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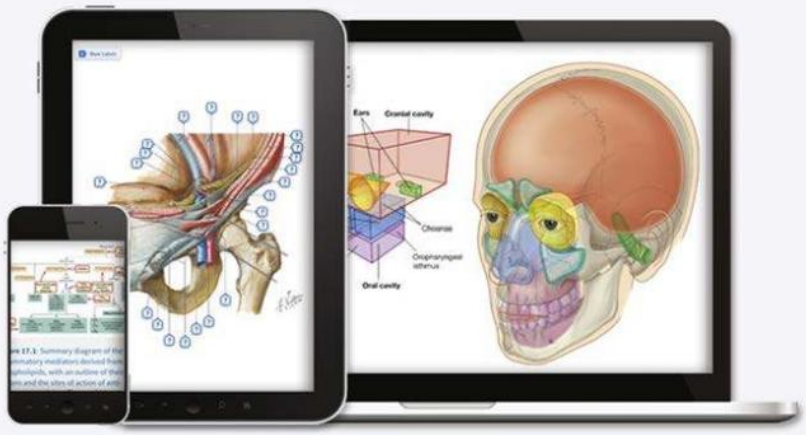

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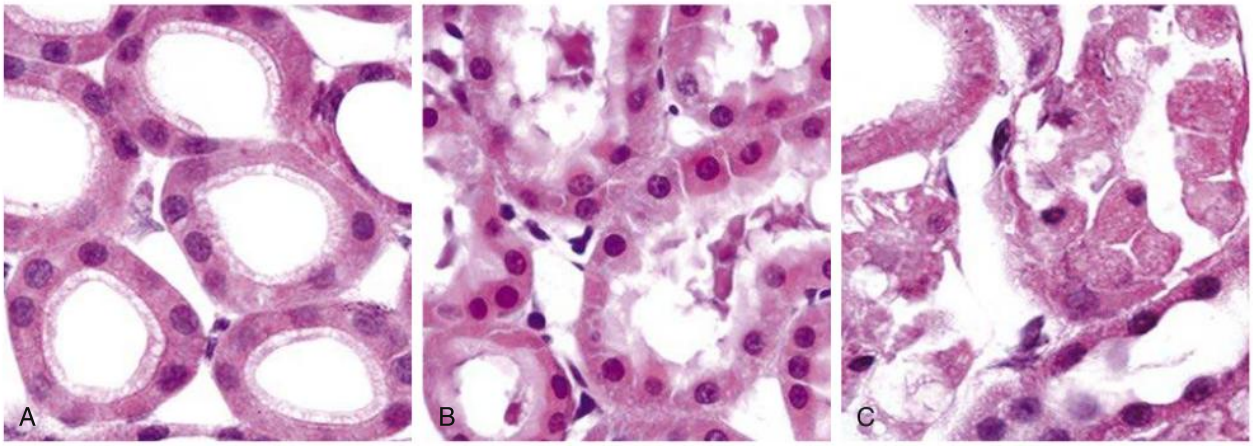


Fig. 1.2 Morphologic changes in reversible and irreversible cell injury (necrosis). (A) Normal kidney tubules with viable epithelial cells. (B) Early (reversible) ischemic injury showing surface blebs, increased eosinophilia of cytoplasm, and swelling of occasional cells. (C) Necrotic (irreversible) injury of epithelial cells, with loss of nuclei and fragmentation of cells and leakage of contents. (Courtesy of Drs. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio.)

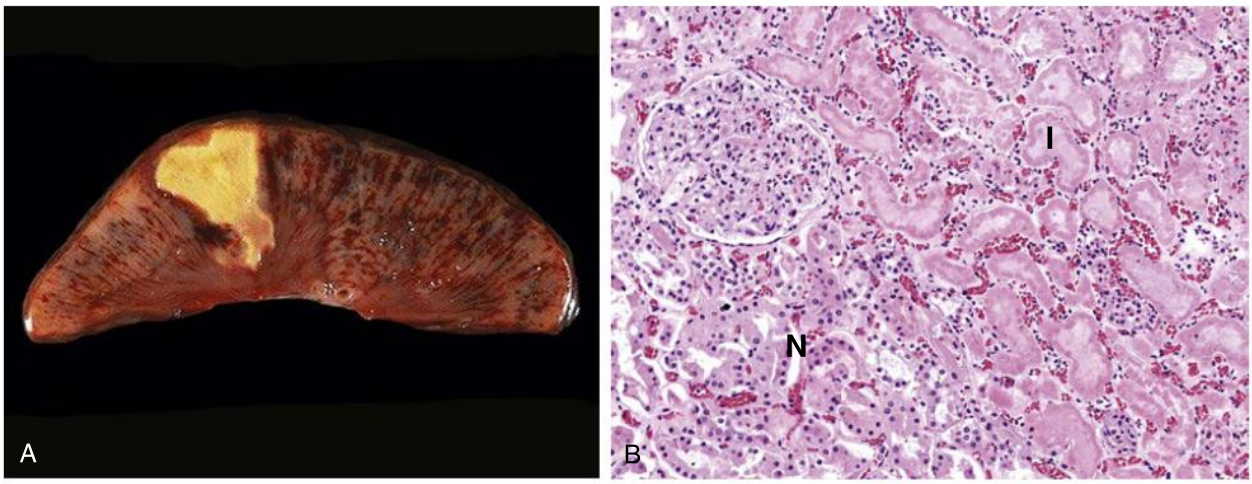


Fig. 1.3 Coagulative necrosis. (A) A wedge-shaped kidney infarct *(yellow).* (B) Microscopic view of the edge of the infarct, with normal kidney *(N)* and necrotic cells in the infarct *(I).* The necrotic cells show preserved outlines with loss of nuclei, and an inflammatory infiltrate (dark nuclei interspersed between necrotic tubules) is present.

In this pathway of cell death, enzymes activated by specific signals dismantle the nucleus and cytoplasm, generating fragments that are recognized and rapidly cleared by phagocytes.

Causes of Apoptosis

Apoptosis occurs in many physiologic situations and serves to eliminate potentially harmful cells and cells that have outlived their usefulness (Table 1.2). It also occurs as a pathologic event when cells are damaged, especially when the damage affects the cell's DNA or proteins; thus, the irreparably damaged cell is eliminated.

- *Physiologic apoptosis*
  - Death of cells during the development of organisms, such as cells of primordial tissues that are replaced by mature tissues
  - Death of leukocytes (neutrophils and lymphocytes) after inflammatory and immune responses have eliminated offending agents
  - Elimination of dysfunctional or autoreactive lymphocytes or lymphocyte precursors, particularly in the bone marrow and the thymus

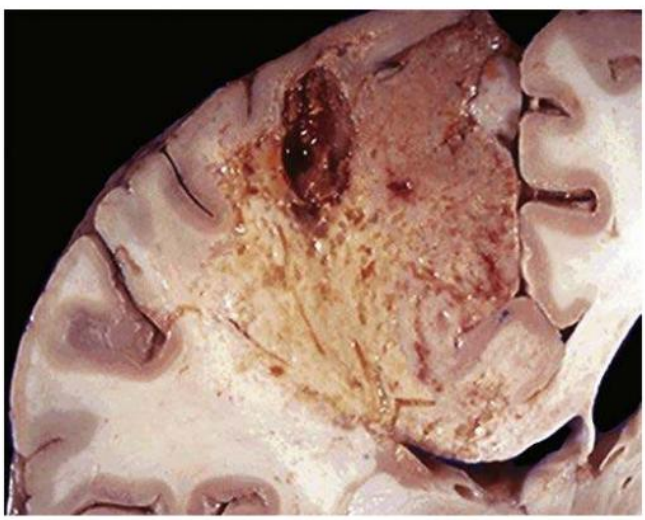


Fig. 1.4 Liquefactive necrosis. An infarct in the brain showing dissolution of the tissue.

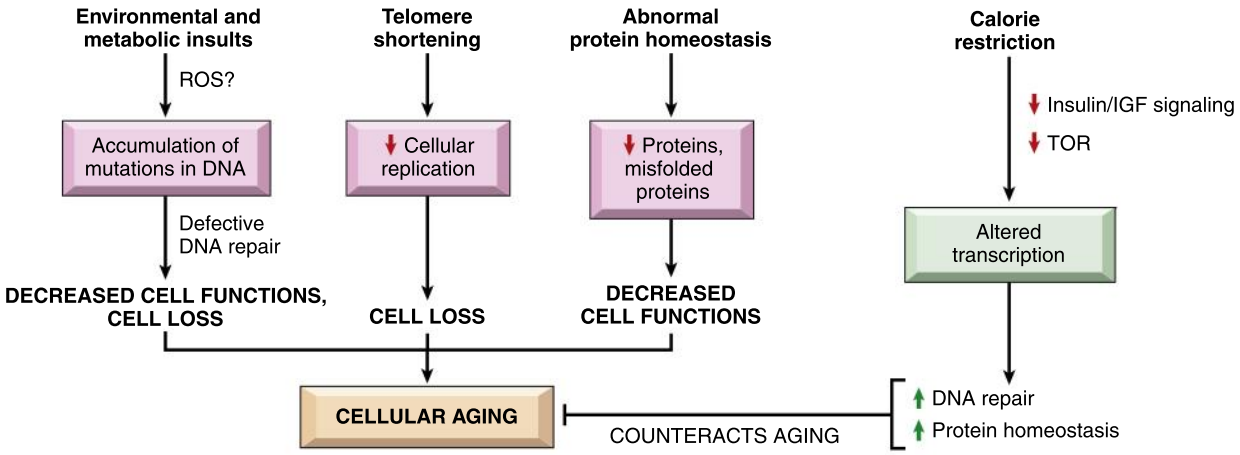


Fig. 1.13 Mechanisms of cellular aging. DNA damage, replicative senescence, and decreased and misfolded proteins are among the best-described mechanisms of cellular aging. Some environmental stresses, such as calorie restriction, counteract aging by activating various signaling pathways and transcription factors. *IGF,* Insulin-like growth factor; *ROS,* reactive oxygen species; *TOR,* target of rapamycin.

aging, the "naked" chromosome ends activate the DNA damage response, causing the cells to enter a state of replicative senescence.

- *Defective protein homeostasis,* due to increased turnover and decreased synthesis of intracellular proteins, together with accumulation of misfolded proteins.
- *Altered signaling pathways* that may affect responses to growth factors. There has been great interest in defining these pathways, in part because of the intriguing observation that calorie restriction prolongs life. One possibility is that calorie restriction reduces signaling by insulin-like growth factor, so cells cycle less and suffer fewer DNA replication–related errors.
- In addition to these intrinsic abnormalities, damaged and dying cells induce low-level *inflammation,* and chronic inflammation predisposes to many diseases, such as atherosclerosis, type 2 diabetes, and some types of cancer.

CELLULAR ADAPTATIONS TO STRESS

Adaptations are reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to changes in their environment.

Cellular adaptations may be part of physiologic cellular responses or may be pathologic. *Physiologic adaptations* usually represent responses of cells to normal stimulation by hormones or endogenous chemical mediators (e.g., the hormone-induced enlargement of the breast and uterus during pregnancy), or to the demands of mechanical stress (in the case of bones and muscles). *Pathologic adaptations* are responses to stress that allow cells to modulate their structure and function and thus escape injury, but at the expense of normal function. Physiologic and pathophysiologic adaptations can take several distinct forms.

- *Hypertrophy* is an increase in the size of cells resulting in enlargement of the organ (Fig. 1.14). It can be physiologic or pathologic and is caused either by an increased functional demand or by hormonal stimulation. For example, physiologic enlargement of the uterus during pregnancy is caused by increased estrogen levels. Muscle hypertrophy following weight lifting is an adaptation to increased mechanical stress. Cardiac hypertrophy in hypertension or aortic valve disease is an example of pathologic hypertrophy resulting from increased work load. In all forms, hormones and mechanical sensors activate signaling pathways that lead to increased protein synthesis and assembly of more organelles, and thus enlargement of the cell. Although an adaptation to stress, hypertrophy can progress to functionally significant cell or organ injury if the stress is not relieved. For example, cardiac hypertrophy can cause myocardial ischemia due to relative lack of oxygen delivery, and eventually give rise to cardiac failure.
- *Hyperplasia* is an increase in the number of cells in an organ that stems from increased proliferation, either of less-differentiated progenitor cells or, in some instances, differentiated cells. Hyperplasia occurs if the tissue contains cell populations capable of replication and may occur concurrently with hypertrophy and often in response to the same stimuli. Hyperplasia can be physiologic or pathologic and, in both situations, cellular proliferation is stimulated by hormones and growth factors that are produced by a variety of cell types. Postpartum enlargement of the breast due to increased proliferation of ductular epithelium is an example of physiologic hyperplasia induced by hormones. Growth factors are responsible for stimulating proliferation of surviving cells after death or removal of some of the cells in an organ (e.g., growth of residual liver following partial hepatectomy, called *compensatory hyperplasia*). Pathologic hyperplasia is typically the result of inappropriate and excessive stimulation by hormones and growth factors, as in endometrial hyperplasia resulting from a disturbed estrogen–progesterone balance. Benign prostatic hyperplasia is induced by androgens and can cause obstruction to the flow of urine and predispose to urinary tract infections. It is important to distinguish hyperplasia from neoplasia: Unlike neoplastic growths, hyperplasia is reversible when the growth signals abate. In some cases, persistent pathologic hyperplasia, such as that affecting the endometrium, sets the stage for the development of cancer because proliferating cells are susceptible to mutations and oncogenic transformation.
- *Atrophy* is a decrease in the number of cells and, hence, may cause an organ to shrink. It is caused by decreased protein synthesis (due to reduced metabolic activity) and increased protein breakdown mediated by the ubiquitin–proteasome pathway. Causes include a decreased workload (as in immobilization or denervation of muscle, leading to disuse atrophy), progressive ischemia, reduced nutrition, and reduced hormone stimulation (as in menopause). Faced with malnutrition, cells undergo atrophy rather than death as an adaptation to reduced energy supply. It is often associated with increased autophagy.
- *Metaplasia* is a change of one adult cell type to another. It is a response to stress in which a cell that is sensitive to that stress is replaced by another cell type that is better able to survive the adverse environment. The mechanism is thought to be reprogramming of tissue stem cells to differentiate along a new pathway. Examples include squamous metaplasia of the bronchial columnar epithelium

Table 2.5 Major Cytokines of Acute and Chronic Inflammation

Cytokine	Principal Cell Sources	Principal Functions and Role in Inflammation	Use of Therapeutic Antagonists[a]
Cytokines in Acute Inflammation			
Tumor necrosis factor (TNF)	Macrophages, dendritic cells, T cells	Endothelial cells: activation → expression of adhesion molecules, secretion of chemokines, reduced anticoagulant properties (inflammation, coagulation) Neutrophils: activation Hypothalamus: fever Muscle, fat: catabolism (cachexia)	Rheumatoid arthritis, inflammatory bowel disease, psoriasis
Interleukin-1 (IL-1)	Macrophages, dendritic cells, fibroblasts, endothelial cells, keratinocytes	Endothelial cells: activation (inflammation, coagulation), similar to TNF Hypothalamus: fever Liver: synthesis of acute-phase proteins T cells: Th17 differentiation	Rheumatoid arthritis, autoinflammatory syndromes (rare genetic diseases)
Interleukin-6 (IL-6)	Macrophages, dendritic cells, T cells	Liver: synthesis of acute-phase protein B cells: proliferation of antibody-producing cells T cells: Th17 differentiation	Rheumatoid arthritis (juvenile and adult)
Chemokines (many)	Virtually all cell types	Recruitment of leukocytes from the circulation into tissues Maintenance of lymphoid tissue architecture (segregation of T and B cells in secondary lymphoid organs)	Inflammatory bowel disease (in clinical trials)
Cytokines in Chronic Inflammation			
Interleukin-2 (IL-2)	T cells (mainly CD4+ helper T cells)	T cells: proliferation and differentiation into effector and memory cells; promotes regulatory T-cell development, survival, and function	Anti-IL-2 receptor used to prevent acute organ transplant rejection
Interleukin-4 (IL-4)	$CD4^+$ T cells (Th2), mast cells	B cells: isotype switching to IgE T cells: Th2 differentiation, proliferation Macrophages: alternative activation Role in allergic inflammation	Asthma, atopic dermatitis
Interleukin-5 (IL-5)	$CD4^+$ T cells (Th2)	Eosinophils: activation, increased generation Role in allergic inflammation	Asthma
Interleukin-12 (IL-12)	Macrophages, dendritic cells	T cells: Th1 differentiation NK cells and T cells: IFN-γ synthesis	
Interleukin-17	$CD4^+$ T cells (Th17)	Epithelial cells, macrophages, and other cell types: increased chemokine and cytokine production; GM-CSF and G-CSF production → recruitment and activation of neutrophils	Psoriasis; some effect in multiple sclerosis
Interferon-γ (IFN-γ)	T cells (Th1, $CD8^+$ T cells), NK cells	Macrophages: classical activation (increased microbicidal functions) T cells: Th1 differentiation	Hemophagocytic syndromes
Interleukin-10 (IL-10)	Macrophages, T cells (mainly regulatory T cells)	Macrophages, dendritic cells: inhibition Role in termination of inflammation	
Transforming growth factor-β (TGF-β)	T cells, macrophages, other cell types	T cells: inhibition of proliferation and effector functions; differentiation of Th17 and Treg Macrophages: inhibition of activation; stimulation of angiogenic factors Fibroblasts: increased collagen synthesis	

[a]Specific for the cytokine or its receptor.

Pentraxins are plasma proteins that include C-reactive protein (CRP) and serum amyloid protein (see below). They recognize phospholipids expressed on bacterial membranes (and apoptotic cells) and promote phagocytosis or activate the complement system, thus causing the elimination of these microbes and dead cells. The plasma levels of these proteins increase during the acute-phase response that accompanies inflammatory reactions, discussed later. *Kinins* are produced from circulating precursor proteins and contribute to vascular dilation and pain at the site of inflammation.

The four major features of inflammation (initially described in the 1st century AD by the Roman encyclopedist Celsus), *rubor* (redness), *calor* (warmth), *tumor* (swelling), and *dolor* (pain), can be explained by the actions of particular mediators (Table 2.6). A fifth sign, loss of function, was added later.

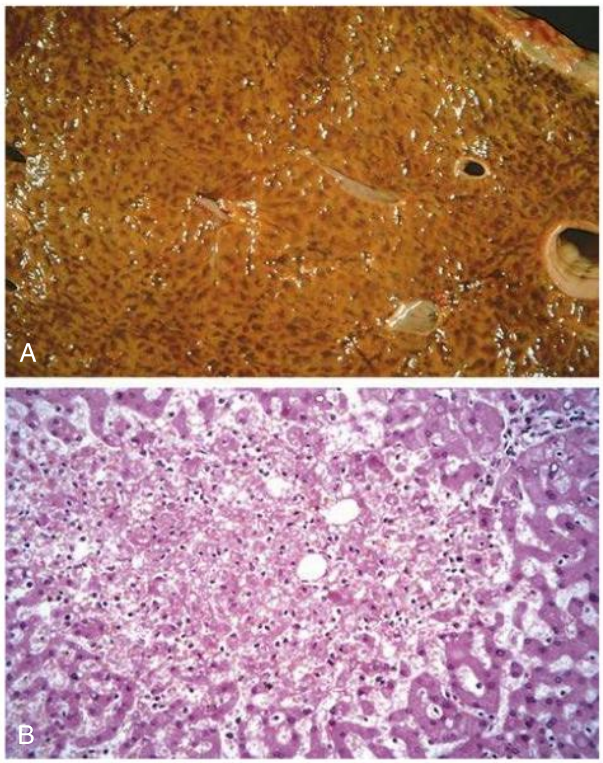


Fig. 3.2 Liver with chronic passive congestion and hemorrhagic necrosis. (A) In this autopsy specimen, central areas are red and slightly depressed compared with the surrounding tan viable parenchyma, creating "nutmeg liver" (so called because it resembles the cut surface of a nutmeg). (B) Microscopic preparation shows centrilobular hepatic necrosis with hemorrhage and scattered inflammatory cells. (Courtesy of Dr. James Crawford, Hofstra/Northwell School of Medicine, Hempstead, NY.)

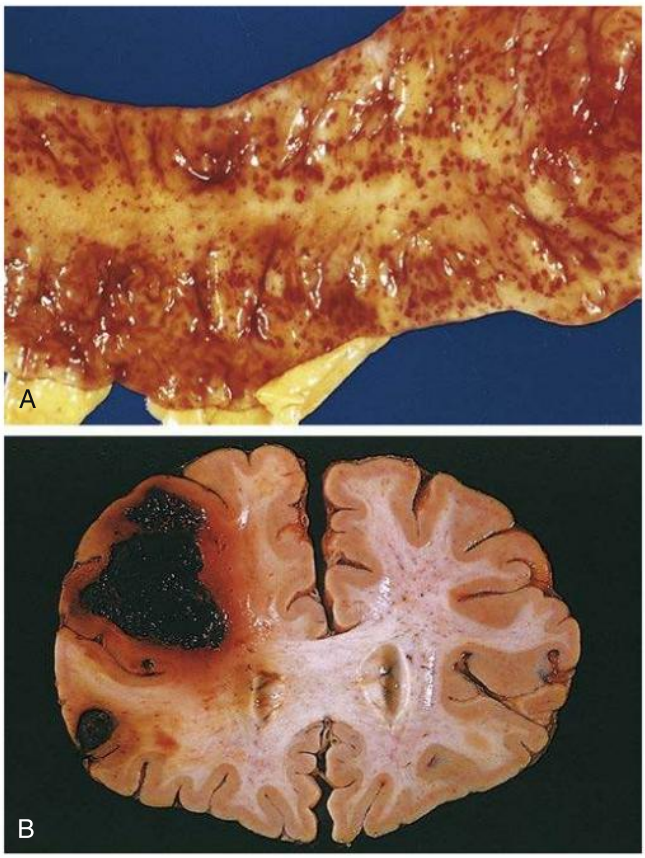


Fig. 3.3 (A) Punctate petechial hemorrhages of the colonic mucosa, a consequence of thrombocytopenia. (B) Fatal intracerebral hemorrhage.

- *Purpura* are 3- to 5-mm bleeds that may stem from defects in platelet function, trauma, vascular inflammation, or vascular fragility.
- *Ecchymoses* are 1-2 cm in size and correspond to "bruises"; they are usually caused by trauma.

Hemostasis, the clotting of blood following blood vessel trauma, is essential for life.

Under normal circumstances, blood clotting occurs at sites where the walls of blood vessels have been physically disrupted. The initial steps in clot formation are two mutually reinforcing processes (Fig. 3.4):

- *Primary hemostasis* is initiated by the exposure of subendothelial collagen and von Willebrand factor (vWF) within injured vessel walls. These factors lead to the adhesion and activation of platelets, which form a platelet-rich plug.
- *Secondary hemostasis* is triggered by the exposure of tissue factor within the subendothelium and tissues. Tissue factor acts in conjunction with factor VII (described later) to initiate the coagulation cascade, which uses cofactors that are present on the surfaces of activated platelets and leads to the deposition of fibrin. Fibrin reinforces and stabilizes the platelet plug, sealing the area of vascular damage and preventing further bleeding.

Once a clot has formed, its extent must be limited to the area of damage. This is mediated by counterregulatory mechanisms, which we will discuss later in this chapter.

Platelets

Platelets are anucleate fragments derived from megakaryocytes that form the primary hemostatic plug and provide a procoagulant surface that promotes secondary hemostasis.

Platelet function depends on surface glycoprotein receptors, a contractile cytoskeleton, and cytoplasmic granules that contain a number of procoagulant substances. In the setting of vascular injury, platelets undergo a series of stereotypic events:

- *Adhesion.* Platelet adhesion is mediated largely by interactions with vWF, which acts as a bridge between exposed subendothelail collagen and platelet surface receptor glycoprotein 1b (Gp1b).
- *Activation.* Platelets change shape from smooth discs to spiky spheres and release the contents of their granules, which include coagulation cofactors (calcium, factor V) and platelet activators such as adenosine diphosphate (ADP), which recruit other platelets to the growing platelet plug.
- *Aggregation.* The shape change associated with activation exposes negatively charged phospholipids, which are required by certain coagulation factors (described later), and also alters the conformation of surface glycoprotein IIb/IIIa (GpIIb/IIIa), converting GpIIa/IIIb to a high-affinity receptor for fibrinogen. Bivalent bridging interactions involving GpIIa/IIIb receptors and fibrinogen then cause platelets to clump into aggregates.

Deficiencies of GpIb, GpIIa/IIIb, or vWF are associated with abnormal bleeding (Fig. 3.5).

4

Diseases of the Immune System

OUTLINE

The immune system protects us against infections and cancers by two types of mechanisms: innate immunity and adaptive immunity.

Innate immunity is the rapid response to infections mediated by cells and plasma proteins that are always present and ready to attack (hence, *innate*). The principal cells of innate immunity are myeloid cells, including macrophages, neutrophils, and dendritic cells, but lymphocytes, epithelial cells, and other cell types also possess intrinsic defense mechanisms. These cells express receptors such as Toll-like receptors that recognize microbial products and products of necrotic cells. These receptors, unlike the antigen receptors of T and B lymphocytes, are not pathogen specific and have limited diversity. They are triggered by molecules shared by many pathogens (pathogen-associated molecular patterns [PAMPs]) and substances released from damaged cells (damage-associated molecular patterns [DAMPs]). The major reaction of innate immunity is acute inflammation (see Chapter 2).

Adaptive immunity is the more powerful and specialized set of responses mediated by T and B lymphocytes. These cells express specific and highly diverse receptors for antigens. Each T and B lymphocyte and its clonal progeny express a unique receptor and, hence, have a unique specificity. The diversity of the receptors is created by rearrangements of antigen-receptor genes that occur during the maturation of the lymphocytes. Thus, the presence of rearranged antigen-receptor genes is a reliable marker of T and B lymphocytes and of tumors derived from these cells. Lymphocytes are normally silent and are activated by (adapt to) antigens (hence, the term adaptive immunity). Following activation, the lymphocytes produce effector cells that possess mechanisms that function to eliminate microbes and tumor cells. These mechanisms include:

- *Humoral immunity* mediated by antibodies, which are produced by B cells and their differentiated progeny, plasma cells. Antibodies neutralize microbes, opsonize them for phagocytosis, and activate the complement system.
- *Cell-mediated immunity* mediated by T cells. T cells are activated by protein antigens displayed by antigen-presenting cells (APCs), and require repeat antigen stimulation to perform their functions. Two major types of T cells, CD4+ and CD8+, function differently in host defense and pathologic reactions. CD4+ helper T cells secrete cytokines that activate macrophages to destroy phagocytosed microbes, help B cells to make potent antibodies, and stimulate inflammation. Helper T cells consist of several subsets that produce different cytokines and induce different types of inflammatory reactions: Th1 cells activate macrophages, Th2 cells activate eosinophils, and Th17 cells stimulate neutrophil-rich inflammation. CD8+ cytotoxic T lymphocytes (CTLs) kill infected and transformed cells.

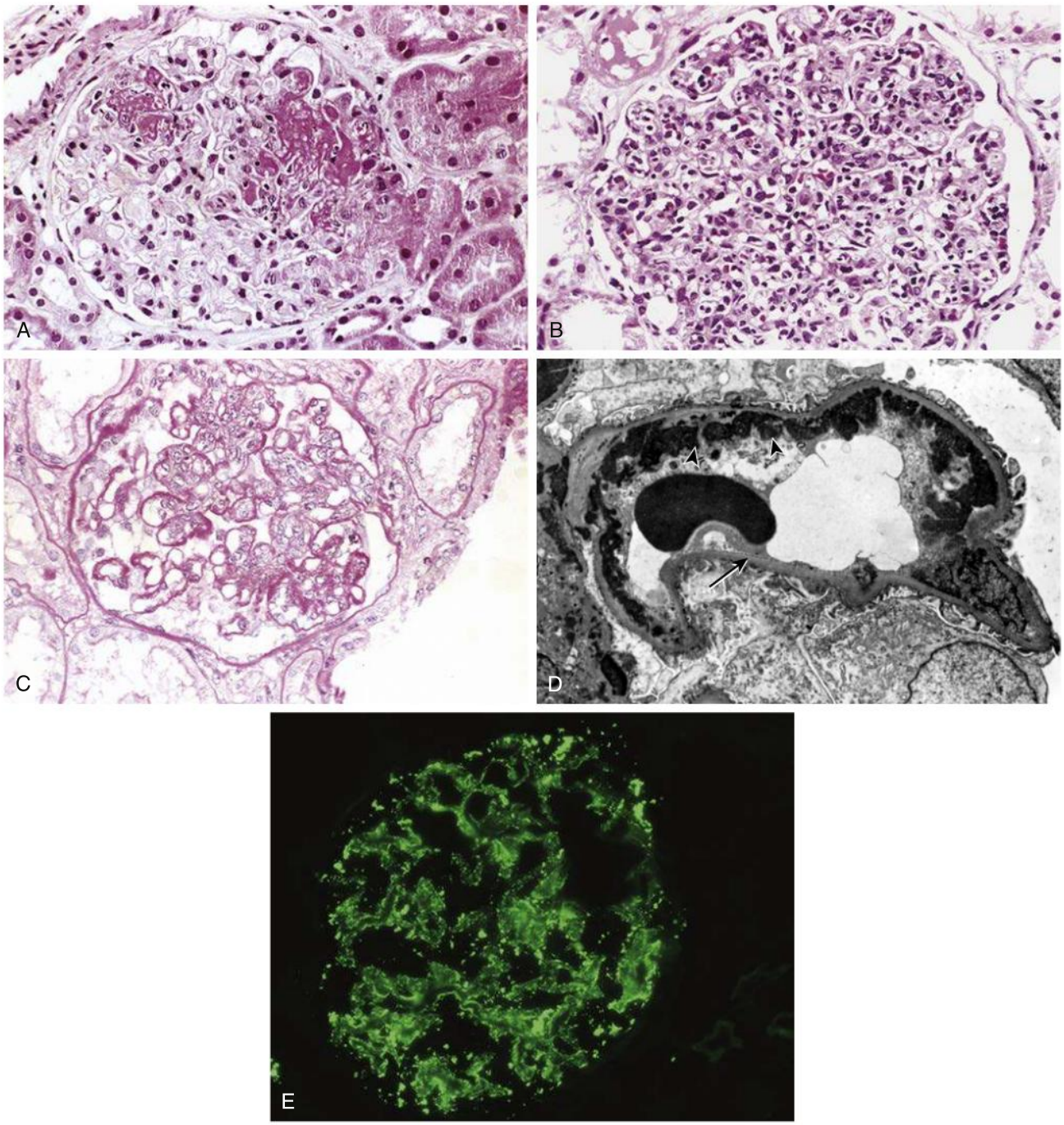
Although the immune system evolved as a protective force, at times it can go awry and cause tissue injury and clinical disease. In this chapter, we discuss the most important pathologic reactions and diseases that are caused by immune responses, mainly adaptive immune responses, as well as deficiencies of the immune system and their consequences.

HYPERSENSITIVITY DISORDERS

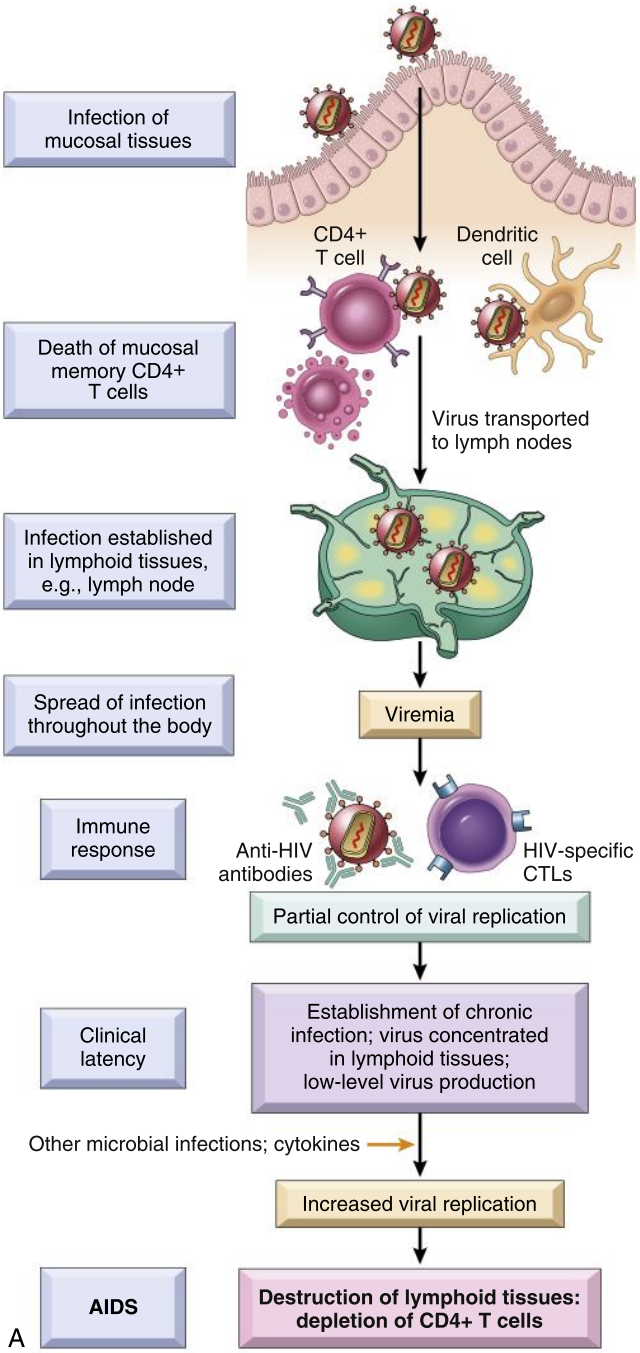
Persistent, misdirected, or inadequately regulated immune reactions against a variety of antigens may cause tissue injury.

An individual who has been exposed to and reacts against an antigen is said to be sensitized, so injurious immune reactions are called *hypersensitivity reactions.* Hypersensitivity diseases tend to be chronic and difficult to control, and are therefore important clinical problems. These diseases may be caused by reactions to three main types of antigens.

- *Reactions against self antigens* are called autoimmunity, and the diseases they cause are *autoimmune diseases.* As we shall discuss later, individuals are normally tolerant to their own (self) antigens, and autoimmunity results when self-tolerance breaks down.



Supplemental eFig. 4.1 Lupus nephritis. (A) Focal proliferative glomerulonephritis, with two focal necrotizing lesions at the 11 o'clock and 2 o'clock positions (H&E stain). Extracapillary proliferation is not prominent in this case. (B) Diffuse proliferative glomerulonephritis. Note the marked increase in cellularity throughout the glomerulus (H&E stain). (C) Lupus nephritis showing a glomerulus with several "wire-loop" lesions representing extensive subendothelial deposits of immune complexes (periodic acid-Schiff stain). (D) Electron micrograph of a renal glomerular capillary loop from a patient with SLE nephritis. Subendothelial dense deposits *(arrowheads)* on basement membrane *(arrow)* correspond to "wire loops" seen by light microscopy. (E) Deposition of IgG antibody in a granular pattern, detected by immunofluorescence. (A to C, Courtesy of Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts. D, Courtesy of Dr. Edwin Eigenbrodt, Department of Pathology, University of Texas, Southwestern Medical School, Dallas, Texas. E, Courtesy of Dr. Jean Olson, Department of Pathology, University of California, San Francisco, California.)



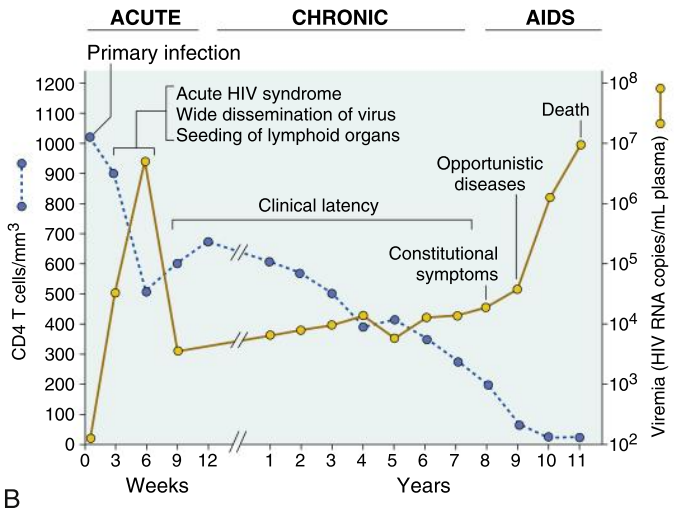


Fig. 4.16 Pathogenesis and clinical course of HIV infection. (A) The initial infection starts in mucosal tissues, involving mainly memory CD4+ T cells and dendritic cells, and spreads to lymph nodes. Viral replication leads to viremia and widespread seeding of lymphoid tissue. The viremia is controlled by the host immune response, and the patient then enters a phase of clinical latency. During this phase, viral replication in both T cells and macrophages continues unabated, but there is some immune containment of virus (not illustrated). There continues a gradual erosion of CD4+ cells, and ultimately, CD4+ T-cell numbers decline and the patient develops clinical symptoms of full-blown AIDS. (B) Clinical course of HIV infection. CTL, Cytotoxic T lymphocyte. (B, from Pantelo G, et al: *N Engl J Med* 328:327, 1993. Copyright 1993 Massachusetts Medical Society. All rights reserved.)

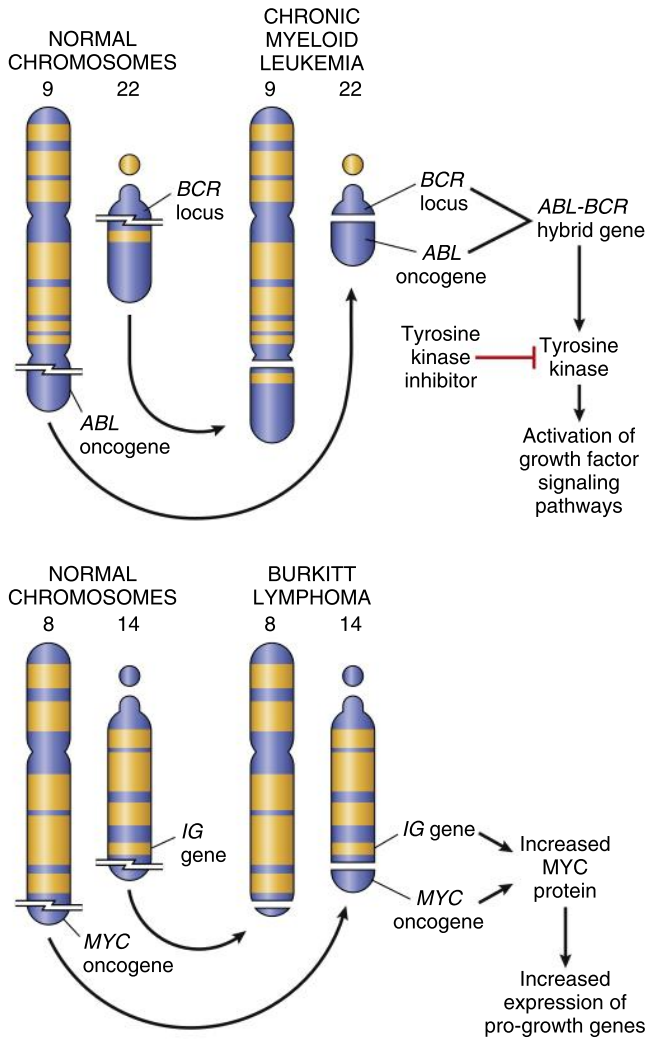


Fig. 5.12 Chromosomal translocations and associated oncogenes. In chronic myeloid leukemia, a balanced translocation involving chromosomes 9 and 22 creates a chimeric gene containing pieces of the *BCR* and *ABL* genes that encode a chimeric BCR-ABL fusion protein with constitutively active tyrosine kinase activity. In Burkitt lymphoma, a balanced translocation involving chromosomes 8 and 14 places the coding sequence for the *MYC* gene adjacent to strong regulatory elements in the immunoglobulin heavy-chain gene, leading to overexpression of MYC, an oncogenic transcription factor.

cancer is incompletely understood, but it is believed to involve changes in the expression of cancer genes that reside in affected chromosomal regions.

Epigenetic Alterations in Cancer

Epigenetic changes are defined as heritable changes in the expression of a gene that occur without mutation of the gene.

Gene expression is regulated by posttranslational modifications of histones and by DNA methylation, both of which are frequently altered in cancer cells when compared with their normal cellular counterparts. How these alterations in the epigenome contribute to neoplasia is poorly understood, but are likely in most, if not all, instances to stem from the altered expression of cancer genes.

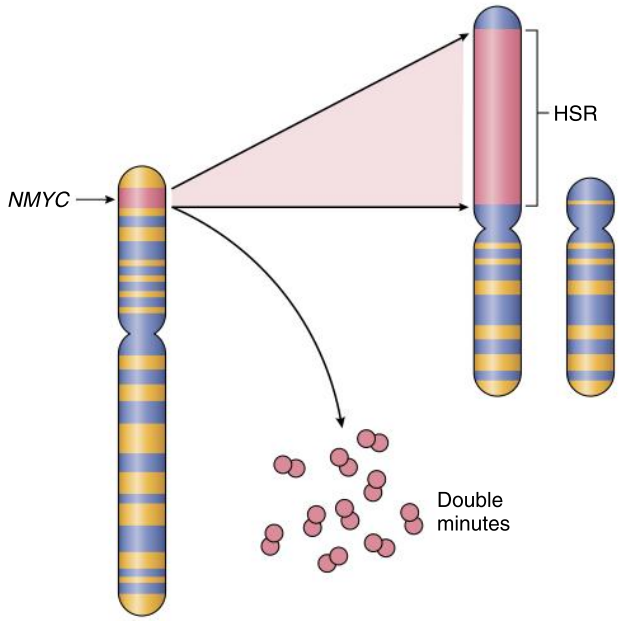


Fig. 5.13 Amplification of the *NMYC* gene in human neuroblastoma. The *NMYC* gene, present normally on chromosome 2p, becomes amplified and is seen either as extrachromosomal double minutes or as a chromosomally integrated homogeneous-staining region, usually on a chromosome other than chromosome 2. NMYC is closely related in structure to MYC and also is an oncogenic transcription factor. (Modified from Brodeur GM, Seeger RC, Sather H, et al: Clinical implications of oncogene activation in human neuroblastomas. *Cancer* 58:541, 1986. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Carcinogenesis: A Multistep Process Directed by Darwinian Evolution

Cancers are initiated and subsequently progress by the stepwise acquisition of multiple genetic aberrations that disrupt sets of cancer genes with complementary prooncogenic functions.

Even though tumor formation is initiated from a single founding cell, cancers continue to evolve genetically (Fig. 5.14), a process that contributes to a phenomenon referred to as tumor progression. At the molecular level, tumor progression is believed to result from additional mutations that accumulate independently in different cancer cells. Some of these mutations may alter the function of cancer genes, thereby making the affected cells more adept at growth, survival, invasion, metastasis, or immune evasion, resulting in progression akin to Darwinian evolution (survival of the fittest). Due to this selective advantage, subclones may come to dominate a tumor, either at the primary site or at sites of metastasis. Because of continuing mutation and selection, malignant tumors that were monoclonal in origin are typically genetically heterogeneous at the time of clinical presentation.

Genetic heterogeneity has implications not only for cancer progression but also for the response to therapy.

When tumors recur after chemotherapy, the recurrent tumor is almost always resistant to the original drug regimen. This acquired resistance stems from the outgrowth of subclones that have mutations (or epigenetic alterations) that impart drug resistance. Thus, genetic evolution forged by darwinian selection can explain the two most

the regression of many tumors, including melanoma, non–small cell lung cancer, bladder cancer, Hodgkin lymphoma, and others. This approach, called checkpoint blockade, is now an important component of anticancer therapy. Because the checkpoints evolved normally to prevent autoimmunity, patients given these treatments often develop autoimmune inflammation, including colitis, as well as inflammation of the endocrine organs, heart, and other tissues.

- *Other mechanisms* by which tumors inhibit immune responses include induction of regulatory T cells and the local production of immunosuppressive cytokines such as TGF-β.

Genomic Instability as an Enabler of Malignancy

Defects in DNA repair pathways enable tumor growth by allowing accumulation of mutations in cancer genes.

The preceding section identified the eight defining features of malignancy, all of which appear to be produced by genetic alterations involving cancer genes. Although humans are awash in environmental mutagens, cancers are relatively rare outcomes of these encounters because normal cells are able to sense and repair DNA damage. The importance of DNA repair in maintaining the integrity of the genome is highlighted by persons born with inherited defects in three types of DNA repair systems (mismatch repair, nucleotide excision repair, and recombination repair), all of which are associated with an increased risk for developing cancer. Although the discussion below focuses on these inherited syndromes, sporadic cancers often incur mutations in DNA repair genes, as well. Presumably, as in individuals with inherited DNA repair defects, these somatic mutations speed the accumulation of driver mutations in cancer genes and thereby the development of cancer.

Hereditary Nonpolyposis Colon Cancer Syndrome

The role of DNA mismatch repair genes in the predisposition to cancer is illustrated by the *hereditary nonpolyposis colon cancer (HNPCC) syndrome,* a disorder characterized by familial carcinoma of the colon. When a strand of DNA is being repaired, the proteins encoded by these genes act as "spell checkers." For example, if there is an erroneous pairing of G with T, rather than the normal A with T, the mismatch repair proteins correct the defect. Without these "proofreaders," errors accumulate at an increased rate. Mutations in at least four mismatch repair genes have been found in patients with HNPCC. One defective copy of a DNA mismatch repair gene is inherited, and a second "hit" in the other allele of the same gene occurs in colonic epithelial cells. In this respect, they resemble tumor suppressor genes. DNA repair genes affect cell growth indirectly by allowing mutations in other genes during the process of normal cell division. A characteristic finding in the genome of patients with mismatch repair defects is microsatellite instability (MSI). Microsatellites are tandem repeats of one to six nucleotides found throughout the genome. Usually, the length of these microsatellites remains constant. However, in patients with HNPCC, these satellites are unstable and increase or decrease in length. HNPCC syndrome accounts for only 2% to 4% of all colonic cancers, but MSI can be detected in about 15% of sporadic cancers. MSI-associated tumors tend to be more responsive to immune checkpoint inhibitor therapies, presumably because the defect in mismatch repair leads to a high burden of mutations producing tumor neoantigens. In fact, this type of immunotherapy is now approved for all recurrent tumors with mismatch repair defects regardless of the tumor type—the first time a treatment has been approved based only on a mutational signature.

Xeroderma Pigmentosum

Patients with the autosomal recessive disorder *xeroderma pigmentosum* are at increased risk for cancers arising in sun-exposed skin. Ultraviolet (UV) rays in sunlight cause cross-linking of pyrimidine residues, preventing normal DNA replication. Such DNA damage is repaired by the nucleotide excision repair system, which is defective in patients with this disease. The rate of somatic mutation in sun-exposed skin is greatly accelerated, resulting in an extraordinarily high incidence of skin cancers such as basal cell carcinoma and squamous cell carcinoma in these patients.

Diseases with Defects in DNA Repair by Homologous Recombination

The autosomal recessive disorders *Bloom syndrome, ataxia-telangiectasia,* and *Fanconi anemia* are characterized by hypersensitivity to DNA-damaging agents, such as ionizing radiation (in Bloom syndrome and ataxia-telangiectasia) or DNA cross-linking agents such as nitrogen mustard (in Fanconi anemia). Each is caused by defects in genes that are required for DNA repair by homologous recombination, in which a "good" strand of DNA is used to repair a damaged piece of DNA that has been broken or covalently cross-linked. The phenotypes of these diseases are complex and include, in addition to a predisposition to cancer, neural symptoms (in ataxia-telangiectasia), anemia (in Fanconi anemia), and developmental defects (in Bloom syndrome).

Evidence of the oncogenic role of defective homologous recombination also comes from the study of hereditary breast cancer. Germline mutations in two genes that also function in homologous recombination, *BRCA1* and *BRCA2,* are found in 50% of familial breast cancers. In addition to breast cancer, women with *BRCA1* mutations have a substantially higher risk of ovarian carcinoma and men have a slightly higher risk of prostate cancer; germline mutations in *BRCA2* increase the risk of breast cancer in both men and women, as well as other carcinomas, melanoma, and lymphomas. Similar to other tumor suppressor genes, both copies of *BRCA1* and *BRCA2* must be inactivated for cancer to develop.

Tumor-Promoting Inflammation as an Enabler of Malignancy

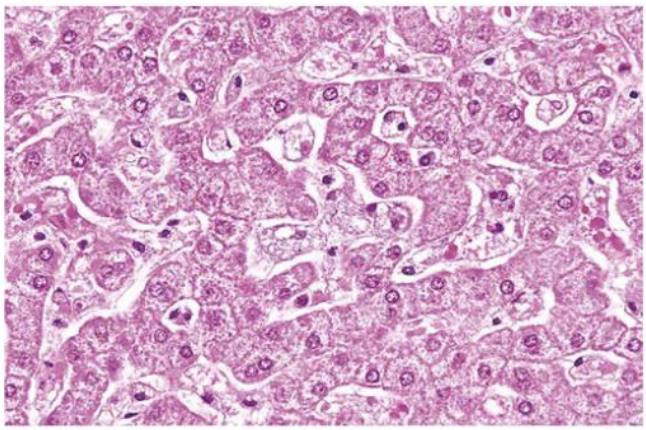
Inflammatory cells can facilitate tumor cell growth and survival by producing soluble factors that influence the hallmarks of cancer.

Infiltrating cancers provoke a chronic inflammatory reaction. In patients with advanced cancers, this inflammatory reaction can be so extensive as to cause systemic signs and symptoms, such as anemia (the anemia of chronic inflammation), fatigue, and cachexia. Animal models suggest that inflammatory cells also modify the tumor microenvironment to enable many of the hallmarks of cancer. These effects may stem from direct interactions between inflammatory cells and tumor cells, or indirect effects of inflammatory cells on other resident stromal cells, particularly cancer-associated fibroblasts and endothelial cells. Inflammatory cells and resident stromal cells may promote cancer development by producing growth factors that act on the neoplastic cells, promoting angiogenesis, activating cell survival pathways in tumors, producing enzymes that enhance local tumor invasion and metastasis, and suppressing effective antitumor immune responses. In this respect, they resemble tumor suppressor genes.

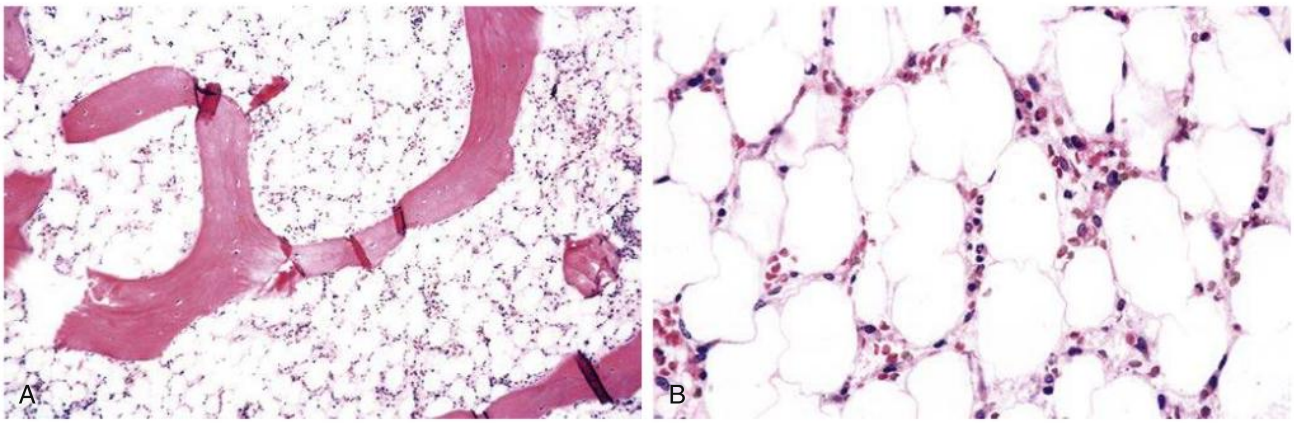
These pathophysiologic concepts have provided a road map for the development of new therapeutic agents for the treatment of cancer (Fig. 5.24). As our understanding of cancer pathogenesis expands, there is reason to hope that the next few years will see the development of many more effective targeted therapies.

CLINICAL ASPECTS OF NEOPLASIA

Ultimately, the importance of cancer is its impact on patients. The following discussion considers the effects of tumors on their hosts, the grading and clinical staging of cancer, and the laboratory diagnosis of neoplasms.



Supplemental eFig. 6.1 Niemann-Pick disease in liver. The hepatocytes and Kupffer cells have a foamy, vacuolated appearance resulting from deposition of lipids. (From Kumar V, Abbas A, Aster J: *Robbins Basic Pathology*, 10th ed., St. Louis, Elsevier, 2018, Fig. 7.10; Courtesy Dr. Arthur Weinberg, Department of Pathology, University of Texas Southwestern Medical Center, Dallas.)



Supplemental eFig. 9.2 Aplastic anemia (bone marrow biopsy). Markedly hypocellular marrow contains mainly fat cells. (A) Low power. (B) High power. (Courtesy Dr. Steven Kroft, Department of Pathology, University of Texas Southwestern Medical School, Dallas.)

Reed-Sternberg cells and variants resemble those seen in the mixed cellularity subtype.

- Set apart from classical Hodgkin lymphoma is the *lymphocyte-predominant subtype,* which accounts for about 5% of cases. It is defined by the presence of lymphohistiocytic (L&H) variant Reed-Sternberg cells with a delicate multilobed, puffy nucleus resembling popped corn (popcorn cell). L&H variants are found within large nodules containing mainly small B cells admixed with variable numbers of macrophages. Unlike the Reed-Sternberg variants in classic Hodgkin lymphoma, L&H variants express B-cell markers (e.g., CD20) and do not express CD15 and CD30.

Regardless of subtype, the diagnosis is based on the identification of Reed-Sternberg cells or variants in the appropriate background of reactive cells. Cells resembling Reed-Sternberg cells may be seen in other cancers and some reactive conditions; thus, immunophenotyping is often required for diagnosis.

Clinical Features. Hodgkin lymphoma usually manifests as painless lymphadenopathy or, with the nodular sclerosis subtype, symptoms related to the presence of a mediastinal mass. The systemic effects of cytokines cause anemia of chronic inflammation, leukocytosis, and so-called B symptoms (fever, weight loss, night sweats). Staging guides therapy and determines the prognosis. Younger patients with more favorable subtypes tend to present with low-stage disease and are free of so-called B symptoms, whereas patients with more extensive disease are more likely to have B symptoms and anemia. Initial treatment is with chemotherapy, sometimes with involved field radiotherapy for large tumor masses.

The overall outlook is excellent. The 5-year survival rate for patients with low-stage disease is over 90%. Even with widespread disease, the overall 5-year disease-free survival rate is around 50%. Immune checkpoint inhibitors have produced excellent responses in patients with relapsed, refractory disease and may soon be added to frontline therapeutic regimens.

Plasma Cell Neoplasms and Related Entities

These B-cell proliferations are composed entirely or in part of plasma cells and virtually always secrete a monoclonal immunoglobulin or immunoglobulin fragments.

Collectively, plasma cell neoplasms and related disorders account for about 15% of the deaths caused by lymphoid neoplasms. The most important of these neoplasms, multiple myeloma, is discussed next.

Multiple Myeloma

Multiple myeloma is one of the most common hematologic malignancies: Approximately 20,000 new cases are diagnosed in the United States each year. The median age at diagnosis is 70 years. It is more common in males and in people of African origin. It principally involves the marrow and usually is associated with lytic lesions throughout the skeletal system.

The most frequent immunoglobulin produced by myeloma cells is IgG (60%), followed by IgA (20% to 25%); in the remaining 15% to 20% of cases, the plasma cells produce only κ or λ immunoglobulin light chains. Only rarely are IgM, IgD, or IgE produced. Even in myelomas that produce complete immunoglobulins, immunoglobulin light chains are often synthesized in excess of immunoglobulin heavy chains, resulting in free, unpaired light chains. Once secreted, the small free light chains are excreted in the urine as *Bence-Jones proteins.* As described in the following, free light chains have important pathologic effects.

Morphology. Myeloma often has chromosomal translocations that fuse the *IGH* locus on chromosome 14 to proto-oncogenes such as the cyclin D1 gene. A wide variety of other driver mutations have been described. Proliferation of myeloma cells is supported by the cytokine interleukin 6 (IL-6).

The proliferating plasma cells have deleterious effects on the skeleton, the immune system, and the kidney, all of which contribute to morbidity and mortality:

- Several factors produced by myeloma cells cause bone resorption and lead to hypercalcemia and pathologic fractures, most frequently in the spine and femur.
- Myeloma causes defects in humoral immunity, increasing the risk for bacterial infections.
- Myeloma leads to renal failure owing to (1) obstructive proteinaceous casts comprised of precipitated Bence-Jones proteins; (2) light-chain deposition in the glomeruli or the interstitium, either as amyloid or linear deposits; (3) hypercalcemia, which leads to dehydration and renal stones; and (4) frequent bouts of bacterial pyelonephritis due to defective humoral immunity.

Morphology. Multiple myeloma usually manifests with multifocal destructive skeletal lesions that most commonly involve the vertebral column, ribs, skull, pelvis, femur, clavicle, and scapula. Radiologically, the bone lesions appear as punched-out defects 1 to 4 cm in diameter (Fig. 9.22A). The marrow contains increased numbers of plasma cells, typically more than 30% of the cellularity (see Fig. 9.22B). Renal involvement *(myeloma nephrosis)* is associated with proteinaceous casts that obstruct the distal convoluted tubules and the collecting ducts. Often, epithelial cells adjacent to the casts become necrotic or atrophic because Bence-Jones proteins are toxic. Other common pathologic processes involving the kidney include metastatic calcification, light-chain (AL) amyloidosis, and bacterial pyelonephritis.

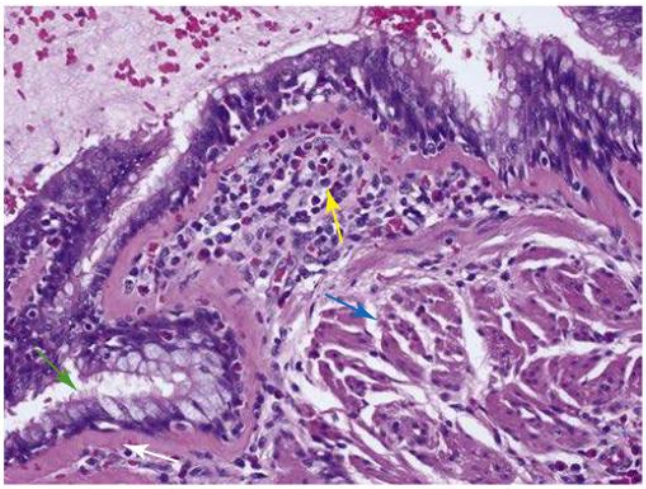
Clinical Features. The diagnosis relies on the detection of a serum monoclonal immunoglobulin (a so-called M protein, for myeloma) and/or high levels of free immunoglobulin light chains in the serum or the urine; the identification of a large number of plasma cells in the marrow; and the characteristic radiologic findings. Hypercalcemia and renal failure also are common at the time of presentation. The prognosis is variable. Patients with multiple bony lesions, if untreated, rarely survive for more than 6 to 12 months, whereas patients with "smoldering myeloma" may be asymptomatic for many years.

Although cures have yet to be achieved, several recently developed therapies have improved outcomes. Misfolded immunoglobulin chains accumulate in myeloma cells and cause cell stress by activating the unfolded protein response (see Chapter 1). Inhibitors of the proteasome, a cellular organelle that disposes of misfolded proteins, induce apoptosis of myeloma cells and are effective therapies. The thalidomide-like compound lenalidomide also has activity against myeloma because of its ability to activate certain ubiquitin ligases, which tag proteins with ubiquitin, thereby marking them for proteasomal degradation. Bisphosphonates, drugs that inhibit bone resorption, reduce pathologic fractures and limit hypercalcemia. Hematopoietic stem cell transplantation prolongs life but has not yet proven to be curative. Trials of CAR-T cells that recognize plasma cell antigens are ongoing.

Other Plasma Cell Neoplasms and Related Entities

All these tumors are associated with the production of monoclonal immunoglobulins, marking them as clonal proliferations of antibody-producing B lymphocytes or plasma cells. Three tumors in this group merit discussion.

- *Monoclonal gammopathy of undetermined significance (MGUS)* is seen in patients without signs or symptoms who have monoclonal immunoglobulins in their blood. MGUS is very common in older adults, and about 1% of cases transform into a symptomatic neoplasm, most often multiple myeloma, each year.



Supplemental eFig. 10.3 Bronchus from an asthmatic patient showing goblet cell hyperplasia *(green arrow),* subbasement membrane fibrosis *(white arrow),* eosinophilic inflammation *(yellow arrow),* and muscle hypertrophy *(blue arrow).*

pathogens (Table 10.5). Thus, the clinical setting can be a helpful guide when antimicrobial therapy has to be given empirically.

With this brief introduction, we turn next to some of the more common forms of pneumonia, starting with bacterial pneumonia.

Community-Acquired Bacterial Pneumonias

***Streptococcus pneumoniae* (pneumococcal) pneumonia is the most common cause of community-acquired bacterial pneumonia.**

Pneumococcal pneumonia occurs with increased frequency in the setting of chronic diseases (e.g., heart failure, COPD, or diabetes) and congenital or acquired defects in immunoglobulin production. Splenic macrophages have an important role in the removal of pneumococci from the blood; individuals with decreased or absent splenic function are at high risk of developing sepsis. These patients benefit from pneumococcal vaccines. The presence of numerous neutrophils in sputum containing gram-positive, lancet-shaped diplococci supports the diagnosis, but false-positive results are common. Isolation of pneumococci from blood cultures is more specific but less sensitive.

Other important causes of community-acquired bacterial pneumonia include the following:

- *Haemophilus influenzae.* Both encapsulated and unencapsulated forms of *H. influenzae* may be responsible. Adults at risk for developing infections include those with chronic pulmonary diseases such as COPD, cystic fibrosis, and bronchiectasis. Encapsulated *H. influenzae* type B was formerly an important cause of epiglottitis and suppurative meningitis in children, but vaccination in infancy has significantly reduced the risk.
- *Moraxella catarrhalis* mainly infects older adults and is a common cause of acute exacerbation of COPD.
- *Staphylococcus aureus* frequently causes secondary bacterial pneumonia after viral respiratory illnesses and is associated with a high incidence of complications, such as lung abscess and empyema. Staphylococcal pneumonia occurring in association with right-sided staphylococcal endocarditis is a serious complication of intravenous drug use.
- *Klebsiella pneumoniae* is the most frequent cause of gram-negative bacterial pneumonia and primarily afflicts debilitated and malnourished individuals, particularly chronic alcoholics. Thick and gelatinous sputum is characteristic because the organism produces an abundant viscid capsular polysaccharide, which is not easily cleared by coughing.
- *Legionella pneumophila* is the agent of Legionnaire disease. *L. pneumophila* flourishes in artificial aquatic environments, such as water-cooling towers and within the tubing system of potable water supplies. Transmission occurs through inhalation of aerosolized organisms or aspiration of contaminated drinking water. *Legionella* pneumonia occurs more frequently in individuals with cardiac, renal, immunologic, or hematologic diseases. It frequently requires hospitalization and has a fatality rate of 30% to 50% in immunosuppressed individuals.
- *Mycoplasma pneumoniae* infections are particularly common among children and young adults. They occur sporadically or as local epidemics in closed communities (schools, military camps, prisons).

Morphology.* Bacterial pneumonia has two anatomic distributions: *bronchopneumonia* and *lobar pneumonia.

Patchy lung involvement is the dominant characteristic of bronchopneumonia (Supplemental eFig. 10.10), whereas involvement of a large portion of a lobe or of an entire lobe defines lobar pneumonia (Supplemental eFig. 10.11). These patterns often overlap, however, and patchy disease may become confluent over time, producing complete lobar consolidation. Most important from the clinical standpoint are identification of the causative agent and determination of the extent of disease.

In lobar pneumonia, the inflammatory response can be divided into four successive stages: (1) congestion; (2) red hepatization, characterized by exuberant alveolar exudates containing neutrophils, red cells, and fibrin (Fig. 10.10A) that create a red, firm, airless, liver-like consistency; (3) gray hepatization, marked by progressive disintegration of red cells and the persistence of a fibrin- and neutrophil-rich exudate (Fig. 10.10B); and (4) resolution, marked by resorption of exudate and clearance of inflammatory cells, sometimes with fibrosis (referred to as organization) (Fig. 10.10C). A pleural fibrinous reaction (pleuritis) is often present in the early stages that may resolve

Table 10.5 The Pneumonia Syndromes and Implicated Pathogens

Community-Acquired Bacterial Pneumonias
Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus
Legionella pneumophila
Enterobacteriaceae *(Klebsiella pneumoniae)* and *Pseudomonas* spp.
Mycoplasma pneumoniae
Chlamydia pneumoniae
Coxiella burnetii (Q fever)
Community-Acquired Viral Pneumonias
Respiratory syncytial virus, human metapneumovirus, parainfluenza virus (children); influenza A and B (adults); adenovirus (military recruits)
Nosocomial Pneumonias
Gram-negative rods belonging to Enterobacteriaceae (*Klebsiella* spp., *Serratia marcescens, Escherichia coli)* and *Pseudomonas* spp.
S. aureus (usually methicillin-resistant)
Aspiration Pneumonias
Anaerobic oral flora *(Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus),* admixed with aerobic bacteria *(S. pneumoniae, S. aureus, H. influenzae,* and *Pseudomonas aeruginosa)*
Chronic Pneumonias
Nocardia
Actinomyces
Granulomatous: *Mycobacterium tuberculosis* and atypical mycobacteria, *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis*
Necrotizing Pneumonias and Lung Abscess
Anaerobic bacteria (extremely common), with or without mixed aerobic infection
S. aureus, K. pneumoniae, Streptococcus pyogenes, and type 3 pneumococcus (uncommon)
Pneumonias in the Immunocompromised Host
Cytomegalovirus
Pneumocystis jiroveci
Mycobacterium avium complex
Invasive aspergillosis
Invasive candidiasis
"Usual" bacterial, viral, and fungal organisms

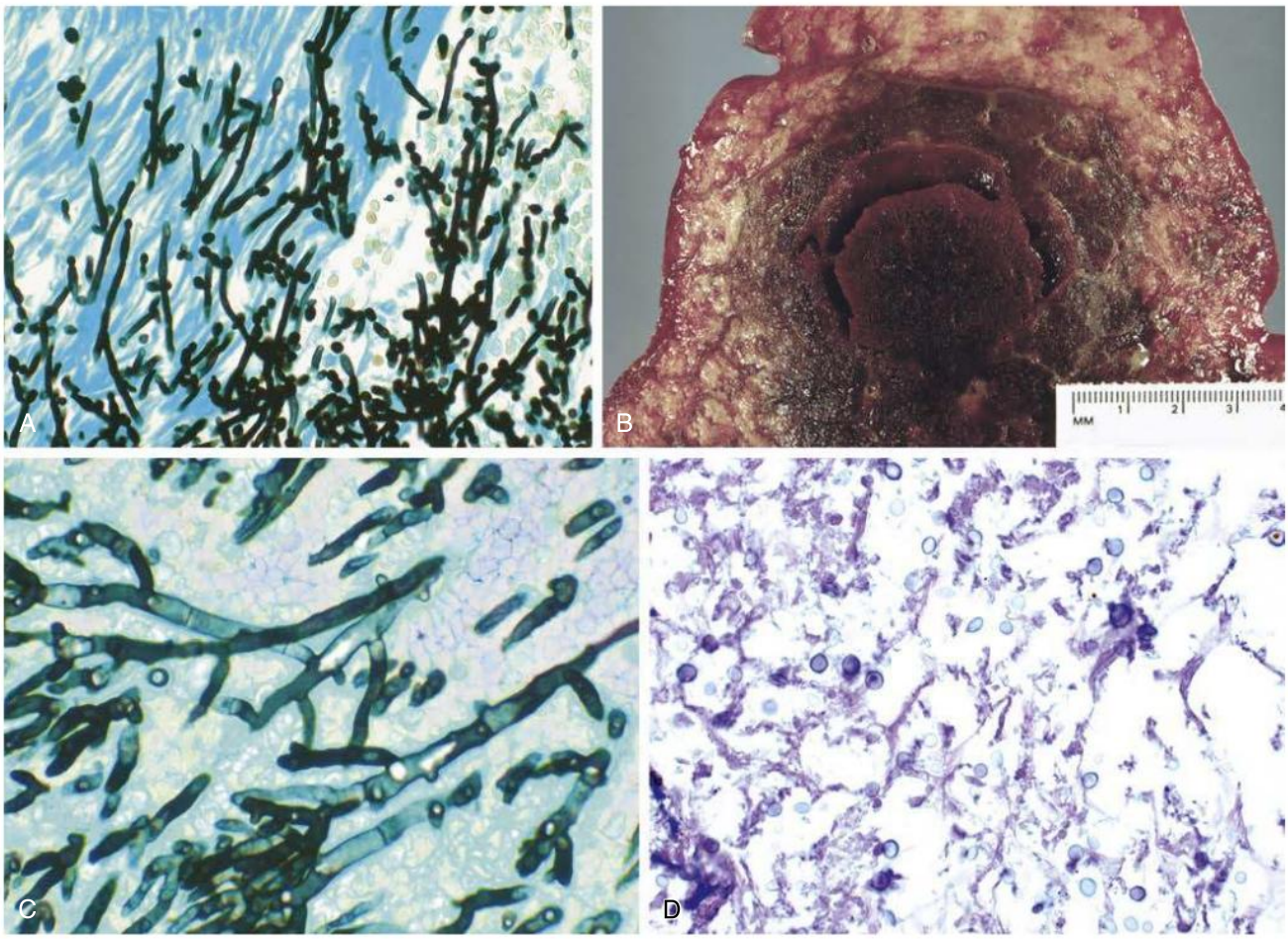


Fig. 10.17 The morphology of fungal infections. (A) *Candida* organism has pseudohyphae and budding yeasts (silver stain). (B) Invasive aspergillosis (gross appearance) of the lung in a hematopoietic stem cell transplant recipient. (C) Gomori methenamine–silver (GMS) stain shows septate hyphae with acute-angle branching, consistent with *Aspergillus*. (D) Cryptococcosis of the lung in a patient with AIDS. The organisms are somewhat variable in size. (B, Courtesy of Dr. Dominick Cavuoti, Department of Pathology, University of Texas Southwestern Medical School, Dallas.)

carcinogens include exposure to radiation (in uranium miners), exposure to asbestos, and inhalation of dusts containing arsenic, chromium, nickel, or vinyl chloride. The risk associated with exposure to asbestos and tobacco smoking is multiplicative: Nonsmokers exposed to asbestos have a 5-fold risk of developing lung cancer, whereas in heavy smokers exposed to asbestos, the risk is elevated approximately 55-fold.

Not all individuals exposed to tobacco smoke develop cancer (~11% of heavy smokers do), and it is likely that the mutagenic effect of carcinogens is modified by hereditary (genetic) factors. Individuals with certain polymorphisms involving the P-450 genes have an increased capacity to activate procarcinogens found in cigarette smoke, and are thus exposed to larger doses of carcinogens and incur a greater risk of developing lung cancer. Similarly, individuals whose peripheral blood lymphocytes undergo chromosomal breakage after exposure to carcinogens in tobacco smoke (mutagen-sensitive genotype) have a greater than 10-fold increased risk for developing lung cancer over control subjects.

Some of the mutations that drive lung cancer growth activate tyrosine kinases, which are excellent drug targets. Tyrosine kinase mutations are most common in adenocarcinomas, particularly those arising in nonsmoking women, and affect several different kinases, such as the epidermal growth factor receptor (EGFR), ALK, ROS1, HER2, and c-MET. Each of these kinases is optimally targeted by a different drug, which has spurred a new era of "personalized" lung cancer treatment, in which the genetics of the tumor guide therapy.

Morphology. Adenocarcinomas are usually peripherally located and may display a variety of growth patterns, including acinar (gland-forming) (Fig. 10.18A and B), papillary, mucinous, and solid types. These tumors often have spread by the time of diagnosis, possibly because they produce few symptoms early in their course due to peripheral location.

Squamous cell carcinomas tend to arise centrally in major bronchi and eventually spread to hilar nodes. Large lesions may undergo central necrosis, giving rise to cavitation. These tumors often become symptomatic when the tumor obstructs a bronchus, leading to distal collapse of alveoli (atelectasis) and superimposed infection (Fig. 10.19A). On histologic examination, these tumors show a wide range of differentiation (Fig. 10.19B).

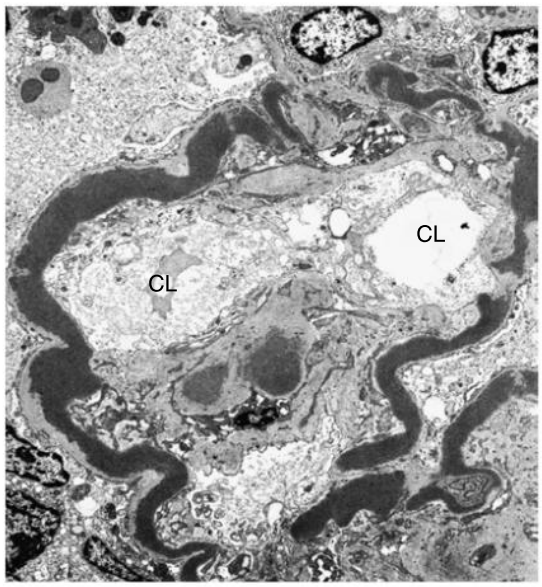


Fig. 11.6 Dense deposit disease. Dense homogeneous deposits in the GBM. CL, capillary lumen.

Clinical Features. Patients present with the acute nephritic syndrome, marked by hematuria, variable, typically mild proteinuria, azotemia, edema, and hypertension. Serum complement levels decrease during the acute phase. Most children with the disease recover, although rarely the disease may evolve into rapidly progressive GN (RPGN, described later). The prognosis in adults is significantly worse; about a third develop end-stage renal disease over 10 to 20 years.

Lupus Nephritis

Renal involvement is common in lupus and usually dominated by immune complex–mediated glomerulonephritis.

Systemic lupus erythematosus (SLE) is an autoimmune disease in which antinuclear autoantibodies are produced that form immune complexes with self nuclear antigens (see Chapter 4). Disease manifestations are mainly due to deposition of these complexes in vessels in different tissues. The kidney is a major site of immune complex deposition, and renal failure is one of the most serious complications of the disease. Autoantibodies against nonnuclear antigens also contribute to the disease, including those that bind to and deplete red cells or platelets (see Chapter 9) and others that affect coagulation, called antiphospholipid antibodies (see Chapter 3). Here we discuss the renal involvement; other aspects of SLE are discussed in Chapter 4.

Pathogenesis. The glomerular lesions are caused by the deposition of immune complexes, activation of complement, and subsequent recruitment and activation of leukocytes via complement products and by the deposited antibodies binding to leukocyte Fc receptors. This is the typical sequence of events in all immune complex diseases (see Chapter 4). Less commonly, there is evidence of tubulointerstitial nephritis and vasculitis, also caused mainly by immune complexes.

Morphology. The glomerular disease caused by the deposition of immune complexes is divided into six classes that have distinct pathologies (Fig. 11.8), clinical features, and prognostic implications. The glomerular lesions are classified on the basis of the site of deposition of the immune complexes (mesangial, subendothelial, subepithelial), the resulting proliferative reaction of the glomeruli (mesangial, focal or diffuse), and the extent of sclerosis of the glomerular tufts.

Of the six classes, *diffuse lupus nephritis* (called class IV) is the most common and severe form. The typical morphologic picture is proliferative GN affecting most glomeruli. The involved glomeruli show proliferation of endothelial, mesangial, and epithelial cells, sometimes with crescent formation (described later). Extensive subendothelial immune complex deposition may lead to GBM thickening, creating the appearance of "wire loops."

Other common renal lesions in SLE are tubulointerstitial inflammation, with or without immune complex deposition along the tubular basement membrane, and vasculitis with immune complex deposition and, sometimes, thrombosis. The prognosis worsens with increased severity of both of these lesions.

Clinical Features. Clinical manifestations range from mild hematuria and proteinuria to massive proteinuria with nephrotic syndrome (as in idiopathic membranous nephropathy) and progressive renal failure.

Rapidly Progressive Glomerulonephritis

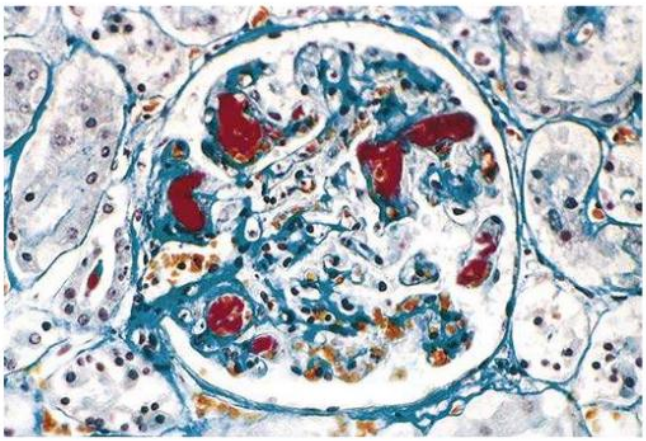
This group of diseases shares clinical and morphologic features (especially the formation of crescents in glomeruli) but may have diverse etiologies.

Because crescents are the *sine qua non* of RPGN, it is also called *crescentic GN.*

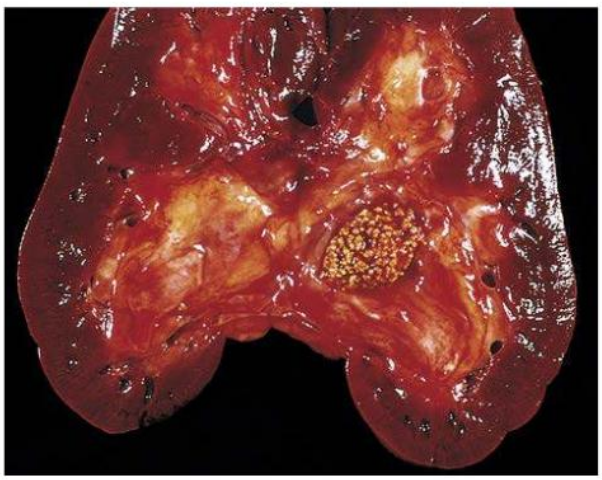
Pathogenesis. RPGN may be caused by different immune mechanisms.

- Anti-GBM autoantibodies, often reactive with antigens in the noncollagenous component of the GBM, are deposited along the GBM, activate complement, and induce destructive inflammation. In some patients, the antibodies also bind to basement membranes of pulmonary alveolar capillaries, causing lung hemorrhages; the combination of renal and pulmonary involvement is called *Goodpasture syndrome.*
- RPGN may be a manifestation of a known immune complex disease, such as acute postinfectious GN or lupus. In some cases of RPGN, immune complexes are detected in the absence of another underlying disease.
- Pauci-immune crescentic GN is defined by the presence of the characteristic glomerular lesion in the absence of detectable antibodies or immune complexes. Anti–neutrophil cytoplasmic antibodies (PR3-ANCAs) are typically present in the serum, with or without associated systemic vasculitis (see Chapter 7). Thus, pauci-immune crescentic GN may be a manifestation of a systemic vasculitis or idiopathic (limited to the kidney).

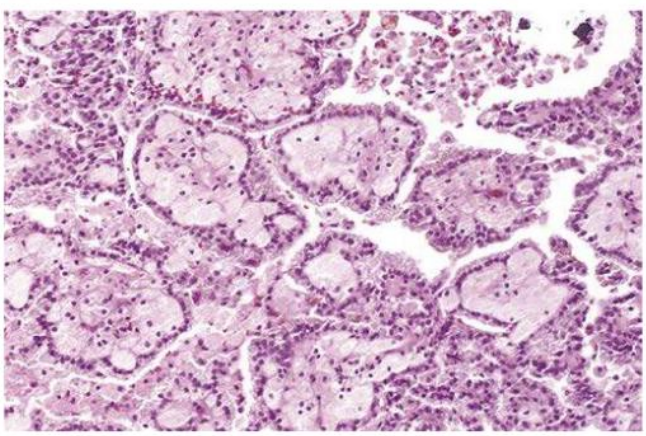
Morphology. The morphologic changes in RPGN are reflections of severe glomerular injury. This is manifested in some cases with segmental capillary necrosis, breaks in the GBM (visible by electron microscopy), and the deposition of fibrin in the Bowman space. The glomeruli show proliferation outside the capillary loops, giving rise to distinctive proliferative lesions called *crescents* that obliterate the Bowman space (Fig. 11.9). Crescents consist of proliferating epithelial cells lining the Bowman capsule and infiltrating monocytes and other leukocytes. In addition to extracapillary proliferation, cellular proliferation may also be seen in the capillary loops and mesangium, similar to what is seen in other forms of immune complex–mediated injury. Immunofluorescence microscopy reveals linear or granular staining for IgG and C3 along the GBM (except in the pauci-immune type). Electron microscopy may show ruptures in the GBM, with or without immune deposits.



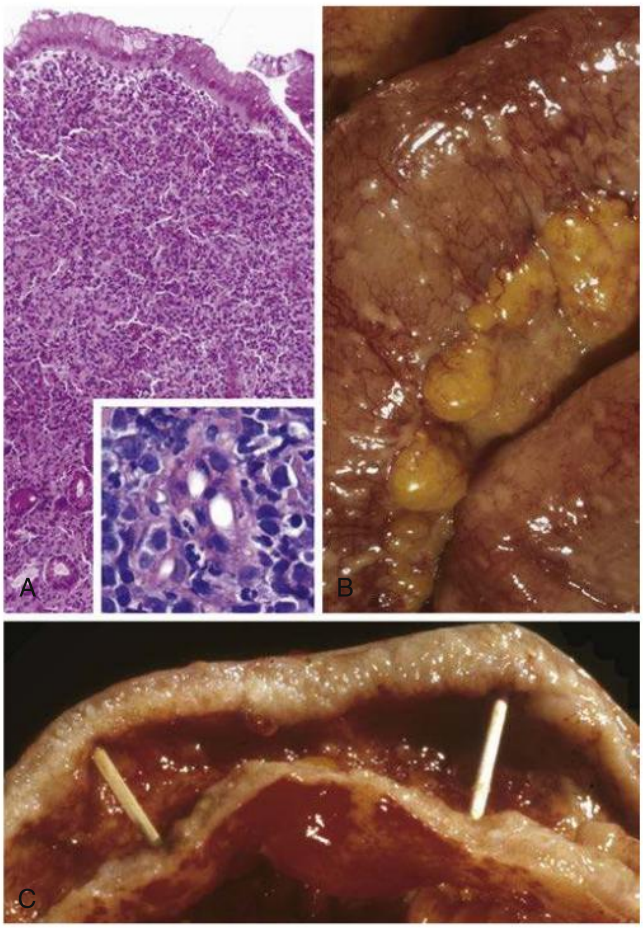
Supplemental eFig. 11.5 Fibrin stain showing platelet-fibrin thrombi *(red)* in the glomerular capillaries, characteristic of thrombotic microangiopathic disorders.



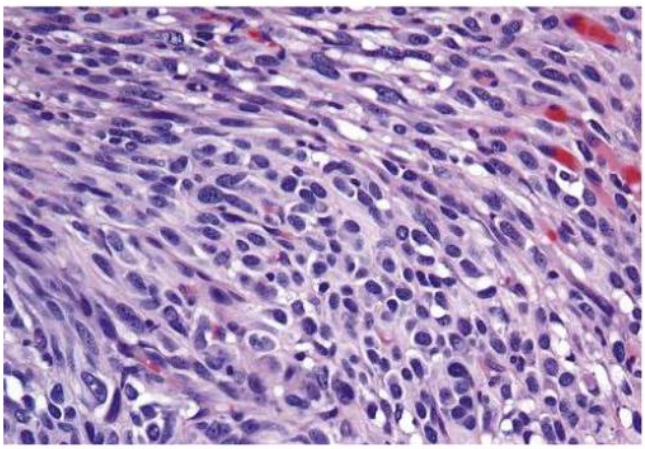
Supplemental eFig. 11.6 Nephrolithiasis. A large stone impacted in the renal pelvis. (Courtesy Dr. E. Mosher, Brigham and Women's Hospital, Boston, Mass.)



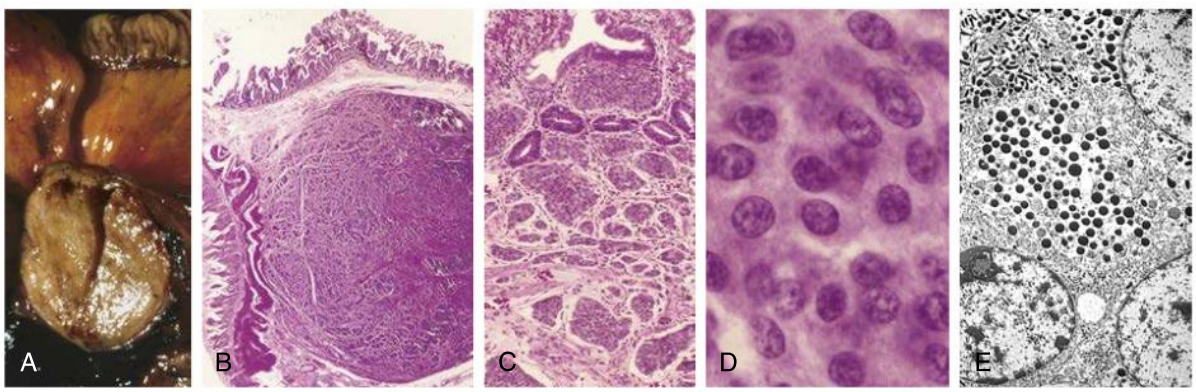
Supplemental eFig. 11.7 Renal cell carcinoma, papillary type. Note the papillae and foamy macrophages in the stalk. (Courtesy Dr. A. Renshaw, Baptist Hospital, Miami.)



Supplemental eFig. 12.9 Lymphoma. (A) Gastric extranodal marginal zone lymphoma replacing much of the gastric epithelium. *Inset* shows lymphoepithelial lesions with neoplastic lymphocytes surrounding and infiltrating gastric glands. (B) Disseminated lymphoma within the small intestine with numerous small serosal nodules. (C) Large B-cell lymphoma infiltrating the small intestinal wall and producing diffuse thickening.



Supplemental eFig. 12.11 GI stromal tumor. Histologically, the tumor is primarily composed of bundles, or fascicles, of spindle-shaped tumor cells. (Courtesy Dr. Christopher Weber, University of Chicago, Chicago.)



Supplemental eFig. 12.10 GI carcinoid tumor (neuroendocrine carcinoma). (A) Gross cross section of a submucosal tumor nodule. (B) Microscopically, the nodule is composed of tumor cells embedded in dense fibrous tissue. (C) In other areas, the tumor has spread extensively within mucosal lymphatic channels. (D) High magnification shows the bland cytology of carcinoid tumors. The chromatin texture, with fine and coarse clumps, is frequently described as a "salt-and-pepper" pattern. Despite their innocuous appearance, carcinoids can be clinically aggressive. (E) Electron microscopy reveals cytoplasmic dense-core eurosecretory granules.

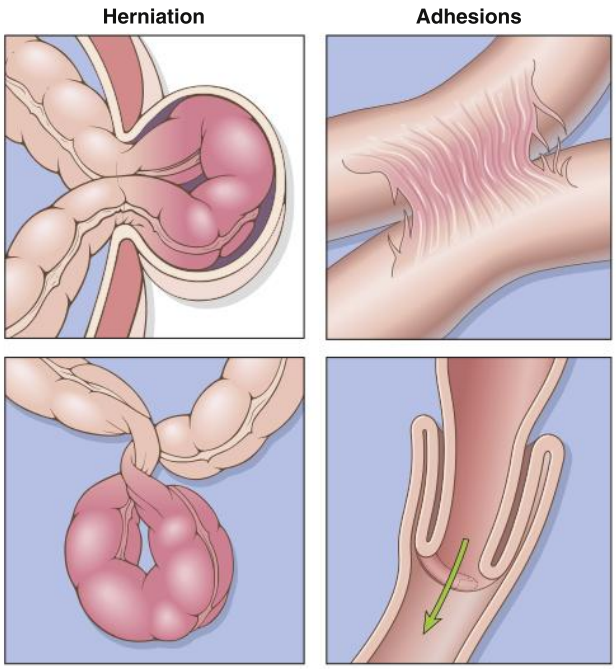


Fig. 12.15 Intestinal obstruction. The four major mechanical causes of intestinal obstruction are (1) herniation of a segment in the umbilical or inguinal regions, (2) adhesion between loops of intestine, (3) volvulus, and (4) intussusception.

Vascular Diseases

The most serious vascular disorder is *ischemic bowel disease.* Acute arterial obstruction, which may be caused by atherosclerosis, an aortic aneurysm, a thrombus, or an embolism, can lead to transmural infarction of segments of the bowel that are supplied by the obstructed vessels (Supplemental eFig. 12.16). Hypoperfusion secondary to cardiac failure, dehydration, or gradual arterial compromise typically causes sub-total mucosal or mural infarction; lesions frequently involve watershed zones that include the splenic flexure, where the superior and inferior mesenteric arterial circulations terminate, and, to a lesser extent, the sigmoid colon and rectum, where inferior mesenteric, pudendal, and iliac arterial circulations end. Patients typically present with abdominal pain. If not treated, the ischemic bowel can perforate, which is a surgical emergency.

DISORDERS OF THE ORAL CAVITY AND SALIVARY GLANDS

The oral cavity and salivary glands are frequent sites of inflammatory diseases and some tumors. The diseases are conceptually simple and are described only briefly.

Inflammatory Disorders of the Oral Cavity

A variety of infectious and noninfectious inflammatory disorders frequently involve the oral cavity. Among the most common are the following:

- *Aphthous ulcers* are painful superficial mucosal ulcerations (Supplemental eFig. 12.17) that affect as much as 40% of the population at some time, and tend to resolve spontaneously but recur. Their cause is not known.
- *Herpes simplex virus infection* presents with vesicles and ulcerations, commonly called *cold sores.* Most orofacial herpetic infections are caused by herpes simplex virus type 1 (HSV-1), with the remainder being caused by HSV-2 (genital herpes). Primary infection occurs usually in childhood, and the virus establishes a latent infection that may persist for life. The infection may be reactivated by virtually any stress, including trauma, exposure to ultraviolet light and temperature extremes, pregnancy, other infections, and immune suppression. The lesions are similar to those in genital herpes (see Chapter 14).
- *Candida infection* occurs when this normal fungal inhabitant of the oral cavity grows excessively, which may occur in immunosuppressed individuals or when the normal microbiota are altered by antibiotic treatment. Some strains of *C. albicans* are more pathogenic than others. The most common type of infection is called *thrush.* Characteristically, a pseudomembrane consisting of fungal hyphae and inflammatory cells trapped within a protein-rich exudate covers the site of infection.
- *Pyogenic granuloma* is a vascular lesion of unknown etiology found on the gums of children, young adults, and pregnant women (Supplemental eFig. 12.18). The lesions consist of proliferating small blood vessels, similar to those in granulation tissue, which may create an alarming red appearance. The lesions may regress or become fibrotic.

Tumors and Tumor-like Lesions of the Oral Cavity

The most important proliferations involving the oral cavity are squamous cell carcinoma and its precursors.

- *Leukoplakia* is defined clinically as a white plaque in the oral cavity with no underlying cause (such as an infection) (Supplemental eFig. 12.19). Microscopically, it is an area of squamous cell hyperplasia. Lesions with dysplastic features may progress to squamous cell carcinoma. Surgical excision is therefore the accepted treatment. A related but less common entity, *erythroplakia,* is a red, velvety, sometimes eroded lesion that is flat or slightly depressed relative to the surrounding mucosa (Supplemental eFig. 12.20). Erythroplakia is associated with a greater risk for malignant transformation than leukoplakia.
- *Squamous cell carcinoma* is the most common malignant tumor of the oropharynx. Two mechanisms are implicated in tumor development: exposure to carcinogens (most commonly in tobacco) and infection with high-risk types of human papillomavirus (HPV) (up to 70% of cases, particularly those of the tonsils, base of tongue, and pharynx). The tumors associated with chemical carcinogens frequently harbor mutations in tumor suppressor genes such as *TP53* and oncogenes such as *RAS.* The prognosis of HPV-associated tumors is better than those that are not associated with HPV. The mechanisms by which HPV causes cancer are discussed in Chapter 5.

This tumor may appear as raised plaques or mucosal thickenings, and may ulcerate as it grows (Fig. 12.16). Histologically, it varies from well-differentiated and keratinizing to poorly differentiated and anaplastic. The most frequent sites of metastases are cervical lymph nodes.

Diseases of the Salivary Glands

The salivary glands are prone to a number of inflammatory and neoplastic disorders.

- *Sialadenitis* (inflammation of the salivary glands) may be caused by bacterial or viral infections (e.g., mumps), autoimmune diseases (e.g., Sjögren syndrome), obstruction by ductal stones, or physical agents (e.g., radiotherapy). A common manifestation of salivary gland damage is *xerostomia,* or dry mouth, caused by a reduced production of saliva. The most common inflammatory lesion of the salivary glands is *mucocele,* a cyst usually in the lower lip that is caused by blockage or rupture of a salivary duct with leakage of saliva into the connective tissue. The cyst is filled with fluid and inflammatory cells and lined by granulation or fibrous tissue.

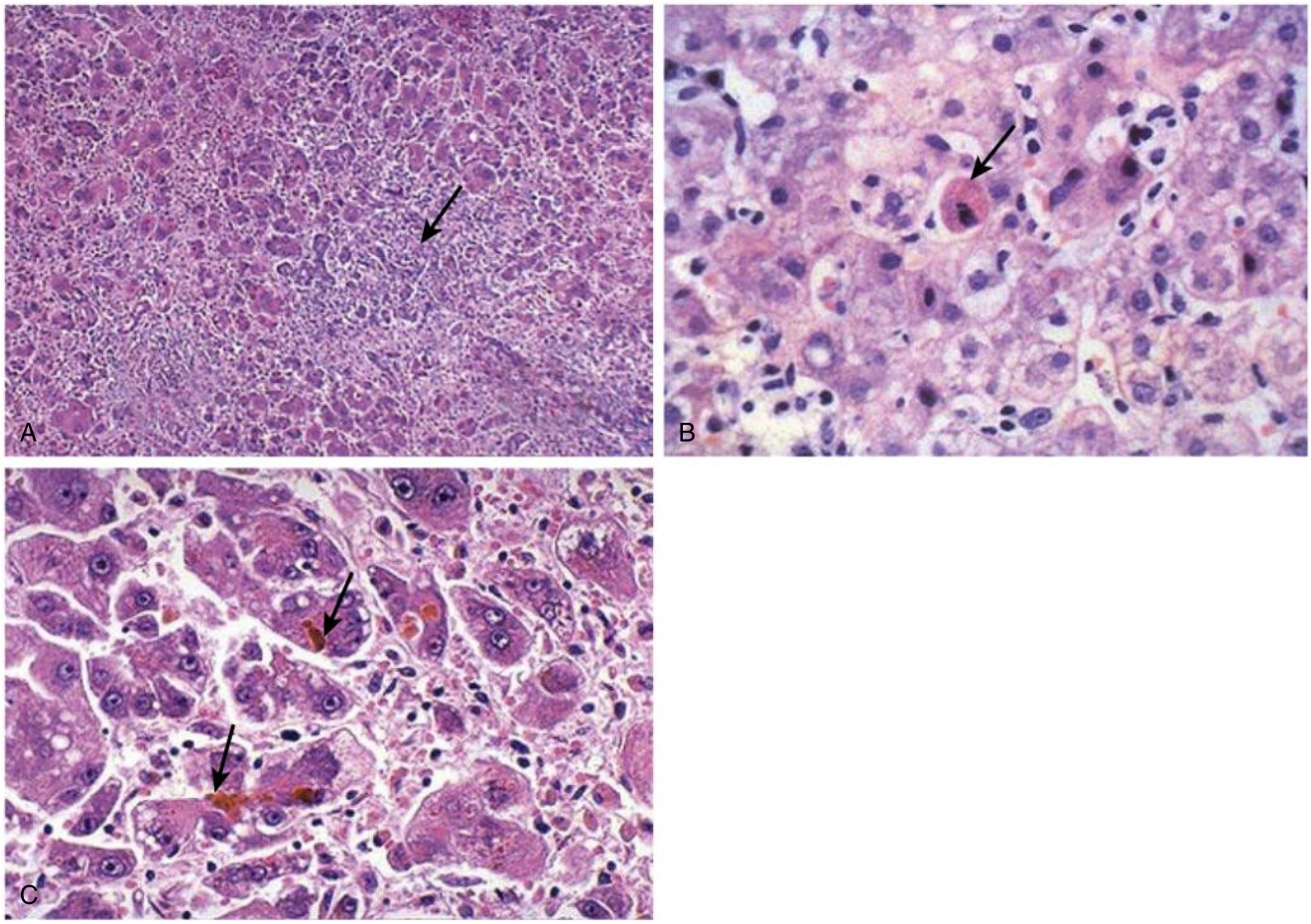


Fig. 13.5 HBV infection. (A) Inflammatory infiltrates in the liver *(arrow)*. (B) Damaged (apoptotic) hepatocytes *(arrow)*. (C) Intracanalicular bile stasis *(arrows)*. (Courtesy Drs. Ryan Gill and Sanjay Kakar, Department of Pathology, University of California San Francisco.)

there are regenerating hepatocytes with large nuclei and prominent nucleoli, often with mitoses. Apoptotic hepatocytes may stain deeply eosinophilic, forming so-called Councilman bodies.

- **Chronic viral hepatitis.** The defining histologic feature of chronic viral hepatitis is variable mononuclear cell infiltration around portal tracts (Fig. 13.6). Progression is marked by scarring, beginning with portal fibrosis and followed by extension of fibrous septa between portal tracts. Continued scarring and nodule formation lead to the development of cirrhosis (Supplemental eFig. 13.2). Certain histologic features suggest the viral etiology: In chronic hepatitis B, "ground-glass" hepatocytes (cells with endoplasmic reticulum swollen by HBsAg) are seen (Supplemental eFig 13.3), whereas chronic hepatitis C is characterized by large lymphoid aggregates and bile duct injury. Fatty change may also be seen.

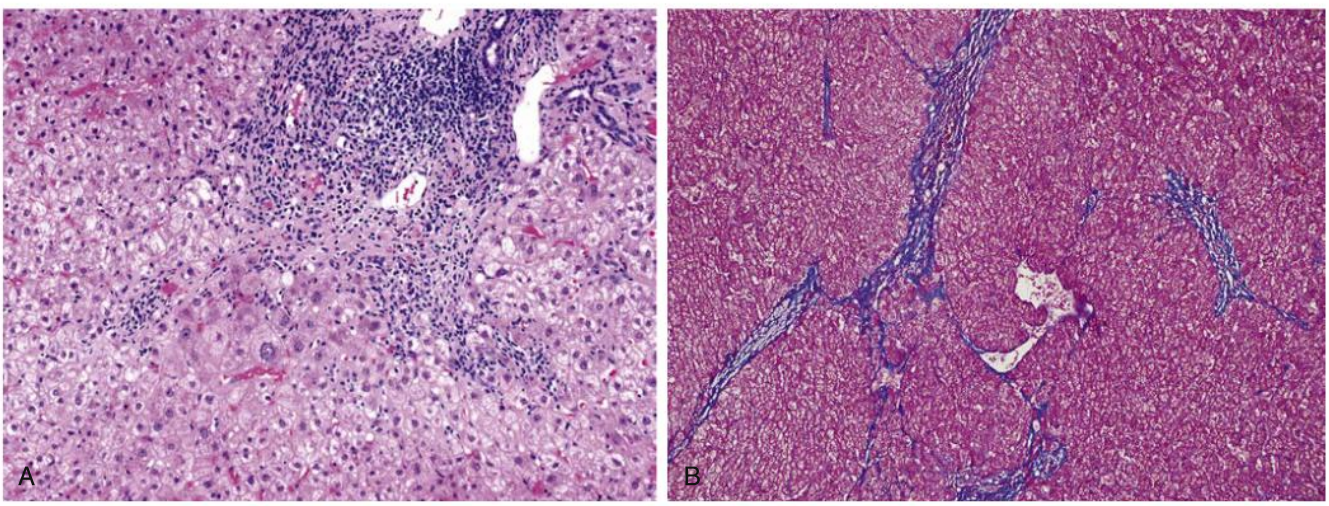
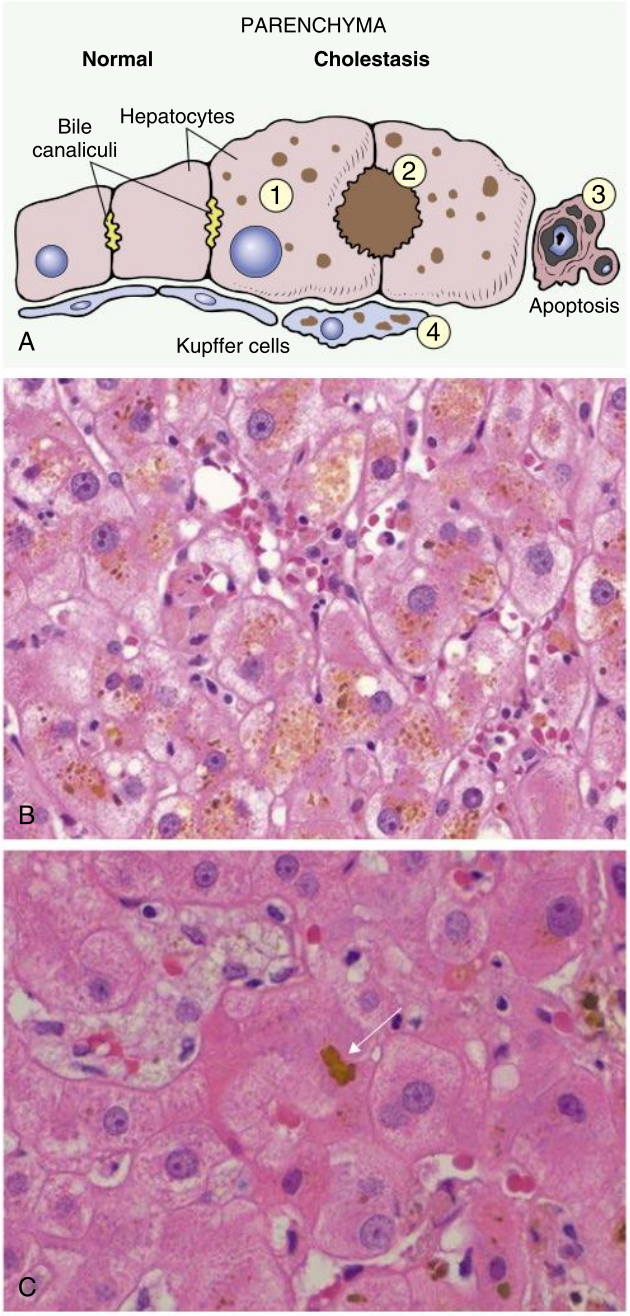
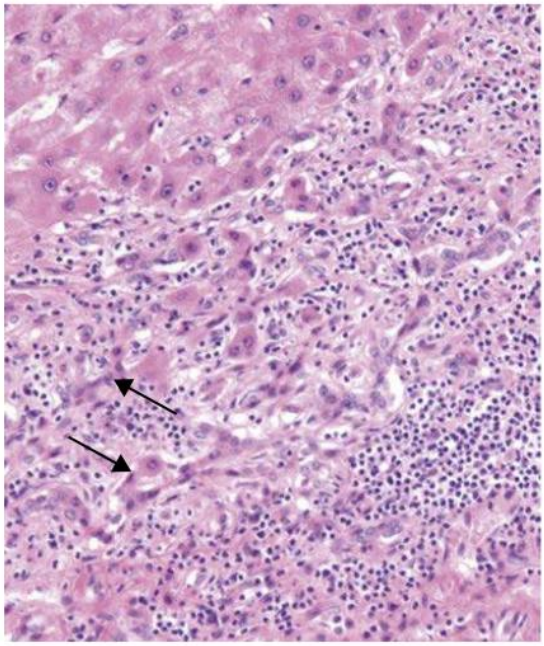


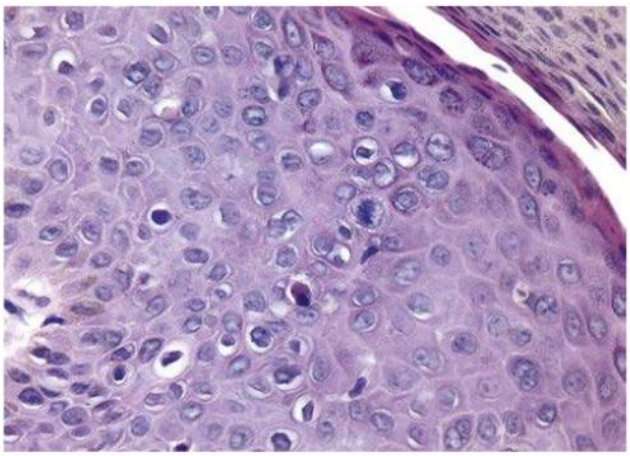
Fig. 13.6 Chronic HCV infection. Chronic hepatitis due to HCV, showing characteristic portal tract expansion by a dense lymphoid infiltrate (A) and bridging fibrosis (stained blue) connecting portal tracts (B).



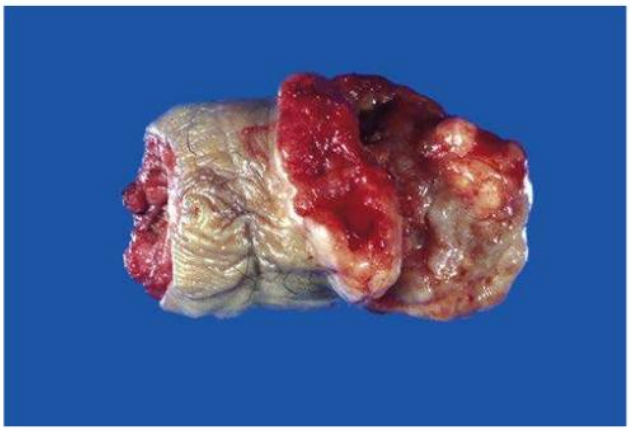
Supplemental eFig. 13.8 Cholestasis. (A) Morphologic features of cholestasis and comparison with normal liver. Cholestatic hepatocytes *(1)* are enlarged with dilated canalicular spaces *(2)*. Apoptotic cells *(3)* may be seen, and Kupffer cells *(4)* frequently contain regurgitated bile pigments. (B) Intracellular cholestasis showing the bile pigments in the cytoplasm. (C) Bile plug *(arrow)* showing the expansion of bile canaliculus by bile.



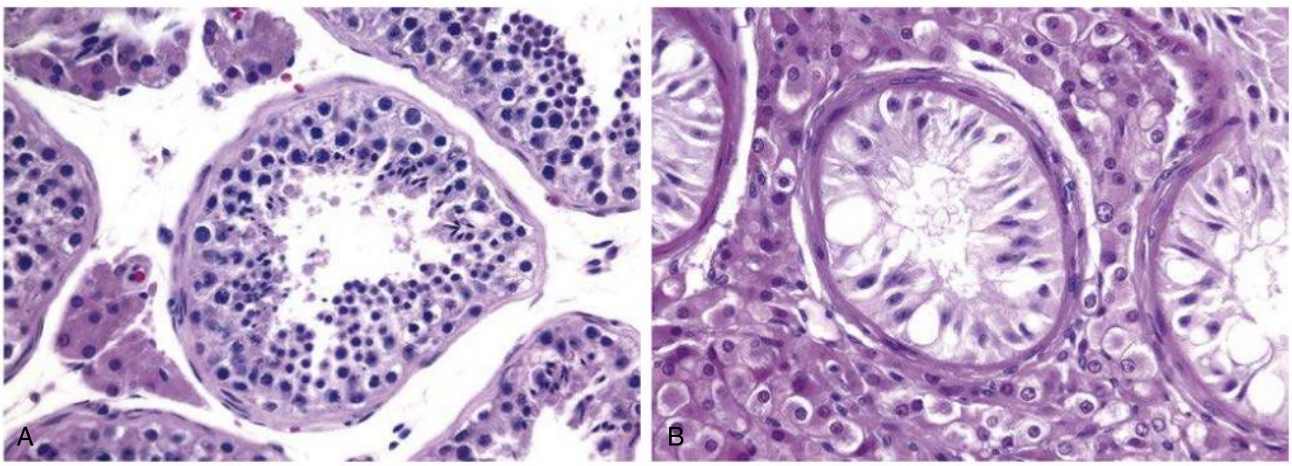
Supplemental eFig. 13.9 Primary biliary cholangitis. The ductular reaction *(arrows)* may help maintain bile flow past destroyed segments of the biliary tree in early stages of the disease, but later it may contribute to scarring.



Supplemental eFig. 14.1 Bowen disease (carcinoma in situ) of the penis. Note the hyperchromatic, dysplastic dyskeratotic epithelial cells with scattered mitoses above the basal layer. The intact basement membrane is not readily seen in this picture.



Supplemental eFig. 14.2 Carcinoma of the penis. The glans penis is deformed by a firm, ulcerated, infiltrative mass.



Supplemental eFig. 14.3 (A) Normal testis shows tubules with active spermatogenesis. (B) Testicular atrophy in cryptorchidism. The tubules show Sertoli cells but no spermatogenesis. There is thickening of basement membranes and an apparent increase in interstitial Leydig cells.