In addition, patients who receive splenic irradiation for a neoplastic or autoimmune disease are also functionally hyposplenic. The 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. The 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.

BIBLIOGRAPHY

BARKUN AN et al: Splenic enlargement and Traube's space: How useful in percussion? Am J Med 87:562, 1989

——— et al: The bedside assessment of splenic enlargement. Am J Med 91:512, 1991

CASTELL DO: The spleen percussion sign: A useful diagnostic technique. Ann Intern Med 67:1265, 1967

GRAVES SA et al: Does this patient have splenomegaly? JAMA 270:2218, 1993

KUBOTA T: The evaluation of peripheral adenopathy. Primary Care 7:461, 1980

MCINTYRE OR, EBAUGH FG JR: Palpable spleens: Ten year follow-up. Ann Intern Med 90:130, 1979

———, ———: Palpable spleens in college freshmen. Ann Intern Med 66:301, 1967

NIXON RK JR: The detection of splenomegaly by percussion. N Engl J Med 250:166, 1954

PANGALIS GA et al: Clinical approach to lymphadenopathy. Semin Oncol 20:570, 1993

SLAP GB et al: Validation of a model to identify young patients for lymph node biopsy. JAMA 255:2768, 1986

WEISS S: Self-observation and psychologic reactions of medical student A.S.R. to the onset and symptoms of subacute bacterial endocarditis. J Mt Sinai Hospital 8:1079, 1942

WILLIAMSON HA JR: Lymphadenopathy in a family practice: A descriptive study of 240 cases. J Fam Pract 20:449, 1985

ZUELZER W, KAPLAN J: The child with lymphadenopathy. Semin Hematol 12:323, 1975

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DISORDERS OF GRANULOCYTES AND MONOCYTES

Leukocytes are the major cellular components of inflammatory and immune responses and include neutrophils, T and B lymphocytes, natural killer (NK) cells, monocytes, eosinophils, and basophils. These cells have been assigned 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 each of the cell types completely established. Thus, whereas neutrophils are classically thought to be critical to host defense against bacteria, there is increasing evidence that neutrophils play important roles in viral infections.

The blood is the most readily obtainable source of leukocytes and serves as the vehicle for their delivery to the various tissues from the bone marrow, where they are produced. Normal blood leukocyte counts are given in the Appendix (Tables A-7 and A-8). The various leukocytes are thought to derive from a common stem cell in the bone marrow. Three-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 and interleukins (see Chap. 105). Because an alteration in the number and type of leukocytes is a frequent association with disease processes, a total white blood count (WBC) (cells per microliter) and differential counts are obtained frequently. The lymphocytes and basophils are discussed in Chaps. 305 and 310, respectively. This chapter focuses on the neutrophils, monocytes, and eosinophils.

NEUTROPHILS

MATURATION Important events in the neutrophil life are summarized in Fig. 62-1. In normal humans, neutrophils are produced only in the bone marrow. Best estimates indicate that the appropriate number of stem cells necessary to support hematopoiesis is between 400 and 500. There is convincing evidence that human blood monocytes and tissue macrophages produce colony stimulating factors, hormones required for the growth of monocytes and neutrophils in the bone marrow. The hematopoietic system not only produces enough neutrophils (approximately 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 *shift to the left*. A diminution in the number of blood neutrophils is referred to as *neutropenia*.

Neutrophils and monocytes evolve from pluripotent stem cells under the influence of cytokines and colony stimulating factors (Fig. 62-2). The myeloblast is the first recognizable precursor cell and is followed by the *promyelocyte* (**Plate IV-15**). The promyelocyte evolves when the classic lysosomal granules, called the *primary* or *azurophil granules*, are produced. The primary granules contain hydrolases, elastase, myeloperoxidase, cationic proteins, and bactericidal/permeability-increasing (BPI) protein important for killing gram-negative bacteria. Azurophil granules also contain *defensins*, a family of cysteine-rich polypeptides with broad antimicrobial activity against bacteria, fungi, and certain enveloped viruses. The promyelocyte divides to produce the *myelocyte*, a cell responsible for the synthesis of the *specific* or *secondary granules* which contain unique (specific) constituents such as lactoferrin, vitamin B_{12}–binding proteins, membrane components of the nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase required for hydrogen peroxide production, histaminase, and receptors for certain chemoattractants and adherence-promoting factors (CR3) as well as receptors for the connective tissue element laminin. The secondary granules do not contain acid hydrolases and therefore are not classic lysosomes. They are readily released extracellularly, and their mobilization is probably important in modulating inflammation. During the final stages of maturation there is no cell division, and the cell passes through the *metamyelocyte* stage and then to the *band* neutrophil with a sausage-shaped nucleus (**Plate IV-17**). As the band cell matures, the nucleus assumes a lobulated configuration. The nucleus of neutrophils normally contains up to four segments. Excessive segmentation (greater than five nuclear lobes) may be a manifestation of folate or vitamin B_{12} deficiency (**Plate IV-18**). The Pelger-Hüet anomaly (**Plate IV-19*B***), an infrequent dominant benign inherited trait, results in neutrophils with distinctive bilobed nuclei that must be distinguished from band forms. The physiologic role of the multilobed nucleus of neutrophils is unknown, but it may allow great deformation of neutrophils during migration into tissues at sites of inflammation.

In settings of severe acute bacterial infection, prominent neutrophil cytoplasmic granules called *toxic granulations* are occasionally seen (**Plate IV-16**). Toxic granulations are thought to be immature or abnormally staining azurophil granules. Cytoplasmic inclusions, also called *Döhle bodies* (**Plate IV-17**), can be seen during infection and probably represent fragments of ribosome-rich endoplasmic reticulum. Large neutrophil vacuoles are often present in acute bacterial infection and probably represent pinocytosed (internalized) membrane.

Neutrophils have long been thought to be a homogeneous population of cells. However, studies of neutrophil function have suggested that they are heterogeneous. Recently, monoclonal antibodies have been developed that recognize only a subset of mature neutrophils. The meaning of neutrophil heterogeneity is not known.

MARROW RELEASE AND CIRCULATING COMPARTMENTS Specific signals, including interleukin (IL) 1, tumor necro-

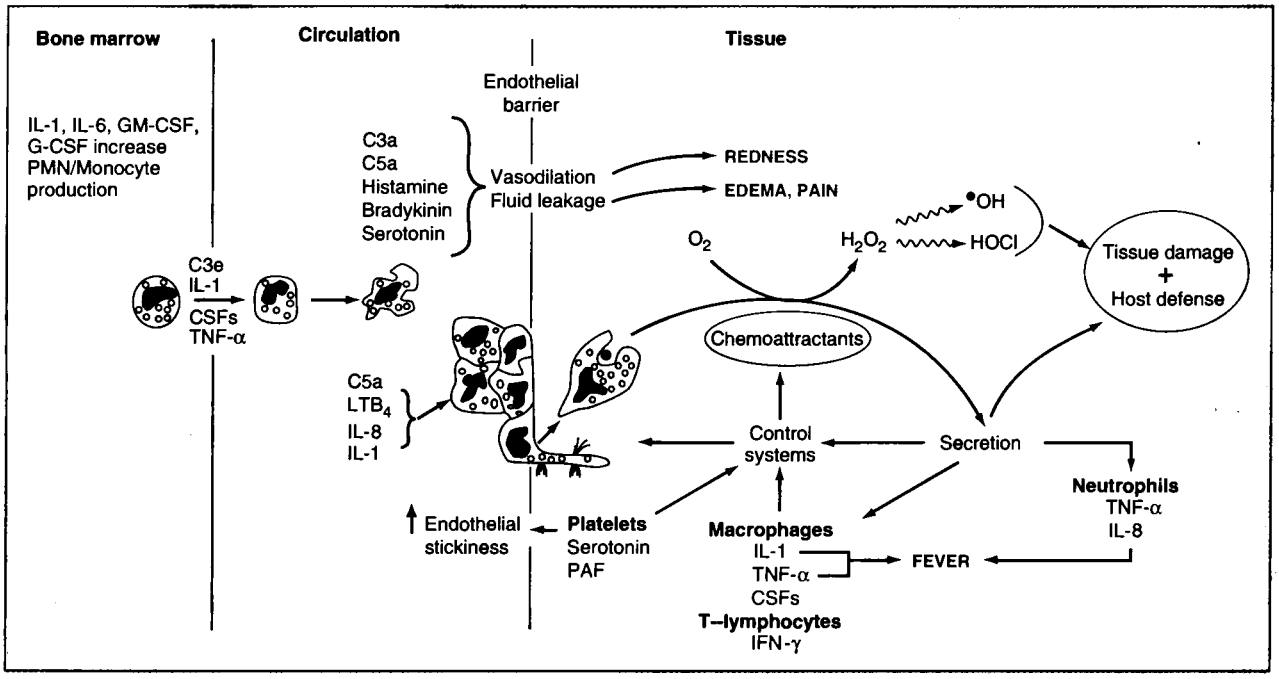

FIGURE 62-1 Events in inflammation. The four basic symptoms of inflammation are indicated by bold blue print.

Cell	Stage	Surface Markers*	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

* CD= Cluster Determinant; ● Nucleolus; ● Primary granule; o Secondary granule.

FIGURE 62-2 Stages of neutrophil development are schematically shown. G-CSF and GM-CSF are critical to this process. Identifying cellular characteristics and specific cell-surface markers are listed for each maturational stage.

sis factor α (TNFα), the colony stimulating factors, the complement fragment C3e, and perhaps other cytokines mobilize leukocytes from the bone marrow and deliver them to the blood in an unstimulated state. Under normal conditions, about 90 percent of the neutrophil pool is in the bone marrow, 2 to 3 percent in the circulation, and the remainder in the tissues (Fig. 62-3).

The circulating pool exists in two dynamic compartments: freely flowing and 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. 62-4). In the pulmonary circulation, where there is an extensive capillary bed (about 1000 capillaries per aleveolus), 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. *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 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 (GlyCAM) 1 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

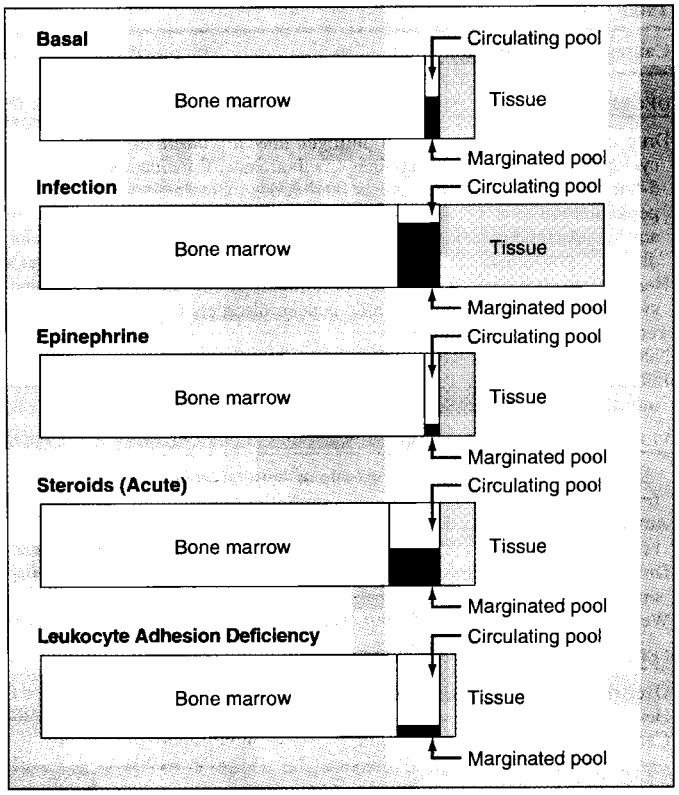

FIGURE 62-3 Schematic neutrophil distribution and kinetics between the different anatomic and functional pools.

chemotactic stimuli from injured tissues (e.g., the complement product C5a, the arachidonic acid derivative leukotriene B_4, the cytokine IL-8) or bacterial products [e.g., *N*-formylmethionylleucylphenylalanine (f-metleuphe)], neutrophil adhesiveness increases and they "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 (also called either Mac-1, CR3, or the C3bi receptor), and CD11c (p150,95). CD11a/CD18 and CD11b/CD18 mediate binding to specific endothelial receptors [intercellular adhesion molecules (ICAM)] 1 and 2.

Receptors for chemoattractants and opsonins are also mobilized; the phagocytes orient toward the chemoattractant source in the extravascular space, increase their motile activity (chemokinesis), and migrate with direction (chemotaxis) into tissues. The biochemistry and cell biology of these processes are rapidly unfolding (see "Bibliography"). The process of migration into tissues is 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 secondary to increased vasodilation and permeability) are mediated by anaphylatoxins (e.g., complement products C3a and C5a) as well as vasodilators such as histamine, bradykinin, serotonin, and prostaglandins E and I. In the healthy adult, most neutrophils leave the body by migration through the mucous membrane of the gastrointestinal tract. Normally, neutrophils spend a relatively short time in the circulation, with a half-life of 6 to 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 (phagocytose) pathogenic materials that have been properly altered (opsonized) by substances such as IgG and the complement product C3b. Fibronectin and the tetrapeptide tuftsin facilitate the phagocytic process.

Concomitant with phagocytosis there is 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 reduction of oxygen to superoxide anion, which is then converted to hydrogen peroxide and other toxic oxygen products (e.g., hydrogen peroxide and hydroxyl radical). Hydrogen peroxide + chloride + neutrophil myeloperoxidase provide a particularly toxic system that generates 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 and defensins also participate in microbial killing. Other enzymes, such as lysozyme and acid proteases, help digest microbial debris. After 1 to 4 days in tissues neutrophils die. Under certain conditions, such as in delayed-type hypersensitivity immunity, monocyte accumulation occurs within 6 to 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. Neutrophils shed their

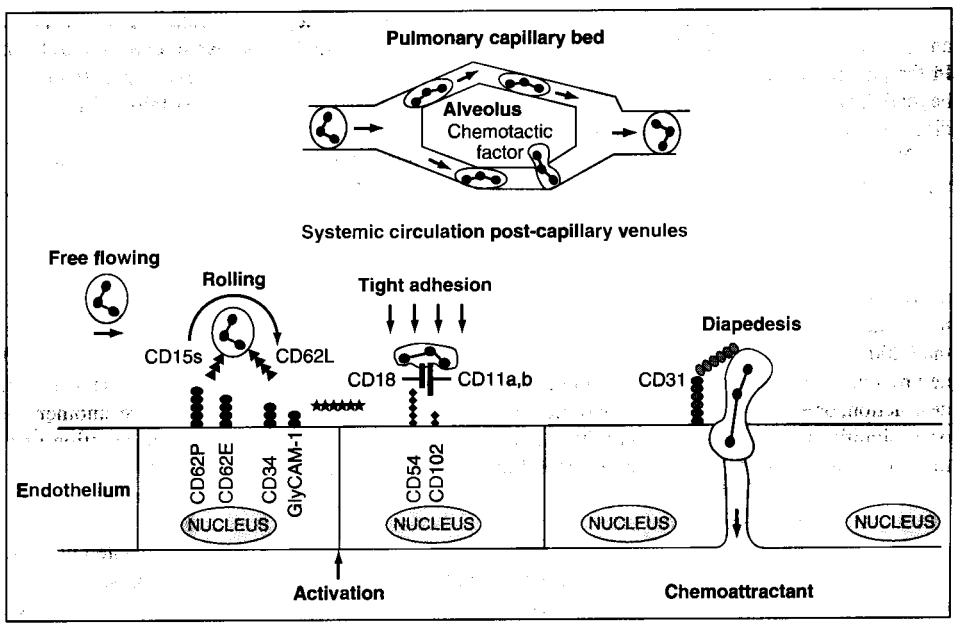

FIGURE 62-4 Neutrophil travel through the pulmonary capillaries is dependent on neutrophil deformability. Neutrophil rigidity (e.g., caused by C5a) enhances pulmonary trapping and response to pulmonary pathogens in a way that is not so dependent upon cell-surface receptors. Intraalveolar chemotactic 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.

L-selectin molecules into the circulation upon entry into inflammatory sites. Myeloperoxidase (previously called verdoperoxidase) confers the characteristic green color to pus and may participate in turning off the inflammatory process by inactivating chemoattractants and immobilizing phagocytic cells.

Neutrophils react to certain cytokines [interferon γ (IFNγ), granulocyte-macrophage colony stimulating factor (GM-CSF), IL-8] and produce cytokines [TNFα, IL-8, macrophage inflammatory protein (MIP) 1α] that modulate the inflammatory response. An expanding class of proinflammatory peptides important for neutrophil and monocyte recruitment and activation are the *chemokines* (*chemo*attractant cyto*kines*). These small proteins are produced by many different cell types, including endothelial cells, fibroblasts, epithelial cells, neutrophils, and monocytes, and are necessary in the development of the inflammatory response. The 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 classical chemoattractants N-f-metleuphe and C5a. There are two major structural and functional classes of chemokines: The α chemokines (e.g., IL-8) are mainly chemoattractant for neutrophils, whereas the β chemokines (e.g., MIP-1α) are more chemoattractant for monocytes and lymphocytes.

NEUTROPHIL ABNORMALITIES A defect anywhere in the neutrophil life cycle can lead to dysfunction and compromised host defenses. Inflammation is often depressed, and the clinical result is often recurrent and severe bacterial and fungal infections creating difficult management problems. Diagnosis of phagocytic cell disorders is suggested by clinical evaluation. Aphthous ulcers of mucous membranes (gray ulcers without pus) and gingivitis and periodontal disease are common. 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. In the past it was unusual for persons with congenital defects to live beyond the age of 30 years. However, aggressive management of these diseases has extended the life span of patients.

Neutropenia The consequences of absent neutrophils are a dramatic demonstration of their importance in host defense. A large body of clinical data indicates that susceptibility to infectious diseases increases sharply when neutrophil levels fall below 1000 cells/μL. When the absolute neutrophil count (ANC; band forms and mature neutrophils combined) falls below 500 cells/μL, control of endogenous microbial flora (e.g., mouth, gut) is impaired; when there are fewer than 200 cells/μL, the inflammatory process is absent. The causes of neutropenia are related to depressed production, increased peripheral destruction, or excessive peripheral pooling. A falling neutrophil count or a significant decrease in neutrophils below steady state levels, together with a failure to increase neutrophil counts in the setting of infection or other challenge to the bone marrow reserve, 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," below).

Some causes of inherited and acquired neutropenia are listed in Table 62-1. The most common neutropenias are iatrogenic, resulting from the widespread use of cytotoxic or immunosuppressive therapies for malignancy or control of autoimmune disorders. These drugs cause neutropenia because they are toxic and result in decreased production of rapidly growing progenitor (stem) cells of the marrow. Cytotoxic chemotherapeutic agents fall into this category, but certain antibiotics such as chloramphenicol, trimethoprim-sulfamethoxazole, flucytosine, vidarabine, and the antiretroviral drug zidovudine may cause neutropenia by inhibiting proliferation of myeloid precursors. The marrow suppression is generally dose-related and dependent on continued administration of the drug. Recombinant human granulocyte colony stimulating factor (G-CSF) is an important drug for reversing this form of neutropenia and is particularly useful in cancer chemotherapy.

Table 62-1

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 (alveolar macrophage) trapping
Autoimmune disorders—Felty's syndrome, rheumatoid arthritis, lupus erythematosus
Drugs as haptens—aminopyrine, α-methyl dopa, phenylbutazone, mercurial diuretics, some phenothiazines
Wegener's granulomatosis
PERIPHERAL POOLING (TRANSIENT NEUTROPENIA)
Overwhelming bacterial infection (acute endotoxemia)
Hemodialysis
Cardiopulmonary bypass

Another important mechanism for iatrogenically induced neutropenia is the effect of drugs that serve as immune haptens and sensitize neutrophils or neutrophil precursors to immune-mediated peripheral destruction. This 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 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 also may be associated 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 to 7 days and is complete by 10 days. Readministration of the sensitizing drug should be avoided, since abrupt neutropenia often will result. For this reason, diagnostic challenge should be avoided in most situations.

Autoimmune neutropenias caused by circulating antineutrophil antibodies are another form of acquired neutropenia that results in increased destruction of neutrophils. Acquired neutropenia also may be seen with viral infections, including those with the human immunodeficiency virus. Rarely, acquired neutropenia may be cyclic in nature, occurring at intervals of several weeks. Acquired cyclic neutropenia may be associated with increased natural NK cells and may be responsive to steroids.

Syndromes have been described in which expansion of large granular lymphocytes (LGL) is associated with neutropenia. Patients with LGL lymphocytosis may have moderate blood and bone marrow lymphocytosis, neutropenia, polyclonal hypergammaglobulinemia, splenomegaly, and absence of lymphadenopathy. Such patients may have a chronic and relatively stable course. Recurrent bacterial infections are frequent. There are both benign and malignant forms of this syndrome. 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.

Hereditary neutropenias are rare and may manifest in early childhood as a profound constant neutropenia or agranulocytosis. Examples of congenital forms of neutropenia include Kostmann's syndrome

Table 62-2

Causes of Neutrophilia

INCREASED PRODUCTION
Idiopathic
Drug-induced—glucocorticoids
Infection—bacterial, fungal, rarely 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 MOBILIZATION
Glucocorticoids
Acute infection (endotoxin)
Inflammation—thermal injury
DEFECTIVE MARGINATION
Drugs—epinephrine, glucocorticoids, nonsteroidal anti-inflammatory agents
Stress, excitement, vigorous exercise
Leukocyte adhesion deficiency type 1 (integrin β chain, CD18), Leukocyte adhesion deficiency type 2 (selectin ligand, CD15s, sialyl-Lewis^x)
MISCELLANEOUS
Metabolic disorders—ketoacidosis, acute renal failure, eclampsia, acute poisoning
Drugs—lithium
Other—metastatic carcinoma, acute hemorrhage or hemolysis

(fewer than 100 neutrophils/μL), which is often fatal; more benign chronic idiopathic neutropenia (300 to 1500 neutrophils/μL); the hair-cartilage-hypoplasia syndrome; Shwachman syndrome associated with pancreatic insufficiency; and neutropenias associated with other immune defects (X-linked agammaglobulinemia, ataxia telangiectasia, IgA deficiency). Recently, forms of severe congenital neutropenia have been identified in which the G-CSF receptor encoded on chromosome 1 is mutated, leading to poor G-CSF responsiveness and apparently predisposing to development of myeloid malignancy. Hereditary cyclic neutropenia, an autosomal dominant trait, may occur in infancy and is characterized by a remarkably regular 3-week cycle. Hereditary cyclic neutropenia actually is cyclic hematopoiesis. Although the mechanism for hereditary cyclic neutropenia is not known, steroids and G-CSF blunt the cycling in some patients. 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., thiazide) ingested during pregnancy can cause neutropenia in the newborn by either depressed production or peripheral destruction.

The presence of immunoglobulin directed toward neutrophils is seen in Felty's syndrome (triad of rheumatoid arthritis, splenomegaly, and neutropenia; see Chap. 61). Patients with Felty's syndrome who respond to splenectomy with an increase in their neutrophil count also have lower postoperative serum neutrophil-binding IgG, a result suggesting that one beneficial effect of splenectomy is reduction in antibodies to neutrophils. 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, marrow release, or defective margination (Table 62-2). The most important acute cause of neutrophilia requiring prompt medical attention 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. Leukocytosis with counts of 10,000 to 25,000 cells/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 of 30,000 to 50,000 cells/μL or greater 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.

Abnormal Neutrophil Function The types of inherited and acquired abnormalities of phagocyte function are described in Table 62-3. 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 62-4, several of which are discussed below.

Two types of leukocyte adhesion deficiency (LAD) have been described: Both are autosomal recessive traits and result in the inability of neutrophils to exit the circulation to sites of infection, leading to constant leukocytosis and increased susceptibility to infection. 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 comple-

Table 62-3

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	Leukoctye adhesion deficiency types 1 and 2
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 syndrome, α-mannosidase deficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome
Microbicidal activity	Colchicine, cyclophosphamide, glucocorticoids (high dose)	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

ment-derived opsonin C3bi (CR3). The CD18 gene is located on distal chromosome 21q. Variable expression of the defect determines the magnitude of clinical disease. Complete lack of expression of the leukocyte adhesion proteins by resting neutrophils results in the severe phenotype in which inflammatory cytokines do not increase the expression of leukocyte adhesion proteins on neutrophils or activated T and B cells. The functional abnormalities are predictable because of the role these molecules play in normal leukocyte function. 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 this syndrome have recurrent bacterial and fungal infections involving skin, oral and genital mucosa, and respiratory and intestinal tracts; persistent leukocytosis (15,000 to 20,000 neutrophils/μL) because cells do not marginate; and, in severe cases, a history of delayed separation of the umbilical stump. Infections, especially of the skin, tend to become necrotic with progressively enlarging borders, slow healing, and the development of dysplastic scars. The most common bacteria are *Staphylococcus aureus* and enteric gram-negative bacteria. LAD 2 is caused by an abnormality of SLe^x (CD15s), the ligand on neutrophils that interacts with selectins on endothelial cells.

Abnormal neutrophil and monocyte chemotaxis occurs in the *hyperimmunoglobulin E–recurrent infection* (HIE) or *Job's syndrome*. The molecular basis for this syndrome is not known, but some cases appear to have autosomal dominant transmission. Patients with this syndrome have coarse facies; bone abnormalities including hyperostosis frontalis externa, hypertelorism, kyphoscoliosis, and osteoporosis; and eczema. They 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." A high degree of suspicion is required to diagnose infections in these patients, who may appear well despite extensive disease. For many years the cold abscesses were thought to be a reflection of impaired chemotaxis with too few phagocytes arriving too late, perhaps secondary to a lymphocyte factor inhibiting chemotaxis. However, it is now clear that the chemotactic defect in these patients is variable and the fundamental basis for the impaired defenses is complex and inadequately delineated.

Table 62-4

Inherited Disorders of Phagocyte Function: Differential Features

Clinical Manifestations	Cellular or Molecular Defects	Diagnosis
CHRONIC GRANULOMATOUS DISEASES OF CHILDHOOD (60% X-LINKED, 40% AUTOSOMAL RECESSIVE)		
Severe infections of skin, ears, lungs, liver, and bone with catalase-positive microorganisms such as *S. aureus*, *Burkholderia cepacia*, *Aspergillus* sp., *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	Absent respiratory burst due to the lack of one of four NADPH oxidase subunits in neutrophils, monocytes, and eosinophils	NBT test; absent superoxide and H_2O_2 production by neutrophils; absent chemiluminescence; immunoblot for NADPH oxidase components
CHÉDIAK-HIGASHI SYNDROME (AUTOSOMAL RECESSIVE)		
Recurrent pyogenic infections, especially with *S. aureus*; many patients get lymphomatous-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	Giant primary granules in neutrophils and other granule-bearing cells (Wright's stain)
SPECIFIC GRANULE DEFICIENCY (AUTOSOMAL RECESSIVE?)		
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	Lack of secondary (specific) granules in neutrophils (Wright's stain), absent neutrophil-specific granule contents (i.e., lactoferrin), absent defensins, platelet alpha granule abnormality
MYELOPEROXIDASE DEFICIENCY (AUTOSOMAL RECESSIVE)		
Clinically normal except in patients with underlying disease such as diabetes mellitus; then candidiasis or other fungal infections	Absent myeloperoxidase due to pre- and posttranslational defects	Absent peroxidase in neutrophils
LEUKOCYTE ADHESION DEFICIENCY (AUTOSOMAL RECESSIVE)		
Type 1 Delayed separation of umbilical cord, sustained granulocytosis, 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 using monoclonal antibodies against LFA-1 (CD18/CD11a), Mac-1 or CR3 (CD18/CD11b), p150,95 (CD18/CD11c)
Type 2 Severe mental retardation, short stature, Bombay (hh) blood phenotype, recurrent infections, granulocytosis	Impaired phagocyte rolling along endothelium	Reduced phagocyte surface expression of Sialyl-$Lewis^x$, using monoclonal antibodies against CD15s
HYPER IgE–RECURRENT INFECTION SYNDROME (AUTOSOMAL) (JOB'S SYNDROME)		
Eczematoid or pruritic dermatitis, "cold" skin abscesses, recurrent pneumonias with *S. aureus* with bronchopleural fistulas and cyst formation, mild eosinophilia, mucocutaneous candidiasis, atopy, coarse facies, restrictive lung disease, scoliosis	Reduced chemotaxis in some patients, reduced suppressor T cell activity	Clinical features, serum IgE > 2000 IU/mL, high serum anti-*S. aureus* IgE, low or absent serum and salivary anti-*S. aureus* IgA

The most common neutrophil defect is *myeloperoxidase deficiency*, which is inherited as an autosomal recessive trait and may have an incidence as high as about 1 in 2000 persons. Isolated myeloperoxidase deficiency is not associated with clinically compromised defenses, because other defense systems such as hydrogen peroxide generation are accelerated. Microbicidal activity of neutrophils is delayed but not absent. However, if another underlying defect in host defense, such as poorly controlled diabetes mellitus, accompanies myeloperoxidase deficiency, then host defenses are likely to be significantly compromised. An acquired form of myeloperoxidase deficiency occurs in myelomonocytic leukemia and acute myeloblastic leukemia.

Chédiak-Higashi syndrome (CHS) is a rare disease with autosomal recessive inheritance. Neutrophils and all cells containing lysosomes from patients with CHS characteristically have large granules (**Plate IV-19A**). CHS patients have increased infections due to a multitude of infectious agents. 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. Natural killer cell function is also impaired.

Chronic granulomatous disease (CGD) represents a group of disorders of granulocyte and monocyte oxidative metabolism. Although CGD is rare, currently estimated to occur once in 250,000 individuals, it is an important model of defective neutrophil oxidative metabolism. Most often CGD is inherited as an X-linked recessive pattern, although in about 40 percent of patients the disease is inherited with an autosomal recessive pattern. Mutations of four genes corresponding to four 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. Two other proteins (47 and 67 kDa, abnormal in the other autosomal recessive forms of CGD) are cytoplasmic in origin and interact with the cytochrome following 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 infection with catalase-positive microorganisms (organisms that destroy their own hydrogen peroxide). 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 usually present. Granulomas are frequent and can obstruct the gastrointestinal or genitourinary tracts. The excessive inflammatory reactions probably reflect abnormal turnoff of inflammation by failure to degrade chemoattractants and failure to degrade antigens that cause persistent neutrophil accumulation. Impaired killing of intracellular microorganisms by macrophages may lead to persistent cell-mediated immunity and granuloma formation.

MONONUCLEAR PHAGOCYTES

The mononuclear phagocyte system is defined as a continuum linking monoblasts, promonocytes, and monocytes with 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. In addition, they are important secretory cells that, through their receptors and secretory products, participate in many complex immunologic and inflammatory processes not attributed to neutrophils. Monocytes leave the circulation by diapedesis more slowly than neutrophils and have a half-life in the blood of 12 to 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, numerous complement components, enzyme inhibitors (plasmin, α_2 macroglobulin), binding proteins (transferrin, fibronectin, transcobalamin II), nucleosides, and cytokines (TNFα, IL-1, -8, -12). Interleukin 1 (see Chaps. 17 and 305) has many important functions, including stimulating the hypothalamus to initiate fever, mobilizing leukocytes from the bone marrow, as well as activating lymphocytes and neutrophils. Tumor necrosis factor α (also called *cachectin*) is a pyrogen that duplicates many of the actions of IL-1 and plays an important role in the pathogenesis of gram-negative shock (see Chap. 124). It can stimulate vigorous production of hydrogen peroxide and related toxic oxygen species by macrophages and neutrophils. In addition, TNFα induces the catabolic responses of chronic inflammation, which contribute to the profound wasting (cachexia) associated with many chronic diseases.

Other macrophage-secreted products include reactive oxygen metabolites, bioactive lipids (arachidonate metabolites and platelet-activating factors), chemokines, bone marrow colony stimulating factors, and factors stimulating fibroblast and microvasculature 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. Their 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 may be under the control of IFNγ.

Macrophages play an important role in the immune response (see Chap. 305). They 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 immunologically active substances from the circulation. Furthermore, they play a role in wound healing, in the disposal of senescent cells, and in the development of atheromas.

DISORDERS OF THE MONONUCLEAR PHAGOCYTE SYSTEM Many disorders of neutrophils extend to mononuclear phagocytes. Thus drugs that suppress neutrophil production in the bone marrow usually lead to monocytopenia. Transient monocytopenia also can be seen after stress or glucocorticoid administration. Monocytosis is associated with certain infections such as tuberculosis, brucellosis, subacute bacterial endocarditis, Rocky Mountain spotted fever, malaria, and visceral leishmaniasis (kala azar). Monocytosis is also seen in 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, HIE (Job's) syndrome, CHS, and chronic granulomatous diseases all have defects in the mononuclear phagocyte system. Impaired monocyte cytokine production has been found in some patients with disseminated nontuberculous mycobacterial infection who are not infected with the human immunodeficiency virus (HIV).

Certain viral infections impair mononuclear phagocyte function. For example, influenza virus infection is associated with abnormal monocyte chemotaxis. Mononuclear phagocytes can be infected by the HIV, and abnormal monocyte chemotaxis and abnormal clearance of IgG-coated erythrocytes (discussed below) by macrophages is also seen in AIDS (see Chap. 308). It is likely that the defects of the monocyte-macrophage system in AIDS contribute to the disordered immunoregulation and increased susceptibility to opportunistic infection due to intracellular microorganisms such as *Pneumocystis carinii* and *M. avium* complex. T lymphocytes produce IFNγ, which induces Fc-receptor expression and phagocytosis and stimulates hydrogen per-

oxide production by mononuclear phagocytes and neutrophils. In certain diseases, such as AIDS, IFNγ production may be deficient, while in other diseases, such as T cell lymphomas, excessive release of IFNγ is thought to cause erythrophagocytosis by splenic macrophages.

Specific defects of mononuclear phagocytes have been described in certain autoimmune diseases. Removal of IgG-coated radiolabeled autologous erythrocytes, presumably via the Fc receptor of splenic macrophages, is profoundly abnormal in patients with active systemic lupus erythematosus. Patients with other autoimmune diseases characterized by tissue deposition of immune complexes, as seen in Sjögren's syndrome, mixed cryoglobulinemia, dermatitis herpetiformis, and chronic progressive multiple sclerosis, also have defects in Fc-receptor function as judged by clearance of IgG-coated erythrocytes (see Chap. 311). Clinically, normal subjects with genetic haplotypes commonly associated with autoimmune disease (i.e., HLA-B8/DRw3) also have an increased incidence of defective Fc-receptor–specific functional activity, suggesting that this defect may predispose individuals with this genetic profile to immune-complex disease.

Monocytopenia occurs with acute infections, with stress, and following administration of glucocorticoids. Monocytopenia also occurs in aplastic anemia, hairy cell leukemia, and acute myelogenous leukemia and as a direct result of myelotoxic and immunosuppressive drugs.

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. However, there are major differences between the two cell types, and little is known about the natural function of eosinophils. Eosinophils are much longer lived than neutrophils, and unlike neutrophils, tissue eosinophils can recirculate. During most infections, eosinophils do not appear to have any important function. However, in invasive helminthic infections, such as hookworm, schistosomiasis, strongyloidiasis, toxocariasis, trichinosis, filariasis, echinococcosis, and cysticercosis, the eosinophil likely plays a central role in host defense. Eosinophils are also associated with bronchial asthma, cutaneous allergic reactions, and other hypersensitivity states.

The characteristic red-staining eosinophil granules (Wright's stain) contain a number of unique constituents. The distinctive feature of the eosinophil granule is its crystalline core consisting of an arginine-rich protein (major basic protein) with histaminase activity, which is probably 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 may contribute to inflammation. Other substances found in eosinophils include cationic proteins, some of which bind to heparin and reduce its anticoagulant activity. Eosinophil cytoplasm contains Charcot-Leyden crystal protein, a hexagonal bipyramidal crystal first described in leukemia and then in sputum from asthma patients, which is lysophospholipase and may function to restrict the toxicity of certain lysophospholipids. Eosinophils also contain a powerful neurotoxin. Patients with hypereosinophilic syndrome and cerebral spinal fluid eosinophilia exhibit varied neurologic abnormalities.

Several factors enhance the eosinophil's function in host defense. For example, stimulated 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. In addition, eosinophil colony stimulating factors (e.g., IL-5) produced by macrophages may not only increase eosinophil production in the bone marrow but also may activate eosinophils to kill parasites.

EOSINOPHILIA Eosinophilia is the presence of more than 500 eosinophils/μL of blood and is common in many settings besides parasite infection. Significant tissue eosinophilia can occur without an elevated blood count. The most common cause of eosinophilia is probably allergic reactions to drugs such as iodides, aspirin, sulfonamides, nitrofurantoin, penicillins, and cephalosporins. Allergies such as hay fever, asthma, eczema, serum sickness, allergic vasculitis, and pemphigus commonly are associated with eosinophilia. Eosinophilia is also seen 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 myelogenous leukemia, and cancer of the lung, stomach, pancreas, ovary, or uterus), as well as in rare diseases such as Job's syndrome and CGD; the mechanisms for the eosinophilia in these diseases are not known. Eosinophilia is commonly seen in the helminthic infections. Therapeutic administration of the cytokines IL-2 and GM-CSF frequently leads to transient eosinophilia. The most dramatic hypereosinophilic syndromes are Loeffler's syndrome, Loeffler's endocarditis, eosinophilic leukemia, and idiopathic hypereosinophilic syndrome (with counts as high as 50,000 to 100,000/μL).

The idiopathic hypereosinophilic syndrome represents a heterogeneous group of disorders with the common feature of prolonged eosinophilia of unknown cause and associated organ system dysfunction, including the heart, central nervous system, kidneys, lungs, gastrointestinal tract, and skin. The bone marrow is involved in all subjects, but the most severe complications involve the heart and central nervous system. Eosinophils are found in the involved tissues and are thought to cause tissue damage by local deposition of toxic eosinophil proteins such as eosinophil cationic protein and eosinophil major basic protein. In the heart, the pathologic changes lead to thrombosis, which may result in endocardial fibrosis and restrictive endomyocardiopathy. Similar pathologic changes are thought to contribute to the damage of tissues in other organ systems. Although the mechanism for the hypereosinophilia is not known, it has been shown that chemotherapy with glucocorticoids usually induces remission. In patients unresponsive to glucocorticoids, a cytotoxic agent such as hydroxyurea has been used successfully to lower the peripheral blood eosinophil counts and to improve markedly the prognosis. Interferon α also is effective in some patients, including those unresponsive to hydroxyurea. Aggressive medical and surgical approaches are employed for management of patients with cardiovascular complications.

The *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. The syndrome is characterized by eosinophilia (greater than 1000 eosinophils/μL) and generalized disabling myalgias without other recognized causes. Eosinophil fasciitis, pneumonitis and myocarditis, neuropathy culminating in respiratory failure, and encephalopathy have been described. The association of the disease with ingestion of L-tryptophan–containing products originating from a single source has led to the identification and characterization of putative etiologic agents present as contaminants in these preparations. Although the accumulation of eosinophils, lymphocytes, macrophages, and fibroblasts in the affected tissues suggests that these cells play important roles in the pathogenesis of the eosinophilia-myalgia syndrome, the precise mechanism of their involvement has not been established. Several studies have demonstrated the activation of eosinophils and the deposition of eosinophil-derived toxic proteins in affected tissues. Fibroblast activation and increased expression of genes coding for various connective tissue molecules have been demonstrated. Furthermore, IL-5 and transforming growth factor β have been implicated as potential mediators. Treatment has included withdrawal of L-tryptophan–containing products and the administration of glucocorticoids. Most patients recover fully, remain stable, or show slow recovery, but in some patients (up to 5 percent) the disease can be fatal. This disease emphasizes the importance of chemical and environmental factors in the development of systemic disorders characterized by chronic inflammation and fibrosis.