for the small intestine and 66 years for the rectum. T e presentation is diverse and is related to the site of origin and the extent of malignant spread. In the appendix, NETs (carcinoids) usually are found incidentally during surgery for suspected appendicitis. SI NETs (carcinoids) in the jejunoileum present with periodic abdominal pain (51%), intestinal obstruction with ileus/invagination (31%), an

abdominal tumor (17%), or GI bleeding (11%). Because of the vagueness of the symptoms, the diagnosis usually is delayed approximately 2 years from onset of the symptoms, with a range up to 20 years. Duodenal, gastric, and rectal NETs (carcinoids) are most frequently found by chance at endoscopy. T e most common symptoms of rectal carcinoids are melena/bleeding (39%), constipation (17%), and diarrhea (12%). Bronchial NETs (carcinoids) frequently are discovered as a lesion on a chest radiograph, and 31% of the patients are asymptomatic. T ymic NETs (carcinoids) present as anterior mediastinal masses, usually on chest radiograph or computed tomography (CT) scan. Ovarian and testicular NETs (carcinoids) usually present as masses discovered on physical examination or ultrasound. Metastatic NETs (carcinoids) in the liver frequently presents as hepatomegaly in a patient who may have minimal symptoms and nearly normal liver function test results.

GI-NETS (CARCINOIDS) WITH SYSTEMIC SYMPTOMS DUE TO SECRETED PRODUCTS

GI/lung NETs (carcinoids) immunocytochemically can contain numerous GI peptides: gastrin, insulin, somatostatin, motilin, neurotensin, tachykinins (substance K, substance P, neuropeptide K), glucagon, gastrin-releasing peptide, vasoactive intestinal peptide (VIP), PP, ghrelin, other biologically active peptides (ACTH, calcitonin, growth hormone), prostaglandins, and bioactive amines (serotonin). T ese substances may or may not be released in sufficient amounts to cause symptoms. In various studies of patients with GI-NETs (carcinoids), elevated serum levels of PP were found in 43%, motilin in 14%, gastrin in 15%, and VIP in 6%. Foregut NETs (carcinoids) are more likely to produce various GI peptides than are midgut NETs (carcinoids). Ectopic ACTH production causing Cushing's syndrome is seen increasingly with foregut carcinoids (respiratory tract primarily) and, in some series, has been the most common cause of the ectopic ACTH syndrome, accounting for 64% of all cases. Acromegaly due to growth hormone–releasing factor release occurs with foregut NETs (carcinoids), as does the somatostatinoma syndrome, but rarely occurs with duodenal NETs (carcinoids). T e most common systemic syndrome with GI-NETs (carcinoids) is the carcinoid syndrome, which is discussed in detail in the next section.

CARCINOID SYNDROME

Clinical features

T e cardinal features from a number of series at presentation as well as during the disease course are shown in Table 51-7. Flushing and diarrhea are the two most common symptoms, occurring in a mean of 69–70% of patients initially and in up to 78% of patients during the course of the disease. T e characteristic f ush is of sudden onset; it is a deep red or violaceous erythema of the upper body, especially the neck and face, often associated with a feeling of warmth and occasionally associated with pruritus, lacrimation, diarrhea, or facial edema. Flushes may be precipitated by stress; alcohol; exercise; certain foods, such as cheese; or certain agents, such as catecholamines, pentagastrin, and serotonin reuptake inhibitors. Flushing episodes may be brief, lasting 2–5 min, especially initially, or may last hours, especially later in the disease course. Flushing usually is associated with metastatic midgut NETs (carcinoids) but can also occur with foregut NETs (carcinoids). With bronchial NETs (carcinoids), the f ushes frequently are prolonged for hours to days, reddish in color, and associated with salivation, lacrimation, diaphoresis, diarrhea, and hypotension. T e f ush associated with gastric NETs (carcinoids) can also be reddish in color, but with a patchy distribution over the face and neck, although the classic f ush seen with midgut NETs (carcinoids) can also be seen with gastric NETs (carcinoids). It may be provoked by food and have accompanying pruritus.

Diarrhea usually occurs with f ushing (85% of cases). T e diarrhea usually is described as watery, with 60% of patients having <1 L/d of diarrhea. Steatorrhea is present in 67%, and in 46%, it is >15 g/d (normal <7 g). Abdominal pain may be present with the diarrhea or independently in 10–34% of cases.

Cardiac manifestations occur initially in 11–40% (mean 26%) of patients with carcinoid syndrome and in 14–41% (mean 30%) at some time in the disease course. T e cardiac disease is due to the formation of fibrotic plaques (composed of smooth-muscle cells, myofibroblasts, and elastic tissue) involving the endocardium, primarily on the right side, although lesions on the left side also occur occasionally, especially if a patent foramen ovale exists. T e dense fibrous deposits are most commonly on the ventricular aspect of the tricuspid valve and less commonly on the pulmonary valve cusps. T ey can result in constriction of the valves, and pulmonic stenosis is usually predominant, whereas the tricuspid valve is often fixed open, resulting in regurgitation predominating. Overall, in patients with carcinoid heart disease, 90–100% have tricuspid insufficiency, 43–59% have tricuspid stenosis, 50–81% have pulmonary insufficiency, 25–59% have pulmonary stenosis, and 11% (0–25%) left-side lesions. Up to 80% of patients with cardiac lesions develop heart failure. Lesions on the left side are much less extensive, occur in 30% at autopsy, and most frequently affect the mitral valve. Up to 80% of patients with cardiac lesions have evidence of heart failure. At diagnosis in various series, 27–43% of patients are in New York Heart Association

class I, 30–40% are in class II, 13–31% are in class III, and 3–12% are in class IV. At present, carcinoid heart disease is reported to be decreasing in frequency and severity, with mean occurrence in 20% of patients and occurrence in as few as 3–4% in some reports. Whether this decrease is due to the widespread use of somatostatin analogues, which control the release of bioactive agents thought involved in mediating the heart disease, is unclear.

Other clinical manifestations include wheezing or asthma-like symptoms (8–18%), pellagra-like skin lesions (2–25%), and impaired cognitive function. A variety of noncardiac problems due to increased fibrous tissue have been reported, including retroperitoneal fibrosis causing urethral obstruction, Peyronie's disease of the penis, intraabdominal fibrosis, and occlusion of the mesenteric arteries or veins.

Pathobiology

Carcinoid syndrome occurred in 8% of 8876 patients with GI-NETs (carcinoids), with a rate of 1.7–18.4% in different studies. It occurs only when sufficient concentrations of products secreted by the tumor reach the systemic circulation. In 91–100% of cases, this occurs after distant metastases to the liver. Rarely, primary GI-NETs (carcinoids) with nodal metastases with extensive retroperitoneal invasion, pNETs (carcinoids) with retroperitoneal lymph nodes, or NETs (carcinoids) of the lung or ovary with direct access to the systemic circulation can cause the carcinoid syndrome without hepatic metastases. All GI-NETs (carcinoids) do not have the same propensity to metastasize and cause the carcinoid syndrome (Table 51-3). Midgut NETs (carcinoids) account for 57–67% of cases of carcinoid syndrome, foregut NETs (carcinoids) for 0–33%, hindgut for 0–8%, and an unknown primary location for 2–26% (Tables 51-3 and 51-7).

One of the main secretory products of GI-NETs (carcinoids) involved in the carcinoid syndrome is serotonin (5-HT) (Fig. 51-1), which is synthesized from tryptophan. Up to 50% of dietary tryptophan can be used in this synthetic pathway by tumor cells, and this can result in inadequate supplies for conversion to niacin; hence, some patients (2.5%) develop pellagra-like lesions. Serotonin has numerous biologic effects, including stimulating intestinal secretion with inhibition of absorption, stimulating increases in intestinal motility, and stimulating fibrogenesis. In various studies, 56–88% of all GI-NETs (carcinoids) were associated with serotonin overproduction; however, 12–26% of the patients did not have the carcinoid syndrome. In one study, platelet serotonin was elevated in 96% of patients with midgut NETs (carcinoids), 43% with foregut tumors, and 0% with hindgut tumors. In 90–100% of patients with the carcinoid syndrome, there is evidence of serotonin overproduction. Serotonin is thought to be predominantly responsible for the diarrhea. Patients with the carcinoid syndrome have increased colonic motility with a shortened transit time and possibly a secretory/absorptive alteration that is compatible with the known actions of serotonin in the gut mediated primarily through 5-HT_3 and, to a lesser degree, 5-HT_4 receptors. Serotonin receptor antagonists (especially 5-HT_3 antagonists) relieve the diarrhea in many, but not all, patients. A tryptophan 5-hydroxylase inhibitor, LX-1031, which inhibits serotonin synthesis in peripheral tissues, is reported to cause a 44% decrease in bowel movement frequency and a 20% improvement in stool form in patients with the carcinoid syndrome. Additional studies suggest that tachykinins may be important mediators of diarrhea in some patients. In one study, plasma tachykinin levels correlated with symptoms of diarrhea. Serotonin does not appear to be involved in the flushing because serotonin receptor antagonists do not relieve flushing. In patients with gastric carcinoids, the characteristic red, patchy pruritic flush is thought due to histamine release because H_1 and H_2 receptor antagonists can prevent it. Numerous studies have shown that tachykinins (substance P, neuropeptide K) are stored in GI-NETs (carcinoids) and released during flushing. However, some studies have demonstrated that octreotide can relieve the flushing induced by pentagastrin in these patients without altering the stimulated increase in plasma substance P, suggesting that other mediators must be involved in the flushing. A correlation between plasma tachykinin levels (but not substance P levels) and flushing has been reported. Prostaglandin release could be involved in mediating either the diarrhea or flush, but conflicting data exist. Both histamine and serotonin may be responsible for the wheezing as well as the fibrotic reactions involving the heart, causing Peyronie's disease and intraabdominal fibrosis.

The exact mechanism of the heart disease remains unclear, although increasing evidence supports a central role for serotonin. Patients with heart disease have higher plasma levels of neurokinin A, substance P, plasma atrial natriuretic peptide (ANP), pro-brain natriuretic peptide, chromogranin A, and activin A as well as higher urinary 5-HIAA excretion.

The valvular heart disease caused by the appetite-suppressant drug dexfenfluramine is histologically indistinguishable from that observed in carcinoid disease. Furthermore, ergot-containing dopamine receptor agonists used for Parkinson's disease (pergolide, cabergoline) cause valvular heart disease that closely resembles that seen in the carcinoid syndrome. Furthermore, in animal studies, the formation of valvular plaques/fibrosis occurs after prolonged treatment with serotonin

as well as in animals with a deficiency of the 5-HIAA transporter gene, which results in an inability to inactivate serotonin. Metabolites of fenfuramine, as well as the dopamine receptor agonists, have high affinity for serotonin receptor subtype 5-HT_{2B} receptors, whose activation is known to cause fibroblast mitogenesis. Serotonin receptor subtypes 5-$HT_{1B,1D,2A,2B}$ normally are expressed in human heart valve interstitial cells. High levels of 5-HT_{2B} receptors are known to occur in heart valves and occur in cardiac fibroblasts and cardiomyocytes. Studies of cultured interstitial cells from human cardiac valves have demonstrated that these valvulopathic drugs induce mitogenesis by activating 5-HT_{2B} receptors and stimulating upregulation of transforming growth factor β and collagen biosynthesis. These observations support the conclusion that serotonin overproduction by GI-NETs (carcinoids) is important in mediating the valvular changes, possibly by activating 5-HT_{2B} receptors in the endocardium. Both the magnitude of serotonin overproduction and prior chemotherapy are important predictors of progression of the heart disease, whereas patients with high plasma levels of ANP have a worse prognosis. Plasma connective tissue growth factor levels are elevated in many fibrotic conditions; elevated levels occur in patients with carcinoid heart disease and correlate with the presence of right ventricular dysfunction and the extent of valvular regurgitation in patients with GI-NETs (carcinoids).

Patients may develop either a typical or, rarely, an atypical carcinoid syndrome (Fig. 51-1). In patients with the typical form, which characteristically is caused by midgut NETs (carcinoids), the conversion of tryptophan to 5-HTP is the rate-limiting step (Fig. 51-1). Once 5-HTP is formed, it is rapidly converted to 5-HT and stored in secretory granules of the tumor or in platelets. A small amount remains in plasma and is converted to 5-HIAA, which appears in large amounts in the urine. These patients have an expanded serotonin pool size, increased blood and platelet serotonin, and increased urinary 5-HIAA. Some GI-NETs (carcinoids) cause an atypical carcinoid syndrome that is thought to be due to a deficiency in the enzyme dopa decarboxylase; thus, 5-HTP cannot be converted to 5-HT (serotonin), and 5-HTP is secreted into the bloodstream (Fig. 51-1). In these patients, plasma serotonin levels are normal but urinary levels may be increased because some 5-HTP is converted to 5-HT in the kidney. Characteristically, urinary 5-HTP and 5-HT are increased, but urinary 5-HIAA levels are only slightly elevated. Foregut carcinoids are the most likely to cause an atypical carcinoid syndrome; however, they also can cause a typical carcinoid syndrome.

One of the most immediate life-threatening complications of the carcinoid syndrome is the development of a carcinoid crisis. This is more common in patients who have intense symptoms or have greatly increased urinary 5-HIAA levels (i.e., >200 mg/d). The crisis may occur spontaneously; however, it is usually provoked by procedures such as anesthesia, chemotherapy, surgery, biopsy, endoscopy, or radiologic examinations such as during biopsies, hepatic artery embolization, and vessel catheterization. It can be provoked by stress or procedures as mild as repeated palpation of the tumor during physical examination. Patients develop intense flushing, diarrhea, abdominal pain, cardiac abnormalities including tachycardia, hypertension, or hypotension, and confusion or stupor. If not adequately treated, this can be a terminal event.

DIAGNOSIS OF THE CARCINOID SYNDROME AND GI-NETS (CARCINOIDS)

The diagnosis of carcinoid syndrome relies on measurement of urinary or plasma serotonin or its metabolites in the urine. The measurement of 5-HIAA is used most frequently. False-positive elevations may occur if the patient is eating serotonin-rich foods such as bananas, pineapples, walnuts, pecans, avocados, or hickory nuts or is taking certain medications (cough syrup containing guaifenesin, acetaminophen, salicylates, serotonin reuptake inhibitors, or l-dopa). The normal range for daily urinary 5-HIAA excretion is 2–8 mg/d. Serotonin overproduction was noted in 92% of patients with carcinoid syndrome in one study, and in another study, 5-HIAA had 73% sensitivity and 100% specificity for carcinoid syndrome. Serotonin overproduction is not synonymous with the presence of clinical carcinoid syndrome because 12–26% of patients with serotonin overproduction do not have clinical evidence of the carcinoid syndrome.

Most physicians use only the urinary 5-HIAA excretion rate; however, plasma and platelet serotonin levels, if available, may provide additional information. Platelet serotonin levels are more sensitive than urinary 5-HIAA but are not generally available. A single plasma 5-HIAA determination was found to correlate with the 24-h urinary values, raising the possibility that this could replace the standard urinary collection because of its greater convenience and avoidance of incomplete or improper collections. Because patients with foregut NETs (carcinoids) may produce an atypical carcinoid syndrome, if this syndrome is suspected and the urinary 5-HIAA is minimally elevated or normal, other urinary metabolites of tryptophan, such as 5-HTP and 5-HT, should be measured (Fig. 51-1).

Flushing occurs in a number of other diseases, including systemic mastocytosis, chronic myeloid leukemia with increased histamine release, menopause, reactions to alcohol or glutamate, and side effects of chlorpropamide, calcium channel blockers, and

nicotinic acid. None of these conditions cause increased urinary 5-HIAA.

The diagnosis of carcinoid tumor can be suggested by the carcinoid syndrome, recurrent abdominal symptoms in a healthy-appearing individual, or the discovery of hepatomegaly or hepatic metastases associated with minimal symptoms. Ileal NETs (carcinoids), which make up 25% of all clinically detected carcinoids, should be suspected in patients with bowel obstruction, abdominal pain, flushing, or diarrhea.

Serum chromogranin A levels are elevated in 56–100% of patients with GI-NETs (carcinoids), and the level correlates with tumor bulk. Serum chromogranin A levels are not specific for GI-NETs (carcinoids) because they are also elevated in patients with pNETs and other NETs. Furthermore, a major problem is caused by potent acid antisecretory drugs such as proton pump inhibitors (omeprazole and related drugs) because they almost invariably cause elevation of plasma chromogranin A levels; the elevation occurs rapidly (3–5 days) with continued use, and the elevated levels overlap with the levels seen in many patients with NETs. Plasma neuron-specific enolase levels are also used as a marker of GI-NETs (carcinoids) but are less sensitive than chromogranin A, being increased in only 17–47% of patients. Newer markers have been proposed including pancreastatin (a chromogranin A breakdown product) and activin A. The former is not affected by proton pump inhibitors; however, its sensitivity and specificity are not established. Plasma activin elevations are reported to correlate with the presence of cardiac disease with a sensitivity of 87% and specificity of 57%.

TREATMENT Carcinoid Syndrome and Nonmetastatic Gastrointestinal Neuroendocrine Tumors (Carcinoids)

CARCINOID SYNDROME Treatment includes avoiding conditions that precipitate flushing, dietary supplementation with nicotinamide, treatment of heart failure with diuretics, treatment of wheezing with oral bronchodilators, and control of the diarrhea with antidiarrheal agents such as loperamide and diphenoxylate. If patients still have symptoms, serotonin receptor antagonists or somatostatin analogues **(Fig. 51-2)** are the drugs of choice.

There are 14 subclasses of serotonin receptors, and antagonists for many are not available. The 5-HT_1 and 5-HT_2 receptor antagonists methysergide, cyproheptadine, and ketanserin have all been used to control the diarrhea but usually do not decrease flushing. The use of methysergide is limited because it can cause or enhance retroperitoneal fibrosis. Ketanserin diminishes diarrhea in 30–100% of patients. 5-HT_3 receptor antagonists (ondansetron, tropisetron, alosetron) can control diarrhea and nausea in up to 100% of patients and occasionally ameliorate the flushing. A combination of histamine H_1 and H_2 receptor antagonists (i.e., diphenhydramine and cimetidine or ranitidine) may control flushing in patients with foregut carcinoids. The tryptophan 5-hydoxylase inhibitor telotristat etiprate decreased bowel frequency in 44% and improved stool consistency in 20%.

Synthetic analogues of somatostatin (octreotide, lanreotide) are now the most widely used agents to control the symptoms of patients with carcinoid syndrome (Fig. 51-2). These drugs are effective at relieving symptoms and decreasing urinary 5-HIAA levels in patients with this syndrome. Octreotide-LAR and lanreotide-SR/autogel (Somatuline)

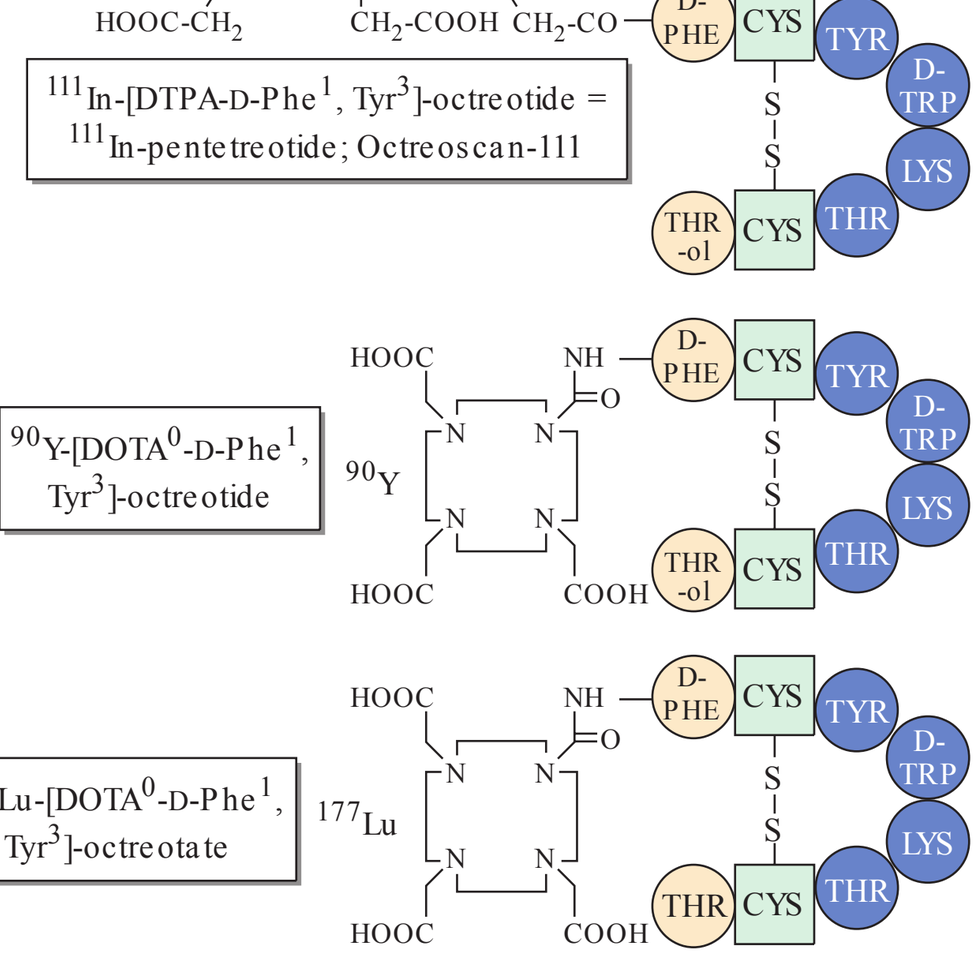


FIGURE 51-2
Structure of somatostatin and synthetic analogues used for diagnostic or therapeutic indications.

(sustained-release formulations allowing monthly injections) control symptoms in 74% and 68% of patients, respectively, with carcinoid syndrome and show a biochemical response in 51% and 64%, respectively. Patients with mild to moderate symptoms usually are treated initially with octreotide 100 μg SC every 8 h and then begun on the long-acting monthly depot forms (octreotide-LAR or lanreotide-autogel). Forty percent of patients escape control after a median time of 4 months, and the depot dosage may have to be increased as well as supplemented with the shorter-acting formulation, SC octreotide. Pasireotide (SOM230) is a somatostatin analogue with broader selectivity (high-affinity somatostatin receptors [sst_1, sst_2, sst_3, sst_5]) than octreotide/lanreotide (sst_2, sst_5). In a phase II study of patients with refractory carcinoid syndrome, pasireotide controlled symptoms in 27%.

Carcinoid heart disease is associated with a decreased mean survival (3.8 years), and therefore, it should be sought for and carefully assessed in all patients with carcinoid syndrome. Transthoracic echocardiography remains a key element in establishing the diagnosis of carcinoid heart disease and determining the extent and type of cardiac abnormalities. Treatment with diuretics and somatostatin analogues can reduce the negative hemodynamic effects and secondary heart failure. It remains unclear whether long-term treatment with these drugs will decrease the progression of carcinoid heart disease. Balloon valvuloplasty for stenotic valves or cardiac valve surgery may be required.

In patients with carcinoid crises, somatostatin analogues are effective at both treating the condition and preventing their development during known precipitating events such as surgery, anesthesia, chemotherapy, and stress. It is recommended that octreotide 150–250 μg SC every 6 to 8 h be used 24–48 h before anesthesia and then continued throughout the procedure.

Currently, sustained-release preparations of both octreotide (octreotide-LAR [long-acting release], 10, 20, 30 mg) and lanreotide (lanreotide-PR [prolonged release, lanreotide-autogel], 60, 90, 120 mg) are available and widely used because their use greatly facilitates long-term treatment. Octreotide-LAR (30 mg/month) gives a plasma level ≥1 ng/mL for 25 days, whereas this requires three to six injections a day of the non-sustained-release form. Lanreotide-autogel (Somatuline) is given every 4–6 weeks.

Short-term side effects occur in up to one-half of patients. Pain at the injection site and side effects related to the GI tract (59% discomfort, 15% nausea, diarrhea) are the most common. T ey are usually short-lived and do not interrupt treatment. Important long-term side effects include gallstone formation, steatorrhea, and deterioration in glucose tolerance. T e overall incidence of gallstones/biliary sludge in one study was 52%, with 7% having symptomatic disease that required surgical treatment.

Interferon α is reported to be effective in controlling symptoms of the carcinoid syndrome either alone or combined with hepatic artery embolization. With interferon α alone, the clinical response rate is 30–70%, and with interferon α with hepatic artery embolization, diarrhea was controlled for 1 year in 43% and f ushing was controlled in 86%. Side effects develop in almost all patients, with the most frequent being a f u-like syndrome (80–100%), followed by anorexia and fatigue, even though these frequently improve with continued treatment. Other more severe side effects include bone marrow toxicity, hepatotoxicity, autoimmune disorders, and rarely CNS side effects (depression, mental disorders, visual problems).

Hepatic artery embolization alone or with chemotherapy (chemoembolization) has been used to control the symptoms of carcinoid syndrome. Embolization alone is reported to control symptoms in up to 76% of patients, and chemoembolization (5-f uorouracil, doxorubicin, cisplatin, mitomycin) controls symptoms in 60–75% of patients. Hepatic artery embolization can have major side effects, including nausea, vomiting, pain, and fever. In two studies, 5–7% of patients died from complications of hepatic artery occlusion.

Other drugs have been used successfully in small numbers of patients to control the symptoms of carcinoid syndrome. Parachlorophenylanine can inhibit tryptophan hydroxylase and therefore the conversion of tryptophan to 5-HTP. However, its severe side effects, including psychiatric disturbances, make it intolerable for long-term use. α-Methyldopa inhibits the conversion of 5-HTP to 5-HT, but its effects are only partial.

Peptide radioreceptor therapy (using radiotherapy with radiolabeled somatostatin analogues), the use of radiolabeled microspheres, and other methods for treatment of advanced metastatic disease may facilitate control of the carcinoid syndrome and are discussed in a later section dealing with treatment of advanced disease.

GI-NETS (CARCINOIDS) (NONMETASTATIC) Surgery is the only potentially curative therapy. Because with most GI-NETs (carcinoids), the probability of metastatic disease increases with increasing size, the extent of surgical resection is determined accordingly. With appendiceal NETs (carcinoids) <1 cm, simple appendectomy was curative in 103 patients followed for up to 35 years. With rectal NETs (carcinoids) <1 cm, local resection is curative. With SI NETs (carcinoids) <1 cm, there is not complete agreement. Because 15–69% of SI NETs (carcinoids) this size have metastases in different studies, some recommend a wide resection with en bloc resection of the adjacent lymph-bearing mesentery. If the tumor is >2 cm for rectal, appendiceal, or SI NETs (carcinoids), a full cancer operation should be done. T is includes a right hemicolectomy for appendiceal NETs (carcinoids), an abdominoperineal resection or low anterior resection for rectal NETs (carcinoids), and an en bloc resection of adjacent lymph nodes for SI NETs (carcinoids). For appendiceal NETs (carcinoids) 1–2 cm in diameter, a simple appendectomy is proposed by some, whereas others favor a formal right hemicolectomy. For 1–2 cm rectal NETs (carcinoids), it is recommended that a wide, local, full-thickness excision be performed.

With type I or II gastric NETs (carcinoids), which are usually <1 cm, endoscopic removal is recommended. In type I or II gastric carcinoids, if the tumor is >2 cm or if there is local invasion, some recommend total gastrectomy, whereas others recommend antrectomy in type I to reduce the hypergastrinemia, which has led to regression of the carcinoids in a number of studies. For types I and II gastric NETs (carcinoids) of 1–2 cm, there is no agreement, with some recommending endoscopic treatment followed by chronic somatostatin treatment and careful follow-up and others recommending surgical treatment. With type III gastric NETs (carcinoids) >2 cm, excision and regional lymph node clearance are recommended. Most tumors <1 cm are treated endoscopically.

Resection of isolated or limited hepatic metastases may be beneficial and will be discussed in a later section on treatment of advanced disease.

PANCREATIC NEUROENDOCRINE TUMORS

Functional pNETs usually present clinically with symptoms due to the hormone-excess state (Table 51-2). Only late in the course of the disease does the tumor per se cause prominent symptoms such as abdominal pain. In contrast, all the symptoms due to nonfunctional pNETs are due to the tumor per se. T e overall result of this is that some functional pNETs may present with severe symptoms with a small or undetectable primary tumor, whereas nonfunctional tumors usually present late in the disease course with large tumors, which are frequently metastatic. T e mean delay between onset of continuous symptoms and diagnosis of a functional pNET syndrome is 4–7 years. T erefore, the diagnoses frequently are missed for extended periods.

TREATMENT Pancreatic Neuroendocrine Tumor (General Points)

Treatment of pNETs requires two different strategies. First, treatment must be directed at the hormone-excess state such as the gastric acid hypersecretion in gastrinomas or the hypoglycemia in insulinomas. Ectopic hormone secretion usually causes the presenting symptoms and can cause life-threatening complications. Second, with all the tumors except insulinomas, >50% are malignant (Table 51-2); therefore, treatment must also be directed against the tumor per se. Because in many patients these tumors are not surgically curable due to the presence of advanced disease at diagnosis, surgical resection for cure, which addresses both treatment aspects, is often not possible.

GASTRINOMA (ZOLLINGER-ELLISON SYNDROME)

A gastrinoma is an NET that secretes gastrin; the resultant hypergastrinemia causes gastric acid hypersecretion (Zollinger-Ellison syndrome [ZES]). T e chronic hypergastrinemia results in marked gastric acid hypersecretion and growth of the gastric mucosa with increased numbers of parietal cells and proliferation of gastric ECL cells. T e gastric acid hypersecretion characteristically causes peptic ulcer disease (PUD), often refractory and severe, as well as diarrhea. T e most common presenting symptoms are abdominal pain (70-100%), diarrhea (37-73%), and gastroesophageal ref ux disease (GERD) (30-35%); 10-20% of patients have diarrhea only. Although peptic ulcers may occur in unusual locations, most patients have a typical duodenal ulcer. Important observations that should suggest this diagnosis include PUD with diarrhea; PUD in an unusual location or with multiple ulcers; PUD refractory to treatment or persistent; PUD associated with prominent gastric folds; PUD associated with findings suggestive of MEN 1 (endocrinopathy, family history of ulcer or endocrinopathy, nephrolithiases); and PUD without Helicobacter pylori present. H. pylori is present in >90% of idiopathic peptic ulcers but is present in <50% of patients with gastrinomas. Chronic unexplained diarrhea also should suggest ZES.

Approximately 20-25% of patients with ZES have MEN 1 (MEN1/ZES), and in most cases, hyperparathyroidism is present before the ZES develops. T ese patients are treated differently from those without MEN 1 (sporadic ZES); therefore, MEN 1 should be sought in all patients with ZES by family history and by measuring plasma ionized calcium and prolactin levels and plasma hormone levels (parathormone, growth hormone).

Most gastrinomas (50–90%) in sporadic ZES are present in the duodenum, followed by the pancreas (10–40%) and other intraabdominal sites (mesentery, lymph nodes, biliary tract, liver, stomach, ovary). Rarely, the tumor may involve extraabdominal sites (heart, lung cancer). In MEN 1/ZES the gastrinomas are also usually in the duodenum (70–90%), followed by the pancreas (10–30%), and are almost always multiple. About 60–90% of gastrinomas are malignant (Table 51-2) with metastatic spread to lymph nodes and liver. Distant metastases to bone occur in 12–30% of patients with liver metastases.

Diagnosis

T e diagnosis of ZES requires the demonstration of inappropriate fasting hypergastrinemia, usually by demonstrating hypergastrinemia occurring with an increased basal gastric acid output (BAO) (hyperchlorhydria).

More than 98% of patients with ZES have fasting hypergastrinemia, although in 40–60% the level may be elevated less than tenfold. T erefore, when the diagnosis is suspected, a fasting gastrin is usually the initial test performed. It is important to remember that potent gastric acid suppressant drugs such as proton pump inhibitors (PPIs) (omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole) can suppress acid secretion sufficiently to cause hypergastrinemia; because of their prolonged duration of action, these drugs have to be tapered or frequently discontinued for a week before the gastrin determination. Withdrawal of PPIs should be performed carefully because PUD complications can rapidly develop in some patients and is best done in consultation with GI units with experience in this area. T e widespread use of PPIs can confound the diagnosis of ZES by raising a false-positive diagnosis by causing hypergastrinemia in a patient being treated with idiopathic PUD (without ZES) and lead to a false-negative diagnosis because at routine doses used to treat patients with idiopathic PUD, PPIs control symptoms in most ZES patients and thus mask the diagnosis. If ZES is suspected and the gastrin level is elevated, it is important to show that it is increased when gastric pH is ≤2.0 because physiologically hypergastrinemia secondary to achlorhydria (atrophic gastritis, pernicious anemia) is one of the most common causes of hypergastrinemia. Nearly all ZES patients have a fasting pH ≤2 when off antisecretory drugs. If the fasting gastrin is >1000 pg/mL (increased tenfold) and the pH is ≤2.0, which occurs in 40–60% of patients with ZES, the diagnosis of ZES is established after the possibility of retained antrum syndrome has been ruled out by history. In patients with hypergastrinemia with fasting gastrins <1000 pg/mL (<10-fold increased) and gastric pH ≤2.0, other conditions, such as H. pylori infections, antral G-cell hyperplasia/hyperfunction, gastric outlet obstruction, and, rarely, renal failure, can masquerade as ZES. To establish the diagnosis in this group, a determination of BAO and a secretin provocative test should be done. In patients with ZES without previous gastric acid–reducing surgery, the BAO is usually (>90%) elevated (i.e., >15 mEq/h). T e secretin provocative test is usually positive, with the criterion of a >120-pg/mL increase over the basal level having the highest sensitivity (94%) and specificity (100%). Unfortunately the diagnosis of ZES is becoming increasing more difficult. T is is due not only to the widespread use of PPIs (leading to false-positive results as well as masking ZES presentation), but also recent studies demonstrate than many of the commercial gastrin kits that are used by most laboratories to measure fasting serum gastrin levels are not reliable. In one study, 7 of the 12 tested commercial gastrin kits inaccurately assessed the true serum concentration of gastrin primarily because the antibodies used had inappropriate specificity for the different circulating forms of gastrin and were not adequately validated. Both underestimation and overestimation of fasting serum gastrin levels occurred using these commercial kits. To circumvent this problem, it is either necessary to use one of the five reliable kits identified or, alternatively, to refer the patient to a center with expertise in making the diagnosis in your area, or if this is not possible, to contact such a center and use the gastrin assay they recommend. An accurate gastrin assay is essential for accurate measurement of fasting serum gastrin level as well as for assessing gastrin levels during the secretin provocative test, and thus, the diagnosis of ZES cannot reliably be made without one.

TREATMENT Zollinger–Ellison Syndrome

Gastric acid hypersecretion in patients with ZES can be controlled in almost every case by oral gastric antisecretory drugs. Because of their long duration of action and potency, which allows dosing once or twice a day, the PPIs (H^+, K^+-ATPase inhibitors) are the drugs of choice. Histamine H_2-receptor antagonists are also effective, although more frequent dosing (q 4–8 h) and high doses are required. In patients with MEN 1/ZES with hyperparathyroidism, correction of the hyperparathyroidism increases the sensitivity to gastric antisecretory drugs and decreases the basal acid output. Long-term treatment with PPIs (>15 years) has proved to be safe and effective, without development of tachyphylaxis. Although patients with ZES, especially those with MEN 1/ZES, more frequently develop gastric NETs (carcinoids), no data suggest that the long-term use of PPIs increases this risk in these patients. With long-term PPI use in ZES patients, vitamin B_{12} deficiency can develop; thus, vitamin B_{12} levels should be assessed during follow-up. Epidemiologic studies suggest that long-term PPI use may be associated with an increased incidence of bone fractures; however, at present, there is no such report in ZES patients.

With the increased ability to control acid hypersecretion, more than 50% of patients who are not cured (>60% of patients) will die from tumor-related causes. At presentation, careful imaging studies are essential to localize the extent of the tumor to determine the appropriate treatment. A third of patients present with hepatic metastases, and in <15% of those patients, the disease is limited, so that surgical resection may be possible. Surgical short-term cure is possible in 60% of all patients without MEN 1/ZES or liver metastases (40% of all patients) and in 30% of patients long term. In patients with MEN 1/ZES, long-term surgical cure is rare because the tumors are multiple, frequently with lymph node metastases. Surgical studies demonstrate that successful resection of the gastrinoma not only decreases the chances of developing liver metastases but also increases the disease-related survival rate. T erefore, all patients with gastrinomas without MEN 1/ZES or a medical condition that limits life expectancy should

undergo surgery by a surgeon experienced in the treatment of these disorders.

INSULINOMAS

An insulinoma is an NET of the pancreas that is thought to be derived from beta cells that ectopically secrete insulin, which results in hypoglycemia. T e average age of occurrence is 40–50 years old. T e most common clinical symptoms are due to the effect of the hypoglycemia on the CNS (neuroglycemic symptoms) and include confusion, headache, disorientation, visual difficulties, irrational behavior, and even coma. Also, most patients have symptoms due to excess catecholamine release secondary to the hypoglycemia, including sweating, tremor, and palpitations. Characteristically, these attacks are associated with fasting.

Insulinomas are generally small (>90% are <2 cm) and usually not multiple (90%); only 5–15% are malignant, and they almost invariably occur only in the pancreas, distributed equally in the pancreatic head, body, and tail.

Insulinomas should be suspected in all patients with hypoglycemia, especially when there is a history suggesting that attacks are provoked by fasting, or with a family history of MEN 1. Insulin is synthesized as proinsulin, which consists of a 21-amino-acid α chain and a 30-amino-acid β chain connected by a 33-amino-acid connecting peptide (C peptide). In insulinomas, in addition to elevated plasma insulin levels, elevated plasma proinsulin levels are found, and C-peptide levels are elevated.

Diagnosis

T e diagnosis of insulinoma requires the demonstration of an elevated plasma insulin level at the time of hypoglycemia. A number of other conditions may cause fasting hypoglycemia, such as the inadvertent or surreptitious use of insulin or oral hypoglycemic agents, severe liver disease, alcoholism, poor nutrition, and other extrapancreatic tumors. Furthermore, postprandial hypoglycemia can be caused by a number of conditions that confuse the diagnosis of insulinoma. Particularly important here is the increased occurrence of hypoglycemia after gastric bypass surgery for obesity, which is now widely performed. A new entity, insulinomatosis, was described that can cause hypoglycemia and mimic insulinomas. It occurs in 10% of patients with persistent hyperinsulinemic hypoglycemia and is characterized by the occurrence of multiple macro-/microadenomas expressing insulin, and it is not clear how to distinguish this entity from insulinoma preoperatively. T e most reliable test to diagnose insulinoma is a fast up to 72 h with serum glucose, C-peptide, proinsulin, and insulin measurements every 4–8 h. If at any point the patient becomes symptomatic or glucose levels are persistently below <2.2 mmol/L (40 mg/dL), the test should be terminated, and repeat samples for the above studies should be obtained before glucose is given. Some 70–80% of patients will develop hypoglycemia during the first 24 h, and 98% by 48 h. In nonobese normal subjects, serum insulin levels should decrease to <43 pmol/L (<6 μU/mL) when blood glucose decreases to <2.2 mmol/L (<40 mg/dL) and the ratio of insulin to glucose is <0.3 (in mg/dL). In addition to having an insulin level >6 μU/mL when blood glucose is <40 mg/dL, some investigators also require an elevated C-peptide and serum proinsulin level, an insulin/glucose ratio >0.3, and a decreased plasma β-hydroxybutyrate level for the diagnosis of insulinomas. Surreptitious use of insulin or hypoglycemic agents may be difficult to distinguish from insulinomas. T e combination of proinsulin levels (normal in exogenous insulin/hypoglycemic agent users), C-peptide levels (low in exogenous insulin users), antibodies to insulin (positive in exogenous insulin users), and measurement of sulfonylurea levels in serum or plasma will allow the correct diagnosis to be made. T e diagnosis of insulinoma has been complicated by the introduction of specific insulin assays that do not also interact with proinsulin, as do many of the older radioimmunoassays (RIAs), and therefore give lower plasma insulin levels. T e increased use of these specific insulin assays has resulted in increased numbers of patients with insulinomas having lower plasma insulin values (<6 μU/mL) than levels proposed to be characteristic of insulinomas by RIA. In these patients, the assessment of proinsulin and C-peptide levels at the time of hypoglycemia is particularly helpful for establishing the correct diagnosis. An elevated proinsulin level when the fasting glucose level is <45 mg/dL is sensitive and specific.

TREATMENT Insulinomas

Only 5–15% of insulinomas are malignant; therefore, after appropriate imaging (see below), surgery should be performed. In different studies, 75–100% of patients are cured by surgery. Before surgery, the hypoglycemia can be controlled by frequent small meals and the use of diazoxide (150–800 mg/d). Diazoxide is a benzothiadiazide whose hyperglycemic effect is attributed to inhibition of insulin release. Its side effects are sodium retention and GI symptoms such as nausea. Approximately 50–60% of patients respond to diazoxide. Other agents effective in some patients to control the hypoglycemia include verapamil and diphenylhydantoin. Long-acting somatostatin analogues such as octreotide and lanreotide are acutely effective in 40% of patients. However, octreotide must be used with care

because it inhibits growth hormone secretion and can alter plasma glucagon levels; therefore, in some patients, it can worsen the hypoglycemia.

For the 5–15% of patients with malignant insulinomas, these drugs or somatostatin analogues are used initially. In a small number of patients with insulinomas, some with malignant tumors, mammalian target of rapamycin (mTOR) inhibitors (everolimus, rapamycin) are reported to control the hypoglycemia. If they are not effective, various antitumor treatments such as hepatic arterial embolization, chemoembolization, chemotherapy, and peptide receptor radiotherapy have been used (see below).

Insulinomas, which are usually benign (>90%) and intrapancreatic in location, are increasingly resected using a laparoscopic approach, which has lower morbidity rates. T is approach requires that the insulinoma be localized on preoperative imaging studies.

GLUCAGONOMAS

A glucagonoma is NET of the pancreas that secretes excessive amounts of glucagon, which causes a distinct syndrome characterized by dermatitis, glucose intolerance or diabetes, and weight loss. Glucagonomas principally occur between 45 and 70 years of age. T e tumor is clinically heralded by a characteristic dermatitis (migratory necrolytic erythema) (67–90%), accompanied by glucose intolerance (40–90%), weight loss (66–96%), anemia (33–85%), diarrhea (15–29%), and thromboembolism (11–24%). T e characteristic rash usually starts as an annular erythema at intertriginous and periorificial sites, especially in the groin or buttock. It subsequently becomes raised, and bullae form; when the bullae rupture, eroded areas form. T e lesions can wax and wane. T e development of a similar rash in patients receiving glucagon therapy suggests that the rash is a direct effect of the hyperglucagonemia. A characteristic laboratory finding is hypoaminoacidemia, which occurs in 26–100% of patients.

Glucagonomas are generally large tumors at diagnosis (5–10 cm). Some 50–80% occur in the pancreatic tail. From 50 to 82% have evidence of metastatic spread at presentation, usually to the liver. Glucagonomas are rarely extrapancreatic and usually occur singly.

Two new entities have been described that can also cause hyperglucagonemia and may mimic glucagonomas. Mahvah disease is due to a homozygous P86S mutation of the human glucagon receptor. It is associated with the development of α-cell hyperplasia, hyperglucagonemia, and the development of nonfunctioning pNETs. A second disease called glucagon cell adenomatosis can mimic glucagonoma syndrome clinically and is characterized by the presence of hyperplastic islets staining positive for glucagon instead of a single glucagonoma.

Diagnosis

T e diagnosis is confirmed by demonstrating an increased plasma glucagon level. Characteristically, plasma glucagon levels exceed 1000 pg/mL (normal is <150 pg/mL) in 90%; 7% are between 500 and 1000 pg/mL, and 3% are <500 pg/mL. A trend toward lower levels at diagnosis has been noted in the last decade. A plasma glucagon level >1000 pg/mL is considered diagnostic of glucagonoma. Other diseases causing increased plasma glucagon levels include cirrhosis, diabetic ketoacidosis, celiac disease, renal insufficiency, acute pancreatitis, hypercorticism, hepatic insufficiency, severe stress, and prolonged fasting or familial hyperglucagonemia, as well as danazol treatment. With the exception of cirrhosis, these disorders do not increase plasma glucagon >500 pg/mL.

Necrolytic migratory erythema is not pathognomonic for glucagonoma and occurs in myeloproliferative disorders, hepatitis B infection, malnutrition, short-bowel syndrome, inf ammatory bowel disease, zinc deficiency, and malabsorption disorders.

TREATMENT Glucagonomas

In 50–80% of patients, hepatic metastases are present, and so curative surgical resection is not possible. Surgical debulking in patients with advanced disease or other antitumor treatments may be beneficial (see below). Long-acting somatostatin analogues such as octreotide and lanreotide improve the skin rash in 75% of patients and may improve the weight loss, pain, and diarrhea, but usually do not improve the glucose intolerance.

SOMATOSTATINOMA SYNDROME

T e somatostatinoma syndrome is due to an NET that secretes excessive amounts of somatostatin, which causes a distinct syndrome characterized by diabetes mellitus, gallbladder disease, diarrhea, and steatorrhea. T ere is no general distinction in the literature between a tumor that contains somatostatin-like immunoreactivity (somatostatinoma) and does (11–45%) or does not (55–90%) produce a clinical syndrome (somatostatinoma syndrome) by secreting somatostatin. In a review of 173 cases of somatostatinomas, only 11% were associated with the somatostatinoma syndrome. T e mean age is 51 years. Somatostatinomas occur primarily in the pancreas and small intestine, and the frequency of the symptoms and occurrence of the somatostatinoma syndrome differ in each. Each of the usual symptoms is more common in pancreatic than in intestinal somatostatinomas: diabetes mellitus (95% vs 21%), gallbladder disease (94% vs 43%), diarrhea (92% vs 38%), steatorrhea (83% vs 12%),

hypochlorhydria (86% vs 12%), and weight loss (90% vs 69%). The somatostatinoma syndrome occurs in 30–90% of pancreatic and 0–5% of SI somatostatinomas. In various series, 43% of all duodenal NETs contain somatostatin; however, the somatostatinoma syndrome is rarely present (<2%). Somatostatinomas occur in the pancreas in 56–74% of cases, with the primary location being the pancreatic head. The tumors are usually solitary (90%) and large (mean size 4.5 cm). Liver metastases are common, being present in 69–84% of patients. Somatostatinomas are rare in patients with MEN 1, occurring in only 0.65%.

Somatostatin is a tetradecapeptide that is widely distributed in the CNS and GI tract, where it functions as a neurotransmitter or has paracrine and autocrine actions. It is a potent inhibitor of many processes, including release of almost all hormones, acid secretion, intestinal and pancreatic secretion, and intestinal absorption. Most of the clinical manifestations are directly related to these inhibitory actions.

Diagnosis

In most cases, somatostatinomas have been found by accident either at the time of cholecystectomy or during endoscopy. The presence of psammoma bodies in a duodenal tumor should particularly raise suspicion. Duodenal somatostatin-containing tumors are increasingly associated with von Recklinghausen's disease (NF-1) (**Table 51-6**). Most of these tumors (>98%) do not cause the somatostatinoma syndrome. The diagnosis of the somatostatinoma syndrome requires the demonstration of elevated plasma somatostatin levels.

TREATMENT Somatostatinomas

Pancreatic tumors are frequently (70–92%) metastatic at presentation, whereas 30–69% of SI somatostatinomas have metastases. Surgery is the treatment of choice for those without widespread hepatic metastases. Symptoms in patients with the somatostatinoma syndrome are also improved by octreotide treatment.

VIPOMAS

VIPomas are NETs that secrete excessive amounts of vasoactive intestinal peptide (VIP), which causes a distinct syndrome characterized by large-volume diarrhea, hypokalemia, and dehydration. This syndrome also is called Verner-Morrison syndrome, pancreatic cholera, and WDHA syndrome for watery diarrhea, hypokalemia, and achlorhydria, which some patients develop. The mean age of patients with this syndrome is 49 years; however, it can occur in children, and when it does, it is usually caused by a ganglioneuroma or ganglioneuroblastoma.

The principal symptoms are large-volume diarrhea (100%) severe enough to cause hypokalemia (80–100%), dehydration (83%), hypochlorhydria (54–76%), and flushing (20%). The diarrhea is secretory in nature, persisting during fasting, and is almost always >1 L/d and in 70% is >3 L/d. In a number of studies, the diarrhea was intermittent initially in up to half the patients. Most patients do not have accompanying steatorrhea (16%), and the increased stool volume is due to increased excretion of sodium and potassium, which, with the anions, accounts for the osmolality of the stool. Patients frequently have hyperglycemia (25–50%) and hypercalcemia (25–50%).

VIP is a 28-amino-acid peptide that is an important neurotransmitter, ubiquitously present in the CNS and GI tract. Its known actions include stimulation of SI chloride secretion as well as effects on smooth-muscle contractility, inhibition of acid secretion, and vasodilatory effects, which explain most features of the clinical syndrome.

In adults, 80–90% of VIPomas are pancreatic in location, with the rest due to VIP-secreting pheochromocytomas, intestinal carcinoids, and rarely ganglioneuromas. These tumors are usually solitary, 50–75% are in the pancreatic tail, and 37–68% have hepatic metastases at diagnosis. In children <10 years old, the syndrome is usually due to ganglioneuromas or ganglioblastomas and is less often malignant (10%).

Diagnosis

The diagnosis requires the demonstration of an elevated plasma VIP level and the presence of large-volume diarrhea. A stool volume <700 mL/d is proposed to exclude the diagnosis of VIPoma. When the patient fasts, a number of diseases can be excluded that can cause marked diarrhea because the high volume of diarrhea is not sustained during the fast. Other diseases that can produce a secretory large-volume diarrhea include gastrinomas, chronic laxative abuse, carcinoid syndrome, systemic mastocytosis, rarely medullary thyroid cancer, diabetic diarrhea, sprue, and AIDS. Among these conditions, only VIPomas caused a marked increase in plasma VIP. Chronic surreptitious use of laxatives/diuretics can be particularly difficult to detect clinically. Hence, in a patient with unexplained chronic diarrhea, screens for laxatives should be performed; they will detect many, but not all, laxative abusers. Elevated plasma levels of VIP should not be the only basis of the diagnosis of VIPomas because they can occur with some diarrheal states including inflammatory bowel disease, post small bowel resection, and radiation enteritis. Furthermore, nesidioblastosis can mimic

VIPomas by causing elevated plasma VIP levels, diarrhea, and even false-positive location in the pancreatic region on somatostatin receptor scintigraphy.

TREATMENT VIPomas

The most important initial treatment in these patients is to correct their dehydration, hypokalemia, and electrolyte losses with fluid and electrolyte replacement. These patients may require 5 L/d of fluid and >350 mEq/d of potassium. Because 37–68% of adults with VIPomas have metastatic disease in the liver at presentation, a significant number of patients cannot be cured surgically. In these patients, long-acting somatostatin analogues such as octreotide and lanreotide are the drugs of choice.

Octreotide/lanreotide will control the diarrhea short- and long-term in 75–100% of patients. In nonresponsive patients, the combination of glucocorticoids and octreotide/lanreotide has proved helpful in a small number of patients. Other drugs reported to be helpful in small numbers of patients include prednisone (60–100 mg/d), clonidine, indomethacin, phenothiazines, loperamide, lidamidine, lithium, propranolol, and metoclopramide. Treatment of advanced disease with cytoreductive surgery, embolization, chemoembolization, chemotherapy, radiotherapy, radiofrequency ablation, and peptide receptor radiotherapy may be helpful (see below).

NONFUNCTIONAL PANCREATIC NEUROENDOCRINE TUMORS (NF-PNETS)

NF-pNETs are NETs that originate in the pancreas and either secrete no products or their products do not cause a specific clinical syndrome. Their symptoms are due entirely to the tumor per se. NF-pNETs secrete chromogranin A (90–100%), chromogranin B (90–100%), α-HCG (human chorionic gonadotropin) (40%), neuron-specific enolase (31%), and β-HCG (20%), and because 40–90% secrete PP, they are also often called PPomas. Because the symptoms are due to the tumor mass, patients with NF-pNETs usually present late in the disease course with invasive tumors and hepatic metastases (64–92%), and the tumors are usually large (72% >5 cm). NF-pNETs are usually solitary except in patients with MEN 1, in which case they are multiple. They occur primarily in the pancreatic head. Even though these tumors do not cause a functional syndrome, immunocytochemical studies show that they synthesize numerous peptides and cannot be distinguished from functional pNETs by immunocytochemistry. In MEN 1, 80–100% of patients have microscopic NF-pNETs, but they become large or symptomatic in a minority (0–13%) of cases. In VHL, 12–17% develop NF-pNETs, and in 4%, they are ≥3 cm in diameter.

The most common symptoms are abdominal pain (30–80%), jaundice (20–35%), and weight loss, fatigue, or bleeding; 10–35% are found incidentally. The average time from the beginning of symptoms to diagnosis is 5 years.

Diagnosis

The diagnosis is established by histologic confirmation in a patient without either the clinical symptoms or the elevated plasma hormone levels of one of the established syndromes. The principal difficulty in diagnosis is to distinguish an NF-pNET from a nonendocrine pancreatic tumor, which is more common, as well as from a functional pNET. Even though chromogranin A levels are elevated in almost every patient, this is not specific for this disease as it can be found in functional pNETs, GI-NETs (carcinoids), and other neuroendocrine disorders. Plasma PP elevations should strongly suggest the diagnosis in a patient with a pancreatic mass because it is usually normal in patients with pancreatic adenocarcinomas. Elevated plasma PP is not diagnostic of this tumor because it is elevated in a number of other conditions, such as chronic renal failure, old age, inflammatory conditions, alcohol abuse, pancreatitis, hypoglycemia, postprandially, and diabetes. A positive somatostatin receptor scan in a patient with a pancreatic mass should suggest the presence of pNET/NF-pNET rather than a nonendocrine tumor.

TREATMENT Nonfunctional Pancreatic Neuroendocrine Tumors (NF-pNETs)

Overall survival in patients with sporadic NF-pNET is 30–63% at 5 years, with a median survival of 6 years. Unfortunately, surgical curative resection can be considered only in a minority of these patients because 64–92% present with diffuse metastatic disease. Treatment needs to be directed against the tumor per se using the various modalities discussed below for advanced disease. The treatment of NF-pNETs in either MEN 1 patients or patients with VHL is controversial. Most recommend surgical resection for any tumor >2–3 cm in diameter; however, there is no consensus on smaller NF-pNETs in these inherited disorders, with most recommending careful surveillance of these patients. The treatment of small sporadic, asymptomatic NF-pNETs (≤2 cm) is also controversial. Most of these are low- or intermediate-grade lesions, and <7% are malignant. Some advocate a nonoperative approach with careful, regular follow-up, whereas other recommend an operative approach with specially consideration for a laparoscopic surgical approach.

GRFOMAS

GRFomas are NETs that secrete excessive amounts of growth hormone–releasing factor (GRF) that cause acromegaly. GRF is a 44-amino-acid peptide,

and 25–44% of pNETs have GRF immunoreactivity, although it is uncommonly secreted. GRFomas are lung tumors in 47–54% of cases, pNETs in 29–30%, and SI carcinoids in 8–10%; up to 12% occur at other sites. Patients have a mean age of 38 years, and the symptoms usually are due to either acromegaly or the tumor per se. The acromegaly caused by GRFomas is indistinguishable from classic acromegaly. The pancreatic tumors are usually large (>6 cm), and liver metastases are present in 39%. They should be suspected in any patient with acromegaly and an abdominal tumor, a patient with MEN 1 with acromegaly, or a patient without a pituitary adenoma with acromegaly or associated with hyperprolactinemia, which occurs in 70% of GRFomas. GRFomas are an uncommon cause of acromegaly. GRFomas occur in <1% of MEN 1 patients. The diagnosis is established by performing plasma assays for GRF and growth hormone. Most GRFomas have a plasma GRF level >300 pg/mL (normal <5 pg/mL men, <10 pg/mL women). Patients with GRFomas also have increased plasma levels of insulin-like growth factor type I (IGF-I) similar to those in classic acromegaly. Surgery is the treatment of choice if diffuse metastases are not present. Long-acting somatostatin analogues such as octreotide and lanreotide are the agents of choice, with 75–100% of patients responding.

OTHER RARE PANCREATIC NEUROENDOCRINE TUMOR SYNDROMES

Cushing's syndrome (ACTHoma) due to a pNET occurs in 4–16% of all ectopic Cushing's syndrome cases. It occurs in 5% of cases of sporadic gastrinomas, almost invariably in patients with hepatic metastases, and is an independent poor prognostic factor. Paraneoplastic hypercalcemia due to pNETs releasing parathyroid hormone–related peptide (PTHrP), a PTH-like material, or unknown factor, is rarely reported. The tumors are usually large, and liver metastases are usually present. Most (88%) appear to be due to release of PTHrP. pNETs occasionally can cause the carcinoid syndrome. A number of very rare pNET syndromes involving a few cases (less than five) have been described; these include a renin-producing pNET in a patient presenting with hypertension; pNETs secreting luteinizing hormone, resulting in masculinization or decreased libido; a pNET secreting erythropoietin, resulting in polycythemia; pNETs secreting IGF-II, causing hypoglycemia; and pNETs secreting enteroglucagon, causing small intestinal hypertrophy, colonic/SI stasis, and malabsorption (Table 51-2). A number of other possible functional pNETs have been proposed, but most authorities classify these as unclear or as a nonfunctional pNET because in each case numerous patients have been described with similar plasma hormone elevations that do not cause any symptoms. These include pNETs secreting calcitonin, neurotensin (neurotensinoma), PP (PPoma), and ghrelin (Table 51-2).

TUMOR LOCALIZATION

Localization of the primary tumor and knowledge of the extent of the disease are essential to the proper management of all GI-NETs (carcinoids) and pNETs. Without proper localization studies, it is not possible to determine whether the patient is a candidate for surgical resection (curative or cytoreductive) or requires antitumor treatment, to determine whether the patient is responding to antitumor therapies, or to appropriately classify/stage the patient's disease to assess prognosis.

Numerous tumor localization methods are used in both types of NETs, including cross-sectional imaging studies (CT, magnetic resonance imaging [MRI], transabdominal ultrasound), selective angiography, somatostatin receptor scintigraphy (SRS), and positron emission tomography. In pNETs, endoscopic ultrasound (EUS) and functional localization by measuring venous hormonal gradients are also reported to be useful. Bronchial carcinoids are usually detected by standard chest radiography and assessed by CT. Rectal, duodenal, colonic, and gastric carcinoids are usually detected by GI endoscopy. Because of their wide availability, CT and MRI are generally initially used to determine the location of the primary NETs and the extent of disease. NETs are hypervascular tumors, and with both MRI and CT, contrast enhancement is essential for maximal sensitivity, and it is recommended that generally triple-phase scanning be used. The ability of cross-sectional imaging and, to a lesser extent, SRS to detect NETs is a function of NET size. With CT and MRI, <10% of tumors <1 cm in diameter are detected, 30–40% of tumors 1–3 cm are detected, and >50% of tumors >3 cm are detected. Many primary GI-NETs (carcinoids) are small, as are insulinomas and duodenal gastrinomas, and are frequently not detected by cross-sectional imaging, whereas most other pNETs present late in the course of their disease and are large (>4 cm). Selective angiography is more sensitive, localizing 60–90% of all NETs; however, it is now used infrequently. For detecting liver metastases, CT and MRI are more sensitive than ultrasound, and with recent improvements, 5–25% of patients with liver metastases will be missed by CT and/or MRI.

pNETs, as well as GI-NETs (carcinoids), frequently (>80%) overexpress high-affinity somatostatin receptors in both the primary tumors and the metastases. Of the five types of somatostatin receptors ($sst_{1–5}$), radiolabeled octreotide binds with high affinity to sst_2 and sst_5, has

a lower affinity for sst_3, and has a very low affinity for sst_1 and sst_4. Between 80 and 100% of GI-NETs (carcinoids) and pNETs possess sst_2, and many also have the other four sst subtypes. Interaction with these receptors can be used to treat these tumors as well as to localize NETs by using radiolabeled somatostatin analogues (SRS). In the United States, [^{111}In-DTPA-d-Phe^1]octreotide (octreoscan) is generally used with gamma camera detection using single-photon emission computed tomography (SPECT) imaging. Numerous studies, primarily in Europe, using gallium-68-labeled somatostatin analogues and positron emission tomography (PET) detection, demonstrate even greater sensitivity than with SRS with ^{111}In-labeled somatostatin analogues. Although not yet approved in the United States, there are a number of centers starting to use this approach. Because of its sensitivity and ability to localize tumor throughout the body, SRS is the initial imaging modality of choice for localizing both the primary tumor and metastatic NETs. SRS localizes tumor in 73–95% of patients with GI-NETs (carcinoids) and in 56–100% of patients with pNETs, except insulinomas. Insulinomas are usually small and have low densities of sst receptors, resulting in SRS being positive in only 12–50% of patients with insulinomas. SRS identifies >90–95% of patients with liver metastases due to NETs. **Figure 51-3** shows an example of the increased sensitivity of SRS in a patient with a GI-NET (carcinoid) tumor. T e CT scan showed a single liver metastasis, whereas the SRS demonstrated three metastases in the liver in multiple locations. Occasional false-positive responses with SRS can occur (12% in one study) because numerous other normal tissues as well as diseases can have high densities of sst receptors, including granulomas (sarcoid, tuberculosis, etc.), thyroid diseases (goiter, thyroiditis), and activated lymphocytes (lymphomas, wound infections). If liver metastases are identified by SRS, to plan the proper treatment, either a CT or an MRI (with contrast enhancement) is recommended to assess the size and exact location of the metastases because SRS does not provide information on tumor size. For pNETs in the pancreas, EUS is highly sensitive, localizing 77–100% of insulinomas, which occur almost exclusively within the pancreas. Endoscopic ultrasound is less sensitive for extrapancreatic tumors. It is increasingly used in patients with MEN 1, and to a lesser extent VHL, to detect small pNETs not seen with other modalities or for serial pNET assessments to determine size changes or rapid growth in patients in whom surgery is deferred. EUS with cytologic evaluation also is used frequently to distinguish an NF-pNET from a pancreatic adenocarcinoma or another nonendocrine pancreatic tumor. Not infrequently patients present with liver metastases due to an NET and the primary site is unclear. Occult small intestinal NETs (carcinoids) are

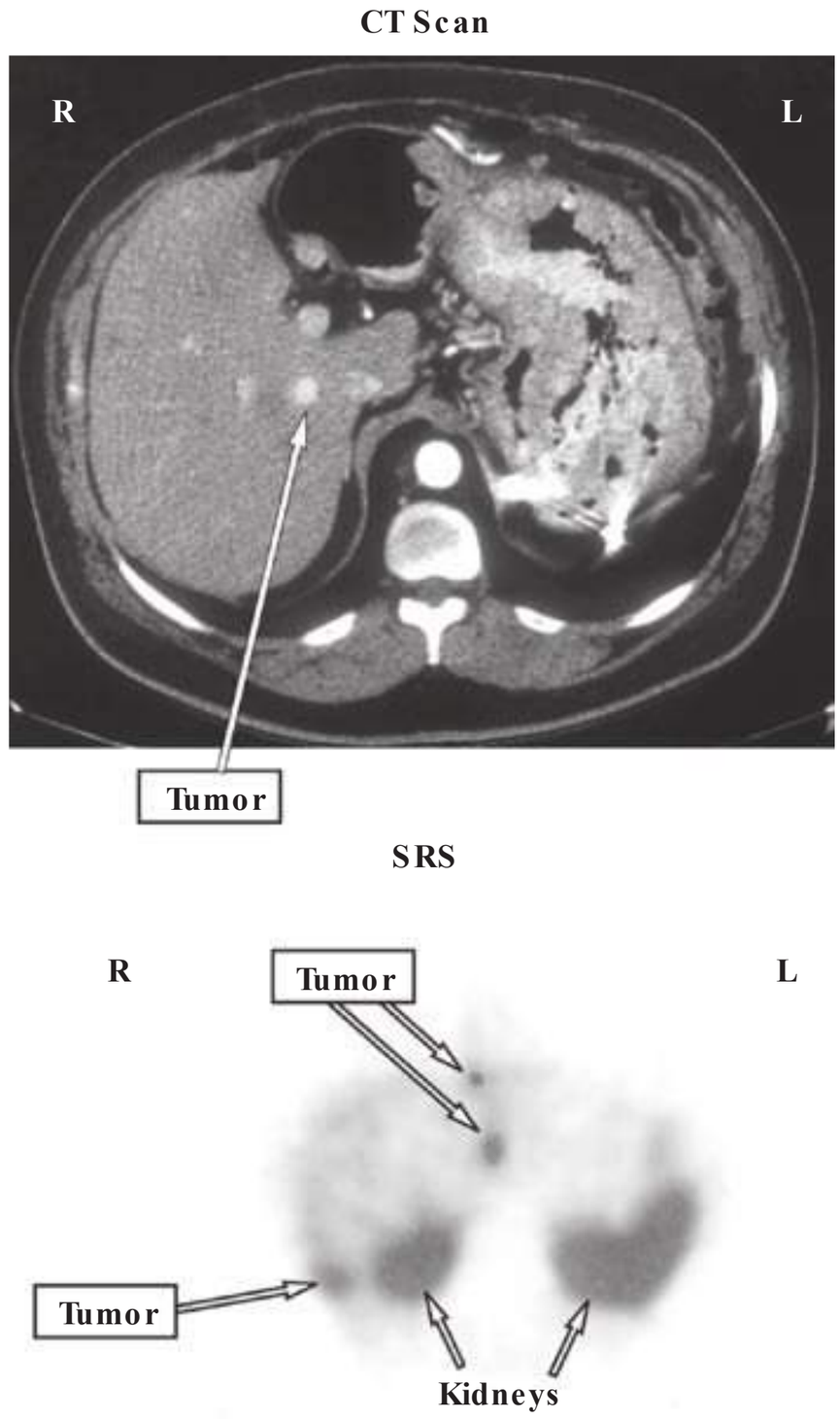


FIGURE 51-3
Ability of computed tomography (CT) scanning (top) or somatostatin receptor scintigraphy (SRS) (bottom) to localize metastatic carcinoid in the liver.

increasingly detected by double-balloon enteroscopy or capsule endoscopy.

Insulinomas frequently overexpress receptors for glucagon-like peptide-1 (GLP-1), and radiolabeled GLP-1 analogues have been developed that can detect occult insulinomas not localized by other imaging modalities. Functional localization by measuring hormonal gradients is now uncommonly used with gastrinomas (after intra-arterial secretin injections) but is still frequently used in insulinoma patients in whom other imaging studies are negative (assessing hepatic vein insulin concentrations post-intra-arterial calcium injections). Functional localization measuring hormone gradients in insulinomas or gastrin gradients in gastrinoma is a sensitive method, being positive in 80–100% of patients. T e intra-arterial calcium test may also allow differentiation of the cause of the hypoglycemia and indicate whether it is due to an insulinoma or a nesidioblastosis. T e latter entity is becoming increasingly important because hypoglycemia after gastric bypass surgery for obesity is increasing in frequency, and it is primarily

due to nesidioblastosis, although it can occasionally be due to an insulinoma.

PET and use of hybrid scanners such as CT and SRS may have increased sensitivity. PET scanning with ^{18}F-fluoro-DOPA in patients with carcinoids or with ^{11}C-5-HTP in patients with pNETs or GI-NETs (carcinoids) has greater sensitivity than cross-sectional imaging studies and may be used increasingly in the future. PET scanning for GI-NETs is not currently approved in the United States.

TREATMENT Advanced Disease (Diffuse Metastatic Disease)

The single most important prognostic factor for survival is the presence of liver metastases **(Fig. 51-4)**. For patients with foregut carcinoids without hepatic metastases, the 5-year survival in one study was 95%, and with distant metastases, it was 20% (Fig. 51-4). With gastrinomas, the 5-year survival without liver metastases is 98%; with limited metastases in one hepatic lobe, it is 78%; and with diffuse metastases, 16% (Fig. 51-4). In a large study of 156 patients (67 pNETs, rest carcinoids), the overall 5-year survival rate was 77%; it was 96% without liver metastases, 73% with liver metastases, and 50% with distant disease. Another very important prognostic factor is whether the NET is well-differentiated (G1/G2) or poorly differentiated (<1% of all NETs) (G3). Well-differentiated NETs have a 5-year survival of 50–80%, whereas poorly differentiated NETs have a 5-year survival of only 0–15%.

Therefore, treatment for advanced metastatic disease is an important challenge. A number of different modalities are reported to be effective, including cytoreductive surgery (surgically or by radiofrequency ablation [RFA]), treatment with chemotherapy, somatostatin analogues, interferon α, hepatic embolization alone or with chemotherapy (chemoembolization), molecular targeted therapy, radiotherapy with radiolabeled beads/microspheres, peptide radioreceptor therapy (PRRT), and liver transplantation.

SPECIFIC ANTITUMOR TREATMENTS

Cytoreductive surgery is considered if either all of the visible metastatic disease or at last 90% is thought resectable; however, unfortunately, this is possible in only the 9–22% of patients who present with limited hepatic metastases. Although no randomized studies have proven that it extends life, results from a number of studies suggest that it may increase survival; therefore, it is recommended, if possible. RFA can be applied to NET liver metastases if they are limited in number (usually less than five) and size (usually <3.5 cm in diameter). It can be used at the time of surgery (either general or laparoscopic) or using radiologic guidance.

Response rates are >80%, the responses can last up to 3 years, the morbidity rate is low, and this procedure may be particularly helpful in patients with functional pNETs that are difficult to control medically. Although RFA has not been established in a controlled trial, both the European and North American Neuroendocrine Tumor Society guidelines (ENETS, NANETS) state it can be an effective antitumor treatment for both refractory functional syndromes and for palliative treatment.

Chemotherapy plays a different role in the treatment of patients with pNETs and GI-NETs (carcinoids). Chemotherapy continues to be widely used in the treatment of patients with advanced pNETs with moderate success (response rates 20–70%); however, in general, its results in patients with metastatic GI-NETs (carcinoids) has been disappointing, with response rates of 0–30% with various two- and three-drug combinations, and thus, it is infrequently used in these patients. An important distinction in patients with pNETs is whether the tumor is well differentiated (G1/G2) or poorly differentiated (G3). The chemotherapeutic approach is different for these two groups. The current regimen of choice for patients with well-differentiated pNETs is the combination of streptozotocin and doxorubicin with or without 5-fluorouracil. Streptozotocin is a glucosamine nitrourea compound originally found to have cytotoxic effects on pancreatic islets, and later in studies with doxorubicin with or without 5-fluorouracil, it produced response rates of 20–45% in advanced pNETs. Streptozotocin causes considerable morbidity, with 70–100% of patients developing side effects (most prominent being nausea/vomiting in 60–100% or leukopenia/thrombocytopenia) and 15–40% of patients developing some degree of renal dysfunction (proteinuria in 40–50%, decreased creatine clearance). The combination of temozolomide (TMZ) with capecitabine produces partial response rates as high as 70% in patients with advance pNETs and a 2-year survival of 92%. The use of TMZ or another alkylating agent in advanced pNETs is supported by studies that show low levels of the DNA repair enzyme O^6-methylguanine DNA methyltransferase in pNETs, but not in GI-NETs (carcinoids), which increases the sensitivity of pNETs to TMZ. In poorly differentiated NETs (G3), chemotherapy with a cisplatin-based regimen with etoposide or other agents (vincristine, paclitaxel) is the recommended treatment, with response rates of 40–70%; however, responses are generally short-lived (<12 months). This chemotherapy regimen can be associated with significant toxicity including GI toxicities (nausea, vomiting), myelosuppression, and renal toxicity.

In addition to the effectiveness in controlling the functional hormonal state, long-acting somatostatin analogues such as octreotide and lanreotide are increasingly used for their antiproliferative effects. Whereas somatostatin analogues rarely decrease tumor size (i.e., 0–17%), these drugs have tumoristatic effects, stopping additional growth in 26–95% of patients with NETs. In a randomized, double-blind study in patients with metastatic midgut carcinoids (PROMID study) octreotide-LAR demonstrated a marked lengthening of time to progression (14.3 vs 6 months, p = .000072). This improvement was seen in patients with limited liver involvement. This study did not assess whether such treatment will extend survival. A double-blind, randomized, placebo-controlled, phase III study in patients with well-differentiated, metastatic, inoperable

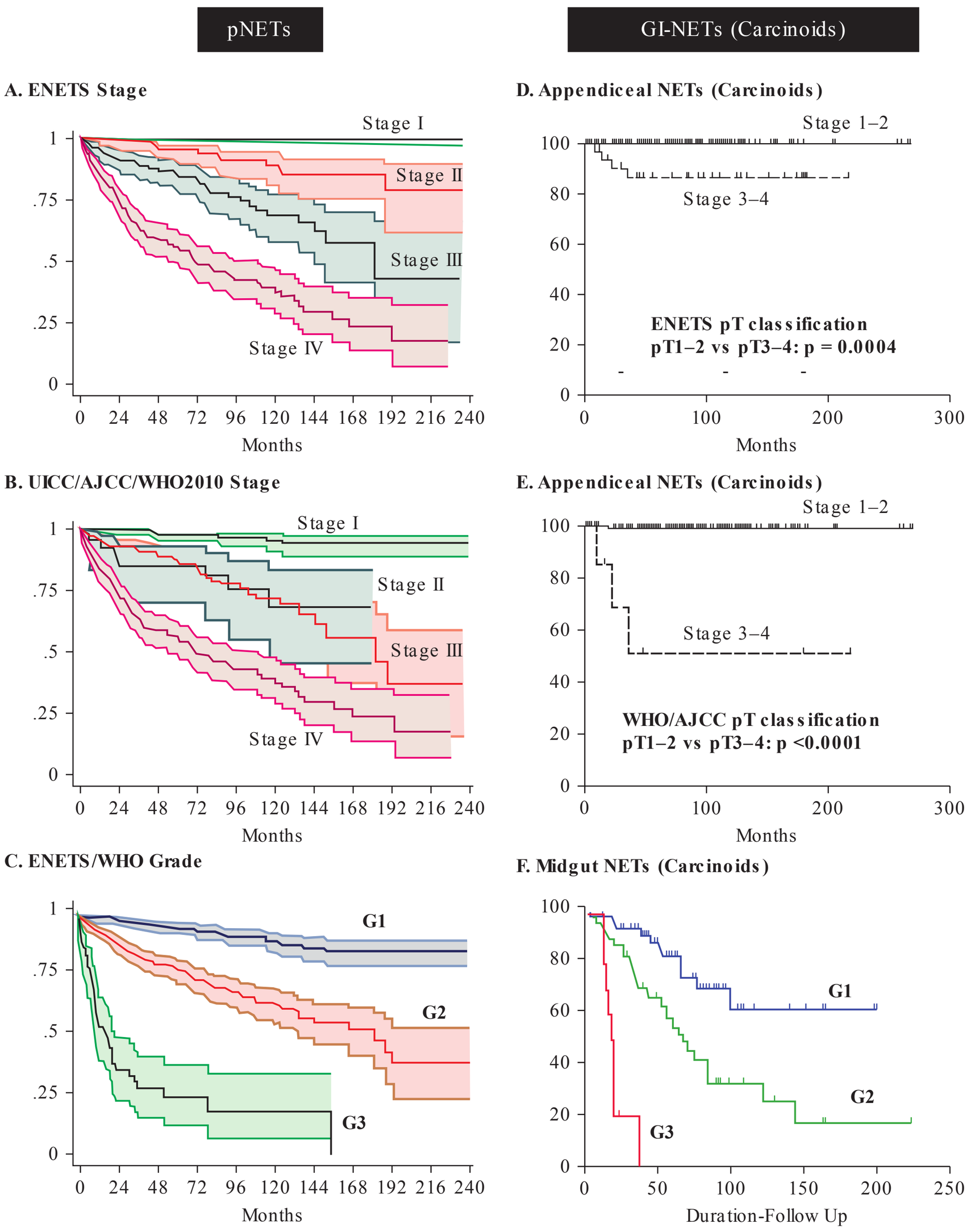


FIGURE 51-4

Survival (Kaplan-Meier plots) of patients with pancreatic neuroendocrine tumors (pNETs; n = 1072) (A–C) or gastrointestinal neuroendocrine tumors (GI-NETs; carcinoids) (appendix, n = 138; midgut, n = 238) (D–F) stratified according to recent proposed classification and grading systems. (Panels A–C are drawn from data in G Rindi et al: J Natl Cancer Inst 104:764, 2012; panels D and E are drawn from data in M Volante et al: Am J Surg Pathol 37:606, 2013; and panel F is drawn from data in MS Khan: Br J Cancer 108:1838, 2013.)

pNETs (45%) or GI-NETs (carcinoids) (55%) (CLARINET study) showed that monthly treatment with lanreotide-autogel reduced tumor progression or death by 53%. Somatostatin analogues can induce apoptosis in GI-NETs (carcinoids), which probably contributes to their tumoristatic effects. Treatment with somatostatin analogues is generally well-tolerated, with most side effects being mild and uncommonly leading to stopping the drug. Potential long-term side effects include diabetes/glucose intolerance, steatorrhea, and the development of gallbladder sludge/gallstones (10–80%), although only 1% of patients develop symptomatic gallbladder disease. Because of these phase III studies, somatostatin analogues are generally recommended as first-line treatment for patients with well-differentiated metastatic NETs.

Interferon α, similar to somatostatin analogues, is effective at controlling the hormonal excess symptoms of NETs and has antiproliferative effects in NETs, which primarily result in disease stabilization (30–80%), with a decrease in tumor size in <15% of patients. Interferon can inhibit DNA synthesis, block cell cycle progression in the G_1 phase, inhibit protein synthesis, inhibit angiogenesis, and induce apoptosis. Interferon α treatment results in side effects in the majority of patients, with the most frequent being a fu-like syndrome (80–100%), anorexia with weight loss, and fatigue. T ese side effects frequently decrease in severity with continued treatment. In addition, patients become accommodated to the symptoms. More serious side effects include hepatotoxicity (31%), hyperlipidemia (31%), bone marrow toxicity, thyroid disease (19%), and rarely CNS side effects (depression, mental/visual disorders). ENETS 2012 guidelines conclude that in patients with well-differentiated NETs that are slowly progressive, interferon α treatment should be considered if the tumor is somatostatin receptor negative or if somatostatin treatment fails.

Selective internal radiation therapy (SIRT) using yttrium-90 (^{90}Y) glass or resin microspheres is a relatively newer approach being evaluated in patients with unresectable NET liver metastases, with approximately 500 NET patients treated. T e treatment requires careful evaluation for vascular shunting before treatment and a pretreatment angiogram to evaluate placement of the catheter and is generally is reserved for patients without extrahepatic metastatic disease and with adequate hepatic reserve. One of two types of ^{90}Y microspheres are used: either microspheres with a 20- to 60-μm diameter and 50 Bq/sphere (SIR-Spheres) or glass microspheres (T eraSpheres) with a 20- to 30-μm diameter and 2500 Bq/sphere. T e ^{90}Y-microspheres are delivered to the liver by intra-arterial injection from percutaneously placed catheters. In four studies involving metastatic NETs, the response rate varied from 50–61% (partial or complete), tumor stabilization occurred in 22–41%, 60–100% had symptomatic improvement, and overall survival varied from 25–70 months. Side effects include postembolization syndrome (pain, fever, nausea/vomiting [frequent]), which is usually mild, although grade 2 (43%) or grade 3 (1%) symptoms can occur; radiation-induced liver disease (<1%); and radiation pneumonitis (<1%). Contraindications to use include excess shunting to the GI tract or lung, inability to isolate the liver arterial supply, and inadequate liver reserve. Because of the limited data available in the ENETS 2012 guidelines, treatment with SIRTs is considered experimental.

Molecular targeted medical treatment with either an mTOR inhibitor (everolimus) or a tyrosine kinase inhibitor (sunitinib) is now approved treatment in the United States and Europe for patients with metastatic unresectable pNET, each supported by a phase III, double-blind, prospective, placebo-controlled trial. mTOR is a serine-threonine kinase that plays an important role in proliferation, cell growth, and apoptosis in both normal and neoplastic cells. Activation of the mTOR cascade is important in mediating NET cell growth, especially in pNETs. A number of mTOR inhibitors have shown promising antitumor activity in NETs including everolimus and temsirolimus, with the former undergoing a phase III trial (RADIANT-3) involving 410 patients with advance progressive pNETs. Everolimus caused significant improvement in progression-free survival (11 vs 4.6 months, p <.001) and increased by a factor of 3.7 the proportion of patients progression-free at 18 months (37% vs 9%). Everolimus treatment was associated with frequent side effects, causing a twofold increase in adverse events, with the most frequent being grade 1 or 2. Grade 3 or 4 side effects included hematologic, GI (diarrhea), stomatitis, or hypoglycemia occurring in 3–7% of patients. Most grade 3 or 4 side effects were controlled by dose reduction or drug interruption. T e ENETS 2012 guidelines conclude that everolimus, similar to sunitinib (below), should be considered as a first-line treatment in selected cases of well-differentiated pNETs that are unresectable. NETs, like other normal and neoplastic cells, frequently possess multiple types of the 20 different tyrosine kinase (TK) receptors that are known and mediate the action of different growth factors. Numerous studies demonstrate that TK receptors in normal and neoplastic tissues as well as NETs are especially important in mediating cell growth, angiogenesis, differentiation, and apoptosis. Whereas a number of TK inhibitors show antiproliferative activity in NETs only sunitinib has undergone a phase III controlled trial. Sunitinib is an orally active small-molecule inhibitor of TK receptors (PDGFRs, VEGFR-1, VEGFR-2, c-KIT, FLT-3). In a phase III study in which 171 patients with progressive, metastatic, nonresectable pNETs were treated with sunitinib (37.5 mg/d) or placebo, sunitinib treatment caused a doubling of progression-free survival (11.4 vs 4.5 months, p <.001), an increase in objective tumor response rate (9% vs 0%, p = .007), and an increase in overall survival. Sunitinib treatment was associated with an overall threefold increase in side effects, although most were grade 1 or 2. T e most frequent grade 3 or 4 side effects were neutropenia (12%) and hypertension (9.6%), which were controlled by dose reduction or temporary interruption. T ere is no consensus regarding the order of sunitinib or everolimus use in patients with advanced, well-differentiated, progressive pNETs.

PRRT for NETs involves treatment with radiolabeled somatostatin analogues. T e success of this approach is based on the finding that somatostatin receptors (sst) are overexpressed or ectopically expressed by 60–100% of all NETs, which allows the targeting of cytotoxic, radiolabeled somatostatin receptor ligands.

T ree different radionuclides are being used. High doses of [^{111}In-DTPA-d-Phe^1]octreotide, which emits γ-rays, internal conversion, and Auger electrons; ^{90}yttrium, which emits high-energy β-particles coupled by a DOTA chelating group to octreotide or octreotate; and ^{177}lutetium-coupled analogues, which emit both, are all in clinical studies. At present, the ^{177}lutetium-coupled analogues are the most widely used. ^{111}Indium-, ^{90}yttrium-, and ^{177}lutetium-labeled compounds caused tumor stabilization in 41–81%, 44–88%, and

23–40%, respectively, and a decrease in tumor size in 8–30%, 6–37%, and 38%, respectively, of patients with advanced metastatic NETs. In one large study involving 504 patients with malignant NETs, ^{177}lutetium-labeled analogues produced a reduction of tumor size of >50% in 30% of patients (2% complete) and tumor stabilization in 51% of patients. An effect on survival has not been established. At present, PRRT is not approved for use in either the United States or Europe, but because of the above promising results, a large phase III study is now being conducted in both the United States and Europe. The ENETS 2012, NANETS 2010, Nordic 2010, and European Society for Medical Oncology (ESMO) guidelines list PRRT as an experimental or investigational treatment at present.

The use of liver transplantation has been abandoned for treatment of most metastatic tumors to the liver. However, for metastatic NETs, it is still a consideration. Among 213 European patients with NETs (50% functional NETs) who had liver transplantation from 1982 to 2009, the overall 5-year survival was 52% and disease free-survival was 30%. In various studies, the postoperative mortality rate is 10–14%. These results are similar to the United Network for Organ Sharing data in the United States in which 150 NET patients had liver transplants and the 5-year survival was 49%. In various studies, important prognostic factors for a poor outcome include a major resection performed in addition at the time of the liver transplant; poor tumor differentiation; hepatomegaly; age >45 years; a primary NET in the duodenum or pancreas; the presence of extrahepatic metastatic disease or extensive liver involvement (>50%); Ki-67 proliferative index >10%; and abnormal E-cadherin staining. The ENETS 2012 guidelines conclude that liver transplantation should be viewed as providing palliative care, with cure an exception, and recommend it be reserved for patients with life-threatening hormonal disturbances refractory to other treatments or for selected patients with a nonfunctional tumor with diffuse liver metastatic disease refractory to all other treatments.

CHAPTER 52

MULTIPLE ENDOCRINE NEOPLASIA

Rajesh V. Thakker

Multiple endocrine neoplasia (MEN) is characterized by a predilection for tumors involving two or more endocrine glands. Four major forms of MEN are recognized and referred to as MEN types 1–4 (MEN 1–4) **(Table 52-1)**. Each type of MEN is inherited as an autosomal dominant syndrome or may occur sporadically; that is, without a family history. However, this distinction between familial and sporadic forms is often difficult because family members with the disease may have died before symptoms developed. In addition to MEN 1–4, at least six other syndromes are associated with multiple endocrine and other organ neoplasias (MEONs) **(Table 52-2)**. T ese MEONs include the hyperparathyroidism-jaw tumor syndrome, Carney complex, von Hippel-Lindau disease **(Chap. 53)**, neurofibromatosis type 1 **(Chap. 48)**, Cowden's syndrome, and McCune-Albright syndrome; all of these are inherited as autosomal dominant disorders, except for McCune-Albright syndrome, which is caused by mosaic expression of a postzygotic somatic cell mutation (Table 52-2).

A diagnosis of a MEN or MEON syndrome may be established in an individual by one of three criteria: (1) clinical features (two or more of the associated tumors [or lesions] in an individual); (2) familial pattern (one of the associated tumors [or lesions] in a first-degree relative of a patient with a clinical diagnosis of the syndrome); and (3) genetic analysis (a germline mutation in the associated gene in an individual, who may be clinically affected or asymptomatic). Mutational analysis in MEN and MEON syndromes is helpful in clinical practice to: (1) confirm the clinical diagnosis; (2) identify family members who harbor the mutation and require screening for relevant tumor detection and early/appropriate treatment; and (3) identify the ~50% of family members who do not harbor the germline mutation and can, therefore, be alleviated of the anxiety of developing associated tumors. T is latter aspect also helps to reduce health care costs by reducing the need for unnecessary biochemical and radiologic investigations.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

Clinical manifestations

MEN type 1 (MEN 1), which is also referred to as Werner's syndrome, is characterized by the triad of tumors involving the parathyroids, pancreatic islets, and anterior pituitary. In addition, adrenal cortical tumors, carcinoid tumors usually of the foregut, meningiomas, facial angiofibromas, collagenomas, and lipomas may also occur in some patients with MEN 1. Combinations of the affected glands and their pathologic features (e.g., hyperplastic adenomas of the parathyroid glands) may differ in members of the same family and even between identical twins. In addition, a nonfamilial (e.g., sporadic) form occurs in 8–14% of patients with MEN 1, and molecular genetic studies have confirmed the occurrence of de novo mutations of the MEN1 gene in approximately 10% of patients with MEN 1. T e prevalence of MEN 1 is approximately 0.25% based on randomly chosen postmortem studies but is 1–18% among patients with primary hyperparathyroidism, 16–38% among patients with pancreatic islet tumors, and <3% among patients with pituitary tumors. T e disorder affects all age groups, with a reported age range of 5 to 81 years, with clinical and biochemical manifestations developing in the vast majority by the fifth decade. T e clinical manifestations of MEN 1 are related to the sites of tumors and their hormonal products. In the absence of treatment, endocrine tumors are associated with an earlier mortality in patients with MEN 1, with a 50% probability of death by the age of 50 years. T e cause of death is usually a malignant tumor, often from a pancreatic neuroendocrine tumor (NET) or foregut carcinoid. In addition, the treatment outcomes of patients with MEN 1–associated tumors are not as successful as those in patients with non–MEN 1 tumors.

TABLE 52-1

MULTIPLE ENDOCRINE NEOPLASIA (MEN) SYNDROMES

TYPE (CHROMOSOMAL LOCATION)	TUMORS (ESTIMATED PENETRANCE)	GENE AND MOST FREQUENTLY MUTATED CODONS
MEN 1 (11q13)	Parathyroid adenoma (90%) Enteropancreatic tumor (30–70%) • Gastrinoma (>50%) • Insulinoma (10–30%) • Nonfunctioning and PPoma (20–55%) • Glucagonoma (<3%) • VIPoma (<1%) Pituitary adenoma (15–50%) • Prolactinoma (60%) • Somatotrophinoma (25%) • Corticotropinoma (<5%) • Nonfunctioning (<5%) Associated tumors • Adrenal cortical tumor (20–70%) • Pheochromocytoma (<1%) • Bronchopulmonary NET (2%) • Thymic NET (2%) • Gastric NET (10%) • Lipomas (>33%) • Angiofibromas (85%) • Collagenomas (70%) • Meningiomas (8%)	MEN1 83/84, 4-bp del (≈4%) 119, 3-bp del (≈3%) 209-211, 4-bp del (≈8%) 418, 3-bp del (≈4%) 514-516, del or ins (≈7%) Intron 4 ss (≈10%)
MEN 2 (10 cen-10q11.2)		
MEN 2A	MTC (90%)	RET
	Pheochromocytoma (>50%)	634, e.g., Cys → Arg (~85%)
	Parathyroid adenoma (10–25%)	
MTC only	MTC (100%)	RET 618, missense (>50%)
MEN 2B (also known as MEN 3)	MTC (>90%)	RET 918, Met → Thr (>95%)
	Pheochromocytoma (>50%)	
	Associated abnormalities (40–50%) • Mucosal neuromas • Marfanoid habitus • Medullated corneal nerve fibers • Megacolon	
MEN 4 (12p13)	Parathyroid adenoma[a]	CDKN1B; no common mutations identified to date
	Pituitary adenoma[a]	
	Reproductive organ tumors[a] (e.g., testicular cancer, neuroendocrine cervical carcinoma)	
	?Adrenal + renal tumors[a]	

[a]Insufficient numbers reported to provide prevalence information.
Note: Autosomal dominant inheritance of the MEN syndromes has been established.
Abbreviations: del, deletion; ins, insertion; MTC, medullary thyroid cancer; NET, neuroendocrine tumor; PPoma, pancreatic polypeptide–secreting tumor; VIPoma, vasoactive intestinal polypeptide–secreting tumor.
Source: Reproduced from RV Thakker et al: J Clin Endocrinol Metab 97:2990, 2012.

This is because MEN 1–associated tumors, with the exception of pituitary NETs, are usually multiple, making it difficult to achieve a successful surgical cure. Occult metastatic disease is also more prevalent in MEN 1, and the tumors may be larger, more aggressive, and resistant to treatment.

Parathyroid tumors

Primary hyperparathyroidism occurs in approximately 90% of patients and is the most common feature of MEN 1. Patients may have asymptomatic hypercalcemia or vague symptoms associated with hypercalcemia

TABLE 52-2

MULTIPLE ENDOCRINE AND OTHER ORGAN NEOPLASIA SYNDROMES (MEONS)

DISEASE[a]	GENE PRODUCT	CHROMOSOMAL LOCATION
Hyperparathyroidism-jaw tumor (HPT-JT)	Parafibromin	1q31.2
Carney complex		
CNC1	PPKAR1A	17q24.2
CNC2	?[b]	2p16
von Hippel-Lindau disease (VHL)	pVHL(elongin)	3p25
Neurofibromatosis type 1 (NF1)	Neurofibromin	17q11.2
Cowden's syndrome (CWD)		
CWD1	PTEN	10q23.31
CWD2	SDHB	1p36.13
CWD3	SDHD	11q23.1
CWD4	KLLN	10q23.31
CWD5	PIK3CA	3q26.32
CWD6	AKT1	14q32.33
McCune-Albright syndrome (MAS)	Gsα	20q13.32

[a]The inheritance for these disorders is autosomal dominant, except MAS, which is due to mosaicism that results from the postzygotic somatic cell mutation of the GNAS1 gene, encoding Gsα.
[b]?, unknown.

(e.g., polyuria, polydipsia, constipation, malaise, or dyspepsia). Nephrolithiasis and osteitis fibrosa cystica (less commonly) may also occur. Biochemical investigations reveal hypercalcemia, usually in association with elevated circulating parathyroid hormone (PTH) **(Table 52-3)**. The hypercalcemia is usually mild, and severe hypercalcemia or parathyroid cancer is a rare occurrence. Additional differences in the primary hyperparathyroidism of patients with MEN 1, as opposed to those without MEN 1, include an earlier age at onset (20–25 years vs 55 years) and an equal male-to-female ratio (1:1 vs 1:3). Preoperative imaging (e.g., neck ultrasound with ^{99m}Tc-sestamibi parathyroid scintigraphy) is of limited benefit because all parathyroid glands may be affected, and neck exploration may be required irrespective of preoperative localization studies.

TREATMENT Parathyroid Tumors

Surgical removal of the abnormally overactive parathyroids in patients with MEN 1 is the definitive treatment. However, it is controversial whether to perform subtotal (e.g., removal of 3.5 glands) or total parathyroidectomy with or without autotransplantation of parathyroid tissue in the forearm, and whether surgery should be performed at an early or late stage. Minimally invasive parathyroidectomy is not recommended because all four parathyroid glands are usually affected with multiple adenomas or hyperplasia. Surgical experience should be taken into account given the variability in pathology in MEN 1. Calcimimetics (e.g., cinacalcet), which act via the calcium-sensing receptor, have been used to treat primary hyperparathyroidism in some patients when surgery is unsuccessful or contraindicated.

TABLE 52-3

BIOCHEMICAL AND RADIOLOGICAL SCREENING IN MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

TUMOR	AGE TO BEGIN (YEARS)	BIOCHEMICAL TEST (PLASMA OR SERUM) ANNUALLY	IMAGING TEST (TIME INTERVAL)
Parathyroid	8	Calcium, PTH	None
Pancreatic NETs			
Gastrinoma	20	Gastrin (± gastric pH)	None
Insulinoma	5	Fasting glucose, insulin	None
Other pancreatic NET	<10	Chromogranin A; pancreatic polypeptide, glucagon, vasoactive intestinal peptide	MRI, CT, or EUS (annually)
Anterior pituitary	5	Prolactin, IGF-I	MRI (every 3 years)
Adrenal	<10	None unless symptoms or signs of functioning tumor and/or tumor >1 cm identified on imaging	MRI or CT (annually with pancreatic imaging)
Thymic and bronchial carcinoid	15	None	CT or MRI (every 1–2 years)

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; IGF-I, insulin-like growth factor I; MRI, magnetic resonance imaging; PTH, parathyroid hormone.
Source: Reproduced from RV Thakker et al: J Clin Endocrinol Metab 97:2990, 2012.

Pancreatic tumors

(See also Chap. 51) The incidence of pancreatic islet cell tumors, which are NETs, in patients with MEN 1 ranges from 30 to 80% in different series. Most of these tumors (Table 52-1) produce excessive amounts of hormone (e.g., gastrin, insulin, glucagon, vasoactive intestinal polypeptide [VIP]) and are associated with distinct clinical syndromes, although some are nonfunctioning or nonsecretory. These pancreatic islet cell tumors have an earlier age at onset in patients with MEN 1 than in patients without MEN 1.

Gastrinoma

Gastrin-secreting tumors (gastrinomas) are associated with marked gastric acid production and recurrent peptic ulcerations, a combination referred to as the Zollinger-Ellison syndrome. Gastrinomas occur more often in patients with MEN 1 who are older than age 30 years. Recurrent severe multiple peptic ulcers, which may perforate, and cachexia are major contributors to the high mortality. Patients with Zollinger-Ellison syndrome may also suffer from diarrhea and steatorrhea. The diagnosis is established by demonstration of an elevated fasting serum gastrin concentration in association with increased basal gastric acid secretion (Table 52-3). However, the diagnosis of Zollinger-Ellison syndrome may be difficult in hypercalcemic MEN 1 patients, because hypercalcemia can also cause hypergastrinemia. Ultrasonography, endoscopic ultrasonography, computed tomography (CT), nuclear magnetic resonance imaging (MRI), selective abdominal angiography, venous sampling, and somatostatin receptor scintigraphy are helpful in localizing the tumor prior to surgery. Gastrinomas represent more than 50% of all pancreatic NETs in patients with MEN 1, and approximately 20% of patients with gastrinomas will be found to have MEN 1. Gastrinomas, which may also occur in the duodenal mucosa, are the major cause of morbidity and mortality in patients with MEN 1. Most MEN 1 gastrinomas are malignant and metastasize before a diagnosis is established.

TREATMENT Gastrinoma

Medical treatment of patients with MEN 1 and Zollinger-Ellison syndrome is directed toward reducing basal acid output to <10 mmol/L. Parietal cell H^+-K^+-adenosine triphosphatase (ATPase) inhibitors (e.g., omeprazole or lansoprazole) reduce acid output and are the drugs of choice for gastrinomas. Some patients may also require additional treatment with the histamine H_2 receptor antagonists, cimetidine or ranitidine. The role of surgery in the treatment of gastrinomas in patients with MEN 1 is controversial. The goal of surgery is to reduce the risk of distant metastatic disease and improve survival. For a nonmetastatic gastrinoma situated in the pancreas, surgical excision is often effective. However, the risk of hepatic metastases increases with tumor size, such that 25–40% of patients with pancreatic NETs >4 cm develop hepatic metastases, and 50–70% of patients with tumors 2–3 cm in size have lymph node metastases. Survival in MEN 1 patients with gastrinomas <2.5 cm in size is 100% at 15 years, but 52% at 15 years, if metastatic disease is present. The presence of lymph node metastases does not appear to adversely affect survival. Surgery for gastrinomas that are >2–2.5 cm has been recommended, because the disease-related survival in these patients is improved following surgery. In addition, duodenal gastrinomas, which occur more frequently in patients with MEN 1, have been treated successfully with surgery. However, in most patients with MEN 1, gastrinomas are multiple or extrapancreatic, and with the exception of duodenal gastrinomas, surgery is rarely successful. For example, the results of one study revealed that only ~15% of patients with MEN 1 were free of disease immediately after surgery, and at 5 years, this number had decreased to ~5%; the respective outcomes in patients without MEN 1 were better, at 45% and 40%. Given these findings, most specialists recommend a nonsurgical management for gastrinomas in MEN 1, except as noted earlier for smaller, isolated lesions. Treatment of disseminated gastrinomas is difficult. Chemotherapy with streptozotocin and 5-fuorouracil; hormonal therapy with octreotide or lanreotide, which are human somatostatin analogues; hepatic artery embolization; administration of human leukocyte interferon; and removal of all resectable tumor have been successful in some patients.

Insulinoma

These β islet cell insulin-secreting tumors represent 10–30% of all pancreatic tumors in patients with MEN 1. Patients with an insulinoma present with hypoglycemic symptoms (e.g., weakness, headaches, sweating, faintness, seizures, altered behavior, weight gain) that typically develop after fasting or exertion and improve after glucose intake. The most reliable test is a supervised 72-h fast. Biochemical investigations reveal increased plasma insulin concentrations in association with hypoglycemia (Table 52-3). Circulating concentrations of C peptide and proinsulin, which are also increased, are useful in establishing the diagnosis. It also is important to demonstrate the absence of sulfonylureas in plasma and urine samples obtained during the investigation of hypoglycemia (Table 52-3). Surgical success is greatly enhanced by preoperative localization by endoscopic ultrasonography, CT scanning, or celiac axis angiography. Additional localization methods may include preoperative and perioperative percutaneous transhepatic portal venous sampling, selective intraarterial stimulation with hepatic venous sampling,

and intraoperative direct pancreatic ultrasonography. Insulinomas occur in association with gastrinomas in 10% of patients with MEN 1, and the two tumors may arise at different times. Insulinomas occur more often in patients with MEN 1 who are younger than 40 years, and some arise in individuals younger than 20 years. In contrast, in patients without MEN 1, insulinomas generally occur in those older than 40 years. Insulinomas may be the first manifestation of MEN 1 in 10% of patients, and approximately 4% of patients with insulinomas will have MEN 1.

TREATMENT Insulinoma

Medical treatment, which consists of frequent carbohydrate meals and diazoxide or octreotide, is not always successful, and surgery is the optimal treatment. Surgical treatment, which ranges from enucleation of a single tumor to a distal pancreatectomy or partial pancreatectomy, has been curative in many patients. Chemotherapy may include streptozotocin, 5-fluorouracil, and doxorubicin. Hepatic artery embolization has been used for metastatic disease.

Glucagonoma

These glucagon-secreting pancreatic NETs occur in <3% of patients with MEN 1. The characteristic clinical manifestations of a skin rash (necrolytic migratory erythema), weight loss, anemia, and stomatitis may be absent. The tumor may have been detected in an asymptomatic patient with MEN 1 undergoing pancreatic imaging or by the finding of glucose intolerence and hyperglucagonemia.

TREATMENT Glucagonoma

Surgical removal of the glucagonoma is the treatment of choice. However, treatment may be difficult because approximately 50–80% of patients have metastases at the time of diagnosis. Medical treatment with somatostatin analogues (e.g., octreotide or lanreotide) or chemotherapy with streptozotocin and 5-fluorouracil has been successful in some patients, and hepatic artery embolization has been used to treat metastatic disease.

Vasoactive intestinal peptide (VIP) tumors (VIPomas)

VIPomas have been reported in only a few patients with MEN 1. This clinical syndrome is characterized by watery diarrhea, hypokalemia, and achlorhydria and is also referred to as the Verner-Morrison syndrome, the WDHA (watery diarrhea, hypokalemia, and achlorhydria) syndrome, or the VIPoma syndrome. The diagnosis is established by excluding laxative and diuretic abuse, by confirming a stool volume in excess of 0.5–1.0 L/d during a fast, and by documenting a markedly increased plasma VIP concentration.

TREATMENT VIPomas

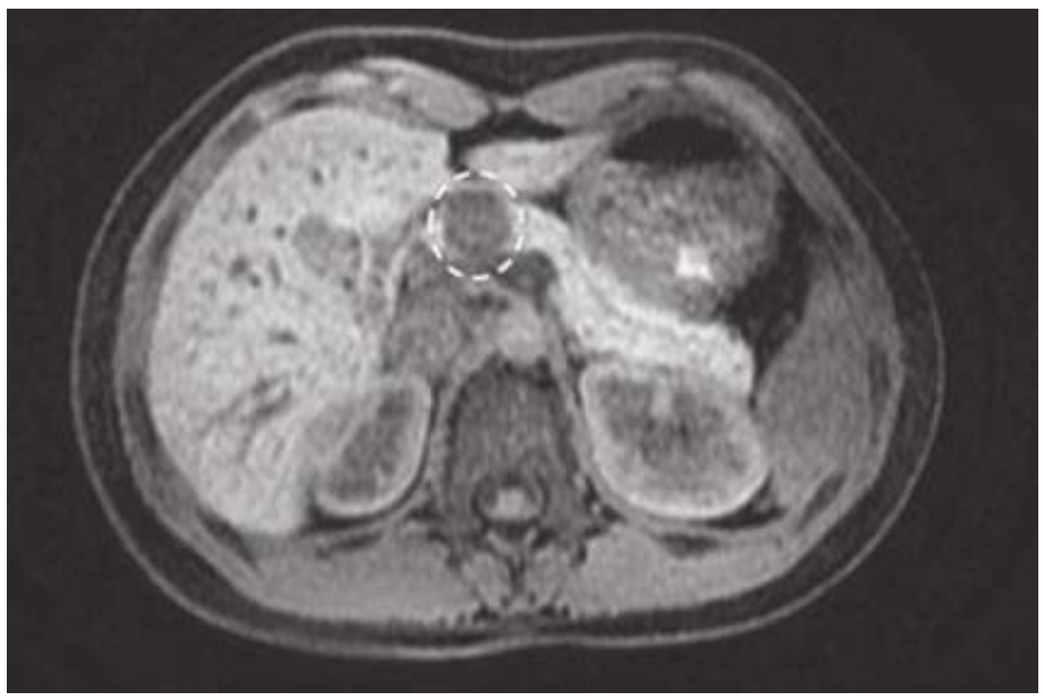
Surgical management of VIPomas, which are mostly located in the tail of the pancreas, can be curative. However, in patients with unresectable tumor, somatostatin analogues, such as octreotide and lanreotide, may be effective. Streptozotocin with 5-fluorouracil may be beneficial, along with hepatic artery embolization for the treatment of metastases.

Pancreatic polypeptide-secreting tumors (Ppomas) and nonfunctioning pancreatic NETs

PPomas are found in a large number of patients with MEN 1. No pathologic sequelae of excessive polypeptide (PP) secretion are apparent, and the clinical significance of PP is unknown. Many PPomas may have been unrecognized or classified as nonfunctioning pancreatic NETs, which likely represent the most common enteropancreatic NET associated with MEN 1 **(Fig. 52-1)**. The absence of both a clinical syndrome and specific biochemical abnormalities may result in a delayed diagnosis of nonfunctioning pancreatic NETs, which are associated with a worse prognosis than other functioning tumors, including insulinoma and gastrinoma. The optimum screening method and its timing interval for nonfunctioning pancreatic NETs remain to be established. At present, endoscopic ultrasound likely represents the most sensitive method of detecting small pancreatic tumors, but somatostatin receptor scintography is the most reliable method for detecting metastatic disease (Table 52-3).

TREATMENT PPomas and Nonfunctioning Pancreatic NETs

The management of nonfunctioning pancreatic NETs in the asymptomatic patient is controversial. One recommendation is to undertake surgery irrespective of tumor size after biochemical assessment is complete. Alternatively, other experts recommend surgery based on tumor size, using either >1 cm or >3 cm at different centers. Pancreatoduodenal surgery is successful in removing the tumors in 80% of patients, but more than 40% of patients develop complications, including diabetes mellitus, frequent steatorrhea, early and late dumping syndromes, and other gastrointestinal symptoms. However, ~50–60% of patients treated surgically survive >5 years. When considering these recommendations, it is important to consider that occult metastatic disease (e.g., tumors not



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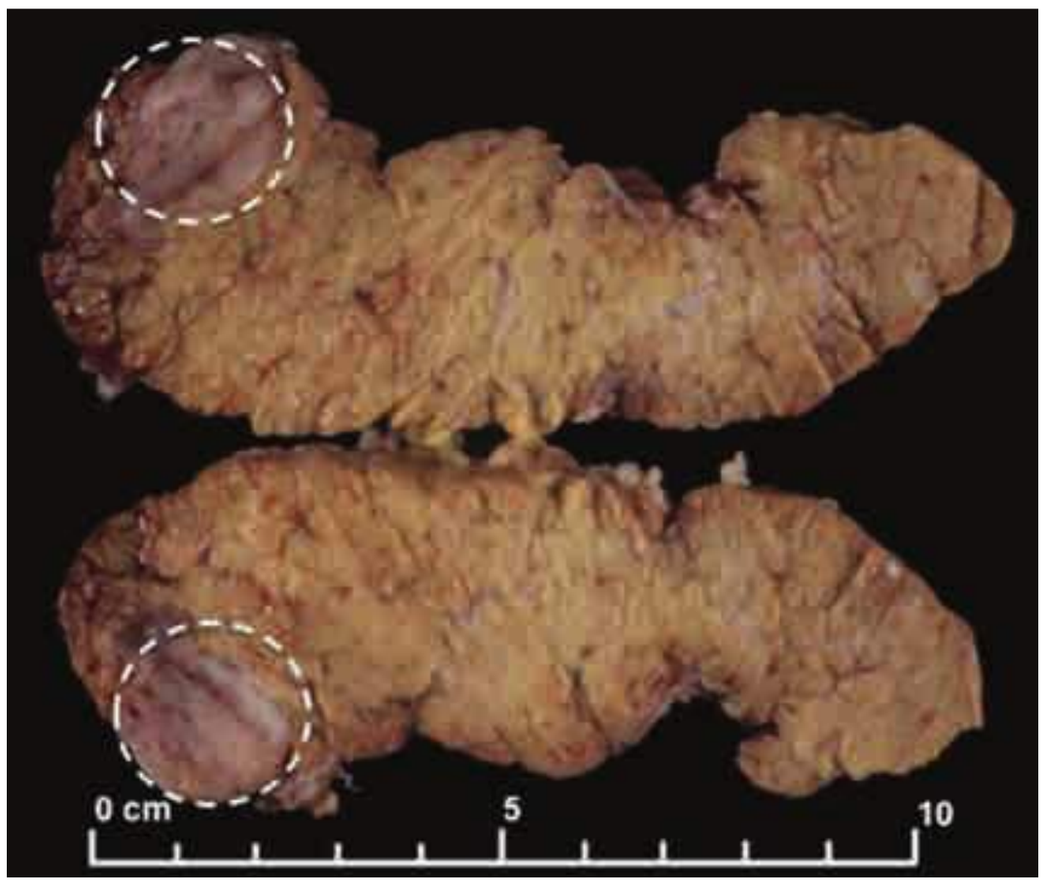

B

FIGURE 52-1
Pancreatic nonfunctioning neuroendocrine tumor (NET) in a 14-year-old patient with multiple endocrine neoplasia type 1 (MEN 1). A. An abdominal magnetic resonance imaging scan revealed a low-intensity >2.0 cm (anteroposterior maximal diameter) tumor within the neck of pancreas. There was no evidence of invasion of adjacent structures or metastases. The tumor is indicated by white dashed circle. B. The pancreatic NET was removed by surgery, and macroscopic examination confirmed the location of the tumor (white dashed circles) in the neck of the pancreas. Immunohistochemistry showed the tumor to immunostain for chromogranin A, but not gastrointestinal peptides or menin, thereby confirming that it was a nonsecreting NET due to loss of menin expression. (Part A adapted with permission from PJ Newey et al: J Clin Endocrinol Metab 10:3640, 2009.)

detected by imaging investigations) is likely to be present in a substantial proportion of these patients at the time of presentation. Inhibitors of tyrosine kinase receptors (TKRs) and of the mammalian target of rapamycin (mTOR) signaling pathway have been reported to be effective in treating pancreatic NETs and in doubling the progression-free survival time.

Other pancreatic NETs

NETs secreting growth hormone–releasing hormone (GHRH), GHRHomas, have been reported rarely in patients with MEN 1. It is estimated that ~33% of patients with GHRHomas have other MEN 1–related tumors. GHRHomas may be diagnosed by demonstrating elevated serum concentrations of growth hormone and GHRH. More than 50% of GHRHomas occur in the lung, 30% occur in the pancreas, and 10% are found in the small intestine. Somatostatinomas secrete somatostatin, a peptide that inhibits the secretion of a variety of hormones, resulting in hyperglycemia, cholelithiasis, low acid output, steatorrhea, diarrhea, abdominal pain, anemia, and weight loss. Although 7% of pancreatic NETs secrete somatostatin, the clinical features of somatostatinoma syndrome are unusual in patients with MEN 1.

Pituitary tumors

Pituitary tumors occur in 15–50% of patients with MEN 1 (Table 52-1). T ese occur as early as 5 years of age or as late as the ninth decade. MEN 1 pituitary adenomas are more frequent in women than men and significantly are macroadenomas (i.e., diameter >1 cm). Moreover, about one-third of these pituitary tumors show invasive features such as infiltration of tumor cells into surrounding normal juxtatumoral pituitary tissue. However, no specific histologic parameters differentiate between MEN 1 and non–MEN 1 pituitary tumors. Approximately 60% of MEN 1–associated pituitary tumors secrete prolactin, <25% secrete growth hormone, 5% secrete adrenocorticotropic hormone (ACTH), and the remainder appear to be nonfunctioning, with some secreting glycoprotein subunits (Table 52-1). However, pituitary tumors derived from MEN 1 patients may exhibit immunoreactivity to several hormones. In particular, there is a greater frequency of somatolactotrope tumors. Prolactinomas are the first manifestation of MEN 1 in ~15% of patients, whereas somatotrope tumors occur more often in patients older than 40 years of age. Fewer than 3% of patients with anterior pituitary tumors will have MEN 1. Clinical manifestations are similar to those in patients with sporadic pituitary tumors without MEN 1 and depend on the hormone secreted and the size of the pituitary tumor. T us, patients may have symptoms of hyperprolactinemia (e.g., amenorrhea, infertility, and galactorrhea in women, or impotence and infertility in men) or have features of acromegaly or Cushing's disease. In addition, enlarging pituitary tumors may compress adjacent structures such as the optic chiasm or normal pituitary tissue, causing visual disturbances and/or hypopituitarism. In asymptomatic patients with MEN 1, periodic biochemical monitoring of serum

prolactin and insulin-like growth factor I (IGF-I) levels, as well as MRI of the pituitary, can lead to early identification of pituitary tumors (Table 52-3). In patients with abnormal results, hypothalamic-pituitary testing should characterize the nature of the pituitary lesion and its effects on the secretion of other pituitary hormones.

TREATMENT Pituitary Tumors

Treatment of pituitary tumors in patients with MEN 1 consists of therapies similar to those used in patients without MEN 1 and includes appropriate medical therapy (e.g., bromocriptine or cabergoline for prolactinoma; or octreotide or lanreotide for somatotrope tumors) or selective transsphenoidal adenomectomy, if feasible, with radiotherapy reserved for residual unresectable tumor tissue. Pituitary tumors in MEN 1 patients may be more aggressive and less responsive to medical or surgical treatments.

Associated tumors

Patients with MEN 1 may also develop carcinoid tumors, adrenal cortical tumors, facial angiofibromas, collagenomas, thyroid tumors, and lipomatous tumors.

Carcinoid tumors

(See also Chap. 51) Carcinoid tumors occur in more than 3% of patients with MEN 1 (Table 52-1). The carcinoid tumor may be located in the bronchi, gastrointestinal tract, pancreas, or thymus. At the time of diagnosis, most patients are asymptomatic and do not have clinical features of the carcinoid syndrome. Importantly, no hormonal or biochemical abnormality (e.g., plasma chromogranin A) is consistently observed in individuals with thymic or bronchial carcinoid tumors. Thus, screening for these tumors is dependent on radiologic imaging. The optimum method for screening has not been established. CT and MRI are sensitive for detecting thymic and bronchial tumors (Table 52-3), although repeated CT scanning raises concern about exposure to repeated doses of ionizing radiation. Octreotide scintigraphy may also reveal some thymic and bronchial carcinoids, although there is insufficient evidence to recommend its routine use. Gastric carcinoids, of which the type II gastric enterochromaffin-like (ECL) cell carcinoids (ECLomas) are associated with MEN 1 and Zollinger-Ellison syndrome, may be detected incidentally at the time of gastric endoscopy for dyspeptic symptoms in MEN 1 patients. These tumors, which may be found in >10% of MEN 1 patients, are usually multiple and smaller than 1.5 cm. Bronchial carcinoids in patients with MEN 1 occur predominantly in women (male-to-female ratio, 1:4). In contrast, thymic carcinoids in European patients with MEN 1 occur predominantly in men (male-to-female ratio, 20:1), with cigarette smokers having a higher risk for these tumors; thymic carcinoids in Japanese patients with MEN 1 have a less marked sex difference (male-to-female ratio 2:1). The course of thymic carcinoids in MEN 1 appears to be particularly aggressive. The presence of thymic tumors in patients with MEN 1 is associated with a median survival after diagnosis of approximately 9.5 years, with 70% of patients dying as a direct result of the tumor.

TREATMENT Carcinoid Tumors

If resectable, surgical removal of carcinoid tumors is the treatment of choice. For unresectable tumors and those with metastatic disease, treatment with radiotherapy or chemotherapeutic agents (e.g., cisplatin, etoposide) may be used. In addition, somatostatin analogues, such as octreotide or lanreotide, have resulted in symptom improvement and regression of some tumors. Little is known about the malignant potential of gastric type II ECLomas, but treatment with somatostatin analogues, such as octreotide or lanreotide, has resulted in regression of these ECLomas.

Adrenocortical tumors

(See also Chap. 53) Asymptomatic adrenocortical tumors occur in 20–70% of patients with MEN 1 depending on the radiologic screening methods used (Table 52-1). Most of these tumors, which include cortical adenomas, hyperplasia, multiple adenomas, nodular hyperplasia, cysts, and carcinomas, are nonfunctioning. Indeed, <10% of patients with enlarged adrenal glands have hormonal hypersecretion, with primary hyperaldosteronism and ACTH-independent Cushing's syndrome being encountered most commonly. Occasionally, hyperandrogenemia may occur in association with adrenocortical carcinoma. Pheochromocytoma in association with MEN 1 is rare. Biochemical investigation (e.g., plasma renin and aldosterone concentrations, low-dose dexamethasone suppression test, urinary catecholamines, and/or metanephrines) should be undertaken in those with symptoms or signs suggestive of functioning adrenal tumors or in those with tumors >1 cm. Adrenocortical carcinoma occurs in approximately 1% of MEN 1 patients but increases to >10% for adrenal tumors larger than 1 cm.

TREATMENT Adrenocortical Tumors

Consensus has not been reached about the management of MEN 1–associated nonfunctioning adrenal tumors, because the majority are benign. However, the risk of malignancy

increases with size, particularly for tumors with a diameter >4 cm. Indications for surgery for adrenal tumors include: size >4 cm in diameter; atypical or suspicious radiologic features (e.g., increased Hounsfield unit on unenhanced CT scan) and size of 1–4 cm in diameter; or significant measurable growth over a 6-month period. T e treatment of functioning (e.g., hormone-secreting) adrenal tumors is similar to that for tumors occurring in non–MEN 1 patients.

Meningioma

Central nervous system (CNS) tumors, including ependymomas, schwannomas, and meningiomas, have been reported in MEN 1 patients (Table 52-1). Meningiomas are found in <10% of patients with other clinical manifestations of MEN 1 (e.g., primary hyperparathyroidism) for >15 years. T e majority of meningiomas are not associated with symptoms, and 60% do not enlarge. T e treatment of MEN 1–associated meningiomas is similar to that in non–MEN 1 patients.

Lipomas

Subcutaneous lipomas occur in >33% of patients with MEN 1 (Table 52-1) and are frequently multiple. In addition, visceral, pleural, or retroperitoneal lipomas may occur in patients with MEN 1. Management is conservative. However, when surgically removed for cosmetic reasons, they typically do not recur.

Facial angiofibromas and collagenomas

T e occurrence of multiple facial angiofibromas in patients with MEN 1 may range from >20 to >90%, and occurrence of collagenomas may range from 0 to >70% (Table 52-1). T ese cutaneous findings may allow presymptomatic diagnosis of MEN 1 in the relatives of a patient with MEN 1. Treatment for these cutaneous lesions is usually not required.

Thyroid tumors

T yroid tumors, including adenomas, colloid goiters, and carcinomas, have been reported to occur in >25% of patients with MEN 1. However, the prevalence of thyroid disorders in the general population is high, and it has been suggested that the association of thyroid abnormalities in patients with MEN 1 may be incidental. T e treatment of thyroid tumors in MEN 1 patients is similar to that for non–MEN 1 patients.

Genetics and screening

T e MEN1 gene is located on chromosome 11q13 and consists of 10 exons, which encode a 610–amino acid protein, menin, that regulates transcription, genome stability, cell division, and proliferation. T e pathophysiology of MEN 1 follows the Knudson two-hit hypothesis with a tumor-suppressor role for menin. Inheritance of a germline MEN1 mutation predisposes an individual to developing a tumor that arises following a somatic mutation, which may be a point mutation or more commonly a deletion, leading to loss of heterozygosity (LOH) in the tumor DNA. T e germline mutations of the MEN1 gene are scattered throughout the entire 1830-bp coding region and splice sites, and there is no apparent correlation between the location of MEN1 mutations and clinical manifestations of the disorder, in contrast with the situation in patients with MEN 2 (Table 52-1). More than 10% of MEN1 germline mutations arise de novo and may be transmitted to subsequent generations. Some families with MEN 1 mutations develop parathyroid tumors as the sole endocrinopathy, and this condition is referred to as familial isolated hyperparathyroidism (FIHP). However, between 5 and 25% of patients with MEN 1 do not harbor germline mutations or deletions of the MEN1 gene. Such patients with MEN 1–associated tumors but without MEN1 mutations may represent phenocopies or have mutations involving other genes. Other genes associated with MEN 1–like features include: CDC73, which encodes parafibromin, whose mutations result in the hyperparathyroid-jaw tumor syndrome; the calcium-sensing receptor gene (CaSR), whose mutations result in familial benign hypocalciuric hypercalcemia (FBHH); and the aryl hydrocarbon receptor interacting protein gene (AIP), a tumor suppressor located on chromosome 11q13 whose mutations are associated with familial isolated pituitary adenomas (FIPA). Genetic testing to determine the MEN1 mutation status in symptomatic family members within a MEN 1 kindred, as well as to all index cases (e.g., patients) with two or more endocrine tumors, is advisable. If an MEN1 mutation is not identified in the index case with two or more endocrine tumors, then clinical and genetic tests for other disorders such as hyperparathyroid-jaw tumor syndrome, FBHH, FIPA, MEN 2, or MEN 4 should be considered, because these patients may represent phenocopies for MEN 1.

T e current guidelines recommend that MEN1 mutational analysis should be undertaken in: (1) an index case with two or more MEN 1–associated endocrine tumors (e.g., parathyroid, pancreatic, or pituitary tumors); (2) asymptomatic first-degree relatives of a known MEN1 mutation carrier; and (3) first-degree relatives of a MEN1 mutation carrier with symptoms, signs, or biochemical or radiologic evidence for one or more MEN 1–associated tumors. In addition, MEN1 mutational analysis should be considered in patients with suspicious or atypical MEN 1. T is would include individuals with parathyroid adenomas before the age of 30 years or multigland parathyroid

disease; individuals with gastrinoma or multiple pancreatic NETs at any age; or individuals who have two or more MEN 1–associated tumors that are not part of the classical triad of parathyroid, pancreatic islet, and anterior pituitary tumors (e.g., parathyroid tumor plus adrenal tumor). Family members, including asymptomatic individuals who have been identified to harbor a MEN1 mutation, will require biochemical and radiologic screening (Table 52-3). In contrast, relatives who do not harbor the MEN1 mutation have a risk of developing MEN 1–associated endocrine tumors that is similar to that of the general population; thus, relatives without the MEN1 mutation do not require repeated screening.

Mutational analysis in asymptomatic individuals should be undertaken at the earliest opportunity and, if possible, in the first decade of life because tumors have developed in some children by the age of 5 years. Appropriate biochemical and radiologic investigations (Table 52-3) aimed at detecting the development of tumors should then be undertaken in affected individuals. Mutant gene carriers should undergo biochemical screening at least once per annum and also have baseline pituitary and abdominal imaging (e.g., MRI or CT), which should then be repeated at 1- to 3-year intervals (Table 52-3). Screening should commence after 5 years of age and should continue for life because the disease may develop as late as the eighth decade. T e screening history and physical examination elicit the symptoms and signs of hypercalcemia, nephrolithiasis, peptic ulcer disease, neuroglycopenia, hypopituitarism, galactorrhea and amenorrhea in women, acromegaly, Cushing's disease, and visual field loss and the presence of subcutaneous lipomas, angiofibromas, and collagenomas. Biochemical screening should include measurements of serum calcium, PTH, gastrointestinal hormones (e.g., gastrin, insulin with a fasting glucose, glucagon, VIP, PP), chromogranin A, prolactin, and IGF-I in all individuals. More specific endocrine function tests should be undertaken in individuals who have symptoms or signs suggestive of a specific clinical syndrome. Biochemical screening for the development of MEN 1 tumors in asymptomatic members of families with MEN 1 is of great importance to reduce morbidity and mortality from the associated tumors.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 AND TYPE 3

Clinical manifestations

MEN type 2 (MEN 2), which is also called Sipple's syndrome, is characterized by the association of medullary thyroid carcinoma (MTC), pheochromocytomas, and parathyroid tumors (Table 52-1). T ree clinical variants of MEN 2 are recognized: MEN 2A, MEN 2B, and MTC only. MEN 2A, which is often referred to as MEN 2, is the most common variant. In MEN 2A, MTC is associated with pheochromocytomas in 50% of patients (may be bilateral) and with parathyroid tumors in 20% of patients. MEN 2A may rarely occur in association with Hirschsprung's disease, caused by the absence of autonomic ganglion cells in the terminal hindgut, resulting in colonic dilatation, severe constipation, and obstruction. MEN 2A may also be associated with cutaneous lichen amyloidosis, which is a pruritic lichenoid lesion that is usually located on the upper back. MEN 2B, which is also referred to as MEN 3, represents 5% of all cases of MEN 2 and is characterized by the occurrence of MTC and pheochromocytoma in association with a Marfanoid habitus; mucosal neuromas of the lips, tongue, and eyelids; medullated corneal fibers; and intestinal autonomic ganglion dysfunction leading to multiple diverticulae and megacolon. Parathyroid tumors do not usually occur in MEN 2B. MTC only (FMTC) is a variant in which MTC is the sole manifestation of the syndrome. However, the distinction between FMTC and MEN 2A is difficult and should only be considered if there are at least four family members above the age of 50 years who are affected by MTC but not pheochromocytomas or primary hyperparathyroidism. All of the MEN 2 variants are due to mutations of the rearranged during transfection (RE*T*) protooncogene, which encodes a TKR. Moreover, there is a correlation between the locations of RE*T* mutations and MEN 2 variants. T us, ~95% of MEN 2A patients have mutations involving the cysteine-rich extracellular domain, with mutations of codon 634 accounting for ~85% of MEN 2A mutations; FMTC patients also have mutations of the cysteine-rich extracellular domain, with most mutations occurring in codon 618. In contrast, ~95% of MEN 2B/MEN 3 patients have mutations of codon 918 of the intracellular tyrosine kinase domain (Table 52-1 and **Table 52-4**).

Medullary thyroid carcinoma

MTC is the most common feature of MEN 2A and MEN 2B and occurs in almost all affected individuals. MTC represents 5–10% of all thyroid gland carcinomas, and 20% of MTC patients have a family history of the disorder. T e use of RE*T* mutational analysis to identify family members at risk for hereditary forms of MTC has altered the presentation of MTC from that of symptomatic tumors to a preclinical disease for which prophylactic thyroidectomy (Table 52-4) is undertaken to improve the prognosis and ideally result in cure. However, in patients who do not have a known family history of MEN 2A, FMTC, or MEN 2B, and therefore have not had RE*T* mutational analysis, MTC may present as a palpable mass in the neck, which may be asymptomatic or associated with symptoms of pressure or dysphagia

TABLE 52-4

RECOMMENDATIONS FOR TESTS AND SURGERY IN MEN 2 AND MEN 3[a]

		RECOMMENDED AGE (YEARS) FOR TEST/INTERVENTION				
RET MUTATION, EXON (EX) LOCATION, AND CODON INVOLVED	RISK[b]	RET MUTATIONAL ANALYSIS	FIRST SERUM CALCITONIN AND NECK ULTRASOUND	PROPHYLACTIC THYROIDECTOMY	SCREENING FOR PHEOCHROMOCYTOMA	SCREENING FOR PHPT
Ex13 (768, 790)[c]; Ex14 (804)[c]; Ex15 (891)[c]	+	<3–5	<3–5	5[d]	20	20
Ex10 (609, 611, 618, 620)[c]; Ex11 (630)[c]	++	<3–5	<3–5	<5[e]	20	20
Ex11 (634)[c]	+++	<3–5	<3–5	<5	8	20
Ex15 (883)[f]; Ex16 (918)[f]	++++	ASAP and by <1	ASAP and by <0.5–1	ASAP and by <1	8	—[g]

[a]Adapted from American Thyroid Association Guidelines, RT Kloos et al: Thyroid 6:565, 2009.
[b]Risk for early development of metastasis and aggressive growth of medullary thyroid cancer: ++++, highest; +++, high; ++, intermediate; and +, lowest.
[c]Mutations associated with MEN 2A (or medullary thyroid carcinoma only).
[d]Consider surgery at 5 years or later if serum calcitonin is normal, neck ultrasound is normal, and there is a less aggressive family history and family preference.
[e]Consider surgery before 5 years or later if serum calcitonin is normal, neck ultrasound is normal, and there is a less aggressive family history and family preference.
[f]Mutations associated with MEN 2B (MEN 3).
[g]Not required because PHPT is not a feature of MEN 2B (MEN 3).
Abbreviations: ASAP, as soon as possible; MEN, multiple endocrine neoplasia; PHPT, primary hyperparathyroidism.

in >15% of patients. Diarrhea occurs in 30% of patients and is associated either with elevated circulating concentrations of calcitonin or tumor-related secretion of serotonin and prostaglandins. Some patients may also experience flushing. In addition, ectopic ACTH production by MTC may cause Cushing's syndrome. The diagnosis of MTC relies on the demonstration of hypercalcitoninemia (>90 pg/mL in the basal state); stimulation tests using IV pentagastrin (0.5 mg/kg) and or calcium infusion (2 mg/kg) are rarely used now, reflecting improvements in the assay for calcitonin. Neck ultrasonography with fine-needle aspiration of the nodules can confirm the diagnosis. Radionucleotide thyroid scans may reveal MTC tumors as "cold" nodules. Radiography may reveal dense irregular calcification within the involved portions of the thyroid gland and in lymph nodes involved with metastases. Positron emission tomography (PET) may help to identify the MTC and metastases **(Fig. 52-2)**. Metastases of MTC usually occur to the cervical lymph nodes in the early stages and to the mediastinal nodes, lung, liver, trachea, adrenal, esophagus, and bone in later stages. Elevations in serum calcitonin concentrations are often the first sign of recurrence or persistent disease, and the serum calcitonin doubling time is useful for determining prognosis. MTC can have an aggressive clinical course, with early metastases and death in approximately 10% of patients. A family history of aggressive MTC or MEN 2B may be elicited.

TREATMENT Medullary Thyroid Carcinoma

Individuals with RE*T* mutations who do not have clinical manifestations of MTC should be offered prophylactic surgery between the ages of <1 and 5 years. The timing of surgery will depend on the type of RE*T* mutation and its associated risk for early development, metastasis, and aggressive growth of MTC (Table 52-4). Such patients should have a total thyroidectomy with a systematic central neck dissection to remove occult nodal metastasis, although the value of undertaking a central neck dissection has been subject to debate. Prophylactic thyroidectomy, with life-long thyroxine replacement, has dramatically improved outcomes in patients with MEN 2 and MEN 3, such that ~90% of young patients with RE*T* mutations who had a prophylactic thyroidectomy have no evidence of persistent or recurrent MTC at 7 years after surgery. In patients with clinically evident MTC, a total thyroidectomy with bilateral central resection is recommended, and an ipsilateral lateral neck dissection should be undertaken if the primary tumor is >1 cm in size or there is evidence of nodal metastasis in the central neck. Surgery is the only curative therapy for MTC. The 10-year survival in patients with metastatic MTC is ~20%. For inoperable MTC or metastatic disease, the tyrosine kinase inhibitors, vandetanib and cabozantinib, have improved the progression-free survival times. Other types of chemotherapy are of limited efficacy, but radiotherapy may help to palliate local disease.

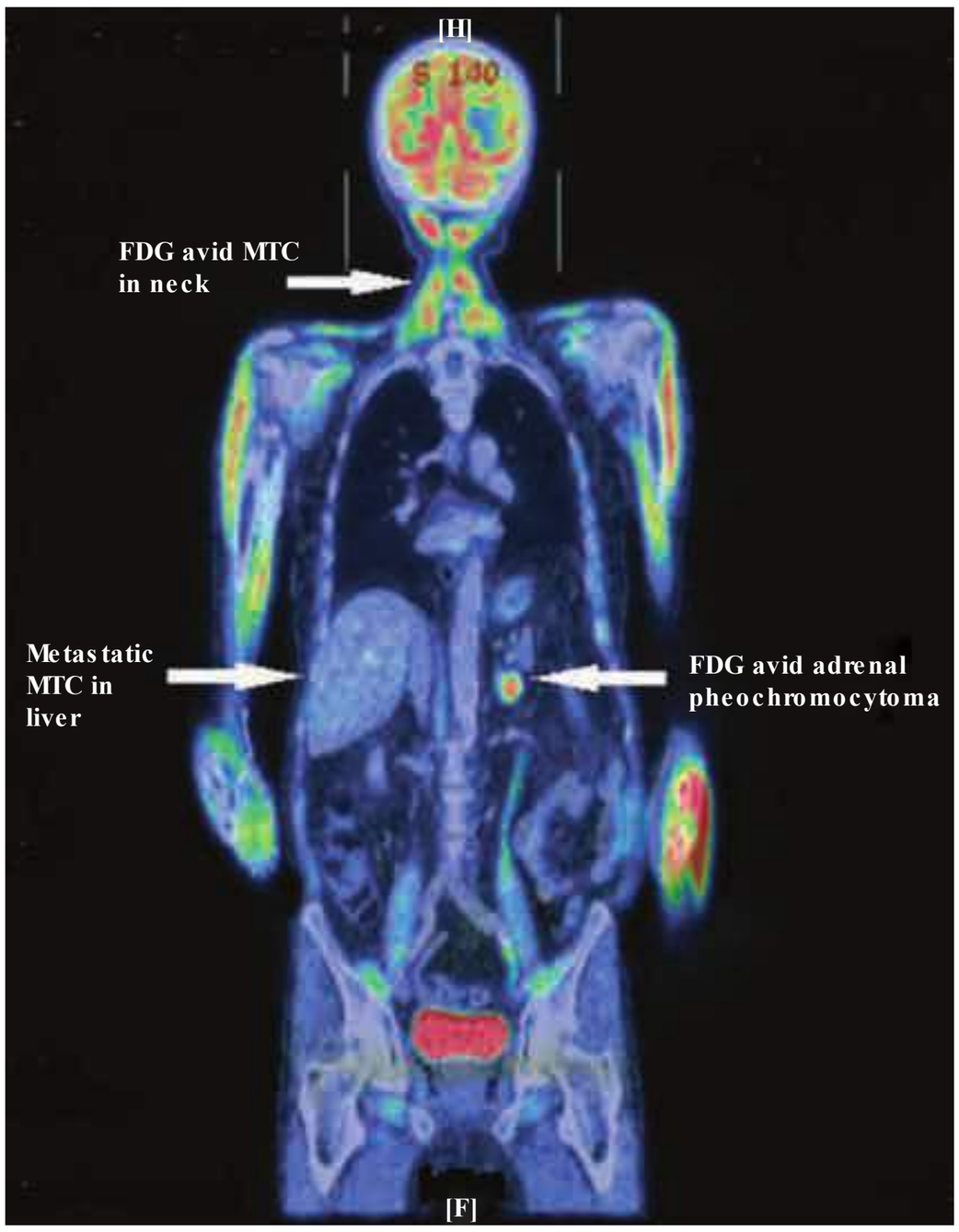

FIGURE 52-2
Fluorodeoxyglucose (FDG) positron emission tomography scan in a patient with multiple endocrine neoplasia type 2A, showing medullary thyroid cancer (MTC) with hepatic and skeletal (left arm) metastasis and a left adrenal pheochromocytoma. Note the presence of excreted FDG compound in the bladder. (Reproduced with permission from A Naziat et al: Clin Endocrinol [Oxf] 78:966, 2013.)

Pheochromocytoma

(See also Chap. 53) T ese noradrenaline- and adrenaline-secreting tumors occur in >50% of patients with MEN 2A and MEN 2B and are a major cause of morbidity and mortality. Patients may have symptoms and signs of catecholamine secretion (e.g., headaches, palpitations, sweating, poorly controlled hypertension), or they may be asymptomatic with detection through biochemical screening based on a history of familial MEN 2A, MEN 2B, or MTC. Pheochromocytomas in patients with MEN 2A and MEN 2B differ significantly in distribution when compared with patients without MEN 2A and MEN 2B. Extra-adrenal pheochromocytomas, which occur in 10% of patients without MEN 2A and MEN 2B, are observed rarely in patients with MEN 2A and MEN 2B. Malignant pheochromocytomas are much less common in patients with MEN 2A and MEN 2B. T e biochemical and radiologic investigation of pheochromocytoma in patients with MEN 2A and MEN 2B is similar to that in non–MEN 2 patients and includes the measurement of plasma (obtained from supine patients) and urinary free fractionated metanephrines (e.g., normetanephrine and metanephrines measured separately), CT or MRI scanning, radionuclide scanning with meta-iodo-(^{123}I or ^{131}I)-benzyl guanidine (MIBG), and PET using (^{18}F)-fuorodopamine or (^{18}F)-fuoro-2-dexoxy-d-glucose (Fig. 52-2).

TREATMENT Pheochromocytoma

Surgical removal of pheochromocytoma, using α and β adrenoreceptor blockade before and during the operation, is the recommended treatment. Endoscopic adrenal-sparing surgery, which decreases postoperative morbidity, hospital stay, and expense, as opposed to open surgery, has become the method of choice.

Parathyroid tumors

Parathyroid tumors occur in 10–25% of patients with MEN 2A. However, >50% of these patients do not have hypercalcemia. T e presence of abnormally enlarged parathyroids, which are unusually hyperplastic, is often seen in the normocalcemic patient undergoing thyroidectomy for MTC. T e biochemical investigation and treatment of hypercalcemic patients with MEN 2A is similar to that of patients with MEN 1.

Genetics and screening

To date, approximately 50 different RE*T* mutations have been reported, and these are located in exons 5, 8, 10, 11, 13, 14, 15, and 16. RE*T* germline mutations are detected in >95% of MEN 2A, FMTC, and MEN 2B families, with Cys634Arg being most common in MEN 2A, Cys618Arg being most common in FMTC, and Met918T r being most common in MEN 2B (Tables 52-1 and 52-4). Between 5 and 10% of patients with MTC or MEN 2A–associated tumors have de novo RE*T* germline mutations, and ~50% of patients with MEN 2B have de novo RE*T* germline mutations. T ese de novo RE*T* germline mutations always occur on the paternal allele. Approximately 5% of patients with sporadic pheochromocytoma have a germline RE*T* mutation, but such germline RE*T* mutations do not appear to be associated with sporadic primary hyperparathyroidism. T us, RE*T* mutational analysis should be performed in: (1) all patients with MTC who have a family history of tumors associated with MEN 2, FMTC, or MEN 3, such that the diagnosis can be confirmed and genetic testing offered to asymptomatic relatives; (2) all patients with MTC and pheochromocytoma without a known family history of MEN 2 or MEN 3; (3) all patients with MTC, but without a family history of MEN 2, FMTC, or MEN 3, because

these patients may have a de novo germline RE*T* mutations; (4) all patients with bilateral pheochromocytoma; and (5) patients with unilateral pheochromocytoma, particularly if this occurs with increased calcitonin levels.

Screening for MEN 2/MEN 3–associated tumors in patients with RE*T* germline mutations should be undertaken annually and include serum calcitonin measurements, a neck ultrasound for MTC, plasma and 24-h urinary fractionated metanephrines for pheochromocytoma, and albumin-corrected serum calcium or ionized calcium with PTH for primary hyperparathyroidism. In patients with MEN 2–associated RE*T* mutations, screening for MTC should begin by 3 to 5 years; for pheochromocytoma by 20 years; and for primary hyperparathyroidism by 20 years of age (Table 52-4).

MULTIPLE ENDOCRINE NEOPLASIA TYPE 4

Clinical manifestations

Patients with MEN 1–associated tumors, such as parathyroid adenomas, pituitary adenomas, and pancreatic NETs, occurring in association with gonadal, adrenal, renal, and thyroid tumors have been reported to have mutations of the gene encoding the 196–amino acid cyclin-dependent kinase inhibitor (CK1) p27 kip1 (CDNKIB). Such families with MEN 1–associated tumors and CDNKIB mutations are designated to have MEN 4 (Table 52-1). T e investigations and treatments for the MEN 4–associated tumors are similar to those for MEN 1 and non–MEN 1 tumors.

Genetics and screening

To date, eight different MEN 4–associated mutations of CDNKIB, which is located on chromosome 12p13, have been reported, and all of these are associated with a loss of function. T ese MEN 4 patients may represent ~3% of the 5–10% of patients with MEN 1 who do not have mutations of the MEN1 gene. Germline CDNKIB mutations may rarely be found in patients with sporadic (i.e., nonfamilial) forms of primary hyperparathyroidism.

HYPERPARATHYROIDISM-JAW TUMOR SYNDROME

Clinical manifestations

Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is an autosomal dominant disorder characterized by the development of parathyroid tumors (15% are carcinomas) and fibro-osseous jaw tumors. In addition, some patients may also develop Wilms' tumors, renal cysts, renal hematomas, renal cortical adenomas, papillary renal cell carcinomas, pancreatic adenocarcinomas, uterine tumors, testicular mixed germ cell tumors with a major seminoma component, and Hürthle cell thyroid adenomas. T e parathyroid tumors may occur in isolation and without any evidence of jaw tumors, and this may cause confusion with other hereditary hypercalcemic disorders, such as MEN 1. However, genetic testing to identify the causative mutation will help to establish the correct diagnosis. T e investigation and treatment for HPT-JT-associated tumors are similar to those in non-HPT-JT patients, except that early parathyroidectomy is advisable because of the increased frequency of parathyroid carcinoma.

Genetics and screening

T e gene that causes HPT-JT is located on chromosome 1q31.2 and encodes a 531–amino acid protein, parafibromin (Table 52-2). Parafibromin is also referred to as cell division cycle protein 73 (CDC73) and has a role in transcription. Genetic testing in families helps to identify mutation carriers who should be periodically screened for the development of tumors **(Table 52-5)**.

VON HIPPEL-LINDAU DISEASE

Clinical manifestations

von Hippel-Lindau (VHL) disease is an autosomal dominant disorder characterized by hemangioblastomas of the retina and CNS; cysts involving the kidneys, pancreas,

TABLE 52-5

HPT-JT SCREENING GUIDELINES

TUMOR[a]	TEST	FREQUENCY[b]
Parathyroid	Serum Ca, PTH	6–12 months
Ossifying jaw fibroma	Panoramic jaw x-ray with neck shielding[c]	5 years
Renal	Abdominal MRI[c,d]	5 years
Uterine	Ultrasound (transvaginal or transabdominal) and additional imaging ± D&C if indicated[e]	Annual

[a]Screening for most common HPT-JT–associated tumors is considered. Assessment for other reported tumor types may be indicated (e.g., pancreatic, thyroid, testicular tumors).
[b]Frequency of repeating test after baseline tests performed.
[c]X-rays and imaging involving ionizing radiation should ideally be avoided to minimize risk of generating subsequent mutations.
[d]Ultrasound scan recommended if MRI unavailable.
[e]Such selective pelvic imaging should be considered after obtaining a detailed menstrual history.
Abbreviations: Ca, calcium; D&C, dilatation and curettage; HPT-JT, hyperparathyroidism-jaw tumor syndrome; MRI, magnetic resonance imaging; PTH, parathyroid hormone.
Source: Reproduced from PJ Newey et al: Hum Mutat 31:295, 2010.

and epididymis; renal cell carcinomas; pheochromocytomas; and pancreatic islet cell tumors **(See also Chap. 53)**. The retinal and CNS hemangioblastomas are benign vascular tumors that may be multiple; those in the CNS may cause symptoms by compressing adjacent structures and/or increasing intracranial pressure. In the CNS, the cerebellum and spinal cord are the most frequently involved sites. The renal abnormalities consist of cysts and carcinomas, and the lifetime risk of a renal cell carcinoma (RCC) in VHL is 70%. The endocrine tumors in VHL consist of pheochromocytomas and pancreatic islet cell tumors. The clinical presentation of pheochromocytoma in VHL disease is similar to that in sporadic cases, except there is a higher frequency of bilateral or multiple tumors, which may involve extra-adrenal sites in VHL disease. The most frequent pancreatic lesions in VHL are multiple cyst-adenomas, which rarely cause clinical disease. However, nonsecreting pancreatic islet cell tumors occur in <10% of VHL patients, who are usually asymptomatic. The pancreatic tumors in these patients are often detected by regular screening using abdominal imaging. Pheochromocytomas should be investigated and treated as described earlier for MEN 2. The pancreatic islet cell tumors frequently become malignant, and early surgery is recommended.

Genetics and screening

The VHL gene, which is located on chromosome 3p26-p25, is widely expressed in human tissues and encodes a 213–amino acid protein (pVHL) (Table 52-2). A wide variety of germline VHL mutations have been identified. VHL acts as a tumor-suppressor gene. A correlation appears to exist between the type of mutation and the clinical phenotype; large deletions and protein-truncating mutations are associated with a low incidence of pheochromocytomas, whereas some missense mutations in VHL patients are associated with pheochromocytoma (referred to as VHL type 2C). Other missense mutations may be associated with hemangioblastomas and RCC but not pheochromocytoma (referred to as VHL type 1), whereas distinct missense mutations are associated with hemangioblastomas, RCC, and pheochromocytoma (VHL type 2B). VHL type 2A, which refers to the occurrence of hemangioblastomas and pheochromocytoma without RCC, is associated with rare missense mutations. The basis for these complex genotype-phenotype relationships remains to be elucidated. One major function of pVHL, which is also referred to as elongin, is to downregulate the expression of vascular endothelial growth factor (VEGF) and other hypoxia-inducible mRNAs. Thus, pVHL, in complex with other proteins, regulates the expression of hypoxia-inducible factors (HIF-1 and HIF-2) such that loss of functional pVHL leads to a stabilization of the HIF protein complexes, resulting in VEGF overexpression and tumor angiogenesis. Screening for the development of pheochromocytomas and pancreatic islet cell tumors is as described earlier for MEN 2 and MEN 1, respectively (Tables 52-3 and 52-4).

NEUROFIBROMATOSIS

Clinical manifestations

Neurofibromatosis type 1 (NF1), which is also referred to as von Recklinghausen's disease, is an autosomal dominant disorder characterized by the following manifestations: neurologic (e.g., peripheral and spinal neurofibromas); ophthalmologic (e.g., optic gliomas and iris hamartomas such as Lisch nodules); dermatologic (e.g., café au lait macules); skeletal (e.g., scoliosis, macrocephaly, short stature, and pseudoarthrosis); vascular (e.g., stenoses of renal and intracranial arteries); and endocrine (e.g., pheochromocytoma, carcinoid tumors, and precocious puberty). Neurofibromatosis type 2 (NF2) is also an autosomal dominant disorder but is characterized by the development of bilateral vestibular schwannomas (acoustic neuromas) that lead to deafness, tinnitus, or vertigo. Some patients with NF2 also develop meningiomas, spinal schwannomas, peripheral nerve neurofibromas, and café au lait macules. Endocrine abnormalities are not found in NF2 and are associated solely with NF1. Pheochromocytomas, carcinoid tumors, and precocious puberty occur in about 1% of patients with NF1, and growth hormone deficiency has been also reported. The features of pheochromocytomas in NF1 are similar to those in non-NF1 patients, with 90% of tumors being located within the adrenal medulla and the remaining 10% at an extra-adrenal location, which often involves the para-aortic region. Primary carcinoid tumors are often periampullary and may also occur in the ileum but rarely in the pancreas, thyroid, or lungs. Hepatic metastases are associated with symptoms of the carcinoid syndrome, which include flushing, diarrhea, bronchoconstriction, and tricuspid valve disease. Precocious puberty is usually associated with the extension of an optic glioma into the hypothalamus with resultant early activation of gonadotropin-releasing hormone secretion. Growth hormone deficiency has also been observed in some NF1 patients, who may or may not have optic chiasmal gliomas, but it is important to note that short stature is frequent in the absence of growth hormone deficiency in patients with NF1. The investigation and treatment for tumors are similar to those undertaken for each respective tumor type in non-NF1 patients.

Genetics and screening

The NF1 gene, which is located on chromosome 17q11.2 and acts as a tumor suppressor, consists of 60 exons that span more than 350 kb of

genomic DNA (Table 52-2). Mutations in NF1 are of diverse types and are scattered throughout the exons. The NF1 gene product is the protein neurofibromin, which has homologies to the p120GAP (GTPase activating protein) and acts on p21ras by converting the active GTP bound form to its inactive GDP form. Mutations of NF1 impair this downregulation of the p21ras signaling pathways, which in turn results in abnormal cell proliferation. Screening for the development of pheochromocytomas and carcinoid tumors is as described earlier for MEN 2 and MEN 1, respectively (Tables 52-3 and 52-4).

CARNEY COMPLEX

Clinical manifestations

Carney complex (CNC) is an autosomal dominant disorder characterized by spotty skin pigmentation (usually of the face, labia, and conjunctiva), myxomas (usually of the eyelids and heart, but also the tongue, palate, breast, and skin), psammomatous melanotic schwannomas (usually of the sympathetic nerve chain and upper gastrointestinal tract), and endocrine tumors that involve the adrenals, Sertoli cells, somatotropes, thyroid, and ovary. Cushing's syndrome, the result of primary pigmented nodular adrenal disease (PPNAD), is the most common endocrine manifestation of CNC and may occur in one-third of patients. Patients with CNC and Cushing's syndrome often have an atypical appearance by being thin (as opposed to having truncal obesity). In addition, they may have short stature, muscle and skin wasting, and osteoporosis. These patients often have levels of urinary free cortisol that are normal or increased only marginally. Cortisol production may fluctuate periodically with days or weeks of hypercortisolism; this pattern is referred to as "periodic Cushing's syndrome." Patients with Cushing's syndrome usually have loss of the circadian rhythm of cortisol production. Acromegaly, the result of a somatotrope tumor, affects ~10% of patients with CNC. Testicular tumors may also occur in one-third of patients with CNC. These may either be large-cell calcifying Sertoli cell tumors, adrenocortical rests, or Leydig cell tumors. The Sertoli cell tumors occasionally may be estrogen-secreting and lead to precocious puberty or gynecomastia. Some patients with CNC have been reported to develop thyroid follicular tumors, ovarian cysts, or breast duct adenomas.

Genetics and screening

CNC type 1 (CNC1) is due to mutations of the protein kinase A (PKA) regulatory subunit 1 α (R1α) (PPKAR1A), a tumor suppressor, whose gene is located on chromosome 17q.24.2 (Table 52-2). The gene causing CNC type 2 (CNC2) is located on chromosome 2p16 and has not yet been identified. It is interesting to note, however, that some tumors do not show LOH of 2p16 but instead show genomic instability, suggesting that this CNC gene may not be a tumor suppressor. Screening and treatment of these endocrine tumors are similar to those described earlier for patients with MEN 1 and MEN 2 (Tables 52-3 and 52-4).

COWDEN'S SYNDROME

Clinical manifestations

Multiple hamartomatous lesions, especially of the skin, mucous membranes (e.g., buccal, intestinal, and colonic), breast, and thyroid are characteristic of Cowden's (CWD) syndrome, which is an autosomal dominant disorder. Thyroid abnormalities occur in two-thirds of patients with CWD syndrome, and these usually consist of multinodular goiters or benign adenomas, although <10% of patients may have a follicular thyroid carcinoma. Breast abnormalities occur in >75% of patients and consist of either fibrocystic disease or adenocarcinomas. The investigation and treatment for CWD tumors are similar to those undertaken for non-CWD patients.

Genetics and screening

CWD syndrome is genetically heterogenous, and six types (CWD1–6) are recognized (Table 52-2). CWD is due to mutations of the phosphate and tensin homologue deleted on chromosome 10 (*PTEN*) gene, located on chromosome 10q23.31. CWD2 is caused by mutations of the succinate dehydrogenase subunit B (SDHB) gene, located on chromosome 1p36.13; and CWD3 is caused by mutations of the SDHD gene, located on chromosome 11q13.1. SDHB and SDHD mutations are also associated with pheochromocytoma. CWD4 is caused by hypermethylation of the Killin (KLLN) gene, the promoter of which shares the same transcription site as *PTEN* on chromosome 10q23.31. CWD5 is caused by mutations of the phosphatidylinositol 3-kinase catalytic alpha (PIK3CA) gene on chromosome 3q26.32, and CWD6 is caused by mutations of the V-Akt murine thymoma viral oncogene homolog 1 (*AKT*1) gene on chromosome 14q32.33. Screening for thyroid abnormalities entails neck ultrasonography and fine-needle aspiration with analysis of cell cytology.

McCUNE-ALBRIGHT SYNDROME

Clinical manifestations

McCune-Albright syndrome (MAS) is characterized by the triad of polyostotic fibrous dysplasia, which may be

associated with hypophosphatemic rickets; café au lait skin pigmentation; and peripheral precocious puberty; other endocrine abnormalities include thyrotoxicosis, which may be associated with a multinodular goiter, somatotrope tumors, and Cushing's syndrome (due to adrenal tumors). Investigation and treatment for each endocrinopathy are similar to those used in patients without MAS.

Genetics and screening

MAS is a disorder of mosaicism that results from postzygotic somatic cell mutations of the G protein α stimulating subunit (Gsα), encoded by the GNAS1 gene, located on chromosome 20q13.32 (Table 52-2). The Gsα mutations, which include Arg201Cys, Arg201His, Glu227Arg, or Glu227His, are activating and are found only in cells of the abnormal tissues. Screening for hyperfunction of relevant endocrine glands and development of hypophosphatemia, which may be associated with elevated serum fibroblast growth factor 23 (FGF23) concentrations, is undertaken in MAS patients.

Acknowledgments

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CHAPTER 53

PHEOCHROMOCYTOMA AND ADRENOCORTICAL CARCINOMA

Hartmut P. H. Neumann

Pheochromocytomas and paragangliomas are catecholamine-producing tumors derived from the sympathetic or parasympathetic nervous system. T ese tumors may arise sporadically or be inherited as features of multiple endocrine neoplasia type 2, von Hippel–Lindau disease, or several other pheochromocytoma-associated syndromes. T e diagnosis of pheochromocytomas identifies a potentially correctable cause of hypertension, and their removal can prevent hypertensive crises that can be lethal. T e clinical presentation is variable, ranging from an adrenal incidentaloma to a hypertensive crisis with associated cerebrovascular or cardiac complications.

EPIDEMIOLOGY

Pheochromocytoma is estimated to occur in 2–8 of 1 million persons per year, and ~0.1% of hypertensive patients harbor a pheochromocytoma. T e mean age at diagnosis is ~40 years, although the tumors can occur from early childhood until late in life. T e classic "rule of tens" for pheochromocytomas states that ~10% are bilateral, 10% are extra-adrenal, and 10% are malignant.

ETIOLOGY AND PATHOGENESIS

Pheochromocytomas and paragangliomas are well-vascularized tumors that arise from cells derived from the sympathetic (e.g., adrenal medulla) or parasympathetic (e.g., carotid body, glomus vagale) paraganglia **(Fig. 53-1)**. T e name pheochromocytoma reflects the black-colored staining caused by chromaffin oxidation of catecholamines; although a variety of terms have been used to describe these tumors, most clinicians use this designation to describe symptomatic catecholamine-producing tumors, including those in extra-adrenal retroperitoneal, pelvic, and thoracic sites. T e term paraganglioma is used to describe catecholamine-producing tumors in the skull base and neck; these tumors may secrete little or no catecholamine. In contrast to common clinical parlance, the World Health Organization (WHO) restricts the term pheochromocytoma to adrenal tumors and applies the term paraganglioma to tumors at all other sites.

T e etiology of sporadic pheochromocytomas and paragangliomas is unknown. However, 25–33% of patients have an inherited condition, including germline mutations in the classically recognized RET, VHL, NF1, SDHB, SDHC, and SDHD genes or in the more recently recognized SDHA, SDHAF2, TMEM127, and MAX genes. Biallelic gene inactivation has been demonstrated for the VHL, NF1, and SDH genes, whereas RET mutations activate receptor tyrosine kinase activity. SDH is an enzyme of the Krebs cycle and the mitochondrial respiratory chain. T e VHL protein is a component of a ubiquitin E3 ligase. VHL mutations reduce protein degradation, resulting in upregulation of components involved in cell cycle progression, glucose metabolism, and oxygen sensing.

CLINICAL FEATURES

Its clinical presentation is so variable that pheochromocytoma has been termed "the great masquerader" **(Table 53-1)**. Among the presenting manifestations, episodes of palpitation, headache, and profuse sweating are typical, and these manifestations constitute a classic triad. T e presence of all three manifestations in association with hypertension makes pheochromocytoma a likely diagnosis. However, a pheochromocytoma can be asymptomatic for years, and some tumors grow to a considerable size before patients note symptoms.

T e dominant sign is hypertension. Classically, patients have episodic hypertension, but sustained hypertension is also common. Catecholamine crises can

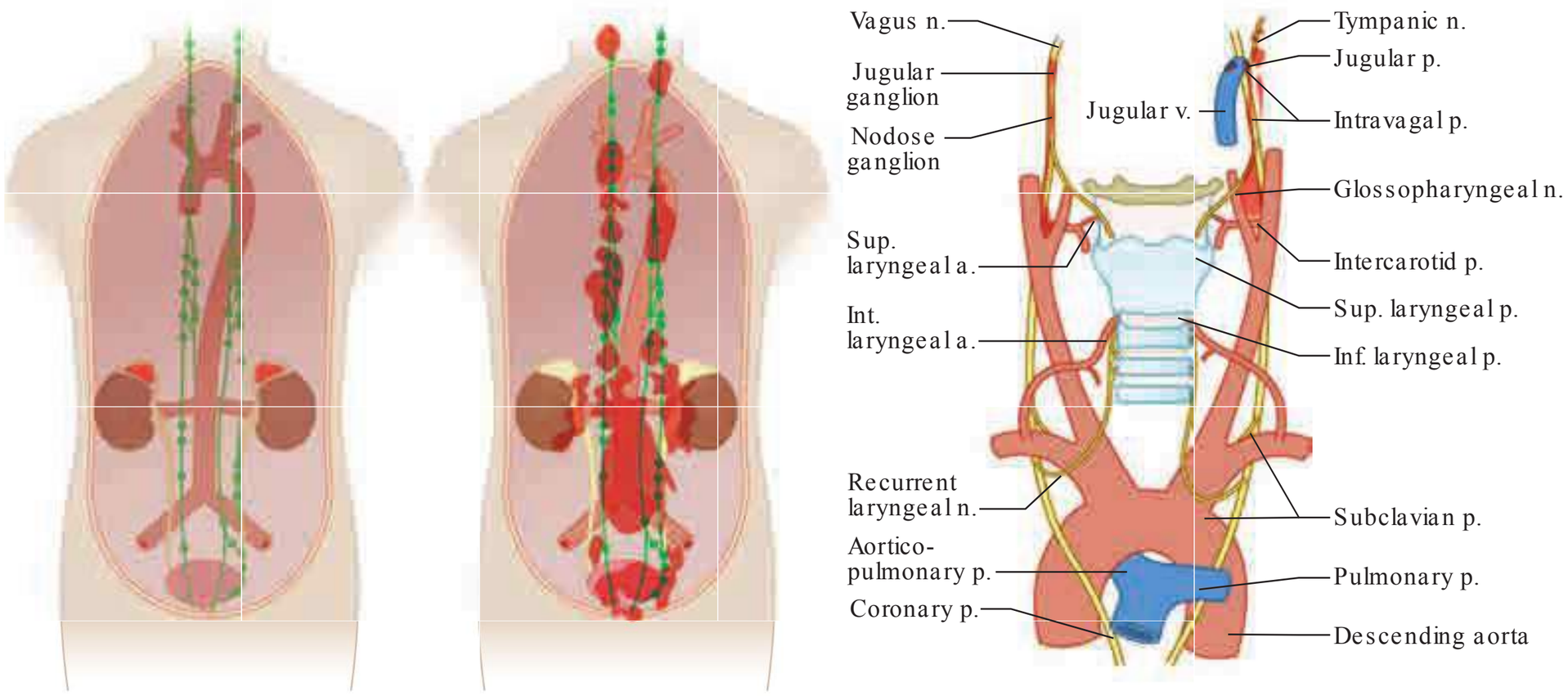


FIGURE 53-1

The paraganglial system and topographic sites (in red) of pheochromocytomas and paragangliomas. (Parts A and B from WM Manger, RW Gifford: Clinical and experimental pheochromocytoma. Cambridge, Blackwell Science, 1996; Part C from GG Glenner, PM Grimley: Tumors of the Extra-adrenal Paraganglion System [Including Chemoreceptors], Atlas of Tumor Pathology, 2nd Series, Fascicle 9. Washington, DC, AFIP, 1974.)

lead to heart failure, pulmonary edema, arrhythmias, and intracranial hemorrhage. During episodes of hormone release, which can occur at widely divergent intervals, patients are anxious and pale, and they experience tachycardia and palpitations. These paroxysms generally last <1 h and may be precipitated by surgery, positional changes, exercise, pregnancy, urination (particularly with bladder pheochromocytomas), and various medications (e.g., tricyclic antidepressants, opiates, metoclopramide).

TABLE 53-1

CLINICAL FEATURES ASSOCIATED WITH PHEOCHROMOCYTOMA, LISTED BY FREQUENCY OF OCCURRENCE
1. Headaches
2. Profuse sweating
3. Palpitations and tachycardia
4. Hypertension, sustained or paroxysmal
5. Anxiety and panic attacks
6. Pallor
7. Nausea
8. Abdominal pain
9. Weakness
10. Weight loss
11. Paradoxical response to antihypertensive drugs
12. Polyuria and polydipsia
13. Constipation
14. Orthostatic hypotension
15. Dilated cardiomyopathy
16. Erythrocytosis
17. Elevated blood sugar
18. Hypercalcemia

DIAGNOSIS

The diagnosis is based on documentation of catecholamine excess by biochemical testing and localization of the tumor by imaging. These two criteria are of equal importance, although measurement of catecholamines or metanephrines (their methylated metabolites) is traditionally the first step in diagnosis.

Biochemical testing

Pheochromocytomas and paragangliomas synthesize and store catecholamines, which include norepinephrine (noradrenaline), epinephrine (adrenaline), and dopamine. Elevated plasma and urinary levels of catecholamines and metanephrines form the cornerstone of diagnosis. The characteristic fluctuations in the hormonal activity of tumors results in considerable variation in serial catecholamine measurements. However, most tumors continuously leak O-methylated metabolites, which are detected by measurement of metanephrines.

Catecholamines and metanephrines can be measured by different methods, including high-performance liquid chromatography, enzyme-linked immunosorbent assay, and liquid chromatography/mass spectrometry. When pheochromocytoma is suspected on clinical grounds (i.e., when values are three times the upper limit of normal), this diagnosis is highly likely regardless of the assay used. However, as summarized in **Table 53-2**, the sensitivity and specificity of available biochemical tests vary greatly, and these differences are

TABLE 53-2

BIOCHEMICAL AND IMAGING METHODS USED FOR DIAGNOSIS OF PHEOCHROMOCYTOMA AND PARAGANGLIOMA

DIAGNOSTIC METHOD	SENSITIVITY	SPECIFICITY
24-h urinary tests		
Catecholamines	+++	+++
Fractionated metanephrines	++++	++
Total metanephrines	+++	++++
Plasma tests		
Catecholamines	+++	++
Free metanephrines	++++	+++
Imaging		
CT	++++	+++
MRI	++++	+++
MIBG scintigraphy	+++	++++
Somatostatin receptor scintigraphy[a]	++	++
^{18}Fluoro-DOPA PET/CT	+++	++++

[a]Values are particularly high in head and neck paragangliomas.
Abbreviations: MIBG, metaiodobenzylguanidine; PET/CT, positron emission tomography plus CT. For the biochemical tests, the ratings correspond globally to sensitivity and specificity rates as follows: ++, <85%; +++, 85–95%; and ++++, >95%.

TABLE 53-3

CLASSIFICATION OF UNILATERAL ADRENAL MASSES

MASS	APPROXIMATE PREVALENCE (%)
Benign	
Adrenocortical adenoma	
Endocrine-inactive	60–85
Cortisol-producing	5–10
Aldosterone-producing	2–5
Pheochromocytoma	5–10
Adrenal myelolipoma	<1
Adrenal ganglioneuroma	<0.1
Adrenal hemangioma	<0.1
Adrenal cyst	<1
Adrenal hematoma/hemorrhagic infarction	<1
Indeterminate	
Adrenocortical oncocytoma	<1
Malignant	
Adrenocortical carcinoma	2–5
Malignant pheochromocytoma	<1
Adrenal neuroblastoma	<0.1
Lymphomas (including primary adrenal lymphoma)	<1
Metastases (most frequent: breast, lung)	15

Note: Bilateral adrenal enlargement/masses may be caused by congenital adrenal hyperplasia, bilateral macronodular hyperplasia, bilateral hemorrhage (due to antiphospholipid syndrome or sepsis-associated Waterhouse-Friderichsen syndrome), granuloma, amyloidosis, or infiltrative disease including tuberculosis.

important in assessing patients with borderline elevations of different compounds. Urinary tests for metanephrines (total or fractionated) and catecholamines are widely available and are used commonly for initial evaluation. Among these tests, those for the fractionated metanephrines and catecholamines are the most sensitive. Plasma tests are more convenient and include measurements of catecholamines and metanephrines. Measurements of plasma metanephrine are the most sensitive and are less susceptible to false-positive elevations from stress, including venipuncture. Although the incidence of false-positive test results has been reduced by the introduction of newer assays, physiologic stress responses and medications that increase catecholamine levels still can confound testing. Because the tumors are relatively rare, borderline elevations are likely to represent false-positive results. In this circumstance, it is important to exclude dietary or drug-related factors (withdrawal of levodopa or use of sympathomimetics, diuretics, tricyclic antidepressants, alpha and beta blockers) that might cause false-positive results and then to repeat testing or perform a clonidine suppression test (i.e., the measurement of plasma normetanephrine 3 h after oral administration of 300 μg of clonidine). Other pharmacologic tests, such as the phentolamine test and the glucagon provocation test, are of relatively low sensitivity and are not recommended.

Diagnostic imaging

A variety of methods have been used to localize pheochromocytomas and paragangliomas (Table 53-2). CT and MRI are similar in sensitivity and should be performed with contrast. T2-weighted MRI with gadolinium contrast is optimal for detecting pheochromocytomas and is somewhat better than CT for imaging extraadrenal pheochromocytomas and paragangliomas. About 5% of adrenal incidentalomas, which usually are detected by CT or MRI, prove to be pheochromocytomas upon endocrinologic evaluation.

Tumors also can be localized by procedures using radioactive tracers, including ^{131}I- or ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, ^{111}In-somatostatin analogue scintigraphy, ^{18}F-DOPA positron emission tomography (PET), or ^{18}F-fluorodeoxyglucose (FDG) PET. Because these agents exhibit selective uptake in

paragangliomas, nuclear imaging is particularly useful in the hereditary syndromes.

Differential diagnosis

When the possibility of a pheochromocytoma is being entertained, other disorders to consider include essential hypertension, anxiety attacks, use of cocaine or amphetamines, mastocytosis or carcinoid syndrome (usually without hypertension), intracranial lesions, clonidine withdrawal, autonomic epilepsy, and factitious crises (usually from use of sympathomimetic amines). When an asymptomatic adrenal mass is identified, likely diagnoses other than pheochromocytoma include a nonfunctioning adrenal adenoma, an aldosteronoma, and a cortisol-producing adenoma (Cushing's syndrome) **(Table 53-3)**.

TREATMENT Pheochromocytoma

Complete tumor removal, the ultimate therapeutic goal, can be achieved by partial or total adrenalectomy. It is important to preserve the normal adrenal cortex, particularly in hereditary disorders in which bilateral pheochromocytomas are most likely. Preoperative preparation of the patient is important. Before surgery, blood pressure should be consistently below 160/90 mmHg. Classically, blood pressure has been controlled by α-adrenergic blockers (oral phenoxybenzamine, 0.5–4 mg/kg of body weight). Because patients are volume-constricted, liberal salt intake and hydration are necessary to avoid severe orthostasis. Oral prazosin or intravenous phentolamine can be used to manage paroxysms while adequate alpha blockade is awaited. Beta blockers (e.g., 10 mg of propranolol three or four times per day) can then be added. Other antihypertensives, such as calcium channel blockers or angiotensin-converting enzyme inhibitors, have also been used effectively.

Surgery should be performed by teams of surgeons and anesthesiologists with experience in the management of pheochromocytomas. Blood pressure can be labile during surgery, particularly at the outset of intubation or when the tumor is manipulated. Nitroprusside infusion is useful for intraoperative hypertensive crises, and hypotension usually responds to volume infusion.

Minimally invasive techniques (laparoscopy or retroperitoneoscopy) have become the standard approaches in pheochromocytoma surgery. They are associated with fewer complications, a faster recovery, and optimal cosmetic results. Extra-adrenal abdominal and most thoracic pheochromocytomas also can also be removed endoscopically. Postoperatively, catecholamine normalization should be documented. An adrenocorticotropic hormone test should be used to exclude cortisol deficiency when bilateral adrenal cortex–sparing surgery has been performed.

MALIGNANT PHEOCHROMOCYTOMA

About 5–10% of pheochromocytomas and paragangliomas are malignant. The diagnosis of malignant pheochromocytoma is problematic. The typical histologic criteria of cellular atypia, presence of mitoses, and invasion of vessels or adjacent tissues are insufficient for the diagnosis of malignancy in pheochromocytoma. Thus, the term malignant pheochromocytoma is restricted to tumors with distant metastases, most commonly found by nuclear medicine imaging in lungs, bone, or liver—locations suggesting a vascular pathway of spread. Because hereditary syndromes are associated with multifocal tumor sites, these features should be anticipated in patients with germ-line mutations of RET, VHL, SDHD, or SDHB. However, distant metastases also occur in these syndromes, especially in carriers of SDHB mutations.

Treatment of malignant pheochromocytoma or paraganglioma is challenging. Options include tumor mass reduction, alpha blockers for symptoms, chemotherapy, and nuclear medicine radiotherapy. The first-line choice is nuclear medicine therapy for scintigraphically documented metastases, preferably with ^{131}I-MIBG in 200-mCi doses at monthly intervals over three to six cycles. Averbuch's chemotherapy protocol includes dacarbazine (600 mg/m^2 on days 1 and 2), cyclophosphamide (750 mg/m^2 on day 1), and vincristine (1.4 mg/m^2 on day 1), all repeated every 21 days for three to six cycles. Palliation (stable disease to shrinkage) is achieved in about one-half of patients. Other chemotherapeutic options are sunitinib and temozolomide/thalidomide. The prognosis of metastatic pheochromocytoma or paraganglioma is variable, with 5-year survival rates of 30–60%.

PHEOCHROMOCYTOMA IN PREGNANCY

Pheochromocytomas occasionally are diagnosed in pregnancy. Endoscopic removal, preferably in the fourth to sixth month of gestation, is possible and can be followed by uneventful childbirth. Regular screening in families with inherited pheochromocytomas provides an opportunity to identify and remove asymptomatic tumors in women of reproductive age.

PHEOCHROMOCYTOMA-ASSOCIATED SYNDROMES

About 25–33% of patients with a pheochromocytoma or paraganglioma have an inherited syndrome. At diagnosis, patients with inherited syndromes are a mean of ~15 years younger than patients with sporadic tumors.

Neurofibromatosis type 1 (NF1) was the first described pheochromocytoma-associated syndrome **(Chap. 48)**. The NF1 gene functions as a tumor

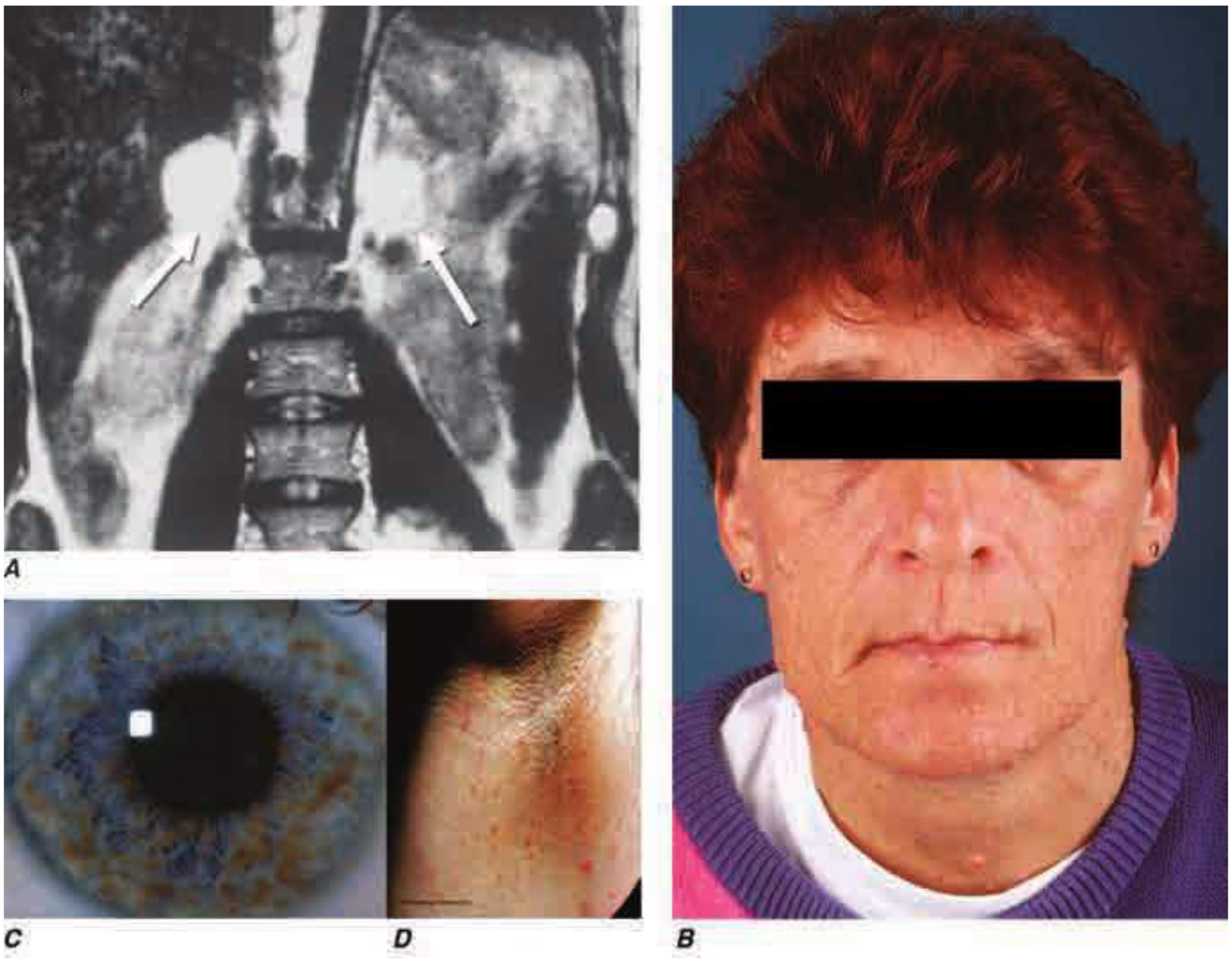


FIGURE 53-2
Neurofibromatosis. A. MRI of bilateral adrenal pheochromocytoma. B. Cutaneous neurofibromas. C. Lisch nodules of the iris. D. Axillary freckling. (Part A from HPH Neumann et al: Keio J Med 54:15, 2005; with permission.)

suppressor by regulating the Ras signaling cascade. Classic features of neurofibromatosis include multiple neurofibromas, café au lait spots, axillary freckling of the skin, and Lisch nodules of the iris **(Fig. 53-2)**. Pheochromocytomas occur in only ~1% of these patients and are located predominantly in the adrenals. Malignant pheochromocytoma is not uncommon.

The best-known pheochromocytoma-associated syndrome is the autosomal dominant disorder multiple endocrine neoplasia type 2 (MEN2) **(Chap. 52)**. Both types of MEN2 (2A and 2B) are caused by mutations in RET (rearranged during transfection), which encodes a tyrosine kinase. The locations of RET mutations correlate with the severity of disease and the type of MEN2 **(Chap. 52)**. MEN2A is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism; MEN2B also includes MTC and pheochromocytoma as well as multiple mucosal neuromas, marfanoid habitus, and other developmental disorders, though it typically lacks hyperparathyroidism. MTC is found in virtually all patients with MEN2, but pheochromocytoma occurs in only ~50% of these patients. Nearly all pheochromocytomas in MEN2 are benign and located in the adrenals, often bilaterally **(Fig. 53-3)**. Pheochromocytoma may be symptomatic before MTC. Prophylactic thyroidectomy is being performed in many carriers of RET mutations; pheochromocytomas should be excluded before any surgery in these patients.

Von Hippel–Lindau syndrome (VHL) is an autosomal dominant disorder that predisposes to retinal and cerebellar hemangioblastomas, which also occur in the brainstem and spinal cord **(Fig. 53-4)**. Other important features of VHL are clear cell renal carcinomas, pancreatic neuroendocrine tumors, endolymphatic sac tumors of the inner ear, cystadenomas of the epididymis and broad ligament, and multiple pancreatic or renal cysts.

The VHL gene (among other genes) encodes an E3 ubiquitin ligase that regulates expression of hypoxia-inducible factor 1. Loss of VHL is associated with increased expression of vascular endothelial growth factor (VEGF), which induces angiogenesis. Although the VHL gene can be inactivated by all types of mutations, patients with pheochromocytoma predominantly have missense mutations. About 20–30% of patients with VHL have pheochromocytomas, but in some families the incidence can reach 90%. The recognition of pheochromocytoma as a VHL-associated feature provides an opportunity to diagnose retinal, central nervous system, renal, and pancreatic tumors at a stage when effective treatment may still be possible.

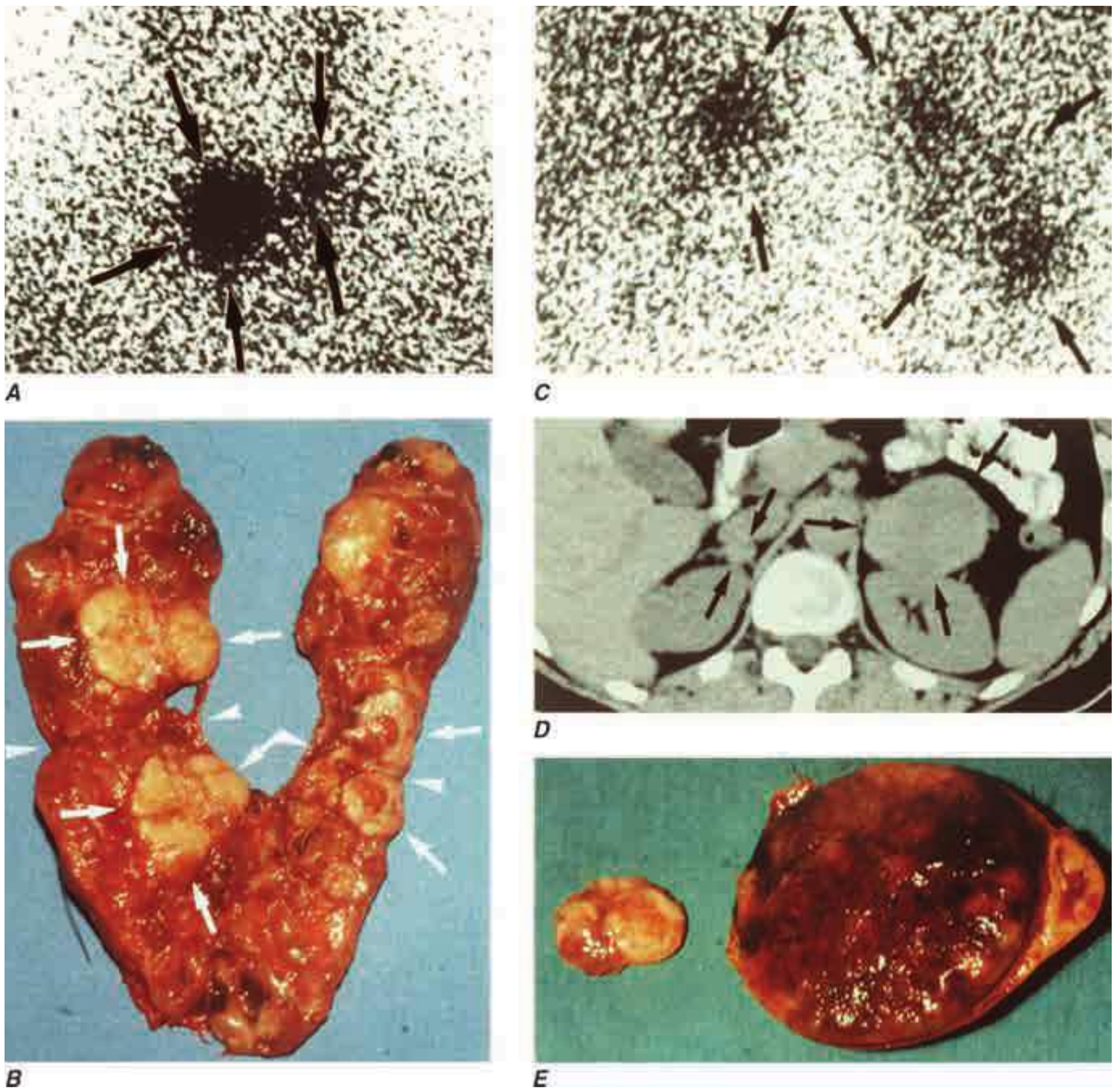


FIGURE 53-3
Multiple endocrine neoplasia type 2. A, B. Multifocal medullary thyroid carcinoma shown by MIBG scintigraphy (A) and operative specimen (B). Arrows demonstrate the tumors; arrowheads show the tissue bridge of the cut specimen. C–E. Bilateral adrenal pheochromocytoma shown by MIBG scintigraphy (C), CT imaging (D), and operative specimens (E). (From HPH Neumann et al: Keio J Med 54:15, 2005; with permission.)

The paraganglioma syndromes (PGLs) have been classified by genetic analyses of families with head and neck paragangliomas. The susceptibility genes encode subunits of the enzyme succinate dehydrogenase (SDH), a component in the Krebs cycle and the mitochondrial electron transport chain. SDH is formed by four subunits (A–D). Mutations of SDHB (PGL4), SDHC (PGL3), SDHD (PGL1), and SDHAF2 (PGL2) predispose to the PGLs. The transmission of the disease in carriers of SDHB and SDHC germ-line mutations is autosomal dominant. In contrast, in SDHD and SDHAF2 families, only the progeny of affected fathers develop tumors if they inherit the mutation. PGL1 is most common, followed by PGL4; PGL2 and PGL3 are rare. Adrenal, extra-adrenal abdominal, and thoracic pheochromocytomas, which are components of PGL1 and PGL4, are rare in PGL3 and absent in PGL2 **(Fig. 53-5)**. About one-third of patients with PGL4 develop metastases.

Familial pheochromocytoma (FP) has been attributed to hereditary, mainly adrenal tumors in patients with germ-line mutations in the genes TMEM127, MAX, and SDHA. Transmission is also autosomal dominant, and mutations of MAX, like those of SDHD, cause tumors only if inherited from the father.

GUIDELINES FOR GENETIC SCREENING OF PATIENTS WITH PHEOCHROMOCYTOMA OR PARAGANGLIOMA

In addition to family history, general features suggesting an inherited syndrome include young age, multifocal tumors, extra-adrenal tumors, and malignant tumors **(Fig. 53-6)**. Because of the relatively high

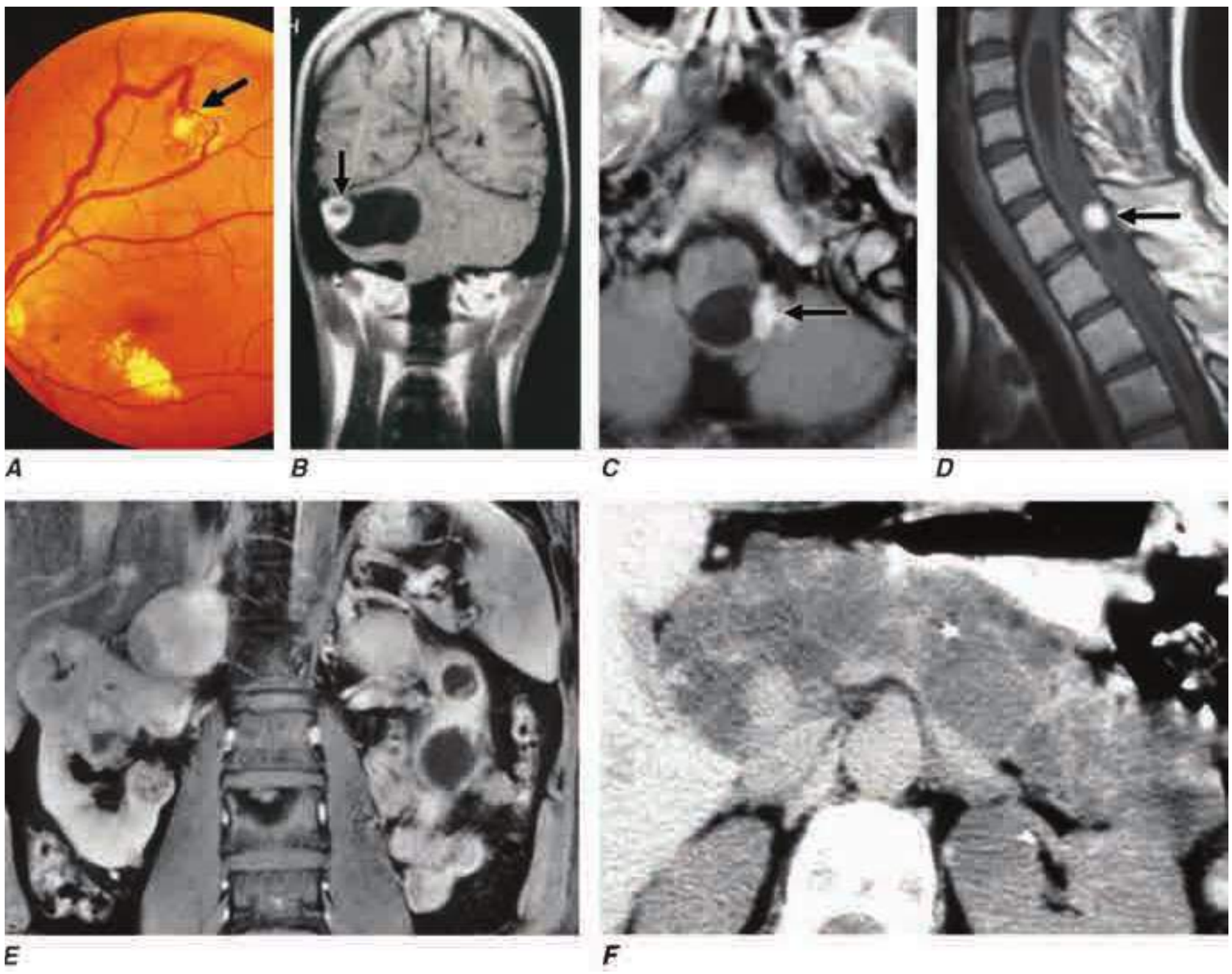


FIGURE 53-4
Von Hippel–Lindau disease. A. Retinal angioma. All subsequent panels show findings on MRI: B–D. Hemangioblastomas of the cerebellum (B) in brainstem (C) and spinal cord (D). E. Bilateral pheochromocytomas and bilateral renal clear cell carcinomas F. Multiple pancreatic cysts. (Parts A and D from HPH Neumann et al: Adv Nephrol Necker Hosp 27:361, 1997. © Elsevier. Part B from SH Morgan, J-P Grunfeld [eds]: Inherited Disorders of the Kidney. Oxford, UK, Oxford University Press, 1998. Part F from HPH Neumann et al: Contrib Nephrol 136:193, 2001. © S. Karger AG, Basel.)

prevalence of familial syndromes among patients who present with pheochromocytoma or paraganglioma, it is useful to identify germ-line mutations even in patients without a known family history. A first step is to search for clinical features of inherited syndromes and to obtain an in-depth, multigenerational family history. Each of these syndromes exhibits autosomal dominant transmission with variable penetrance, but a proband with a mother affected by paraganglial tumors is not predisposed to PLG1 (SDHD mutation carrier). Cutaneous neurofibromas, café au lait spots, and axillary freckling suggest neurofibromatosis. Germ-line mutations in NF1 have not been reported in patients with sporadic pheochromocytomas. Thus, NF1 testing need not be performed in the absence of other clinical features of neurofibromatosis. A personal or family history of MTC or an elevation of serum calcitonin strongly suggests MEN 2 and should prompt testing for RET mutations. A history of visual impairment or tumors of the cerebellum, kidney, brainstem, or spinal cord suggests the possibility of VHL. A personal and/or family history of head and neck paraganglioma suggests PGL1 or PGL4.

A single adrenal pheochromocytoma in a patient with an otherwise unremarkable history may still be associated with mutations of VHL, RET, SDHB, or SDHD (in decreasing order of frequency). Two-thirds of extra-adrenal tumors are associated with one of these syndromes, and multifocal tumors occur with decreasing frequency in carriers of RET, SDHD, VHL, and SDHB mutations. About 30% of head and neck paragangliomas are associated with germ-line mutations of one of the SDH subunit genes (most often SDHD) and are rare in carriers of VHL, RET, and TMEM127 mutations (Fig. 53-6F).

Immunohistochemistry is helpful in the preselection of hereditary pheochromocytoma. Negative immunostaining with antibodies to SDHB, TMEM127, and MAX may predict mutations of the SDH, TMEM127, and MAX genes, respectively.

Once the underlying syndrome is diagnosed, the benefit of genetic testing can be extended to relatives. For this purpose, it is necessary to identify the germ-line mutation in the proband and, after genetic counseling, to perform DNA sequence analyses of the responsible gene in relatives to determine whether they

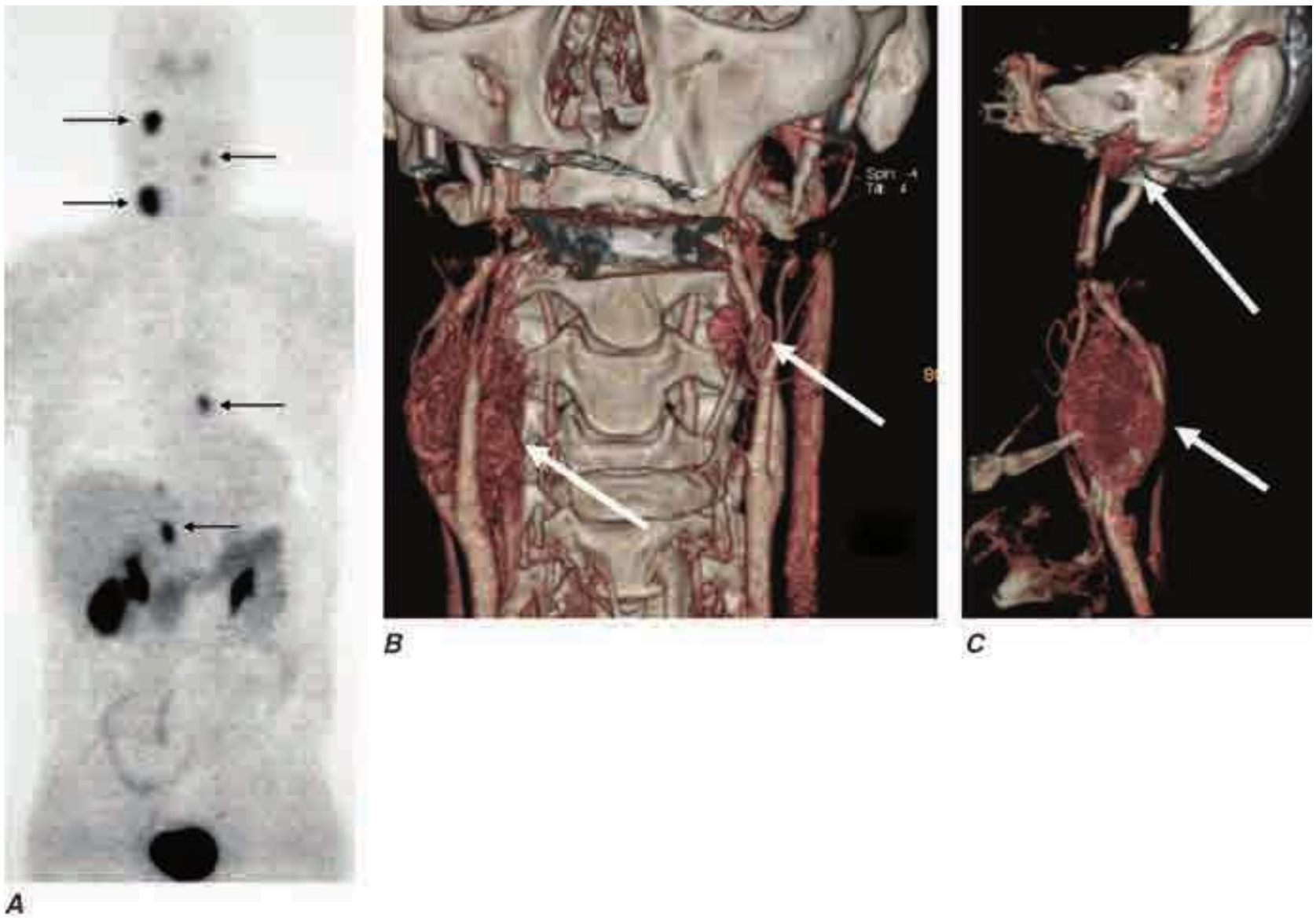


FIGURE 53-5
Paraganglioma syndrome. A patient with the SDHD W5X mutation and PGL1 underwent incomplete resection of a left carotid body tumor. A. ^{18}F-DOPA positron emission tomography demonstrating tumor uptake in the right jugular glomus, the right carotid body, the left carotid body, the left coronary glomus, and the right adrenal gland. Note the physiologic accumulation of the radiopharmaceutical agent in the kidneys, liver, gallbladder, renal pelvis, and urinary bladder. B and C. CT angiography with three-dimensional reconstruction. Arrows point to the paraganglial tumors. (From S Hoegerle et al: Eur J Nucl Med Mol Imaging 30:689, 2003; with permission.)

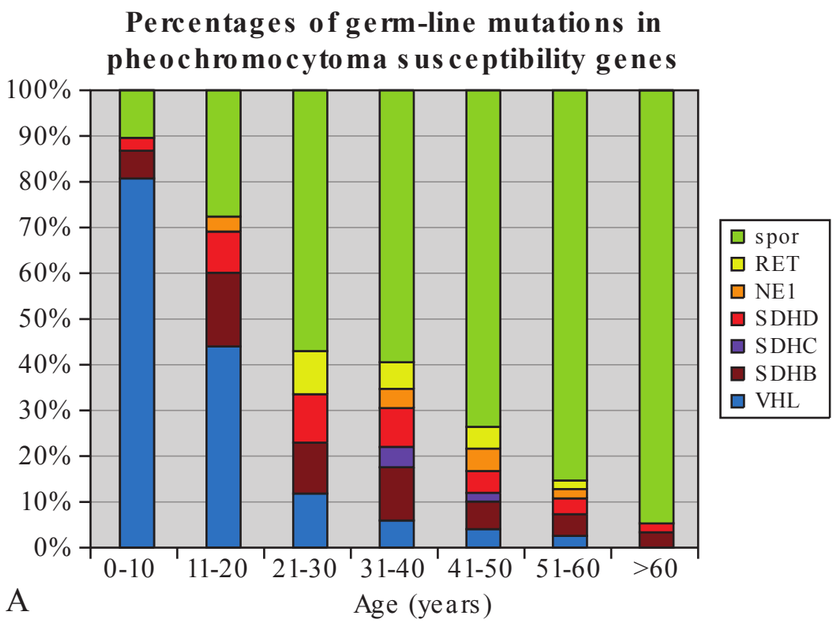
are affected. Other family members may benefit when individuals who carry a germ-line mutation are biochemically screened for paraganglial tumors.

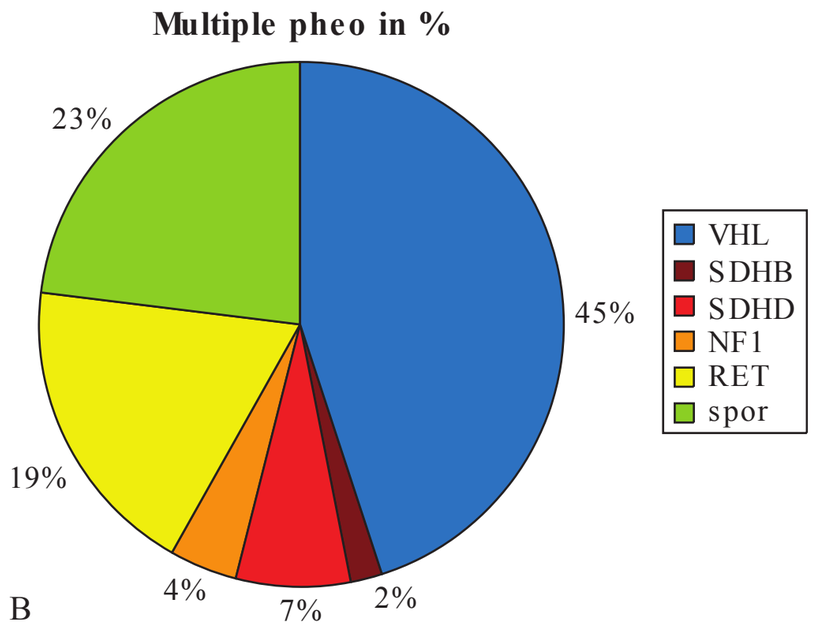
Asymptomatic paraganglial tumors, now often detected in patients with hereditary tumors and their relatives, are challenging to manage. Watchful waiting strategies have been introduced. Head and neck paragangliomas—mainly carotid body, jugular, and vagal tumors—are increasingly treated by radiation, since surgery is frequently associated with permanent palsy of cranial nerves II, VII, IX, X, XI, and XII. Nevertheless, tympanic paragangliomas are symptomatic early, and most of these tumors can easily be resected, with subsequent improvement of hearing and alleviation of tinnitus.

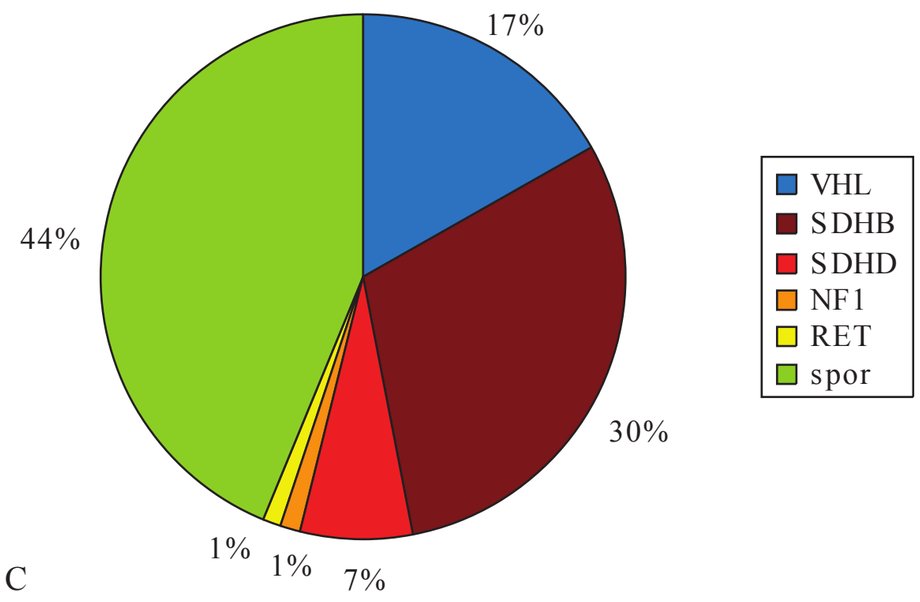
ADRENOCORTICAL CARCINOMA

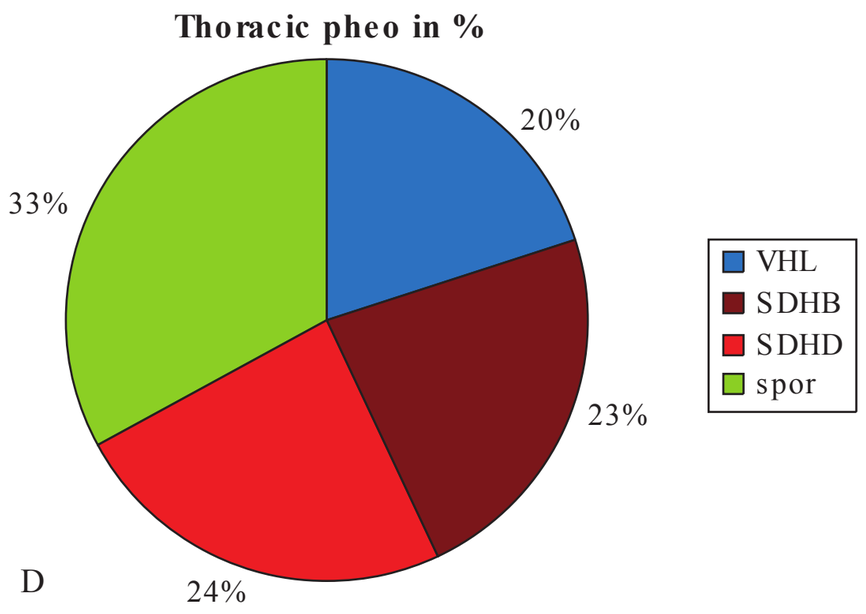
Adrenocortical carcinoma (ACC) is a rare malignancy with an annual incidence of 1–2 per million population. ACC is generally considered a highly malignant tumor; however, it presents with broad interindividual variability with regard to biologic characteristics and clinical behavior. Somatic mutations in the tumor-suppressor gene TP53 are found in 25% of apparently sporadic ACC. Germline TP53 mutations are the cause of the Li-Fraumeni syndrome associated with multiple solid organ cancers including ACC and are found in 25% of pediatric ACC cases; the TP53 mutation R337H is found in almost all pediatric ACC in Brazil. Other genetic changes identified in ACC include alterations in the Wnt/β-catenin pathway and in the insulin-like growth factor 2 (IGF2) cluster; IGF2 overexpression is found in 90% of ACC.

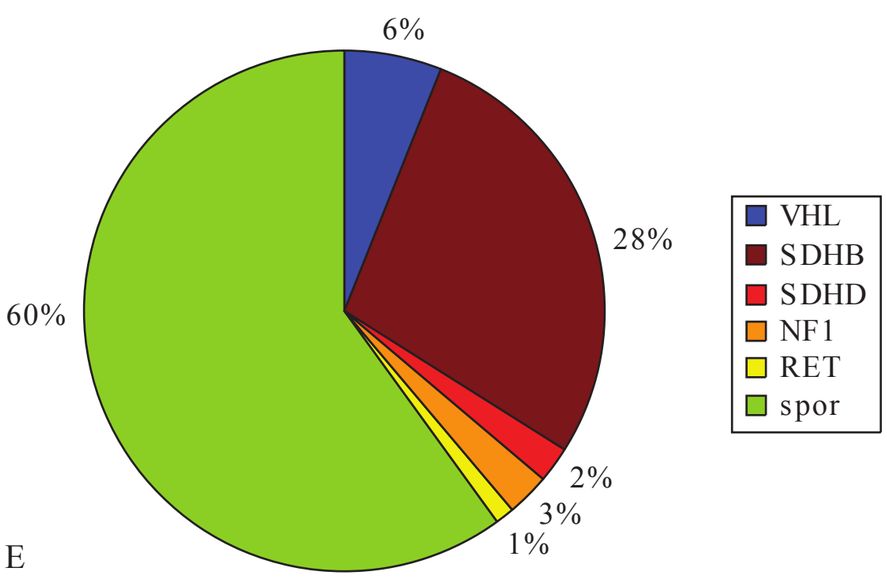
Patients with large adrenal tumors suspicious of malignancy should be managed by a multidisciplinary specialist team, including an endocrinologist, an oncologist, a surgeon, a radiologist, and a histopathologist. FNA is not indicated in suspected ACC: first, cytology and also histopathology of a core biopsy cannot differentiate between benign and malignant primary adrenal masses; second, FNA violates the tumor capsule and may even cause needle canal metastasis. Even when the entire tumor specimen is available, the histopathologic differentiation between benign and malignant lesions is a diagnostic challenge. T e most common histopathologic classification is the Weiss score, taking into account high nuclear grade; mitotic rate (>5/HPF);











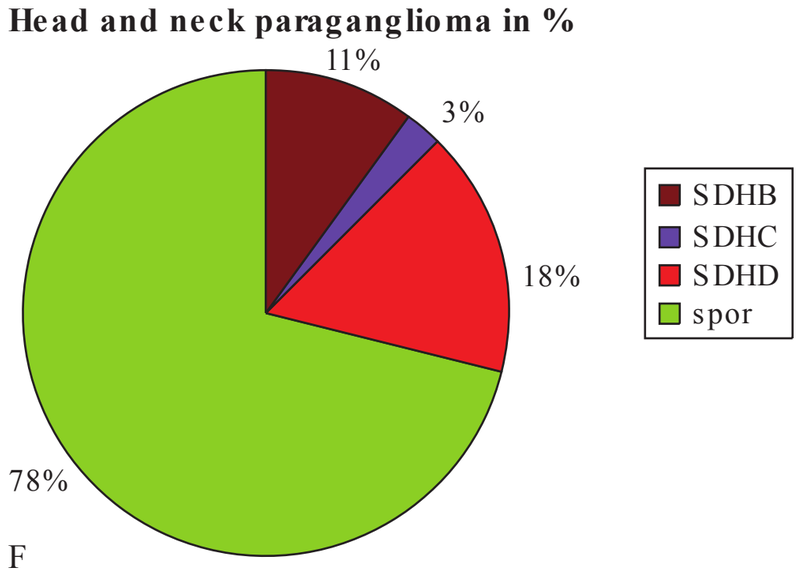


FIGURE 53-6
Mutation distribution in the VHL, RET, SDHB, SDHC, SDHD, and NF1 genes in 2021 patients with pheochromocytomas and paragangliomas from the European-American Pheochromocytoma-Paraganglioma Registry based in Freiburg, Germany, as updated on March 1, 2014. A. Correlation with age. The bars depict the frequency of sporadic (spor) or various inherited forms of pheochromocytoma in different age groups. The inherited disorders are much more common among younger individuals presenting with pheochromocytoma. Patients with mutations in the TMEM127, MAX, and SDHA genes are not included, since they contribute <1% in decades 4–7 only. B–F. Germ-line mutations according to multiple (B), extra-adrenal retroperitoneal (C), thoracic (D), and malignant (E) pheochromocytomas and head and neck paragangliomas (F). (Data from the Freiburg International Pheochromocytoma and Paraganglioma Registry, 2014.)

atypical mitosis; <25% clear cells; diffuse architecture; and presence of necrosis, venous invasion, and invasion of sinusoidal structures and tumor capsule. The presence of three or more elements suggests ACC.

Although 60–70% of ACCs show biochemical evidence of steroid overproduction, in many patients, this is not clinically apparent due to the relatively inefficient steroid production by the adrenocortical cancer cells. Excess production of glucocorticoids and adrenal androgen precursors are most common. Mixed excess production of several corticosteroid classes by an adrenal tumor is generally indicative of malignancy.

Tumor staging at diagnosis **(Table 53-4)** has important prognostic implications and requires scanning

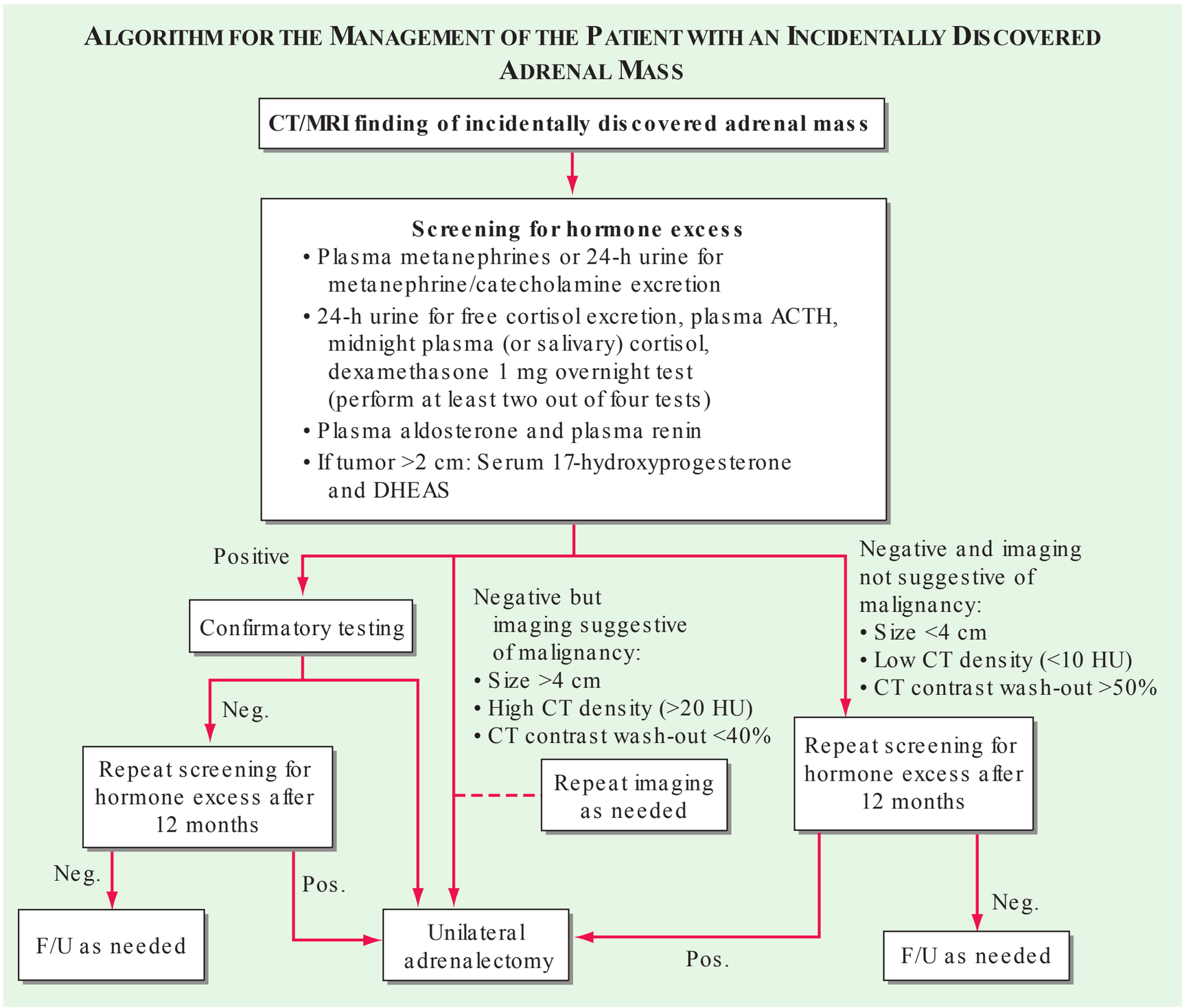


FIGURE 53-7

Management of the patient with an incidentally discovered adrenal mass. CT, computed tomography; F/U, follow-up; MRI, magnetic resonance imaging.

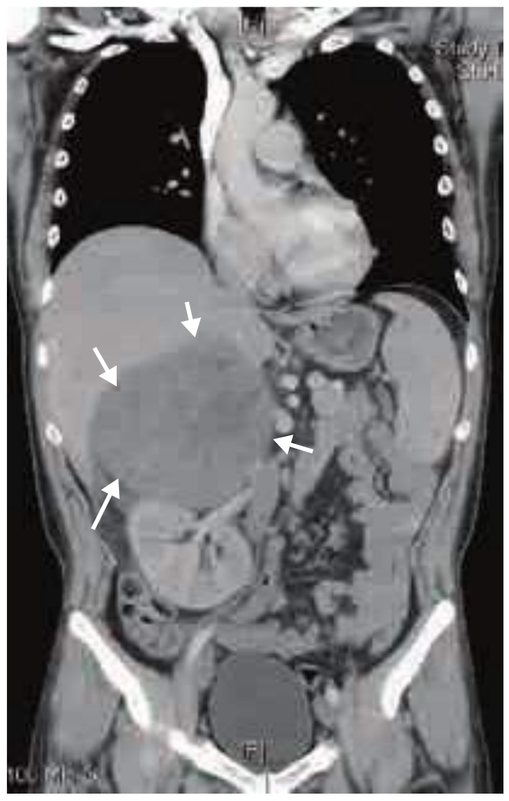
of the chest and abdomen for local organ invasion, lymphadenopathy, and metastases. Intravenous contrast medium is necessary for maximum sensitivity for hepatic metastases. An adrenal origin may be difficult to determine on standard axial CT imaging if the tumors are large and invasive, but CT reconstructions

TABLE 53-4

CLASSIFICATION SYSTEM FOR STAGING OF ADRENOCORTICAL CARCINOMA

ENSAT STAGE	TNM STAGE	TNM DEFINITIONS
I	T1,N0,M0	T1, tumor ≤5 cm
		N0, no positive lymph node
		M0, no distant metastases
II	T2,N0,M0	T2, tumor >5 cm
		N0, no positive lymph node
		M0, no distant metastases
III	T1–T2,N1,M0	N1, positive lymph node(s)
	T3–T4,N0–N1,M0	M0, no distant metastases
		T3, tumor infiltration into surrounding tissue
		T4, tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein
IV	T1–T4,N0–N1,M1	M1, presence of distant metastases

Abbreviations: ENSAT, European Network for the Study of Adrenal Tumors; TNM, tumor, node, metastasis.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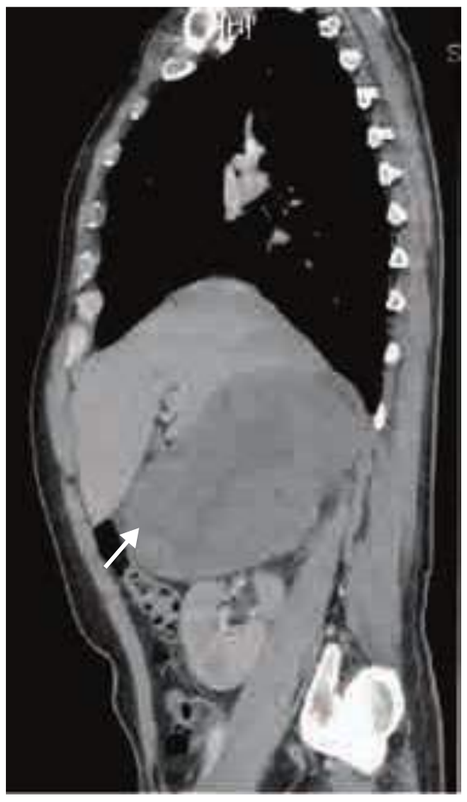
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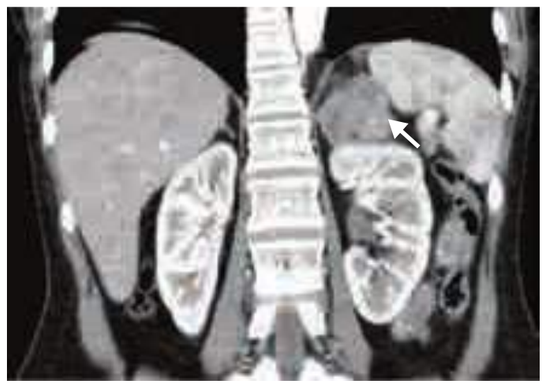
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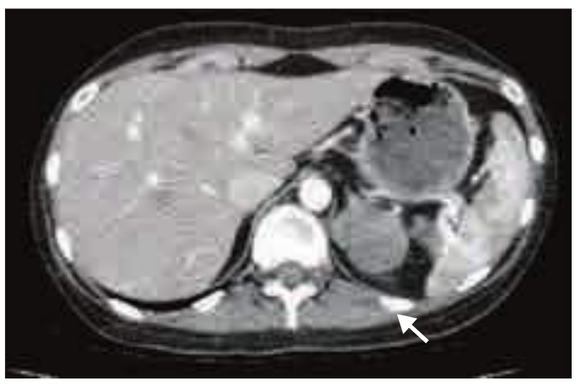
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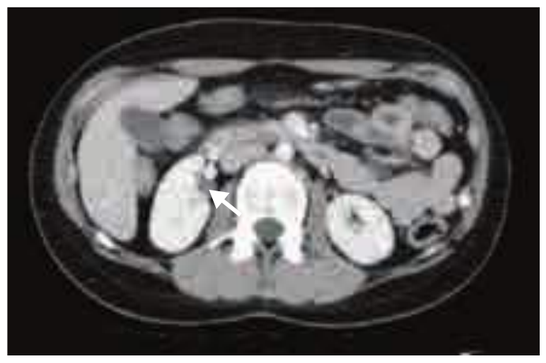
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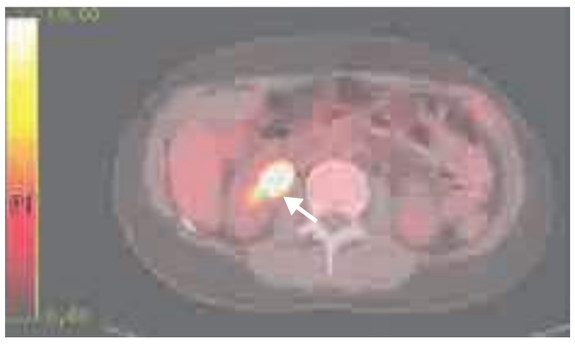
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FIGURE 53-8

Imaging in adrenocortical carcinoma. Magnetic resonance imaging scan with A. frontal and B. lateral views of a right adrenocortical carcinoma that was detected incidentally. Computed tomography (CT) scan with C. coronal and D. transverse views depicting a right-sided adrenocortical carcinoma. Note the irregular border and inhomogeneous structure. CT scan E. and positron emission tomography/CT F. visualizing a peritoneal metastasis of an adrenocortical carcinoma in close proximity to the right kidney (arrow).

and MRI are more informative **(Fig. 53-8)** using multiple planes and different sequences. Vascular and adjacent organ invasion is diagnostic of malignancy. 18-Fluoro-2-deoxy-D-glucose positron emission tomography (18-FDG PET) is highly sensitive for the detection of malignancy and can be used to detect small metastases or local recurrence that may not be obvious on CT (Fig. 53-8). However, FDG PET is not specific and therefore cannot be used for differentiating benign from malignant adrenal lesions. Metastasis in ACC most frequently occurs to liver and lung.

T ere is no established grading system for ACC, and the Weiss score carries no prognostic value; the most important prognostic histopathologic parameter is the Ki67 proliferation index, with Ki67 <10% indicative of slow to moderate growth velocity, whereas a Ki67 ≥10% is associated with poor prognosis including high risk of recurrence and rapid progression.

Cure of ACC can only be achieved by early detection and complete surgical removal. Capsule violation during primary surgery, metastasis at diagnosis, and primary treatment in a nonspecialist center are major determinants of poor survival. If the primary tumor invades adjacent organs, en bloc removal of kidney and spleen should be considered to reduce the risk of recurrence. Surgery can also be considered in a patient with metastases if there is severe tumor-related hormone excess. T is indication needs to be carefully weighed against surgical risk, including thromboembolic complications, and the resulting delay in the introduction of other therapeutic options. Patients with confirmed ACC and successful removal of the primary tumor should receive adjuvant treatment with mitotane (o,p'DDD), particularly in patients with a high risk of recurrence as determined by tumor size >8 cm, histopathologic signs of vascular invasion, capsule invasion or violation, and a Ki67 proliferation index ≥10%. Adjuvant mitotane should be continued for at least 2 years, if the patient can tolerate side effects. Regular monitoring of plasma mitotane levels is mandatory (therapeutic range 14–20 mg/L; neurotoxic complications more frequent at >20 mg/L). Mitotane is usually started at 500 mg tid, with stepwise increases to a maximum dose of 2000 mg tid in days (high-dose saturation) or weeks (low-dose saturation) as tolerated. Once therapeutic range plasma mitotane levels are achieved, the dose can be tapered to maintenance doses mostly ranging from 1000 to 1500 mg tid. Mitotane treatment results in disruption of cortisol synthesis and thus requires glucocorticoid replacement; glucocorticoid replacement dose should be at least double of that usually used in adrenal insufficiency (i.e., 20 mg tid) because mitotane induces hepatic CYP3A4 activity resulting in rapid inactivation of glucocorticoids. Mitotane also increases circulating CBG, thereby decreasing the available free cortisol fraction. Single metastases can be addressed surgically or with radiofrequency ablation as appropriate. If the tumor recurs or progresses during mitotane treatment, chemotherapy should be considered; the established first-line chemotherapy regimen is the combination of cisplatin, etoposide, and doxorubicin plus continuing mitotane. Painful bone metastasis responds to irradiation. Overall survival in ACC is still poor, with 5-year survival rates of 30–40% and a median survival of 15 months in metastatic ACC.

SECTION XI

REMOTE EFFECTS OF CANCER

CHAPTER 54

PARANEOPLASTIC SYNDROMES: ENDOCRINOLOGIC/HEMATOLOGIC

J. Larry Jameson ■ Dan L. Longo

Neoplastic cells can produce a variety of products that can stimulate hormonal, hematologic, dermatologic, and neurologic responses. Paraneoplastic syndromes is the term used to refer to the disorders that accompany benign or malignant tumors but are not directly related to mass effects or invasion. Tumors of neuroendocrine origin, such as small-cell lung carcinoma (SCLC) and carcinoids, produce a wide array of peptide hormones and are common causes of paraneoplastic syndromes. However, almost every type of tumor has the potential to produce hormones or to induce cytokine and immunologic responses. Careful studies of the prevalence of paraneoplastic syndromes indicate that they are more common than is generally appreciated. The signs, symptoms, and metabolic alterations associated with paraneoplastic disorders may be overlooked in the context of a malignancy and its treatment. Consequently, atypical clinical manifestations in a patient with cancer should prompt consideration of a paraneoplastic syndrome. The most common endocrinologic and hematologic syndromes associated with underlying neoplasia will be discussed here.

ENDOCRINE PARANEOPLASTIC SYNDROMES

Etiology

Hormones can be produced from eutopic or ectopic sources. Eutopic refers to the expression of a hormone from its normal tissue of origin, whereas ectopic refers to hormone production from an atypical tissue source. For example, adrenocorticotropic hormone (ACTH) is expressed eutopically by the corticotrope cells of the anterior pituitary, but it can be expressed ectopically in SCLC. Many hormones are produced at low levels from a wide array of tissues in addition to the classic endocrine source. Thus, ectopic expression is often a quantitative change rather than an absolute change in tissue expression. Nevertheless, the term ectopic expression is firmly entrenched and conveys the abnormal physiology associated with hormone production by neoplastic cells. In addition to high levels of hormones, ectopic expression typically is characterized by abnormal regulation of hormone production (e.g., defective feedback control) and peptide processing (resulting in large, unprocessed precursors).

A diverse array of molecular mechanisms has been suggested to cause ectopic hormone production. In rare instances, genetic rearrangements explain aberrant hormone expression. For example, translocation of the parathyroid hormone (*PTH*) gene can result in high levels of PTH expression in tissues other than the parathyroid gland because the genetic rearrangement brings the *PTH* gene under the control of atypical regulatory elements. A related phenomenon is well documented in many forms of leukemia and lymphoma, in which somatic genetic rearrangements confer a growth advantage and alter cellular differentiation and function **(Chap. 16)**. Although genetic rearrangements cause selected cases of ectopic hormone production, this mechanism is rare, as many tumors are associated with excessive production of numerous peptides. Cellular dedifferentiation probably underlies most cases of ectopic hormone production. Many cancers are poorly differentiated, and certain tumor products, such as human chorionic gonadotropin (hCG), parathyroid hormone–related protein (PTHrP), and α fetoprotein, are characteristic

of gene expression at earlier developmental stages. In contrast, the propensity of certain cancers to produce particular hormones (e.g., squamous cell carcinomas produce PTHrP) suggests that dedifferentiation is partial or that selective pathways are derepressed. T ese expression profiles probably reflect epigenetic modifications that alter transcriptional repression, microRNA expression, and other pathways that govern cell differentiation.

In SCLC, the pathway of differentiation has been relatively well defined. T e neuroendocrine phenotype is dictated in part by the basic-helix-loop-helix (bHLH) transcription factor human achaete-scute homologue 1 (hASH-1), which is expressed at abnormally high levels in SCLC associated with ectopic ACTH. T e activity of hASH-1 is inhibited by hairy enhancer of split 1 (HES-1) and by Notch proteins, which also are capable of inducing growth arrest. T us, abnormal expression of these developmental transcription factors appears to provide a link between cell proliferation and differentiation.

Ectopic hormone production would be merely an epiphenomenon associated with cancer if it did not result in clinical manifestations. Excessive and unregulated production of hormones such as ACTH, PTHrP, and vasopressin can lead to substantial morbidity and complicate the cancer treatment plan. Moreover, the paraneoplastic endocrinopathies may be a presenting clinical feature of underlying malignancy and prompt the search for an unrecognized tumor.

A large number of paraneoplastic endocrine syndromes have been described, linking overproduction of particular hormones with specific types of tumors. However, certain recurring syndromes emerge from this group **(Table 54-1)**. T e most common paraneoplastic endocrine syndromes include hypercalcemia from overproduction of PTHrP and other factors, hyponatremia from excess vasopressin, and Cushing's syndrome from ectopic ACTH.

HYPERCALCEMIA CAUSED BY ECTOPIC PRODUCTION OF PTHRP

Etiology

Humoral hypercalcemia of malignancy (HHM) occurs in up to 20% of patients with cancer. HHM is most common in cancers of the lung, head and neck, skin, esophagus, breast, and genitourinary tract and in multiple myeloma and lymphomas. T ere are several distinct humoral causes of HHM, but it is caused most commonly by overproduction of PTHrP. In addition to acting as a circulating humoral factor, bone metastases (e.g., breast, multiple myeloma) may produce PTHrP, leading to local osteolysis and hypercalcemia. PTHrP may also affect the initiation and progression of tumors by acting through pro-survival and chemokine pathways.

PTHrP is structurally related to PTH and binds to the PTH receptor, explaining the similar biochemical features of HHM and hyperparathyroidism. PTHrP plays a key role in skeletal development and regulates cellular proliferation and differentiation in other tissues, including skin, bone marrow, breast, and hair follicles. T e mechanism of PTHrP induction in malignancy is incompletely understood; however, tumor-bearing tissues commonly associated with HHM normally produce PTHrP during development or cell renewal. PTHrP expression is stimulated by hedgehog pathways and Gli transcription factors that are active in many malignancies. Transforming growth factor β (TGF-β), which is produced by many tumors, also stimulates PTHrP, in part by activating the Gli pathway. Mutations in certain oncogenes, such as Ras, also can activate PTHrP expression. In adult T cell lymphoma, the transactivating Tax protein produced by human T cell lymphotropic virus 1 (HTLV-1) stimulates PTHrP promoter activity. Metastatic lesions to bone are more likely to produce PTHrP than are metastases in other tissues, suggesting that bone produces factors (e.g., TGF-β) that enhance PTHrP production or that PTHrP-producing metastases have a selective growth advantage in bone. PTHrP activates the pro-survival AKT pathway and the chemokine receptor CXCR4. T us, PTHrP production can be stimulated by mutations in oncogenes, altered expression of viral or cellular transcription factors, and local growth factors. In addition to its role in HHM, the PTHrP pathway may also provide a potential target for therapeutic intervention to impede cancer growth.

Another relatively common cause of HHM is excess production of 1,25-dihydroxyvitamin D. Like granulomatous disorders associated with hypercalcemia, lymphomas can produce an enzyme that converts 25-hydroxyvitamin D to the more active 1,25-dihydroxyvitamin D, leading to enhanced gastrointestinal calcium absorption. Other causes of HHM include tumor-mediated production of osteolytic cytokines and inflammatory mediators.

Clinical manifestations

T e typical presentation of HHM is a patient with a known malignancy who is found to be hypercalcemic on routine laboratory tests. Less often, hypercalcemia is the initial presenting feature of malignancy. Particularly when calcium levels are markedly increased (>3.5 mmol/L [>14 mg/dL]), patients may experience fatigue, mental status changes, dehydration, or symptoms of nephrolithiasis.

TABLE 54-1

PARANEOPLASTIC SYNDROMES CAUSED BY ECTOPIC HORMONE PRODUCTION

PARANEOPLASTIC SYNDROME	ECTOPIC HORMONE	TYPICAL TUMOR TYPES[a]
Common		
Hypercalcemia of malignancy	Parathyroid hormone–related protein (PTHrP)	Squamous cell (head and neck, lung, skin), breast, genitourinary, gastrointestinal
	1,25-dihydroxyvitamin D	Lymphomas
	Parathyroid hormone (PTH) (rare)	Lung, ovary
	Prostaglandin E_2 (PGE_2) (rare)	Renal, lung
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Vasopressin	Lung (squamous, small cell), gastrointestinal, genitourinary, ovary
Cushing's syndrome	Adrenocorticotropic hormone (ACTH)	Lung (small cell, bronchial carcinoid, adenocarcinoma, squamous), thymus, pancreatic islet, medullary thyroid carcinoma
	Corticotropin-releasing hormone (CRH) (rare)	Pancreatic islet, carcinoid, lung, prostate
	Ectopic expression of gastric inhibitory peptide (GIP), luteinizing hormone (LH)/human chorionic gonadotropin (hCG), other G protein–coupled receptors (rare)	Macronodular adrenal hyperplasia
Less Common		
Non–islet cell hypoglycemia	Insulin-like growth factor type II (IGF-II)	Mesenchymal tumors, sarcomas, adrenal, hepatic, gastrointestinal, kidney, prostate
	Insulin (rare)	Cervix (small-cell carcinoma)
Male feminization	hCG[b]	Testis (embryonal, seminomas), germinomas, choriocarcinoma, lung, hepatic, pancreatic islet
Diarrhea or intestinal hypermotility	Calcitonin[c]	Lung, colon, breast, medullary thyroid carcinoma
	Vasoactive intestinal peptide (VIP)	Pancreas, pheochromocytoma, esophagus
Rare		
Oncogenic osteomalacia	Phosphatonin (fibroblast growth factor 23 [FGF23])	Hemangiopericytomas, osteoblastomas, fibromas, sarcomas, giant cell tumors, prostate, lung
Acromegaly	Growth hormone–releasing hormone (GHRH)	Pancreatic islet, bronchial, and other carcinoids
	Growth hormone (GH)	Lung, pancreatic islet
Hyperthyroidism	Thyroid-stimulating hormone (TSH)	Hydatidiform mole, embryonal tumors, struma ovarii
Hypertension	Renin	Juxtaglomerular tumors, kidney, lung, pancreas, ovary

[a]Only the most common tumor types are listed. For most ectopic hormone syndromes, an extensive list of tumors has been reported to produce one or more hormones.
[b]hCG is produced eutopically by trophoblastic tumors. Certain tumors produce disproportionate amounts of the hCG α or hCG β subunit. High levels of hCG rarely cause hyperthyroidism because of weak binding to the TSH receptor.
[c]Calcitonin is produced eutopically by medullary thyroid carcinoma and is used as a tumor marker.

Diagnosis

Features that favor HHM, as opposed to primary hyperparathyroidism, include known malignancy, recent onset of hypercalcemia, and very high serum calcium levels. Like hyperparathyroidism, hypercalcemia caused by PTHrP is accompanied by hypercalciuria and hypophosphatemia. Patients with HHM typically have metabolic alkalosis rather than hyperchloremic acidosis, as is seen in hyperparathyroidism. Measurement of PTH is useful to exclude primary hyperparathyroidism; the PTH level should be suppressed in HHM. An elevated PTHrP level confirms the diagnosis, and it is increased in ~80% of hypercalcemic patients with cancer. 1,25-Dihydroxyvitamin D levels may be increased in patients with lymphoma.

TREATMENT Humoral Hypercalcemia of Malignancy

The management of HHM begins with removal of excess calcium in the diet, medications, or IV solutions. Saline rehydration (typically 200–500 mL/h) is used to dilute serum calcium and promote calciuresis; exercise caution in patients with cardiac, hepatic, or renal insufficiency. Forced diuresis with furosemide (20–80 mg IV in escalating doses) or other loop diuretics can enhance calcium excretion but provides relatively little value except in life-threatening hypercalcemia. When used, loop diuretics should be administered only after complete rehydration and with careful monitoring of fluid balance. Oral phosphorus (e.g., 250 mg Neutra-Phos 3–4 times daily) should be given until serum phosphorus is >1 mmol/L (>3 mg/dL). Bisphosphonates such as pamidronate (60–90 mg IV), zoledronate (4–8 mg IV), and etidronate (7.5 mg/kg per day PO for 3–7 consecutive days) can reduce serum calcium within 1–2 days and suppress calcium release for several weeks. Bisphosphonate infusions can be repeated, or oral bisphosphonates can be used for chronic treatment. Dialysis should be considered in severe hypercalcemia when saline hydration and bisphosphonate treatments are not possible or are too slow in onset. Previously used agents such as calcitonin and mithramycin have little utility now that bisphosphonates are available. Calcitonin (2–8 U/kg SC every 6–12 h) should be considered when rapid correction of severe hypercalcemia is needed. Hypercalcemia associated with lymphomas, multiple myeloma, or leukemia may respond to glucocorticoid treatment (e.g., prednisone 40–100 mg PO in four divided doses).

ECTOPIC VASOPRESSIN: TUMOR-ASSOCIATED SIADH

Etiology

Vasopressin is an antidiuretic hormone normally produced by the posterior pituitary gland. Ectopic vasopressin production by tumors is a common cause of the syndrome of inappropriate antidiuretic hormone (SIADH), occurring in at least half of patients with SCLC. SIADH also can be caused by a number of nonneoplastic conditions, including central nervous system (CNS) trauma, infections, and medications. Compensatory responses to SIADH, such as decreased thirst, may mitigate the development of hyponatremia. However, with prolonged production of excessive vasopressin, the osmostat controlling thirst and hypothalamic vasopressin secretion may become reset. In addition, intake of free water, orally or intravenously, can quickly worsen hyponatremia because of reduced renal diuresis.

Tumors with neuroendocrine features, such as SCLC and carcinoids, are the most common sources of ectopic vasopressin production, but it also occurs in other forms of lung cancer and with CNS lesions, head and neck cancer, and genitourinary, gastrointestinal, and ovarian cancers. The mechanism of activation of the vasopressin gene in these tumors is unknown but often involves concomitant expression of the adjacent oxytocin gene, suggesting derepression of this locus.

Clinical manifestations

Most patients with ectopic vasopressin secretion are asymptomatic and are identified because of the presence of hyponatremia on routine chemistry testing. Symptoms may include weakness, lethargy, nausea, confusion, depressed mental status, and seizures. The severity of symptoms reflects the rapidity of onset as well as the severity of hyponatremia. Hyponatremia usually develops slowly but may be exacerbated by the administration of IV fluids or the institution of new medications.

Diagnosis

The diagnostic features of ectopic vasopressin production are the same as those of other causes of SIADH. Hyponatremia and reduced serum osmolality occur in the setting of an inappropriately normal or increased urine osmolality. Urine sodium excretion is normal or increased unless volume depletion is present. Other causes of hyponatremia should be excluded, including renal, adrenal, or thyroid insufficiency. Physiologic sources of vasopressin stimulation (CNS lesions, pulmonary disease, nausea), adaptive circulatory mechanisms (hypotension, heart failure, hepatic cirrhosis), and medications, including many chemotherapeutic agents, also should be considered as possible causes of hyponatremia. Vasopressin measurements are not usually necessary to make the diagnosis.

TREATMENT Ectopic Vasopressin: Tumor-Associated SIADH

Most patients with ectopic vasopressin production develop hyponatremia over several weeks or months. The disorder should be corrected gradually unless mental status is altered or there is risk of seizures. Treatment of the underlying malignancy may reduce ectopic vasopressin production, but this response is slow if it occurs at all. Fluid restriction to less than urine output, plus insensible losses, is often sufficient to correct hyponatremia partially. However, strict monitoring of the amount and types of liquids consumed or administered intravenously is required for fluid restriction to be effective. Salt tablets and saline are not helpful unless volume depletion is also present. Demeclocycline (150–300 mg orally three to four times daily) can be used to inhibit vasopressin action on the renal distal tubule, but its onset of action is relatively

slow (1–2 weeks). Conivaptan, a nonpeptide V_2-receptor antagonist, can be administered either PO (20–120 mg bid) or IV (10–40 mg) and is particularly effective when used in combination with fluid restriction in euvolemic hyponatremia. Tolvaptan (15 mg PO daily) is another vasopressin antagonist. T e dose can be increased to 30–60 mg/d based on response. Severe hyponatremia (Na <115 meq/L) or mental status changes may require treatment with hypertonic (3%) or normal saline infusion together with furosemide to enhance free water clearance. T e rate of sodium correction should be slow (0.5–1 meq/L per hour) to prevent rapid fluid shifts and the possible development of central pontine myelinolysis.

CUSHING'S SYNDROME CAUSED BY ECTOPIC ACTH PRODUCTION

Etiology

Ectopic ACTH production accounts for 10–20% of cases of Cushing's syndrome. T e syndrome is particularly common in neuroendocrine tumors. SCLC is the most common cause of ectopic ACTH, followed by bronchial and thymic carcinoids, islet cell tumors, other carcinoids, and pheochromocytomas. Ectopic ACTH production is caused by increased expression of the proopiomelanocortin (POMC) gene, which encodes ACTH, along with melanocyte-stimulating hormone (MSH), β lipotropin, and several other peptides. In many tumors, there is abundant but aberrant expression of the POMC gene from an internal promoter, proximal to the third exon, which encodes ACTH. However, because this product lacks the signal sequence necessary for protein processing, it is not secreted. Increased production of ACTH arises instead from less abundant, but unregulated, POMC expression from the same promoter site used in the pituitary. However, because the tumors lack many of the enzymes needed to process the POMC polypeptide, it is typically released as multiple large, biologically inactive fragments along with relatively small amounts of fully processed, active ACTH.

Rarely, corticotropin-releasing hormone (CRH) is produced by pancreatic islet cell tumors, SCLC, medullary thyroid cancer, carcinoids, or prostate cancer. When levels are high enough, CRH can cause pituitary corticotrope hyperplasia and Cushing's syndrome. Tumors that produce CRH sometimes also produce ACTH, raising the possibility of a paracrine mechanism for ACTH production.

A distinct mechanism for ACTH-independent Cushing's syndrome involves ectopic expression of various G protein–coupled receptors in the adrenal nodules. Ectopic expression of the gastric inhibitory peptide (GIP) receptor is the best-characterized example of this mechanism. In this case, meals induce GIP secretion, which inappropriately stimulates adrenal growth and glucocorticoid production.

Clinical manifestations

T e clinical features of hypercortisolemia are detected in only a small fraction of patients with documented ectopic ACTH production. Patients with ectopic ACTH syndrome generally exhibit less marked weight gain and centripetal fat redistribution, probably because the exposure to excess glucocorticoids is relatively brief and because cachexia reduces the propensity for weight gain and fat deposition. T e ectopic ACTH syndrome is associated with several clinical features that distinguish it from other causes of Cushing's syndrome (e.g., pituitary adenomas, adrenal adenomas, iatrogenic glucocorticoid excess). T e metabolic manifestations of ectopic ACTH syndrome are dominated by fluid retention and hypertension, hypokalemia, metabolic alkalosis, glucose intolerance, and occasionally steroid psychosis. T e very high ACTH levels often cause increased pigmentation, and melanotrope-stimulating hormone (MSH) activity derived from the POMC precursor peptide is also increased. T e extraordinarily high glucocorticoid levels in patients with ectopic sources of ACTH can lead to marked skin fragility and easy bruising. In addition, the high cortisol levels often overwhelm the renal 11β-hydroxysteroid dehydrogenase type II enzyme, which normally inactivates cortisol and prevents it from binding to renal mineralocorticoid receptors. Consequently, in addition to the excess mineralocorticoids produced by ACTH stimulation of the adrenal gland, high levels of cortisol exert activity through the mineralocorticoid receptor, leading to severe hypokalemia.

Diagnosis

T e diagnosis of ectopic ACTH syndrome is usually not dif cult in the setting of a known malignancy. Urine free cortisol levels fluctuate but are typically greater than two to four times normal, and the plasma ACTH level is usually >22 pmol/L (>100 pg/mL). A suppressed ACTH level excludes this diagnosis and indicates an ACTH-independent cause of Cushing's syndrome (e.g., adrenal or exogenous glucocorticoid). In contrast to pituitary sources of ACTH, most ectopic sources of ACTH do not respond to glucocorticoid suppression. T erefore, high-dose dexamethasone (8 mg PO) suppresses 8:00 a.m. serum cortisol (50% decrease from baseline) in ~80% of pituitary ACTH-producing adenomas but fails to suppress ectopic ACTH in ~90%

of cases. Bronchial and other carcinoids are well-documented exceptions to these general guidelines, as these ectopic sources of ACTH may exhibit feedback regulation indistinguishable from pituitary adenomas, including suppression by high-dose dexamethasone, and ACTH responsiveness to adrenal blockade with metyrapone. If necessary, petrosal sinus catheterization can be used to evaluate a patient with ACTH-dependent Cushing's syndrome when the source of ACTH is unclear. After CRH stimulation, a 3:1 petrosal sinus:peripheral ACTH ratio strongly suggests a pituitary ACTH source. Imaging studies (computed tomography or magnetic resonance imaging) are also useful in the evaluation of suspected carcinoid lesions, allowing biopsy and characterization of hormone production using special stains. If available, positron emission tomography or octreotide scanning may identify some sources of ACTH production.

TREATMENT Cushing's Syndrome Caused by Ectopic ACTH Production

The morbidity associated with the ectopic ACTH syndrome can be substantial. Patients may experience depression or personality changes because of extreme cortisol excess. Metabolic derangements, including diabetes mellitus and hypokalemia, can worsen fatigue. Poor wound healing and predisposition to infections can complicate the surgical management of tumors, and opportunistic infections caused by organisms such as Pneumocystis carinii and mycoses are often the cause of death in patients with ectopic ACTH production. These patients likely have increased risk of venous thromboembolism reflecting the combination of malignancy and altered coagulation factor profiles. Depending on prognosis and treatment plans for the underlying malignancy, measures to reduce cortisol levels are often indicated. Treatment of the underlying malignancy may reduce ACTH levels but is rarely sufficient to reduce cortisol levels to normal. Adrenalectomy is not practical for most of these patients but should be considered during surgery for the malignancy or if the underlying tumor is not resectable and the prognosis is otherwise favorable (e.g., carcinoid). Medical therapy with ketoconazole (300–600 mg PO bid), metyrapone (250–500 mg PO every 6 h), mitotane (3–6 g PO in four divided doses, tapered to maintain low cortisol production), or other agents that block steroid synthesis or action is often the most practical strategy for managing the hypercortisolism associated with ectopic ACTH production. Glucocorticoid replacement should be provided to prevent adrenal insufficiency. Unfortunately, many patients eventually progress despite medical blockade.

TUMOR-INDUCED HYPOGLYCEMIA CAUSED BY EXCESS PRODUCTION OF IGF-II

Mesenchymal tumors, hemangiopericytomas, hepatocellular tumors, adrenal carcinomas, and a variety of other large tumors have been reported to produce excessive amounts of insulin-like growth factor type II (IGF-II) precursor, which binds weakly to insulin receptors and more strongly to IGF-I receptors, leading to insulin-like actions. The gene encoding IGF-II resides on a chromosome 11p15 locus that is normally imprinted (that is, expression is exclusively from a single parental allele). Biallelic expression of the IGF-II gene occurs in a subset of tumors, suggesting loss of methylation and loss of imprinting as a mechanism for gene induction. In addition to increased IGF-II production, IGF-II bioavailability is increased due to complex alterations in circulating binding proteins. Increased IGF-II suppresses growth hormone (GH) and insulin, resulting in reduced IGF binding protein 3 (IGFBP-3), IGF-I, and acid-labile subunit (ALS). The reduction in ALS and IGFBP-3, which normally sequester IGF-II, causes it to be displaced to a small circulating complex that has greater access to insulin target tissues. For this reason, circulating IGF-II levels may not be markedly increased despite causing hypoglycemia. In addition to IGF-II–mediated hypoglycemia, tumors may occupy enough of the liver to impair gluconeogenesis.

In most cases, a tumor causing hypoglycemia is clinically apparent (usually >10 cm in size) and hypoglycemia develops in association with fasting. The diagnosis is made by documenting low serum glucose and suppressed insulin levels in association with symptoms of hypoglycemia. Serum IGF-II levels may not be increased (IGF-II assays may not detect IGF-II precursors). Increased IGF-II mRNA expression is found in most of these tumors. Any medications associated with hypoglycemia should be eliminated. Treatment of the underlying malignancy, if possible, may reduce the predisposition to hypoglycemia. Frequent meals and IV glucose, especially during sleep or fasting, are often necessary to prevent hypoglycemia. Glucagon and glucocorticoids have also been used to enhance glucose production.

HUMAN CHORIONIC GONADOTROPIN

hCG is composed of α and β subunits and can be produced as intact hormone, which is biologically active, or as uncombined biologically inert subunits. Ectopic production of intact hCG occurs most often in association with testicular embryonal tumors, germ cell tumors, extragonadal germinomas, lung cancer, hepatoma, and pancreatic islet tumors. Eutopic production of hCG occurs with trophoblastic malignancies. hCG α subunit

production is particularly common in lung cancer and pancreatic islet cancer. In men, high hCG levels stimulate steroidogenesis and aromatase activity in testicular Leydig cells, resulting in increased estrogen production and the development of gynecomastia. Precocious puberty in boys or gynecomastia in men should prompt measurement of hCG and consideration of a testicular tumor or another source of ectopic hCG production. Most women are asymptomatic. hCG is easily measured. Treatment should be directed at the underlying malignancy.

ONCOGENIC OSTEOMALACIA

Hypophosphatemic oncogenic osteomalacia, also called tumor-induced osteomalacia (TIO), is characterized by markedly reduced serum phosphorus and renal phosphate wasting, leading to muscle weakness, bone pain, and osteomalacia. Serum calcium and PTH levels are normal, and 1,25-dihydroxyvitamin D is low. Oncogenic osteomalacia is usually caused by benign mesenchymal tumors, such as hemangiopericytomas, fibromas, and giant cell tumors, often of the skeletal extremities or head. It has also been described in sarcomas and in patients with prostate and lung cancer. Resection of the tumor reverses the disorder, confirming its humoral basis. T e circulating phosphaturic factor is called phosphatonin—a factor that inhibits renal tubular reabsorption of phosphate and renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Phosphatonin has been identified as fibroblast growth factor 23 (FGF23). FGF23 levels are increased in some, but not all, patients with osteogenic osteomalacia. FGF23 forms a ternary complex with the klotho protein and renal FGF receptors to reduce renal phosphate reabsorption. Treatment involves removal of the tumor, if possible, and supplementation with phosphate and vitamin D. Octreotide treatment reduces phosphate wasting in some patients with tumors that express somatostatin receptor subtype 2. Octreotide scans may also be useful in detecting these tumors.

HEMATOLOGIC SYNDROMES

T e elevation of granulocyte, platelet, and eosinophil counts in most patients with myeloproliferative disorders is caused by the proliferation of the myeloid elements due to the underlying disease rather than to a paraneoplastic syndrome. T e paraneoplastic hematologic syndromes in patients with solid tumors are less well characterized than are the endocrine syndromes because the ectopic hormone(s) or cytokines responsible have not been identified in most of these tumors **(Table 54-2)**. T e extent of the paraneoplastic syndromes parallels the course of the cancer.

ERYTHROCYTOSIS

Ectopic production of erythropoietin by cancer cells causes most paraneoplastic erythrocytosis. T e ectopically produced erythropoietin stimulates the production of red blood cells (RBCs) in the bone marrow and raises the hematocrit. Other lymphokines and hormones produced by cancer cells may stimulate erythropoietin release but have not been proved to cause erythrocytosis.

Most patients with erythrocytosis have an elevated hematocrit (>52% in men, >48% in women) that is detected on a routine blood count. Approximately 3% of patients with renal cell cancer, 10% of patients with hepatoma, and 15% of patients with cerebellar hemangioblastomas have erythrocytosis. In most cases, the erythrocytosis is asymptomatic.

Patients with erythrocytosis due to a renal cell cancer, hepatoma, or CNS cancer should have measurement of red cell mass. If the red cell mass is elevated, the serum erythropoietin level should be measured. Patients with an appropriate cancer, elevated erythropoietin levels, and no other explanation for erythrocytosis (e.g., hemoglobinopathy that causes increased O_2 af nity; **Chap. 2**) have the paraneoplastic syndrome.

TABLE 54-2

PARANEOPLASTIC HEMATOLOGIC SYNDROMES

SYNDROME	PROTEINS	CANCERS TYPICALLY ASSOCIATED WITH SYNDROME
Erythrocytosis	Erythropoietin	Renal cancers, hepatocarcinoma, cerebellar hemangioblastomas
Granulocytosis	G-CSF, GM-CSF, IL-6	Lung cancer, gastrointestinal cancer, ovarian cancer, genitourinary cancer, Hodgkin's disease
Thrombocytosis	IL-6	Lung cancer, gastrointestinal cancer, breast cancer, ovarian cancer, lymphoma
Eosinophilia	IL-5	Lymphoma, leukemia, lung cancer
Thrombophlebitis	Unknown	Lung cancer, pancreatic cancer, gastrointestinal cancer, breast cancer, genitourinary cancer, ovarian cancer, prostate cancer, lymphoma

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin.

TREATMENT Erythrocytosis

Successful resection of the cancer usually resolves the erythrocytosis. If the tumor cannot be resected or treated effectively with radiation therapy or chemotherapy, phlebotomy may control any symptoms related to erythrocytosis.

GRANULOCYTOSIS

Approximately 30% of patients with solid tumors have granulocytosis (granulocyte count >8000/μL). In about half of patients with granulocytosis and cancer, the granulocytosis has an identifiable nonparaneoplastic etiology (infection, tumor necrosis, glucocorticoid administration, etc.). T e other patients have proteins in urine and serum that stimulate the growth of bone marrow cells. Tumors and tumor cell lines from patients with lung, ovarian, and bladder cancers have been documented to produce granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and/or interleukin 6 (IL-6). However, the etiology of granulocytosis has not been characterized in most patients.

Patients with granulocytosis are nearly all asymptomatic, and the differential white blood cell count does not have a shift to immature forms of neutrophils. Granulocytosis occurs in 40% of patients with lung and gastrointestinal cancers, 20% of patients with breast cancer, 30% of patients with brain tumors and ovarian cancers, 20% of patients with Hodgkin's disease, and 10% of patients with renal cell carcinoma. Patients with advanced-stage disease are more likely to have granulocytosis than are those with early-stage disease.

Paraneoplastic granulocytosis does not require treatment. T e granulocytosis resolves when the underlying cancer is treated.

THROMBOCYTOSIS

Some 35% of patients with thrombocytosis (platelet count >400,000/μL) have an underlying diagnosis of cancer. IL-6, a candidate molecule for the etiology of paraneoplastic thrombocytosis, stimulates the production of platelets in vitro and in vivo. Some patients with cancer and thrombocytosis have elevated levels of IL-6 in plasma. Another candidate molecule is thrombopoietin, a peptide hormone that stimulates megakaryocyte proliferation and platelet production. T e etiology of thrombocytosis has not been established in most cases.

Patients with thrombocytosis are nearly all asymptomatic. T rombocytosis is not clearly linked to thrombosis in patients with cancer. T rombocytosis is present in 40% of patients with lung and gastrointestinal cancers; 20% of patients with breast, endometrial, and ovarian cancers; and 10% of patients with lymphoma. Patients with thrombocytosis are more likely to have advanced-stage disease and have a poorer prognosis than do patients without thrombocytosis. In ovarian cancer, IL-6 has been shown to directly promote tumor growth. Paraneoplastic thrombocytosis does not require treatment other than treatment of the underlying tumor.

EOSINOPHILIA

Eosinophilia is present in ~1% of patients with cancer. Tumors and tumor cell lines from patients with lymphomas or leukemia may produce IL-5, which stimulates eosinophil growth. Activation of IL-5 transcription in lymphomas and leukemias may involve translocation of the long arm of chromosome 5, to which the genes for IL-5 and other cytokines map.

Patients with eosinophilia are typically asymptomatic. Eosinophilia is present in 10% of patients with lymphoma, 3% of patients with lung cancer, and occasional patients with cervical, gastrointestinal, renal, and breast cancer. Patients with markedly elevated eosinophil counts (>5000/μL) can develop shortness of breath and wheezing. A chest radiograph may reveal diffuse pulmonary infiltrates from eosinophil infiltration and activation in the lungs.

TREATMENT Eosinophilia

Definitive treatment is directed at the underlying malignancy: Tumors should be resected or treated with radiation or chemotherapy. In most patients who develop shortness of breath related to eosinophilia, symptoms resolve with the use of oral or inhaled glucocorticoids. IL-5 antagonists exist but have not been evaluated in this clinical setting.

THROMBOPHLEBITIS

Deep venous thrombosis and pulmonary embolism are the most common thrombotic conditions in patients with cancer. Migratory or recurrent thrombophlebitis may be the initial manifestation of cancer. Nearly 15% of patients who develop deep venous thrombosis or pulmonary embolism have a diagnosis of cancer **(Chap. 22)**. T e coexistence of peripheral venous thrombosis with visceral carcinoma, particularly pancreatic cancer, is called *T*rousseau's syndrome.

Pathogenesis

Patients with cancer are predisposed to thromboembolism because they are often at bed rest or immobilized, and tumors may obstruct or slow blood flow. Postoperative deep venous thrombosis is twice as common in cancer

patients who undergo surgery. Chronic IV catheters also predispose to clotting. In addition, clotting may be promoted by release of procoagulants or cytokines from tumor cells or associated inflammatory cells or by platelet adhesion or aggregation. T e specific molecules that promote thromboembolism have not been identified.

Chemotherapeutic agents, particularly those associated with endothelial damage, can induce venous thrombosis. T e annual risk of venous thrombosis in patients with cancer receiving chemotherapy is about 11%, sixfold higher than the risk in the general population. Bleomycin, l-asparaginase, thalidomide analogues, cisplatin-based regimens, and high doses of busulfan and carmustine are all associated with an increased risk.

In addition to cancer and its treatment causing secondary thrombosis, primary thrombophilic diseases may be associated with cancer. For example, the antiphospholipid antibody syndrome is associated with a wide range of pathologic manifestations. About 20% of patients with this syndrome have cancers. Among patients with cancer and antiphospholipid antibodies, 35–45% develop thrombosis.

Clinical manifestations

Patients with cancer who develop deep venous thrombosis usually develop swelling or pain in the leg, and physical examination reveals tenderness, warmth, and redness. Patients who present with pulmonary embolism develop dyspnea, chest pain, and syncope, and physical examination shows tachycardia, cyanosis, and hypotension. Some 5% of patients with no history of cancer who have a diagnosis of deep venous thrombosis or pulmonary embolism will have a diagnosis of cancer within 1 year. T e most common cancers associated with thromboembolic episodes include lung, pancreatic, gastrointestinal, breast, ovarian, and genitourinary cancers; lymphomas; and brain tumors. Patients with cancer who undergo surgical procedures requiring general anesthesia have a 20–30% risk of deep venous thrombosis.

Diagnosis

T e diagnosis of deep venous thrombosis in patients with cancer is made by impedance plethysmography or bilateral compression ultrasonography of the leg veins. Patients with a noncompressible venous segment have deep venous thrombosis. If compression ultrasonography is normal and there is a high clinical suspicion for deep venous thrombosis, venography should be done to look for a luminal filling defect. Elevation of d-dimer is not as predictive of deep venous thrombosis in patients with cancer as it is in patients without cancer; elevations are seen in people over age 65 years without concomitant evidence of thrombosis, probably as a consequence of increased thrombin deposition and turnover in aging.

Patients with symptoms and signs suggesting a pulmonary embolism should be evaluated with a chest radiograph, electrocardiogram, arterial blood gas analysis, and ventilation-perfusion scan. Patients with mismatched segmental perfusion defects have a pulmonary embolus. Patients with equivocal ventilation-perfusion findings should be evaluated as described above for deep venous thrombosis in their legs. If deep venous thrombosis is detected, they should be anticoagulated. If deep venous thrombosis is not detected, they should be considered for a pulmonary angiogram.

Patients without a diagnosis of cancer who present with an initial episode of thrombophlebitis or pulmonary embolus need no additional tests for cancer other than a careful history and physical examination. In light of the many possible primary sites, diagnostic testing in asymptomatic patients is wasteful. However, if the clot is refractory to standard treatment or is in an unusual site or if the thrombophlebitis is migratory or recurrent, efforts to find an underlying cancer are indicated.

TREATMENT Thrombophlebitis

Patients with cancer and a diagnosis of deep venous thrombosis or pulmonary embolism should be treated initially with IV unfractionated heparin or low-molecular-weight heparin for at least 5 days, and warfarin should be started within 1 or 2 days. T e warfarin dose should be adjusted so that the international normalized ratio (INR) is 2–3. Patients with proximal deep venous thrombosis and a relative contraindication to heparin anticoagulation (hemorrhagic brain metastases or pericardial effusion) should be considered for placement of a filter in the inferior vena cava (Greenfield filter) to prevent pulmonary embolism. Warfarin should be administered for 3–6 months. An alternative approach is to use low-molecular-weight heparin for 6 months. Patients with cancer who undergo a major surgical procedure should be considered for heparin prophylaxis or pneumatic boots. Breast cancer patients undergoing chemotherapy and patients with implanted catheters should be considered for prophylaxis. Guidelines recommend that hospitalized patients with cancer and patients receiving a thalidomide analogue receive prophylaxis with low-molecular-weight heparin or low-dose aspirin. Use of prophylaxis routinely during chemotherapy is controversial and not recommended by the American Society of Clinical Oncology.

Neurologic paraneoplastic syndromes are discussed in Chap. 55.

Acknowledgment

T e authors acknowledge the contributions of Bruce E. Johnson to prior versions of this chapter.

CHAPTER 55

PARANEOPLASTIC NEUROLOGIC SYNDROMES AND AUTOIMMUNE ENCEPHALITIS

Josep Dalmau ■ Myrna R. Rosenfeld

Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect any part of the nervous system **(Table 55-1)**. They are caused by mechanisms other than metastasis or by any of the complications of cancer such as coagulopathy, stroke, metabolic and nutritional conditions, infections, and side effects of cancer therapy. In 60% of patients, the neurologic symptoms precede the cancer diagnosis. Clinically disabling PNDs occur in 0.5–1% of all cancer patients, but they affect 2–3% of patients with neuroblastoma or small-cell lung cancer (SCLC) and 30–50% of patients with thymoma or sclerotic myeloma.

PATHOGENESIS

Most PNDs are mediated by immune responses triggered by neuronal proteins (onconeuronal antigens) expressed by tumors. In PNDs of the central nervous system (CNS), many antibody-associated immune responses have been identified **(Table 55-2)**. These antibodies react with the patient's tumor, and their detection in serum or cerebrospinal fluid (CSF) usually predicts the presence of cancer. When the antigens are intracellular, most syndromes are associated with extensive infiltrates of CD4+ and CD8+ T cells, microglial activation, gliosis, and variable neuronal loss. The infiltrating T cells are often in close contact with neurons undergoing degeneration, suggesting a primary pathogenic role. T cell–mediated cytotoxicity may contribute directly to cell death in these PNDs. Thus both humoral and cellular immune mechanisms participate in the pathogenesis of many PNDs. This complex immunopathogenesis may underlie the resistance of many of these conditions to therapy.

In contrast to the disorders associated with immune responses against intracellular antigens, those associated with antibodies to antigens expressed on the neuronal cell surface of the CNS or at the neuromuscular junction are more responsive to immunotherapy **(Table 55-3, Fig. 55-1)**. These disorders occur with and without a cancer association and may affect children and young adults, and there is increasing evidence that they are mediated by the antibodies.

Other PNDs are likely immune-mediated, although their antigens are unknown. These include several syndromes of inflammatory neuropathies and myopathies. In addition, many patients with typical PND syndromes are antibody-negative.

For still other PNDs, the cause remains quite obscure. These include, among others, several neuropathies that occur in the terminal stages of cancer and a number of neuropathies associated with plasma cell dyscrasias or lymphoma without evidence of inflammatory infiltrates or deposits of immunoglobulin, cryoglobulin, or amyloid.

APPROACH TO THE PATIENT: Paraneoplastic Neurologic Disorders

Three key concepts are important for the diagnosis and management of PNDs. First, it is common for symptoms to appear before the presence of a tumor is known; second, the neurologic syndrome usually develops rapidly, producing severe deficits in a short period of time; and third, there is evidence that prompt tumor control improves the neurologic outcome. Therefore, the major concern of the physician is to recognize a disorder promptly as paraneoplastic and to identify and treat the tumor.

TABLE 55-1

PARANEOPLASTIC SYNDROMES OF THE NERVOUS SYSTEM

CLASSIC SYNDROMES: USUALLY OCCUR WITH CANCER ASSOCIATION	NONCLASSIC SYNDROMES: MAY OCCUR WITH AND WITHOUT CANCER ASSOCIATION
Encephalomyelitis	Brainstem encephalitis
Limbic encephalitis	Stiff-person syndrome
Cerebellar degeneration (adults)	Necrotizing myelopathy
Opsoclonus-myoclonus	Motor neuron disease
Subacute sensory neuronopathy	Guillain-Barré syndrome
Gastrointestinal paresis or pseudo-obstruction	Subacute and chronic mixed sensory-motor neuropathies
Dermatomyositis (adults)	Neuropathy associated with plasma cell dyscrasias and lymphoma
Lambert-Eaton myasthenic syndrome	Vasculitis of nerve
Cancer- or melanoma-associated retinopathy	Pure autonomic neuropathy
	Acute necrotizing myopathy
	Polymyositis
	Vasculitis of muscle
	Optic neuropathy
	BDUMP

Abbreviation: BDUMP, bilateral diffuse uveal melanocytic proliferation.

PND OF THE CENTRAL NERVOUS SYSTEM AND DORSAL ROOT GANGLIA When symptoms involve brain, spinal cord, or dorsal root ganglia, the suspicion of PND is usually based on a combination of clinical, radiologic, and CSF findings. Presence of antineuronal antibodies (Tables 55-2 and 55-3) may help in the diagnosis, but only 60–70% of PNDs of the CNS and less than 20% of those involving the peripheral nervous system have neuronal or neuromuscular junction antibodies that can be used as diagnostic tests.

Magnetic resonance imaging (MRI) and CSF studies are important to rule out neurologic complications due to the direct spread of cancer, particularly metastatic and leptomeningeal disease. In most PNDs, the MRI findings are nonspecific. Paraneoplastic limbic encephalitis is usually associated with characteristic MRI abnormalities in the mesial temporal lobes (see below), but similar findings can occur with other disorders (e.g., nonparaneoplastic autoimmune limbic encephalitis and human herpesvirus type 6 [HHV-6] encephalitis) **(Fig. 55-2)**. The CSF profile of patients with PND of the CNS or dorsal root ganglia typically consists of mild to moderate pleocytosis (<200 mononuclear cells, predominantly lymphocytes), an increase in the protein concentration, and a variable presence of oligoclonal bands. There are no specific electrophysiologic tests that are diagnostic of PND. Moreover, a biopsy of the affected tissue is often difficult to obtain, and although useful to rule out other disorders (e.g., metastasis) the pathologic findings are not specific for PND.

PND OF NERVE AND MUSCLE If symptoms involve peripheral nerve, neuromuscular junction, or muscle, the diagnosis of a specific PND is usually established on clinical, electrophysiologic, and pathologic grounds. The clinical history, accompanying symptoms (e.g., anorexia, weight loss), and type of syndrome dictate the studies and degree of effort needed to demonstrate a neoplasm. For example, the frequent association of Lambert-Eaton myasthenic syndrome (LEMS) with SCLC should lead to a chest and abdomen computed tomography (CT) or body positron emission tomography (PET) scan and, if negative, periodic tumor screening for at least 3 years after the neurologic diagnosis. In contrast, the weak association of polymyositis with cancer calls into question the need for repeated cancer screenings in this situation. Serum and urine immunofixation

TABLE 55-2

ANTIBODIES TO INTRACELLULAR ANTIGENS, SYNDROMES, AND ASSOCIATED CANCERS

ANTIBODY	ASSOCIATED NEUROLOGIC SYNDROME(S)	TUMORS
Anti-Hu (ANNA1)	Encephalomyelitis, subacute sensory neuronopathy	SCLC
Anti-Yo (PCA1)	Cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA2)	Cerebellar degeneration, opsoclonus, brainstem encephalitis	Breast, gynecologic, SCLC
Anti-Tr	Cerebellar degeneration	Hodgkin's lymphoma
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis, uveitis, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins	Limbic, hypothalamic, brainstem encephalitis	Testicular (Ma2), other (Ma)
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, SCLC
Recoverin, bipolar cell antibodies, others[a]	Cancer-associated retinopathy (CAR) Melanoma-associated retinopathy (MAR)	SCLC (CAR), melanoma (MAR)
Anti-GAD	Stiff-person, cerebellar syndromes, limbic encephalitis	Infrequent tumor association (thymoma)

[a] A variety of target antigens have been identified.
Abbreviations: CRMP, collapsing response-mediator protein; SCLC, small-cell lung cancer.

TABLE 55-3

ANTIBODIES TO CELL SURFACE OR SYNAPTIC ANTIGENS, SYNDROMES, AND ASSOCIATED TUMORS

ANTIBODY	NEUROLOGIC SYNDROME	TUMOR TYPE WHEN ASSOCIATED
Anti-AChR (muscle)[a]	Myasthenia gravis	Thymoma
Anti-AChR (neuronal)[a]	Autonomic ganglionopathy	SCLC
Anti-VGCC[b]	LEMS, cerebellar degeneration	SCLC
Anti-NMDAR[a]	Anti-NMDAR encephalitis	Teratoma in young women (children and men rarely have tumors)
Anti-LGI1[c]	Limbic encephalitis, hyponatremia, faciobrachial tonic or dystonic seizures	Rarely thymoma
Anti-Caspr2[c]	Morvan's syndrome, neuromyotonia	Thymoma, prostate cancer
Anti-$GABA_BR$[d]	Limbic encephalitis, seizures	SCLC, neuroendocrine
Anti-$GABA_AR$[d]	Encephalitis with prominent seizures and status epilepticus; less often opsoclonus and stiff-person syndrome	Rarely thymoma
Anti-AMPAR[d]	Limbic encephalitis with relapses	SCLC, thymoma, breast
Glycine receptor[d]	Encephalomyelitis with rigidity, stiff-person syndrome	Rarely, thymoma, lung cancer
Anti-DPPX[d]	Agitation, myoclonus, tremor, seizures, hyperekplexia, encephalomyelitis with rigidity	No cancer, but frequent diarrhea or cachexia suggesting paraneoplasia

[a]A direct pathogenic role of these antibodies has been demonstrated.
[b]Anti-VGCC antibodies are pathogenic for LEMS.
[c]Previously named voltage-gated potassium channel antibodies (VGKC); currently included under the term VGKC-complex proteins. Of note, the significance of antibodies to VGKC-complex proteins other than LGI1 and Caspr2 is uncertain (the antigens are unknown, and the response to immunotherapy is variable)
[d]These antibodies are strongly suspected to be pathogenic.
Abbreviations: AChR, acetylcholine receptor; AMPAR, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; $GABA_BR$, γ-aminobutyric acid B receptor; GAD, glutamic acid decarboxylase; LEMS, Lambert-Eaton myasthenic syndrome; LGI1, leucine-rich glioma-inactivated 1; NMDAR, N-methyl-d-aspartate receptor; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel.

studies should be considered in patients with peripheral neuropathy of unknown cause; detection of a monoclonal gammopathy suggests the need for additional studies to uncover a B cell or plasma cell malignancy. In paraneoplastic neuropathies, diagnostically useful antineuronal antibodies are limited to anti-CV_2/CRMP5 and anti-Hu.

For any type of PND, if antineuronal antibodies are negative, the diagnosis relies on the demonstration of cancer and the exclusion of other cancer-related or independent neurologic disorders. Combined CT and PET scans often uncover tumors undetected by other tests. For germ cell tumors of the testis and teratomas of the ovary, ultrasound and CT or MRI of the abdomen and pelvis may reveal tumors undetectable by PET.

SPECIFIC PARANEOPLASTIC NEUROLOGIC SYNDROMES

PARANEOPLASTIC ENCEPHALOMYELITIS AND FOCAL ENCEPHALITIS

The term encephalomyelitis describes an inflammatory process with multifocal involvement of the nervous system, including brain, brainstem, cerebellum, and spinal cord. It is often associated with dorsal root ganglia and autonomic dysfunction. For any given patient, the clinical manifestations are determined by the areas predominantly involved, but pathologic studies almost always reveal abnormalities beyond the symptomatic regions. Several clinicopathologic syndromes may occur alone or in combination: (1) cortical encephalitis, which may present as "epilepsia partialis continua"; (2) limbic encephalitis, characterized by confusion, depression, agitation, anxiety, severe short-term memory deficits, partial complex seizures, and sometimes dementia (the MRI usually shows unilateral or bilateral medial temporal lobe abnormalities, best seen with T2 and fluid-attenuated inversion recovery sequences); (3) brainstem encephalitis, resulting in eye movement disorders (nystagmus, opsoclonus, supranuclear or nuclear paresis), cranial nerve paresis, dysarthria, dysphagia, and central autonomic dysfunction; (4) cerebellar gait and limb ataxia; (5) myelitis, which may cause lower or upper motor neuron symptoms, myoclonus, muscle rigidity, and spasms; and (6) autonomic dysfunction as a result of involvement of the neuraxis at multiple levels, including hypothalamus, brainstem, and autonomic nerves (see Paraneoplastic Peripheral Neuropathies, below). Cardiac arrhythmias, postural hypotension, and central

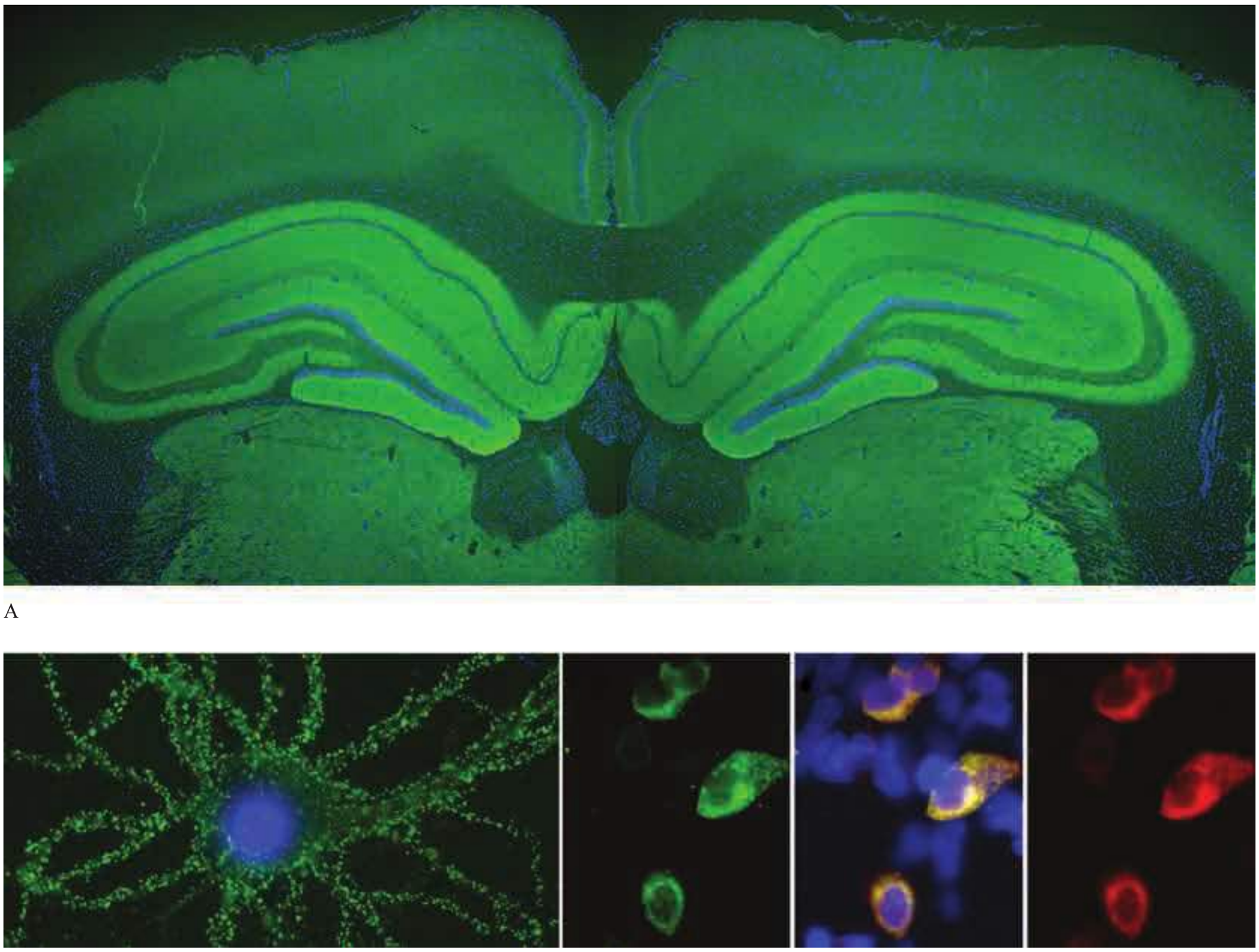


FIGURE 55-1
Antibodies to the GluN1 subunit of the N-methyl-D-aspartate (NMDA) receptor in a patient with anti-NMDA receptor encephalitis and ovarian teratoma. A. Coronal section of rat brain immunolabeled (green fuorescence) with the patient's antibodies. The reactivity predominates in the hippocampus, which is highly enriched in NMDA receptors. B. This image shows the antibody reactivity with cultures of rat hippocampal neurons; the intense green immunolabeling is due to the antibodies against the GluN1 subunit of NMDA receptors. (C–E) Images of HEKcells (a human kidney cell line) transfected to express NMDA receptors, showing reactivity with patient's antibodies C. and with a commercial monoclonal antibody against NMDA receptors D. the patient's antibody reactivity co-labels only the cells that express NMDA receptors E. (From J Dalmau et al: Lancet Neurol 7:1091, 2008; with permission.)

hypoventilation are frequent causes of death in patients with encephalomyelitis.

Paraneoplastic encephalomyelitis and focal encephalitis are usually associated with SCLC, but many other cancers have been implicated. Patients with SCLC and these syndromes usually have anti-Hu antibodies in serum and CSF. Anti-CRMP5 antibodies occur less frequently; some of these patients may develop chorea, uveitis, or optic neuritis. Antibodies to Ma proteins are associated with limbic, hypothalamic, and brainstem encephalitis and occasionally with cerebellar symptoms **(Fig. 55-3)**; some patients develop hypersomnia, cataplexy, and severe hypokinesia. MRI abnormalities are frequent, including those described with limbic encephalitis and variable involvement of the hypothalamus, basal ganglia, or upper brainstem. T e oncologic associations of these antibodies are shown in Table 55-2.

TREATMENT Encephalomyelitis and Focal Encephalitis

Most types of paraneoplastic encephalitis and encephalomyelitis respond poorly to treatment. Stabilization of symptoms or partial neurologic improvement may occasionally occur, particularly if there is a satisfactory response of the tumor to treatment. Controlled trials of therapy are lacking, but

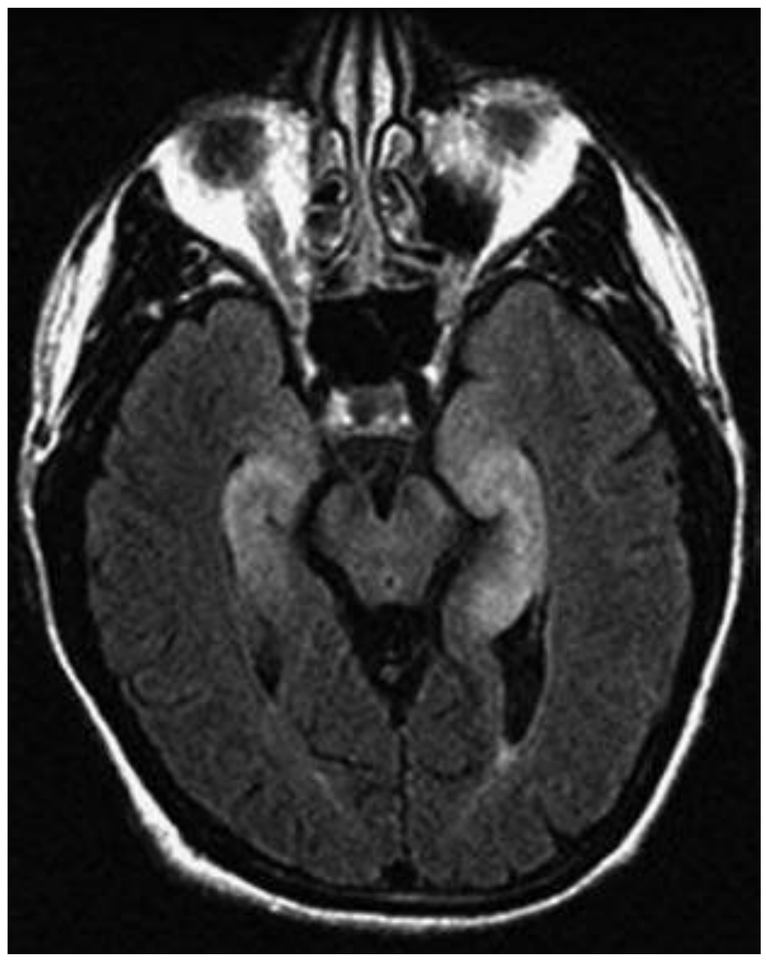


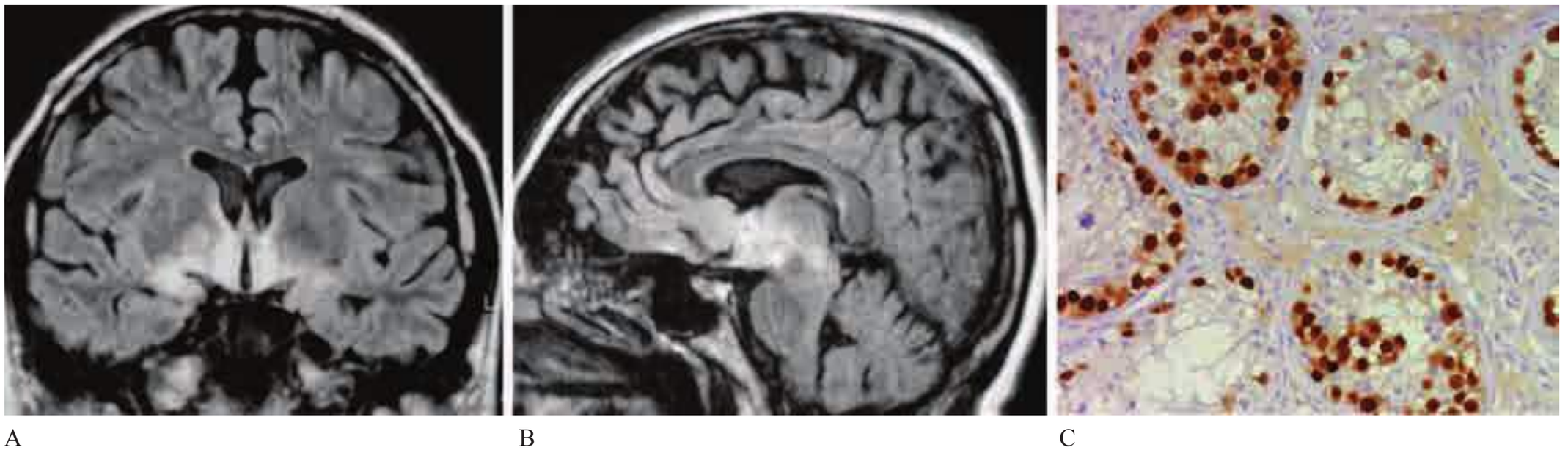
FIGURE 55-2
Fluid-attenuated inversion recovery sequence magnetic resonance imaging of a patient with limbic encephalitis and LGI1 antibodies. Note the abnormal hyperintensity involving the medial aspect of the temporal lobes.

many experts recommend treatment initially with glucocorticoids. If there is no response within several days, one can advance to intravenous immunoglobulin (IVIg) or plasma exchange, and then to immunosuppression with either rituximab or cyclophosphamide. Approximately 30% of patients with anti-Ma2-associated encephalitis respond to treatment of the tumor (usually a germ cell neoplasm of the testis) and immunotherapy.

ENCEPHALITIDES WITH ANTIBODIES TO CELL-SURFACE OR SYNAPTIC PROTEINS

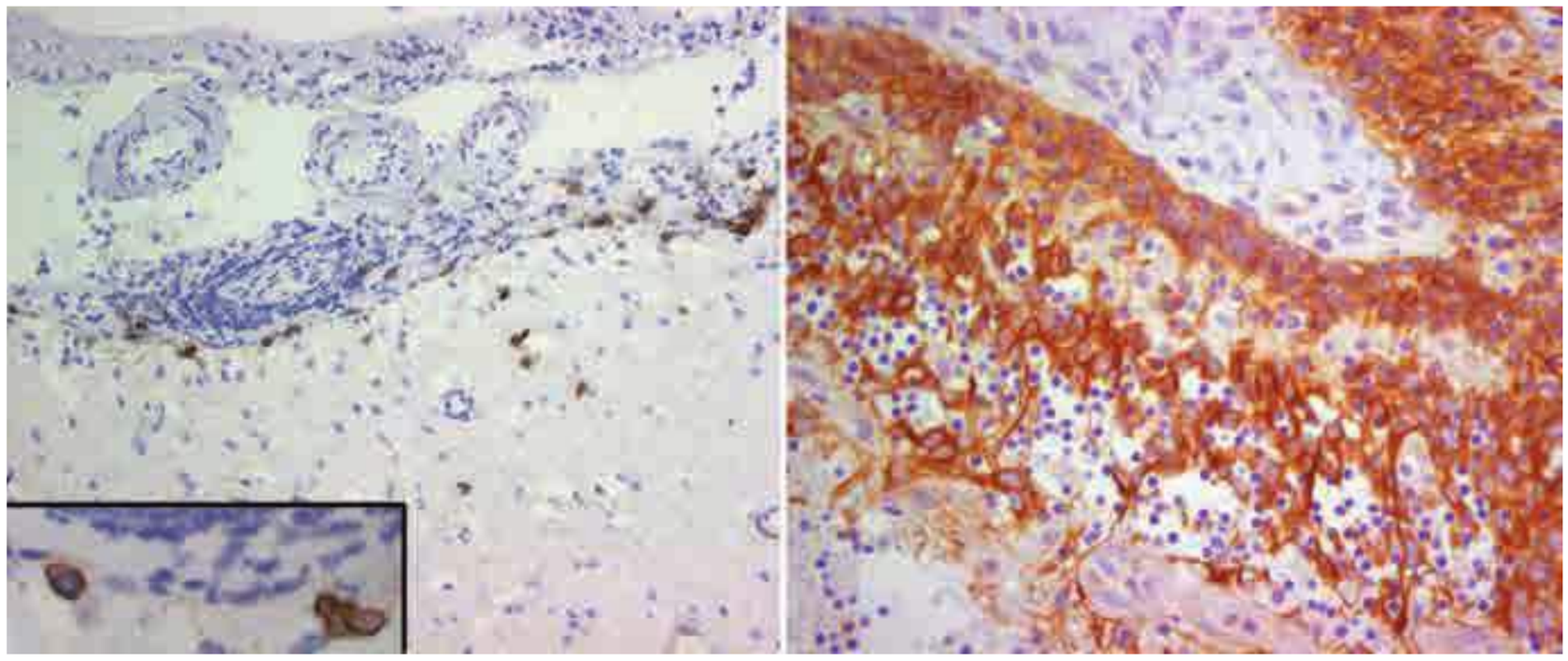
These disorders are important for three reasons: (1) they can occur with and without tumor association, (2) some syndromes predominate in young individuals and children, and (3) despite the severity of the symptoms patients usually respond to treatment of the tumor, if found, and immunotherapy (e.g., glucocorticoids, IVIg, plasma exchange, rituximab, or cyclophosphamide) (Table 55-3).

Encephalitis with N-methyl-d-aspartate (NMDA) receptor antibodies (Fig. 55-1) usually occurs in young women and children, but men and older patients of both sexes can be affected. The disorder has a characteristic pattern of symptom progression that includes a prodrome resembling a viral process, followed in a few days by the onset of severe psychiatric symptoms, memory loss, seizures, decreased level of consciousness, abnormal movements (orofacial, limb, and trunk dyskinesias, dystonic postures), autonomic instability, and frequent hypoventilation. Monosymptomatic episodes, such as pure psychosis, occur in 4% of the patients. Clinical relapses occur in 12–24% of patients (12% during the first 2 years after initial presentation). Most patients have intrathecal synthesis of antibodies, likely by infiltrating plasma cells in brain and meninges **(Fig. 55-4A)**. The syndrome is often misdiagnosed as a viral or idiopathic encephalitis, neuroleptic malignant syndrome, or encephalitis lethargica, and many patients are initially evaluated by psychiatrists with the suspicion of acute psychosis. The detection of an associated teratoma is dependent on age and gender: 46% of female patients 12 years or older have uni- or bilateral ovarian teratomas, whereas less than 7% of girls younger than 12 have a teratoma **(Fig. 55-4B)**. In male patients, the detection of a tumor is rare. Patients older



A B C

FIGURE 55-3
Magnetic resonance imaging (MRI) and tumor of a patient with anti-Ma2-associated encephalitis. A. and B. Fluid-attenuated inversion recovery MRI sequences showing abnormal hyperintensities in the medial temporal lobes, hypothalamus, and upper brainstem. C. This image corresponds to a section of the patient's orchiectomy incubated with a specific marker (Oct4) of germ cell tumors. The positive (brown) cells correspond to an intratubular germ cell neoplasm.



A B

FIGURE 55-4
Pathologic findings in anti–N-methyl-d-aspartate (NMDA) receptor encephalitis. Infiltrates of plasma cells (brown cells; stained for CD138) in the meninges and brain of a patient A. the inset is a magnification of some plasma cells. B. Neurons and neuronal processes in the teratoma of a patient (brown cells; stained with MAP2); these neurons express NMDA receptors (not shown). (From E Martinez-Hernandez et al: Neurology 77:589, 2011, with permission.)

than 45 years are more frequently male; about 20% of these patients have tumors (e.g., cancer of the breast, ovary, or lung).

Encephalitis with leucine-rich glioma-inactivated 1 (LGI1) antibodies predominates in patients older than 50 years (65% male) and frequently presents with memory loss and seizures (limbic encephalopathy), along with hyponatremia and sleep dysfunction. In a small number of patients, the encephalitis is preceded by or occurs with myoclonic-like movements called faciobrachial dystonic or tonic seizures. Less than 10% of patients have thymoma.

Encephalitis with contactin-associated protein-like 2 (Caspr2) antibodies predominates in patients older than 50 years and is associated with Morvan's syndrome (encephalitis, insomnia, confusion, hallucinations, autonomic dysfunction, and neuromyotonia) and, less frequently, with limbic encephalitis, neuromyotonia, and neuropathic pain. About 30–40% of patients have thymoma.

Encephalitis with γ-aminobutyric acid type B ($GABA_B$) receptor antibodies is usually associated with limbic encephalitis and seizures. In rare instances, patients develop cerebellar symptoms and opsoclonus. Fifty percent of patients have SCLC or a neuroendocrine tumor of the lung. Patients may have additional antibodies to glutamic acid decarboxylase (GAD), which are of unclear significance. Other antibodies to non-neuronal proteins are often found in these patients as well as in patients with α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antibodies, indicating a general tendency to autoimmunity.

Encephalitis with GABAA receptor antibodies may affect children and adults. When antibodies are present at high titer in serum and CSF, the disorder associates with prominent seizures and status epilepticus, often requiring pharmacologically induced coma. Low titer antibodies in serum are often associated with other autoimmune conditions, and the spectrum of symptoms is wider, including encephalitis, seizures, opsoclonus, or stiff-person syndrome. Most patients do not have an underlying tumor, but some may have thymoma.

Encephalitis with AMPA receptor antibodies affects middle-aged women, who develop acute limbic dysfunction or, less frequently, prominent psychiatric symptoms; 70% of the patients have an underlying tumor in the lung, breast, or thymus. Neurologic relapses may occur; these also respond to immunotherapy and are not necessarily associated with tumor recurrence.

Encephalitis with glycine receptor (GlyR) antibodies has been described in adults with progressive encephalomyelitis with rigidity and myoclonus (PERM) and stiff-person spectrum of symptoms (with or without GAD antibodies). T e disorder usually occurs without tumor association, although some patients have lung cancer, thymoma, or Hodgkin's lymphoma.

Encephalitis with dipeptidyl-peptidase-like protein-6 (or DPPX) antibodies results in symptoms of CNS hyperexcitability including agitation, hallucinations, paranoid delusions, tremor, myoclonus, nystagmus, seizures, and sometimes hyperekplexia. Some patients develop progressive encephalomyelitis with rigidity and myoclonus. Diarrhea, other gastrointestinal symptoms,

and substantial loss of weight often suggest the presence of an underlying tumor, but no tumor association has been identified. T e disorder responds to immunotherapy.

PARANEOPLASTIC CEREBELLAR DEGENERATION

T is disorder is often preceded by a prodrome that may include dizziness, oscillopsia, blurry or double vision, nausea, and vomiting. A few days or weeks later, patients develop dysarthria, gait and limb ataxia, and variable dysphagia. T e examination usually shows downbeating nystagmus and, rarely, opsoclonus. Brainstem dysfunction, upgoing toes, or a mild neuropathy may occur. Early in the course, MRI studies are usually normal; later, the MRI reveals cerebellar atrophy. T e disorder results from extensive degeneration of Purkinje cells, with variable involvement of other cerebellar cortical neurons, deep cerebellar nuclei, and spinocerebellar tracts. T e tumors more frequently involved are SCLC, cancer of the breast and ovary, and Hodgkin's lymphoma.

Anti-Yo antibodies in patients with breast and gynecologic cancers and anti-Tr antibodies in patients with Hodgkin's lymphoma are the two immune responses typically associated with prominent or pure cerebellar degeneration. Antibodies to P/Q-type voltage-gated calcium channels (VGCC) occur in some patients with SCLC and cerebellar dysfunction; only some of these patients develop LEMS. A variable degree of cerebellar dysfunction can be associated with virtually any of the antibodies and PND of the CNS shown in Table 55-2.

A number of single case reports have described neurologic improvement after tumor removal, plasma exchange, IVIg, cyclophosphamide, rituximab, or glucocorticoids. However, most patients with paraneoplastic cerebellar degeneration do not improve with treatment.

PARANEOPLASTIC OPSOCLONUS-MYOCLONUS SYNDROME

Opsoclonus is a disorder of eye movement characterized by involuntary, chaotic saccades that occur in all directions of gaze; it is frequently associated with myoclonus and ataxia. Opsoclonus-myoclonus may be cancer-related or idiopathic. When the cause is paraneoplastic, the tumors involved are usually cancer of the lung and breast in adults, neuroblastoma in children, and ovarian teratoma in adolescents and young women. T e pathologic substrate of opsoclonus-myoclonus is unclear, but studies suggest that disinhibition of the fastigial nucleus of the cerebellum is involved. Most patients do not have antineuronal antibodies. A small subset of patients with ataxia, opsoclonus, and other eye-movement disorders develop anti-Ri antibodies; in rare instances, muscle rigidity, laryngeal spasms, autonomic dysfunction, and dementia also occur. T e tumors most frequently involved in anti-Ri-associated syndromes are breast and ovarian cancer. If the tumor is not successfully treated, the syndrome in adults often progresses to encephalopathy, coma, and death. In addition to treating the tumor, symptoms may respond to immunotherapy (glucocorticoids, plasma exchange, and/or IVIg).

At least 50% of children with opsoclonus-myoclonus have an underlying neuroblastoma. Hypotonia, ataxia, behavioral changes, and irritability are frequent accompanying symptoms. Neurologic symptoms often improve with treatment of the tumor and glucocorticoids, adrenocorticotropic hormone (ACTH), plasma exchange, IVIg, and rituximab. Many patients are left with psychomotor retardation and behavioral and sleep problems.

PARANEOPLASTIC SYNDROMES OF THE SPINAL CORD

T e number of reports of paraneoplastic spinal cord syndromes, such as subacute motor neuronopathy and acute necrotizing myelopathy, has decreased in recent years. T is may represent a true decrease in incidence, due to improved and prompt oncologic interventions, or the identification of nonparaneoplastic etiologies. Some patients with cancer develop upper or lower motor neuron dysfunction or both, resembling amyotrophic lateral sclerosis. It is unclear whether these disorders have a paraneoplastic etiology or simply coincide with the presence of cancer. T ere are isolated case reports of cancer patients with motor neuron dysfunction who had neurologic improvement after tumor treatment. A search for lymphoma should be undertaken in patients with a rapidly progressive motor neuron syndrome and a monoclonal protein in serum or CSF.

Paraneoplastic myelitis may present with upper or lower motor neuron symptoms, segmental myoclonus, and rigidity, and can be the first manifestation of encephalomyelitis. Neuromyelitis optica (NMO) with aquaporin 4 antibodies may occur in rare instances as a paraneoplastic manifestation of a cancer.

PARANEOPLASTIC STIFF-PERSON SYNDROME

T is disorder is characterized by progressive muscle rigidity, stiffness, and painful spasms triggered by auditory, sensory, or emotional stimuli. Rigidity mainly involves the lower trunk and legs, but it can affect the upper extremities and neck. Sometimes, only one extremity is affected (stif-limb syndrome). Symptoms

improve with sleep and general anesthetics. Electrophysiologic studies demonstrate continuous motor unit activity. T e associated antibodies target proteins (GAD, amphiphysin) involved in the function of inhibitory synapses using γ-aminobutyric acid (GABA) or glycine as neurotransmitters. T e presence of amphiphysin antibodies usually indicates a paraneoplastic etiology related to SCLC and breast cancer. By contrast, GAD antibodies may occur in some cancer patients but are much more frequently present in the nonparaneoplastic disorder. GlyR antibodies may occur in some patients with stiff-person syndrome; these antibodies are also detectable in patients with PERM.

Optimal treatment of stiff-person syndrome requires therapy of the underlying tumor, glucocorticoids, and symptomatic use of drugs that enhance GABA-ergic transmission (diazepam, baclofen, sodium valproate, tiagabine, vigabatrin). IVIg and plasma exchange are transiently effective in some patients.

PARANEOPLASTIC SENSORY NEURONOPATHY OR DORSAL ROOT GANGLIONOPATHY

T is syndrome is characterized by sensory deficits that may be symmetric or asymmetric, painful dysesthesias, radicular pain, and decreased or absent reflexes. All modalities of sensation and any part of the body including face and trunk can be involved. Specialized sensations such as taste and hearing can also be affected. Electrophysiologic studies show decreased or absent sensory nerve potentials with normal or near-normal motor conduction velocities. Symptoms result from an inflammatory, likely immune-mediated, process that targets the dorsal root ganglia, causing neuronal loss and secondary degeneration of the posterior columns of the spinal cord. T e dorsal and, less frequently, the anterior nerve roots and peripheral nerves may also be involved. T is disorder often precedes or is associated with encephalomyelitis and autonomic dysfunction and has the same immunologic and oncologic associations (Hu antibodies, SCLC).

As with anti-Hu-associated encephalomyelitis, the therapeutic approach focuses on prompt treatment of the tumor. Glucocorticoids occasionally produce clinical stabilization or improvement. T e benefit of IVIg and plasma exchange is not proven.

PARANEOPLASTIC PERIPHERAL NEUROPATHIES

T ese disorders may develop any time during the course of the neoplastic disease. Neuropathies occurring at late stages of cancer or lymphoma usually cause mild to moderate sensorimotor deficits due to axonal degeneration of unclear etiology. T ese neuropathies are often masked by concurrent neurotoxicity from chemotherapy and other cancer therapies. In contrast, the neuropathies that develop in the early stages of cancer frequently show a rapid progression, sometimes with a relapsing and remitting course, and evidence of inflammatory infiltrates and axonal loss or demyelination. If demyelinating features predominate, IVIg, plasma exchange, or glucocorticoids may improve symptoms. Occasionally anti-CRMP5 antibodies are present; detection of anti-Hu suggests concurrent dorsal root ganglionitis.

Guillain-Barré syndrome and brachial plexitis have occasionally been reported in patients with lymphoma, but there is no clear evidence of a paraneoplastic association.

Malignant monoclonal gammopathies include: (1) multiple myeloma and sclerotic myeloma associated with IgG or IgA monoclonal proteins; and (2) Waldenström's macroglobulinemia, B cell lymphoma, and chronic B cell lymphocytic leukemia associated with IgM monoclonal proteins. T ese disorders may cause neuropathy by a variety of mechanisms, including compression of roots and plexuses by metastasis to vertebral bodies and pelvis, deposits of amyloid in peripheral nerves, and paraneoplastic mechanisms. T e paraneoplastic variety has several distinctive features. Approximately half of patients with sclerotic myeloma develop a sensorimotor neuropathy with predominantly motor deficits, resembling a chronic inflammatory demyelinating neuropathy; some patients develop elements of the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes). Treatment of the plasmacytoma or sclerotic lesions usually improves the neuropathy. In contrast, the sensorimotor or sensory neuropathy associated with multiple myeloma is more refractory to treatment. Between 5 and 10% of patients with Waldenström's macroglobulinemia develop a distal symmetric sensorimotor neuropathy with predominant involvement of large sensory fibers. T ese patients may have IgM antibodies in their serum against myelin-associated glycoprotein and various gangliosides. In addition to treating the Waldenström's macroglobulinemia, other therapies may improve the neuropathy, including plasma exchange, IVIg, chlorambucil, cyclophosphamide, fludarabine, or rituximab.

Vasculitis *of* the nerve and muscle causes a painful symmetric or asymmetric distal axonal sensorimotor neuropathy with variable proximal weakness. It predominantly affects elderly men and is associated with an elevated erythrocyte sedimentation rate and increased CSF protein concentration. SCLC and lymphoma are the primary tumors involved. Glucocorticoids and cyclophosphamide often result in neurologic improvement.

Peripheral nerve hyperexcitability (neuromyotonia, or Isaacs' syndrome) is characterized by spontaneous and continuous muscle fiber activity of peripheral nerve origin. Clinical features include cramps, muscle twitching (fasciculations or myokymia), stiffness, delayed muscle relaxation (pseudomyotonia), and spontaneous or evoked carpal or pedal spasms. The involved muscles may be hypertrophic, and some patients develop paresthesias and hyperhidrosis. CNS dysfunction, including mood changes, sleep disorder, hallucinations, and autonomic symptoms may occur. The electromyogram (EMG) shows fibrillations; fasciculations; and doublet, triplet, or multiplet single-unit (myokymic) discharges that have a high intraburst frequency. Some patients have Caspr2 antibodies in the context of Morvan's syndrome, but most cases of isolated neuromyotonia are antibody negative. The disorder often occurs without cancer; if paraneoplastic, benign and malignant thymomas and SCLC are the usual tumors. Phenytoin, carbamazepine, and plasma exchange improve symptoms.

Paraneoplastic autonomic neuropathy usually develops as a component of other disorders, such as LEMS and encephalomyelitis. It may rarely occur as a pure or predominantly autonomic neuropathy with cholinergic or adrenergic dysfunction at the pre- or postganglionic levels. Patients can develop several life-threatening complications, such as gastrointestinal paresis with pseudo-obstruction, cardiac dysrhythmias, and postural hypotension. Other clinical features include abnormal pupillary responses, dry mouth, anhidrosis, erectile dysfunction, and problems in sphincter control. The disorder occurs in association with several tumors, including SCLC, cancer of the pancreas or testis, carcinoid tumors, and lymphoma. Because autonomic symptoms can be the presenting feature of encephalomyelitis, serum anti-Hu and anti-CRMP5 antibodies should be sought. Antibodies to ganglionic (alpha3-type) neuronal acetylcholine receptors are the cause of autoimmune autonomic ganglionopathy, a disorder that frequently occurs without cancer association.

Patients with this syndrome develop myalgias and rapid progression of weakness involving the extremities and the pharyngeal and respiratory muscles, often resulting in death. Serum muscle enzymes are elevated, and muscle biopsy shows extensive necrosis with minimal or absent inflammation and sometimes deposits of complement. The disorder occurs as a paraneoplastic manifestation of a variety of cancers including SCLC and cancer of the gastrointestinal tract, breast, kidney, and prostate, among others. Glucocorticoids and treatment of the underlying tumor rarely control the disorder.

PARANEOPLASTIC VISUAL SYNDROMES

This group of disorders involves the retina and, less frequently, the uvea and optic nerves. The term cancer-associated retinopathy is used to describe paraneoplastic cone and rod dysfunction characterized by photosensitivity, progressive loss of vision and color perception, central or ring scotomas, night blindness, and attenuation of photopic and scotopic responses in the electroretinogram (ERG). The most commonly associated tumor is SCLC. Melanoma-associated retinopathy affects patients with metastatic cutaneous melanoma. Patients develop acute onset of night blindness and shimmering, flickering, or pulsating photopsias that often progress to visual loss. The ERG shows reduced b waves with normal dark adapted a waves. Paraneoplastic optic neuritis and uveitis are very uncommon and can develop in association with encephalomyelitis. Some patients with paraneoplastic uveitis and optic neuritis have anti-CRMP5 antibodies.

Some paraneoplastic retinopathies are associated with serum antibodies that specifically react with the subset of retinal cells undergoing degeneration, supporting an immune-mediated pathogenesis (Table 55-2). Paraneoplastic retinopathies usually fail to improve with treatment, although rare responses to glucocorticoids, plasma exchange, and IVIg have been reported.

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SECTION XII

ONCOLOGIC EMERGENCIES AND LATE EFFECTS AND COMPLICATIONS OF CANCER AND ITS TREATMENT

CHAPTER 56

ONCOLOGIC EMERGENCIES

Rasim Gucalp ■ Janice P. Dutcher

Emergencies in patients with cancer may be classified into three groups: pressure or obstruction caused by a space-occupying lesion, metabolic or hormonal problems (paraneoplastic syndromes, **Chap. 54**), and treatment-related complications.

STRUCTURAL-OBSTRUCTIVE ONCOLOGIC EMERGENCIES

SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome (SVCS) is the clinical manifestation of superior vena cava (SVC) obstruction, with severe reduction in venous return from the head, neck, and upper extremities. Malignant tumors, such as lung cancer, lymphoma, and metastatic tumors, are responsible for the majority of SVCS cases. With the expanding use of intravascular devices (e.g., permanent central venous access catheters, pacemaker/defibrillator leads), the prevalence of benign causes of SVCS is increasing now, accounting for at least 40% of cases. Lung cancer, particularly of small-cell and squamous cell histologies, accounts for approximately 85% of all cases of malignant origin. In young adults, malignant lymphoma is a leading cause of SVCS. Hodgkin's lymphoma involves the mediastinum more commonly than other lymphomas but rarely causes SVCS. When SVCS is noted in a young man with a mediastinal mass, the differential diagnosis is lymphoma versus primary mediastinal germ cell tumor. Metastatic cancers to the mediastinal lymph nodes, such as testicular and breast carcinomas, account for a small proportion of cases. Other causes include benign tumors, aortic aneurysm, thyromegaly, thrombosis, and fibrosing mediastinitis from prior irradiation, histoplasmosis, or Behçet's syndrome. SVCS as the initial manifestation of Behçet's syndrome may be due to inflammation of the SVC associated with thrombosis.

Patients with SVCS usually present with neck and facial swelling (especially around the eyes), dyspnea, and cough. Other symptoms include hoarseness, tongue swelling, headaches, nasal congestion, epistaxis, hemoptysis, dysphagia, pain, dizziness, syncope, and lethargy. Bending forward or lying down may aggravate the symptoms. T e characteristic physical findings are dilated neck veins; an increased number of collateral veins covering the anterior chest wall; cyanosis; and edema of the face, arms, and chest. Facial swelling and plethora are typically exacerbated when the patient is supine. More severe cases include proptosis, glossal and laryngeal edema, and obtundation. T e clinical picture is milder if the obstruction is located above the azygos vein. Symptoms are usually progressive, but in some cases, they may improve as collateral circulation develops.

Signs and symptoms of cerebral and/or laryngeal edema, though rare, are associated with a poorer prognosis and require urgent evaluation. Seizures are more likely related to brain metastases than to cerebral edema from venous occlusion. Patients with small-cell lung cancer and SVCS have a higher incidence of brain metastases than those without SVCS.

Cardiorespiratory symptoms at rest, particularly with positional changes, suggest significant airway and vascular obstruction and limited physiologic reserve. Cardiac arrest or respiratory failure can occur, particularly in patients receiving sedatives or undergoing general anesthesia.

Rarely, esophageal varices may develop. T ese are "downhill" varices based on the direction of blood flow from cephalad to caudad (in contrast to "uphill" varices associated with caudad to cephalad flow from portal hypertension). If the obstruction to the SVC is proximal to the azygous vein, varices develop in the upper one-third of the esophagus. If the obstruction involves or is distal to the azygous vein, varices occur in the entire length of the esophagus. Variceal bleeding may be a late complication of chronic SVCS.

Superior vena cava obstruction may lead to bilateral breast edema with bilateral enlarged breast. Unilateral breast dilatation may be seen as a consequence of axillary or subclavian vein blockage.

T e diagnosis of SVCS is a clinical one. T e most significant chest radiographic finding is widening of the superior mediastinum, most commonly on the right side. Pleural effusion occurs in only 25% of patients, often on the right side. T e majority of these effusions are exudative and occasionally chylous. However, a normal chest radiograph is still compatible with the diagnosis if other characteristic findings are present. Computed tomography (CT) provides the most reliable view of the mediastinal anatomy. T e diagnosis of SVCS requires diminished or absent opacification of central venous structures with prominent collateral venous circulation. Magnetic resonance imaging (MRI) has no advantages over CT. Invasive procedures, including bronchoscopy, percutaneous needle biopsy, mediastinoscopy, and even thoracotomy, can be performed by a skilled clinician without any major risk of bleeding. Endobronchial or esophageal ultrasound-guided needle aspiration may establish the diagnosis safely. For patients with a known cancer, a detailed workup usually is not necessary, and appropriate treatment may be started after obtaining a CT scan of the thorax. For those with no history of malignancy, a detailed evaluation is essential to rule out benign causes and determine a specific diagnosis to direct the appropriate therapy.

TREATMENT Superior Vena Cava Syndrome

T e one potentially life-threatening complication of a superior mediastinal mass is tracheal obstruction. Upper airway obstruction demands emergent therapy. Diuretics with a low-salt diet, head elevation, and oxygen may produce temporary symptomatic relief. Glucocorticoids may be useful at shrinking lymphoma masses; they are of no benefit in patients with lung cancer.

Radiation therapy is the primary treatment for SVCS caused by non-small-cell lung cancer and other metastatic solid tumors. Chemotherapy is effective when the underlying cancer is small-cell carcinoma of the lung, lymphoma, or germ cell tumor. SVCS recurs in 10–30% of patients; it may be palliated with the use of intravascular self-expanding stents **(Fig. 56-1)**. Early stenting may be necessary in patients with severe symptoms; however, the prompt increase in venous return after stenting may precipitate heart failure and pulmonary edema. Other complications of stent placement include hematoma at the insertion site, SVC perforation, stent migration in the right ventricle, stent fracture, and pulmonary embolism. Surgery may provide immediate relief for patients in whom a benign process is the cause.

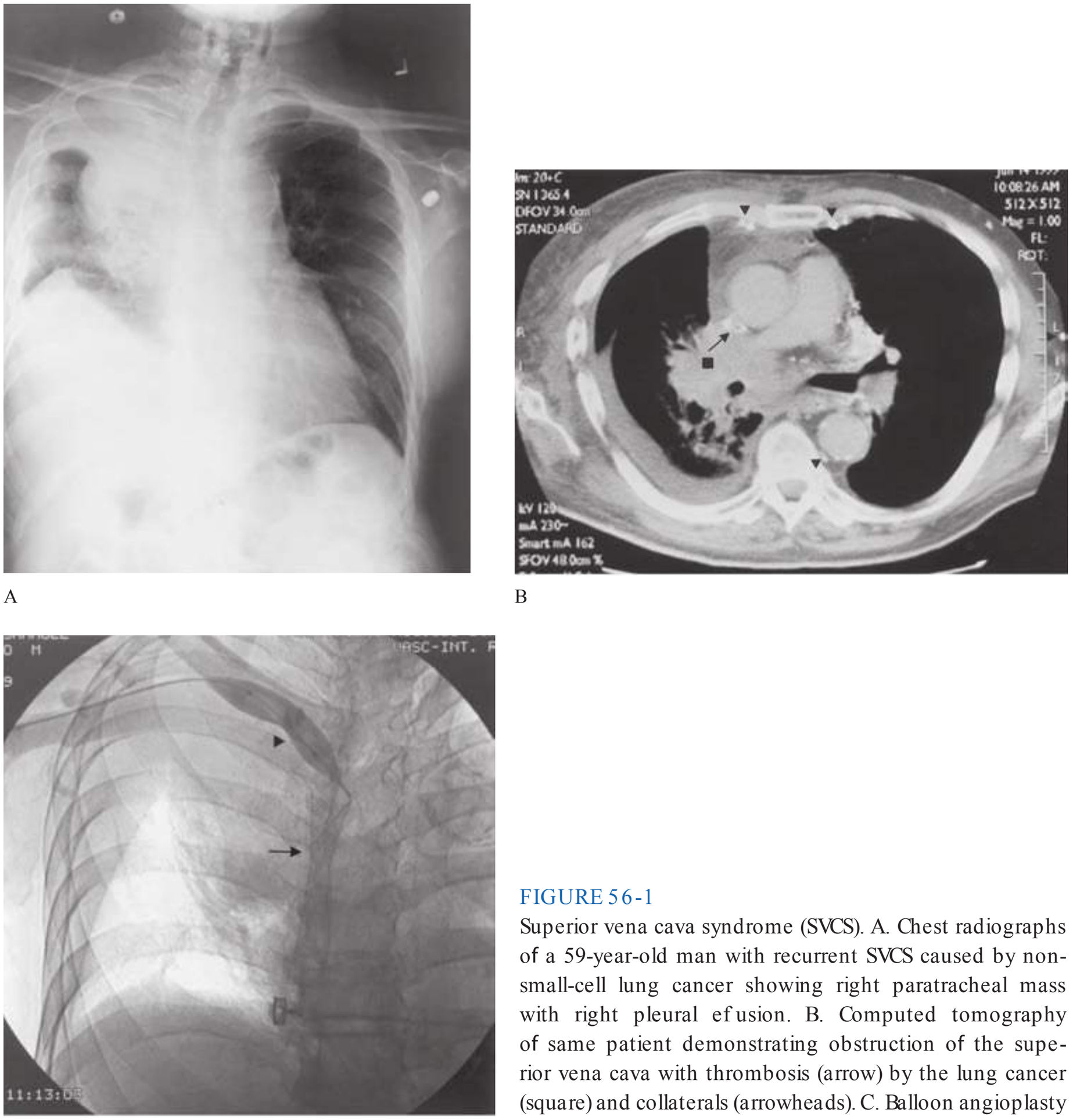
Clinical improvement occurs in most patients, although this improvement may be due to the development of adequate collateral circulation. T e mortality associated with SVCS does not relate to caval obstruction but rather to the underlying cause.

SVCS AND CENTRAL VENOUS CATHETERS IN ADULTS T e use of long-term central venous catheters has become common practice in patients with cancer. Major vessel thrombosis may occur. In these cases, catheter removal should be combined with anticoagulation to prevent embolization. SVCS in this setting, if detected early, can be treated by fibrinolytic therapy without sacrificing the catheter. T e routine use of low-dose warfarin or low-molecular-weight heparin to prevent thrombosis related to permanent central venous access catheters in cancer patients is not recommended.

PERICARDIAL EFFUSION/TAMPONADE

Malignant pericardial disease is found at autopsy in 5–10% of patients with cancer, most frequently with lung cancer, breast cancer, leukemias, and lymphomas. Cardiac tamponade as the initial presentation of extrathoracic malignancy is rare. T e origin is not malignancy in about 50% of cancer patients with symptomatic pericardial disease, but it can be related to irradiation, drug-induced pericarditis, hypothyroidism, idiopathic pericarditis, infection, or autoimmune diseases. Two types of radiation pericarditis occur: an acute inflammatory, effusive pericarditis occurring within months of irradiation, which usually resolves spontaneously, and a chronic effusive pericarditis that may appear up to 20 years after radiation therapy and is accompanied by a thickened pericardium.

Most patients with pericardial metastasis are asymptomatic. However, the common symptoms are dyspnea, cough, chest pain, orthopnea, and weakness. Pleural effusion, sinus tachycardia, jugular venous distention, hepatomegaly, peripheral edema, and cyanosis are the most frequent physical findings. Relatively specific diagnostic findings, such as paradoxical pulse, diminished heart sounds, pulsus alternans (pulse waves alternating between those of greater and lesser amplitude with successive beats), and friction rub are less common than with nonmalignant pericardial disease. Chest radiographs and electrocardiogram (ECG) reveal abnormalities in 90% of patients, but half of these abnormalities are nonspecific. Echocardiography is the most helpful diagnostic test. Pericardial fluid may be serous, serosanguineous, or hemorrhagic, and cytologic examination of pericardial fluid is diagnostic in most patients. Measurements of tumor markers in the pericardial fluid are not helpful in the diagnosis of malignant pericardial fluid. Pericardioscopy (not widely available) with targeted pericardial and epicardial biopsy may differentiate



A B C

FIGURE 56-1
Superior vena cava syndrome (SVCS). A. Chest radiographs of a 59-year-old man with recurrent SVCS caused by non-small-cell lung cancer showing right paratracheal mass with right pleural effusion. B. Computed tomography of same patient demonstrating obstruction of the superior vena cava with thrombosis (arrow) by the lung cancer (square) and collaterals (arrowheads). C. Balloon angioplasty (arrowhead) with Wallstent (arrow) in same patient.

neoplastic and benign pericardial disease. A combination of cytology, pericardial and epicardial biopsy, and guided pericardioscopy gives the best diagnostic yield. CT scan findings of irregular pericardial thickening and mediastinal lymphadenopathy suggest this is a malignant pericardial effusion. Cancer patients with pericardial effusion containing malignant cells on cytology have a very poor survival, about 7 weeks.

TREATMENT Pericardial Effusion/Tamponade

Pericardiocentesis with or without the introduction of sclerosing agents, the creation of a pericardial window, complete pericardial stripping, cardiac irradiation, or systemic chemotherapy are effective treatments. Acute pericardial tamponade with life-threatening hemodynamic instability requires immediate drainage of fluid. This can be quickly achieved by pericardiocentesis. The recurrence rate after percutaneous catheter drainage is about 20%. Sclerotherapy (pericardial instillation of bleomycin, mitomycin C, or tetracycline) may decrease recurrences. Alternatively, subxiphoid pericardiotomy can be performed in 45 min under local anesthesia. Thoracoscopic pericardial fenestration can be employed for benign causes; however, 60% of malignant pericardial effusions recur after this procedure. In a subset of patients, drainage of the pericardial effusion is paradoxically followed by worsening hemodynamic instability. This is so-called "postoperative low cardiac output syndrome" occurs in up to 10% of patients undergoing surgical drainage and carries poor short-term survival.

INTESTINAL OBSTRUCTION

Intestinal obstruction and reobstruction are common problems in patients with advanced cancer, particularly colorectal or ovarian carcinoma. However, other cancers, such as lung or breast cancer and melanoma, can metastasize within the abdomen, leading to intestinal obstruction. Metastatic disease from colorectal, ovarian, pancreatic, gastric, and occasionally breast cancer can lead to peritoneal carcinomatosis, with infiltration of the omentum and peritoneal surface, thus limiting bowel motility. Typically, obstruction occurs at multiple sites in peritoneal carcinomatosis. Melanoma has a predilection to involve the small bowel; this involvement may be isolated, and resection may result in prolonged survival. Intestinal pseudoobstruction is caused by infiltration of the mesentery or bowel muscle by tumor, involvement of the celiac plexus, or paraneoplastic neuropathy in patients with small-cell lung cancer. Paraneoplastic neuropathy is associated with IgG antibodies reactive to neurons of the myenteric and submucosal plexuses of the jejunum and stomach. Ovarian cancer can lead to authentic luminal obstruction or to pseudoobstruction that results when circumferential invasion of a bowel segment arrests the forward progression of peristaltic contractions.

T e onset of obstruction is usually insidious. Pain is the most common symptom and is usually colicky in nature. Pain can also be due to abdominal distention, tumor masses, or hepatomegaly. Vomiting can be intermittent or continuous. Patients with complete obstruction usually have constipation. Physical examination may reveal abdominal distention with tympany, ascites, visible peristalsis, high-pitched bowel sounds, and tumor masses. Erect plain abdominal films may reveal multiple air-fluid levels and dilation of the small or large bowel. Acute cecal dilation to >12–14 cm is considered a surgical emergency because of the high likelihood of rupture. CT scan is useful in defining the extent of disease and the exact nature of the obstruction and differentiating benign from malignant causes of obstruction in patients who have undergone surgery for malignancy. Malignant obstruction is suggested by a mass at the site of obstruction or prior surgery, adenopathy, or an abrupt transition zone and irregular bowel thickening at the obstruction site. Benign obstruction is more likely when CT shows mesenteric vascular changes, a large volume of ascites, or a smooth transition zone and smooth bowel thickening at the obstruction site. In challenging patients with obstructive symptoms, particularly low-grade small-bowel obstruction (SBO), CT enteroclysis often can help establish the diagnosis by providing distention of small-bowel loops. In this technique, water-soluble contrast is infused through a nasoenteric tube into the duodenum or proximal small bowel followed by CT images. T e prognosis for the patient with cancer who develops intestinal obstruction is poor; median survival is 3–4 months. About 25–30% of patients are found to have intestinal obstruction due to causes other than cancer. Adhesions from previous operations are a common benign cause. Ileus induced by vinca alkaloids, narcotics, or other drugs is another reversible cause.

TREATMENT Intestinal Obstruction

T e management of intestinal obstruction in patients with advanced malignancy depends on the extent of the underlying malignancy, options for further antineoplastic therapy, estimated life expectancy, the functional status of the major organs, and the extent of the obstruction. T e initial management should include surgical evaluation. Operation is not always successful and may lead to further complications with a substantial mortality rate (10–20%). Laparoscopy can diagnose and treat malignant bowel obstruction in some cases. Self-expanding metal stents placed in the gastric outlet, duodenum, proximal jejunum, colon, or rectum may palliate obstructive symptoms at those sites without major surgery. Patients known to have advanced intraabdominal malignancy should receive a prolonged course of conservative management, including nasogastric decompression. Percutaneous endoscopic or surgical gastrostomy tube placement is an option for palliation of nausea and vomiting, the so-called "venting gastrostomy." Treatment with antiemetics, antispasmodics, and analgesics may allow patients to remain outside the hospital. Octreotide may relieve obstructive symptoms through its inhibitory effect on gastrointestinal secretion. Glucocorticoids have anti-inflammatory effects and may help the resolution of bowel obstruction. T ey also have antiemetic effects.

URINARY OBSTRUCTION

Urinary obstruction may occur in patients with prostatic or gynecologic malignancies, particularly cervical carcinoma; metastatic disease from other primary sites such as carcinomas of the breast, stomach, lung, colon, and pancreas; or lymphomas. Radiation therapy to pelvic tumors may cause fibrosis and subsequent ureteral obstruction. Bladder outlet obstruction is usually due to prostate and cervical cancers and may lead to bilateral hydronephrosis and renal failure.

Flank pain is the most common symptom. Persistent urinary tract infection, persistent proteinuria, or hematuria in patients with cancer should raise suspicion of ureteral obstruction. Total anuria and/or anuria alternating with polyuria may occur. A slow, continuous rise in the serum creatinine level necessitates immediate evaluation. Renal ultrasound is the safest and cheapest way to identify hydronephrosis. T e function of an

obstructed kidney can be evaluated by a nuclear scan. CT scan can reveal the point of obstruction and identify a retroperitoneal mass or adenopathy.

TREATMENT Urinary Obstruction

Obstruction associated with flank pain, sepsis, or fistula formation is an indication for immediate palliative urinary diversion. Internal ureteral stents can be placed under local anesthesia. Percutaneous nephrostomy offers an alternative approach for drainage. The placement of a nephrostomy is associated with a significant rate of pyelonephritis. In the case of bladder outlet obstruction due to malignancy, a suprapubic cystostomy can be used for urinary drainage. An aggressive intervention with invasive approaches to improve the obstruction should be weighed against the likelihood of antitumor response, and the ability to reverse renal insufficiency should be evaluated.

MALIGNANT BILIARY OBSTRUCTION

This is common clinical problem can be caused by a primary carcinoma arising in the pancreas, ampulla of Vater, bile duct, or liver or by metastatic disease to the periductal lymph nodes or liver parenchyma. The most common metastatic tumors causing biliary obstruction are gastric, colon, breast, and lung cancers. Jaundice, light-colored stools, dark urine, pruritus, and weight loss due to malabsorption are usual symptoms. Pain and secondary infection are uncommon in malignant biliary obstruction. Ultrasound, CT scan, or percutaneous transhepatic or endoscopic retrograde cholangiography will identify the site and nature of the biliary obstruction.

TREATMENT Malignant Biliary Obstruction

Palliative intervention is indicated only in patients with disabling pruritus resistant to medical treatment, severe malabsorption, or infection. Stenting under radiographic control, surgical bypass, or radiation therapy with or without chemotherapy may alleviate the obstruction. The choice of therapy should be based on the site of obstruction (proximal vs distal), the type of tumor (sensitive to radiotherapy, chemotherapy, or neither), and the general condition of the patient. In the absence of pruritus, biliary obstruction may be a largely asymptomatic cause of death.

SPINAL CORD COMPRESSION

Malignant spinal cord compression (MSCC) is defined as compression of the spinal cord and/or cauda equina by an extradural tumor mass. The minimum radiologic evidence for cord compression is indentation of the theca at the level of clinical features. Spinal cord compression occurs in 5–10% of patients with cancer. Epidural tumor is the first manifestation of malignancy in about 10% of patients. The underlying cancer is usually identified during the initial evaluation; lung cancer is the most common cause of MSCC.

Metastatic tumor involves the vertebral column more often than any other part of the bony skeleton. Lung, breast, and prostate cancer are the most frequent offenders. Multiple myeloma also has a high incidence of spine involvement. Lymphomas, melanoma, renal cell cancer, and genitourinary cancers also cause cord compression. The thoracic spine is the most common site (70%), followed by the lumbosacral spine (20%) and the cervical spine (10%). Involvement of multiple sites is most frequent in patients with breast and prostate carcinoma. Cord injury develops when metastases to the vertebral body or pedicle enlarge and compress the underlying dura. Another cause of cord compression is direct extension of a paravertebral lesion through the intervertebral foramen. These cases usually involve a lymphoma, myeloma, or pediatric neoplasm. Parenchymal spinal cord metastasis due to hematogenous spread is rare. Intramedullary metastases can be seen in lung cancer, breast cancer, renal cancer, melanoma, and lymphoma and are frequently associated with brain metastases and leptomeningeal disease.

Expanding extradural tumors induce injury through several mechanisms. Obstruction of the epidural venous plexus leads to edema. Local production of inflammatory cytokines enhances blood flow and edema formation. Compression compromises blood flow, leading to ischemia. Production of vascular endothelial growth factor is associated with spinal cord hypoxia and has been implicated as a potential cause of damage after spinal cord injury.

The most common initial symptom in patients with spinal cord compression is localized back pain and tenderness due to involvement of vertebrae by tumor. Pain is usually present for days or months before other neurologic findings appear. It is exacerbated by movement and by coughing or sneezing. It can be differentiated from the pain of disk disease by the fact that it worsens when the patient is supine. Radicular pain is less common than localized back pain and usually develops later. Radicular pain in the cervical or lumbosacral areas may be unilateral or bilateral. Radicular pain from the thoracic roots is often bilateral and is described by patients as a feeling of tight, band-like constriction around the thorax and abdomen. Typical cervical radicular pain radiates down the arm; in the lumbar region, the radiation is down the legs. Lhermitte's sign, a tingling or electric sensation down the back and upper and lower limbs upon flexing or extending the neck, may be an early sign of cord

compression. Loss of bowel or bladder control may be the presenting symptom but usually occurs late in the course. Occasionally patients present with ataxia of gait without motor and sensory involvement due to involvement of the spinocerebellar tract.

On physical examination, pain induced by straight leg raising, neck flexion, or vertebral percussion may help to determine the level of cord compression. Patients develop numbness and paresthesias in the extremities or trunk. Loss of sensibility to pinprick is as common as loss of sensibility to vibration or position. The upper limit of the zone of sensory loss is often one or two vertebrae below the site of compression. Motor findings include weakness, spasticity, and abnormal muscle stretching. An extensor plantar reflex reflects significant compression. Deep tendon reflexes may be brisk. Motor and sensory loss usually precedes sphincter disturbance. Patients with autonomic dysfunction may present with decreased anal tonus, decreased perineal sensibility, and a distended bladder. The absence of the anal wink reflex or the bulbocavernosus reflex confirms cord involvement. In doubtful cases, evaluation of postvoiding urinary residual volume can be helpful. A residual volume of >150 mL suggests bladder dysfunction. Autonomic dysfunction is an unfavorable prognostic factor. Patients with progressive neurologic symptoms should have frequent neurologic examinations and rapid therapeutic intervention. Other illnesses that may mimic cord compression include osteoporotic vertebral collapse, disk disease, pyogenic abscess or vertebral tuberculosis, radiation myelopathy, neoplastic leptomeningitis, benign tumors, epidural hematoma, and spinal lipomatosis.

Cauda equina syndrome is characterized by low back pain; diminished sensation over the buttocks, posterior-superior thighs, and perineal area in a saddle distribution; rectal and bladder dysfunction; sexual impotence; absent bulbocavernous, patellar, and Achilles' reflexes; and variable amount of lower-extremity weakness. This reflects compression of nerve roots as they form the cauda equina after leaving the spinal cord. The majority of cauda equine tumors are primary tumors of glial or nerve sheath origin; metastases are very rare.

Patients with cancer who develop back pain should be evaluated for spinal cord compression as quickly as possible **(Fig. 56-2)**. Treatment is more often successful in patients who are ambulatory and still have sphincter control at the time treatment is initiated. Patients should have a neurologic examination and plain films of the spine. Those whose physical examination suggests cord compression should receive dexamethasone (6 mg intravenously every 6 h), starting immediately.

Erosion of the pedicles (the "winking owl" sign) is the earliest radiologic finding of vertebral tumor. Other radiographic changes include increased intrapedicular distance, vertebral destruction, lytic or sclerotic lesions, scalloped vertebral bodies, and vertebral body collapse. Vertebral collapse is not a reliable indicator of the presence of tumor; about 20% of cases of vertebral collapse, particularly those in older patients and postmenopausal women, are due not to cancer but to osteoporosis. Also, a normal appearance on plain films of the spine does not exclude the diagnosis of cancer. The role of bone scans in the detection of cord compression is not clear; this method is sensitive but less specific than spinal radiography.

The full-length image of the cord provided by MRI is the imaging procedure of choice. Multiple epidural metastases are noted in 25% of patients with cord compression, and their presence influences treatment plans. On T1-weighted images, good contrast is noted between the cord, cerebrospinal fluid, and extradural lesions. Owing to its sensitivity in demonstrating the replacement of bone marrow by tumor, MRI can show which parts of a vertebra are involved by tumor. MRI also visualizes intraspinal extradural masses compressing the cord. T2-weighted images are most useful for the demonstration of intramedullary pathology. Gadolinium-enhanced MRI can help to delineate intramedullary disease. MRI is as good as or better than myelography plus postmyelogram CT scan in detecting metastatic epidural disease with cord compression. Myelography should be reserved for patients who have poor MRIs or who cannot undergo MRI promptly. CT scan in conjunction with myelography enhances the detection of small areas of spinal destruction.

In patients with cord compression and an unknown primary tumor, a simple workup including chest radiography, mammography, measurement of prostate-specific antigen, and abdominal CT usually reveals the underlying malignancy.

TREATMENT Spinal Cord Compression

The treatment of patients with spinal cord compression is aimed at relief of pain and restoration/preservation of neurologic function (Fig. 56-2). Management of MSCC requires a multidisciplinary approach.

Radiation therapy plus glucocorticoids is generally the initial treatment of choice for most patients with spinal cord compression. Up to 75% of patients treated when still ambulatory remain ambulatory, but only 10% of patients with paraplegia recover walking capacity. Indications for surgical intervention include unknown etiology, failure of radiation therapy, a radioresistant tumor type (e.g., melanoma or renal cell cancer), pathologic fracture dislocation, and rapidly evolving neurologic symptoms. Laminectomy is done for tissue diagnosis and for the removal of posteriorly localized epidural deposits in the absence of vertebral body disease. Because most cases of epidural spinal cord compression are

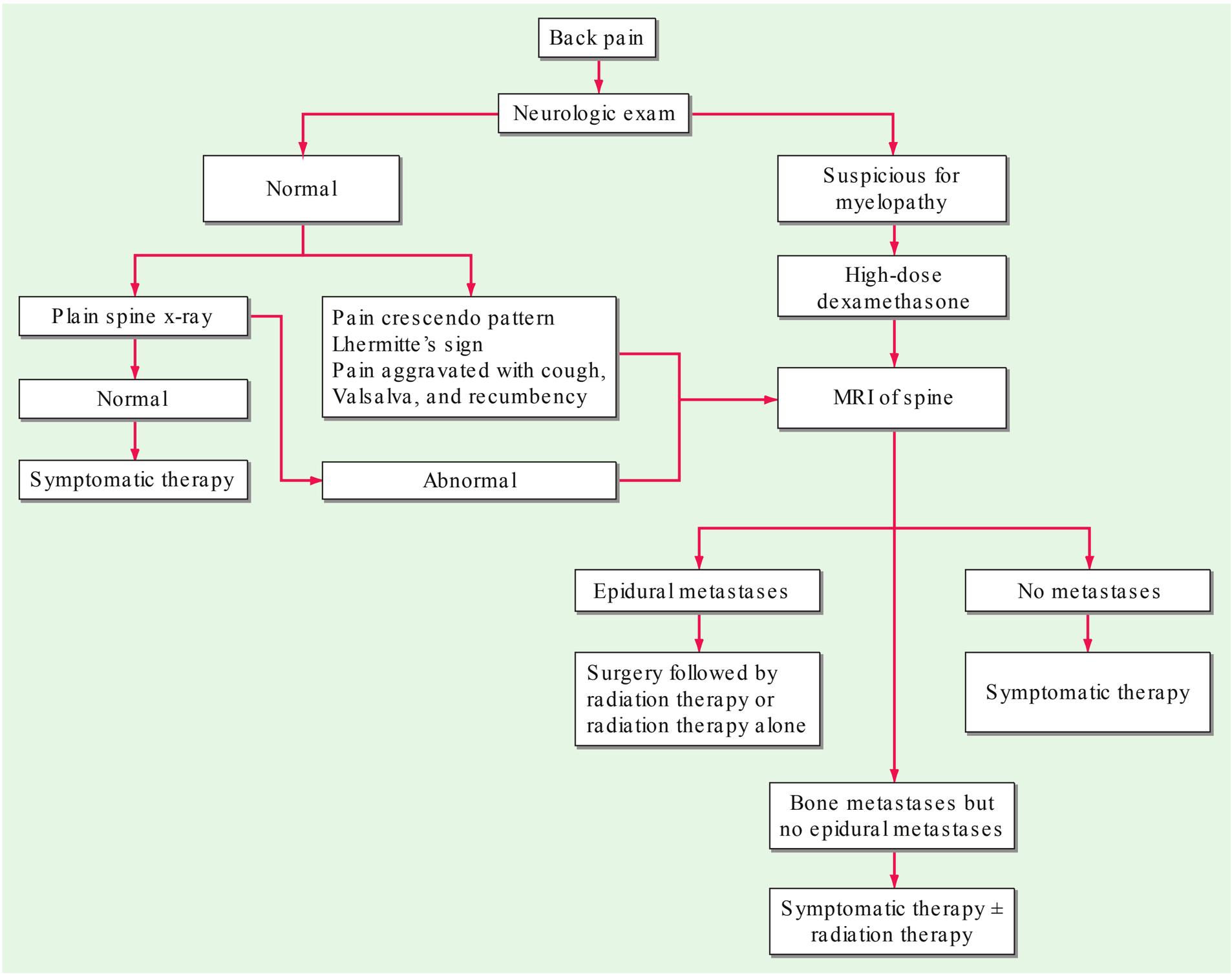


FIGURE 56-2
Management of cancer patients with back pain.

due to anterior or anterolateral extradural disease, resection of the anterior vertebral body along with the tumor, followed by spinal stabilization, has achieved good results. A randomized trial showed that patients who underwent an operation followed by radiotherapy (within 14 days) retained the ability to walk significantly longer than those treated with radiotherapy alone. Surgically treated patients also maintained continence and neurologic function significantly longer than patients in the radiation group. T e length of survival was not significantly different in the two groups, although there was a trend toward longer survival in the surgery group. T e study drew some criticism for the poorer than expected results in the patients who did not go to surgery. T e benefit of surgery over radiotherapy decreased in patients over age 65 years. However, patients should be evaluated for surgery if they are expected to survive longer than 3 months. Conventional radiotherapy has a role after surgery. Chemotherapy may have a role in patients with chemosensitive tumors who have had prior radiotherapy to the same region and who are not candidates for surgery. Most patients with prostate cancer who develop cord compression have already had hormonal therapy; however, for those who have not, androgen deprivation is combined with surgery and radiotherapy. Patients who previously received radiotherapy for MSCC with an in-field tumor progression can be treated with reirradiation if they are not surgical candidates.

Patients with metastatic vertebral tumors may benefit from percutaneous vertebroplasty or kyphoplasty, the injection of acrylic cement into a collapsed vertebra to stabilize the fracture. Pain palliation is common, and local antitumor effects have been noted. Cement leakage may cause symptoms in about 10% of patients. Bisphosphonates may be helpful in prevention of SCC in patients with bony involvement.

T e histology of the tumor is an important determinant of both recovery and survival. Rapid onset and progression of signs and symptoms are poor prognostic features.

INCREASED INTRACRANIAL PRESSURE

About 25% of patients with cancer die with intracranial metastases. T e cancers that most often metastasize to the brain are lung and breast cancers and melanoma. Brain metastases often occur in the presence of systemic disease, and they frequently cause major symptoms, disability, and early death. T e initial presentation of brain metastases from a previously

unknown primary cancer is common. Lung cancer is most commonly the primary malignancy. Chest/abdomen CT scans and brain MRI as the initial diagnostic studies can identify a biopsy site in most patients.

The signs and symptoms of a metastatic brain tumor are similar to those of other intracranial expanding lesions: headache, nausea, vomiting, behavioral changes, seizures, and focal, progressive neurologic changes. Occasionally the onset is abrupt, resembling a stroke, with the sudden appearance of headache, nausea, vomiting, and neurologic deficits. This picture is usually due to hemorrhage into the metastasis. Melanoma, germ cell tumors, and renal cell cancers have a particularly high incidence of intracranial bleeding. The tumor mass and surrounding edema may cause obstruction of the circulation of cerebrospinal fluid, with resulting hydrocephalus. Patients with increased intracranial pressure may have papilledema with visual disturbances and neck stiffness. As the mass enlarges, brain tissue may be displaced through the fixed cranial openings, producing various herniation syndromes.

CT scan and MRI are equally effective in the diagnosis of brain metastases. CT scan with contrast should be used as a screening procedure. The CT scan shows brain metastases as multiple enhancing lesions of various sizes with surrounding areas of low-density edema. If a single lesion or no metastases are visualized by contrast-enhanced CT, MRI of the brain should be performed. Gadolinium-enhanced MRI is more sensitive than CT at revealing meningeal involvement and small lesions, particularly in the brainstem or cerebellum.

Intracranial hypertension ("pseudotumor cerebri") secondary to tretinoin therapy has been reported.

TREATMENT Increased Intracranial Pressure

Dexamethasone is the best initial treatment for all symptomatic patients with brain metastases. Patients with multiple lesions should usually receive whole-brain radiation. Patients with a single brain metastasis and with controlled extracranial disease may be treated with surgical excision followed by whole-brain radiation therapy, especially if they are younger than 60 years. Radioresistant tumors should be resected if possible. Stereotactic radiosurgery (SRS) is recommended in patients with a limited number of brain metastases (one to four) who have stable, systemic disease or reasonable systemic treatment options and for patients who have a small number of metastatic lesions in whom whole-brain radiation therapy has failed. With a gamma knife or linear accelerator, multiple small, well-collimated beams of ionizing radiation destroy lesions seen on MRI. Some patients with increased intracranial pressure associated with hydrocephalus may benefit from shunt placement. If neurologic deterioration is not reversed with medical therapy, ventriculotomy to remove cerebrospinal fluid (CSF) or craniotomy to remove tumors or hematomas may be necessary.

NEOPLASTIC MENINGITIS

Tumor involving the leptomeninges is a complication of both primary central nervous system (CNS) tumors and tumors that metastasize to the CNS. The incidence is estimated at 3–8% of patients with cancer. Melanoma, breast and lung cancer, lymphoma (including AIDS-associated), and acute leukemia are the most common causes. Synchronous intraparenchymal brain metastases are evident in 11–31% of patients with neoplastic meningitis. Leptomeningeal seeding is frequent in patients undergoing resection of brain metastases or receiving stereotactic radiotherapy for brain metastases.

Patients typically present with multifocal neurologic signs and symptoms, including headache, gait abnormality, mental changes, nausea, vomiting, seizures, back or radicular pain, and limb weakness. Signs include cranial nerve palsies, extremity weakness, paresthesia, and decreased deep tendon reflexes.

Diagnosis is made by demonstrating malignant cells in the CSF; however, up to 40% of patients may have false-negative CSF cytology. An elevated CSF protein level is nearly always present (except in HTLV-1–associated adult T cell leukemia). Patients with neurologic signs and symptoms consistent with neoplastic meningitis who have a negative CSF cytology but an elevated CSF protein level should have the spinal tap repeated at least three times for cytologic examination before the diagnosis is rejected. MRI findings suggestive of neoplastic meningitis include leptomeningeal, subependymal, dural, or cranial nerve enhancement; superficial cerebral lesions; intradural nodules; and communicating hydrocephalus. Spinal cord imaging by MRI is a necessary component of the evaluation of nonleukemia neoplastic meningitis because ~20% of patients have cord abnormalities, including intradural enhancing nodules that are diagnostic for leptomeningeal involvement. Cauda equina lesions are common, but lesions may be seen anywhere in the spinal canal. The value of MRI for the diagnosis of leptomeningeal disease is limited in patients with hematopoietic malignancy. Radiolabeled CSF flow studies are abnormal in up to 70% of patients with neoplastic meningitis; ventricular outlet obstruction, abnormal flow in the spinal canal, or impaired flow over the cerebral convexities may affect distribution of intrathecal chemotherapy, resulting in decreased efficacy or increased toxicity. Radiation therapy may correct CSF flow abnormalities before use of intrathecal chemotherapy. Neoplastic meningitis can also lead to intracranial hypertension and hydrocephalus.

Placement of a ventriculoperitoneal shunt may effectively palliate symptoms in these patients.

The development of neoplastic meningitis usually occurs in the setting of uncontrolled cancer outside the CNS; thus, prognosis is poor (median survival 10–12 weeks). However, treatment of the neoplastic meningitis may successfully alleviate symptoms and control the CNS spread.

TREATMENT Neoplastic Meningitis

Intrathecal chemotherapy, usually methotrexate, cytarabine, or thiotepa, is delivered by lumbar puncture or by an intraventricular reservoir (Ommaya). An extended-release preparation of cytarabine (Depocyte) has a longer half-life and is more effective than other formulations. Among solid tumors, breast cancer responds best to therapy. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) may be effective in non-small-cell lung cancer patients with EGFR mutations and leptomeningeal involvement. Patients with neoplastic meningitis from either acute leukemia or lymphoma may be cured of their CNS disease if the systemic disease can be eliminated.

SEIZURES

Seizures occurring in a patient with cancer can be caused by the tumor itself, by metabolic disturbances, by radiation injury, by cerebral infarctions, by chemotherapy-related encephalopathies, or by CNS infections. Metastatic disease to the CNS is the most common cause of seizures in patients with cancer. However, seizures occur more frequently in primary brain tumors than in metastatic brain lesions. Seizures are a presenting symptom of CNS metastasis in 6–29% of cases. Approximately 10% of patients with CNS metastasis eventually develop seizures. Tumors that affect the frontal, temporal, and parietal lobes are more commonly associated with seizures than are occipital lesions. The presence of frontal lesions correlates with early seizures, and the presence of hemispheric symptoms increases the risk for late seizures. Both early and late seizures are uncommon in patients with posterior fossa and sellar lesions. Seizures are common in patients with CNS metastases from melanoma and low-grade primary brain tumors. Very rarely, cytotoxic drugs such as etoposide, busulfan, ifosfamide, and chlorambucil cause seizures. Another cause of seizures related to drug therapy is reversible posterior leukoencephalopathy syndrome (RPLS). RPLS is associated rarely with administration of cisplatin, 5-fluorouracil, bleomycin, vinblastine, vincristine, etoposide, paclitaxel, ifosfamide, cyclophosphamide, doxorubicin, cytarabine, methotrexate, oxaliplatin, cyclosporine, tacrolimus, and vascular endothelial growth factor inhibitors including bevacizumab, aflibercept, sunitinib, sorafenib, pazopanib, and axitinib. RPLS occurs in patients undergoing allogeneic bone marrow or solid-organ transplantation. RPLS is characterized by headache, altered consciousness, generalized seizures, visual disturbances, hypertension, and posterior cerebral white matter vasogenic edema on CT/MRI. Seizures may begin focally but are typically generalized.

TREATMENT Seizures

Patients in whom seizures due to CNS metastases have been demonstrated should receive anticonvulsive treatment with phenytoin or levetiracetam. If this is not effective, valproic acid can be added. Prophylactic anticonvulsant therapy is not recommended. In postcraniotomy patients, prophylactic antiepileptic drugs should be withdrawn during the first week after surgery. Most antiseizure medications including phenytoin induce cytochrome P450 (CYP450), which alters the metabolism of many antitumor agents, including irinotecan, taxanes, and etoposide as well as molecular targeted agents, including imatinib, gefitinib, erlotinib, tipifarnib, sorafenib, sunitinib, temsirolimus, everolimus, and vemurafenib. Levetiracetam and topiramate are anticonvulsant agents not metabolized by the hepatic CYP450 system and do not alter the metabolism of antitumor agents. They have become the preferred drugs. Surgical resection and other antitumor treatments such as radiotherapy and chemotherapy may improve seizure control.

PULMONARY AND INTRACEREBRAL LEUKOSTASIS

Hyperleukocytosis and the leukostasis syndrome associated with it is a potentially fatal complication of acute leukemia (particularly myeloid leukemia) that can occur when the peripheral blast cell count is >100,000/mL. The frequency of hyperleukocytosis is 5–13% in acute myeloid leukemia (AML) and 10–30% in acute lymphoid leukemia; however, leukostasis is rare in lymphoid leukemia. At such high blast cell counts, blood viscosity is increased, blood flow is slowed by aggregates of tumor cells, and the primitive myeloid leukemic cells are capable of invading through the endothelium and causing hemorrhage. Brain and lung are most commonly affected. Patients with brain leukostasis may experience stupor, headache, dizziness, tinnitus, visual disturbances, ataxia, confusion, coma, or sudden death. On examination, papilledema, retinal vein distension, retinal hemorrhages, and focal deficit may be present. Administration of 600 cGy of whole-brain irradiation can protect against this complication and can be followed by rapid institution of antileukemic

therapy. Hydroxyurea, 3–5 g, can rapidly reduce a high blast cell count while the accurate diagnostic workup is in progress. Pulmonary leukostasis may present as respiratory distress and hypoxemia, and progress to respiratory failure. Chest radiographs may be normal but usually show interstitial or alveolar infiltrates. Hyperleukocytosis rarely may cause acute leg ischemia, renal vein thrombosis, myocardial ischemia, bowel infraction, and priapism. Arterial blood gas results should be interpreted cautiously. Rapid consumption of plasma oxygen by the markedly increased number of white blood cells can cause spuriously low arterial oxygen tension. Pulse oximetry is the most accurate way of assessing oxygenation in patients with hyperleukocytosis. Leukapheresis may be helpful in decreasing circulating blast counts. Treatment of the leukemia can result in pulmonary hemorrhage from lysis of blasts in the lung, called leukemic cell lysis pneumopathy. Intravascular volume depletion and unnecessary blood transfusions may increase blood viscosity and worsen the leukostasis syndrome. Leukostasis is very rarely a feature of the high white cell counts associated with chronic lymphoid or chronic myeloid leukemia.

When acute promyelocytic leukemia is treated with differentiating agents like tretinoin and arsenic trioxide, cerebral or pulmonary leukostasis may occur as tumor cells differentiate into mature neutrophils. T is complication can be largely avoided by using cytotoxic chemotherapy or arsenic together with the differentiating agents.

HEMOPTYSIS

Hemoptysis may be caused by nonmalignant conditions, but lung cancer accounts for a large proportion of cases. Up to 20% of patients with lung cancer have hemoptysis some time in their course. Endobronchial metastases from carcinoid tumors, breast cancer, colon cancer, kidney cancer, and melanoma may also cause hemoptysis. T e volume of bleeding is often dif cult to gauge. Massive hemoptysis is defined as >200–600 mL of blood produced in 24 h. However, any hemoptysis should be considered massive if it threatens life. When respiratory dif culty occurs, hemoptysis should be treated emergently. T e first priorities are to maintain the airway, optimize oxygenation, and stabilize the hemodynamic status. If the bleeding side is known, the patient should be placed in a lateral decubitus position, with the bleeding side down to prevent aspiration into the unaffected lung, and given supplemental oxygen. If large-volume bleeding continues or the airway is compromised, the patient should be intubated and undergo emergency bronchoscopy. If the site of bleeding is detected, either the patient undergoes a definitive surgical procedure or the lesion is treated with a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, argon plasma coagulation, or electrocautery. In stable patients, multidetector CT angiography delineates bronchial and nonbronchial systemic arteries and identifies the source of bleeding and underlying pathology with high sensitivity. Massive hemoptysis usually originates from the high-pressure bronchial circulation. Bronchial artery embolization is considered a first-line definite procedure for managing hemoptysis. Bronchial artery embolization may control brisk bleeding in 75–90% of patients, permitting the definitive surgical procedure to be done more safely.

Embolization without definitive surgery is associated with rebleeding in 20–50% of patients. Recurrent hemoptysis usually responds to a second embolization procedure. A postembolization syndrome characterized by pleuritic pain, fever, dysphagia, and leukocytosis may occur; it lasts 5–7 days and resolves with symptomatic treatment. Bronchial or esophageal wall necrosis, myocardial infarction, and spinal cord infarction are rare complications. Surgery, as a salvage strategy, is indicated after failure of embolization and is associated with better survival when performed in a nonurgent setting.

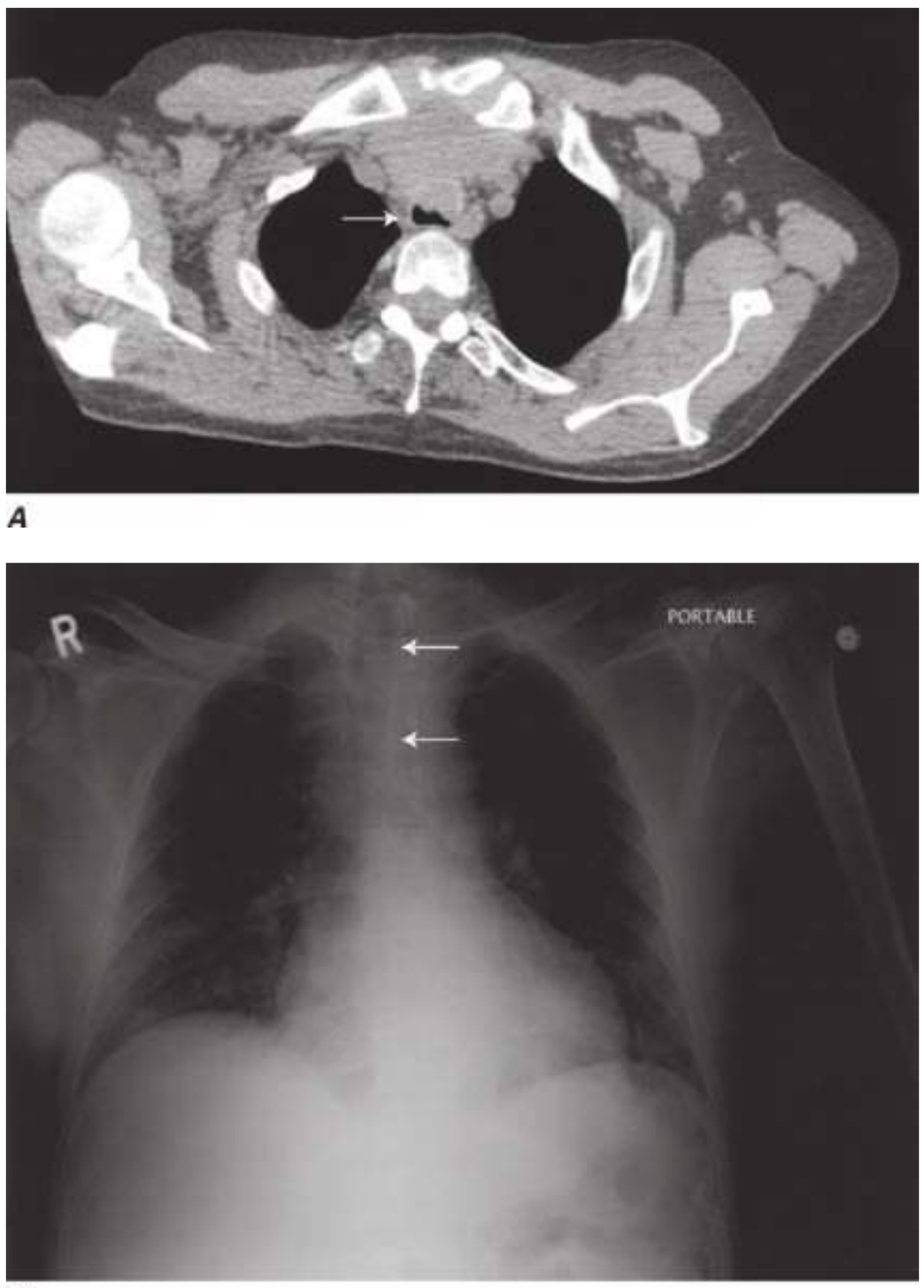
Pulmonary hemorrhage with or without hemoptysis in hematologic malignancies is often associated with fungal infections, particularly Aspergillus sp. After granulocytopenia resolves, the lung infiltrates in aspergillosis may cavitate and cause massive hemoptysis. T rombocytopenia and coagulation defects should be corrected, if possible. Surgical evaluation is recommended in patients with aspergillosis-related cavitary lesions.

Bevacizumab, an antibody to vascular endothelial growth factor (VEGF) that inhibits angiogenesis, has been associated with life-threatening hemoptysis in patients with non-small-cell lung cancer, particularly of squamous cell histology. Non-small-cell lung cancer patients with cavitary lesions or previous hemoptysis (≥2.5 mL) within the past 3 months have higher risk for pulmonary hemorrhage.

AIRWAY OBSTRUCTION

Airway obstruction refers to a blockage at the level of the mainstem bronchi or above. It may result either from intraluminal tumor growth or from extrinsic compression of the airway. T e most common cause of malignant upper airway obstruction is invasion from an adjacent primary tumor, most commonly lung cancer, followed by esophageal, thyroid, and mediastinal malignancies including lymphomas. Extrathoracic primary tumors such as renal, colon, or breast cancer can cause airway obstruction through endobronchial and/or mediastinal lymph node metastases. Patients

may present with dyspnea, hemoptysis, stridor, wheezing, intractable cough, postobstructive pneumonia, or hoarseness. Chest radiographs usually demonstrate obstructing lesions. CT scans reveal the extent of tumor. Cool, humidified oxygen, glucocorticoids, and ventilation with a mixture of helium and oxygen (Heliox) may provide temporary relief. If the obstruction is proximal to the larynx, a tracheostomy may be lifesaving. For more distal obstructions, particularly intrinsic lesions incompletely obstructing the airway, bronchoscopy with mechanical debulking and dilatation or ablational treatments including laser treatment, photodynamic therapy, argon plasma coagulation, electrocautery, or stenting can produce immediate relief in most patients **(Fig. 56-3)**. However, radiation therapy (either external-beam irradiation or brachytherapy) given together with glucocorticoids may also open the airway. Symptomatic extrinsic compression may be palliated by stenting. Patients with primary airway tumors such as squamous cell carcinoma, carcinoid tumor, adenocystic carcinoma, or non-small-cell lung cancer, if resectable, should have surgery.



A

B

FIGURE 56-3
Airway obstruction. A. Computed tomography scan of a 62-year-old man with tracheal obstruction caused by renal carcinoma showing paratracheal mass with tracheal invasion/obstruction (arrow). B. Chest x-ray of same patient after stent (arrows) placement.

METABOLIC EMERGENCIES

HYPERCALCEMIA

Hypercalcemia is the most common paraneoplastic syndrome. **Its pathogenesis and management are discussed fully in Chap. 54.**

SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH)

Hyponatremia is a common electrolyte abnormality in cancer patients, and SIADH is the most common cause among patients with cancer. **SIADH is discussed fully in Chap. 54.**

LACTIC ACIDOSIS

Lactic acidosis is a rare and potentially fatal metabolic complication of cancer. Lactic acidosis associated with sepsis and circulatory failure is a common preterminal event in many malignancies. Lactic acidosis in the absence of hypoxemia may occur in patients with leukemia, lymphoma, or solid tumors. In some cases, hypoglycemia also is present. Extensive involvement of the liver by tumor is often present. In most cases, decreased metabolism and increased production by the tumor both contribute to lactate accumulation. Tumor cell overexpression of certain glycolytic enzymes and mitochondrial dysfunction can contribute to its increased lactate production. HIV-infected patients have an increased risk of aggressive lymphoma; lactic acidosis that occurs in such patients may be related either to the rapid growth of the tumor or from toxicity of nucleoside reverse transcriptase inhibitors. Symptoms of lactic acidosis include tachypnea, tachycardia, change of mental status, and hepatomegaly. T e serum level of lactic acid may reach 10–20 mmol/L (90–180 mg/dL). Treatment is aimed at the underlying disease. T e danger *f*rom lactic acidosis is *f*rom the acidosis, not the lactate. Sodium bicarbonate should be added if acidosis is very severe or if hydrogen ion production is very rapid and uncontrolled. Other treatment options include renal replacement therapy, such as hemodialysis, and thiamine replacement. T e prognosis is poor regardless of the treatment offered.

HYPOGLYCEMIA

Persistent hypoglycemia is occasionally associated with tumors other than pancreatic islet cell tumors.

Usually these tumors are large; tumors of mesenchymal origin, hepatomas, or adrenocortical tumors may cause hypoglycemia. Mesenchymal tumors are usually located in the retroperitoneum or thorax. Obtundation, confusion, and behavioral aberrations occur in the postabsorptive period and may precede the diagnosis of the tumor. These tumors often secrete incompletely processed insulin-like growth factor II (IGF-II), a hormone capable of activating insulin receptors and causing hypoglycemia. Tumors secreting incompletely processed big IGF-II are characterized by an increased IGF-II to IGF-I ratio, suppressed insulin and C-peptide level, and inappropriately low growth hormone and β-hydroxybutyrate concentrations. Rarely, hypoglycemia is due to insulin secretion by a non-islet cell carcinoma. The development of hepatic dysfunction from liver metastases and increased glucose consumption by the tumor can contribute to hypoglycemia. If the tumor cannot be resected, hypoglycemia symptoms may be relieved by the administration of glucose, glucocorticoids, or glucagon.

Hypoglycemia can be artifactual; hyperleukocytosis from leukemia, myeloproliferative diseases, leukemoid reactions, or colony-stimulating factor treatment can increase glucose consumption in the test tube after blood is drawn, leading to pseudohypoglycemia.

ADRENAL INSUFFICIENCY

In patients with cancer, adrenal insufficiency may go unrecognized because the symptoms, such as nausea, vomiting, anorexia, and orthostatic hypotension, are nonspecific and may be mistakenly attributed to progressive cancer or to therapy. Primary adrenal insufficiency may develop owing to replacement of both glands by metastases (lung, breast, colon, or kidney cancer; lymphoma), to removal of both glands, or to hemorrhagic necrosis in association with sepsis or anticoagulation. Impaired adrenal steroid synthesis occurs in patients being treated for cancer with mitotane, ketoconazole, or aminoglutethimide or undergoing rapid reduction in glucocorticoid therapy. Rarely, metastatic replacement causes primary adrenal insufficiency as the first manifestation of an occult malignancy. Metastasis to the pituitary or hypothalamus is found at autopsy in up to 5% of patients with cancer, but associated secondary adrenal insufficiency is rare. On the other hand, ipilimumab, an anti-CTLA-4 antibody used for treatment of malignant melanoma, may cause autoimmunity including autoimmune-like enterocolitis, hypophysitis, and hepatitis. Autoimmune hypophysitis may present with headache, visual field defects, and pituitary hormone deficiencies manifesting as hypopituitarism, adrenal insufficiency (including adrenal crisis), or hypothyroidism. Anti-CTLA-4-associated hypophysitis symptoms occur at an average of 6–12 weeks after initiation of therapy. The treatment of severe autoimmune toxicity is glucocorticoids. Almost all patients with hypophysitis respond to withdrawal of ipilimumab and glucocorticoid therapy in several days. However, pituitary dysfunction may resolve or may be permanent, requiring long-term therapy and thyroid and testosterone replacement. Peripheral Addison's disease can also be observed with anti-CTLA-4 antibodies. Megestrol acetate, used to manage cancer and HIV-related cachexia, may suppress plasma levels of cortisol and adrenocorticotropic hormone (ACTH). Patients taking megestrol may develop adrenal insufficiency, and even those whose adrenal dysfunction is not symptomatic may have inadequate adrenal reserve if they become seriously ill. Paradoxically, some patients may develop Cushing's syndrome and/or hyperglycemia because of the glucocorticoid-like activity of megestrol acetate. Cranial irradiation for childhood brain tumors may affect the hypothalamus-pituitary-adrenal axis, resulting in secondary adrenal insufficiency.

Acute adrenal insufficiency is potentially lethal. Treatment of suspected adrenal crisis is initiated after the sampling of serum cortisol and ACTH levels.

TREATMENT-RELATED EMERGENCIES

TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia and is caused by the destruction of a large number of rapidly proliferating neoplastic cells. Acidosis may also develop. Acute renal failure occurs frequently.

TLS is most often associated with the treatment of Burkitt's lymphoma, acute lymphoblastic leukemia, and other rapidly proliferating lymphomas, but it also may be seen with chronic leukemias and, rarely, with solid tumors. This syndrome has been seen in patients with chronic lymphocytic leukemia after treatment with nucleosides like fludarabine. TLS has been observed with administration of glucocorticoids, hormonal agents such as letrozole and tamoxifen, and monoclonal antibodies such as rituximab and gemtuzumab. TLS usually occurs during or shortly (1–5 days) after chemotherapy. Rarely, spontaneous necrosis of malignancies causes TLS.

Hyperuricemia may be present at the time of chemotherapy. Effective treatment kills malignant cells and leads to increased serum uric acid levels from the turnover of nucleic acids. Owing to the acidic local environment, uric acid can precipitate in the tubules, medulla, and collecting ducts of the kidney, leading to renal

failure. Lactic acidosis and dehydration may contribute to the precipitation of uric acid in the renal tubules. The finding of uric acid crystals in the urine is strong evidence for uric acid nephropathy. The ratio of urinary uric acid to urinary creatinine is >1 in patients with acute hyperuricemic nephropathy and <1 in patients with renal failure due to other causes.

Hyperphosphatemia, which can be caused by the release of intracellular phosphate pools by tumor lysis, produces a reciprocal depression in serum calcium, which causes severe neuromuscular irritability and tetany. Deposition of calcium phosphate in the kidney and hyperphosphatemia may cause renal failure. Potassium is the principal intracellular cation, and massive destruction of malignant cells may lead to hyperkalemia. Hyperkalemia in patients with renal failure may rapidly become life-threatening by causing ventricular arrhythmias and sudden death.

The likelihood that TLS will occur in patients with Burkitt's lymphoma is related to the tumor burden and renal function. Hyperuricemia and high serum levels of lactate dehydrogenase (LDH >1500 U/L), both of which correlate with total tumor burden, also correlate with the risk of TLS. In patients at risk for TLS, pretreatment evaluations should include a complete blood count, serum chemistry evaluation, and urine analysis. High leukocyte and platelet counts may artificially elevate potassium levels ("pseudohyperkalemia") due to lysis of these cells after the blood is drawn. In these cases, plasma potassium instead of serum potassium should be followed. In pseudohyperkalemia, no electrocardiographic abnormalities are present. In patients with abnormal baseline renal function, the kidneys and retroperitoneal area should be evaluated by sonography and/or CT to rule out obstructive uropathy. Urine output should be watched closely.

TREATMENT Tumor Lysis Syndrome

Recognition of risk and prevention are the most important steps in the management of this syndrome **(Fig. 56-4)**. The standard preventive approach consists of allopurinol, urinary alkalinization, and aggressive hydration. Urinary alkalization

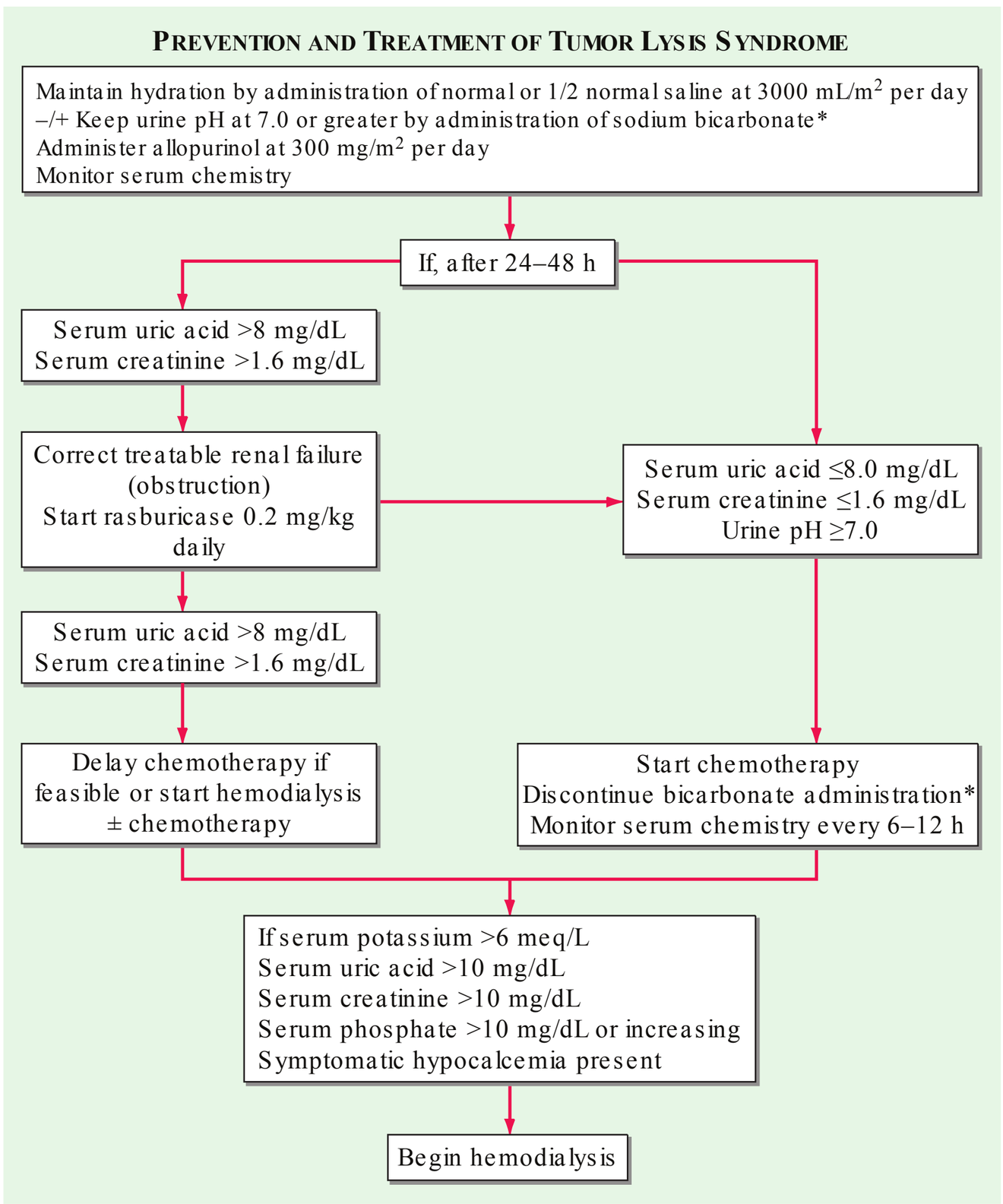


FIGURE 56-4
Management of patients at high risk for the tumor lysis syndrome. *See text.

with sodium bicarbonate is controversial. It increases uric acid solubility, but decreases calcium phosphate solubility. If it is used, it should be discontinued when hyperphosphatemia develops. Intravenous allopurinol may be given in patients who cannot tolerate oral therapy. In some cases, uric acid levels cannot be lowered suf ciently with the standard preventive approach. Rasburicase (recombinant urate oxidase) can be effective in these instances, particularly when renal failure is present. Urate oxidase is missing from primates and catalyzes the conversion of poorly soluble uric acid to readily soluble allantoin. Rasburicase acts rapidly, decreasing uric acid levels within hours; however, it may cause hypersensitivity reactions such as bronchospasm, hypoxemia, and hypotension. Rasburicase should also be administered to high-risk patients for TLS prophylaxis. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency who are unable to break down hydrogen peroxide, an end product of the urate oxidase reaction. Rasburicase is known to cause ex vivo enzymatic degradation of uric acid in test tube at room temperature. T is leads to spuriously low uric acid levels during laboratory monitoring of the patient with TLS. Samples must be cooled immediately to deactivate the urate oxidase. Despite aggressive prophylaxis, TLS and/or oliguric or anuric renal failure may occur. Care should be taken to prevent worsening of symptomatic hypocalcemia by induction of alkalosis during bicarbonate infusion. Administration of sodium bicarbonate may also lead to urinary precipitation of calcium phosphate, which is less soluble at alkaline pH. Dialysis is often necessary and should be considered early in the course. Hemodialysis is preferred. Hemofiltration offers a gradual, continuous method of removing cellular by-products and fluid. T e prognosis is excellent, and renal function recovers after the uric acid level is lowered to ≤10 mg/dL.

HUMAN ANTIBODY INFUSION REACTIONS

T e initial infusion of human or humanized antibodies (e.g., rituximab, gemtuzumab, trastuzumab, alemtuzumab, panitumumab, brentuximab vedotin) is associated with fever, chills, nausea, asthenia, and headache in up to half of treated patients. Bronchospasm and hypotension occur in 1% of patients. Severe manifestations including pulmonary infiltrates, acute respiratory distress syndrome, and cardiogenic shock occur rarely. Laboratory manifestations include elevated hepatic aminotransferase levels, thrombocytopenia, and prolongation of prothrombin time. T e pathogenesis is thought to be activation of immune effector processes (cells and complement) and release of inflammatory cytokines, such as tumor necrosis factor α, interferon gamma, interleukin 6, and interleukin 10 (cytokine release syndrome [CRS]). Although its origins are not completely understood, CRS is believed to be due to activation of a variety of cell types including monocytes/macrophages and T and B lymphocytes. Severe reactions from rituximab have occurred with high numbers (>50 × 10^9lymphocytes) of circulating cells bearing the target antigen (CD20) and have been associated with a rapid fall in circulating tumor cells, mild electrolyte evidence of TLS, and very rarely, death. In addition, increased liver enzymes, D-dimer, and LDH and prolongation of the prothrombin time may occur. Diphenhydramine, hydrocortisone, and acetaminophen can often prevent or suppress the infusion-related symptoms. If they occur, the infusion is stopped and restarted at half the initial infusion rate after the symptoms have abated. Severe CRS may require intensive support for acute respiratory distress syndrome (ARDS) and resistant hypotension.

HEMOLYTIC-UREMIC SYNDROME

Hemolytic-uremic syndrome (HUS) and, less commonly, thrombotic thrombocytopenic purpura (TTP) may rarely occur after treatment with antineoplastic drugs, including mitomycin, gemcitabine, cisplatin, and bleomycin, and with VEGF inhibitors. It occurs most often in patients with gastric, lung, colorectal, pancreatic, and breast carcinoma. In one series, 35% of patients were without evident cancer at the time this syndrome appeared. Secondary HUS/TTP has also been reported as a rare but sometimes fatal complication of bone marrow transplantation.

HUS usually has its onset 4–8 weeks after the last dose of chemotherapy, but it is not rare to detect it several months later. HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Dyspnea, weakness, fatigue, oliguria, and purpura are also common initial symptoms and findings. Systemic hypertension and pulmonary edema frequently occur. Severe hypertension, pulmonary edema, and rapid worsening of hemolysis and renal function may occur after a blood or blood product transfusion. Cardiac findings include atrial arrhythmias, pericardial friction rub, and pericardial effusion. Raynaud's phenomenon is part of the syndrome in patients treated with bleomycin.

Laboratory findings include severe to moderate anemia associated with red blood cell fragmentation and numerous schistocytes on peripheral smear. Reticulocytosis, decreased plasma haptoglobin, and an LDH level document hemolysis. T e serum bilirubin level is usually normal or slightly elevated. T e Coombs' test is negative. T e white cell count is usually normal, and thrombocytopenia (<100,000/μL) is almost always present. Most patients have a normal coagulation profile, although some have mild elevations in thrombin time and in levels of fibrin degradation products. T e serum creatinine level is elevated at presentation and shows a

pattern of subacute worsening within weeks of the initial azotemia. T e urinalysis reveals hematuria, proteinuria, and granular or hyaline casts; and circulating immune complexes may be present.

T e basic pathologic lesion appears to be deposition of fibrin in the walls of capillaries and arterioles, and these deposits are similar to those seen in HUS due to other causes. T ese microvascular abnormalities involve mainly the kidneys and rarely occur in other organs. T e pathogenesis of cancer treatment–related HUS is not completely understood, but probably the most important factor is endothelial damage. Primary forms of HUS/TTP are related to a decrease in processing of von Willebrand factor by a protease called ADAMTS13.

T e case fatality rate is high; most patients die within a few months. T ere is no consensus on the optimal treatment for chemotherapy-induced HUS. Treatment modalities for HUS/TTP including immunocomplex removal (plasmapheresis, immunoadsorption, or exchange transfusion), antiplatelet/anticoagulant therapies, immunosuppressive therapies, and plasma exchange have varying degrees of success. T e outcome with plasma exchange is generally poor, as in many other cases of secondary TTP. Rituximab is successfully used in patients with chemotherapy-induced HUS as well as in ADAMTS13-deficient TTP.

NEUTROPENIA AND INFECTION

T ese remain the most common serious complications of cancer therapy. **T ey are covered in detail in Chap. 30**.

PULMONARY INFILTRATES

Patients with cancer may present with dyspnea associated with diffuse interstitial infiltrates on chest radiographs. Such infiltrates may be due to progression of the underlying malignancy, treatment-related toxicities, infection, and/or unrelated diseases. T e cause may be multifactorial; however, most commonly they occur as a consequence of treatment. Infiltration of the lung by malignancy has been described in patients with leukemia, lymphoma, and breast and other solid cancers. Pulmonary lymphatics may be involved diffusely by neoplasm (pulmonary lymphangitic carcinomatosis), resulting in a diffuse increase in interstitial markings on chest radiographs. T e patient is often mildly dyspneic at the onset, but pulmonary failure develops over a period of weeks. In some patients, dyspnea precedes changes on the chest radiographs and is accompanied by a nonproductive cough. T is syndrome is characteristic of solid tumors. In patients with leukemia, diffuse microscopic neoplastic peribronchial and peribronchiolar infiltration is frequent but may be asymptomatic. However, some patients present with diffuse interstitial infiltrates, an alveolar capillary block syndrome, and respiratory distress. In these situations, glucocorticoids can provide symptomatic relief, but specific chemotherapy should always be started promptly.

Several cytotoxic agents, such as bleomycin, methotrexate, busulfan, nitrosoureas, gemcitabine, mitomycin, vinorelbine, docetaxel, paclitaxel, fludarabine, pentostatin, and ifosfamide may cause pulmonary damage. T e most frequent presentations are interstitial pneumonitis, alveolitis, and pulmonary fibrosis. Some cytotoxic agents, including methotrexate and procarbazine, may cause an acute hypersensitivity reaction. Cytosine arabinoside has been associated with noncardiogenic pulmonary edema. Administration of multiple cytotoxic drugs, as well as radiotherapy and preexisting lung disease, may potentiate the pulmonary toxicity. Supplemental oxygen may potentiate the effects of drugs and radiation injury. Patients should always be managed with the lowest FIO2 that is suf cient to maintain hemoglobin saturation.

T e onset of symptoms may be insidious, with symptoms including dyspnea, nonproductive cough, and tachycardia. Patients may have bibasilar crepitant rales, end-inspiratory crackles, fever, and cyanosis. T e chest radiograph generally shows an interstitial and sometimes an intraalveolar pattern that is strongest at the lung bases and may be symmetric. A small effusion may occur. Hypoxemia with decreased carbon monoxide diffusing capacity is always present. Glucocorticoids may be helpful in patients in whom pulmonary toxicity is related to radiation therapy or to chemotherapy. Treatment is otherwise supportive.

Molecular targeted agents, imatinib, erlotinib, and gefitinib are potent inhibitors of tyrosine kinases. T ese drugs may cause interstitial lung disease (ILD). In the case of gefitinib, preexisting fibrosis, poor performance status, and prior thoracic irradiation are independent risk factors; this complication has a high fatality rate. In Japan, incidence of interstitial lung disease associated with gefitinib was about 4.5% compared to 0.5% in the United States. Temsirolimus and everolimus, both esters a derivative of rapamycin, are agents that block the effects of mammalian target of rapamycin (mTOR), an enzyme that has an important role in regulating the synthesis of proteins that control cell division. It may cause ground-glass opacities in the lung with or without diffuse interstitial disease and lung parenchymal consolidation. Patients may be asymptomatic with only radiologic findings or may be symptomatic. Symptoms include cough, dyspnea, and/or hypoxemia, and sometimes patients present with systemic symptoms such as fever and fatigue. T e incidence of everolimus-induced interstitial lung disease also appears to be higher in Japanese patients. Treatment includes dose reduction or withdrawal and, in some cases, the addition of glucocorticoids.

Radiation pneumonitis and/or fibrosis is a relatively frequent side effect of thoracic radiation therapy. It may be acute or chronic. Radiation-induced lung toxicity is a function of the irradiated lung volume, dose per fraction, and radiation dose. T e larger the irradiated lung field, the higher is the risk for radiation pneumonitis. T e use of concurrent chemoradiation, particularly regimens including paclitaxel, increases pulmonary toxicity. Radiation pneumonitis usually develops 2–6 months after completion of radiotherapy. T e clinical syndrome, which varies in severity, consists of dyspnea, cough with scanty sputum, low-grade fever, and an initial hazy infiltrate on chest radiographs. T e infiltrate and tissue damage usually are confined to the radiation field. T e patients subsequently may develop a patchy alveolar infiltrate and air bronchograms, which may progress to acute respiratory failure that is sometimes fatal. A lung biopsy may be necessary to make the diagnosis. Asymptomatic infiltrates found incidentally after radiation therapy need not be treated. However, prednisone should be administered to patients with fever or other symptoms. T e dosage should be tapered slowly after the resolution of radiation pneumonitis, because abrupt withdrawal of glucocorticoids may cause an exacerbation of pneumonia. Delayed radiation fibrosis may occur years after radiation therapy and is signaled by dyspnea on exertion. Often it is mild, but it can progress to chronic respiratory failure. T erapy is supportive.

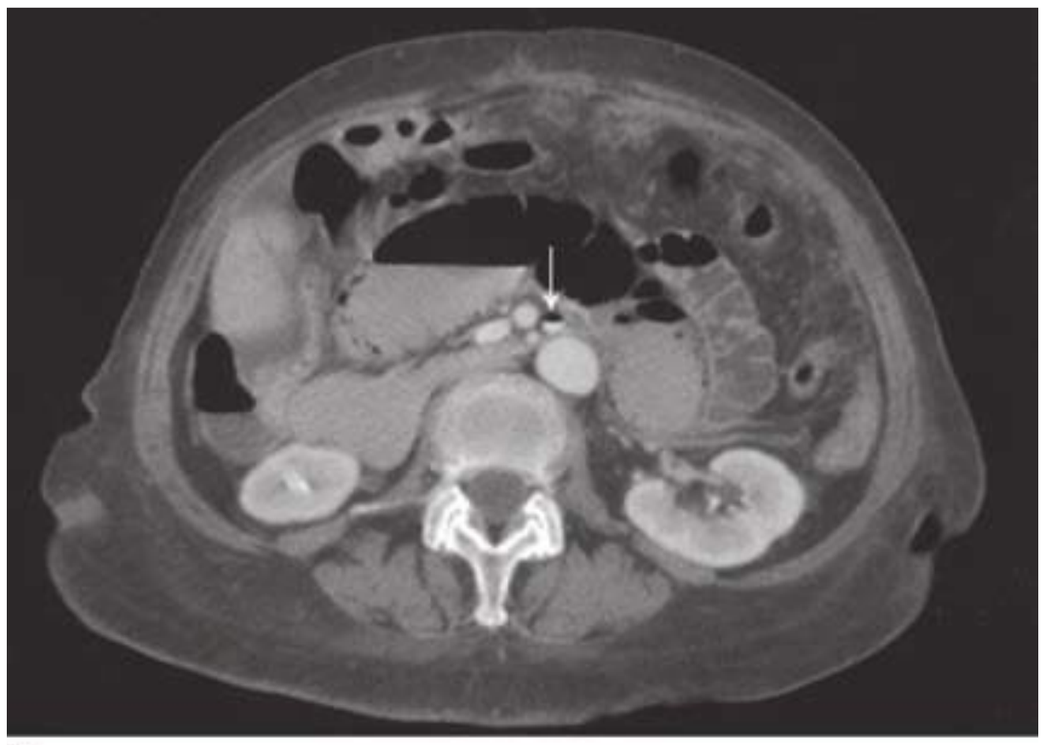
Classical radiation pneumonitis that leads to pulmonary fibrosis is due to radiation-induced production of local cytokines such as platelet-derived growth factor β, tumor necrosis factor, interleukins, and transforming growth factor β in the radiation field. An immunologically mediated sporadic radiation pneumonitis occurs in about 10% of patients; bilateral alveolitis mediated by T cells results in infiltrates outside the radiation field. T is form of radiation pneumonitis usually resolves without sequelae.

Pneumonia is a common problem in patients undergoing treatment for cancer. Bacterial pneumonia typically causes a localized infiltrate on chest radiographs. T erapy is tailored to the causative organism. When diffuse interstitial infiltrates appear in a febrile patient, the differential diagnosis is extensive and includes pneumonia due to infection with Pneumocystis carinii; viral infections including cytomegalovirus, adenovirus, herpes simplex virus, herpes zoster, respiratory syncytial virus, or intracellular pathogens such as Mycoplasma and Legionella; effects of drugs or radiation; tumor progression; nonspecific pneumonitis; and fungal disease. Detection of opportunistic pathogens in pulmonary infections is still a challenge. Diagnostic tools include chest radiographs, CT scans, bronchoscopy with bronchoalveolar lavage, brush cytology, transbronchial biopsy, fine-needle aspiration, and open lung biopsy. In addition to the culture, evaluation of bronchoalveolar lavage fluid for P. carinii by polymerase chain reaction (PCR) and serum galactomannan test improve the diagnostic yield. Patients with cancer who are neutropenic and have fever and local infiltrates on chest radiograph should be treated initially with broad-spectrum antibiotics. A new or persistent focal infiltrate not responding to broad-spectrum antibiotics argues for initiation of empiric antifungal therapy. When diffuse bilateral infiltrates develop in patients with febrile neutropenia, broad-spectrum antibiotics plus trimethoprim-sulfamethoxazole, with or without erythromycin, should be initiated. Addition of an antiviral agent is necessary in some settings, such as patients undergoing allogeneic hematopoietic stem cell transplantation. If the patient does not improve in 4 days, open lung biopsy is the procedure of choice. Bronchoscopy with bronchoalveolar lavage may be used in patients who are poor candidates for surgery.

In patients with pulmonary infiltrates who are afebrile, heart failure and multiple pulmonary emboli are in the differential diagnosis.

NEUTROPENIC ENTEROCOLITIS

Neutropenic enterocolitis (typhlitis) is the inflammation and necrosis of the cecum and surrounding tissues that may complicate the treatment of acute leukemia. Nevertheless, it may involve any segment of the gastrointestinal tract including small intestine, appendix, and colon. T is complication has also been seen in patients with other forms of cancer treated with taxanes, 5-fluorouracil, irinotecan, vinorelbine, cisplatin, carboplatin, and high-dose chemotherapy **(Fig. 56-5)**. It also has been reported in patients with AIDS, aplastic anemia, cyclic neutropenia, idiosyncratic drug reactions involving antibiotics, and immunosuppressive therapies. T e patient develops right lower quadrant abdominal pain, often with rebound tenderness and a tense, distended abdomen, in a setting of fever and neutropenia. Watery diarrhea (often containing sloughed mucosa) and bacteremia are common, and bleeding may occur. Plain abdominal films are generally of little value in the diagnosis; CT scan may show marked bowel wall thickening, particularly in the cecum, with bowel wall edema, mesenteric stranding, and ascites, and may help to differentiate neutropenic colitis from other abdominal disorders such as appendicitis, diverticulitis, and Clostridium dif cile–associated colitis in this high-risk population. Patients with bowel wall thickness >10 mm on ultrasonogram have higher mortality rates. However, bowel wall thickening is significantly more prominent in patients with C. dif cile colitis. Pneumatosis intestinalis is a more specific finding, seen only in those with neutropenic enterocolitis and ischemia.



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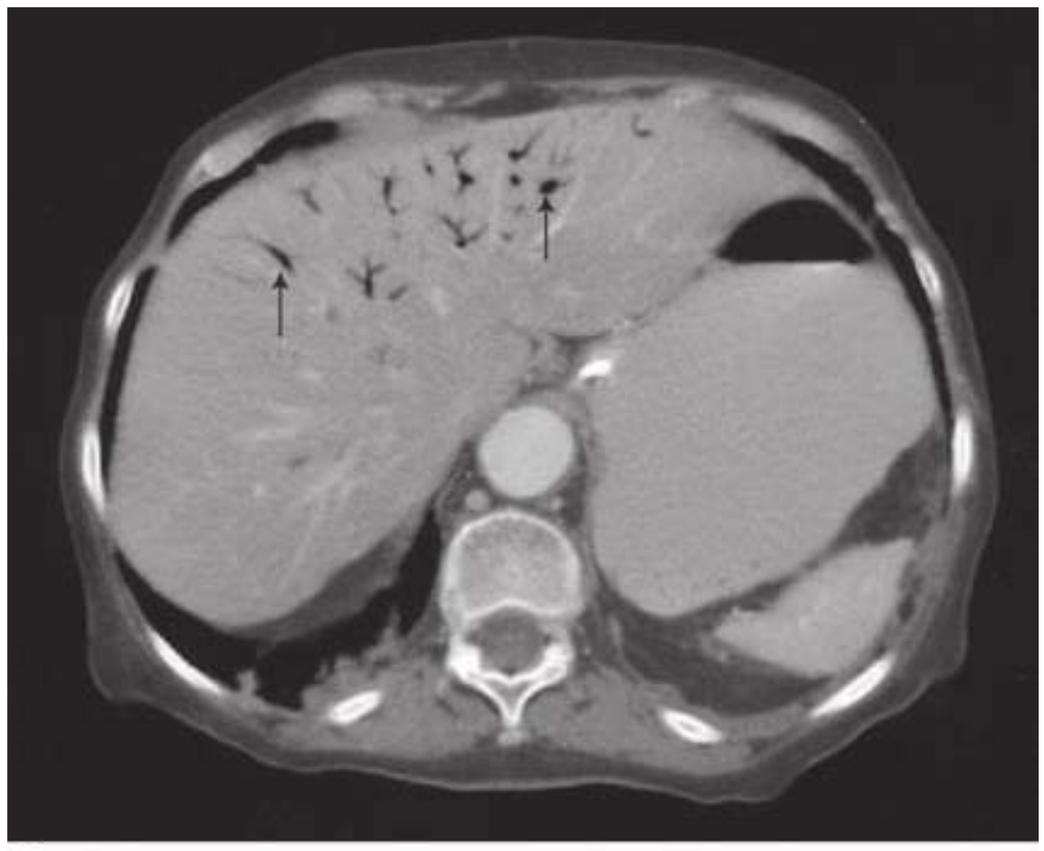


B

FIGURE 56-5
Abdominal computed tomography (CT) scans of a 72-year-old woman with neutropenic enterocolitis secondary to chemotherapy. A. Air in inferior mesenteric vein (arrow) and bowel wall with pneumatosis intestinalis. B. CT scan of upper abdomen demonstrating air in portal vein (arrows).

T e combined involvement of the small and large bowel suggests a diagnosis of neutropenic enterocolitis. Rapid institution of broad-spectrum antibiotics, bowel rest, and nasogastric suction may reverse the process. Use of myeloid growth factors improved outcome significantly. Surgical intervention is reserved for severe cases of neutropenic enterocolitis with evidence of perforation, peritonitis, gangrenous bowel, or gastrointestinal hemorrhage despite correction of any coagulopathy.

C. dif cile colitis is increasing in incidence. Newer strains of C. dif cile produce about 20 times more of toxins A and B compared to previously studied strains. C. dif cile risk is also increased with chemotherapy. Antibiotic coverage for C. dif cile should be added if pseudomembranous colitis cannot be excluded.

HEMORRHAGIC CYSTITIS

Hemorrhagic cystitis can develop in patients receiving cyclophosphamide or ifosfamide. Both drugs are metabolized to acrolein, which is a strong chemical irritant that is excreted in the urine. Prolonged contact or high concentrations may lead to bladder irritation and hemorrhage. Symptoms include gross hematuria, frequency, dysuria, burning, urgency, incontinence, and nocturia. T e best management is prevention. Maintaining a high rate of urine flow minimizes exposure. In addition, 2-mercaptoethanesulfonate (mesna) detoxifies the metabolites and can be coadministered with the instigating drugs. Mesna usually is given three times on the day of ifosfamide administration in doses that are each 20% of the total ifosfamide dose. If hemorrhagic cystitis develops, the maintenance of a high urine flow may be suf cient supportive care. If conservative management is not effective, irrigation of the bladder with a 0.37–0.74% formalin solution for 10 min stops the bleeding in most cases. N-Acetylcysteine may also be an effective irrigant. Prostaglandin (carboprost) can inhibit the process. In extreme cases, ligation of the hypogastric arteries, urinary diversion, or cystectomy may be necessary.

Hemorrhagic cystitis also occurs in patients who undergo bone marrow transplantation (BMT). In the BMT setting, early-onset hemorrhagic cystitis is related to drugs in the treatment regimen (e.g., cyclophosphamide), and late-onset hemorrhagic cystitis is usually due to the polyoma virus BKV or adenovirus type 11. BKV load in urine alone or in combination with acute graft-versus-host disease correlates with development of hemorrhagic cystitis. Viral causes are usually detected by PCR-based diagnostic tests. Treatment of viral hemorrhagic cystitis is largely supportive, with reduction in doses of immunosuppressive agents, if possible. No antiviral therapy is approved, although cidofovir is reported to be effective in a small series. Hyperbaric oxygen therapy has been used successfully in patients with BKV-associated and cyclophosphamide-induced hemorrhagic cystitis during hematopoietic stem cell transplantation, as well as in hemorrhagic radiation cystitis.

HYPERSENSITIVITY REACTIONS TO ANTINEOPLASTIC DRUGS

Many antineoplastic drugs may cause hypersensitivity reaction. T ese reactions are unpredictable and potentially life-threatening. Most reactions occur during or within hours of parenteral drug administration. Taxanes, platinum compounds, asparaginase, etoposide, procarbazine, and biologic agents, including rituximab, bevacizumab, trastuzumab, gemtuzumab, cetuximab, and alemtuzumab, are more commonly associated with acute hypersensitivity reactions than

are other agents. Acute hypersensitivity reactions to some drugs, such as taxanes, occur during the first or second dose administered. Hypersensitivity to platinum compounds occurs after prolonged exposure. Skin testing may identify patients with high risk for hypersensitivity after carboplatin exposure. Premedication with histamine H_1 and H_2 receptor antagonists and glucocorticoids reduces the incidence of hypersensitivity reaction to taxanes, particularly paclitaxel. Despite premedication, hypersensitivity reactions may still occur. In these cases, rapid desensitization in the intensive care unit setting or re-treatment may be attempted with care, but the use of alternative agents may be required. Candidate patients for desensitization include those who have mild to severe hypersensitivity type I, with mast cell–mediated and IgE-dependent reactions occurring during a chemotherapy infusion or shortly thereafter.

CHAPTER 57

LATE CONSEQUENCES OF CANCER AND ITS TREATMENT

Carl E. Freter ■ Dan L. Longo

There are over 10 million American cancer survivors. The vast majority of these will bear some mark of their cancer and its treatment, and a large proportion will experience long-term consequences including medical problems, psychosocial dysfunction, economic hardship, sexual dysfunction, and discrimination regarding employment and insurance. Many of these problems are directly related to cancer treatment. As patients survive longer from more types of malignancies, we are increasingly recognizing the biologic toll our very imperfect therapies take in terms of morbidity and mortality. The human face of these consequences of therapy confronts the cancer specialist who treats them every day. Although long-term survivors of childhood leukemias, Hodgkin's lymphoma, and testicular cancer, as examples, have taught us much about the consequences of cancer treatment, we keep learning more as patients survive longer with newer therapies. Newer "targeted" chemotherapy drugs have their own, often unique, long-term toxicities about which we remain in a learning process. Cancer "survivorship" clinics are increasing to expressly follow patients for long-term toxicities of cancer treatment.

The pace of developing therapies that mitigate treatment-related consequences has been slow, partly due to an understandable aversion to alter regimens that work and partly due to a lack of new, effective, less toxic therapeutic agents with less "collateral damage" to replace known agents with known toxicities. The types of damage from cancer treatment vary. Often, a final common pathway is irreparable damage to DNA. Surgery can create dysfunction, including blind gut loops with absorption problems and loss of function of removed body parts. Radiation may damage end-organ function, for example, loss of potency in prostate cancer patients, pulmonary fibrosis, and neurocognitive impairment, and may act as a direct carcinogen. Cancer chemotherapy can be a direct carcinogen and has a kaleidoscope of other toxicities discussed in this chapter. **Table 57-1** lists the late effects of cancer treatment.

The first goal of therapy is to eradicate or control the malignancy. Late treatment consequences are, indeed, testimony to the increasing success of such treatment. Their occurrence sharply underlines the necessity to develop more effective therapies with less long-term morbidity and mortality. At the same time, a sense of perspective and relative risk is necessary; fear of long-term complications should not prevent the application of effective, particularly curative, cancer treatment.

CARDIOVASCULAR DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Cardiovascular toxicity of cancer chemotherapeutic agents includes dysrhythmias, cardiac ischemia, cardiomyopathic congestive heart failure (CHF), pericardial disease, and peripheral vascular disease. Because these cardiac toxicities are difficult to distinguish from disease that is not associated with cancer treatment, clear etiologic implication of cancer chemotherapeutic agents may be difficult. Cardiovascular complications occurring in an unexpected clinical setting in patients who have undergone cancer therapy are often important in raising suspicion. Dose-dependent myocardial toxicity of anthracyclines with characteristic myofibrillar dropout is pathologically pathognomonic on endomyocardial biopsy. Anthracycline cardiotoxicity occurs through a root mechanism of chemical free radical damage. Fe^{3+}-doxorubicin complexes damage DNA, nuclear and cytoplasmic membranes, and mitochondria. About 5% of patients receiving >450–550 mg/m^2 of doxorubicin will develop CHF. Cardiotoxicity in relation to the dose of

TABLE 57-1

LATE EFFECTS OF CANCER THERAPY

SURGICAL PROCEDURE	EFFECT
Amputation	Functional loss
Lymph node dissection	Risk of lymphedema
Ostomy	Psychosocial impact
Splenectomy	Risk of sepsis
Adhesions	Risk of obstruction
Bowel anastomoses	Malabsorption syndromes
RADIATION THERAPY	**EFFECT**
Organ	
Bone	Premature termination of growth, osteonecrosis
Soft tissues	Atrophy, fibrosis
Brain	Neuropsychiatric deficits, cognitive dysfunction
Thyroid	Hypothyroidism, Graves' disease, cancer
Salivary glands	Dry mouth, caries, dysgeusia
Eyes	Cataracts
Heart	Pericarditis, myocarditis, coronary artery disease
Lung	Pulmonary fibrosis
Kidney	Decreased function, hypertension
Liver	Decreased function
Intestine	Malabsorption, stricture
Gonads	Infertility, premature menopause
Any	Secondary neoplasia

CHEMOTHERAPY		EFFECT
Organ	Drug	
Bone	Glucocorticoids	Osteoporosis, avascular necrosis
Brain	Methotrexate, cytarabine, others	Neuropsychiatric deficits, cognitive decline?
Peripheral nerves	Vincristine, platinum, taxanes	Neuropathy, hearing loss
Eyes	Glucocorticoids	Cataracts
Heart	Anthracyclines, trastuzumab	Cardiomyopathy
Lung	Bleomycin	Pulmonary fibrosis
	Methotrexate	Pulmonary hypersensitivity
Kidney	Platinum, others	Decreased function, hypomagnesemia
Liver	Various	Altered function
Gonads	Alkylating agents, others	Infertility, premature menopause
Bone marrow	Various	Aplasia, myelodysplasia, secondary leukemia

anthracycline is clearly not a step function, but rather a continuous function, and occasional patients are seen with CHF at substantially lower doses. Advanced age, other concomitant cardiac disease, hypertension, diabetes, and thoracic radiation therapy are all important cofactors in promoting anthracycline-associated CHF. The risk of cardiac failure appears to be substantially lower when doxorubicin is administered by continuous infusion. Anthracycline-related CHF is difficult to reverse and has a mortality rate as high as 50%, making prevention crucial. Some anthracyclines such as mitoxantrone are associated with less cardiotoxicity, and continuous-infusion regimens and liposomally encapsulated doxorubicin are associated with less cardiotoxicity. Dexrazoxane, an intracellular iron chelator, may limit anthracycline toxicity, but the concern of limiting chemotherapeutic efficacy has somewhat limited its use. Monitoring patients for cardiac toxicity typically involves periodic gated nuclear cardiac blood pool ejection fraction testing (multigated acquisition scan [MUGA]) or cardiac ultrasonography. More recently, cardiac magnetic resonance imaging (MRI) has been used, but MRI is not standard or widespread. Testing is performed more frequently at higher cumulative doses, with additional risk factors, and certainly for any newly developing CHF or other symptoms of cardiac dysfunction.

After anthracyclines, trastuzumab is the next most frequent cardiotoxic drug currently in use. Trastuzumab is frequently used as adjuvant breast cancer therapy, sometimes in conjunction with anthracyclines, which is believed to result in additive or possibly synergistic toxicity. In contrast to anthracyclines, cardiotoxicity is not dose-related, is usually reversible, is not associated with pathologic changes of anthracyclines on cardiac myofibrils, and has a different biochemical mechanism inhibiting intrinsic cardiac repair mechanisms. Toxicity

is typically routinely monitored every three to four doses using functional cardiac testing as mentioned earlier for anthracyclines.

Other cardiotoxic drugs include lapatinib, phosphoramide mustards (cyclophosphamide), ifosfamide, interleukin 2, ponatinib, imatinib, and sunitinib.

RADIATION THERAPY

Radiation therapy that includes the heart can cause interstitial myocardial fibrosis, acute and chronic pericarditis, valvular disease, and accelerated premature atherosclerotic coronary artery disease. Repeated or high (>6000 cGy) radiation doses are associated with greater risk, as is concomitant or distant cardiotoxic cancer chemotherapy exposure. Symptoms of acute pericarditis, which peaks about 9 months after treatment, include dyspnea, chest pain, and fever. Chronic constrictive pericarditis may develop 5–10 years following radiation therapy. Cardiac valvular disease includes aortic insufficiency from fibrosis or papillary muscle dysfunction resulting in mitral regurgitation. A threefold increased risk of fatal myocardial infarction is associated with mantle field radiation with accelerated coronary artery disease. Carotid radiation similarly increases the risk of embolic stroke.

TREATMENT Chemotherapeutic/Radiation-Induced Cardiovascular Disease

Therapy for chemotherapeutic/radiation-induced cardiovascular disease is essentially the same as therapy for disease not associated with cancer treatment. Discontinuation of the offending agent is the first step. Diuretics, fluid and sodium restriction, and antiarrhythmic agents are often useful for acute symptoms. Afterload reduction with angiotensin-converting enzyme (ACE) inhibitors or, in some cases, β-adrenergic blockers (carvedilol) often is of significant benefit, and digitalis may be helpful as well.

A hybrid discipline of "cardio-oncology" has been developing in clinics to expressly follow chemotherapy-treated patients for cardiotoxicity. The goals are early intervention using more sensitive techniques, management of cardiotoxicity before it becomes symptomatic, and using clinical trials to identify cardioprotective strategies.

PULMONARY DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Bleomycin generates activated free radical oxygen species and causes pneumonitis associated with a radiographic or interstitial ground-glass appearance diffusely throughout both lungs, often worse in the lower lobes. A nonproductive cough with or without fever may be an early sign. This toxicity is dose-related and dose-limiting. The diffusion capacity of the lungs for carbon dioxide (DL_{CO}) is a sensitive measure of toxicity and recovery, and a baseline value is generally obtained for future comparison prior to bleomycin therapy. Additive or synergistic risk factors include age, prior lung disease, and concomitant use of other chemotherapy, lung irradiation, and high concentrations of inspired oxygen. Other chemotherapeutic agents notable for pulmonary toxicity include mitomycin, nitrosoureas, doxorubicin with radiation, gemcitabine combined with weekly docetaxel, methotrexate, and fludarabine. High-dose alkylating agents, cyclophosphamide, ifosfamide, and melphalan are frequently used in the hematopoietic stem cell transplant setting, often with whole-body radiation. This therapy may result in severe pulmonary fibrosis and/or pulmonary venoocclusive disease.

RADIATION THERAPY

Risk factors for radiation pneumonitis include advanced age, poor performance status, preexisting compromised pulmonary function, and radiation volume and dose. The dose "threshold" is thought to be in the range of 5 to 20 Gy. Hypoxemia and dyspnea on exertion are characteristic. Fine, high-pitched "Velcro rales" may be an accompanying physical finding, and fever, cough, and pleuritic chest pain are common symptoms. The DL_{CO} is the most sensitive measure of pulmonary functional impairment, and ground-glass infiltrates often correspond with relatively sharp edges to the irradiated volume, although the pneumonitis may progress beyond the field and even occasionally involve the contralateral unirradiated lung.

TREATMENT Pulmonary Dysfunction

Chemotherapy- and radiation-induced pneumonitis is generally very corticosteroid responsive, except in the case of nitrosoureas. Prednisone 1 mg/kg is often used to control acute symptoms and pulmonary dysfunction with a generally slow taper. Prolonged glucocorticoid therapy requires gastrointestinal protection with proton pump inhibitors, management of hyperglycemia, heightened infection management, and treatment of steroid-induced osteoporosis. Antibiotics, bronchodilators, oxygen in only necessary doses, and diuretics may all play an important role in management of pneumonitis, and consultation with a pulmonologist should be routinely undertaken. Amifostine has been studied as a pulmonary radioprotectant, with inconclusive results, and is associated with skin rash, fatigue, and nausea; hence, it is not considered standard therapy at this time. Transforming

growth factor β (TGF-β) is believed to be a major inducer of radiation fibrosis and represents a therapeutic target for development of anti-TGF-β therapies.

NEUROLOGIC DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Chemotherapy- and radiation-induced neurologic dysfunction is unfortunately increasing in both incidence and severity as a result of improved supportive care leading to more aggressive regimens and longer cancer survivorship allowing the development of late toxicity. Direct effects on myelin, glial cells, and neurons have all been implicated, with alterations in cellular cytoskeleton, axonal transport, and cellular metabolism as mechanisms.

Vinca alkaloids produce a characteristic "stocking-glove" neuropathy with numbness and tingling advancing to loss of motor function, which is highly dose related. Distal sensorimotor polyneuropathy prominently involves loss of deep tendon reflexes with initially loss of pain and temperature sensation, followed by proprioceptive and vibratory loss. This requires careful patient history and physical examination by experienced oncologists to decide when the drug must be stopped due to toxicity. Milder toxicity often slowly completely resolves. Vinca alkaloids may sometimes be associated with jaw claudication, autonomic neuropathy, ileus, cranial nerve palsies, and, in severe cases, encephalopathy, seizures, and coma.

Cisplatin is associated with sensorimotor neuropathy and hearing loss, especially at doses >400 mg/m^2, requiring audiometry in patients with preexisting hearing compromise. Carboplatin is often substituted in such cases given its lesser effect on hearing.

Many of the agents that target kinase enzymes in tumor cells and 5-fluorouracil congeners produce dysesthesias and painful hands and feet known as hand-foot syndrome or palmar-plantar erythrodysesthesia. Symptoms usually abate when the agent is stopped.

Neurocognitive dysfunction has been well described in childhood survivors of acute lymphoblastic leukemia (ALL) treatment, including intrathecal methotrexate or cytosine arabinoside in conjunction with prophylactic cranial irradiation. Methotrexate alone may cause acute leukoencephalopathy characterized by somnolence and confusion that is often reversible. Acute toxicity is dose related, especially at doses >3 g/m^2, with younger patients being at greater risk. Subacute methotrexate toxicity occurs weeks after therapy and is often ameliorated with glucocorticoid therapy. Chronic methotrexate toxicity (leukoencephalopathy) develops months or years after treatment and is characterized clinically as progressive loss of cognitive function and focal neurologic signs, which are irreversible, promoted by synchronous or metachronous radiation therapy, and more pronounced at a younger age.

Neurocognitive decline following chemotherapy alone occurs notably in breast cancer patients receiving adjuvant chemotherapy; this has been referred to as "chemo brain." It is clinically associated with impaired memory, learning, attention, and speed of information processing. There is no clear mechanistic explanation for its cause and no clearly effective therapy. This entity is justifiably attracting more attention and clearly needs to be studied to develop effective therapy or prophylaxis.

Many cancer patients experience intrusive or debilitating concerns about cancer recurrence following successful therapy. In addition, these patients may experience job, insurance, stress, relationship, financial, and sexual difficulties. Oncologists need to ask about and address these issues explicitly with patients and provide appropriate counseling or support systems. Suicidal ideation and suicide have an increased incidence in cancer patients and survivors.

RADIATION THERAPY

Acute radiation central nervous system (CNS) toxicity occurs within weeks; is characterized by nausea, drowsiness, hypersomnia, and ataxia; and is most often associated with recovery. Early delayed toxicity occurring weeks to 3 months following therapy is associated with similar symptoms as acute toxicity and is pathologically associated with reversible demyelination. Chronic, late radiation injury occurs 9 months to up to 10 years following therapy. Focal necrosis is a common pathologic finding, and glucocorticoid therapy may be helpful. Diffuse radiation injury is associated with global CNS neurologic dysfunction and diffuse white matter changes on computed tomography (CT) or MRI. Pathologically, small vessel changes are prominent. Glucocorticoids may be symptomatically useful but do not alter the course. Necrotizing encephalopathy is the most severe form of radiation injury and almost always is associated with chemotherapy, notably methotrexate.

Cranial radiation may also be associated with an array of endocrine abnormalities with disruption of normal pituitary/hypothalamic axis function, and a high index of suspicion needs to be maintained to identify and treat this toxicity.

Radiation-associated spinal cord injury (myelopathy) is highly dose-dependent and rarely occurs with modern radiation therapy. An early, self-limited form involving electric sensations down the spine on neck flexion (Lhermitte's sign) is seen 6–12 weeks after treatment and generally resolves over weeks. Peripheral nerve toxicity is quite rare owing to relative radiation resistance.

HEPATIC DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Long-term hepatic damage from standard chemotherapy regimens is rare. Long-term methotrexate or high-dose chemotherapy alone or with radiation therapy, for example, in preparative regimens for bone marrow transplantation, may result in venoocclusive disease of the liver. T is potentially lethal complication classically presents with anicteric ascites, elevated alkaline phosphatase, and hepatosplenomegaly. Pathologically, there is venous congestion, epithelial cell proliferation, and hepatocyte atrophy progressing to frank fibrosis. Frequent monitoring of liver function tests during any chemotherapy is necessary to avoid both idiosyncratic and expected toxicities.

Certain nucleoside drugs have been associated with hepatic dysfunction; however, this complication is rare in oncology.

RADIATION THERAPY

Hepatic radiation damage depends on dose, volume, fractionation, preexisting liver disease, and synchronous or metachronous chemotherapy. In general, radiation doses to the liver >1500 cGy can produce hepatic dysfunction with a steep dose-injury curve. Radiation-induced liver disease closely mimics hepatic venoocclusive disease.

RENAL/BLADDER DYSFUNCTION

Cisplatin produces reversible decrements in renal function, but may also produce severe irreversible toxicity in the presence of renal disease and may predispose to accentuated damage with subsequent renal insults. Cyclophosphamide and ifosfamide, as prodrugs primarily activated in the liver, have cleavage products (acrolein) that can produce hemorrhagic cystitis. T is can be prevented with the free radical scavenger MESNA (mercaptoethane sulfonate), which is required for ifosfamide administration. Hemorrhagic cystitis caused by these agents may predispose to bladder cancer.

REPRODUCTIVE AND ENDOCRINE DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Alkylating agents are associated with the highest rates of male and female infertility, which is directly dependent on age, dose, and duration of treatment. T e age at treatment is an important determinant of fertility outcome, with prepubertal patients having the highest tolerance. Ovarian failure is age related, and females who resume menses after treatment are still at increased risk for premature menopause. Males generally have reversible azoospermia during lower intensity alkylator chemotherapy, and long-term infertility is associated with doses of cyclophosphamide >9 g/m^2 and with high-intensity therapy, such as that used in hematopoietic stem cell transplantation. Males undergoing potentially sterilizing chemotherapy should be offered sperm banking. Gonadotropin-releasing hormone (GnRH) analogs remain experimental to preserve ovarian function. Assisted reproductive technologies can be helpful to couples with chemotherapy-induced infertility.

RADIATION THERAPY

Testicles and ovaries in prepubertal patients are less sensitive to radiation damage; spermatogenesis is affected by low doses of radiation, and complete azoospermia occurs at 600–700 cGy. Leydig cell dysfunction, in contrast, occurs at <2000 cGy, and hence, endocrine function is lost at much higher radiation doses than spermatogenesis. Erectile dysfunction occurs in up to 80% of men treated with external-beam radiation therapy for prostate cancer. Sildenafil may be useful in reversing erectile dysfunction. Ovarian function damage with radiation is age related and occurs at doses of 150–500 cGy. Premature induction of menopause can have serious medical and psychological sequelae. Hormone replacement therapy is often contraindicated (as in estrogen receptor–positive breast cancer). Attention must be paid to maintenance of bone mass with calcium and vitamin D supplements and oral bisphosphonates, and bone mass should be monitored using bone density determinations. Paroxetine, clonidine, pregabalin, and other drugs may be useful in symptomatically controlling hot f ashes.

Long-term survivors of childhood cancer (e.g., ALL) who have received cranial radiation may have altered leptin biology and growth hormone deficiency, leading to obesity and reduced strength, exercise tolerance, and bone density.

Radiation therapy to the neck (e.g., in Hodgkin's lymphoma) may lead to hypothyroidism, Graves' disease, thyroiditis, and thyroid malignancies. T yroid-stimulating hormone (TSH) is followed routinely in such patients to prevent hypothyroidism, and to suppress persistently elevated levels of TSH which may cause or drive thyroid cancer.

OCULAR COMPLICATIONS

Cataracts may be caused by glucocorticoids, depending on duration and dose; radiation therapy; and uncommonly tamoxifen. Orbital radiation therapy may cause blindness.

ORAL COMPLICATIONS

Radiation therapy can produce xerostomia (dry mouth), with an attendant increase in caries and poor dentition. Taste and appetite may be suppressed. Bisphosphonate use may result in osteonecrosis of the jaw.

RAYNAUD'S PHENOMENON

Up to 40% of patients treated with bleomycin may develop Raynaud's phenomenon as a result of an unknown mechanism.

SECOND MALIGNANCIES

Second malignancies in patients cured of cancer are a major cause of death, and treated cancer patients must be monitored for their occurrence. T e induction of second malignancies is governed by the complex interplay of a number of factors including age, gender, environmental exposures, genetic susceptibility, and cancer treatment itself. In a number of settings, the events leading to the primary cancer themselves increase the risk of second malignancies. Patients with lung cancer are at increased risk of esophageal and head and neck cancers, and vice versa, due to shared risk factors including alcohol and tobacco abuse. Indeed, the risk of developing a second primary head and neck, esophageal, or lung cancer is also increased in these patients. Patients with breast cancer are at increased risk of breast cancer in the opposite breast. Patients with Hodgkin's lymphoma are at risk for non-Hodgkin's lymphomas. Genetic cancer syndromes (e.g., multiple endocrine neoplasia or Li-Fraumeni, Lynch's, Cowden's, and Gardner's syndromes) are examples of genetically based second malignancies of specific types. Cancer treatment itself does not appear to be responsible for the risk of these secondary malignancies. Deficient DNA repair can greatly increase the risk of cancers from DNA-damaging agents, as in ataxia-telangiectasia. Importantly, the risk of treatment-related second malignancies is at least additive and often synergistic with combined chemotherapy and radiation therapy, and hence for such combined-therapy treatment approaches, it is important to establish the necessity of each in the treatment program. All of these patients require special surveillance or, in some cases, prophylactic surgery as part of appropriate treatment and follow-up.

CHEMOTHERAPEUTIC AGENTS

Chemotherapy is significantly associated with two fatal second malignancies, acute leukemia and myelodysplastic syndromes. Two types of leukemia have been described; in patients treated with alkylating agents, acute myeloid leukemia is associated with deletions in chromosome 5 or 7. T e lifetime risk is about 1–5%, is increased by radiation therapy, and increases with age. T e incidence of these leukemias peaks at 4–6 years, with risk returning close to baseline at 10 years. T e other type of acute myeloid leukemia is related to therapy with topoisomerase inhibitors, is associated with chromosome 10q23 translocations, has an incidence of <1%, and generally occurs 1.5–3 years after treatment. Both of these acute myeloid leukemias are refractory to treatment and have a high mortality. T e development of myelodysplastic syndromes is increased following chemotherapy, and these are often associated with leukemic progression and a dismal prognosis.

RADIATION THERAPY

Patients receiving radiation have an increasing and lifelong risk of second malignancies that is 1–2% in the second decade following treatment but increases to >25% after 25 years. T ese malignancies include cancers of the thyroid and breast, sarcomas, and CNS cancers, which often tend to be aggressive and have a poor prognosis. An example of organ-, age-, and sex-dependent radiation-induced secondary malignancy is breast cancer, in which the risk is small with radiation in women under age 30 but increases about 20-fold over baseline in women over 30. A 25-year-old woman treated with mantle radiation for Hodgkin's lymphoma has a 29% actuarial risk of developing breast cancer by age 55.

HORMONAL THERAPY

Treatment of breast cancer with tamoxifen for 5 years or longer is associated with a 1–2% risk of endometrial cancer. Surveillance is generally effective at finding these cancers at an early stage. T e risk of mortality from tamoxifen-induced endometrial cancer is low compared to the benefit of tamoxifen as adjuvant therapy for breast cancer.

IMMUNOSUPPRESSIVE THERAPY

Immunosuppressive therapy, as used in allogeneic bone marrow transplantation, particularly with T cell depletion using antithymocyte globulin or other means, increases the risk of Epstein Barr virus–associated B cell lymphoproliferative disorder. T e incidence at 10 years after T cell depletion is 9–12%. Discontinuing immunosuppressive therapy, if possible, is often associated with complete disease regression.

RECOMMENDATIONS FOR FOLLOW-UP

All former cancer patients should be followed indefinitely. T is is most often done by oncologists, but demographic changes suggest that more primary care physicians will need to be trained in the follow-up of treated cancer patients in remission. Cancer patients need to be educated about signs and symptoms of recurrence and potentially adverse effects related to therapy. Localized pain or palpable abnormality in a previously radiated field should prompt radiographic evaluation. Screening tests, when available and validated, should be used on a routine and regular basis (e.g., mammography and Pap smear), particularly in patients receiving radiation to specific organs. Annual mammography should start no later than 10 years after breast radiation. Patients receiving radiation fields encompassing thyroid tissue should have regular thyroid exams and TSH testing. Patients treated with alkylating agents or topoisomerase inhibitors should have a complete blood count every 6–12 months, and cytopenias, abnormal cells on peripheral smear, or macrocytosis should be evaluated with bone marrow biopsy and aspirate, to include cytogenetics, f ow cytometry, or f uorescence in situ hybridization (FISH) studies as appropriate.

As the population of cancer survivors lives longer and grows, cancer survivorship has become an increasingly recognized subject, and the Institute of Medicine and National Research Council have published a monograph entitled From Cancer Patient to Cancer Survivor: Lost in Transition. T e monograph proposes a plan that would inform clinicians caring for cancer survivors in complete detail of their previous treatments, complications thereof, signs and symptoms of late effects, and recommended screening and follow-up procedures. **Table 57-2** lists long-term treatment effects by cancer type.

OUTLOOK

Clearly, the challenge for the future is to combine chemotherapy, targeted agents, biologic therapies, radiation, and surgery to produce better outcomes with less toxicity, including late effects of therapy. T is is easily said but less easily accomplished. As treatment becomes more effective in new patient populations (ovarian, bladder, anal, and laryngeal cancers, for example), we will expect to discover new populations at risk for late effects. T ese populations will need to be followed carefully, so that such effects are recognized and treated. Cancer survivors represent an underused resource for prevention studies. Childhood cancer survivors, especially, suffer multiple chronic health impairments. T e incidence of these late treatment consequences appears to have no plateau with age, throwing in stark relief the necessity of close monitoring and therapies with fewer late consequences of treatment.

TABLE 57-2

LONG-TERM TREATMENT EFFECTS BY CANCER TYPE

CANCER TYPE	LATE EFFECTS
Pediatric cancers	Majority have at least one late effect 30% with moderate/severe problems Cardiovascular: radiation, anthracyclines Lungs: radiation Skeletal abnormalities: radiation Psychological, cognitive, and sexual problems Second neoplasms significant cause of death
Hodgkin's lymphoma	Thyroid dysfunction: radiation Premature coronary artery disease: radiation Gonadal dysfunction: chemotherapy Postsplenectomy sepsis Myelodysplasia Acute myeloid leukemia Non-Hodgkin's lymphomas Breast cancer, lung cancer, and melanoma Fatigue, psychological and sexual problems Peripheral neuropathy
Non-Hodgkin's lymphoma	Myelodysplasia Acute leukemia Bladder cancer Peripheral neuropathy
Acute leukemia	Second malignancies: hematologic, solid tumors Neuropsychiatric dysfunction Subnormal growth Thyroid abnormalities Infertility
Bone marrow stem cell transplantation	Infertility Graft-versus-host disease (allogeneic transplant) Psychosexual dysfunction.
Head and neck cancer	Poor dentition, dry mouth, poor nutrition: radiation
Breast cancer	Tamoxifen: endometrial cancer, blood clots Aromatase inhibitors: osteoporosis, arthritis Cardiomyopathy: anthracycline ± radiation, trastuzumab Acute leukemia Hormone deficiency symptoms: hot f ashes, vaginal dryness, dyspareunia Psychosocial dysfunction "Chemo brain"
Testicular cancer	Raynaud's phenomenon Renal dysfunction Pulmonary dysfunction Retrograde ejaculation: surgery 15% sexual dysfunction
Colon cancer	Major risk is second colon cance. Quality of life high in survivors
Prostate cancer	Impotence Urinary incontinence (0–15%) Chronic proctitis, prostatitis/cystitis: radiation

REVIEW AND SELF-ASSESSMENT*

Charles M. Wiener ■ Cynthia D. Brown ■ Brian Houston

QUESTIONS

DIRECTIONS: Choose the **one best** response to each question.

1. Which of the following statements regarding erythropoiesis is TRUE?

A. Hypoxia-inducible factor-1α is downregulated in response to hypoxia and results in increased production of erythropoietin.
B. In response to erythropoietin, red blood cell production can increase to by a maximum factor of 2 over a 3–6 day period.
C. Normal red blood cell production results in replacement of approximately 1% of all circulating red blood cells each week.
D. T e erythroid precursor, the pronormoblast, can produce 16–32 mature red blood cells.
E. With increased erythropoietin, each progenitor cell is stimulated to produce additional red blood cells.

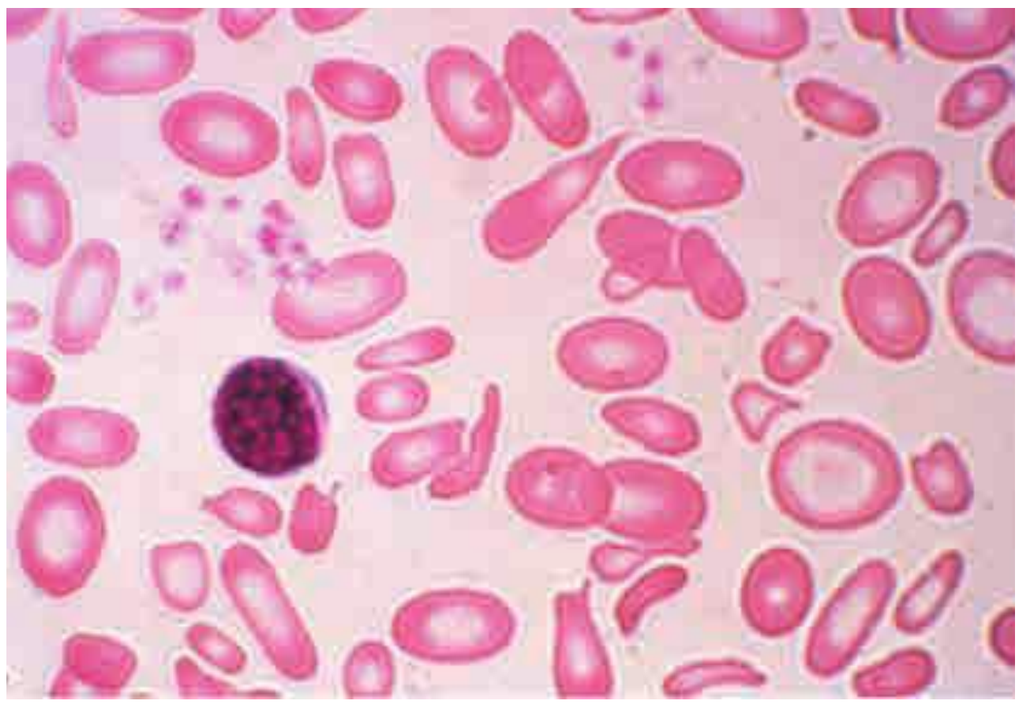


FIGURE 2 (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

2. A 36-year-old woman presents to your office complaining of easy fatigability. She is found to have anemia. On further questioning, she does report heavy menses and has been following a vegetarian diet. Her physical examination is normal with the exception of mildly pale conjunctiva. Her hemoglobin is 9.1 g/dL, hematocrit is 27.6%. T e MCV is 65 fL, MCH is 24 pg, and MCHC is 26%. T e red cell distribution width is 16.7%. T e peripheral blood smear is shown in Figure 2.

Which of the following is present on the peripheral blood smear?

A. Anisocytosis
B. Hypochromia
C. Poikilocytosis
D. A and B
E. All of the above

3. A 24-year-old woman is 12 weeks' pregnant with her first child. She is referred for evaluation of an abnormal finding on complete blood count. She is asymptomatic and has had no complications thus far. She is of Turkish descent. She has no family members with significant anemias. Her hemoglobin is 12.2 g/dL and hematocrit is 37%. T e MCV is 60 fL and MCH is 25 pg. Her ferritin is 50 µg/L and iron is 15 µmol/L. What is the characteristic finding expected on peripheral blood smear?

A. Burr cells
B. Howell-Jolly bodies
C. Schistocytes
D. Spherocytes
E. Target cells

4. You are asked to review the peripheral blood smear (see Figure 4) from a patient with anemia.

Serum lactate dehydrogenase and total bilirubin are elevated and there is hemoglobinuria. T is patient is likely to have which physical examination finding?

*Questions and answers were taken from Wiener C et al. (eds). Harrison's Principles *of* Internal Medicine Self-Assessment and Board Review. 19th ed. New York: McGraw-Hill; 2017.

4. (Continued)

A. Goiter
B. Heme-positive stools
C. Mechanical second heart sound
D. Splenomegaly
E. T ickened calvarium

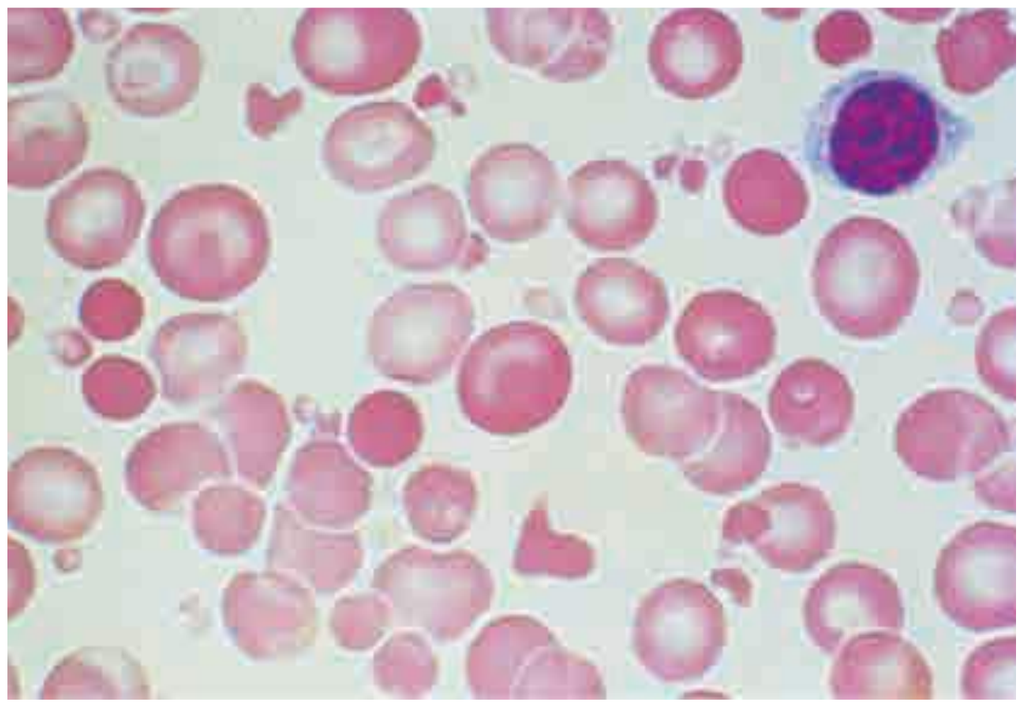


FIGURE 4 (From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)

5. You are seeing a patient in follow-up in whom you have begun an evaluation for an elevated hematocrit. You suspect polycythemia vera based on a history of aquagenic pruritus and splenomegaly. Which set of laboratory tests are consistent with the diagnosis of polycythemia vera?

A. Elevated red blood cell mass, high serum erythropoietin levels, normal oxygen saturation
B. Elevated red blood cell mass, low serum erythropoietin levels, normal oxygen saturation
C. Normal red blood cell mass, high serum erythropoietin levels, low arterial oxygen saturation
D. Normal red blood cell mass, low serum erythropoietin levels, low arterial oxygen saturation

6. Which protein is the primary mediating factor for platelet adhesion?

A. Collagen
B. Endothelin
C. Tissue factor
D. T rombin
E. Von Willebrand factor

Match the following proteins involved in hemostasis with their definition:

7. Glycoprotein IIb/IIIa
8. Tissue factor
9. Plasmin
10. Protein S

A. A vitamin-K–dependent cofactor that accelerates the anticoagulant action of protein C on factors V and VIII
B. T e most abundant receptor on the surface of platelets that binds VWF and fibrinogen
C. T e major protease enzyme of the fibrinolytic system
D. Primary trigger for activation of the coagulation system

11. You are consulted after an episode of postpartum hemorrhage in a 24-year-old woman. T is was her first pregnancy, and she successfully delivered a healthy child at 39 weeks and 4 days. T e child weighed 7 lb 12 oz, and the delivery was an uncomplicated spontaneous vaginal delivery. T e uterine fundus contracted appropriately, but over the course of the next 12 hours, the patient had more than 1 L of bloody discharge. She has felt increasingly weak and has lightheadedness on standing. Her heart rate is 126 bpm and blood pressure is 92/50. She appears pale. Her pulses are thready. Cardiovascular examination shows regular tachycardia. Her hemoglobin prior to delivery was 9.2 g/dL. It is now 6.0 g/dL. Her prothrombin time (PT) is 12.0/INR 1.1, and the activated partial thromboplastin time (aPTT) is 42.5 seconds. Upon further questioning, the patient describes one other episode of prolonged oral bleeding in childhood at about age 7. At that time, she had a cap placed on a tooth and subsequently experienced significant bleeding. She bruises easily, but has not had hemarthroses. She says she stopped playing soccer in grade school due to large bruises after minor injuries that were painful and embarrassing to her. She has had no other surgeries. She is taking iron supplements and prenatal vitamins. She has no allergies. She has a family history of excessive bleeding after a surgical procedure in her father from whom she is estranged. What do you suspect as the cause of the patient's illness?

A. Acquired inhibitor of coagulation
B. Factor VIII deficiency
C. Factor IX deficiency
D. Surreptitious ingestion of an anticoagulant
E. Von Willebrand disease

12. A 68-year-old man is undergoing a total knee replacement for degenerative arthritis. His past medical history is significant for hypertension,

12. (Continued)
diabetes mellitus, hyperlipidemia, gout, and obesity. His medication list includes metoprolol, sitagliptin, metformin, allopurinol, rosuvastatin, and aspirin daily. He is asked to stop his aspirin in preparation for surgery. Which of the following tests are indicated prior to surgery to ensure that the patient is not at increased risk of postoperative bleeding complications?

A. Activated partial thromboplastin time (aPTT)
B. Bleeding time
C. Prothrombin time (PT)
D. A and C
E. A, B, and C

13. A 62-year-old woman is evaluated in hematology clinic after a second episode of deep venous thrombosis. Her first episode occurred at age 34 following a pregnancy, and this episode occurred following an automobile accident that resulted in a femur fracture. She has no family history of DVT or pulmonary embolus. She is requesting a work up for hypercoagulability. Her automobile accident was 2 months ago. She remains casted and has undergone surgical intervention on her fracture 4 weeks prior. She remains on low molecular weight heparin. What do you advise at the current time?

A. Do nothing. No further testing is indicated
B. Send Factor V Leiden and prothrombin 20210
C. Send protein C and S levels
D. Send antithrombin III levels
E. Have the patient return in 3–6 months for further testing

14. A 24-year-old woman seeks evaluation from her primary care provider for a "swollen gland" on the right side of her neck. She first noticed it about 2 weeks ago and has felt fatigued with a sore throat and low-grade fevers throughout this time. On examination, there is dominant 2.0 cm right posterior cervical lymph node that is rubbery and mobile. It is tender to palpation. In addition, there are also several 0.5–1 cm lymph nodes in the bilateral anterior and posterior cervical chains as well as the occipital area. All of the following findings favor a benign diagnosis EXCEPT:

A. Age <50
B. Multiple lymph node involvement
C. Presence of mobility on examination
D. Presence of tenderness to palpation
E. Size of dominant node 2 cm or greater

15. A 58-year-old man presents with complaints of fatigue, dyspnea on exertion, and abdominal pain that is worst on the left side of his abdomen. He has a medical history of difficult to treat hypertension. His medical regimen includes lisinopril 40 mg daily, amlodipine 10 mg daily, hydrochlorothiazide 25 mg daily, and methyldopa 250 mg twice daily. He has been intolerant of beta blockers due to bradycardia. T e most recent medication change was addition of the methyldopa approximately 6 months ago. His vital signs are: HR 110 bpm, RR 18/min, Temp 37.0°C, BP 148/84, and SaO_2 95% on room air. He appears pale with mild jaundice. Scleral icterus is present. His chest examination is clear, and cardiovascular examination shows only a regular tachycardia. T e liver is 10 cm to percussion and palpable 1 cm below the right costal margin. T e spleen is palpable 10 cm below the left costal margin. T ere is no edema. On laboratory examination, the hemoglobin is 7.5 g/dL and hematocrit is 23.2%. T e white blood cell count is 8300/μL with a normal differential and platelets are 123,000/μL. T e peripheral smear shows spherocytes and anisocytosis. AST, ALT, and alkaline phosphatase are normal. T e total bilirubin is 3.3 mg/dL, and the direct bilirubin is 0.4 mg/dL. What is the most likely cause of the patient's splenomegaly?

A. Autoimmune hemolytic anemia
B. Chronic myeloid leukemia
C. Hodgkin's lymphoma
D. Myelofibrosis with myeloid metaplasia
E. Passive congestion due to portal hypertension

16. T e presence of Howell-Jolly bodies, Heinz bodies, basophilic stippling, and nucleated red blood cells in a patient with hairy cell leukemia prior to any treatment intervention implies which of the following?

A. Diffuse splenic infiltration by tumor
B. Disseminated intravascular coagulation (DIC)
C. Hemolytic anemia
D. Pancytopenia
E. Transformation to acute leukemia

17. Which of the following is true regarding infection risk after elective splenectomy?

A. Patients are at no increased risk of viral infection after splenectomy.
B. Patients should be vaccinated 2 weeks after splenectomy.
C. Splenectomy patients over the age of 50 are at greatest risk for postsplenectomy sepsis.
D. Staphylococcus aureus is the most commonly implicated organism in postsplenectomy sepsis.
E. T e risk of infection after splenectomy increases with time.

18. You are an internist at a community hospital and are asked to consult regarding an abnormality seen on a peripheral blood smear. A 64-year-old man was admitted to the orthopedic surgery service for a right total hip replacement surgery. His postoperative course was complicated by an aspiration event and subsequent pneumonia. His white blood cell count rose from 6.3/μL to 12.1/μL with 83% neutrophil and 10% bands. T ere was comment of an abnormal bilobed nucleus in a polymorphonuclear cell seen on the peripheral smear in the majority of granulocytes. T e initial cbc did not have a differential or peripheral smear performed. When you evaluate the smear, you see the following in Figure 18. What is your recommendation?

A. A bone marrow biopsy should be performed
B. A follow-up cbc with differential and peripheral smear should be evaluated in 4–6 weeks to ensure a return to normal
C. No further follow-up is required. T is is a benign inherited disorder
D. No further follow-up is required. T is is an expected reaction to the patient's infection
E. Without a prior peripheral smear for comparison, the acuity of the change is unable to be determined. Either C or D could be correct

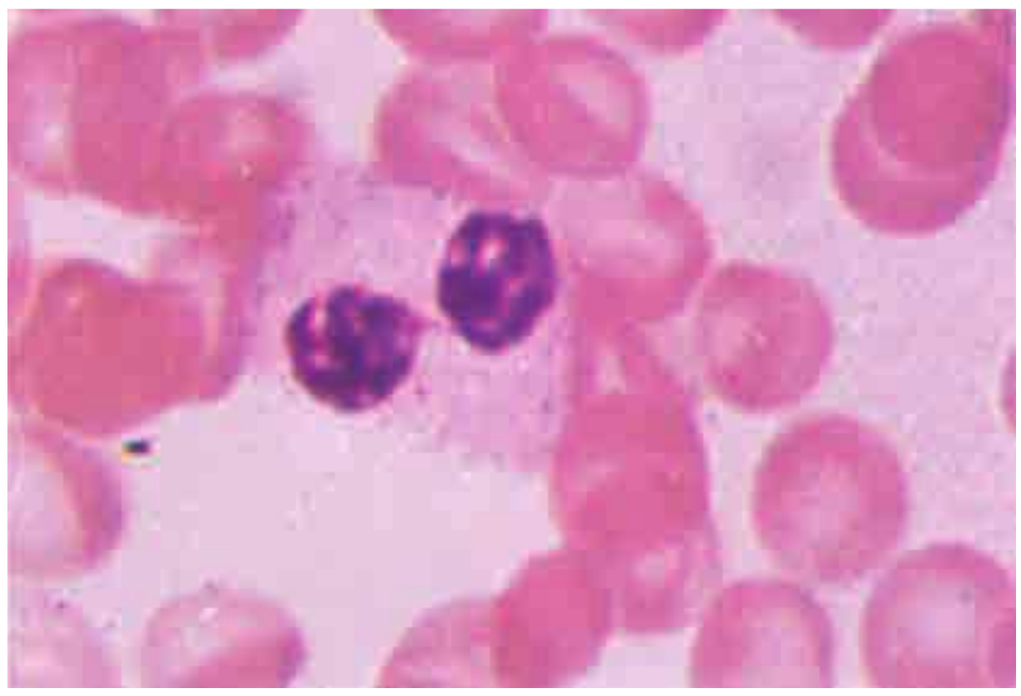


FIGURE 18

19. An 18-year-old man presents with a gastric outlet obstruction. He has had frequent episodes of abdominal pain, diarrhea, and proctitis. A prior colonic biopsy has demonstrated sharply defined granulomas in the colon. In addition, he has had recurrent episodes of pneumonia. He has grown both Staphylococcus aureus and Burkholderia cepacia from his lungs. A dihydrorhodamine oxidation test shows no shift in fuorescence in response to

19. (Continued)
neutrophil stimulation, confirming the suspected diagnosis of chronic granulomatous disease. All of the following would be potentially considered for initial treatment in this patient EXCEPT:

A. Glucocorticoids
B. Inf iximab
C. Interferon-gamma
D. Prophylactic itraconazole
E. Prophylactic trimethoprim-sulfamethoxazole

20. A patient with longstanding HIV infection, alcoholism, and asthma is seen in the emergency room for 1–2 days of severe wheezing. He has not been taking any medicines for months. He is admitted to the hospital and treated with nebulized therapy and systemic glucocorticoids. His CD4 count is 8 and viral load is >750,000. His total white blood cell (WBC) count is 5200 cells /μL with 90% neutrophils. He is accepted into an inpatient substance abuse rehabilitation program and before discharge is started on opportunistic infection prophylaxis, bronchodilators, a prednisone taper over 2 weeks, ranitidine, and highly active antiretroviral therapy. T e rehabilitation center pages you 2 weeks later; a routine laboratory check reveals a total WBC count of 900 cells/μL with 5% neutrophils. Which of the following new drugs would most likely explain this patient's neutropenia?

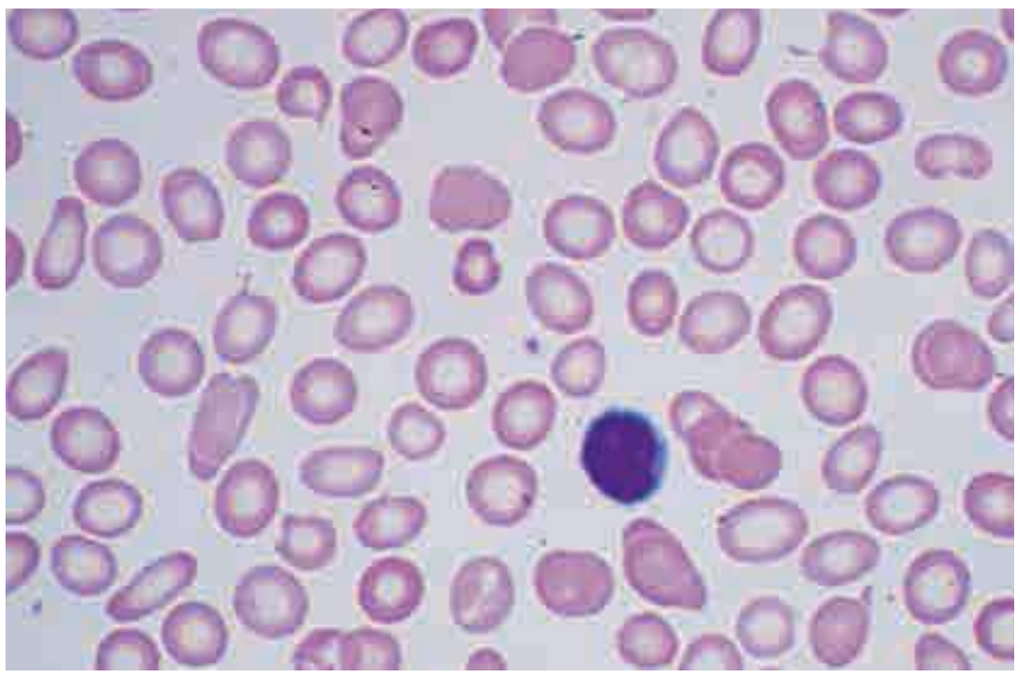
A. Darunavir
B. Efavirenz
C. Ranitidine
D. Prednisone
E. Trimethoprim-sulfamethoxazole

Questions 21 through 25
For each patient below, choose the most likely peripheral blood smear (Figures A through E):

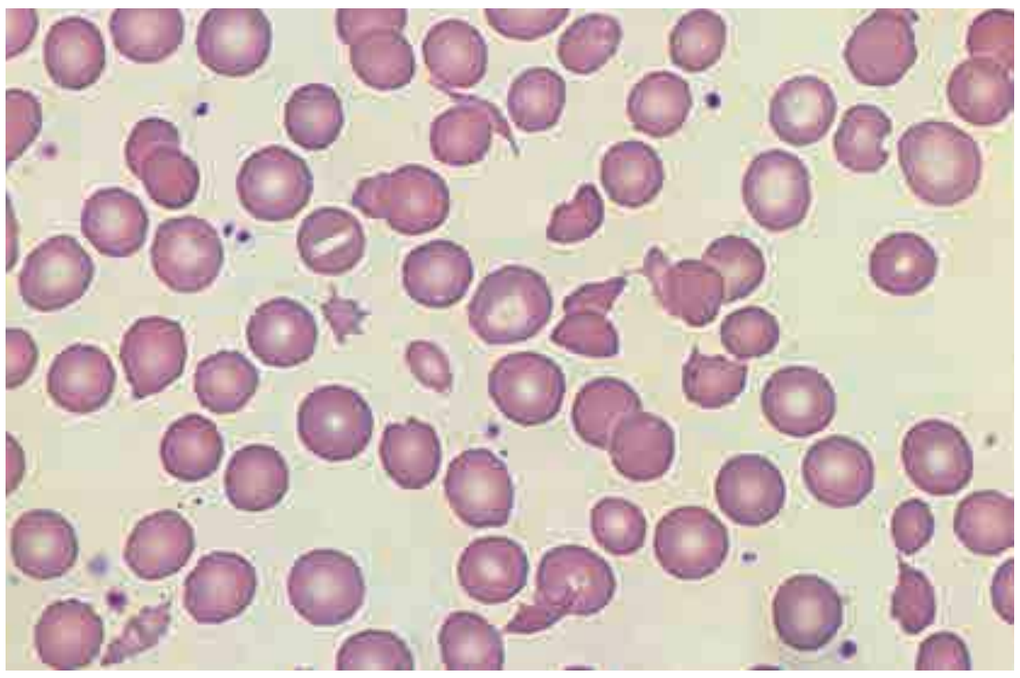
21. A 22-year-old man with a hematocrit of 17%. He has sickle cell disease and is admitted with a vaso-occlusive crisis after an upper respiratory illness.
22. A 36-year-old woman with a hematocrit of 32%. She had a splenectomy 5 years ago after a motor vehicle accident.
23. A 55-year-old man with a hematocrit of 28%. He has advanced alcoholic liver disease with cirrhosis and is awaiting liver transplantation.
24. A 64-year-old woman with a hematocrit of 28%. She has heme-positive stool and a 2-cm adenomatous colonic polyp at colonoscopy.

25. A 72-year-old man with a hematocrit of 33%. Four years ago he received a mechanical prosthetic aortic valve because of aortic stenosis due to a congenital bicuspid valve.

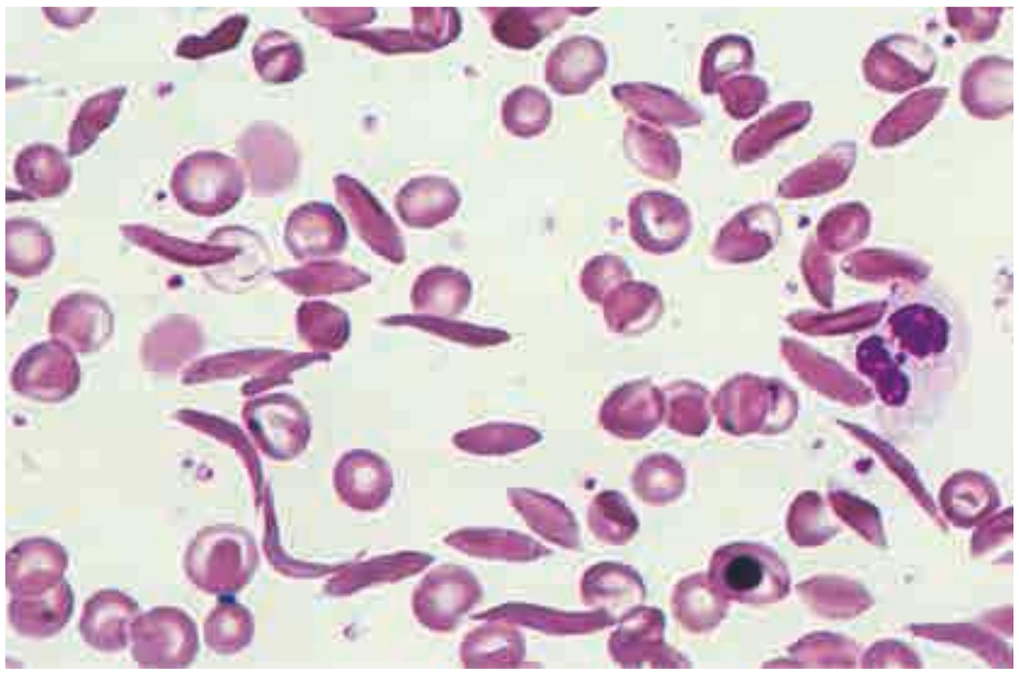
A.



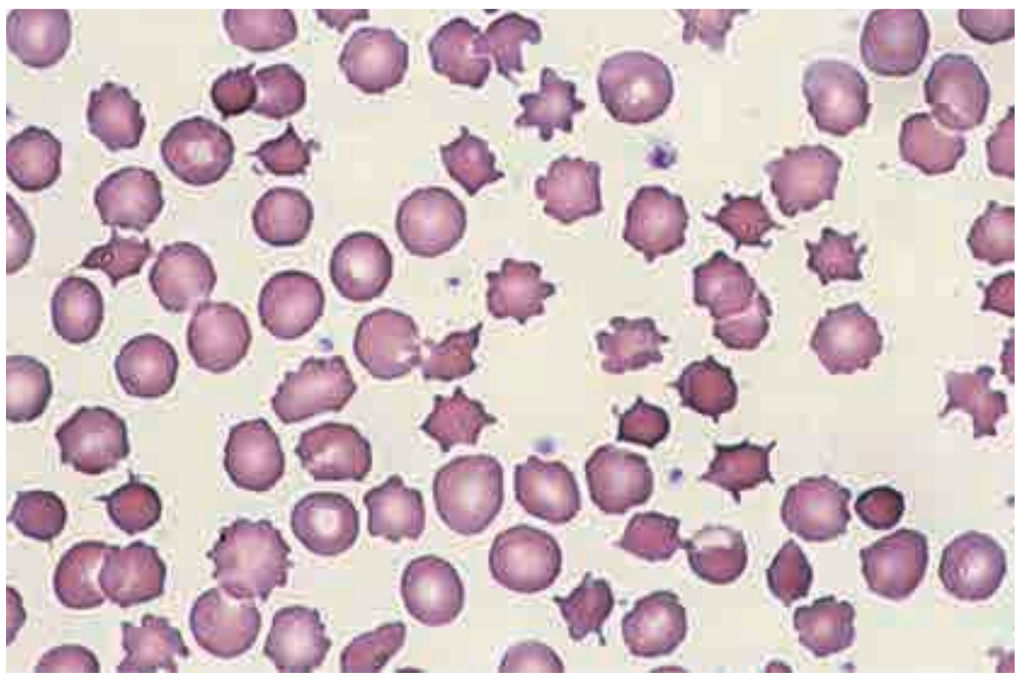
B.



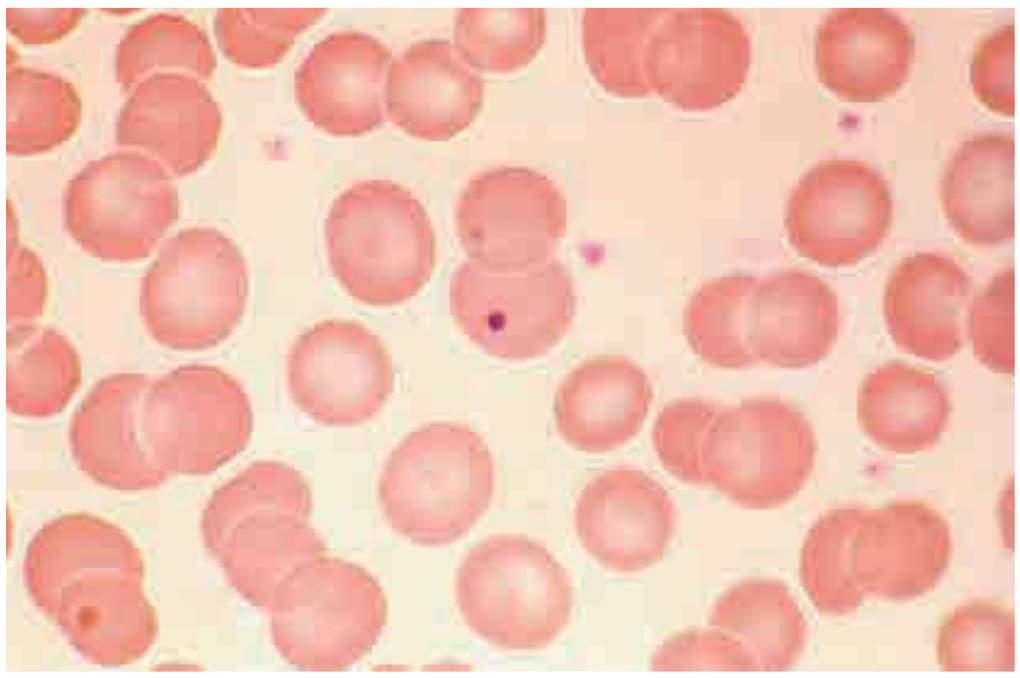
C.



D.



E.



26. Which of the following statements regarding the epidemiology of cancer is true?

A. Cancer has equal mortality rates across all racial groups
B. Cancer is responsible for one out of four deaths in the United States
C. Cancer is the third leading cause of death in the United States
D. Since 1992, the incidence of cancer has been increasing by about 2% each year
E. T e greatest number of cancers in the world occurs in Europe or North America

27. A 42-year-old woman is treated with carboplatin and paclitaxel for stage III ovarian cancer. CT imaging after completing six cycles of therapy shows that the tumor burden has decreased by 25%. What is the best assessment of her response to therapy?

A. Complete response
B. Partial response
C. Progressive disease
D. Stable disease

28. A 68-year-old woman is diagnosed with stage II breast cancer. She has a history of severe chronic obstructive pulmonary disease with an FEV_1 of 32% predicted, coronary artery disease with prior stenting of the left anterior descending artery, peripheral vascular disease, and obesity. She continues to smoke 1–2 packs of cigarettes every day. She requires oxygen at 2 L/min continuously and is functionally quite limited. She currently is able to attend to all of her activities of daily living, including showering and dressing. She retired from her work as a waitress 10 years previously due to her lung disease. At home, she does perform some of the household chores, but is not able to use a vacuum. She does go out once or twice weekly to run typical errands and does drive. She feels short of breath with most of these activities and often utilizes a motorized cart when out and about. How would you categorize her performance status and prognosis for treatment taking this into consideration?

A. She has an Eastern Cooperative Oncology Group (ECOG) grade of 1 and has a good prognosis with appropriate therapy
B. She has an ECOG grade of 2 and has a good prognosis with appropriate therapy
C. She has an ECOG grade of 3 and has a good prognosis with appropriate therapy
D. She has an ECOG grade of 3 and has a poor prognosis despite therapy
E. She has an ECOG grade of 4 and has a poor prognosis that precludes therapy

29. Among women younger than 60 who die from cancer, which of the following is the most common organ of origin?

A. Breast
B. Cervical
C. Colon
D. Leukemia
E. Lung

30. A 24-year-old woman is seen in follow-up 12 months after an allogeneic stem cell transplant for acute myeloid leukemia. She is doing well without evidence of recurrent disease, but has had manifestations of chronic graft versus host disease. She should be administered all of the following vaccines EXCEPT:

A. Diphtheria-tetanus
B. Influenza
C. Measles, mumps, and rubella
D. Poliomyelitis via injection
E. 23-valent pneumococcal polysaccharide

31. A 63-year-old man is treated with paclitaxel and carboplatin chemotherapy for stage IIIB adenocarcinoma of the lung. He presents for evaluation of a fever to 38.3°C (100.9°F). He is found to have erythema at the exit site of his tunneled catheter although the tunnel itself is not tender or red. Blood cultures are negative at 48 hours. His neutrophil count is 1550/μL. What is the best approach to the management of this patient?

A. Removal of catheter alone
B. Treatment with ceftazidime and vancomycin
C. Treatment with topical antibiotics at the catheter site
D. Treatment with vancomycin alone
E. Treatment with vancomycin and removal of catheter

32. A 44-year-old woman has myelodysplastic syndrome and has undergone myeloablative allogeneic stem cell transplant. She has been neutropenic for 10 days and has developed a fever to 39.5°C (103.1°F). She has had a Port-a-cath inserted for her intravenous access for the past 6 months. Her catheter site does not appear inflamed, and she has never tested positive for methicillin-resistant Staphylococcus aureus. What is the best initial choice of antibiotics for this patient?

A. Cefepime
B. Meropenem
C. Piperacillin-tazobactam
D. Any of the above would be acceptable choices
E. Any of the above would be acceptable choice with the addition of vancomycin

33. A 42-year-old man is diagnosed with a stage I malignant melanoma on his left upper arm. Which of the following represents the strongest risk factor(s) for the development of this disease?

A. First degree relative with melanoma
B. Light skin/hair/eye color
C. Number of total body nevi
D. Poor tanning ability
E. A and C

34. A 55-year-old woman presents to her dermatologist with a lesion on her leg that is 8 mm in largest diameter and irregular in shape. She reports this mole has become larger and darker and wants to have it evaluated. Biopsy confirms melanoma that extends 0.5 mm from the surface and into the dermis with <1 mitosis/mm. Which of the following factors has the greatest impact on the patient's prognosis?

34. (Continued)

A. Anatomic site
B. Breslow thickness
C. Clark level
D. Number of mitoses
E. Sex

35. A 46-year-old woman has previously had stage IIb melanoma removed from her upper back. She presents to the emergency room with dyspnea and is found to have multiple lung lesions concerning for metastatic disease. Prior to embarking upon chemotherapy for her disease, the presence of which genetic mutation is an indication for specific therapy?

A. BRAF
B. C-kit
C. ERK
D. N-RAS
E. MEK

36. You confirm the patient has the mutation of interest. Which of the following is recommended?

A. Dacarbazine
B. Interleukin-2
C. Ipilimumab
D. Vemurafenib
E. T e specific therapy depends upon the functional status and desires of the patient

37. All of the following statements regarding nonmelanoma skin cancer are true, EXCEPT:

A. Actinic keratoses and cheilitis are both premalignant forms of squamous cell carcinoma
B. All forms of UV light exposure, including tanning beds, increase the risk of nonmelanoma skin cancers
C. Basal cell carcinoma is most likely to become a metastatic malignancy
D. Keratoacanthomas that regress spontaneously should be treated as aggressively as other squamous cell cancers as they progress to metastatic disease
E. Solid organ transplantation is associated with a marked increased risk of both squamous and basal cell carcinoma that can be aggressive and lead to death

38. A 65-year-old man presents to his primary care physician complaining of a hoarse voice for 6 months. He smokes 1 pack of cigarettes daily and also drinks at least a 6 pack of beer daily. His physical examination

38. (Continued)
reveals a thin man with a weak voice in no distress. No stridor is heard. T e head and neck examination is normal. No cervical lymphadenopathy is present. He is referred to otolaryngologist who discovered a laryngeal lesion. Biopsy reveals squamous cell carcinoma. On imaging, the mass measures 2.8 cm. No suspicious lymphadenopathy is present on PET imaging. What is the best choice of therapy for this patient?

A. Concomitant chemotherapy and radiation therapy
B. Chemotherapy alone
C. Radiation therapy alone
D. Radical neck dissection alone
E. Radical neck dissection followed by concomitant chemotherapy and radiation

39. All of the following have been identified as risk factors for the development of head and neck cancers EXCEPT:

A. Alcohol consumption
B. Epstein-Barr virus infection
C. Helicobacter pylori infection
D. Human papilloma virus infection
E. Tobacco consumption

40. Which of the following statements regarding to a solitary pulmonary nodule is true?

A. A lobulated and irregular contour is more indicative of malignancy than a smooth one
B. About 80% of incidentally found pulmonary nodules are benign
C. Absence of growth over a period of 6–12 months is sufficient to determine if a solitary pulmonary nodule is benign.
D. Ground glass nodules should be regarded as benign
E. Multiple nodules indicate malignant disease

41. A 64-year-old man seeks evaluation for a solitary pulmonary nodule that was found incidentally. He had presented to the emergency department for shortness of breath and chest. A CT pulmonary angiogram did not show any evidence of pulmonary embolism; however, a 9 mm nodule is seen in the periphery of the left lower lobe. No enlarged mediastinal lymph nodes are present. He is a current smoker of 2 packs of cigarettes daily and has done so since the age of 16. He generally reports no functional limitation related to respiratory symptoms. His FEV_1 is 88% predicted, FVC is 92% predicted, and diffusion capacity is 80% predicted.

41. (Continued)
He previously had a normal chest x-ray 3 years previously. What is the next best step in the evaluation and treatment of this patient?

A. Perform a bronchoscopy with biopsy for diagnosis
B. Perform a combined PET/CT to assess for uptake in the nodule and assess for lymph node metastases
C. Perform a follow-up CT scan in 3 months to assess for interval growth
D. Refer the patient to radiation oncology for stereotactic radiation of the dominant nodule
E. Refer the patient to thoracic surgery for video-assisted thoracoscopic biopsy and resection of lung nodule if malignancy is diagnosed

42. A 62-year-old man presents to the emergency room complaining of a droopy right eye and blurred vision for the past day. The symptoms started abruptly, and he denies any antecedent illness. For the past 4 months, he has been complaining of increasing pain in his right arm and shoulder. His primary care physician has treated him for shoulder bursitis without relief. His past medical history is significant for COPD and hypertension. He smokes 1 pack of cigarettes daily. He has chronic daily sputum production and stable dyspnea on exertion. On physical examination, he has right eye ptosis with unequal pupils. His pupil is 2 mm on the right and not reactive whereas the pupil is 4 mm and reactive on the left. However, his ocular movements appear intact. His lung fields are clear to auscultation. On extremity examination, there is wasting of the intrinsic muscles of the hand. Which of the following would be most likely to explain the patient's constellation of symptoms?

A. Enlarged mediastinal lymph nodes causing occlusion of the superior vena cava
B. Metastases to the midbrain from small cell lung cancer
C. Paraneoplastic syndrome caused by antibodies to voltage-gated calcium channels
D. Presence of a cervical rib on chest x-ray
E. Right apical pleural thickening with a mass-like density measuring 1 cm in thickness

43. As an oncologist you are considering treatment options for your patients with lung cancer, including small molecule therapy targeting the epidermal growth factor receptor (EGFR). Which of the following patients is most likely to have an EGFR mutation?

A. A 23-year-old man with a hamartoma
B. A 33-year-old woman with a carcinoid tumor

43. (Continued)
C. A 45-year-old woman who has never smoked with an adenocarcinoma
D. A 56-year-old man with a 100 pack-year history of tobacco with small cell lung carcinoma
E. A 76-year-old man with squamous cell carcinoma and a history of asbestos exposure

44. You are meeting today with Mr. Takei to discuss his recent diagnosis of small cell lung cancer. On reviewing his PET/CT results from earlier today, you note that he has a mass in the hilar region of his left lung, and that he has a moderate pleural effusion there. You know that he underwent thoracentesis of that effusion last week, and so you call the pathologist to get a cytopathology report. He reports the presence of hyperchromic, small basophilic atypical cells in the pleural fluid, consistent with small cell lung cancer. You now know which of the following is true?

A. Thirty percent of patients with SCLC are diagnosed with the same stage of disease as Mr. Takei.
B. Mr. Takei has extensive stage disease.
C. Surgical therapy alone has a high curative rate for Mr. Takei's stage of SCLC.
D. The majority of patients with SCLC of this stage respond to chemotherapy alone and go into remission with a high 2-year survival.
E. Radiation plays no role in therapy for this disease.

45. Which of the following statements regarding screening for lung cancer in the National Lung Screening Trial using low-dose CT scanning is true?

A. Greater than 80% of positive results were found to be malignant after biopsy
B. Positive results were found in approximately 5% of patients over the 3-year trial
C. The trial compared the use of chest radiograph vs low-dose CT scan in patients 30–50 years old
D. There was a reduction in lung cancer mortality in the low-dose CT group
E. There was no difference in all-cause mortality between the CT and radiograph groups

46. A 34-year-old woman is seen by her internist for evaluation of right breast mass. This is was noted approximately 1 week ago when she was showering. She has not had any nipple discharge or discomfort. She has no other medical problems. On examination her right breast has a soft 1 cm by 2 cm mass in the right upper quadrant. There is no axillary lymphadenopathy present. The contralateral breast is normal. The breast is re-examined in 3 weeks and the same

46. (Continued)
findings are present. T e cyst is aspirated and clear fuid is removed. T e mass is no longer palpable. Which of the following statements is true?

A. Breast MRI should be obtained to discern for residual fuid collection
B. Mammography is required to further evaluate the lesion
C. She should be evaluated in 1 month for recurrence
D. She should be referred to a breast surgeon for resection
E. She should not breastfeed any more children

47. Which of the following women has the lowest risk of breast cancer?

A. A woman with menarche at 12 years, first child at 24 years and menopause at 47 years
B. A woman with menarche at 14 years, first child at 17 years and menopause at 52 years
C. A woman with menarche at 16 years, first child at 17 years and menopause at 42 years
D. A woman with menarche at 16 years, first child at 32 years and menopause at 52 years
E. T ey are all equal

48. Which of the following history or physical findings should prompt investigation for hereditary non-polyposis colon cancer screening in a 32-year-old man?

A. Father, paternal aunt, and paternal cousin with colon cancer with ages of diagnosis of 54, 68, and 37 years, respectively
B. Innumerable polyps visualized on routine colonoscopy
C. Mucocutaneous pigmentation
D. New diagnosis of ulcerative colitis
E. None of the above

49. A 64-year-old woman presents with complaints of a change in stool caliber for the past 2 months. T e stools now have a diameter of only the size of her fifth digit. Over this same period, she feels she has to exert increasing strain to have a bowel movement and sometimes has associated abdominal cramping. She often has blood on the toilet paper when she wipes. During this time, she has lost about 20 lb with a decreased appetite. On physical examination, the patient appears cachectic with a body mass index of 22.5 kg/m^2. T e abdomen is f at and nontender. T e liver span is 12 cm to percussion. On digital rectal examination, a mass lesion is palpated approximately 6 cm into the rectum.

49. (Continued)
A colonoscopy is attempted which demonstrates a 2.5-cm sessile mass that narrows the distal colonic lumen. T e biopsy confirms adenocarcinoma. T e colonoscope is not able to traverse the mass. A CT scan of the abdomen does not show evidence of metastatic disease. Liver function tests are normal. A carcinoembryonic antigen level is 4.2 ng/mL. T e patient is referred for surgery and undergoes rectosigmoidectomy with pelvic lymph node dissection. Final pathology demonstrates extension of the primary tumor into the muscularis propria, but not the serosa. Of 15 lymph nodes removed, 2 are positive for tumor. What do you recommend for this patient following surgery?

A. Chemotherapy with a regimen containing 5-fuorouracil
B. Complete colonoscopy within 3 months
C. Measurement of CEA levels at 3 month intervals
D. Radiation therapy to the pelvis
E. All of the above

50. A 56-year-old man presents to a physician with weight loss and dysphagia. He feels that food gets stuck in his mid-chest such that he no longer is able to eat meats. He reports his diet consists primarily of soft foods and liquids. T e symptoms have progressively worsened over 6 months. During this time, he has lost about 50 lb. He occasionally gets pain in his mid-chest that radiates to his back and also occasionally feels that he regurgitates undigested foods. He does not have a history of gastroesophageal ref ux disease. He does not regularly seek medical care. He is known to have hypertension, but takes no medications. He drinks 500 cc or more of whiskey daily and also smokes 1.5 packs of cigarettes per day. On physical examination, the patient appears cachectic with temporal wasting. He has a body mass index of 19.4 kg/m^2. His blood pressure is 198/110, heart rate 110 bpm, respiratory rate 18/min, temperature 37.4°C (99.2°F), and oxygen saturation is 93% on room air. His pulmonary examination shows decreased breath sounds at the apices with scattered expiratory wheezes. His cardiovascular examination demonstrates an S4 gallop with a hyperdynamic precordium. A regular tachycardia is present. Blood pressures are equal in both arms. Liver span is not enlarged. T ere are no palpable abdominal masses. What is the most likely cause of the patient's presentation?

A. Adenocarcinoma of the esophagus
B. Ascending aortic aneurysm
C. Esophageal stricture
D. Gastric cancer
E. Squamous cell carcinoma of the esophagus

51. Which of the following risk factors is associated with BOTH adenocarcinoma and squamous cell carcinoma of the esophagus?

A. Barrett's esophagus
B. Chronic gastroesophageal ref ux disease
C. Cigarette smoking
D. Lye ingestion
E. Male sex

52. All of the following conditions are known to increase the risk of developing hepatocellular carcinoma EXCEPT:

A. Cirrhosis from any cause
B. Hepatitis C infection
C. Malaria
D. Nonalcoholic fatty liver (NAFL)
E. Nonalcoholic steatohepatitis (NASH)

53. A 59-year-old man with known cirrhosis due to prior hepatitis C infection is brought to the clinic by his family due to complaints of 1 month of worsening malaise, abdominal bloating, and nausea with 1 week of right upper quadrant pain. His physical examination is notable for normal vital signs (baseline low blood pressure) and new hepatomegaly. Which of the following statements is true regarding the possibility of hepatocellular carcinoma?

A. FDG-PET scan is more sensitive for showing primary tumor than CT or ultrasound
B. Hepatomegaly is an uncommon finding in hepatocellular carcinoma
C. Imaging criteria alone (without biopsy) have a <75% specificity for the diagnosis
D. Serum alfa-fetoprotein (AFP) is the most sensitive but nonspecific test
E. Ultrasound is an excellent screening test for this patient

54. T e patient described above is found to have a 4-cm single lesion hepatocellular carcinoma. His performance status is excellent despite his recent decline. He still works as a web designer and walks over 10,000 steps daily. Based on this information, he may be eligible for all of the following therapies EXCEPT:

A. Cadaveric liver transplant
B. Living donor liver transplant
C. Local ablation with ethanol injection
D. Local radiofrequency ablation
E. Primary resection

55. All of the following statements regarding cholangiocarcinoma are true EXCEPT:

A. Asians infected with liver f ukes have an increased risk of cholangiocarcinoma
B. In eligible patients with cholangiocarcinoma, liver transplant plus radiation has a >60% 5-year recurrence-free survival
C. Most patients present due to an abnormal screening ultrasound, without symptoms
D. Primary biliary cirrhosis and hepatitis C virus infection are associated with cholangiocarcinoma
E. T e incidence of cholangiocarcinomas is increasing in recent years

56. All of the following statements regarding pancreatic cancer are true EXCEPT:

A. Alcohol consumption is not a risk factor for pancreatic cancer
B. Cigarette smoking is a risk factor for pancreatic cancer
C. Despite accounting for <5% of malignancies diagnosed in the United States, pancreatic cancer is the 4th leading cause of cancer death
D. If detected early, the 5-year survival is up to 20%
E. T e 5-year survival rates for pancreatic cancer have improved substantially in the last decade

57. A 65-year-old man is evaluated in clinic for 1 month of progressive painless jaundice and 10 lb unintentional weight loss. His physical examination is unremarkable. A dual phase contrast CT shows a suspicious mass in the head of the pancreas with biliary ductal dilation. Which of the following is the best diagnostic test to evaluate for suspected pancreatic cancer?

A. CT guided percutaneous needle biopsy
B. Endoscopic ultrasound guided needle biopsy
C. ERCP with pancreatic juice sampling for cytopathology
D. FDG-PET imaging
E. Serum CA 19-9

58. A 63-year-old man presents to his internist with 3 months of worsening painless jaundice and anorexia. Further evaluation reveals a 1.5-cm obstructing lesion in the head of the pancreas that is confirmed as pancreatic adenocarcinoma by endoscopic ultrasound biopsy. T e patient undergoes a modified Whipple procedure and is found to have a 1.6-cm primary tumor with no microscopic residual disease and negative lymph nodes. Which of the following statements regarding this patient is true?

58. (Continued)

A. He has a >75% expected 5-year survival after surgery
B. He has pathologic stage 2 disease
C. He should receive adjuvant chemotherapy
D. T e presence of SMAD4 gene inactivation in the tumor is a positive prognostic sign
E. T is presentation accounts for approximately 25% of patients with pancreatic cancer

59. A 63-year-old man complains of notable pink tinged urine for the last month. At first he thought it was due to eating beets, but has not cleared. His medical history is notable for hypertension and cigarette smoking. He does report some worsening urinary frequency and hesitancy over the last 2 years. Physical examination is unremarkable. Urinalysis is notable for gross hematuria with no white cells or casts. Renal function is normal. Which of the following statements regarding this patient is true?

A. Cigarette smoking is not a risk for bladder cancer
B. Gross hematuria makes prostate cancer more likely than bladder cancer
C. If invasive bladder cancer with nodal involvement but no distant metastases is found, 5-year survival is 20%
D. If superficial bladder cancer is found, intravesicular BCG may be used as adjuvant therapy
E. Radical cystectomy is generally recommended for invasive bladder cancer

60. A 68-year-old man comes to his physician complaining of 2 months of increasing right f ank pain with 1 month of worsening hematuria. He was treated for cystitis at a walk-in clinic 3 weeks ago with no improvement. He also reports poor appetite and 5 lb weight loss. His physical examination is notable for a palpable mass in the right f ank measuring >5 cm. His renal function is normal. All of the following are true about this patient's likely diagnosis EXCEPT:

A. Anemia is more common than erythrocytosis
B. Cigarette smoking increased his risk
C. If his disease has metastasized, with best therapy 5-year survival is >50%
D. If his disease is confined to the kidney, 5-year survival is >80%
E. T e most likely pathology is clear cell carcinoma

61. In the patient described above, imaging shows a 10-cm solid mass in the right kidney and multiple nodules in the lungs consistent with metastatic disease. Needle biopsy of a lung lesion confirms the

61. (Continued)
diagnosis of renal cell carcinoma. Which of the following is recommended therapy?

A. Gemcitabine
B. Interferon gamma
C. Interleukin-2
D. Radical nephrectomy
E. Sunitinib

62. Which of the following has been shown in randomized trials to reduce the future risk of pancreatic cancer diagnosis?

A. Finasteride
B. Selenium
C. Testosterone
D. Vitamin C
E. Vitamin E

63. A 54-year-old man is evaluated in an executive health program. On physical examination he is noted to have an enlarged prostate with a right lobe nodule. He does not recall his last digital rectal examination and has never had prostate-specific antigen (PSA) tested. Based on this evaluation, which of the following is next recommended?

A. Bone scan to evaluate for metastasis
B. PSA
C. PSA now and in 3 months to measure PSA velocity
D. Repeat digital rectal examination in 3 months
E. Transrectal ultrasound guided biopsy

64. Which of the following statements regarding use of prostate-specific antigen (PSA) is true?

A. Asymptomatic men with an elevated PSA should receive a 2-week course of antibiotics before repeating PSA and considering biopsy
B. Most prostate cancer deaths occur in men with PSA levels below the top quartile
C. PSA is produced by malignant and nonmalignant prostate cells
D. T e American Urological Association recommends PSA screening in men 40–55 years of age
E. T e US Preventive Services Task Force recommends PSA screening in men between 55 and 69 years of age

65. All of the following medications may be useful in the treatment of benign prostatic hypertrophy EXCEPT:

65. (Continued)

A. Alfuzosin
B. Bosentan
C. Dutasteride
D. Finasteride
E. Sildenafil

66. A 26-year-old man presents with pain and swelling of his right testicle that has persisted after an empiric treatment for epididymitis. Ultrasound confirms a 1.5 × 2 cm solid mass, suspicious for testicular cancer. Radical inguinal orchiectomy confirms the mass as a seminoma with disease limited to the testis (tumor stage pT1). Chest, abdomen, and pelvis CT shows no evidence of metastatic disease or lymphadenopathy. Results of serum tumor markers demonstrate the following: AFP 5 ng/mL (<10 ng/mL), β-human chorionic gonadotropin (β-hCG) 182 U/L (0.2–0.8 U/L), and LDH 432 U/L (100–190 U/L). Following resection, all tumor markers become undetectable after an appropriate interval. Which is the next best step in this patient's treatment?

A. Immediate retroperitoneal radiation therapy
B. Nerve-sparing retroperitoneal lymph node dissection
C. Single dose therapy with cisplatin
D. Surveillance alone with treatment only if relapse detected
E. Either A or D are associated with a near 100% cure rate

67. Which of the following statements describes the relationship between testicular tumors and serum markers?

A. β-hCG and AFP should be measured in following the progress of a tumor
B. β-hCG is limited in its usefulness as a marker because it is identical to human luteinizing hormone
C. Measurement of tumor markers the day after surgery for localized disease is useful in determining completeness of the resection.
D. More than 40% of nonseminomatous germ cell tumors produce no cell markers
E. Pure seminomas produce AFP or β-hCG in more than 90% of cases.

68. All of the following statements regarding the risk of ovarian cancer are true EXCEPT:

A. Ten percent of women with ovarian cancer have a germline mutation in either BRACA1 or BRACA2
B. Early prophylactic oophorectomy in women with BRACA1 or BRACA2 mutations reduces the risk of developing subsequent breast cancer
C. Individuals with a single copy of a BRACA1 or BRACA2 mutant allele have an increased risk of breast and ovarian cancer
D. Women with a mutation in BRACA1 have a higher risk of ovarian cancer than woman with a mutation in BRACA2
E. Women with BRACA1, BRACA2, or other at risk germ line mutations should be screened with serial measurement of the CA-125 tumor marker

69. A 42-year-old woman seeks evaluation for over 6 months of post-coital bleeding without dyspareunia. She also notes some recent spotting between her regular menses. She has no past medical history, is unmarried with multiple sexual partners and unprotected sex, and works as an accountant. She has not sought gynecologic evaluation for over 10 years. Pelvic examination reveals an abnormal appearance of the cervix with an abnormal Pap smear, positive HPV test, and negative HIV, chlamydia, gonorrhea, and syphilis studies. A cervical biopsy shows squamous cell carcinoma confined to the cervix. All of the following statements regarding this woman's condition are true EXCEPT:

A. Cervical cancer is an uncommon cancer worldwide
B. Her cancer is related to HPV infection
C. HPV vaccination before initiation of sexual activity can decrease the risk of developing an abnormal Pap smear
D. She has stage 1 cervical cancer
E. With surgical therapy her 5-year survival is >80%

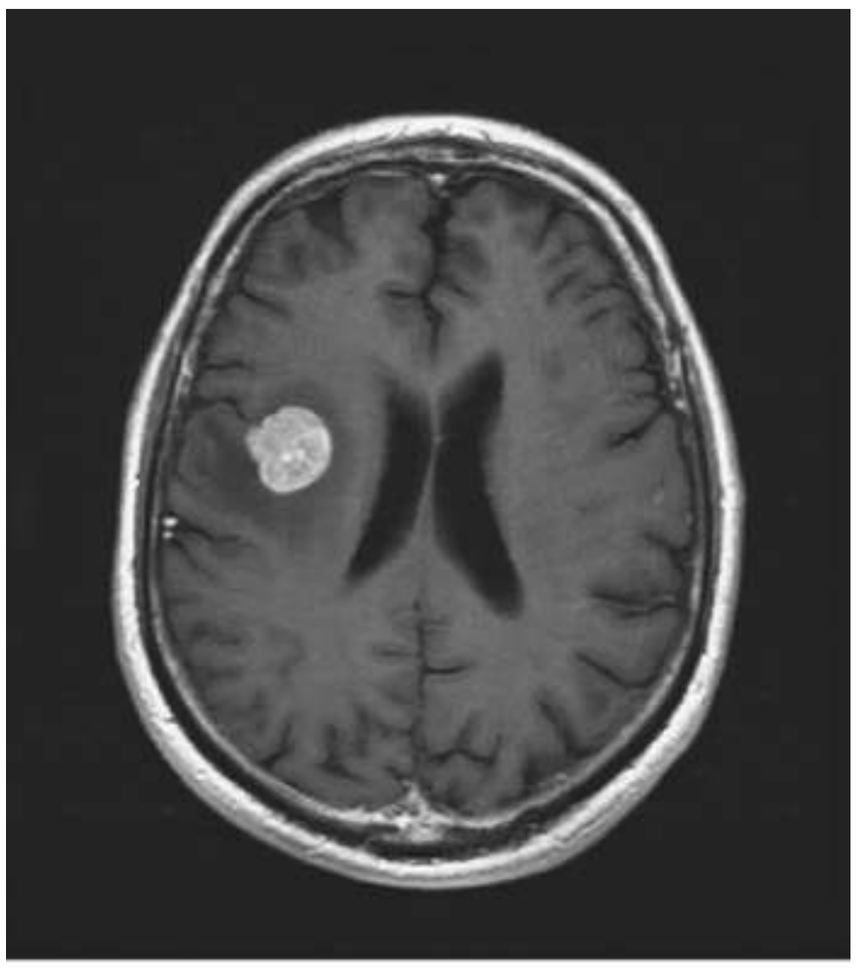
70. Which of the following statements regarding the presentation and evaluation of suspected brain malignancy is true?

A. A low grade glioma is more likely to present with a new seizure than a high grade glioma
B. Approximately half of all malignant brain lesions are metastatic with the other half being all primary brain tumors combined
C. CT with intravenous contrast is the preferred radiologic study to evaluate a suspected intracranial tumor
D. Headache is present at presentation in over 75% of patients with brain tumors
E. High grade gliomas are more likely to present with headache and alteration in cognitive function than metastatic lesions

71. A 63-year-old woman presents to the emergency department after developing a new onset seizure. Family members came to her when they heard a

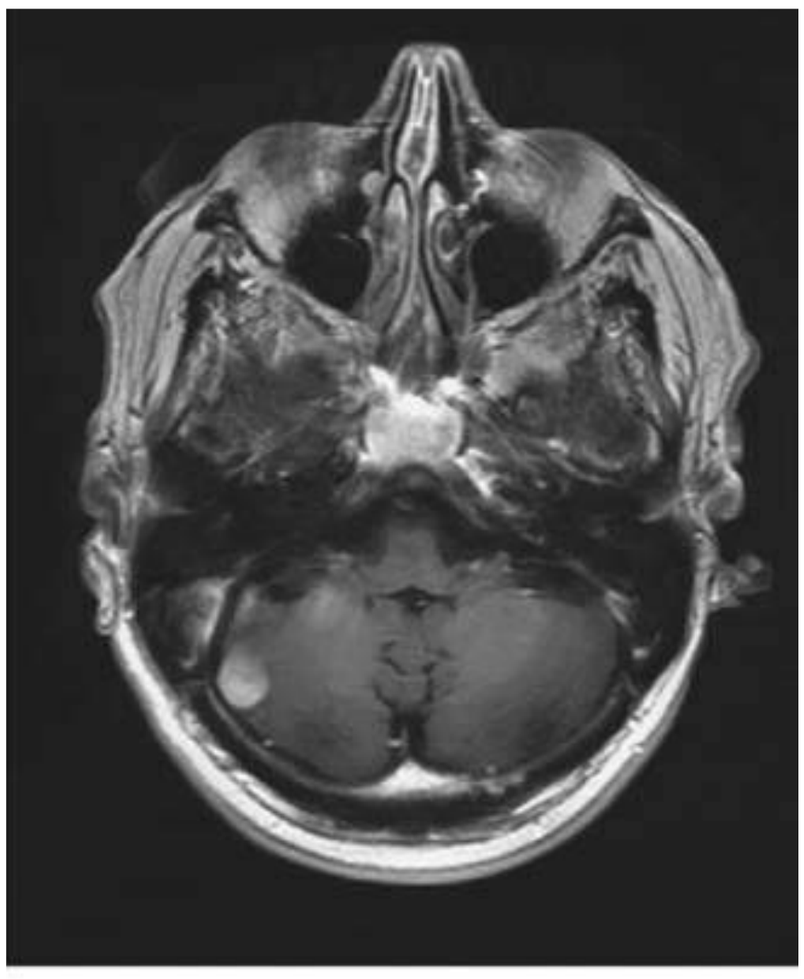
71. (Continued)

commotion in her bedroom and found her having a tonic-clonic seizure that spontaneously ended after about 1 minute. She has no prior neurologic history, her medical history is only notable for hypertension controlled with a diuretic and 40 pack years of cigarette smoking. T ere is no history of illicit drug



A

FIGURE 71A



B

FIGURE 71B

71. (Continued)

use and she has been in excellent health until this episode. She works as a congressional staffer in a legislative office. Her physical examination is unremarkable; she is somnolent and disoriented after receiving lorazepam by the emergency medical team. She receives an urgent head MRI with contrast (see Figures 71A and 71B). T e largest lesion visualized is less than 3 cm in diameter. Which of the following statements is true about her likely diagnosis?

A. Metastatic lesions due to ovarian carcinoma are more likely than metastatic lesions due to a lung carcinoma
B. She is likely a candidate for platinum-based chemotherapy
C. She likely has a primary brain malignancy
D. She may be a candidate for stereotactic radiosurgery
E. Stereotactic radiosurgery and whole brain radiation have similar mortality outcomes for metastatic disease

72. A 55-year-old woman presents to the emergency department after a minor motorcycle collision complaining of diffuse chest pain. Her chest radiograph shows multiple 2–4 cm nodules and masses without cavitation in all lobes. Her physical examination is totally normal other than some diffuse chest. She has no past medical history and takes no medications, other than a multivitamin. She exercises regularly and had negative colonoscopy and mammogram within the last 2 years. She works as a librarian and rides motorcycles for recreation. T ere is no history of cigarette or illicit drug use. Abdominal, pelvic, and head imaging shows no likely primary lesions. A bronchoscopic biopsy of a lung lesion is performed and shows histology consistent with moderately well differentiated adenocarcinoma. T ere were no airway abnormalities. Her FDG-PET scan shows no lesions other than those in the lung, and repeat colonoscopy and mammography are normal. All of the following statements regarding her carcinoma are true EXCEPT:

A. Gene expression profiles may help determine the original primary carcinoma and aid in determining the most appropriate therapy
B. Immunohistochemical staining of cytokeratin 7 (CK 7) and cytokeratin 20 (CK 20) may help determine the most appropriate therapy
C. Median survival of patients with carcinoma of uncertain primary is approximately 18 months
D. Moderately differentiated adenocarcinoma is the most common histology of carcinoma of unknown primary
E. Prognostic factors including performance status and LDH level may identify patients most amenable to therapy

73. A 63-year-old woman is brought to the emergency room by her nephew because of severe confusion and obtundation. Her vital signs are normal and there are no focal physical findings. She is found to have hypercalcemia with a serum level of 14.8 mg/dL along with minimal elevation of BUN and creatinine. Initial evaluation reveals a chest radiograph with multiple nodules suggestive of metastatic disease. Unfortunately the nephew does not know anything about his aunt's medical history. He reports that she was in town attending a healing yoga conference. Subsequent laboratory testing reveals a normal parathyroid hormone level and an elevated parathyroid hormone-related protein level. All of the following are a likely primary malignancy in this woman EXCEPT:

A. Adenocarcinoma of the breast
B. Mantle cell lymphoma
C. Squamous cell of the lung
D. Squamous cell of the piriform sinus
E. Transitional cell of the bladder

74. In the patient described above, she should receive treatment with all of the following for her hypercalcemia EXCEPT:

A. Calcitonin
B. Furosemide
C. Normal saline
D. Pamidronate
E. Prednisone

75. A 61-year-old woman is diagnosed with stage 2 breast carcinoma. She receives a mastectomy where she is found to have 1 positive lymph node. T e tumor is positive for estrogen-receptor, progestin-receptor, and overexpression of Her2/Neu. She receives adjuvant chemotherapy with doxorubicin, cisplatin, and trastuzumab. Match the concerning toxicity with the appropriate agent.

1. Cisplatin
2. Doxorubicin
3. Trastuzumab

A. Reversible cardiomyopathy
B. Irreversible cardiomyopathy
C. Sensorimotor neuropathy

ANSWERS

1. **T e answer is D.**
(Chap. 2) Normal erythropoiesis requires proper erythropoietin (EPO) production, proliferative capacity of the bone marrow, availability of iron and other cofactors, and effective maturation of red blood cell (RBC) precursors. T e physiologic regulator of RBC production is EPO, a glycoprotein produced in the peritubular capillary lining cells of the kidney. EPO production and gene regulation is controlled by hypoxia inducible factor-1α, which is upregulated in response to hypoxia. EPO then stimulates the early progenitor cells in the bone marrow to increase in number and, in turn, to produce more RBCs. T e first morphologically recognizable RBC precursor is the pronormoblast. T is cell divides 4–5 times to generate a total of 16–32 mature RBCs. With EPO stimulation, red cell production increases markedly up to 4–5 fold, reaching maximum capacity within a 1–2 week period. In the absence of EPO, however, erythroid progenitor cells will undergo apoptosis or programmed cell death. Overall, normal red cell production and turnover result in the replacement of 0.8–1.0% of the red cell population on a daily basis.

2. **T e answer is E.**
(Chap. 2) T e patient presents with a microcytic anemia in the setting of heavy menses and a vegetarian diet that may be low in iron. She is most likely to have an iron deficiency anemia, which results in a hypoproliferative bone marrow relative to the degree of anemia. At least 75% of all anemias are hypoproliferative in nature, with iron deficiency being the most common cause. Iron deficiency anemia results in a characteristic microcytic hypochromic anemia. On laboratory examination, this is manifest as a low mean corpuscular volume, low mean corpuscular hemoglobin, and low mean corpuscular hemoglobin concentration. T e peripheral blood smear in iron deficiency anemia characteristically shows microcytosis (small cells) and hypochromia (pale cells) with small cells with central pallor. However, there is also marked anisocytosis (unequal size cells) and poikilocytosis (abnormal shape cells) with cells of many different sizes and shapes. T e degree of anisocytosis typically correlates with the red cell distribution width (RDW) as measured on the complete blood count. Poikilocytosis results in cells of many different shapes and represents a defect of red cell maturation in the bone marrow or fragmentation or circulating red cells. T us, all of the findings can be seen in severe iron deficiency anemia. T e next step in the workup of this patient would be to perform iron studies, including ferritin, iron, transferrin, and total iron binding capacity.

3. **T e answer is E.**
(Chap. 2) T is patient has an asymptomatic microcytosis and hypochromia as evidenced by a low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH), but is not anemic. T is is typical of individuals with alpha thalassemia trait. T alassemias are inherited disorders of hemoglobin production that results in production of an abnormal alpha or beta globin. Alpha thalassemias are most common in individuals of African, Asian, Middle Eastern, or Mediterranean descent. T e production of alpha globulin is encoded by 4 α-globin genes, 2 each on chromosome 16 (α α/ α α). Alpha thalassemia trait results when there is a defect in 2 of the α-globin genes (-α/-α or --/α α). Overall, the production of the α-globin is adequate to yield normal hemoglobin and not result in excessive hemolysis. However, microcytosis and hypochromia are seen. Hematocrit is normal or only minimally reduced while RBC count may be increased. In addition, to microcytosis and hypochromia, the characteristic finding on peripheral smear is the target cell. T ese cells have a bulls-eye appearance and can also be seen in liver disease. Burr cells are typically seen in uremia and show multiple spiny projections. Howell-Jolly bodies are nuclear remnants that can be seen in some RBCs in individuals who have undergone splenomegaly as these proteins are not easily cleared in these individuals. Schistocytes are RBC fragments that can be seen in individuals who are experiencing intravascular hemolysis. Spherocytes are small dense red cells that lack central pallor and biconcavity. T ey are typically seen in hereditary spherocytosis, but can also be seen in other autoimmune hemolytic anemias (AIHAs).

4. **T e answer is C.**
(Chap. 2) T is blood smear shows fragmented RBCs of varying size and shape. In the presence of a foreign body within the circulation (prosthetic heart valve, vascular graft), RBCs can become destroyed. Such intravascular hemolysis will also cause serum lactate dehydrogenase to be elevated and hemoglobinuria. In isolated extravascular hemolysis, there is no hemoglobin or hemosiderin released into the urine. T e characteristic peripheral blood smear in splenomegaly is the presence of Howell-Jolly bodies (nuclear remnants within RBCs). Certain diseases

are associated with extramedullary hematopoiesis (e.g., chronic hemolytic anemias), which can be detected by an enlarged spleen, thickened calvarium, myelofibrosis, or hepatomegaly. T e peripheral blood smear may show tear-drop cells or nucleated RBCs. Hypothyroidism is associated with macrocytosis, which is not demonstrated here. Chronic gastrointestinal blood loss will cause microcytosis, not schistocytes.

5. T e answer is B.
(Chap. 2) T e first step in diagnosing polycythemia vera is to document an elevated RBC mass. A normal RBC mass suggests spurious polycythemia. Next, serum EPO levels should be measured. If EPO levels are low, the diagnosis is polycythemia vera. Confirmatory tests include JAK-2 mutation analysis, leukocytosis, and thrombocytosis. Elevated EPO levels are seen in the normal physiologic response to hypoxia as well as in autonomous production of EPO. Further steps in the workup include evaluation for hypoxia with an arterial blood gas, consideration of smoker's polycythemia (elevated carboxyhemoglobin levels) and disorders of increased hemoglobin affinity for oxygen. Low serum EPO levels with low oxygen saturation suggest inadequate renal production (renal failure). High RBC mass and high EPO levels with normal oxygen saturation may be seen with autonomous EPO production, such as in renal cell carcinoma.

6. T e answer is E.
(Chap. 3) Upon injury, hemostasis is achieved via platelet adhesion and aggregation along with fibrin clot formation. T e initial step in the process of hemostasis is platelet adhesion. T is is primarily mediated by von Willebrand factor (vWF). vWF is a very large multimeric protein that is found in both the plasma and in the extracellular matrix of the subendothelial vessel wall. It acts almost like "molecular glue" as it binds the platelets with enough strength to allow them to withstand shear stress and prevent detachment. Platelet adhesion also occurs to a lesser degree with subendothelial collagen through specific platelet membrane collagen receptors.

7. T e answer is B.

8. T e answer is D.

9. T e answer is C.

10. T e answer is A.
(Chap. 3) Hemostasis involves a balance of procoagulant and anticoagulant forces. T e procoagulant forces include platelet adhesion and aggregation and fibrin clot formation whereas the anticoagulant system includes the natural inhibitors of coagulation and the process of fibrinolysis. T ere are many proteins required to balance this system which is finely tuned to be ready to initiate coagulation upon injury and arrest bleeding quickly. Upon injury, platelets quickly adhere to the site of injury by binding to vWF primarily and to exposed subepithelial collagen to a lesser extent. After the initial platelet adhesion, platelets become activated to promote further aggregation to promulgate the clot. T is process is mediated in part through the action of the glycoprotein IIb/IIIa receptor on the platelet surface. T e protein is the most abundant receptor on the platelet surface. Upon platelet activation, the glycoprotein IIb/IIIa receptor can bind vWF and fibrinogen, furthering platelet aggregation. Fibrin clot formation is classically thought of occurring via the intrinsic and extrinsic pathways. It is now known that coagulation is normally initiated through exposure to tissue factor (the classic extrinsic pathway) with important amplification through the element of the intrinsic pathway. T ere are many dynamic interactions that occur with tissue factor activation. Tissue factor binds the cofactor VIIa and can act to directly activate factor X or it can activate factor IX, which in turn acts with factor VIIIa to activate factor X. Activated factor X then converts prothrombin to thrombin, which in turn has a positive feedback on the coagulant system by activating factor XI (the classic intrinsic pathway) (see **Figure 3-1**). T rombin is a multifunctional enzyme which also converts fibrinogen to fibrin to promulgate clot formation. T e body has several antithrombotic mechanisms to counteract the coagulant system. Antithrombin is the major protease inhibitor of thrombin and the other clotting factors of the coagulation system. Protein C is a plasma glycoprotein that is activated by thrombin and acts to inactivate factors V and VIII. T is process is accelerated by the cofactor protein S, which is a glycoprotein that like protein C undergoes vitamin-K–dependent post-translational modification. Tissue factor pathway inhibitor (TFPI) is a protease that acts near the binding site for TF and factor VIIa to down regulate the coagulation pathway. In addition to these anticoagulants, there is an active process of fibrin degradation. Plasmin is the major protease of the fibrinolytic system, breaking fibrin down to fibrin degradation products.

11. T e answer is E.
(Chap. 3) T is individual has experienced significant bleeding that is primarily mucosal in origin (postpartum hemorrhage, prior oral bleeding). T is

suggests a disorder of primary hemostasis, or platelet plug formation. von Willebrand disease (vWD) is the only disease listed that is a disorder of primary hemostasis. Bleeding symptoms that are common in vWD include prolonged bleeding after surgery, including dental procedures, menorrhagia, postpartum hemorrhage, and large bruises or hematomas, even with minor trauma. Epistaxis is also common, but occurs in many other diseases as well. So a clinician should assess for other symptoms prior to ascribing the symptom to a disorder of platelet function. T e postpartum hemorrhage can be delayed beyond the immediate period of delivery. Hemarthroses are rare in vWD unless the disease is very severe. All of the other disorders listed affect anticoagulant levels.

12. T e answer is C.
(Chap. 3) T e most important part of determining bleeding risk prior to surgery is a careful history and physical examination. Routine testing for preoperative evaluation should include a prothrombin time as this test may detect a previously unknown vitamin K deficiency or unsuspected liver disease. Although it is commonplace to concomitantly assess the activated partial thromboplastin time, the utility of this practice has not been validated in patients undergoing surgery in the absence of a bleeding history. T e bleeding time has previously been used to assess bleeding risk, but has not been shown to have any predictive value in determining individuals at increased bleeding risk during surgery. So it should not be ordered.

13. T e answer is A.
(Chap. 3) Deciding which individuals require workup for hypercoagulability and the timing of the workup is a difficult diagnostic dilemma. T is scenario presents an individual with two clotting episodes separated in time by a prolonged period and with clear risk factors. It is not likely that she would have a hypercoagulable state and would not require further workup. However, limited testing could be performed at this point. Laboratory assays for thrombophilia include both molecular diagnostics for inherited risk factors for thrombophilia as well as immunologic and functional assays. Molecular diagnostics are not indicated in the absence of a strong family history of thrombosis. Levels of coagulation factors are affected by acute thrombosis, acute illness, inf ammatory conditions, pregnancy, and medications. Antithrombin levels are decreased by heparin and in the setting of acute thrombosis. Protein C and S levels are decreased by warfarin and increased in the setting of acute thrombosis. Antiphospholipid antibody levels may even be transiently positive in acute illness. In most instances of acute thrombosis, anticoagulation with warfarin would be continued for 3–6 months. If a decision is made to perform a workup for a hypercoagulable state, it can be done at least 3 weeks after discontinuation of warfarin.

14. T e answer is E.
(Chap. 4) Evaluation of enlarged lymph nodes is a common reason for evaluation in a primary care practice. Most of the time the cause of an enlarged lymph node is benign. In one study, 84% of patients were found to have benign causes of lymphadenopathy, and only 16% had malignancy. Moreover, in more than half of cases, the lymphadenopathy is deemed to be "reactive," and no specific cause is identified. When evaluating an individual for lymphadenopathy, a careful history and physical examination often provides clues to whether the individual is at risk for a malignant cause of disease. Children and young adults usually have benign causes of lymphadenopathy, including viral or bacterial upper respiratory tract infections, infectious mononucleosis, toxoplasmosis, or tuberculosis. After the age of 50, however, the incidence of malignant disorders increases. Other factors in medical history that favor a benign diagnosis include sore throat, cough, fever, night sweats, and fatigue. Localized or regional lymphadenopathy implies involvement of a single anatomic area whereas generalized lymphadenopathy involves three or more noncontiguous lymph node areas. Many etiologies of lymphadenopathy can cause either localized/regional or generalized lymphadenopathy. So the distinction is of limited utility in determining benign from malignant disorders. Size, texture, and the presence of pain can be helpful in assessing whether a lymph node may be malignant, and size is often the most useful of these. Lymph nodes that are <1 cm in size are almost always due to benign causes whereas size greater than 2 to 2.25 cm carries a much greater likelihood of malignancy or granulomatous disease. If the size is ≤1 cm, then watchful waiting is prudent. When describing the texture of a lymph node, typical descriptions include so*ft*, *fi*rm, rubbery, hard, discrete, matted, tender, movable, or *fi*xed. It can be difficult to use these terms to distinguish benign from malignant disease by description alone, specifically in the case of lymphoma. Lymphomatous lymph nodes are most often firm, rubbery, discrete, and mobile. Depending upon the rapidity of enlargement, they may or may not be tender. In comparison, lymph nodes in

infection or infectious mononucleosis appear similarly but are frequently tender. However, metastatic lymph nodes often feel distinctly different. T ey are often hard, fixed, and nontender. In this patient, the diagnosis was most likely a benign case of infectious mononucleosis with the only concerning factor being a single lymph node that is 2 cm in size. A simple blood test will provide a diagnostic answer, but you would want to follow-up the lymph node to ensure that the size diminished as the patient healed from her disease.

15. T e answer is A.
(Chap. 4) T is patient presents with splenomegaly and a constellation of finding suggestive of AIHA including anemia, indirect hyperbilirubinemia, and a peripheral blood smear showing spherocytosis and anisocytosis. T e presenting clinical symptoms may be nonspecific and are related to the degree of anemia. T ese include fatigue, dyspnea on exertion, weakness, tachycardia, and angina. In long-standing cases of AIHA, the patient may be asymptomatic. Physical examination often reveals mild jaundice and scleral icterus. Laboratory studies would confirm the findings as noted above. Additional testing would include a positive direct Coombs test, low serum haptoglobin, and elevated lactate dehydrogenase testing. T e most likely cause of AIHA in this case would be the use of methyldopa as an antihypertensive agent. T is drug is a known cause of AIHA, typically within a few months of starting the medication although some cases have been described as long as several years later. All of the other choices are associated with splenomegaly that may be massive, but are associated with other abnormalities that are not described in this patient. Chronic myeloid leukemia results in an elevation in the white blood cell count, predominantly neutrophils, typically to the range of 20,000–60,000/μL. A mild increase in basophils and eosinophils may also be seen while the lymphocytes numbers are normal. Lymphoma of all types can be associated with splenomegaly, but the patient would be expected to have other symptoms of lymphoma, including fever, chills, night sweats, and weight loss. Hodgkin's lymphoma is also not frequently associated with evidence of hemolysis that was present in this cause. Myelofibrosis with myeloid metaplasia is a clonal disorder that is associated with massive splenomegaly. It may be asymptomatic or associated with symptoms related to the splenomegaly, anemia, or bleeding related to platelet dysfunction. T e anemia related to myelofibrosis is due to bone marrow fibrosis and would not be expected to be associated with hemolysis. T e peripheral smear in myelofibrosis typically demonstrates tear drop RBCs, nucleated RBCs, and immature myeloid cells. Passive congestion of the spleen due to portal hypertension is also a common cause of splenomegaly, but this patient has normal liver function testing. T e elevated bilirubin is due to indirect hyperbilirubinemia due to hemolysis rather than elevated direct bilirubin that would be expected with liver disease.

16. T e answer is A.
(Chap. 4) T e presence of Howell-Jolly bodies (nuclear remnants), Heinz bodies (denatured hemoglobin), basophilic stippling, and nucleated RBCs in the peripheral blood implies that the spleen is not properly clearing senescent or damaged RBCs from the circulation. T is usually occurs because of surgical splenectomy but is also possible when there is diffuse infiltration of the spleen with malignant cells. Hemolytic anemia can have various peripheral smear findings depending on the etiology of the hemolysis. Spherocytes and bite cells are an example of damaged red cells that might appear due to AIHA and oxidative damage, respectively. Disseminated intravascular coagulation (DIC) is characterized by schistocytes and thrombocytopenia on smear, with elevated INR and activated partial thromboplastin time as well. However, in these conditions, damaged red cells are still cleared effectively by the spleen. Transformation to acute leukemia does not lead to splenic damage.

17. T e answer is A.
(Chap. 4) Splenectomy leads to an increased risk of overwhelming postsplenectomy sepsis, an infection that carries an extremely high mortality rate. T e most commonly implicated organisms are encapsulated. Streptococcus pneumoniae, Haemophilus infuenzae, and sometime gram-negative enteric organisms are most frequently isolated. T ere is no known increased risk for any viral infections. Vaccination for S. pneumoniae, H. infuenzae, and Neisseria meningitidis is indicated for any patient who may undergo splenectomy. T e vaccines should be given at least 2 weeks before surgery. T e highest risk of sepsis occurs in patients under 20 because the spleen is responsible for first-pass immunity and younger patients are more likely to have primary exposure to implicated organisms. T e risk is highest during the first 3 years after splenectomy and persists at a lower rate until death.

18. T e answer is E.
(Chap. 5) T e figure shows the characteristic bilobed nucleus of a neutrophil in the Pelger-Hüet anomaly.

T is finding has been described as appearing like spectacles or a pince-nez, popular 19th century reading glasses that did not have earpieces. T e Pelger-Hüet anomaly can be inherited or acquired. T e inherited form is a benign autosomal dominant trait whereas the acquired form is called the pseudo Pelger-Hüet anomaly. It occurs following acute infections or in myelodysplastic syndromes. As this patient did not have a differential or peripheral smear performed prior to his acute infection, it is not possible to determine from the information provided whether he has the inherited or acquired anomaly.

19. T e answer is B.

(Chap. 5) Chronic granulomatous disease (CGD) is a rare disorder of granulocyte and monocyte oxidation with an incidence of 1 in 200,000 individuals. In about two-thirds of individuals, it is inherited in an X-linked recessive fashion, and 30% inherit the disorder as an autosomal recessive trait. Leukocytes affected by CGD have impaired function of NADPH oxidase and severely diminished ability to produce hydrogen peroxide. Clinically, individuals with CGD typically present in early childhood with recurrent infections with S. aureus, Burkholderia cepacia, and Aspergillus species. T e sites of infection in CGD are most commonly skin and lungs. Granulomas are frequent, and gastrointestinal inf ammation including chronic abdominal pain, nausea, and diarrhea are common. Symptoms of inf ammatory bowel disease can occur with obstruction of the bowel. Diagnosis of CGD is made through either the nitroblue tetrazolium dye test (NBT) or the dihydrorhodamine (DHR) oxidation test. T e fundamental property underlying these tests is the ability of the neutrophil to respond with an oxidative burst when stimulated, and these oxidative responses can be detected microscopically (NBT) or by f ow cytometry (DHR). Treatment of CGD includes use of prophylactic trimethoprim-sulfamethoxazole and itraconazole to decrease the frequency of life-threatening infections. In addition, interferon-gamma at a dose of 50 $\mu g/m^2$ subcutaneously three times weekly has been demonstrated to decrease the frequency of infections in CGD by 70% and also decreases the severity of infections. T e mechanism of action of interferon-gamma is to nonspecifically improve phagocytic cell function, and its effect is additive to the effect of prophylactic antibiotics. Glucocorticoids, initially at doses of 1 mg/kg/d, are used for treating inf ammatory bowel disease and bowel obstructions due to CGD. TNF-α-blocking agents, such as inf iximab, are successful in relieving these symptoms as well. However, they markedly increase the risk of life-threatening infections and should not be used as first-line treatment in this disease.

20. T e answer is E.

(Chap. 5) Many drugs can lead to neutropenia, most commonly via retarding neutrophil production in the bone marrow. Of the list above, trimethoprim-sulfamethoxazole is the most likely culprit. Other common causes of drug-induced neutropenia include alkylating agents such as cyclophosphamide or busulfan, antimetabolites including methotrexate and 5-f ucytosine, penicillin and sulfonamide antibiotics, antithyroid drugs, antipsychotics, and anti-inf ammatory agents. Prednisone, when used systemically, often causes an increase in the circulating neutrophil count as it leads to demargination of neutrophils and bone marrow stimulation. Ranitidine, an H_2 blocker, is a well-described cause of thrombocytopenia but has not been implicated in neutropenia. Efavirenz is a nonnucleoside reverse transcriptase inhibitor whose main side effects include a morbilliform rash and central nervous system effects including strange dreams and confusion. T e presence of these symptoms does not require drug cessation. Darunavir is a protease inhibitor that is well tolerated. Common side effects include a maculopapular rash and lipodystrophy, a class effect for all protease inhibitors.

21. through 25. T e answers are: 21:C; 22:E; 23:D; 24:A; 25:B.

(Chap. 6) Patients with homozygous sickle cell disease have RBCs that are less pliable and more "sticky" than normal RBCs. Vaso-occlusive crisis is often precipitated by infection, fever, excessive exercise, anxiety, abrupt changes in temperature, hypoxia, or hypertonic dyes. Peripheral blood smear will show the typical elongated, crescent shaped red cells. T ere is also a nucleated red cell at the bottom of the figure which may occur due to increased bone marrow production. Howell-Jolly bodies, small nuclear remnants normally removed by the intact spleen, are seen in red cells in patients after splenectomy and with maturation/dysplastic disorders characterized by excess production. Acanthocytes are contracted dense red cells with irregular membrane projections that vary in width and length. T ey are seen in patients with severe liver disease, abetalipoproteinemia, and in rare patients with McLeod blood group. Iron deficiency, often due to chronic stool blood loss in patients with colonic polyps or adenocarcinoma, causes a hypochromic microcytic anemia characterized by small pale red cells (a small lymphocyte is

present on the smear to assess red cell size). Red cells are never hyperchromic, if more than the normal amount of hemoglobin is made, the cells get larger not darker. Fragmented red cells, or schistocytes, are helmet-shaped cells that reflect microangiopathic hemolytic anemia (e.g., TTP, DIC, HUS, scleroderma crisis) or shear damage from a prosthetic heart valve.

26. The answer is B.
(Chap. 27) Worldwide, there are more than 12.7 million new cases of cancer and 7.6 million cancer deaths each year, according to estimates provided by the International Agency for Research on Cancer. Most new cases of cancer occur in Asia (45%), with 26% occurring in Europe, and 14.5% in North America. Worldwide, lung cancer is both the most common cause of cancer and the most common cause of cancer deaths. In the United States, lung cancer is the most common cause of cancer death, but is not the most commonly diagnosed cancer. For men, the most commonly diagnosed cancer is prostate cancer, and for women, it is breast cancer. However, overall, in the United States, the incidence of cancer has been declining by about 2% each year since 1992. Despite the declining incidence, cancer is the second leading cause of death in the United States behind heart disease and is responsible for one out every four deaths. In individuals younger than 85 years, cancer is the leading cause of death. However, 5-year survival rates for cancer are generally improving over time. In 1960–1963, the 5-year survival for all cancers in white patients was 39%. By 2003–2009, this had increased to 69%. African-American individuals with cancer fare more poorly with cancer. Over the same interval from 2003 to 2009, the 5-year survival was only 61% for black individuals. Racial differences in survival also, however, are narrowing over time.

27. The answer is D.
(Chap. 27) Assessing response to treatment is an essential component of cancer treatment and compares repeat imaging to the imaging that was used to initially stage the disease. A complete response (option A) is defined as the disappearance of all evidence of disease. To qualify as a partial response (option B), an individual must experience at least a 50% reduction in tumor burden. This reduction is measured as the sum of the products of the perpendicular diameters of all measurable lesions. Another way that partial response can be measured is based upon a 30% decrease in the sum of the longest diameters of the lesions. Progressive disease (option C) is identified when there are any new lesions or if there has been >25% increase in the sum of the products of the perpendicular diameters of all measurable lesions. The scenario proposed in the clinical history meets none of these criteria, and therefore, would be classified as stable disease (option D), which refers to tumor growth or shrinkage that fails to meet any of the definitions for response or progression.

28. The answer is B.
(Chap. 27) While tumor burden is certainly a major factor in determining cancer outcomes, it is also important to consider the functional status of the patient when generating a therapeutic plan. The physiologic stresses of undergoing surgical interventions, radiation therapy, and chemotherapy can exhaust the limited reserves of a patient with multiple medical problems. It is clearly difficult to adequately measure the physiologic reserves of a patient, and most oncologists utilize performance status measures as a surrogate. Two of the most commonly used measures of performance status are the Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status. The ECOG scale provides a grade between 0 (fully active) and 5 (dead). Most patients are considered to have adequate reserve for undergoing treatment if the performance status is 0–2, with a grade 2 indicating someone who is ambulatory and capable of all self-care, but unable to carry out work activities. These individuals are up and about more than 50% of waking hours. A grade 3 performance score would indicate someone who is capable of only limited self-care and is confined to bed or chair more than 50% of waking hours. The Karnofsky score ranges from 0 (dead) to 100 (normal) and is graded at 10 point intervals. A Karnofsky score of <70 also indicates someone with poor performance status and would confer a worse prognosis.

29. The answer is A.
(Chap. 27) The cause of cancer death differs across the lifespan and between genders. In both men and women who are under 20, the primary cause of cancer death is leukemia. In women between the ages of 20 and 59, breast cancer (option A) becomes the leading cause of cancer death. In men, leukemia remains the leading cause of cancer death until the age of 40. After age 40, lung cancer becomes the leading cause of cancer death in men, and in women, it becomes the leading cause of cancer death after age 60.

30. The answer is C.
(Chap. 30) Patients who have undergone allogeneic stem cell transplant remain at risk for infectious complications for an extended period despite

engraftment and apparent return of normal hematopoietic capacity. Individuals with graft versus host disease (GVHD) often require immunosuppressive treatment that further increases infectious risk. Prevention of infection is the goal in these individuals, and the clinician should ensure appropriate vaccinations for all patients who have undergone intensive chemotherapy, have been treated for Hodgkin's disease, or have undergone hematopoietic stem cell transplant. In hematopoietic stem cell transplants, the timeline for vaccination varies after transplant. Pneumococcal vaccination (PCV13) can be given as early as 3–6 months after transplant, but most vaccines are delayed until 6–12 months after transplant. In general, the only vaccines that are given contain inactivated organisms. T erefore, oral vaccine for poliomyelitis and the varicella zoster vaccine are contraindicated. T e measles, mumps, and rubella vaccine is also a live virus vaccine, but can be safely given after 24 months if the patient does not have GVHD. Other recommended vaccines include diphtheria-tetanus, inactivated poliomyelitis (by injection), Haemophilus inf uenzae type B, hepatitis B, and 23-valent pneumococcal polysaccharide vaccine. Meningococcal vaccination is recommended in the splenectomized patients and in those living in endemic areas, including college dormitories.

31. T e answer is D.
(Chap. 30) Clinicians are often faced with treatment decisions regarding catheter-related infections in patients who are immunocompromised from cancer and chemotherapy. As many patients are requiring several weeks of chemotherapy, tunneled catheters are often placed, and determining the need for catheter removal is an important consideration. When blood cultures are positive or there is evidence of infection along the track of the tunnel, catheter removal is recommended. When the erythema is limited to the exit site only, then it is not necessary to remove the catheter unless the erythema fails to respond to treatment. T e recommended treatment for an exit site infection should be directed against coagulase-negative staphylococci. In the options presented, vancomycin alone is the best option for treatment. T ere is no need to add therapy for gram-negative organisms as the patient does not have neutropenia and has negative cultures.

32. T e answer is D.
(Chap. 30) General guidelines for the treatment of febrile neutropenia depend upon the expected duration of neutropenia, previous infections, and recent antibiotic exposures. Each febrile neutropenic patient should be approached as a unique problem. However, several general guidelines can help in treating these patients. T e initial regimen should include antibiotics with activity against both gram-negative and gram-positive bacteria. If the expected duration of neutropenia is expected to be greater than 7 days as in this scenario, then the initial antibiotic choice could be (1) ceftazidime or cefepime, (2) piperacillin/tazobactam, or (3) imipenem/cilastatin or meropenem as any of these regimens have shown equal efficacy in large clinical trials. T ese antibiotics exhibit broad spectrum efficacy against gram-positive and gram-negative organisms, including Pseudomonas aeruginosa. Double coverage of Pseudomonas aeruginosa is not necessary, and use of aminoglycosides alone is contraindicated as these do not provide coverage of gram-positive organisms. Other antibiotics not providing adequate gram-positive coverage include aztreonam and f uoroquinolones. In addition, routine addition of vancomycin is also not indicated as studies have not shown improved outcomes with increased toxic effects. Vancomycin should only be added with there is high suspicion of coagulase-negative Staphylococcal infection or specific concerns regarding methicillin-resistant Staphylococcal aureus infection. However, the treating physician needs to be knowledgeable about his or her local epidemiology and resistance patterns and prescribe in accordance with this knowledge. Antifungal therapy is often added when there is persistent fever at 4–7 days without a known source of infection. T e choice of specific antifungal agent (echinocandin, azole, lipid formulation of amphotericin B) would depend upon whether the patient was receiving antifungal prophylaxis and whether there were reasons to suspect a specific source of infection, such as a pulmonary source.

33. T e answer is E.
(Chap. 34) Melanoma is an aggressive malignancy of the melanocytes that is seen predominantly in white-skinned individuals (approximately 98% of cases) and has had more than 17-fold increase in men and 9-fold increase in women in recent years. T e strongest risk factors for the development of melanoma are the presence of multiple benign or atypical nevi and a family or personal history of the disease. Atypical nevi are often referred to as precursor lesions to melanoma although the specific risk for any individual nevus is quite low. Only about 25% of melanomas arise from nevi; most arise de novo. Other risk factor for melanoma include presence of dysplastic nevi, ultraviolet exposure (including tanning beds),

fair complexion, poor tanning ability, freckling, and specific genetic mutations, including CDKN2A, CDK4, and MITF.

34. T e answer is B.
(Chap. 34) T e best predictor of metastatic risk in melanoma is Breslow thickness, which defines the absolute extent of tumor extension into the tissue. T e Clark level defines the extent of invasion of the melanoma based upon the layer of the skin involved, but does not add significant prognostic information beyond the Breslow thickness. T e number of mitoses is used in staging of tumors <1 mm thickness to provide additional prognostic information about the likelihood of metastatic disease as those with fewer mitoses have better long-term outcomes. Favorable anatomic sites for prognosis are the forearm and leg with less favorable sites being the scalp, hands, feet, and mucous membranes. Women generally have better outcomes than men and are frequently diagnosed at earlier stages than men. T e effect of age is not straight forward. Older patients are usually diagnosed with thicker primary tumors and have a later diagnosis but younger patients have a greater risk of lymph node metastases.

35. and 36. T e answers are A and E, respectively.
(Chap. 34) Treatment of metastatic melanoma has largely shown very little improvements on mortality in this disease with median survival following diagnosis of metastatic disease from 6 to 15 months depending upon organs involved. T e prognosis is better for those with skin or subcutaneous metastases (M1a) than for those with lung metastases (M1b) and worst for those with liver, bone, or brain disease (M1c). Historically, no traditional chemotherapy regimen has had any effect on the outcome of metastatic melanoma, and these drugs are typically used only for symptom palliation. T e agent with the most use in metastatic melanoma is interleukin-2 (IL-2). T is cytokine requires individuals to be in good performance status, and the drug is often administered in an intensive-care like setting due to the high incidence of serious, but expected, side effects. IL-2 is not chemotherapy in the traditional sense, and the mechanism by which it kills tumor cells is not fully explained. It is thought to induce the activity of melanoma-specific T cells and leads to long-term disease-free survival in about 5% of treated patients. Other agents that alter the immune response to the tumor cells are the agents that cause immune checkpoint blockade. T e only FDA approved agent in this class is ipilimumab. T is treatment is a monoclonal antibody that blocks CTLA-4 and results in improved T cell function with eradication of tumor cells. T is medication was the first treatment of any kind to show a survival benefit in metastatic melanoma. However, the response rate is only approximately 10%, and there is a significant side effect profile including induced autoimmunity that has limited the enthusiasm for the clinical use of the drug. In the past few years, two new classes of targeted therapies for melanoma have been introduced that have had fewer side effects although the durability of response is unknown. It is now recommended that all newly diagnosed metastatic lesions undergo molecular testing for BRAF mutation. BRAF mutations are found in 40–60% of melanomas and result in constitutive activation of the MAP kinase pathway. T ere are two currently approved BRAF inhibitors, vemurafenib and dabrafenib. T ese oral medications have shown tumor regression in approximately 50% of treated patients although they are associated with a class-specific complication of the development of numerous skin lesions, which can include squamous cell cancer. A MEK inhibitor acts one step farther down the MAP kinase pathway and has also been approved by the FDA. Trametinib is less effective than the BRAF inhibitors as single agent therapy but may improve survival when added to the BRAF inhibitors. T us, the current recommended approach to the patient with metastatic melanoma is to test every patient for the presence of a "druggable" (BRAF) mutation. If the mutation is not present, the immunotherapy would be offered if the patient had an acceptable functional status. If the mutation is present, then the patient and physician would have to consider the pros and cons of the targeted therapy versus immunotherapy as either could be acceptable. Targeted therapy has fewer side effects but long-term durability of response is unknown. In contrast, immunotherapy has many more side effects and a lower initial response rate, but among responders, long-term durable responses can be achieved.

37. T e answer is C.
(Chap. 34) Nonmelanoma skin cancer (NMSC) is the most common cancer in the United States with an estimated annual incidence of 1.5–2 million cases yearly. However, most of these cases represent very limited disease with a low metastatic potential and account for only 2400 deaths yearly. T e vast majority of NMSC are basal cell carcinomas (BCC, 70–80%) or squamous cell carcinomas (SCC, approximately 20%). T e primary risk factor for all NMSC is UV light exposure. UV exposure can occur either through direct exposure to sunlight (UVA and UVB exposure) or via tanning beds (97% UVA exposure).

Other risk factors for NMSC include inherited disorders of nucleotide excision repair such as xeroderma pigmentosum, fair complexion, light hair/eyes, cigarette smoking, HIV infection, exposure to ionizing radiation, thermal burn scars, Albinism, chronic ulcerations. In addition, recipients of solid organ transplants on chronic immunosuppression have a 65-fold increase in SCC and 10-fold increase in BCC. Moreover, NMSC in those with solid organ transplant is more likely to be aggressive with higher rates of local recurrence, metastasis, and mortality. When comparing BCC to SCC, BCC is the less aggressive of the NMSCs and is typically a slowly enlarging, locally invasive neoplasm. T e metastatic potential of BCC is <0.1%. SCC has a more variable natural history, depending upon the lesion and host factors. Keratoacanthomas are very rapidly growing, low-grade SCCs that can regress spontaneously without therapy. However, progression to metastatic disease has been reported after regression so treatment for keratoacanthoma should be similar to other SCCs. Actinic keratoses and cheilitis are premalignant forms of SCC with transformation to malignancy occurring in 0.25–20%. In general, the metastatic potential of SCC ranges from 0.3–5.2% with the greatest risk of metastases in tumors arising from non-sun-exposed tissues. T e approach to treating NMSC depends upon the size, depth, location, and host factors with the primary goal being eradication of tumor with wide local margins.

38. T e answer is C.

(Chap. 35) Cancers of the larynx often present with the subacute onset of hoarseness that does not resolve over time, but symptoms of head and neck cancer can be rather nonspecific. In more advanced cases, pain, stridor, dysphagia, odynophagia, and cranial neuropathies can occur. Diagnosis of head and neck cancer should include a computed tomography (CT) of the head and neck and endoscopic examination under anesthesia to perform biopsies. Positron emission tomography scans may be used as adjunctive therapy. T e staging of head and neck cancers follow a TNM staging guideline (see **Figure 35-2**). T is patient would be staged as T2N0M0 based upon a tumor size without evidence of lymph node involvement or distant metastatic disease. With this designation, the patient's overall stage would be stage II and classified as localized disease. T e intent of therapy at this stage of disease is cure of cancer, and overall 5-year survival is 60–90%. T e choice of therapy for laryngeal cancer is radiation therapy to preserve voice. Surgical therapy could be chosen by the patient as well, but is less desirable. In locally or regionally advanced disease, patients can still be approached with curative intent, but this requires multimodality therapy with surgery followed by concomitant chemotherapy and radiation treatment.

39. T e answer is C.

(Chap. 35) T e number of new cases of head and neck cancers (oral cavity, pharynx, and larynx) in the United States was 53,640 in 2013, accounting for about 3% of adult malignancies; 11,520 people died from the disease. T e worldwide incidence exceeds half a million cases annually. In North America and Europe, the tumors usually arise from the oral cavity, oropharynx, or larynx. T e incidence of oropharyngeal cancers is increasing in recent years. Nasopharyngeal cancer is more commonly seen in the Mediterranean countries and in the Far East, where it is endemic in some areas. Alcohol and tobacco use are the most significant risk factors for head and neck cancer, and when used together, they act synergistically. Smokeless tobacco is an etiologic agent for oral cancers. Other potential carcinogens include marijuana and occupational exposures such as nickel refining, exposure to textile fibers, and woodworking. Some head and neck cancers have a viral etiology. Epstein-Barr virus (EBV) infection is frequently associated with nasopharyngeal cancer, especially in endemic areas of the Mediterranean and Far East. In Western countries, the human papilloma virus (HPV) is associated with a rising incidence of tumors arising from the oropharynx, i.e., the tonsillar bed and base of tongue. Over 50% of oropharyngeal tumors are caused by HPV in the United States. HPV 16 is the dominant viral subtype, although HPV 18 and other oncogenic subtypes are seen as well. Alcohol- and tobacco-related cancers, on the other hand, have decreased in incidence. HPV-related oropharyngeal cancer occurs in a younger patient population and is associated with increased numbers of sexual partners and oral sexual practices. It is associated with a better prognosis, especially for nonsmokers.

40. T e answer is A.

(Chap. 36) A solitary pulmonary nodule is a frequent reason for referral to a pulmonologist, but most solitary pulmonary nodules are benign. In fact, over 90% of incidentally identified nodules are of benign origin. Features that are more likely to be present in a malignant lesion are: size >3 cm, eccentric calcification, rapid doubling time, and lobulated and irregular contour. Ground glass appearance on CT

imaging can be either malignant or benign. Among malignant lesions, ground glass infiltrate is seen more commonly in bronchoalveolar cell carcinoma. When multiple pulmonary nodules are identified, this most commonly represents prior granulomatous disease from healed infections. If multiple nodules are malignant in origin, this usually indicates disease metastatic to the lung, but can be simultaneous lung primary lesions or lesions metastatic from a primary lung cancer. Many incidentally identified nodules are too small to be diagnosed by biopsy and are nonspecific in nature. In this situation, it is prudent to follow the lesions for a period of 2 years, especially in a patient who is high risk for lung cancer to allow for a proper doubling time to occur. If the lesion remains stable for 2 years, it is most likely benign although some slow-growing tumors such bronchoalveolar cell carcinoma can have a slower growth rate.

41. T e answer is E.
(Chap. 36) T e evaluation and treatment of solitary pulmonary nodules is important to understand. T is patient has a long smoking history with a new nodule that was not apparent by chest x-ray 3 years previously. T is should be assumed to be a malignant nodule, and definitive diagnosis and treatment should be attempted. T e option for diagnostic and staging procedures include PET/CT, bronchoscopic biopsy, percutaneous needle biopsy, or surgical biopsy with concomitant resection if positive. PET/CT would be low yield in this patient given the small size of the primary lesion (<1 cm) and the lack of enlarged mediastinal lymph nodes. Likewise, bronchoscopy would not provide a good yield because the lesion is very peripheral in origin, and a negative biopsy for malignancy would not be definitive. Appropriate approaches would be to either perform a percutaneous needle biopsy with CT guidance or perform a surgical biopsy with definitive resection if positive. As this patient has preserved lung function, surgical biopsy and resection is a good treatment option for this patient. A repeat CT scan assessing for interval growth would only be appropriate if the patient declined further workup at this time. Referral for treatment with radiation therapy is not appropriate in the absence of tissue diagnosis of malignancy, and surgical resection is the preferred primary treatment as the patient has no contraindications to surgical intervention.

42. T e answer is E.
(Chap. 36) Pancoast syndrome results from apical extension of a lung mass into the brachial plexus with frequent involvement of the 8th cervical and 1st and 2nd thoracic nerves. As the tumor continues to grow, it will also involve the sympathetic ganglia of the thoracic chain. T e clinical manifestations of a Pancoast tumor include shoulder and arm pain and Horner's syndrome (ipsilateral ptosis, miosis, and anhidrosis). Often times, the shoulder and arm present several months prior to diagnosis. T e most common cause of Pancoast syndrome is an apical lung tumor, usually non-small cell lung cancer. Other causes include mesothelioma and infection among others. While midbrain lesions can cause Horner's syndrome, other cranial nerve abnormalities would be expected.

Enlarged mediastinal lymph nodes and masses in the middle mediastinum can occlude the superior vena cava, leading to superior vena cava syndrome. Individuals with SVC syndrome typically present with dyspnea and have evidence of facial and upper extremity swelling. Eaton Lambert myasthenic syndrome is caused by antibodies to voltage gated calcium channels and is characterized by generalized weakness of muscles that increases with repetitive nerve stimulation. Cervical ribs can cause thoracic outlet syndrome by compression of nerves or vasculature as they exit the chest. T is typically presents with ischemic symptoms to the affected limb, but intrinsic wasting of the muscles of the hand can be seen due to neurologic compromise.

43. T e answer is C.
(Chap. 36) Mutations of the epidermal growth factor receptor (EGFR) have recently been recognized as important mutations that affect the response of non-small cell lung cancers to treatment with EGFR tyrosine kinase inhibitors. Initial studies of erlotinib in all patients with advanced non-small cell lung cancer failed to show a treatment benefit; however, when only those patients with EGFR mutations were considered, treatment with anti-EGFR therapy improved progression-free and overall survival. Patients who are more likely to have EGFR mutations are women, nonsmokers, Asians, and adenocarcinoma histopathology.

44. T e answer is B.
(Chap. 36) T e Veterans Administration staging system for small cell lung cancer (SCLC) is a distinct two-stage system dividing patients into those with limited- or extensive-stage disease. Patients with limited-stage disease (LD) have cancer that is confined to the ipsilateral hemithorax and can be encompassed within a tolerable radiation port. T us, contralateral supraclavicular nodes, recurrent

laryngeal nerve involvement, and superior vena caval obstruction can all be part of LD. Patients with extensive-stage disease (ED) have overt metastatic disease by imaging or physical examination. Cardiac tamponade, malignant pleural effusion, and bilateral pulmonary parenchymal involvement generally qualify disease as ED, because the involved organs cannot be encompassed safely or effectively within a single radiation therapy port. From 60 to 70% of patients are diagnosed with ED at presentation. In general, surgical resection is not routinely recommended for patients because even patients with LD-SCLC still have occult micrometastases. Chemotherapy significantly prolongs survival in patients with SCLC. Despite response rates to first-line therapy as high as 80%, the median survival ranges from 12 to 20 months for patients with LD and from 7 to 11 months for patients with ED. Regardless of disease extent, the majority of patients relapse and develop chemotherapy-resistant disease. Only 6–12% of patients with LD-SCLC and 2% of patients with ED-SCLC live beyond 5 years. T e role of radiotherapy in ED-SCLC is largely restricted to palliation of tumor related symptoms such as bone pain and bronchial obstruction.

45. T e answer is D.
(Chap. 36 and N Engl J Med 2011;365:395-409) T e National Lung Screening Trial (NLST), a randomized study designed to determine if low-dose CT scan (LDCT) screening could reduce mortality from lung cancer in high-risk populations as compared with standard posterior anterior CXR was published in 2011. High-risk patients were defined as individuals between 55 and 74 years of age, with a ≥30 pack-year history of cigarette smoking; former smokers must have quit within the previous 15 years. Excluded from the trial were individuals with a previous lung cancer diagnosis, a history of hemoptysis, an unexplained weight loss of >15 lb in the preceding year, or a chest CT within 18 months of enrollment. A total of 53,454 persons were enrolled and randomized to annual screening yearly for 3 years (LDCT screening, n = 26,722; CXR screening, n = 26,732). Any noncalcified nodule measuring ≥4 mm in any diameter found on LDCT and CXR images with any noncalcified nodule or mass were classified as "positive." Overall, 39.1% of participants in the LDCT group and 16% in the CXR group had at least one positive screening result. Of those who screened positive, the false-positive rate was 96.4% in the LDCT group and 94.5% in the CXR group. A greater number of cancers were found in the LDCT group. Nearly twice as many early-stage IA cancers were detected in the LDCT group compared with the CXR group (40% vs 21%). T e overall rates of lung cancer death were 247 and 309 deaths per 100,000 participants in the LDCT and CXR groups, respectively, representing a 20% reduction in lung cancer mortality in the LDCT-screened population (95% CI, 6.8–26.7%; p = 0.004). Compared with the CXR group, the rate of death in the LDCT group from any cause was reduced by 6.7% (95% CI, 1.2–13.6; p = 0.02). Despite the aforementioned caveats, screening of individuals who meet the NLST criteria for lung cancer risk seems warranted, provided comprehensive multidisciplinary coordinated care and follow-up similar to those provided to NLST participants are available (see **Table 36-2**).

46. T e answer is C.
(Chap. 38) T e patient has a breast cyst. T is has a benign feel on examination and aspiration of the mass showed nonbloody f uid with resolution of the mass. If there were residual mass or bloody f uid, mammogram and biopsy would be the next step. In patients such as this with nonbloody f uid in whom aspiration clears the mass, re-examination in 1 month is indicated. If the mass recurs, then aspiration should be repeated. If f uid recurs, mammography and biopsy would be indicated at that point. T ere is no indication at this point to refer for advanced imaging or surgical evaluation. Breastfeeding is not affected by breast cyst presence.

47. T e answer is C.
(Chap. 38) Breast cancer risk is related to many factors, but age of menarche, age of first full-term pregnancy and age and menopause together account for 70–80% of all breast cancer risk. T e lowest risk patients have the shortest duration of total menses, i.e., later menarche and earlier menopause, as well as early first full term pregnancy. Specifically, the lowest risks are menarche at age 16 years old or older, first pregnancy by the age of 18 years and menopause that begins 10 years before the median age of menopause of 52 years. T us patient C meets these criteria.

48. T e answer is A.
(Chap. 39) A strong family history of colon cancer should prompt consideration for hereditary nonpolyposis colon cancer (HNPCC), or Lynch syndrome, particularly if diffuse polyposis is not noted on colonoscopy. HNPCC is characterized by (1) three or more relatives with histologically proven colorectal

cancer, one of whom is a first-degree relative and of the other two, at least one with the diagnosis before age 50; and (2) colorectal cancer in at least two generations. T e disease is an autosomal dominant trait and is associated with other tumors, including in the endometrium and ovary. T e proximal colon is most frequently involved, and cancer occurs with a median age of 50 years, 15 years earlier than in sporadic colon cancer. Patients with HNPCC are recommended to receive biennial colonoscopy and pelvic ultrasound beginning at age 25. Innumerable polyps suggest the presence of one of the autosomal dominant polyposis syndromes, many of which carry a high malignant potential. T ese include familial adenomatous polyposis, Gardner's syndrome (associated with osteomas, fibromas, epidermoid cysts), or Turcot's syndrome (associated with brain cancer). Peutz-Jeghers syndrome is associated with mucocutaneous pigmentation and hamartomas. Tumors may develop in the ovary, breast, pancreas, and endometrium; however, malignant colon cancers are not common. Ulcerative colitis is strongly associated with development of colon cancer, but it is unusual for colon cancer to be the presenting finding in ulcerative colitis. Patients are generally symptomatic from their inf ammatory bowel disease long before cancer risk develops.

49. T e answer is E.
(Chap. 39) Colorectal cancer is the second most common cause of cancer death in the United States, and the mortality related to the disease has been decreasing in recent years. When colorectal cancer is identified, patients should be referred for surgical intervention as proper staging and prognosis cannot be determined without pathologic specimens if there is no gross evidence of metastatic disease. T e preoperative workup to assess for metastatic or synchronous disease includes a complete colonoscopy if possible, chest radiograph, liver function testing, carcinoembryonic antigen (CEA) testing, and CT imaging of the abdomen. Staging of colorectal cancer follows a TNM staging system. However, the T staging is not based upon absolute size of the tumor rather it is based upon the extension of the tumor through the colonic wall. T1 tumors can extend into the submucosa, but not beyond, T2 tumors extend into the muscularis propria, and T3 tumors involve the serosa and beyond. Nodal metastases are graded as N1 (1–3 lymph nodes positive) and N2 (≥4 lymph nodes positive). T is patient's stage of cancer would be T2N1M0 and would stage this as a stage III cancer. Despite the relatively advanced stage, the overall 5-year survival would be 50–70% due to improvements in overall care of the patient with colorectal cancer. Since the patient had an occluding lesion that prevents preoperative colonoscopy, the patient needs to have a complete colonoscopy performed within the first several months following surgery and every 3 years thereafter. Serial measurements of CEA every 3 months have also been advocated by some specialists. Annual CT scanning may be performed for the first 3 years following resection although the utility of the practice is debated. Radiation therapy to the pelvis is recommended for all patients with rectal cancer because it reduces local recurrence rate, especially in stage II and III tumors. When postoperative radiation therapy is combined with chemotherapeutic regimens containing 5-f uorouracil, the local recurrence rate is further reduced and increases overall survival as well.

50. T e answer is E.
(Chap. 39) Esophageal cancer has a high mortality rate as most patients do not present until advanced disease is present. T e typical presenting symptoms of esophageal cancer are dysphagia with significant weight loss. Dysphagia is typically fairly rapidly progressive over a period of weeks to months. Dysphagia initially in only to solid foods, but progresses to include semisolids and liquids. For dysphagia to occur, an estimated 60% of the esophageal lumen must be occluded. Weight loss occurs due to decreased oral intake in addition to the cachexia that is common with cancer. Associated symptoms may include pain with swallowing that can radiate to the back, regurgitation or vomiting of undigested food, and aspiration pneumonia. T e two major cell types of esophageal cancer in the United States are adenocarcinoma and squamous cell carcinoma, which have different risk factors. Individuals with squamous cell carcinomas typically have a history of both tobacco and alcohol abuse whereas those with adenocarcinoma more often have a history of long-standing gastroesophageal ref ux disease and Barrett's esophagitis. Among those with a history of alcohol and tobacco abuse, there is an increased risk with increased intake and interestingly is more associated with whiskey drinking when compared to wine or beer. Other risk factors for squamous cell carcinoma of the esophagus include ingestion of nitrites, smoked opiates, fungal toxins in pickled vegetables, and physical insults that include long-standing ingestion of very hot tea or lye.

51. T e answer is C.
(Chap. 39) A variety of causative factors have been implicated in the development of squamous cell cancers of the esophagus. In the United States, the etiology of such cancers is primarily related to excess alcohol consumption and/or cigarette smoking. T e relative risk increases with the amount of tobacco smoked or alcohol consumed, with these factors acting synergistically. Squamous cell esophageal carcinoma has also been associated with the ingestion of nitrates, smoked opiates, and fungal toxins in pickled vegetables, as well as mucosal damage caused by such physical insults as long-term exposure to extremely hot tea, the ingestion of lye, radiation-induced strictures, and chronic achalasia. T e presence of an esophageal web in association with glossitis and iron deficiency (i.e., Plummer-Vinson or Paterson-Kelly syndrome) and congenital hyperkeratosis and pitting of the palms and soles (i.e., tylosis palmaris et plantaris) have each been linked with squamous cell esophageal cancer, as have dietary deficiencies of molybdenum, zinc, selenium, and vitamin A. Several strong etiologic associations have been observed to account for the development of adenocarcinoma of the esophagus. Such tumors arise in the distal esophagus in association with chronic gastric ref ux, often in the presence of Barrett's esophagus (replacement of the normal squamous epithelium of the distal esophagus by columnar mucosa), which occurs more commonly in obese individuals. Adenocarcinomas arise within dysplastic columnar epithelium in the distal esophagus. Cigarette smoking is associated with the development of adenocarcinoma of the esophagus as well.

52. T e answer is C.
(Chap. 41) Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection both have a clear relationship with the subsequent development of hepatocellular carcinoma (HCC). Both case-control and cohort studies have shown a strong association between chronic hepatitis B carrier rates and increased incidence of HCC. In Taiwanese male postal carriers who were hepatitis B surface antigen (HBsAg)-positive, a 98-fold greater risk for HCC was found compared to HbsAg-negative individuals. HBV-based HCC may involve rounds of hepatic destruction with subsequent proliferation and not necessarily frank cirrhosis. T e latency of HCV infection and development of HCC is approximately 30 years. HCV associated HCC patients tend to have more frequent and advanced cirrhosis, but in HBV-associated HCC, only half the patients have cirrhosis, with the remainder having chronic active hepatitis. Approximately 75–80% of patients with HCC have cirrhosis, and other liver conditions without cirrhosis, such as, NAFL and NASH, are associated with the development of HCC. Natural chemical carcinogens, such as af atoxin B1, are strongly associated with HCC. It can be found in a variety of stored grains in hot, humid places, where peanuts and rice are stored in unrefrigerated conditions. Af atoxin contamination of foodstuffs correlates well with incidence rates in Africa and to some extent in China. In endemic areas of China, even farm animals such as ducks have HCC. Malaria is not associated with HCC (see **Table 41-2**).

53. T e answer is E.
(Chap. 41) Hepatomegaly is the most common physical sign in patients with hepatocellular carcinoma (HCC), occurring in 50–90% of the patients. Abdominal bruits are noted in 6–25%, and ascites occurs in 30–60% of patients. Alfa-fetoprotein (AFP) is a serum tumor marker for hepatocellular carcinoma (HCC); however, it is only increased in approximately one-half of the U.S. patients. Rising AFP in a patient at risk of HCC may be a marker of development of disease and, in some cases, serial measurement of AFP may be used as a marker of response to therapy. An ultrasound examination of the liver is an excellent screening tool. T e two characteristic vascular abnormalities are hypervascularity of the tumor mass (neovascularization or abnormal tumor-feeding arterial vessels) and thrombosis by tumor invasion of otherwise normal portal veins. To determine tumor size and extent and the presence of portal vein invasion accurately, a helical/triphasic CT scan of the abdomen and pelvis, with fast-contrast bolus technique, should be performed to detect the vascular lesions typical of HCC. Portal vein invasion is normally detected as an obstruction and expansion of the vessel. Magnetic resonance imaging (MRI) can also provide detailed information, especially with the newer contrast agents. A prospective comparison of triphasic CT, gadolinium-enhanced MRI, ultrasound, and f uorodeoxyglucose positron emission tomography (FDG-PET) showed similar results for CT, MRI, and ultrasound; PET imaging appears to be positive in only a subset of HCC patients. MRI is better able to distinguish dysplastic or regenerative nodules from HCC. Imaging criteria have been developed for HCC that do not require biopsy proof, as they have >90% specificity. T e criteria include nodules >1 cm with arterial enhancement and portal venous washout and, for small tumors, specified

growth rates on two scans performed less than 6 months apart (Organ Procurement and Transplant Network). Nevertheless, explant pathology after liver transplant for HCC has shown that □20% of patients diagnosed without biopsy did not actually have a tumor.

54. T e answer is E.
(Chap. 41) Because this patient has a tumor >3 cm, he is not a candidate for primary radical resection. However, with his otherwise good prognosis and excellent performance status, he may be a candidate for liver transplantation that would cure his cirrhosis and his carcinoma. T ere are also evolving local ablative modalities that he would be eligible to receive (see **Figure 41-1**).

55. T e answer is C.
(Chap. 41) Cholangiocarcinoma (CCC) typically refers to mucin-producing adenocarcinomas (different from hepatocellular carcinoma [HCC]) that arise from the biliary tract and have features of cholangiocyte differentiation. T ey are grouped by their anatomic site of origin, as intrahepatic (IHC), perihilar (central, □65% of CCCs), and peripheral (or distal, □30% of CCCs). IHC is the second most common primary liver tumor. T ey arise on the basis of cirrhosis less frequently than HCC, but may complicate primary biliary cirrhosis. However, cirrhosis and both primary biliary cirrhosis and HCV predispose to IHC. Nodular tumors arising at the bifurcation of the common bile duct are called Klatskin tumors and are often associated with a collapsed gallbladder, a finding that mandates visualization of the entire biliary tree. Incidence is increasing. Although most CCCs have no obvious cause, a number of predisposing factors have been identified, including primary sclerosing cholangitis (10–20% of primary sclerosing cholangitis [PSC] patients), an autoimmune disease, and liver fuke in Asians, especially Opisthorchis viverrini and Clonorchis sinensis. CCC seems also to be associated with any cause of chronic biliary inf ammation and injury, with alcoholic liver disease, choledocholithiasis, choledochal cysts (10%), and Caroli's disease (a rare inherited form of bile duct ectasia). CCC most typically presents as painless jaundice, often with pruritus or weight loss. Incidence has been increasing in recent decades; few patients survive 5 years. T e usual treatment is surgical, but combination systemic chemotherapy may be effective. After complete surgical resection for IHC, 5-year survival is 25–30%. Combination radiation therapy with liver transplant has produced a 5-year recurrence-free survival rate of 65%.

56. T e answer is E.
(Chap. 42) Pancreatic cancer is the fourth leading cause of cancer death in the United States, despite representing only 3% of all newly diagnosed malignancies. Infiltrating ductal adenocarcinomas account for the vast majority of cases and arise most frequently in the head of pancreas. At the time of diagnosis 85–90% of patients have inoperable or metastatic disease, which is ref ected in the 5-year survival rate of only 5% for all stages combined. An improved 5-year survival of up to 20% may be achieved when the tumor is detected at an early stage and when complete surgical resection is accomplished. Over the past 30 years, 5-year survival rates have not improved substantially. Cigarette smoking may be the cause of up to 20–25% of all pancreatic cancers and is the most common environmental risk factor for this disease. Other risk factors are not well established due to inconsistent results from epidemiological studies, but include chronic pancreatitis and diabetes. Alcohol does not appear to be a risk factor unless excess consumption gives rise to chronic pancreatitis.

57. T e answer is B.
(Chap. 42) Dual phase, contrast-enhanced spiral CT is the imaging modality of choice to visualize suspected pancreatic masses. In addition to imaging the pancreas, it also provides accurate visualization of surrounding viscera, vessels, and lymph nodes. In most cases, this study can determine surgical resectability. T ere is no advantage of MRI over CT in predicting tumor resectability, but selected cases may benefit from MRI to characterize the nature of small indeterminate liver lesions and to evaluate the cause of biliary dilatation when no obvious mass is seen on CT. Preoperative confirmation of malignancy is not always necessary in patients with radiological appearances consistent with operable pancreatic cancer. Endoscopic ultrasound-guided needle biopsy is the most effective technique to evaluate the mass for malignancy. It has an accuracy of approximately 90% and has a smaller risk of intraperitoneal dissemination compared with CT-guided percutaneous biopsy. ERCP is a useful method for obtaining ductal brushings, but the diagnostic value of pancreatic juice sampling is only 25–30%. CA 19-9 is elevated in approximately 70–80% of patients with pancreatic carcinoma, but is not recommended as a routine diagnostic or screening test as its sensitivity and specificity are inadequate for accurate diagnosis. Preoperative CA 19-9 levels correlate with tumor stage and prognosis. It is also an indicator

of asymptomatic recurrence in patients with completely resected tumors. FDG-PET should be considered before surgery for detecting distant metastases.

58. The answer is C.
(Chap. 42) This patient has a <2 cm tumor with no microscopic residual disease and therefore is stage 1 with a 20% 5-year survival after surgery and a gemcitabine containing adjuvant chemotherapy regimen. This presentation accounts for <10% of patients with newly diagnosed pancreatic cancer. Most patients present with advanced stage 4 disease with a <5% 5-year survival. The four genes most commonly mutated or inactivated in pancreatic cancer are KRAS, the tumor-suppressor genes p16 (deleted in 95% of tumors), p53 (inactivated or mutated in 50–70% of tumors), and SMAD4 (deleted in 55% of tumors). Typically, the cancer precursor lesions acquire these genetic abnormalities in a progressive manner that is associated with increasing dysplasia. SMAD4 gene inactivation is associated with a pattern of widespread metastatic disease in advanced-stage patients and poorer survival in patients with surgically resected pancreatic adenocarcinoma (see **Figure 42-3**).

59. The answer is D.
(Chap. 43) Bladder cancer is the fourth most common cancer in men and the thirteenth most common cancer in women. Cigarette smoking has a strong association with bladder cancer, particularly in men. The increased risk persists for at least 10 years after quitting. Bladder cancer is a small cause of cancer deaths because most detected cases are superficial with an excellent prognosis. Most cases of bladder cancer come to medical attention by the presence of gross hematuria emanating from exophytic lesions. Microscopic hematuria is more likely due to prostate cancer than bladder cancer. Cystoscopy under anesthesia is indicated to evaluate for bladder cancer. In cases of superficial disease, BCG is an effective adjuvant to decrease recurrence or treat unresectable superficial disease. In the United States, cystectomy is generally recommended for invasive disease. Even invasive cancer with nodal involvement has a >40% 10-year survival after surgery and adjuvant therapy.

60. and 61. The answers are C and E, respectively.
(Chap. 43) The incidence of renal cell carcinoma continues to rise and is now nearly 58,000 cases annually in the United States, resulting in 13,000 deaths. The male to female ratio is 2:1. Incidence peaks between the ages of 50 and 70 years, although this malignancy may be diagnosed at any age. Many environmental factors have been investigated as possible contributing causes; the strongest association is with cigarette smoking. Risk is also increased for patients who have acquired cystic disease of the kidney associated with end-stage renal disease, and for those with tuberous sclerosis. Most renal cell carcinomas are clear cell tumors (60%) with papillary and chromophobic tumors less common. Clear cell tumors account for >80% of patients that develop metastases. The classic triad of hematuria, flank pain, and palpable mass is only present in 10–20% of cases initially. Most cases currently are found as incidental findings on CTs or ultrasounds obtained for different reasons. The increasing number of incidentally discovered low-stage tumors has contributed to an improved 5-year survival. The paraneoplastic phenomenon of erythrocytosis due to increased production of EPO is only found in 3% of cases; anemia due to advanced disease is far more common. Stages 1 and 2 tumors are confined to the kidney and have a >80% survival after radical nephrectomy. Stage 4 tumors with distant metastases have a 5-year survival of 10%. Renal cell carcinoma is notably resistant to traditional chemotherapeutic agents. Until recently, cytokine therapy with IL-2 or interferon gamma was utilized to produce regression in 10–20% of patients with metastatic disease. Antiangiogenic medications have changed the treatment of advance renal cell carcinoma. Sunitinib was demonstrated to be superior to interferon gamma and it is now first line therapy for patients with advanced metastatic disease. Pazopanib and axitinib are newer agents of the same class as sunitinib. Pazopanib was compared to sunitinib in a randomized first-line phase III trial. Efficacy was similar, and there was less fatigue and skin toxicity, resulting in better quality of life scores for pazopanib compared with sunitinib. Temsirolimus and everolimus, inhibitors of the mammalian target of rapamycin (mTOR), show activity in patients with untreated poor prognosis tumors and in sunitinib/sorafenib refractory tumors. Patients may benefit from the sequential use of axitinib and everolimus following progression after first-line therapy. The prognosis of metastatic renal cell carcinoma is variable.

62. The answer is A.
(Chap. 44) The results from several large double-blind, randomized chemoprevention trials have established 5 alpha-reductase inhibitors as the predominant therapy to reduce the future risk of a prostate cancer diagnosis. Randomized placebo controlled trials have shown finasteride and dutasteride

reduce the period prevalence of prostate cancer. Trials of selenium, vitamin C, and vitamin E have shown no benefit versus placebo.

63. T e answer is E.
(Chap. 44) Transrectal ultrasound guided biopsy is recommended for men with either an abnormal digital rectal examination. Carcinomas are characteristically hard, nodular, and irregular, while induration may also be due to benign prostatic hypertrophy (BPH) or calculi. Overall, 20–25% of men with an abnormal DRE have cancer. A diagnosis of cancer is established by an image-guided needle biopsy. Direct visualization by transrectal ultrasound (TRUS) or MRI assures that all areas of the gland are sampled. Contemporary schemas advise an extended pattern 12-core biopsy that includes sampling from the peripheral zone as well as a lesion-directed palpable nodule or suspicious image-guided sampling. Men with an abnormal PSA and negative biopsy are advised to undergo a repeat biopsy. When prostate cancer is diagnosed, a measure of histologic aggressiveness is assigned using the Gleason grading system, in which the dominant and secondary glandular histologic patterns are scored from 1 (well-differentiated) to 5 (undifferentiated) and summed to give a total score of 2–10 for each tumor. T e most poorly differentiated area of tumor (i.e., the area with the highest histologic grade) often determines biologic behavior. T e presence or absence of perineural invasion and extracapsular spread is also recorded.

64. T e answer is C.
(Chap. 44) Prostate-specific antigen (PSA) is a serine protease that causes liquefaction of seminal coagulum. It is produced by both nonmalignant and malignant epithelial cells and, as such, is prostate-specific, not prostate cancer–specific. Serum levels may also increase from prostatitis and benign prostatic hypertrophy. Serum levels are not significantly affected by digital rectal examination, but the performance of a prostate biopsy can increase PSA levels up to tenfold for 8–10 weeks. PSA testing was approved by the U.S. FDA in 1994 for early detection of prostate cancer, and the widespread use of the test has played a significant role in the proportion of men diagnosed with early-stage cancers: more than 70–80% of newly diagnosed cancers are clinically organ-confined. T e level of PSA in blood is strongly associated with the risk and outcome of prostate cancer. Most prostate cancer deaths (90%) occur among men with PSA levels in the top quartile (>2 ng/mL), although only a minority of men with PSA >2 ng/mL will develop lethal prostate cancer. Despite this and mortality rate reductions reported from large randomized prostate cancer screening trials, routine use of the test remains controversial. T e U.S. Preventive Services Task Force (USPSTF) recently made a clear recommendation against screening. By giving a grade of "D" in the recommendation statement that was based on this review, the USPSTF concluded that "there is moderate or high certainty that this service has no net benefit or that the harms outweigh the benefits." Whether the harms of screening, overdiagnosis, and overtreatment are justified by the benefits in terms of reduced prostate cancer mortality is open to reasonable doubt. In response to the USPSTF, the American Urological Association (AUA) updated their consensus statement regarding prostate cancer screening. T ey concluded that the quality of evidence for the benefits of screening was moderate, and evidence for harm was high for men age 55–69 years. For men outside this age range, evidence was lacking for benefit, but the harms of screening, including overdiagnosis and overtreatment, remained. T e AUA recommends shared decision-making considering PSA-based screening for men age 55–69, a target age group for whom benefits may outweigh harms. Outside this age range, PSA-based screening as a routine test was not recommended based on the available evidence. T e PSA criteria used to recommend a diagnostic prostate biopsy have evolved over time. However, based on the commonly used cut point for prostate biopsy (a total PSA ≥4 ng/mL), most men with a PSA elevation do not have histologic evidence of prostate cancer at biopsy. In addition, many men with PSA levels below this cut point harbor cancer cells in their prostate. T ere is no PSA below which the risk of prostate cancer is zero. T e routine use of antibiotics in an asymptomatic man with an elevated PSA level is strongly discouraged and should not affect the decision to pursue further evaluation.

65. T e answer is B.
(Chap. 44) Benign prostatic hypertrophy (BPH) is a pathologic process that contributes to the development of lower urinary tract symptoms in men. Such symptoms, arising from lower urinary tract dysfunction, are further subdivided into obstructive symptoms (urinary hesitancy, straining, weak stream, terminal dribbling, prolonged voiding, incomplete emptying) and irritative symptoms (urinary frequency, urgency, nocturia, urge incontinence, small voided volumes). Lower urinary tract symptoms and other sequelae of BPH are not just due to a mass effect, but are also likely due to a combination of

the prostatic enlargement and age-related detrusor dysfunction. Asymptomatic patients do not require treatment regardless of the size of the prostate gland. Symptomatic relief is the most common reason men seek treatment for BPH, and therefore, the goal of therapy for BPH is usually relief of these symptoms. Selective alpha-adrenergic receptor antagonists, such as alfuzosin, are thought to treat the dynamic aspect of BPH by reducing sympathetic tone of the bladder outlet, thereby decreasing resistance and improving urinary f ow. 5-alpha reductase inhibitors (5ARIs), such as dutasteride and finasteride, are thought to treat the static aspect of BPH by reducing prostate volume and having a similar, albeit delayed effect. T ey have also proven to be beneficial in the prevention of BPH progression, as measured by prostate volume, the risk of developing acute urinary retention, and the risk of having BPH-related surgery. T e use of an alpha-adrenergic receptor antagonist and a 5ARI as combination therapy seeks to provide symptomatic relief while preventing progression of BPH.

Another class of medications that has shown improvement in lower urinary tract symptoms secondary to BPH is PDE5 inhibitors, used currently in the treatment of erectile dysfunction. All three of the PDE5 inhibitors available in the United States, sildenafil, vardenafil, and tadalafil, appear to be effective in the treatment of symptoms secondary to BPH. T e use of PDE5 inhibitors is not without controversy, however, given the fact that short-acting phosphodiesterase inhibitors such as sildenafil need to be dosed separately from alpha blockers because of potential hypotensive effects. Bosentan is a nonselective endothelin receptor antagonist used in the treatment of pulmonary arterial hypertension.

66. T e answer is E.

(Chap. 45) Pure seminomas have the best survival of all forms of testicular cancer and represents approximately 50% of all germ cell tumors (GCTs). T e median age of presentation is the 4th decade of life, and approximately 80% of individuals present with stage I disease, indicating any disease limited to the testis no matter the size at initial presentation. All men presenting with a testicular mass should be referred for radical inguinal orchiectomy as this approach mirrors the embryonic development of the testis and does not breach anatomic barriers to allow for other pathways of spread. In the staging workup of testicular cancers, men should undergo CT imaging of the chest, abdomen, and pelvis as well as measurement of the serum tumor markers AFP and β-human chorionic gonadotropin (β-hCG) hormone in addition to LDH levels. T ese tumor markers assist with both diagnosis and prognosis in testicular cancer and help with determining the appropriate post-orchiectomy treatment. In pure seminomas, AFP levels should not be elevated. If the AFP level were to be elevated, this would indicate an occult nonseminomatous component, which may require more aggressive initial treatment with either retroperitoneal lymph node dissection or adjuvant chemotherapy depending upon local surgical expertise and preference of the patient and treating physician. B-hCG levels may be elevated in pure seminomas although this too is infrequent in men without advanced disease. LDH levels are less specific, but are increased in up to 80% of patients with advanced seminoma. After resection, the tumor markers should return to normal values within their expected half-lives following first order kinetics. T e half-life of β-hCG is 24–36 hours, and AFB is 5–7 days. In stage I seminoma, survival is near 100% with either immediate post-orchiectomy radiation or with surveillance alone (option E). Given the concern about secondary malignancy due to radiation exposure, many providers chose watchful waiting with surveillance alone in men who are compliant with follow-ups. However, approximately 15% of patients will have relapse, and 5% of relapses occur after 5 years. So extended follow-up is required. A single dose of carboplatin has been investigated as an alternative to radiation therapy, but long-term outcomes are as yet unknown.

67. T e answer is A.

(Chap. 45) Ninety percent of persons with nonseminomatous germ cell tumors produce either AFP or β-hCG; in contrast, persons with pure seminomas usually produce neither. T ese tumor markers are present for some time after surgery; if the presurgical levels are high, 30 days or more may be required before meaningful postsurgical levels can be obtained. T e half-lives of AFP and β-hCG are 6 days and 1 day, respectively. After treatment, unequal reduction of β-hCG and AFP may occur, suggesting that the two markers are synthesized by heterogeneous clones of cells within the tumor; thus, both markers should be followed. β-hCG is similar to luteinizing hormone except for its distinctive beta subunit.

68. T e answer is E.

(Chap. 46) A variety of genetic syndromes substantially increase a woman's risk of developing ovarian cancer. Approximately 10% of women with ovarian

cancer have a germline mutation in one of two DNA repair genes: BRCA1 (chromosome 17q12-21) or BRCA2 (chromosome 13q12-13). Individuals inheriting a single copy of a mutant allele have a very high incidence of breast and ovarian cancer. Most of these women have a family history that is notable for multiple cases of breast and/or ovarian cancer, although inheritance through male members of the family can camouf age this genotype through several generations. T e most common malignancy in these women is breast carcinoma, although women harboring germline BRCA1 mutations have a marked increased risk of developing ovarian malignancies in their forties and fifties with a 30–50% lifetime risk of developing ovarian cancer. Women harboring a mutation in BRCA2 have a lower penetrance of ovarian cancer with perhaps a 20–40% chance of developing this malignancy, with onset typically in their fifties or sixties. Women with a BRCA2 mutation also are at slightly increased risk of pancreatic cancer. Likewise women with mutations in the DNA mismatch repair genes associated with Lynch syndrome, type 2 (MSH2, MLH1, MLH6, PMS1, PMS2) may have a risk of ovarian cancer as high as 1% per year in their forties and fifties. Finally, a small group of women with familial ovarian cancer may have mutations in other BRCA-associated genes such as RAD51, CHK2, and others. Screening studies in this select population suggest that current screening techniques, including serial evaluation of the CA-125 tumor marker and ultrasound, are insufficient at detecting early-stage and curable disease, so women with these germline mutations are advised to undergo prophylactic removal of ovaries and fallopian tubes typically after completing childbearing and ideally before age 35–40 years. Early prophylactic oophorectomy also protects these women from subsequent breast cancer with a reduction of breast cancer risk of approximately 50%.

69. T e answer is A.

(Chap. 46) Cervical cancer is the second most common and most lethal malignancy in women worldwide likely due to the widespread infection with high-risk strains of human papillomavirus (HPV) and limited utilization of or access to Pap smear screening in many nations throughout the world. Nearly 500,000 cases of cervical cancer are expected worldwide, with approximately 240,000 deaths annually. Cancer incidence is particularly high in women residing in Central and South America, the Caribbean, and southern and eastern Africa. Mortality rate is disproportionately high in Africa. In the United States, 12,360 women were diagnosed with cervical cancer and 4020 women died in 2014. HPV is the primary neoplastic-initiating event in the vast majority of women with invasive cervical cancer. T is double-strand DNA virus infects epithelium near the transformation zone of the cervix. More than 60 types of HPV are known, with approximately 20 types having the ability to generate high-grade dysplasia and malignancy. HPV-16 and -18 are the types most frequently associated with high-grade dysplasia and targeted by both U.S. Food and Drug Administration-approved vaccines. T e large majority of sexually active adults are exposed to HPV, and most women clear the infection without specific intervention. Risk factors for HPV infection and, in particular, dysplasia include a high number of sexual partners, early age of first intercourse, and history of venereal disease. Smoking is a cofactor; heavy smokers have a higher risk of dysplasia with HPV infection. HIV infection, especially when associated with low $CD4^+$ T cell counts, is associated with a higher rate of high-grade dysplasia and likely a shorter latency period between infection and invasive disease. T e administration of highly active antiretroviral therapy reduces the risk of high-grade dysplasia associated with HPV infection. Currently approved vaccines include the recombinant proteins to the late proteins, L1 and L2, of HPV-16 and -18. Vaccination of women before the initiation of sexual activity dramatically reduces the rate of HPV-16 and -18 infection and subsequent dysplasia. Stage 1 disease, which accounts for almost half of staging at presentation, is defined by carcinoma confined to the cervix and has a >80% 5-year survival (see **Figure 46-1**).

70. T e answer is A.

(Chap. 48) Primary brain tumors are diagnosed in approximately 52,000 people each year in the United States. At least one-half of these tumors are malignant and associated with a high mortality. Glial tumors account for about 30% of all primary brain tumors, and 80% of those are malignant. Meningiomas account for 35%, vestibular schwannomas 10%, and central nervous system (CNS) lymphomas about 2%. Brain metastases are three times more common than all primary brain tumors combined and are diagnosed in approximately 150,000 people each year. Brain tumors of any type can present with a variety of symptoms and signs that fall into two categories: general and focal; patients often have a combination of the two (see **Table 48-1**). Seizures are a common presentation of brain tumors, occurring in about 25% of patients with brain metastases or malignant

gliomas but can be the presenting symptom in up to 90% of patients with a low-grade glioma. All seizures that arise from a brain tumor will have a focal onset whether or not it is apparent clinically. Cranial MRI is the preferred diagnostic test for any patient suspected of having a brain tumor and should be performed with gadolinium contrast administration. CT scan should be reserved for those patients unable to undergo MRI (e.g., pacemaker). Malignant brain tumors—whether primary or metastatic—typically enhance with gadolinium and may have central areas of necrosis; they are characteristically surrounded by edema of the neighboring white matter. Low-grade gliomas usually do not enhance with gadolinium and are best appreciated on fluid-attenuated inversion recovery (FLAIR) MRIs. Meningiomas have a characteristic appearance on MRI because they are dural-based with a dural tail and compress but do not invade the brain.

71. The answer is D.
(Chap. 48) This patient presents with at least two presumed metastatic lesions in the right frontal and right cerebellar lobes. The multiple lesions make a primary brain tumor unlikely. The distribution of metastases in the brain approximates the proportion of blood flow such that about 85% of all metastases are supratentorial and 15% occur in the posterior fossa. The most common sources of brain metastases are lung and breast carcinomas; melanoma has the greatest propensity to metastasize to the brain, being found in 80% of patients at autopsy. The standard treatment for brain metastases has been whole-brain radiotherapy (WBRT) usually administered to a total dose of 3000 cGy in 10 fractions. This affords rapid palliation, and approximately 80% of patients improve with glucocorticoids and RT. However, it is not curative. Median survival is only 4–6 months. More recently, stereotactic radiosurgery (SRS) delivered through a variety of techniques including the gamma knife, linear accelerator, proton beam, and CyberKnife all can deliver highly focused doses of radiation therapy, usually in a single fraction. SRS can effectively sterilize the visible lesions and afford local disease control in 80–90% of patients. In addition, there are some patients who have clearly been cured of their brain metastases using SRS, whereas this is distinctly rare with WBRT. However, SRS can be used only for lesions 3 cm or less in diameter and should be confined to patients with only one to three metastases. The addition of WBRT to SRS improves disease control in the nervous system but does not prolong survival. Randomized controlled trials have demonstrated that surgical extirpation of a single brain metastasis followed by WBRT is superior to WBRT alone. Removal of two lesions or a single symptomatic mass, particularly if compressing the ventricular system, can also be useful. Chemotherapy is rarely useful for brain metastases (see **Table 48-3**).

72. The answer is C.
(Chap. 49) Carcinoma of unknown primary (CUP) is a biopsy-proven malignancy for which the anatomic site of origin remains unidentified after an intensive search. CUP is one of the 10 most frequently diagnosed cancers worldwide, accounting for 3–5% of all cancers. CUP is limited to epithelial cancers and does not include lymphomas, metastatic melanomas, and metastatic sarcomas because these cancers have specific histology- and stage-based treatments that guide management. The emergence of sophisticated imaging, robust immunohistochemistry (IHC), and genomic and proteomic tools has challenged the "unknown" designation. Additionally, effective targeted therapies in several cancers have moved the paradigm from empiricism to considering an individualized approach to CUP management. The reasons cancers present as CUP remain unclear. One hypothesis is that the primary tumor either regresses after seeding the metastasis or remains so small that it is not detected. It is possible that CUP falls on the continuum of cancer presentation where the primary has been contained or eliminated by the natural immune defenses. Alternatively, CUP may represent a specific malignant event that results in an increase in metastatic spread or survival relative to the primary. Most tumor markers, including CEA, CA-125, CA 19-9, and CA 15-3, when elevated, are nonspecific and not helpful in determining the primary tumor site. Men who present with adenocarcinoma and osteoblastic metastasis should undergo a prostate-specific antigen (PSA) test. In patients with undifferentiated or poorly differentiated carcinoma (especially with a midline tumor), elevated β-hCG and AFP levels suggest the possibility of an extragonadal germ cell (testicular) tumor. Monoclonal antibodies to specific cytokeratin (CK) subtypes have been used to help classify tumors according to their site of origin; commonly used CK stains in adenocarcinoma CUP are CK7 and CK20. CK7 is found in tumors of the lung, ovary, endometrium, breast, and upper gastrointestinal tract including pancreaticobiliary cancers, whereas CK20 is normally expressed in the gastrointestinal epithelium, urothelium, and Merkel cells. Gene expression profiling offers the promise of substantially increasing the yield of CUP.

T e median survival duration of most patients with disseminated CUP is approximately 6–10 months. Systemic chemotherapy is the primary treatment modality in most patients with disseminated disease, but the careful integration of surgery, radiation therapy, and even periods of observation is important in the overall management of this condition. Prognostic factors include performance status, site and number of metastases, response to chemotherapy, and serum lactate dehydrogenase (LDH) levels (see **Figure 49-2**).

73. T e answer is B.
(Chap. 54) Humoral hypercalcemia of malignancy (HHM) occurs in up to 20% of patients with cancer. HHM is most common in cancers of the lung, head and neck, skin, esophagus, breast, and genitourinary tract and in multiple myeloma and lymphomas. T ere are several distinct humoral causes of HHM, but it is caused most commonly by overproduction of parathyroid hormone related-protein (PTHrP). In addition to acting as a circulating humoral factor, bone metastases (e.g., breast, multiple myeloma) may produce PTHrP, leading to local osteolysis and hypercalcemia. PTHrP is structurally related to parathyroid hormone (PTH) and binds to the PTH receptor, explaining the similar biochemical features of HHM and hyperparathyroidism. Metastatic lesions to bone are more likely to produce PTHrP than are metastases in other tissues. Another relatively common cause of HHM is excess production of 1,25-dihydroxyvitamin D. Like granulomatous disorders associated with hypercalcemia, lymphomas can produce an enzyme that converts 25-hydroxyvitamin D to the more active 1,25-dihydroxyvitamin D, leading to enhanced gastrointestinal calcium absorption. Other causes of HHM include tumor-mediated production of osteolytic cytokines and inf ammatory mediators. In this case the multiple metastatic nodules and elevated PTHrP make lymphoma the least likely malignancy.

74. T e answer is E.
(Chap. 54) T e management of severe symptomatic humoral hypercalcemia of malignancy (HHM) begins saline rehydration (typically 200–500 mL/h) to dilute serum calcium and promote calciuresis. Forced diuresis with furosemide or other loop diuretics can enhance calcium excretion but provides relatively little value except in life-threatening hypercalcemia. When used, loop diuretics should be administered only after complete rehydration and with careful monitoring of f uid balance. Oral phosphorus should be given until serum phosphorus is >1 mmol/L (>3 mg/dL). Bisphosphonates such as pamidronate, zoledronate, and etidronate can reduce serum calcium within 1–2 days and suppress calcium release for several weeks. Bisphosphonate infusions can be repeated, or oral bisphosphonates can be used for chronic treatment. Dialysis should be considered in severe hypercalcemia when saline hydration and bisphosphonate treatments are not possible or are too slow in onset. Previously used agents such as calcitonin and mithramycin have little utility now that bisphosphonates are available. Calcitonin should be considered when rapid correction of severe hypercalcemia is needed. Hypercalcemia associated with lymphomas, multiple myeloma, or leukemia may respond to glucocorticoid treatment. T is patient most likely does not have lymphoma so initial treatment should not include corticosteroids.

75. T e answers are: 1-C; 2-B; 3-A.
(Chap. 57) Dose-dependent myocardial toxicity of anthracyclines with characteristic myofibrillar dropout is pathologically pathognomonic on endomyocardial biopsy. Anthracycline cardiotoxicity occurs through a root mechanism of chemical-free radical damage. $Fe3^{+}$-doxorubicin complexes damage DNA, nuclear and cytoplasmic membranes, and mitochondria. About 5% of patients receiving >450–550 mg/m^2 of doxorubicin will develop CHF. Cardiotoxicity in relation to the dose of anthracycline is clearly not a step function, but rather a continuous function, and occasional patients are seen with CHF at substantially lower doses. Advanced age, other concomitant cardiac disease, hypertension, diabetes, and thoracic radiation therapy are all important cofactors in promoting anthracycline-associated CHF. T e risk of cardiac failure appears to be substantially lower when doxorubicin is administered by continuous infusion. Anthracycline-related CHF is difficult to reverse and has a mortality rate as high as 50%, making prevention crucial. Monitoring patients for cardiac toxicity typically involves periodic gated nuclear cardiac blood pool ejection fraction testing (multigated acquisition scan [MUGA]) or cardiac ultrasonography. More recently, cardiac MRI has been used, but MRI is not standard or widespread. After anthracyclines, trastuzumab is the next most frequent cardiotoxic drug currently in use. Trastuzumab is frequently used as adjuvant breast cancer therapy, sometimes in conjunction with anthracyclines, which is believed to result in additive or possibly synergistic toxicity. In contrast to anthracyclines, cardiotoxicity is not dose-related, is usually reversible, is not associated with pathologic changes of anthracyclines on cardiac

myofibrils, and has a different biochemical mechanism inhibiting intrinsic cardiac repair mechanisms. Toxicity is typically routinely monitored every three to four doses using functional cardiac testing as mentioned earlier for anthracyclines. Cisplatin is associated with sensorimotor neuropathy and hearing loss, especially at doses >400 mg/m^2, requiring audiometry in patients with preexisting hearing compromise. Carboplatin is often substituted in such cases given its lesser effect on hearing.

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