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Steven M. Holland, John I. Gallin*

Disorders of Granulocytes

and Monocytes Leukocytes, the major cells comprising inflammatory and immune responses, include neutrophils, T and B lymphocytes, natural killer (NK) cells, mononuclear phagocytes (blood monocytes and tissue macrophages), eosinophils, and basophils. These cells have specific functions, such as antibody production by B lymphocytes or destruc tion of bacteria by neutrophils, but in no single infectious disease is the exact role of the cell types completely established. Thus, whereas neutrophils are classically thought to be critical to host defense against bacteria, they may also play important roles in defense against viral infections. The blood delivers leukocytes to the various tissues from the bone marrow, where they are produced. Normal blood leukocyte counts are 4.3–10.8 × 109/L, with neutrophils representing 45–74% of the cells, bands 0–4%, lymphocytes 16–45%, monocytes 4–10%, eosinophils 0–7%, and basophils 0–2%. Variation among individuals and among different ethnic groups can be substantial, with lower leukocyte num bers for certain African-American ethnic groups. Lower granulocyte numbers in African Americans are often in the 1500–2000/μL range and are generally without sequelae, a condition termed benign ethnic neutropenia. The lower number of granulocytes is associated with null expression of the Duffy antigen receptor for cytokines (DARC) gene, a receptor for Plasmodium vivax, the absence of which conveys resis tance to this form of malaria. The various leukocytes are derived 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 (CSFs) and interleukins (ILs). Because an alteration in the number and type of leukocytes is often associated with disease processes, total white blood cell (WBC) count (cells per μL) and differential counts are informative. This chapter focuses on neutrophils, monocytes, and eosinophils. Lymphocytes and basophils are discussed in Chaps. 360 and 364, respectively. NEUTROPHILS ■ ■MATURATION Important events in neutrophil life are summarized in Fig. 67-1. In normal humans, neutrophils are produced only in the bone marrow. The minimum number of stem cells necessary to support hematopoi esis is estimated to be 400–500 at any one time. Human blood mono cytes, tissue

macrophages, and stromal cells produce CSFs, hormones required for the growth of monocytes and neutrophils in the bone mar row. The hematopoietic system not only produces enough neutrophils (~1.3 × 1011 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 pres ence of immature cells is termed a shift to the left. A decrease in the number of blood neutrophils is called neutropenia. Neutrophils and monocytes evolve from pluripotent stem cells under the influence of cytokines and CSFs (Fig. 67-2). The prolifera tion phase through the metamyelocyte takes about 1 week, while the maturation phase from metamyelocyte to mature neutrophil takes another week. The myeloblast is the first recognizable precursor cell and is followed by the promyelocyte. The promyelocyte evolves when the classic lysosomal granules, called the primary, or azurophil, granules are produced. The primary granules contain hydrolases, elastase, *Deceased

myeloperoxidase, cathepsin G, cationic proteins, and bactericidal/

permeability-increasing protein, which is 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 B12–binding protein, mem brane components of the reduced nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase (NOX2) required for hydrogen peroxide production, histaminase, and receptors for certain chemoattractants and adherence-promoting factors (e.g., CR3) as well as receptors for the basement membrane component, laminin. The secondary granules do not contain acid hydrolases and therefore are not classic lysosomes. Packaging of secondary granule contents during myelopoiesis is con trolled by CCAAT/enhancer binding protein-ε (encoded by CEBPE). Secondary granule contents are readily released extracellularly, and their mobilization is important in modulating inflammation. During the final stages of maturation, no cell division occurs, and the cell passes through the metamyelocyte stage and then to the band neutrophil with a sausage-shaped nucleus (Fig. 67-3). As the band cell matures, the nucleus assumes a lobulated configuration. The nucleus of neutrophils normally contains up to four segments (Fig. 67-4). Excessive segmen tation (>5 nuclear lobes) may be a manifestation of folate or vitamin B12 deficiency or the congenital neutropenia syndrome of warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) described below. The Pelger-Hüet anomaly (Fig. 67-5), an infrequent dominant benign inherited trait caused by heterozygous mutations in the lamin B receptor, results in neutrophils with distinctive bilobed nuclei that must be distinguished from band forms. Acquired bilobed nuclei, pseudo-Pelger-Hüet anomaly, can occur with acute infections or in myelodysplastic syndromes. The physiologic role of the normal multilobed nucleus of neutrophils is unknown, but it may allow great deformation of neutrophils during migration into tissues at sites of inflammation and facilitate production of neutrophil nets.

 In severe acute bacterial infection, prominent neutrophil cytoplas mic granules, called toxic granulations, are occasionally seen. Toxic granulations are immature or abnormally staining azurophil granules. Cytoplasmic inclusions, also called Döhle bodies (Fig. 67-3), can be seen during infection and are fragments of ribosome-rich

endoplasmic reticulum. Large neutrophil vacuoles are often present in acute bacte rial infection in some viral infections such as COVID-19 and probably represent pinocytosed (internalized) membrane (Fig. 67-6). Neutrophils are heterogeneous in function. Monoclonal antibodies have been developed that recognize only a subset of mature neutro phils. The meaning of neutrophil heterogeneity is not known. The morphology of eosinophils is shown in Fig. 67-7. ■ ■MARROW RELEASE AND CIRCULATING COMPARTMENTS Specific signals, including IL-1, tumor necrosis factor α (TNF-α), the CSFs, complement fragments, and chemokines, mobilize leukocytes from the bone marrow and deliver them to the blood in an unstimu lated state. Under normal conditions, ~90% of the neutrophil pool is in the bone marrow, 2–3% in the circulation, and the remainder in the tissues (Fig. 67-8). The circulating pool exists in two dynamic compartments: one freely flowing and one marginated. The freely flowing pool is about one-half the neutrophils in the basal state and is composed of those cells that are in the blood and not in contact with the endothelium. Marginated leukocytes are those that are in close physical contact with the endothelium (Fig. 67-9). In the pulmonary circulation, where an extensive capillary bed (~1000 capillaries per alveolus) exists, margin ation occurs because the capillaries are about the same size as a mature neutrophil. Therefore, neutrophil fluidity and deformability are neces sary to make the transit through the pulmonary bed. Increased neutro phil rigidity and decreased deformability lead to augmented neutrophil trapping and margination in the lung. In contrast, in the systemic post capillary venules, margination is mediated by the interaction of specific

BONE MARROW CIRCULATION Stem cell C3a C5a Histamine Bradykinin Serotonin PART 2 Cardinal Manifestations and Presentation of Diseases PMN Diapedesis G-CSF Steroids Endotoxin Integrins Increased endothelial stickiness Vessel wall IL-1, TNF-α Endothelium FIGURE 67-1 Schematic events in neutrophil production, recruitment, and inflammation. The four cardinal signs of inflammation (rubor, tumor, calor, dolor) are indicated, as are the interactions of neutrophils with other cells and cytokines. G-CSF, granulocyte colony-stimulating factor; IL, interleukin; PMN, polymorphonuclear leukocyte; TNF-α, tumor necrosis factor α. Cell Stage Surface Markersa 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 Condensed, band– shaped nucleus BAND FORM CD33, CD13, CD15, CD14, CD11b, CD10, CD16 Condensed, multilobed nucleus CD33, CD13, CD15, CD14, CD11b, CD10, CD16 NEUTROPHIL aCD = Cluster Determinant; Nucleolus; Primary granule; Secondary granule. FIGURE 67-2 Stages of neutrophil development shown schematically. Granulocyte colonystimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are critical to this process. Identifying cellular characteristics and specific cell-surface markers are listed for each maturational stage.

Microbial killing tissue damage Activation of other limbs of host defense Redness (Rubor) Edema (Tumor) Pain (Dolor) Warmth (Calor) O2 –, H2O2, .OH, HOCl (bleach) Vasodilation Fluid Leakage Ingestion Chemokines, other chemoattractants Bacteria or fungi Cytokine secretion Fever IL-8, TNF-α, IL-12 Recruitment Selectins Macrophages Lymphocytes cell-surface molecules called selectins. Selectins are glycoproteins expressed on neutrophils and endothelial cells, among others, that cause a low-affinity interaction, resulting in “rolling” of the neutrophil along the endo thelial surface. On neutrophils, the molecule L-selectin (cluster determinant [CD] 62L) binds to glycosylated proteins on endothelial cells (e.g., glycosylation-depen dent cell adhesion molecule [GlyCAM1] and CD34). Glycoproteins on neutrophils, most importantly sialylLewisx (SLex, CD15s),

are targets for binding of selectins expressed on endothelial cells (E-selectin [CD62E] and P-selectin [CD62P]) and other leukocytes. In response to chemotactic stimuli from injured tissues (e.g., com plement product C5a, leukotriene B4, IL-8) or bacterial products (e.g., N-formylmethionylleucylphenylalanine [f-met-leu-phe of fMLF]), neutrophil adhesiveness increases through mobilization of intracellular adhesion proteins stored in specific granules to the cell surface, and the cells “stick” to the endothelium through integ rins. The integrins are leukocyte glycoproteins that exist as complexes of a common CD18 β chain with CD11a (LFA-1), CD11b (called Mac-1, CR3, or the C3bi recep tor), and CD11c (called p150,95 or CR4). CD11a/CD18 and CD11b/CD18 bind to specific endothelial receptors (intercellular adhesion molecules [ICAM] 1 and 2). On cell stimulation, L-selectin is shed from neutro phils, and E-selectin increases in the blood, presumably because it is shed from endothelial cells; receptors for chemoattractants and opsonins are mobilized; and the phagocytes orient toward the chemoattractant source in the extravascular space, increase their motile activ ity (chemokinesis), and migrate directionally (che motaxis) into tissues. 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 leuko cyte passage. Diapedesis involves platelet/endothelial cell adhesion molecule (PECAM) 1 (CD31), which is expressed on both the emigrating leukocyte and the

FIGURE 67-3 Neutrophil band with Döhle body. The neutrophil with a sausageshaped nucleus in the center of the field is a band form. Döhle bodies (arrow) are discrete, blue-staining, nongranular areas found in the periphery of the cytoplasm of the neutrophil in infections and other toxic states. They represent aggregates of rough endoplasmic reticulum. FIGURE 67-5 Pelger-Hüet anomaly. In this disorder, granulocytes are bilobed. In the benign, genetic form (due to mutations in LBR), most granulocytes have this appearance. In the acquired form, which is associated with myelodysplastic syndrome, it may be more occasional. The nucleus frequently has a spectacle-like, or “pince-nez,” configuration. (Courtesy of Dr. Katherine Calvo, Hematopathology Laboratory, Department of Laboratory Medicine, Clinical Center, NIH.) endothelial cells. The endothelial responses (increased blood flow from increased vasodilation and permeability) are mediated by anaphyla toxins (e.g., C3a and C5a) as well as vasodilators such as histamine, bradykinin, serotonin, nitric oxide, vascular endothelial growth factor (VEGF), and prostaglandins E and I. Cytokines regulate some of these processes (e.g., TNF-α induction of VEGF, interferon [IFN] γ inhibi tion of prostaglandin E). In the healthy adult, most neutrophils leave the body by migration through the mucous membrane of the oral cavity and especially the gastrointestinal tract. Normally, neutrophils spend a short time in the circulation (half-life, 6–7 h). Senescent neutrophils are cleared from the circulation by macrophages in the lung and spleen. Once in the tissues, neutrophils release enzymes, such as collagenase and elastase, which may help establish abscess cavities. Neutrophils ingest pathogenic materials that have been opsonized by IgG and C3b. Fibro nectin and the tetrapeptide tuftsin also facilitate phagocytosis. FIGURE 67-4 Normal granulocyte. The normal granulocyte has a segmented nucleus with heavy, clumped chromatin; fine neutrophilic granules are dispersed throughout the cytoplasm.

 With phagocytosis comes a burst of oxygen consumption and acti vation of the hexose-monophosphate shunt. A membrane-associated NADPH oxidase called NOX2, consisting of membrane and cytosolic components, is assembled and catalyzes the univalent reduction of oxygen to superoxide anion, which is then converted by superoxide dismutase to hydrogen peroxide and other toxic oxygen products (e.g., hydroxyl radical). Hydrogen peroxide + chloride + neutrophil myelo peroxidase 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, defensins, elastase, cathepsins, and probably nitric oxide also participate in microbial killing. Lactoferrin chelates iron, an important growth factor for microorganisms, especially fungi. Other enzymes, such as lysozyme and acid proteases, help digest microbial debris. After 1–4 days in tissues, neutrophils die. The apoptosis of neutrophils is also cytokine-regulated; granulocyte colony-stimulating factor (G-CSF) and IFN-γ prolong their life span. Neutrophil extra cellular traps (NETs) consisting of a DNA scaffold decorated with neutrophil-granule derived proteins, such as enzymatically active proteases and antimicrobial peptides, are thought to be formed as a defense mechanism to immobilize invading microorganisms. Under certain conditions, such as in delayed-type hypersensitivity, monocyte accumulation occurs within 6–12 h of initiation of inflammation. Neutrophils, monocytes, microorganisms in various states of diges tion, and altered local tissue cells make up the inflammatory exudate, pus. Myeloperoxidase confers the characteristic green color to pus and may participate in turning off the inflammatory process by inactivating chemoattractants and immobilizing phagocytic cells. Neutrophils respond to certain cytokines (IFN-γ, granulocyte-

macrophage colony-stimulating factor [GM-CSF], IL-8) and produce cytokines and chemotactic signals (TNF-α, IL-8, macrophage inflam matory protein [MIP] 1) that modulate the inflammatory response. In the presence of fibrinogen, fMLF, or leukotriene B4, IL-8 production by neutrophils is induced, providing autocrine amplification of inflam mation. Chemokines (chemoattractant cytokines) are small proteins produced by many different cell types, including endothelial cells, fibroblasts, epithelial cells, neutrophils, and monocytes, that regulate neutrophil, monocyte, eosinophil, and lymphocyte recruitment and activation. Chemokines transduce their signals through heterotrimeric G protein–linked receptors that have seven cell membrane–spanning domains, the same type of cell-surface receptor that mediates the response to the classic chemoattractants fMLF and C5a. Four major groups of chemokines are recognized based on the cysteine structure near the N terminus: C, CC, CXC, and CXXXC. The C chemokine

Normal monocytes A Normal neutrophils COVID-19 neutrophils PART 2 Cardinal Manifestations and Presentation of Diseases B FIGURE 67-6 COVID-19: Vacuolization in peripheral blood monocytes and neutrophils of COVID-19 patients. Peripheral blood smear showing vacuolization in (A) monocytes and (B) neutrophils from hospitalized hypoxemic COVID-19 patients relative to healthy volunteers. Increased vacuoles were noted in ~80% of monocytes and ~50% of neutrophils in each COVID-19 patient throughout their hospitalization. lymphotactin is T-cell tropic; CC chemokines such as MIP-1 attract lymphocytes, monocytes, eosinophils, and basophils; CXC cytokines such as IL-8 mainly attract neutrophils; while the CXXXC chemokine fractalkine attracts neutrophils, monocytes, and T cells. Not only do these molecules and their receptors regulate the trafficking and acti vation of inflammatory cells, but also specific chemokine receptors serve as co-receptors for HIV infection (Chap. 208), while others have roles in other viral infections (e.g., West Nile virus), susceptibility and response to Candida, and atherogenesis. ■ ■NEUTROPHIL ABNORMALITIES Defects in the neutrophil life cycle can lead to dysfunction and com promised host defenses. When inflammation is severely depressed, the clinical result is often recurrent, severe bacterial and fungal infections. Aphthous ulcers of mucous membranes (gray ulcers without pus) and gingivitis and periodontal disease suggest a phagocytic cell disorder. Patients with congenital phagocyte defects can have infections within the first few days of life. Skin, ear, upper and lower respiratory

tract, and bone infections are common. Sepsis and meningitis are rare. In some disorders, the frequency of infection is variable, and patients can go for months or even years without major infection. Aggressive man agement of these congenital diseases, including hematopoietic stem cell transplantation and gene therapy, has extended the life span of patients well into adulthood. FIGURE 67-7 The normal eosinophil seen here contains large, bright orange granules and usually a bilobed nucleus. (Courtesy of Dr. Katherine Calvo, Hematopathology Laboratory, Department of Laboratory Medicine, Clinical Center, NIH.)

COVID-19 monocytes Neutropenia The consequences of absent neutrophils are dra matic. Susceptibility to infectious diseases increases sharply when neutrophil counts fall to <1000 cells/μL. When the absolute neutrophil count (ANC; band forms and mature neutrophils combined) falls to <500 cells/μL, control of endogenous microbial flora (e.g., mouth, gut) is impaired; when the ANC is <200/μL, the local inflammatory process is absent. Neutropenia can be due to depressed production, increased peripheral destruction, or excessive peripheral pooling. A falling neu trophil count or a significant decrease in the number of neutrophils below steady-state levels, together with a failure to increase neutrophil counts in the setting of infection or other challenge, requires investiga tion. Acute neutropenia, such as that caused by cancer chemotherapy, is more likely to be associated with increased risk of infection than chronic neutropenia (months to years) that reverses in response to infection or carefully controlled administration of endotoxin (see “Laboratory Diagnosis and Management,” below). Some causes of inherited and acquired neutropenia are listed in Table 67-1. The most common neutropenias are iatrogenic, result ing from the use of cytotoxic or immunosuppressive therapies for malignancy or control of autoimmune disorders. These drugs cause Circulating pool Basal Tissue Bone marrow Marginated pool Circulating pool Infection Bone marrow Tissue Marginated pool Circulating pool Epinephrine Bone marrow Tissue Marginated pool Circulating pool Steroids (Acute) Bone marrow Tissue Marginated pool Circulating pool Leukocyte Adhesion Deficiency Bone marrow Tissue Marginated pool FIGURE 67-8 Schematic neutrophil distribution and kinetics between the different anatomic and functional pools.

Pulmonary capillary bed Alveolus Chemotactic factor Free flowing Rolling Systemic circulation postcapillary venules Tight adhesion CD15s CD62L CD18 CD11a,b CD31 CD54 CD102 GlyCAM-1 CD34 CD62P CD62E Activation Chemoattractant FIGURE 67-9 Neutrophil travel through the pulmonary capillaries is dependent on neutrophil deformability. Neutrophil rigidity (e.g., caused by C5a) enhances pulmonary trapping and response to pulmonary pathogens in a way that is not so dependent on cell-surface receptors. Intraalveolar chemotactic factors, such as those caused by certain bacteria (e.g., Streptococcus pneumoniae), lead to diapedesis of neutrophils from the pulmonary capillaries into the alveolar space. Neutrophil interaction with the endothelium of the systemic postcapillary venules is dependent on molecules of attachment. The neutrophil “rolls” along the endothelium using selectins: neutrophil CD15s (sialyl-Lewisx) binds to CD62E (E-selectin) and CD62P (P-selectin) on endothelial cells; CD62L (L-selectin) on neutrophils binds to CD34 and other molecules (e.g., GlyCAM-1) expressed on endothelium. Chemokines or other activation factors stimulate integrin-mediated “tight adhesion”: CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1, CR3) bind to CD54 (ICAM-1) and CD102 (ICAM-2) on the endothelium. Diapedesis occurs between endothelial cells: CD31 (PECAM-1) expressed by the emigrating neutrophil interacts with CD31 expressed at the endothelial cell-cell junction. CD, cluster determinant; GlyCAM, glycosylation-dependent cell adhesion molecule; ICAM, intercellular adhesion molecule; PECAM,

platelet/ endothelial cell adhesion molecule. neutropenia because they result in decreased production of rapidly growing progenitor (stem) cells of the marrow. Certain antibiotics such as chloramphenicol, trimethoprim-sulfamethoxazole, flucytosine, vidarabine, and the antiretroviral drug zidovudine may cause neutro penia by inhibiting proliferation of myeloid precursors. Azathioprine TABLE 67-1 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 B12, folate (especially alcoholics) Infection—tuberculosis, typhoid fever, brucellosis, tularemia, measles, infectious mononucleosis, malaria, viral hepatitis, leishmaniasis, AIDS Peripheral Destruction Antineutrophil antibodies and/or splenic or lung trapping Autoimmune disorders—Felty syndrome, rheumatoid arthritis, lupus erythematosus Drugs as haptens—aminopyrine, α-methyldopa, phenylbutazone, mercurial diuretics, some phenothiazines Granulomatosis with polyangiitis (Wegener) Peripheral Pooling (Transient Neutropenia) Overwhelming bacterial infection (acute endotoxemia) Hemodialysis Cardiopulmonary bypass

and 6-mercaptopurine are metabolized by the enzyme thiopurine methyltrans ferase (TMPT); hypofunctional polymor phisms that are found in 11% of whites can lead to accumulation of 6-thioguanine and profound marrow toxicity, which is why pharmacogenomic testing is recom mended before initiating these drugs. The marrow suppression is generally doserelated and resolves after cessation of the drug.

Disorders of Granulocytes and Monocytes CHAPTER 67 Another important mechanism for iat rogenic 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, neutro penia may occur a few hours after adminis tration of the drug. Although any drug can cause this form of neutropenia, the most frequent causes are commonly used antibi otics, such as sulfa-containing compounds, penicillins, and cephalosporins. Fever and eosinophilia may also be associated with drug reactions, but often these signs are not present. Drug-induced neutropenia can be severe, but discontinuation of the sensitizing drug is sufficient for recovery, which is usually seen within 5–7 days and is complete by 10 days. Readministration of the sensitizing drug should be avoided, because abrupt neutropenia will often result. For this reason, diagnostic challenge should be avoided. Diapedesis Endothelium Nucleus Autoimmune neutropenias caused by circulating antineutrophil antibodies are another form of acquired neutropenia that results in increased destruction of neutrophils. Acquired neutropenia may also be seen with viral infections, including acute infection with HIV. Acquired neutropenia may be cyclic in nature, occurring at intervals of several weeks. Acquired cyclic or stable neutropenia may be associated with an expansion of large granular lymphocytes (LGLs), which may be T cells, NK cells, or NK-like cells. Patients with large granular lym phocytosis may have moderate blood and bone marrow lymphocyto sis, neutropenia, polyclonal hypergammaglobulinemia, splenomegaly, rheumatoid arthritis, and absence of lymphadenopathy.

Such patients may have a chronic and relatively stable course. Recurrent bacterial infections are frequent. Benign and malignant forms of this syndrome occur. In some patients, spontaneous regression has occurred even after 11 years, suggesting an immunoregulatory defect as the basis for at least one form of the disorder. Glucocorticoids, cyclosporine, methotrexate, and monoclonals are commonly used to manage these cytopenias. Hereditary Neutropenias Hereditary neutropenias are rare and may manifest in early childhood as a profound constant neutropenia or agranulocytosis. Congenital forms of neutropenia include Kost mann's syndrome (neutrophil count <100/μL), which is often fatal and due to mutations in the anti-apoptosis gene HAX-1; severe chronic neutropenia (neutrophil count of 300–1500/μL) due to mutations in neutrophil elastase (ELANE); hereditary cyclic neutropenia or, more appropriately, cyclic hematopoiesis, also due to mutations in neutro phil elastase (ELANE); the cartilage-hair hypoplasia syndrome due to mutations in the mitochondrial RNA-processing endoribonuclease RMRP; Shwachman-Diamond syndrome associated with pancreatic insufficiency due to mutations in the Shwachman-Bodian-Diamond syndrome gene SBDS; the WHIM syndrome (warts, hypogamma globulinemia, infections, myelokathexis [retention of WBCs in the

marrow]), characterized by neutrophil hypersegmentation and bone marrow myeloid arrest due to mutations in the chemokine receptor CXCR4; and neutropenias associated with other immune defects, such as GATA2 deficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and CD40 ligand deficiency. Mutations in the G-CSF recep tor can develop in severe congenital neutropenia and are linked to the development of leukemia. Absence of both myeloid and lymphoid cells is seen in reticular dysgenesis, due to mutations in the nuclear genomeencoded mitochondrial enzyme adenylate kinase-2 (AK2).

Maternal factors can be associated with neutropenia in the new born. Transplacental transfer of IgG directed against antigens on fetal neutrophils can result in peripheral destruction. Drugs (e.g., thiazides) ingested during pregnancy can cause neutropenia in the newborn by either depressed production or peripheral destruction. PART 2 Cardinal Manifestations and Presentation of Diseases In Felty syndrome—the triad of rheumatoid arthritis, splenomegaly, and neutropenia (Chap. 370)—antibodies can shorten neutrophil life span, while large granular lymphocytes can attack marrow neutrophil precursors. Splenectomy may increase the neutrophil count in Felty syndrome and lower serum neutrophil-binding IgG. Some Felty syn drome patients also have autoantibodies to G-CSF, while others have increased numbers of LGLs. Splenomegaly with peripheral trapping and destruction of neutrophils is also seen in lysosomal storage dis eases and commonly in portal hypertension. Neutrophilia Neutrophilia results from increased neutrophil pro duction, increased marrow release, or defective margination (Table 67-2). The most important acute cause of neutrophilia is infection. Neutro philia from acute infection represents both increased production and increased marrow release. Increased production is also associated with chronic inflammation and certain myeloproliferative diseases. Increased marrow release and mobilization of the marginated leukocyte pool are induced by glucocorticoids. Release of epinephrine, as with vigorous exercise, excitement, or stress, will demarginate neutrophils in the spleen and lungs and double the neutrophil count in minutes. Cigarette smoking can elevate neutrophil counts above the normal range. Leu kocytosis with cell counts of 10,000–25,000/μL occurs in response to infection and other forms of acute inflammation and results from both release of the marginated pool and mobilization of marrow reserves. Persistent neutrophilia with cell counts of ≥30,000–50,000/μL is called a leukemoid reaction, a term often used to distinguish this degree of neutrophilia from leukemia. In a

leukemoid reaction, the circulating neutrophils are usually mature and not clonally derived. Abnormal Neutrophil Function Inherited and acquired abnor malities of phagocyte function are listed in Table 67-3. The resulting diseases are best considered in terms of the functional defects of adher ence, chemotaxis, and microbicidal activity. The distinguishing features of the important inherited disorders of phagocyte function are shown in Table 67-4. TABLE 67-3 Types of Granulocyte and Monocyte Disorders CAUSE OF INDICATED DYSFUNCTION FUNCTION DRUG-INDUCED ACQUIRED INHERITED Adherence-aggregation Aspirin, colchicine, alcohol, glucocorticoids, ibuprofen, piroxicam Neonatal state, hemodialysis Leukocyte adhesion deficiency types 1, 2, and 3 Deformability Leukemia, neonatal state, diabetes mellitus, immature neutrophils Chemokinesischemotaxis 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 Microbicidal activity Colchicine, cyclophosphamide, glucocorticoids (high dose), TNFα-blocking antibodies Leukemia, aplastic anemia, certain neutropenias, tuftsin deficiency, thermal injury, sepsis, neonatal state, diabetes mellitus, malnutrition, AIDS Abbreviations: IFNγ, interferon γ; IL, interleukin; TNF-α, tumor necrosis factor alpha.

TABLE 67-2 Causes of Neutrophilia Increased Production Idiopathic Drug-induced—glucocorticoids, G-CSF Infection—bacterial, fungal, sometimes viral Inflammation—thermal injury, tissue necrosis, myocardial and pulmonary infarction, hypersensitivity states, collagen vascular diseases Myeloproliferative diseases—myelocytic leukemia, myeloid metaplasia, polycythemia vera Increased Marrow Release Glucocorticoids Acute infection (endotoxin) Inflammation—thermal injury Decreased or Defective Margination Drugs—epinephrine, glucocorticoids, nonsteroidal anti-inflammatory agents Stress, excitement, vigorous exercise Leukocyte adhesion deficiency type 1 (CD18); leukocyte adhesion deficiency type 2 (selectin ligand, CD15s); leukocyte adhesion deficiency type 3 (FERMT3) Miscellaneous Metabolic disorders—ketoacidosis, acute renal failure, eclampsia, acute poisoning Drugs—lithium Other—metastatic carcinoma, acute hemorrhage or hemolysis Abbreviation: G-CSF, granulocyte colony-stimulating factor. DISORDERS OF ADHESION Three main types of leukocyte adhesion deficiency (LAD) have been described. All are autosomal recessive and result in the impairment of neutrophil exit from the circulation to sites of infection, leading to leukocytosis and increased susceptibil ity to infection (Fig. 67-9). Patients with LAD 1 have mutations in CD18, the common component of the integrins LFA-1, Mac-1, and p150,95, leading to a defect in tight adhesion between neutrophils and the endothelium. The heterodimer formed by CD18/CD11b (Mac-1) is also the receptor for the complement-derived opsonin C3bi (CR3). The CD18 gene is located on distal chromosome 21q. The severity of the defect determines the severity of clinical disease. Complete lack of expression of the leukocyte integrins results in a severe phenotype in which inflammatory stimuli do not increase the expression of leuko cyte integrins on neutrophils or activated T and B cells. Neutrophils (and monocytes) from patients with LAD 1 adhere poorly to endothe lial cells and protein-coated surfaces and exhibit defective spreading, aggregation, and chemotaxis. The inability of neutrophils to exit the vasculature to the tissue deprives the tissue macrophage of its expected neutrophil ingestion, leading to macrophage production of IL-23, Chédiak-Higashi syndrome, neutrophil-specific granule deficiency, WDR1 deficiency, Job’s syndrome (in some patients), Down syndrome, α-mannosidase deficiency, leukocyte adhesion deficiencies, Wiskott-Aldrich syndrome Chédiak-Higashi syndrome, neutrophil-specific granule deficiency, chronic granulomatous disease, defects in IFNγ/IL-12 axis, Anti-IFNγ

autoantibodies

TABLE 67-4 Inherited Disorders of Phagocyte Function: Differential Features CLINICAL MANIFESTATIONS CELLULAR OR MOLECULAR DEFECTS DIAGNOSIS Chronic Granulomatous Diseases (70% X-Linked, 30% Autosomal Recessive) Severe infections of skin, ears, lungs, liver, and bone with microorganisms such as Staphylococcus aureus, Burkholderia cepacia complex, Aspergillus spp., Chromobacterium violaceum; often hard to culture organism; excessive inflammation with granulomas, frequent lymph node suppuration; granulomas can obstruct GI or GU tracts; gingivitis, aphthous ulcers Chédiak-Higashi Syndrome (Autosomal Recessive) Recurrent pyogenic infections, especially with S. aureus; many patients get lymphoma-like illness during adolescence; periodontal disease; partial oculocutaneous albinism, nystagmus, progressive peripheral neuropathy, cognitive impairment in some patients Specific Granule Deficiency (Autosomal Recessive and Dominant) Recurrent infections of skin, ears, and sinopulmonary tract; delayed wound healing; decreased inflammation; bleeding diathesis Myeloperoxidase Deficiency (Autosomal Recessive) Clinically normal except in patients with underlying disease such as diabetes mellitus; then candidiasis or other fungal infections Leukocyte Adhesion Deficiency Type 1: Delayed separation of umbilical cord, sustained neutrophilia, recurrent infections of skin and mucosa, gingivitis, periodontal disease Type 2: Cognitive impairment, short stature, Bombay (hh) blood phenotype, recurrent infections, neutrophilia Type 3: Petechial hemorrhage, recurrent infections Impaired signaling for integrin activation resulting in impaired adhesion. Mutations in FERMT3 Phagocyte Activation Defects (X-Linked and Autosomal Recessive) NEMO deficiency: mild hypohidrotic ectodermal dysplasia; broad-based immune defect: pyogenic and encapsulated bacteria, viruses, Pneumocystis, mycobacteria; X-linked IRAK4 and MyD88 deficiency: susceptibility to pyogenic bacteria such as staphylococci, streptococci, clostridia; resistant to Candida; autosomal recessive Hyper IgE–Recurrent Infection Syndrome (Autosomal Dominant) (Job’s Syndrome) Eczematoid or pruritic dermatitis, “cold” skin abscesses, recurrent pneumonias with S. aureus with bronchopleural fistulae and cyst formation, mild eosinophilia, mucocutaneous candidiasis, characteristic facies, restrictive lung disease, scoliosis, delayed primary dental deciduation DOCK8 deficiency (autosomal recessive), severe eczema, atopic dermatitis, cutaneous abscesses, HSV, HPV, and molluscum infections, severe allergies, cancer Mycobacterial Susceptibility (Autosomal Dominant and Recessive Forms) Severe extrapulmonary or disseminated infections with bacille CalmetteGuérin (BCG), nontuberculous mycobacteria, salmonella, histoplasmosis, coccidioidomycosis, poor granuloma formation GATA2 Deficiency (Autosomal Dominant) Persistent or disseminated warts, disseminated mycobacterial disease, low monocytes, NK cells, B cells; hypoplastic myelodysplasia, leukemia, cytogenetic abnormalities, pulmonary alveolar proteinosis Abbreviations: C/EBPε, CCAAT/enhancer binding protein-ε; DHR, dihydrorhodamine (oxidation test); DOCK8, dedicator of cytokinesis 8; GI, gastrointestinal; GU, genitourinary; HPV, human papillomavirus; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; IRAK4, IL-1 receptor–associated kinase 4; LFA-1, leukocyte function– associated antigen 1; MyD88, myeloid differentiation primary response gene 88; NADPH, nicotinamide–adenine dinucleotide phosphate; NBT, nitroblue tetrazolium (dye test); NEMO, NF-κB essential modulator; NF-κB, nuclear factor-κB; NK, natural killer; STAT1–3, signal transducer and activator of transcription 1–3; TLR, Toll-like receptor; TNF, tumor necrosis factor.

No respiratory burst due to impaired of NADPH oxidase in neutrophils, monocytes, and eosinophils. Mutations in CYBB, CYBA, NCF1, NCF2, NCF4, or CYBC1 DHR or NBT test; no superoxide and H_2O_2

production by neutrophils; immunoblot for NADPH oxidase components; genetic detection Reduced chemotaxis and phagolysosome fusion, increased respiratory burst activity, defective egress from marrow, abnormal skin window; defect in CHS1 Giant primary granules in neutrophils and other granule-bearing cells (Wright stain); genetic detection Disorders of Granulocytes and Monocytes CHAPTER 67 Abnormal chemotaxis, impaired respiratory burst and bacterial killing, failure to upregulate chemotactic and adhesion receptors with stimulation, defect in transcription of granule proteins. Mutations in CEBPE or SMARCD2 Lack of secondary (specific) granules in neutrophils (Wright stain), no neutrophilspecific granule contents (i.e., lactoferrin), no defensins, platelet α granule abnormality; genetic detection No myeloperoxidase due to pre- and posttranslational defects in myeloperoxidase deficiency. Mutations in MPO No peroxidase in neutrophils; genetic detection Impaired phagocyte adherence, aggregation, spreading, chemotaxis, phagocytosis of C3bi-coated particles; defective production of CD18 subunit common to leukocyte integrins. Mutations in ITGB2 Reduced phagocyte surface expression of the CD18-containing integrins with monoclonal antibodies against LFA-1 (CD18/CD11a), Mac-1 or CR3 (CD18/ CD11b), p150,95 (CD18/CD11c); genetic detection Impaired phagocyte rolling along endothelium; due to defects in fucose transporter. Mutations in SLC35C1 Reduced phagocyte surface expression of Sialyl-Lewisx, with monoclonal antibodies against CD15s; genetic detection Reduced signaling for adhesion through integrins; genetic detection Impaired phagocyte activation by IL-1, IL-18, TLR, CD40L, TNF-α leading to problems with inflammation and antibody production. Mutations in IKBKG Poor in vitro response to endotoxin; impaired NF-κB activation; genetic detection Impaired phagocyte activation by endotoxin through TLR and other pathways; TNF-α signaling preserved. Mutations in IRAK4 or MYD88 Poor in vitro response to endotoxin; lack of NF-κB activation by endotoxin; genetic detection Reduced chemotaxis in some patients, reduced memory T and B cells. Mutations in STAT3 Somatic and immune features involving lungs, skeleton, and immune system; serum IgE >2000 IU/mL; genetic testing Impaired T-cell proliferation to mitogens. Mutations in DOCK8 Severe allergies, viral infections, high IgE, eosinophilia, low IgM, progressive lymphopenia, genetic detection Inability to kill intracellular organisms due to low IFN-γ production or response. Mutations in IFN-γ receptors, IL-12 receptors, IL-12 p40, STAT1, NEMO, ISG15, and others Abnormally low or very high levels of IFN-γ receptor 1; functional assays of cytokine production and response; genetic detection Impaired macrophage activity, cytopenias. Mutations in GATA2 Profound circulating monocytopenia, NK and B-cell cytopenias; genetic detection

which induces T-cell production of IL-17, a potent proinflammatory cytokine. These processes conspire to drive inflammation in LAD 1. Patients with LAD 1 have recurrent bacterial infections involving the skin, oral and genital mucosa, and respiratory and intestinal tracts; persistent leukocytosis (resting neutrophil counts of 15,000–20,000/μL) because cells do not marginate; and, in severe cases, a history of delayed separation of the umbilical stump. Infections, especially of the skin, may become necrotic with progressively enlarging borders, slow heal ing, and development of dysplastic scars. The most common bacteria are Staphylococcus aureus and enteric gram-negative bacteria. LAD 2 is caused by an abnormality of fucosylation of SLex (CD15s), the ligand on neutrophils that interacts with selectins on endothelial cells and is responsible for neutrophil rolling along the endothelium. Infection susceptibility in LAD 2 appears to be less severe than in LAD 1. LAD 2 is also known as congenital disorder of glycosylation IIc (CDGIIc) due to mutation in a GDP-fucose transporter (SLC35C1). LAD 3 is character ized by infection susceptibility, leukocytosis, and petechial hemorrhage due to impaired integrin activation caused by mutations in FERMT3.

PART 2 Cardinal Manifestations and Presentation of Diseases DISORDERS OF NEUTROPHIL GRANULES The most common neu trophil defect is myeloperoxidase deficiency, a primary granule defect inherited as an autosomal recessive trait; the incidence is ~1 in 2000 persons. Myeloperoxidase deficiency is not associated with clinically compromised defenses unless there is another contributing factor such as diabetes. In myeloperoxidase deficiency, neutrophil microbicidal activity is delayed but not absent. Patients with myeloperoxidase defi ciency and diabetes are more susceptible to Candida infections. An acquired form of myeloperoxidase deficiency occurs in myelomono cytic leukemia and acute myeloid leukemia. Importantly, myeloper oxidase deficiency gives an abnormal dihydrorhodamine (DHR) assay (see chronic granulomatous disease below). Chédiak-Higashi syndrome (CHS) is a rare disease with autosomal recessive inheritance due to defects in the lysosomal transport protein LYST, encoded by the gene CHS1 at 1q42. This protein is required for normal packaging and disbursement of granules. Neutrophils (and all cells containing lysosomes) from patients with CHS characteristically have large granules (Fig. 67-10), making it a systemic disease. Patients with CHS have nystagmus, partial oculocutaneous albinism, and an increased number of infections resulting from many bacterial agents. Some CHS patients develop an “accelerated phase” in childhood with a hemophagocytic syndrome and an aggressive lymphoma requiring FIGURE 67-10 Chédiak-Higashi syndrome. The granulocytes contain huge cytoplasmic granules formed from aggregation and fusion of azurophilic and specific granules. Large abnormal granules are found in other granule-containing cells throughout the body.

bone marrow transplantation. CHS neutrophils and monocytes have impaired chemotaxis and abnormal rates of microbial killing due to slow rates of fusion of the lysosomal granules with phagosomes. NK cell function is also impaired. CHS patients may develop a severe dis abling peripheral neuropathy in adulthood. Specific granule deficiency is a rare autosomal recessive disease in which the production of secondary granules and their contents, as well as the primary granule component defensins, is defective. The defect in killing leads to severe bacterial infections. One type of specific granule deficiency is due to a mutation in CEBPE, which regulates expression of granule components. A dominant mutation in CEBPE has also been described. Specific granule deficiency can also be caused by mutations in SMARCD2. CHRONIC GRANULOMATOUS DISEASE Chronic granulomatous dis ease (CGD) is a group of genetic disorders of granulocyte and mono cyte oxidative metabolism due to defects in the enzyme NADPH oxidase, also called NOX2. CGD has an incidence of ~1 in 100,000– 200,000 individuals. In about two-thirds of patients, CGD is inherited as an X-linked recessive trait; the remainder inherit their disease in autosomal recessive patterns. Mutations in the genes encoding the six proteins that allow assembly at the plasma membrane of NOX2 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. The protein essential for reactive oxidant signaling (EROS) is encoded by CYBC1, which is required to transport the 91- and 22-kDa proteins to the endoplasmic reticulum. Three other proteins (40, 47, and 67 kDa, abnormal in the other autosomal reces sive forms of CGD) are cytoplasmic and interact with the cytochrome after cell activation to form the NADPH oxidase, which is required for phagocyte hydrogen peroxide production. Therefore, leukocytes from patients with CGD have severely diminished hydrogen perox ide production. Patients with CGD characteristically have increased numbers of infections due to a relatively narrow range of microorgan isms (in North America, S. aureus, Serratia marsescens, Burkholderia cepacia complex, and Nocardia and Aspergillus species). Outside of

North America, Salmonella, tuberculosis, and bacillus CalmetteGuérin (BCG) are important pathogens. When patients with CGD become infected, they often have extensive inflammatory reactions, and suppuration is common despite the administration of appropri ate antibiotics. Aphthous ulcers and chronic infection of the nares are often present. Granulomas are frequent and can obstruct the gastroin testinal or genitourinary tracts. The excessive inflammation is due to failure to downregulate inflammation, reflecting a failure to inhibit the synthesis of, degradation of, or response to interleukins or chemoat tractants, leading to persistent myeloid reaction. Impaired killing of intracellular microorganisms by macrophages may lead to persistent cell-mediated immune activation and granuloma formation. Autoim mune complications such as immune thrombocytopenic purpura and juvenile idiopathic arthritis are also increased in CGD. In addition, for unexplained reasons, discoid lupus is more common in X-linked car riers. Late complications, including nodular regenerative hyperplasia and portal hypertension, are increasingly recognized in adolescent and adult patients with CGD. Interestingly, patients with CGD have been reported to be protected from atherosclerosis, suggesting an important role for NADPH oxidase (NOX2) in the pathogenesis of this inflamma tory disease of arteries. DISORDERS OF PHAGOCYTE ACTIVATION Phagocytes depend on cell-surface stimulation to induce signals that evoke multiple levels of the inflammatory response, including cytokine synthesis, chemotaxis, and antigen presentation. Mutations affecting the major pathway that signals through NF-κB have been noted in patients with a variety of infection susceptibility syndromes. If the defects are at a very late stage of signal transduction, in the protein critical for NF-κB activation known as the NF-κB essential modulator (NEMO), then affected males develop ectodermal dysplasia and severe immune deficiency with susceptibility to bacteria, fungi, mycobacteria, and viruses. There are several other proteins that interact with NEMO, mutations in which are

autosomal and can be phenocopies of NEMO deficiency. If the defects in NF-κB activation are closer to the cell-surface receptors, in the pro teins transducing Toll-like receptor signals, IL-1 receptor–associated kinase 4 (IRAK4), and myeloid differentiation primary response gene 88 (MyD88), then children have a marked susceptibility to pyogenic infections associated with a striking blunting of the febrile and inflam matory responses early in life but develop resistance to infection later. The small Rho-family GTPase, RAC2, is involved in actin assem bly, intracellular signaling, and superoxide production. Given these multiple roles, it is not surprising that different mutations in RAC2 can have different effects on its functions. Accordingly, different RAC2 mutations present, ranging from early-onset sepsis (constitutively active mutations), to abscesses with impaired superoxide production (dominant negative mutations), to common variable immunodefi ciency (hyperactive mutations). MONONUCLEAR PHAGOCYTES The mononuclear phagocyte system is composed of monoblasts, pro monocytes, and monocytes, in addition to the structurally diverse tis sue macrophages that make up what was previously referred to as the reticuloendothelial system. Monocytes, which leave the circulation by diapedesis more slowly than neutrophils and have a half-life of 12–24 h, migrate into tissues and differentiate into macrophages. Macrophages are long-lived phagocytic cells capable of many of the functions of neutrophils. They are also secretory cells that participate in many immunologic and inflammatory processes distinct from neutrophils. Many tissue macrophages (“big eaters”) arise in the embryonic yolk sac outside of conventional hematopoiesis and then go on to take up residence in tissues. In addition, there are macrophages derived from monocytes, which may have specialized functions suited for specific anatomic locations. Macrophages are particularly abundant in capil lary 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 macro phages, peritoneal macrophages, bone marrow macrophages, lym phatic macrophages, brain microglial cells, and dendritic macrophages all have specialized functions. Macrophage-secreted products include lysozyme, neutral proteases, acid hydrolases, arginase, complement components, enzyme inhibitors (plasmin, α2-macroglobulin), binding proteins (transferrin, fibronectin, transcobalamin II), nucleosides, and cytokines (TNF-α; IL-1, 8, 12, 18). IL-1 (Chaps. 20 and 360) has many functions, including initiating fever in the hypothalamus, mobilizing leukocytes from the bone marrow, and activating lymphocytes and neutrophils. TNF-α is a pyrogen that duplicates many of the actions of IL-1 and plays an important role in the pathogenesis of gram-negative shock (Chap. 315). TNF-α stimulates production of hydrogen perox ide and related toxic oxygen species by macrophages and neutrophils. In addition, TNF-α induces catabolic changes that contribute to the profound wasting (cachexia) associated with many chronic diseases. Other macrophage-secreted products include reactive oxygen and nitrogen metabolites, bioactive lipids (arachidonic acid metabolites and platelet-activating factors), chemokines, CSFs, and factors stimu lating fibroblast and vessel proliferation. Macrophages help regulate the replication of lymphocytes and participate in the killing of tumors, viruses, and certain bacteria (Mycobacterium tuberculosis and Listeria monocytogenes). Macrophages are key effector cells in the elimination of intracellular microorganisms. 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 is under the control of IFN-γ. Nitric oxide induced by IFN-γ may be an important effector against intracellular parasites, including tuberculo sis and Leishmania. Macrophages play an important role in the immune response (Chap. 360). 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 substances from the circula tion. Polymorphisms in macrophage receptors for immunoglobulin (FcγRII) determine susceptibility to some infections and autoimmune

diseases. In wound healing, they dispose of senescent cells, and they also contribute to atheroma development. Macrophage elastase medi ates development of emphysema from cigarette smoking.

■ ■DISORDERS OF THE MONONUCLEAR PHAGOCYTE SYSTEM Many disorders of neutrophils extend to mononuclear phagocytes. Monocytosis is associated with tuberculosis, brucellosis, subacute bac terial endocarditis, Rocky Mountain spotted fever, malaria, and visceral leishmaniasis (kala-azar). Monocytosis also occurs with certain malig nancies, leukemias, myeloproliferative syndromes, hemolytic anemias, chronic idiopathic neutropenias, and granulomatous diseases such as sarcoidosis, Crohn disease, and some collagen vascular diseases. Patients with LAD1, hyperimmunoglobulin E–recurrent infection (Job’s) syndrome, CHS, and CGD all have defects in the mononuclear phagocyte system. Disorders of Granulocytes and Monocytes CHAPTER 67 Monocyte cytokine production or response is impaired in some patients with disseminated nontuberculous mycobacterial infection who are not infected with HIV. Genetic defects in the pathways regulated by IFN-γ and IL-12 lead to impaired killing of intracellular bacteria, mycobacteria, salmonellae, and certain viruses (Fig. 67-11). Autoantibodies to IFN-γ, IL-23, and GM-CSF can block critical signals for macrophage intracellular killing and are associated with mycobac terial, fungal, and Nocardia infections. Certain viral infections impair mononuclear phagocyte function. For example, influenza virus infection causes abnormal monocyte chemotaxis. Mononuclear phagocytes can be infected by

HIV using CCR5, the chemokine receptor that acts as a co-receptor with CD4 for HIV. T lymphocytes produce IFN-γ, which induces FcR expression and phagocytosis and stimulates hydrogen peroxide production by mononuclear phagocytes and neutrophils. In certain diseases, such as AIDS, IFN-γ production may be deficient, whereas in other diseases, such as T-cell lymphomas, excessive release of IFN-γ may be associated with erythrophagocytosis by splenic macrophages. IL-2 IL-2R IFNγ T/NK β1 IL-12R β2 IL-15

? IFNγR STAT1 1 2 GATA2 ISG15 IL-12 IRF8 TNFα AFB Salm. NEMO NRAMP1 MΦ TNFαR TLR LPS CD14 FIGURE 67-11 Lymphocyte-macrophage interactions underlying resistance to mycobacteria and other intracellular pathogens such as Salmonella, Histoplasma, and Coccidioides. Mycobacteria (and others) infect macrophages, leading to the production of IL-12, which activates T or NK cells through its receptor, leading to production of IL-2 and IFN-γ. IFN-γ acts through its receptor on macrophages to upregulate TNF-γ and IL-12 and kill intracellular pathogens. Other critical interacting molecules include signal transducer and activator of transcription 1 (STAT1), interferon regulatory factor 8 (IRF8), GATA2, and ISG15. Mutant forms of the cytokines and receptors shown in bold type have been found in severe cases of nontuberculous mycobacterial infection, salmonellosis, and other intracellular pathogens. AFB, acid-fast bacilli; IFN, interferon; IL, interleukin; NEMO, nuclear factor-κB essential modulator; NK, natural killer; TLR, Toll-like receptor; TNF, tumor necrosis factor.

Autoinflammatory diseases are characterized by abnormal cytokine regulation, leading to excess inflammation in the absence of infection. These diseases can mimic infectious or immunodeficient syndromes. Gain-of-function mutations in the TNF-α receptor cause TNF-α receptor–associated periodic syndrome (TRAPS), which is character ized by recurrent fever in the absence of infection, due to persistent stimulation of the TNF-α receptor (Chap. 381). Diseases with abnor mal IL-1 regulation leading to fever include familial Mediterranean fever due to mutations in PYRIN. Mutations in cold-induced autoin flammatory syndrome 1 (CIAS1) lead to neonatal-onset multisystem autoinflammatory disease, familial cold urticaria, and Muckle-Wells syndrome. The syndrome of pyoderma gangrenosum, acne, and sterile pyogenic arthritis (PAPA syndrome) is caused by mutations in PSTPIP1. In contrast to these syndromes of overexpression of proin flammatory cytokines, blockade of TNF-α by the antagonists inflix imab, adalimumab, certolizumab, golimumab, or etanercept has been associated with severe infections due to tuberculosis, nontuberculous mycobacteria, and fungi (Chap. 381).

PART 2 Cardinal Manifestations and Presentation of Diseases Monocytopenia occurs with acute infections, with stress, and after treatment with glucocorticoids. Drugs that suppress neutrophil production in the bone marrow can cause monocytopenia. Persistent severe circulating monocytopenia is seen in GATA2 deficiency, even though macrophages are found at the sites of inflammation. Mono cytopenia also occurs in aplastic anemia, hairy cell leukemia, acute myeloid leukemia, and as a direct result of myelotoxic drugs. EOSINOPHILS Eosinophils and neutrophils share similar morphology, many lyso somal constituents, phagocytic capacity, and oxidative metabolism. Eosinophils express a specific chemoattractant receptor and respond to a specific chemokine, eotaxin, but little is known about their required role. Eosinophils are much longer lived than neutrophils, and unlike neutrophils, tissue eosinophils can recirculate. During most infections, eosinophils appear unimportant. However, in invasive helminthic infections, such as hookworm, schistosomiasis, strongyloidiasis, toxo cariasis, trichinosis, filariasis, echinococcosis, and

cysticercosis, the eosinophil plays a central role in host defense. Recently, eosinophils have been recognized as important in the host response to tuberculosis. Eosinophils are associated with bronchial asthma, cutaneous allergic reactions, and other hypersensitivity states. The distinctive feature of the red-staining (Wright's stain) eosino phil granule is its crystalline core consisting of an arginine-rich pro tein (major basic protein) with histaminase activity, important in host defense against parasites. Eosinophil granules also contain a unique eosinophil peroxidase that catalyzes the oxidation of many substances by hydrogen peroxide and may facilitate killing of microorganisms. Eosinophil peroxidase, in the presence of hydrogen peroxide and halide, initiates mast cell secretion in vitro and thereby promotes inflammation. Eosinophils contain cationic proteins, some of which bind to heparin and reduce its anticoagulant activity. Eosinophil-derived neurotoxin and eosinophil cationic protein are ribonucleases that can kill respiratory syncytial virus. Eosinophil cytoplasm contains CharcotLeyden crystal protein, a hexagonal bipyramidal crystal first observed in a patient with leukemia and then in sputum of patients with asthma; this protein is lysophospholipase and may function to detoxify certain lysophospholipids. Several factors enhance the eosinophil's function in host defense. T cell–derived factors enhance the ability of eosinophils to kill para sites. Mast cell–derived eosinophil chemotactic factor of anaphylaxis (ECFa) increases the number of eosinophil complement receptors and enhances eosinophil killing of parasites. Eosinophil CSFs (e.g., IL-5) produced by macrophages increase eosinophil production in the bone marrow and activate eosinophils to kill parasites. ■ ■EOSINOPHILIA Eosinophilia is the presence of >500 eosinophils per µL of blood and is common in many settings besides parasite infection. Significant tissue eosinophilia can occur without an elevated blood count. A common cause of eosinophilia is allergic reaction to drugs (iodides,

aspirin, sulfonamides, nitrofurantoin, penicillins, and cephalospo rins). Allergies such as hay fever, asthma, eczema, serum sickness, allergic vasculitis, and pemphigus are associated with eosinophilia. Eosinophilia also occurs in collagen vascular diseases (e.g., rheuma toid arthritis, eosinophilic fasciitis, allergic angiitis, and periarteritis nodosa) and malignancies (e.g., Hodgkin disease; mycosis fungoides; chronic myeloid leukemia; and cancer of the lung, stomach, pan creas, ovary, or uterus), as well as in dominant negative STAT3 (Job's syndrome), DOCK8 deficiency (see below), and CGD. Eosinophilia is commonly present in helminthic infections. IL-5 is the dominant eosinophil growth factor. Therapeutic administration of the cyto kines IL-2 or GM-CSF frequently leads to transient eosinophilia. The most dramatic hypereosinophilic syndromes are Loeffler's syndrome, tropical pulmonary eosinophilia, Loeffler's endocarditis, eosinophilic leukemia, and idiopathic hypereosinophilic syndrome (50,000–100,000/µL). IL-5 is the dominant eosinophil growth factor and can be specifically inhibited with monoclonal antibodies against it or its receptor. The idiopathic hypereosinophilic syndromes are a heterogeneous group of disorders with the common feature of prolonged eosinophilia of unknown cause and organ system dysfunction, including the heart, central nervous system, kidneys, lungs, gastrointestinal tract, and skin. The bone marrow is involved in all affected individuals, but the most severe complications involve the heart and central nervous system. Clinical manifestations and organ dysfunction are highly variable. Eosinophils are found in the involved tissues and likely cause tissue damage by local deposition of toxic eosinophil proteins such as eosino phil cationic protein and major basic protein. In the heart, the patho logic changes lead to thrombosis, endocardial fibrosis, and restrictive endomyocardiopathy. The damage to tissues in other organ systems is similar. Some cases are due to mutations involving the platelet-

derived growth factor receptor, and these are extremely sensitive to the tyrosine kinase inhibitor imatinib. Glucocorticoids, hydroxyurea, and IFN-α each have been used successfully, as have therapeutic antibodies against IL-5 or its receptor. Cardiovascular complications are managed aggressively. 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 (eosinophil count

> 1000/μL) and generalized disabling myalgias without other recog nized causes. Eosinophilic fasciitis, pneumonitis, and myocarditis; neuropathy culminating in respiratory failure; and encephalopathy may occur. The disease is thought to be caused by ingesting con taminants in L-tryptophan–containing products. Eosinophils, lym phocytes, macrophages, and fibroblasts accumulate in the affected tissues, but their role in pathogenesis is unclear. Activation of eosino phils and fibroblasts and the deposition of eosinophil-derived toxic proteins in affected tissues may contribute. IL-5 and transforming growth factor β have been implicated as potential mediators. Treat ment is withdrawal of products containing L-tryptophan and the administration of glucocorticoids. Most patients recover fully, remain stable, or show slow recovery, but the disease can be fatal in up to 5% of patients. Eosinophilic neoplasms are discussed in Chap. 115. ■ ■EOSINOPENIA Eosinopenia occurs with stress, such as acute bacterial infection, and after treatment with glucocorticoids. The mechanism of eosinopenia of acute bacterial infection is unknown but is independent of endogenous glucocorticoids, because it occurs in animals after total adrenalectomy. There is no known adverse effect of eosinopenia. HYPERIMMUNOGLOBULIN E–RECURRENT INFECTION SYNDROME The hyperimmunoglobulin E–recurrent infection syndrome, Job's syndrome, is a rare multisystem disease in which the immune and somatic systems are affected, including neutrophils, monocytes, T cells, B cells, and osteoclasts. Autosomal dominant negative

mutations in signal transducer and activator of transcription 3 (STAT3) impair normal STAT signaling with broad and profound effects. Patients have characteristic facies with broad nose, kypho scoliosis, and eczema. Primary teeth erupt normally but do not deciduate, often requiring extraction. Recurrent sinopulmonary and cutaneous infections tend to elicit much less inflammation than appropriate for the degree of infection, leading to "cold abscesses." Pneumonias typically cavitate, leading to pneumatoceles. Coronary artery aneurysms are common, as are cerebral demyelinated plaques that accumulate with age. IL-17–producing T cells, which are thought responsible for protection against extracellular and muco sal infections, are reduced in Job's syndrome. Despite very high IgE levels, Job's patients have only mildly elevated levels of allergy. Patients with autosomal recessive defects in dedicator of cytokinesis 8 (DOCK8) also have very high IgE levels joined to severe allergy, extensive viral susceptibility, and increased rates of cancer. Autoso mal dominant gain-of-function (GOF) mutations in STAT3 lead to a disease characterized by onset in childhood of lymphadenopathy, autoimmune cytopenias, multiorgan autoimmunity, infections, and interstitial lung disease. LABORATORY DIAGNOSIS AND MANAGEMENT A complete blood count (CBC) and differential are essential. Careful examination of

neutrophils on peripheral blood smears can diagnose CHS and suggest other neutrophil granule abnormalities such as spe cific granule deficiency. Bone marrow examination, where indicated, should be accompanied by either gene panel or whole exome/genome sequencing if genetic defects are suspected. Bone marrow reserves (ste roid challenge test), marginated circulating pool of cells (epinephrine challenge test), and marginating ability (endotoxin challenge test) are also doable (Fig. 67-8). In vivo assessment of inflammation is possible with a Rebuck skin window test or an in vivo skin blister assay, which measure the ability of leukocytes and inflammatory mediators to accumulate locally in the skin. In vitro tests of phagocyte aggregation, adherence, chemotaxis, phagocytosis, degranulation, and microbicidal activity may help pinpoint cellular or humoral lesions. CGD is detected with either the nitroblue tetrazolium (NBT) dye test or the DHR oxida tion test. These tests are based on the ability of products of oxidative metabolism to alter the oxidation states of reporter molecules so that they can be detected microscopically (NBT) or by flow cytometry (DHR). While the DHR is very sensitive for CGD, impaired DHR responses are seen in myeloperoxidase deficiency and with acetamino phen ingestion. Patients with leukopenias or leukocyte dysfunction often have delayed inflammatory responses. Therefore, clinical manifestations may be minimal despite overwhelming infection, and unusual infec tions must always be suspected. Early signs of infection demand prompt, aggressive culturing for microorganisms, use of antibiotics, and drainage of abscesses. Prolonged courses of antibiotics are often required. In patients with CGD, prophylactic antibiotics (trime thoprim-sulfamethoxazole) and antifungals (itraconazole) markedly diminish the frequency of life-threatening infections. Glucocorti coids may relieve gastrointestinal or genitourinary tract obstruction by granulomas in patients with CGD. Although TNF-α-blocking agents may markedly relieve inflammatory bowel symptoms, extreme caution must be exercised in their use in CGD inflammatory bowel disease, because it profoundly increases these patients’ already heightened susceptibility to infection. Recombinant human IFN-γ, which nonspecifically stimulates phagocytic cell function, reduces the frequency of infections in patients with CGD by 70% and reduces the severity of infection. This effect of IFN-γ in CGD is additive to the effect of prophylactic antibiotics. The recommended dose is 50 μg/m2 subcutaneously three times weekly. IFN-γ has also been used success fully in the treatment of leprosy, nontuberculous mycobacteria, and visceral leishmaniasis.

Rigorous oral hygiene reduces but does not eliminate the dis comfort of gingivitis, periodontal disease, and aphthous ulcers; chlorhexidine mouthwash and tooth brushing with a hydrogen peroxide–sodium bicarbonate paste also helps many patients. Oral antifungal agents (fluconazole, itraconazole, voriconazole, posacon azole) have reduced mucocutaneous candidiasis in patients with Job’s syndrome. Recombinant G-CSF is useful in the management of certain forms of neutropenia due to depressed neutrophil production, including those related to cancer chemotherapy. Patients with chronic neutropenia with evidence of a good bone marrow reserve need not receive prophylactic antibiotics. Patients with chronic or cyclic neutrophil counts <500/μL may benefit from prophylactic antibiot ics and G-CSF during periods of neutropenia. Oral trimethoprimsulfamethoxazole (160/800 mg) twice daily can prevent infection. Increased numbers of fungal infections are not seen in patients with CGD on this regimen. Oral quinolones such as levofloxacin and cip rofloxacin are alternatives.

Disorders of Granulocytes and Monocytes CHAPTER 67 In the setting of cytotoxic chemotherapy with severe, persistent lymphocyte dysfunction, trimethoprim-sulfamethoxazole prevents Pneumocystis jirovecii pneumonia. These patients, and patients with phagocytic cell dysfunction,

should avoid heavy exposure to airborne soil, dust, or decaying matter (mulch, manure), which are often rich in Nocardia and the spores of Aspergillus and other fungi. Restriction of activities or social contact has no proven role in reducing risk of infec tion for phagocyte defects. Although aggressive medical care for many patients with phagocytic disorders can allow them to go for years without a life-threatening infection, there may still be delayed effects of prolonged antimicrobi als and other inflammatory complications. Cure of most congenital phagocyte defects is possible by bone marrow transplantation, and rates of success are improving (Chap. 119). The identification of spe cific gene defects in patients with LAD1, CGD, and other immunode ficiencies has led to gene therapy trials in a number of genetic white cell disorders. ■ ■FURTHER READING

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