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as long as 24 hours before migrating through the vascular endothelium into the extravascular space, where they may survive for 1 to 3 days. Neutrophilia—defined as an increase in the circulating neutrophil count to greater than $7.5 \times 10^6/\mu\text{l}$, usually occurs as an acquired re- active response to underlying disease. Causes include (1) infection, particularly bacterial—the commonest cause of an elevated leuco- cyte count; (2) drugs (e.g. steroids); (3) malignancies—including myeloproliferative disorders and nonhaematological cancers; and (much less commonly) (4) hereditary conditions—including heredi- tary neutrophilia, leucocyte adhesion deficiency, and chronic idio- pathic neutrophilia. Neutropenia—defined as a reduction in the absolute neutrophil count to less than $1.5 \times 10^6/\mu\text{l}$, is of particular importance because, when severe ($<0.5 \times 10^6/\mu\text{l}$), it markedly increases the risk of life- threatening infection. Causes include (1) drugs and toxins. Mechanisms of drug-induced neutropenia include (a) direct marrow suppression, (b) immune destruction with antibody- or complement-mediated damage of myeloid precursors, and (c) peripheral destruction of neu- trophils; common offending drugs that cause dose-dependent neu- tropenia include cancer chemotherapeutic agents, phenothiazines, anticonvulsants, and ganciclovir; (2) postinfectious—particularly after viral infections; (3) nutritional deficiencies (e.g. vitamins B12, folic acid); (4) autoimmune—usually attributable in adults to disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis; (5) large granular lymphocytosis; and (6) congenital—including se- vere congenital neutropenia and cyclic neutropenia. Disorders of neutrophil function include (1) chronic granu- lomatous disease—a heterogeneous group of rare disorders (most X-linked) characterized by defective production of superoxide by neutrophils, monocytes, and eosinophils; patients usually present in childhood with severe infections, often with catalase-negative pathogens; (2) leucocyte adhesion deficiency; (3) myeloperoxidase deficiency; and (4) Chediak-Higashi syndrome. Monocytes and their disorders Monocytes share a common myeloid precursor with granulocytes, present antigens to T cells, produce several important cytokines with immunomodulatory and inflammatory functions, and are the 22.3 Myeloid disease

SECTION 22 Haematological disorders 5190 precursors to resident tissue macrophages. They are especially im- portant in defence against intracellular pathogens. Causes of monocytosis ($>0.9 \times 10^6/\mu\text{l}$) include (1) chronic in- fection (e.g. tuberculosis, endocarditis), (2) autoimmune diseases (e.g. SLE), and (3) malignancy (e.g. primary malignancies of the marrow or marrow infiltration with solid tumours). Basophils and their disorders Basophils are nonphagocytic granulocytes that function in immediate-type hypersensitivity. Basophilia ($> 0.2 \times 10^6/\mu\text{l}$) is seen in myeloproliferative disorders, hypersensitivity reactions, and with some viral infections. Introduction Leucocytes perform a critical role in the host defence against patho- gens. They mediate inflammation and modulate the immune re- sponse. Leucocytes can be divided into granulocytes (neutrophils, eosinophils, and basophils; Fig. 22.3.1.1), monocytes, and lympho- cytes. This chapter will focus on the role of granulocytes and mono- cytes in the normal host response and pathological manifestations of abnormalities of their number and/or function. Lymphocytes are discussed elsewhere. Neutrophils Morphology Under normal conditions, neutrophils make up over one-half of the leucocytes in the peripheral blood. The morphological hallmarks of these cells include heterogeneous granules and a multilobated or segmented nucleus. The two predominant types of granules in the neutrophil's cytoplasm are the azurophilic (or primary) granules and the specific (or secondary) granules. Azurophilic granules arise at the promyelocytic stage of differentiation. They contain myeloperoxidase, proteases, acid hydrolases, and microbicidal proteins. Specific granules and their content proteins are synthesized at the myelocytic stage of differentiation. Their contents include lactoferrin, lysozyme, vitamin B12-binding protein,

gelatinase, and neutrophil collagenase. The specific granules are not a uniform population, and their variable content is determined mainly by the timing of their formation. Those formed early in the myelocyte stage contain abundant lactoferrin, while those formed later are enriched for gelatinase, and are often referred to as 'tertiary' granules or gelatinase granules. The specific granule membrane contains the cytochrome b-558 component of the respiratory burst oxidase, as well as chemotactic and opsonic receptors, which are transferred to the plasma membrane upon activation of the neutrophil. Finally, the neutrophil cytoplasm also contains secretory vesicles that are endocytic vesicles containing primarily plasma proteins, and are the most rapidly mobilized fraction of cytoplasmic granules in the neutrophil. The membrane of secretory vesicles is rich in receptors and cytochrome b, and the vesicles contribute these proteins to the plasma membrane upon neutrophil activation. Common variants of neutrophil morphology include the Pelger-Huet anomaly, hypersegmentation of the nucleus, Dohle bodies, and toxic granulations. The Pelger-Huet anomaly is a dominantly inherited defect in nuclear segmentation that results in a dumb-bell- or rod-shaped nucleus. Neutrophils with nuclei similar to this ('pseudo-Pelger-Huet anomaly') may be seen in acquired myelodysplastic syndromes. Hypersegmented nuclei (containing five or more segments) are characteristic of megaloblastic haematopoiesis due to folic acid or vitamin B12 deficiency. Dohle bodies are large basophilic inclusions that may be seen in sepsis, pregnancy, and following cytotoxic chemotherapy. Toxic granulations are abnormally staining primary granules that arise when neutrophils are released prematurely from the marrow, as in severe bacterial infections.

Maturation There are three cellular compartments that contain myeloid cells: the marrow, the intravascular compartment, and the extravascular space. Maturation from the haematopoietic stem cell occurs in the bone marrow and takes from 10 to 14 days. The marrow compartment can be subdivided into the mitotic compartment and the postmitotic and storage compartment. In the marrow mitotic compartment, neutrophils arise through serial division of myeloid precursors. The mitotic compartment contains myeloid cells with the ability to replicate: myeloblasts, promyelocytes, and myelocytes. The marrow postmitotic and storage compartment contains myeloid elements that have lost the ability to divide, including metamyelocytes, bands, and segmented neutrophils. Neutrophils are released from the storage pool into the intravascular space, where they remain for 4 to 24 h. Within this space, approximately one-half of the neutrophils circulate freely in the peripheral blood while the other half remain 'marginated' along the vascular endothelium. The marginated and circulating cells are in dynamic equilibrium with one another. Neutrophils then migrate through the vascular endothelium into the extravascular space, where they survive for 1 to 3 days. At any given time, approximately 90% of neutrophils are in the marrow compartment and 2 to 3% are in the intravascular space, with the remainder in the extravascular space.

Neutrophilia Neutrophilia is defined as an elevation of the circulating neutrophil count ($>7.5 \times 10^6/\mu\text{l}$). Although it may reflect a primary haematological process, it usually occurs as a secondary manifestation of an underlying disease process or drug. The causes of an elevated neutrophil count are summarized in Box 22.3.1.1.

(a) (b) (c) Fig. 22.3.1.1 Peripheral blood granulocytes: (a) polymorphonuclear leucocyte (neutrophil), (b) eosinophil, (c) basophil.

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Hereditary neutrophilias Hereditary neutrophilia This is a dominantly inherited syndrome manifested by leucocytosis, splenomegaly, and widened diploë of the skull. Laboratory evaluation reveals a white blood count of 20 000 to 70 000/ μl with a neutrophilic predominance, and an elevated leucocyte alkaline phosphatase. Its clinical course is benign.

Chronic idiopathic neutrophilia This is a sporadically occurring condition that manifests as a white blood count of 11 000 to 40 000/ μl with a neutrophilic predominance. Patients are otherwise

well and have been followed for up to 20 years without the development of significant pathology.

Leucocyte adhesion deficiency This is a rare inherited disorder characterized by recurrent life-threatening bacterial and fungal infections, cutaneous abscesses, gingivitis, or periodontal infections. Expression of the CD11b/CD18 integrin is deficient, resulting in the inability of neutrophils to migrate to sites of infection (see 'Disorders of neutrophil function' for further discussion).

Acquired neutrophilias

Infection The most common cause of an elevated leucocyte count is infection. Acute infection often causes a modest rise in the white blood count, which may be accompanied by an increase in circulating immature precursors ('left shift'). This occurs more commonly with bacterial infection but can also occur with viral processes. Along with a left shift, morphological changes in the neutrophil may be seen with bacterial infection, including toxic granulation, Dohle bodies, and cytoplasmic vacuoles. Neutrophilia resolves with treatment or resolution of the infectious process. In chronic inflammation, marrow granulocyte production is stimulated, resulting in moderate neutrophilia, sometimes with monocytosis. Chronic infections such as osteomyelitis, empyema, and tuberculosis can also give rise to a leukaemoid reaction with white blood counts markedly elevated ($>50\,000/\mu\text{l}$), usually associated with a marked left shift.

Drugs Drugs can cause leucocytosis by several different mechanisms. Steroids increase the release of mature neutrophils from the marrow and should not cause a left shift. β -Agonists acutely raise the neutrophil count by inducing the demargination of neutrophils adherent to the vascular endothelium, and may result in a neutrophil count twice that of baseline. Acute stress also results in demargination of neutrophils, which is probably mediated by adrenergic stimulation. Stresses that can cause this include exercise, surgery, seizure, and myocardial infarction. The cytokines granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulate marrow production of neutrophils and can cause dramatic elevations in the white blood count. The majority of white cells formed are neutrophils and a left shift is often seen. The use of these cytokines therefore requires careful monitoring.

Primary haematological conditions In other situations, neutrophilia may reflect a primary haematological condition. Marrow hyperstimulation in the setting of autoimmune haemolytic anaemia, immune thrombocytopenia, or recovery following chemotherapy or toxic insult to the marrow may result in a reactive leucocytosis. In autoimmune haemolytic anaemia and immune thrombocytopenia, neutrophilia may reflect disease activity, but steroid therapy or splenectomy may contribute. Splenectomy or hyposplenic states (e.g. sickle cell disease) may also result in modest neutrophilia at baseline with more marked neutrophilia at times of stress or infection, reflective of the loss of the spleen as a site of margination and sequestration of leucocytes.

Myeloproliferative disorders Neutrophilia is a common feature of the myeloproliferative disorders chronic myeloid leukaemia, polycythaemia vera, and myelofibrosis as well as familial myeloproliferative disorders. Elevated eosinophil and basophil counts are also often seen in these disorders. Leucocyte alkaline phosphatase may be low or undetectable in chronic myeloid leukaemia. The myeloproliferative disorders are discussed in further detail elsewhere.

Nonhaematological malignancies Various nonhaematological malignancies including lung and breast tumours may also cause neutrophilia. Tumours may secrete colony-stimulating factors or may cause a leukaemoid reaction.

Tumour

Box 22.3.1.1 Differential diagnosis of neutrophilia

Primary haematological disease

- Chronic idiopathic neutrophilia
- Hereditary neutrophilia
- Leucocyte adhesion deficiency
- Myeloproliferative disorders:

— Chronic myeloid leukaemia

- Polycythaemia vera
- Myelofibrosis Secondary to other disease processes or drugs • Infection:
- Acute
- Chronic • Acute stress:
- Exercise
- Surgery
- Seizure
- Myocardial infarction • Drugs:
- Steroids
- Lithium
- β -Agonists
- Cytokines (G-CSF, GM-CSF) • Chronic inflammation • Marrow infiltration • Marrow hyperstimulation:
- Chronic haemolysis
- Immune thrombocytopenia
- Recovery from marrow suppression • Postsplenectomy/hyposplenism • Nonhaematological neoplasms

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chronic myeloid leukaemia in this setting), and assay for mutations in JAK2 (for diagnosis of polycythemia vera and other non-bcr-abl-positive myeloproliferative syndromes). Evaluation for myeloproliferative disease is discussed in detail elsewhere.

Neutropenia Neutropenia is defined as an absolute neutrophil count (ANC) of less than $1.5 \times 10^6/\mu\text{l}$. In some populations, such as Africans and Yemeni Jews, normal ANCs are lower, with a lower limit of normal of $1.2 \times 10^6/\mu\text{l}$. Neutropenia may pose a risk of serious bacterial infection, and this risk is directly related to the degree of neutropenia. In mild neutropenia (ANC $1000\text{--}1500 \times 10^6/\mu\text{l}$) the risk of life-threatening infection is not increased, and in moderate neutropenia (ANC $500\text{--}1000 \times 10^6/\mu\text{l}$) the risk of severe infection is only mildly elevated. Severe neutropenia (ANC $<500 \times 10^6/\mu\text{l}$) markedly increases the risk of life-threatening infection. The duration and timecourse of neutropenia may also be important, as the acute onset of severe neutropenia is associated with a higher risk of serious infection than is chronic neutropenia of similar severity. Neutropenia in the setting of marrow failure is more threatening than neutropenia with an intact marrow, as the marrow reserve pool may afford protection. Fever of new onset in the setting of severe neutropenia is a medical emergency requiring immediate evaluation and treatment. Common causes of infection in these patients include Gram-negative enteric pathogens such as *Escherichia coli*, *Pseudomonas*, and *Klebsiella pneumoniae*, as well as *Staphylococcus aureus*. The causes of neutropenia are summarized in Box 22.3.1.2.

Congenital neutropenia Severe congenital neutropenia Severe congenital neutropenia (SCN), originally characterized by Rolf Kostmann as an autosomal recessive disorder (Kostmann's syndrome), is characterized by severe persistent neutropenia, and the early onset of frequent, life-threatening infections. Bone marrow aspirate reveals a maturation arrest at the promyelocyte stage. This syndrome was originally described as an autosomal recessive disorder, but recent evidence suggests that SCN is a heterogeneous disorder with autosomal dominant, autosomal recessive, X-linked, and sporadic forms. Autosomal dominant SCN has been linked to mutations in the gene encoding neutrophil elastase (ELANE), a primary granule protein gene expressed at high levels at the promyelocyte stage of differentiation. Current evidence suggests that the impact of the mutations is not related to the enzymatic function of elastase, but rather reflects the failure of the protein to fold properly. This induces the 'unfolded protein response', a protective response to cellular stress that leads to decreased protein synthesis, degradation of unfolded proteins in the endoplasmic reticulum, and increased apoptosis. Autosomal recessive SCN (Kostmann's syndrome) is caused by mutations in HAX-1, a mitochondrial protein that is important for stabilizing the inner mitochondrial membrane. Homozygous loss of HAX-1 leads to loss of mitochondrial membrane potential, and also Box 22.3.1.2

Differential diagnosis of neutropenia

Decreased production of neutrophils • Constitutional neutropenia • Congenital neutropenias:

- Severe congenital neutropenia (including Kostmann's syndrome)
- Shwachman-Diamond-Oski syndrome
- Chediak-Higashi syndrome
- Reticular dysgenesis
- Dyskeratosis congenita • Cyclic neutropenia • Postinfectious • Nutritional deficiency:
- Vitamin B12

- Folic acid
- Copper • Anorexia nervosa • Drug or toxin induced • Primary marrow failure:
- Aplastic anaemia
- Myelodysplastic syndromes
- Acute leukaemia
- Paroxysmal nocturnal haemoglobinuria
- Pure white-cell aplasia
- Shwachman-Diamond-Oski syndrome
- Chediak-Higashi syndrome
- Reticular dysgenesis
- Dyskeratosis congenita
- Large granular lymphocytosis Increased peripheral destruction of neutrophils • Overwhelming infection • Immune destruction:
- Drug related
- Collagen vascular disease associated
- Large granular lymphocytosis
- Felty's syndrome
- Isoimmune • Hypersplenism/sequestration

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and lasting 3 to 7 days. Along with the neutropenia, cyclic drops in the reticulocyte and monocyte counts are also observed. Episodes of neutropenia may be severe, often with an ANC less than $200 \times 10^6/\mu\text{l}$, and may be accompanied by fevers, pharyngitis, stomatitis, and other bacterial infections. Cyclic neutropenia has also been linked to mutations in the neutrophil elastase gene. Why some mutations give rise to cyclic haemato- poiesis and others to SCN is still a matter of speculation. This has led to the hypothesis that the severity of the phenotype is re- lated to the degree of abnormal protein folding and induction of the unfolded protein response associated with different ELANE mutations. Cyclic neutropenia can be treated safely and effect- ively with G-CSF. Unlike Kostmann's syndrome, cyclic haemato- poiesis is not associated with an increased incidence of AML and MDS.

Acquired neutropenias

Postinfectious neutropenia This is commonly seen following viral infections. It usually occurs several days after the onset of infection and may last several weeks. Varicella zoster, measles, Epstein-Barr, cytomegalovirus, influenza A and B, and hepatitis A and B are some of the viruses most com- monly associated with postinfectious neutropenia. The neutropenia resolves spontaneously. Transient neutropenia may also be seen with parvovirus infection. Neutropenia occurs commonly in patients with HIV. The causes are multifactorial and may be related directly to the viral infection, to opportunistic infections or associated con- ditions, or to the treatment of the virus or its complications. Several bacterial infections can cause neutropenia, including rickettsial infections, typhoid fever, brucellosis, and tularaemia. Bacterial sepsis of any cause can also result in acute neutropenia. This occurs both as a result of marrow suppression and increased destruction of neutrophils. Acute neutropenia in bacterial infections suggest that egress to tissue exceeds the capacity of the marrow re- serve pool. The neutropenia may be severe and it portends a poor prognosis. Fungal infections, such as disseminated histoplasmosis, and mycobacterial diseases may also cause neutropenia.

Nutritional deficiencies Nutritional deficiencies of vitamins B12 and folic acid result in meg- aloblastic haematopoiesis with ineffective myelopoiesis. Deficiency of copper is a rare nutritional cause of neutropenia seen in the set- ting of severe malnutrition or long-term parenteral alimentation. Mild neutropenia may also be seen with anorexia nervosa.

Drugs and toxins Numerous drugs and toxins are known to cause neutropenia. Mechanisms of drug-induced neutropenia include (1) direct marrow suppression, (2) immune destruction with antibody- or complement-mediated damage of myeloid precursors, and (3) per- ipheral destruction of neutrophils. In most cases, direct marrow suppression is dose dependent. Common offending drugs that cause dose-dependent neutropenia include cancer chemotherapeutic agents, phenothiazines, anticonvulsants, and ganciclovir. Alcohol can also cause neutropenia by marrow suppression. If a drug is suspected of causing dose-dependent neutropenia, resolution will occur promptly upon discontinuation of the offending agent. However, if it is not possible to stop the drug and the neutropenia is not severe, the drug may be continued with careful monitoring. Neutropenia is often related to the dose and duration of therapy. In contrast, those drugs that cause immune neutropenia usually cause profound agranulocytosis, resulting from both intramedullary destruction of myeloid precursors and peripheral destruction of mature neutrophils. Such drugs include antithyroid medications, sulphonamides, and semisynthetic penicillins. Examination of the bone marrow shows a maturation arrest of the myeloid lineage, re- flecting immune destruction of myeloid precursors. The offending agent must be stopped and rechallenge should not be attempted. Recovery of the neutrophil count can be accelerated by the admin- istration of G-CSF.

Autoimmune neutropenia Primary autoimmune neutropenia is a disease of childhood, with an average age of onset of 6 to 12 months. Patients present with mod- erate to severe neutropenia that spontaneously remits within 2 years in 95% of patients. Treatment with prophylactic

antibiotics prevents most serious complications, and G-CSF therapy is recommended only in the setting of severe or recurrent infections. Secondary autoimmune neutropenia is seen primarily in adults, and may occur in association with collagen vascular disorders such as systemic lupus erythematosus and rheumatoid arthritis, as well as with immune thrombocytopenia and autoimmune haemolytic anaemia. Destruction may be mediated by IgG or IgM antibodies. The neutropenia may be severe but the degree of neutropenia frequently does not correlate as well with the risk of infection as in other conditions. The marrow typically is hypercellular with a late myeloid maturation arrest. Treatment is indicated in the setting of severe, recurrent infections. Treatment options include intravenous immunoglobulin, splenectomy, and other therapies directed at the underlying collagen vascular disorder. In Felty's syndrome, neutropenia accompanies rheumatoid arthritis and splenomegaly and neutropenia probably reflects both immune destruction and splenic sequestration. Granulopoiesis is inhibited by either antibodies or T-cells. This can lead to severe and recurrent infections. It may be managed with G-CSF.

Splenectomy

SECTION 22 Haematological disorders 5194 relieves the neutropenia in the majority of cases. However, given its close association with large granular lymphocytosis (see following section), treatment with low-dose methotrexate or cyclophosphamide is the chosen approach in many patients. Large granular lymphocytosis Large granular lymphocytosis occurs in an older population, and is frequently seen in association with rheumatological diseases such as rheumatoid arthritis. Due to the association with systemic inflammatory disease, large granular lymphocytosis was originally hypothesized to be a polyclonal abnormal immune response. However, gene rearrangement studies have confirmed that large granular lymphocytosis is frequently a clonal disease representing a form of T-cell lymphoma. There are two distinct subtypes, with cells expressing either an unusual T γ phenotype (CD3+CD8+CD56-) or a natural killer (NK) phenotype (CD56+). When seen in association with rheumatoid arthritis, the disease has significant overlap with Felty's syndrome. Both large granular lymphocytosis and Felty's syndrome are associated with a very high frequency (80–90%) of HLA D4, and investigators now believe that these diseases represent a spectrum of a single disease. Neutropenia related to large granular lymphocytosis is associated with a myeloid maturation arrest in the marrow, consistent with immune-mediated neutrophil destruction. Surprisingly, however, the neutrophil count will often respond to G-CSF. The neutropenia responds well to low-dose methotrexate or cyclophosphamide in 50% of patients, and other immunosuppressive agents also have activity in restoring neutrophil counts. The course of lymphoma in large granular lymphocytosis varies from indolent to rapidly progressive. Other causes Aplastic anaemia reflects a primary failure of haematopoiesis with neutropenia, anaemia, and thrombocytopenia. In the myelodysplastic syndromes and acute leukaemias, the marrow does not produce adequate numbers of neutrophils. Isoimmune neutropenia occurs in 1 in 500 babies born alive. It is caused by placental transfer of maternal IgG directed against fetal neutrophils, and it presents in the first days of life. Hypersplenism usually causes mild or moderate neutropenia along with anaemia and thrombocytopenia. Normal myeloid maturation is seen in the marrow. The neutropenia is rarely severe. Evaluation of neutropenia In contrast to the evaluation of neutrophilia, most patients with confirmed neutropenia require bone marrow examination. A comprehensive history and physical examination may identify the occasional patient with mild neutropenia and no other evidence of disease that may warrant close observation only. However, recurrent infections, including oral and mucosal infections, abnormalities observed in a peripheral blood smear, or severe neutropenia increase the likelihood of significant marrow

pathology and marrow aspiration and biopsy is indicated. If neutropenia is accompanied by anaemia or thrombocytopenia, marrow examination is required to rule out aplasia, leukaemia, myelodysplasia, or other primary marrow malignancy. A marrow that shows hyperplastic myeloid precursors and a maturation arrest supports a diagnosis of peripheral neutrophil destruction and/or immune neutropenia, which should lead to a search for an underlying collagen vascular disorder or drug-induced neutropenia. Management of neutropenia

Fever of new onset in the setting of severe neutropenia ($\text{ANC} < 500 \times 10^6/\mu\text{l}$) is a medical emergency. A careful history and physical examination should be performed in a timely fashion. Due to the lack of neutrophils, sites of infection may be difficult to find as significant inflammation or tissue infiltration by neutrophils may not occur. Blood and bodily fluids should be cultured. Empirical broad-spectrum antibiotics should be initiated without delay. In patients with fever in the setting of neutropenia that is expected to resolve (usually neutropenia induced by chemotherapy or drug reaction), antibiotics should be continued until the neutrophil count recovers to over $500/\mu\text{l}$. In patients with chronic neutropenia that is expected to persist indefinitely, antibiotics should be continued for several days past the resolution of fever. If fever persists for more than 1 week despite antibiotic therapy, empirical antifungal therapy should be given. Granulocyte transfusion should be considered in culture-positive Gram-negative sepsis not responsive to antibiotics in the setting of continued neutropenia. Granulocyte colony-stimulating factor G-CSF (filgrastim) is a haematopoietic growth factor that has effects primarily on the neutrophilic myeloid lineage. G-CSF reduces the time of maturation of committed neutrophil precursors, prolongs the lifespan of mature neutrophils, and primes them for enhanced function of the respiratory burst, phagocytosis, and chemotaxis. Clinically, G-CSF is used in the treatment and prevention of neutropenia. When used in conjunction with myelosuppressive chemotherapy, G-CSF has been shown to reduce the severity of neutropenia, shorten the duration of neutropenia, reduce the risk of developing neutropenic fever, and reduce the length of stay in hospital. G-CSF has also been utilized successfully in the treatment of severe neutropenia secondary to congenital disorders such as cyclic neutropenia and SCN, and may be useful in the treatment of autoimmune neutropenia as seen in Felty's syndrome and systemic lupus erythematosus. The neutropenia of marrow failure states, such as the myelodysplastic syndromes, may respond to G-CSF. Neutropenia secondary to the treatment of HIV infection can also be controlled with G-CSF. The other major use of G-CSF is in the mobilization of haematopoietic progenitor cells from the bone marrow to the peripheral blood. While in the peripheral blood, these cells can be collected by cytopheresis for use in haematopoietic cell transplantation.

Disorders of neutrophil function

Chronic granulomatous disease

Chronic granulomatous disease is a heterogeneous group of rare disorders characterized by defective production of superoxide (O_2^-) by neutrophils, monocytes, and eosinophils. The majority of cases are inherited in an X-linked fashion, but autosomal recessive inheritance also occurs. The genetic lesions causing chronic granulomatous disease have been characterized, and involve mutations in any of four genes encoding the proteins of the respiratory burst oxidase. These include the 91-kDa (X-linked) and 22-kDa (autosomal) components of the membrane cytochrome b-558 complex, and the 47- and 67-kDa soluble components (autosomal) of the

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oxidase complex. Patients usually present in childhood with severe infections, often with catalase-negative pathogens. The most common infection in patients with chronic granulomatous disease is pneumonia, with *S. aureus*, *Burkholderia cepacia*, *aspergillus*, and enteric Gram-negative bacteria often implicated. Other common infections in chronic granulomatous disease include lymphadenitis, cutaneous infections,

hepatic abscesses, and osteomyelitis. Noninfectious inflammatory conditions, such as aphthous ulceration of the oral mucosa are common, as are chronic mucosal inflammation, perirectal abscesses or fissures, and granulomas of the gastrointestinal and genitourinary tract. The diagnosis of chronic granulomatous disease should be considered in an individual with a history of multiple severe bacterial and fungal infections or a family history of the disorder. The diagnosis is established by confirming abnormal neutrophil oxidative metabolism with tests such as the nitroblue tetrazolium slide test or measurements of superoxide or peroxide production. The management of chronic granulomatous disease is based on aggressive prophylaxis and prompt treatment of infection. Prophylactic trimethoprim-sulphamethoxazole or penicillin can significantly decrease the number of bacterial infections in patients with chronic granulomatous disease. Potentially serious infections require the prompt initiation of parenteral antibiotics. Surgical interventions including drainage of abscesses and resection of infected tissue are an important adjunct to antimicrobial chemotherapy. Prophylaxis with recombinant human interferon- γ was shown in a phase III trial to decrease substantially the number of serious infections in patients with chronic granulomatous disease, although oxidase activity was unaffected. Chronic granulomatous disease has also been a target of early gene therapy trials.

Leucocyte adhesion deficiency Leucocyte adhesion deficiency is an inherited disorder of neutrophil function. Two types of leucocyte adhesion deficiency have been characterized. Type 1 deficiency is a rare autosomal recessive disorder resulting from mutations in CD18, the gene encoding the β -chain of leucocyte function antigen-1 (LFA-1, CD11a/CD18), Mac-1 (CD11b/CD18, CR3, the receptor for the opsonin C3Bi), and gp150,95 (CD11c/CD18). Deficient expression of these three integrin complexes on the neutrophil cell surface results in decreased neutrophil adhesion to the endothelium, impaired chemotaxis, and defective C3Bi-mediated pathogen ingestion, degranulation, and respiratory burst activation. Patients with leucocyte adhesion deficiency typically present in early childhood with recurrent pyogenic infections of the skin, respiratory and digestive tracts, and mucosal membranes. A history of delayed umbilical cord separation is also often noted. Common pathogens in patients with type 1 leucocyte adhesion deficiency include *S. aureus* and Gram-negative enterics. Foci of infection notably lack neutrophil infiltration. A mild leucocytosis persists due to impaired margination. The diagnosis is confirmed by flow cytometric measurement of neutrophil CD11b/CD18 expression. The treatment of type 1 leucocyte adhesion deficiency includes aggressive use of parenteral antibiotics for pyogenic infections. Prophylactic trimethoprim-sulphamethoxazole may benefit some patients. Patients with a severe phenotype often die in the first 2 years of life, but patients with mild disease may survive to early adulthood.

Type 2 leucocyte adhesion deficiency is caused by a deficiency of sialyl-Lewis X moieties on neutrophil selectins. In addition to neutrophil function abnormalities, this extremely rare syndrome also is characterized by mental retardation, short stature, and the rare Bombay erythrocyte phenotype.

Myeloperoxidase deficiency Myeloperoxidase deficiency is a relatively common, autosomal recessively inherited disorder of neutrophil function. Complete deficiency occurs in 1 in 2000 individuals and partial deficiency occurs twice as frequently. Myeloperoxidase catalyses the production of hypochlorous acid, which is an antimicrobial agent. Myeloperoxidase deficiency is often of no clinical consequence because other host defence mechanisms can adequately compensate for the defective myeloperoxidase; however, when myeloperoxidase deficiency coexists with another defect in host defence, such as diabetes mellitus, disseminated candidal or fungal infections may occur. The diagnosis of myeloperoxidase deficiency is made by histochemical staining of neutrophils and monocytes. Therapy consists of aggressive treatment of fungal infections as well as careful control of glucose levels in patients with diabetes. An acquired form of

myeloperoxidase deficiency occurs in some myeloid leukaemias. Chediak-Higashi syndrome (OMIM 214500) is a rare disorder of neutrophil function. Neutrophils and monocytes contain giant primary granules and demonstrate impaired degranulation and fusion with phagosomes. Chemotaxis is also defective. Neutropenia results from defective granulopoiesis. Chediak-Higashi syndrome is inherited in an autosomal recessive manner. The gene responsible, *LYST*, has been cloned, and is homologous to a murine lysosomal trafficking protein. Chediak-Higashi syndrome manifests in childhood or infancy with infections of the skin, lungs, and mucous membranes. *S. aureus*, Gram-negative enterics, candida, and aspergillus species are responsible for most infections in this syndrome. Nonhaematological manifestations of Chediak-Higashi syndrome include partial oculocutaneous albinism, progressive peripheral and cranial neuropathies, and in some cases, mental disability. The majority of patients will develop an accelerated phase of the syndrome, manifested by lymphohistiocytic proliferation in the liver, spleen, bone marrow, and lymphatics. The diagnosis of Chediak-Higashi syndrome is made by the demonstration of giant peroxidase-containing granules in peripheral blood or bone marrow myeloid cells, outside of the setting of myelogenous leukaemia. Chediak-Higashi syndrome is treated in the early or stable phase with prophylactic antibiotics and aggressive parenteral antibiotics for infections. Ascorbic acid may also be of benefit. The accelerated phase is treated with vinca alkaloids and glucocorticoids, but often responds poorly to these measures. Allogeneic haematopoietic cell transplantation from HLA-compatible donors is the only potentially curative therapy for Chediak-Higashi syndrome.

Specific granule deficiency An extremely rare disorder, neutrophil-specific granule deficiency is characterized by absent or empty neutrophil-specific granules. Specific granule deficiency is manifested clinically as recurrent skin and pulmonary infections resulting from the absence of antimicrobial neutrophil granule proteins such as lactoferrin and defensins. An inability to upregulate the expression of integrins stored on the specific granule membrane may also be responsible for the impairment

SECTION 22 Haematological disorders 5196 of host defence. The diagnosis of specific granule deficiency is made by microscopic examination of neutrophils. With appropriate antibiotic prophylaxis and aggressive treatment of infections, patients usually live to adulthood. A truncation mutation in the transcription factor *C/EBPε* has been demonstrated to be responsible for some, but not all, cases of specific granule deficiency.

Monocytes Monocytes are large circulating cells with a nonsegmented nucleus and cytoplasmic granules. They function as phagocytes both in antimicrobial defence and in clearing cellular debris. Their granules are essentially identical to neutrophil azurophilic granules, and contain acid hydrolases and myeloperoxidase. Monocytes are also capable of producing reactive oxygen and nitrogen compounds with microbicidal activity. Monocytes play a critical role in the immune response as they present antigens in the context of MHC to T-cells. They also produce a variety of immunomodulatory cytokines including interleukin (IL)-1 and -6, tumour necrosis factor- α , and interferon- β . Monocytes arise from bone marrow stem cells. They share a common myeloid precursor with granulocytes. The differentiation to the monocyte is modulated by several cytokines, most importantly monocyte CSF and granulocyte-monocyte CSF. The majority of monocytes are marginated to the vascular endothelium. Upon stimulation, they migrate to the tissue where they develop into macrophages. In the tissue they kill bacteria, mycobacteria, fungi, and protozoa. They are especially important in defence against intracellular pathogens. Specialized resident tissue macrophages include the Langerhans' cells of the skin, dendritic cells of lymph nodes, Kupffer's cells of the liver, and alveolar macrophages. Monocytosis is defined as a monocyte count of greater than $0.9 \times 10^6/\mu\text{l}$.

Disorders causing monocytosis are heterogeneous. Recovery of the marrow following chemotherapy or agranulocytosis is heralded by monocytosis prior to the return of neutrophils. Monocytosis is also seen in syndromes such as cyclic neutropenia, SCN, and idiopathic neutropenia. The most common causes of monocytosis include chronic infection, inflammation, or tumour, as well as some primary haematological disorders (Box 22.3.1.3). Chronic infections leading to monocytosis include subacute bacterial endocarditis and mycobacterial diseases. Monocytosis is typically moderate and resolves with treatment of the infection. Autoimmune processes such as systemic lupus erythematosus, rheumatoid arthritis, and vasculitis also cause moderate monocytosis. Monocytosis may arise from primary malignancies of the marrow or in the setting of marrow infiltration with solid tumours. Primary marrow disorders causing monocytosis include acute monocytic leukaemia, chronic myeloid leukaemia and other myeloproliferative disorders, and chronic myelomonocytic leukaemia, which has features of both myelodysplastic and myeloproliferative disorders. Juvenile chronic myeloid leukaemia is a rare disorder occurring in children less than 4 years of age. Lymphadenopathy and splenomegaly are also prominent features. Monocytopenia in isolation is uncommon. Monocytopenia is sometimes seen following steroid administration, endotoxaemia, or in marrow failure syndromes such as aplastic anaemia. It is also characteristic of hairy cell leukaemia.

Eosinophils Morphology Eosinophils have a bilobate nucleus and contain characteristic elliptical granules that stain with eosin. There are three types of eosinophil granules. Primary granules are round in shape. Secondary granules are abundant and contain crystalloid material, and account for the eosinophil's staining properties. The third type of granule is small and contains lysosomal enzymes. Granules contain high concentrations of eosinophil major basic protein, histaminase, eosinophil cationic protein, hydrolases, and peroxidase. Eosinophils are capable of phagocytic function but more commonly release their granule contents to the environment. Eosinophils are also capable of producing reactive oxygen species, and produce prostaglandins, thromboxane A₂, and leukotriene C₄. Eosinophils play a prominent role in defence against helminths and parasites. They arise in the marrow from a common myeloid precursor, and their production is dependent on GM-CSF, IL-3, and IL-5. Disorders associated with eosinophilia are discussed elsewhere (see Chapter 22.3.8); causes of eosinophilia are listed in Box 22.3.1.4.

Basophils Basophils are rare circulating cells, accounting for less than 0.1% of white blood cells. They are nonphagocytic granulocytes. Their large heterogeneous granules account for their purple-black staining. Their granules contain histamine, heparin, tryptase, chemotactic factors

Box 22.3.1.3 Causes of monocytosis

Inflammatory diseases

- Infectious diseases:

- Tuberculosis

- Syphilis

- Subacute bacterial endocarditis

- Fungal infections

- Kala-azar

- Brucellosis
- Autoimmune processes:

— Systemic lupus erythematosus

— Rheumatoid arthritis

— Polyarteritis

— Inflammatory bowel disease

— Sarcoidosis Malignancy • Acute myeloid leukaemia • Chronic myeloid leukaemia • Chronic myelomonocytic leukaemia • Juvenile chronic myeloid leukaemia • Hodgkin disease • Non-Hodgkin lymphoma • Histiocytoses • Solid tumours Miscellaneous • Chronic neutropenia • Post-splenectomy • Marrow recovery

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