Chapter 12

The Hematopoietic and Lymphoid Systems

JON C. ASTER, MD, PhD

RED CELL DISORDERS

Anemia of Blood Loss: Hemorrhage
The Hemolytic Anemias
Hereditary Spherocytosis
Sickle Cell Anemia
Thalassemia
  β-Thalassemia
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Glucose-6-Phosphate Dehydrogenase Deficiency
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Aplastic Anemia
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Laboratory Diagnosis of Anemias

Polycythemia

WHITE CELL DISORDERS

Non-Neoplastic Disorders of White Cells
Leukopenia
  Neutropenia/Agranulocytosis
Reactive Leukocytosis
  Infectious Mononucleosis
Reactive Lymphadenitis
  Acute Nonspecific Lymphadenitis
  Chronic Nonspecific Lymphadenitis
  Cat Scratch Disease

Neoplastic Proliferations of White Cells
Lymphoid Neoplasms
  Precursor B- and T-Cell Lymphoblastic

Leukemia/Lymphoma
Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia
Follicular Lymphoma
Mantle Cell Lymphoma
Diffuse Large B-Cell Lymphoma
Burkitt Lymphoma
Multiple Myeloma and Related Plasma Cell Disorders
Hodgkin Lymphoma
Miscellaneous Lymphoid Neoplasms
Myeloid Neoplasms
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BLEEDING DISORDERS

Disseminated Intravascular Coagulation
Thrombocytopenia
  Immune Thrombocytopenic Purpura
  Heparin-Induced Thrombocytopenia
  Thrombotic Microangiopathies: Thrombotic
    Thrombocytopenic Purpura and Hemolytic-Uremic Syndrome
**Coagulation Disorders**
Deficiencies of Factor VIII/von Willebrand Factor Complex
- von Willebrand Disease
- Factor VIII Deficiency (Hemophilia A, Classic Hemophilia)
- Factor IX Deficiency (Hemophilia B, Christmas Disease)

Disorders of the hematopoietic and lymphoid systems encompass a wide range of diseases that are traditionally sorted into disorders that primarily affect red cells, white cells, or the hemostatic system, which includes platelets and clotting factors. The most common red cell disorders lead to anemia, a state of red cell deficiency. White cell disorders, in contrast, are most often caused by excess proliferation, which usually has a neoplastic basis. Hemostatic derangements result in hemorrhagic diatheses (bleeding disorders). Finally, splenomegaly, a feature of several hematopoietic diseases, is discussed at the end of the chapter, as are tumors of the thymus.

Although these divisions are useful, in reality the production, function, and destruction of red cells, white cells, and components of the hemostatic system are closely linked, and pathogenic derangements primarily affecting one cell type or component of the system often lead to alterations in others. For example, in certain conditions B lymphocytes make autoantibodies against components of the red cell membrane. The opsonized red cells are recognized and destroyed by phagocytes in the spleen, which becomes enlarged. The increased red cell destruction causes anemia, which in turn drives a compensatory hyperplasia of red cell progenitors in the bone marrow.

Other levels of interplay and complexity stem from the dispersed nature of the lymphohematopoietic system, which is not confined to a single anatomic site. When considering hematopoietic disorders, it is important to remember that both normal and malignant lymphoid and hematopoietic cells “traffic” between various compartments. Hence, a patient who is diagnosed by lymph node biopsy to have a malignant lymphoma may also be found to have neoplastic lymphocytes in the bone marrow and blood. The malignant lymphoid cells in the marrow may suppress hematopoiesis, giving rise to cytopenias, and the further seeding of tumor cells to the liver and spleen may cause organomegaly. Thus, in both benign and malignant hematolymphoid disorders, a single underlying abnormality can result in diverse systemic manifestations.

**RED CELL DISORDERS**

Disorders of red cells can result in anemia or, less commonly, polycythemia (i.e., an increase in the number of red cells). Anemia is a reduction in the oxygen-transporting capacity of blood, which usually stems from a reduction of the total circulating red cell mass to below-normal amounts.

Anemia can result from excessive bleeding, increased red cell destruction, or decreased red cell production. These mechanisms serve as a basis for classifying anemias (Table 12–1). With the exception of the anemia of chronic renal failure, in which erythropoietin-producing cells in the kidney are lost, the decrease in tissue oxygen tension that attends anemia usually triggers increased erythropoietin production. This drives a compensatory hyperplasia of erythroid precursors in the bone marrow and, in severe anemias, the appearance of extramedullary hematopoiesis within the secondary hematopoietic organs (the spleen, liver, and lymph nodes). In well-nourished individuals who become anemic because of acute bleeding or increased red cell destruction (hemolysis), the compensatory response can increase the regeneration of red cells fivefold to eightfold. The hallmark of increased marrow output is reticulocytosis, the appearance of increased numbers of newly formed red cells (reticulocytes) in the peripheral blood. In contrast, disorders of decreased red cell production (aregenerative anemias) are characterized by reticulocytopenia.

Another classification of anemias is based on the morphology of red cells, which often correlates with the cause of their deficiency. Specific red cell features that provide etiologic clues include the cell size (normocytic, microcytic, or macrocytic), the degree of hemoglobinization—which is reflected in the color of the cells (normochromic or hypochromic)—and the shape of the cells. These features are judged subjectively by visual inspection of peripheral smears and are also expressed quantitatively through the following indices:

- **Mean cell volume** (MCV): the average volume per red cell, expressed in femtoliters (cubic microns)
- **Mean cell hemoglobin** (MCH): the average content (mass) of hemoglobin per red cell, expressed in picograms
- **Mean cell hemoglobin concentration** (MCHC): the average concentration of hemoglobin in a given volume of packed red cells, expressed in grams per deciliter
healthy individuals, but are less effective in those with
igate the effects of mild to moderate anemia in otherwise
volumes take place that partially compensate for the deficit
mellitic anemia) are associated with hyperbilirubinemia, jaundice, and pigment gallstones. Anemias that stem from ineffective hematopoiesis (the premature death of erythroid progenitors in the marrow) are associated with inappropriately high levels of iron absorption from the gut, which can lead to iron overload (secondary hemochromatosis) and eventual damage to endocrine organs and the heart. If left untreated, severe congenital anemias, such as β-thalassemia major, inevitably result in growth retardation, skeletal abnormalities, and cachexia.

**SUMMARY**

**Pathology of Anemias**

**CAUSES**
- Blood loss (hemorrhage)
- Increased red cell destruction (hemolysis)
- Decreased red cell production

**MORPHOLOGY**
- Microcytic (iron deficiency, thalassemia)
- Macrocytic (folate or B12 deficiency)
- Normocytic but with abnormal shapes (hereditary spherocytosis, sickle cell disease)

**CLINICAL MANIFESTATIONS**
- Acute: shortness of breath, organ failure, shock
- Chronic:
  - With hemolysis: skeletal abnormalities because of expansion of marrow; growth retardation; jaundice and gallstones
  - With defective erythropoiesis: iron overload, heart and endocrine failure

**ANEMIA OF BLOOD LOSS: HEMORRHAGE**

With acute blood loss, the immediate threat to the patient is hypovolemia (shock) rather than anemia. If the patient survives, hemodilution begins at once and achieves its full effect within 2 to 3 days, unmasking the extent of the red cell loss. The anemia is normocytic and normochromic. Recovery from blood loss anemia is enhanced by a rise in the erythropoietin level, which stimulates increased red cell production within several days. The onset of the marrow response is marked by reticulocytosis.

With chronic blood loss, iron stores are gradually depleted. Iron is essential for hemoglobin synthesis and effective erythropoiesis, and its deficiency thus leads to a chronic anemia of underproduction. Iron deficiency

### Table 12-1 Classification of Anemia According to Underlying Mechanism

<table>
<thead>
<tr>
<th>Blood Loss</th>
<th>Increased Destruction (Hemolytic Anemias)</th>
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<tbody>
<tr>
<td>Acute: trauma, Chronic: lesions of gastrointestinal tract, gynecologic disturbances</td>
<td>Intrinsic (intracorpuscular) abnormalities</td>
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<tr>
<td></td>
<td>Membrane abnormalities</td>
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<td></td>
<td>Membrane skeleton proteins: spherocytosis, elliptocytosis</td>
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<td></td>
<td>Enzyme deficiencies</td>
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<td></td>
<td>Glycolytic enzymes: pyruvate kinase, hexokinase</td>
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<td>Enzymes of hexose monophosphate shunt: glucose-6-phosphate dehydrogenase, glutathione synthetase</td>
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<td>Disorders of hemoglobin synthesis</td>
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<td>Deficient globin synthesis: thalassemia syndromes</td>
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<td></td>
<td>Structurally abnormal globin synthesis (hemoglobinopathies): sickle cell anemia, unstable hemoglobin</td>
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<tr>
<td></td>
<td>Acquired</td>
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<tr>
<td></td>
<td>Membrane defec: paroxysmal nocturnal hemoglobinuria</td>
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</tbody>
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**Impaired Red Cell Production**

Disturbance of proliferation and differentiation of stem cells:
- aplastic anemia, pure red cell aplasia, anemia of renal failure, anemia of endocrine disorders
- Defective DNA synthesis: deficiency or impaired utilization of vitamin B12 and folic acid (megaloblastic anemias)
- Defective hemoglobin synthesis
- Deficient heme synthesis: iron deficiency
- Deficient globin synthesis: thalassemias

**Extrinsic (extracorpuscular) abnormalities**

- Antibody mediated
- Isohemagglutinins: transfusion reactions, erythroblastosis fetalis (Rh disease of the newborn)
- Autoantibodies: idiopathic (primary), drug-associated, systemic lupus erythematosus
- Mechanical trauma to red cells
- Microangiopathic hemolytic anemias: thrombotic thrombocytopenic purpura, disseminated intravascular coagulation
- Infections: malaria

**Impaired Red Cell Production**

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- Defective hemoglobin synthesis
- Deficient heme synthesis: iron deficiency
- Deficient globin synthesis: thalassemias

**Unknown or multiple mechanisms: myelodysplastic syndrome, anemia of chronic inflammation, myeloproliferative anemias due to marrow infiltrations**

- Red cell distribution width (RDW): the coefficient of variation of red cell volume.

In modern clinical laboratories, specialized instruments directly measure or automatically calculate the red cell indices. Adult reference ranges are shown in Table 12-2.

As we will discuss, the clinical consequences of anemia are determined by its severity, speed of onset, and underlying pathogenic mechanism. If the onset is slow, adaptations take place that partially compensate for the deficit in O2 carrying capacity, such as increases in plasma volume, cardiac output, respiratory rate, and red cell 2,3-diphosphoglycerate levels. These changes can largely mitigate the effects of mild to moderate anemia in otherwise healthy individuals, but are less effective in those with compromised pulmonary or cardiac function. Pallor, fatigue, and lassitude are common to all anemias, and are the primary presenting symptoms of the most common types, such as that caused by iron deficiency. Anemias caused by the premature destruction of red cells in the peripheral blood (hemolytic anemias) are associated with hyperbilirubinemia, jaundice, and pigment gallstones. Anemias that stem from ineffective hematopoiesis (the premature death of erythroid progenitors in the marrow) are associated with inappropriately high levels of iron absorption from the gut, which can lead to iron overload (secondary hemochromatosis) and eventual damage to endocrine organs and the heart. If left untreated, severe congenital anemias, such as β-thalassemia major, inevitably result in growth retardation, skeletal abnormalities, and cachexia.
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hemolysis, and hemosiderinuria. The conversion of the
erythrocyte skeleton have also been described. In all types of HS the
primary abnormality resides in the membrane skeleton and the intrinsic membrane proteins.

Pathogenesis. In HS the primary abnormality resides in one of a group of proteins that form a meshlike support-
itive skeleton on the intracellular face of the red cell membrane (Fig. 12–1). The major protein in this skele-
ton is spectrin, a long, flexible heterodimer that is linked
to the membrane at two points: through ankyrin and
membrane skeleton and the intrinsic membrane proteins.

Hereditary Spherocytosis

This disorder is characterized by an inherited (intrinsic)
defect in the red cell membrane that renders the cells
spheroidal, less deformable, and vulnerable to splenic
sequestration and destruction. Hereditary spherocytosis
(HS) is transmitted most commonly as an autosomal
dominant trait; approximately 25% of patients have a
more severe autosomal recessive form of the disease.

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portive skeleton on the intracellular face of the red cell
membrane (Fig. 12–1). The major protein in this skele-
ton is spectrin, a long, flexible heterodimer that is linked
to the membrane at two points: through ankyrin and
band 4.2 to the intrinsic membrane protein band 3; and
through band 4.1 to the intrinsic membrane protein
glycophorin. The horizontal spectrin–spectrin and verti-
cal spectrin–intrinsic membrane protein interactions
serve to stabilize the membrane and are responsible
for the normal shape, strength, and flexibility of the red
cell. The conversion of the heme pigment to bilirubin can result in unconjugated hyperbilirubinemia and jaundice. Massive intravascular
hemolysis sometimes leads to acute tubular necrosis
(Chapter 14). Haptoglobin, a circulating protein that
binds and clears free hemoglobin, is often absent from the
plasma.

Extravascular hemolysis, the more common mode of
red cell destruction, takes place largely within the phy-
cytic cells of the spleen and liver. The mononuclear
phagocyte system removes damaged or immunologically
targeted red cells from the circulation. Because extreme
alterations of shape are necessary for red cells to suc-
sessfully navigate the splenic sinusoids, any reduction in
red cell deformability makes this passage difficult and
leads to splenic sequestration, followed by phagocytosis.
As will be described, diminished deformability is an
important cause of red cell destruction in a variety of
hemolytic anemias. Extravascular hemolysis is not asso-
ciated with hemoglobinemia and hemoglobinuria, but it
often produces jaundice and, if long-standing, can lead to
the formation of bilirubin-rich galluria (so-called
pigment stones). Haptoglobin amounts are always
decreased, because some hemoglobin invariably escapes
into the plasma. In most forms of hemolytic anemia there
is a reactive hyperplasia of the mononuclear phagocyte
system, which results in splenomegaly.

In chronic hemolytic anemias, changes in iron metab-
olism lead to increases in iron absorption from the gut.
Because the pathways for the excretion of excess iron are
limited, this often causes iron to accumulate, giving rise
to systemic hemosiderosis (Chapter 1) or, in very severe
cases, secondary hemochromatosis (Chapter 16).

We will now discuss some of the common hemolytic
anemias.

### The Hemolytic Anemias

Normal red cells have a life span of about 120 days.
Anemias that are associated with accelerated destruction of
red cells are termed hemolytic anemias. Destruction
can be caused by either inherent (intracorporeal) red
cell defects, which are usually inherited, or external (extracorporeal) factors, which are usually acquired.

<table>
<thead>
<tr>
<th>Table 12–2</th>
<th>Adult Reference Ranges for Red Blood Cells*</th>
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<tbody>
<tr>
<td></td>
<td>Units</td>
</tr>
<tr>
<td>Hemoglobin (Hb)</td>
<td>g/dL</td>
</tr>
<tr>
<td>Hematocrit (HCT)</td>
<td>%</td>
</tr>
<tr>
<td>Red cell count</td>
<td>× 10⁶/mm³</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>%</td>
</tr>
<tr>
<td>Mean cell volume (MCV)</td>
<td>fl</td>
</tr>
<tr>
<td>Mean cell Hb (MCH)</td>
<td>pg</td>
</tr>
<tr>
<td>Mean cell Hb concentration (MCHC)</td>
<td>g/dL</td>
</tr>
<tr>
<td>Red cell distribution width (RDW)</td>
<td>11.5–14.5</td>
</tr>
</tbody>
</table>

*Reference ranges vary among laboratories. The reference ranges for the laboratory providing the result should always be used when interpreting a laboratory test.

anemia can occur in other clinical settings as well, and it is
described later in this chapter along with other anemias
diminished erythropoiesis.
quently lose membrane fragments after their release into the periphery, while retaining most of their volume. As a result, the ratio of surface area to volume of HS cells decreases until the cells become spherical, at which point no further membrane loss is possible (see Fig. 12–1).

The spleen plays a major role in the destruction of spherocytes. Red cells must undergo extreme degrees of deformation to leave the cords of Billroth and enter the splenic sinusoids. The discoid shape of normal red cells allows considerable latitude for changes in cell shape. In contrast, because of their spheroidal shape and limited deformability, spherocytes are sequestered in the splenic cords and eventually destroyed by macrophages, which are plentiful. The critical role of the spleen is illustrated by the invariably beneficial effect of splenectomy; although the red cell defect and spherocytes persist, the anemia is corrected.

Clinical Course. The characteristic clinical features are anemia, splenomegaly, and jaundice. The severity of the anemia is highly variable, ranging from subclinical to profound; most commonly it is moderate in severity. Because of their spheroidal shape, HS red cells show increased osmotic fragility when placed in hypotonic salt solutions, a characteristic that is helpful for diagnosis.

The clinical course is often stable but may be punctuated by aplastic crises. Such episodes are often triggered by the infection of bone marrow erythroblasts by parvovirus B19, which causes a transient cessation of red cell production. Because HS red cells have a shortened life span, the failure of erythropoiesis for even a few days results in a rapid worsening of the anemia. Such episodes are self-limited, but some patients need blood transfusions until the infection clears.

Morphology

On smears, the red cells lack the central zone of pallor because of their spheroidal shape (Fig. 12–2). Spherocytosis, though distinctive, is not diagnostic; it is seen in other conditions, such as immune hemolytic anemias (discussed later), in which there is a loss of cell membrane relative to cell volume. The excessive red cell destruction and resultant anemia lead to a compensatory hyperplasia of marrow red cell progenitors and an increase in red cell production, which is marked by peripheral blood reticulocytosis. Splenomegaly is greater and more common in HS than in any other form of hemolytic anemia. The splenic weight is usually between 500 and 1000 gm and can be even greater. The enlargement results from marked congestion of the cords of Billroth and increased numbers of mononuclear phagocytes. Phagocytosed red cells are frequently seen within macrophages lining the sinusoids and, in particular, within the cords. In long-standing cases there is prominent systemic hemosiderosis. The other general features of hemolytic anemias described earlier are also present, including cholelithiasis, which occurs in 40% to 50% of HS patients.
There is no specific treatment for HS. Splenectomy is beneficial for those who are symptomatic, because the major site of red cell destruction is removed. The benefits of splenectomy must be weighed against the risk of increased susceptibility to infections, particularly in children.

**Sickle Cell Anemia**

The hemoglobinopathies are a group of hereditary disorders that are defined by the presence of structurally abnormal hemoglobins. Of the more than 300 variant hemoglobins that have been discovered, one-third are associated with significant clinical manifestations. The prototypical (and most prevalent) hemoglobinopathy is caused by a mutation in the β-globin chain gene that creates sickle hemoglobin (HbS). The disease associated with HbS, sickle cell anemia, is discussed here; other hemoglobinopathies are infrequent and beyond our scope.

HbS, like 90% of other abnormal hemoglobins, results from a single amino acid substitution in the globin chain. Normal hemoglobins, as may be recalled, are tetramers composed of two pairs of similar chains. On average, the normal adult red cell contains 96% HbA (α2β2), 3% HbA2 (α2δ2), and 1% fetal Hb (Hbf, α2γ2). Substitution of valine for glutamic acid at the sixth position of the β-chain produces HbS. In homozygotes all HbA is replaced by HbS, whereas in heterozygotes only about half is replaced.

**Incidence.** Approximately 8% of American blacks are heterozygous for HbS. In parts of Africa where malaria is endemic the gene frequency approaches 30%, as a result of a small but significant protective effect of HbS against *Plasmodium falciparum* malaria. In the United States sickle cell anemia affects approximately one of every 600 blacks, and worldwide, sickle cell anemia is the most common form of familial hemolytic anemia.

**Etiology and Pathogenesis.** Upon deoxygenation, HbS molecules undergo polymerization, a process also referred to as *gelation* or *crystallization*. These polymers distort the red cell, which assumes an elongated crescentic, or sickle, shape (Fig. 12–3). Sickling of red cells is initially reversible upon reoxygenation; however, membrane damage occurs with each episode of sickling, and eventually the cells accumulate calcium, lose potassium and water, and become irreversibly sickled.

Many variables influence sickling of red cells in vivo. The three most important ones are as follows:

- **The presence of hemoglobins other than HbS.** In heterozygotes approximately 40% of Hb is HbS; the remainder is HbA, which interacts only weakly with deoxygenated HbS. The presence of HbA slows the rate of polymerization greatly, and as a result the red cells of heterozygotes have little tendency to sickle in vivo. Such individuals are said to have the *sickle cell trait*. HbC, another mutant β-globin, is fairly common. The carrier rate for HbC in American blacks is about 2.3%; as a result about one in 1250 newborns are double heterozygotes because they have inherited HbS from one parent and HbC from the other. HbC has a greater tendency to aggregate with HbS than does HbA, and those with HbS and HbC (called *HbSC disease*) are symptomatic. Conversely, HbF interacts more weakly with HbS, and therefore newborns with sickle cell anemia do not manifest the disease until they are 5 to 6 months old, when the HbF falls to adult levels.

- **The concentration of HbS in the cell.** The tendency for deoxygenated HbS to form the insoluble polymers that create sickle cells is strongly dependent on the concentration of HbS. Thus, red cell dehydration, which increases the Hb concentration, greatly facilitates sickling and can trigger occlusion of small blood vessels. Conversely, the coexistence of α-thalassemia (described later) reduces the Hb concentration and therefore the severity of sickling. The relatively low concentration of HbS also contributes to the lack of sickling in heterozygotes with sickle cell trait.

- **The length of time that red cells are exposed to low oxygen tension.** Normal transit times for red cells

![Figure 12-3](image-url)
passing through capillaries are not sufficient for significant aggregation of deoxygenated HbS to occur. Hence, sickling is confined to microvascular beds where blood flow is sluggish. This is normally the case in the spleen and the bone marrow, which are prominently affected by sickle cell disease. In other vascular beds, it has been suggested that particularly important pathogenic roles are played by two factors: inflammation and increased red cell adhesion. As you will recall, blood flow in inflamed tissues is slowed, as a result of the adhesion of leukocytes and red cells to activated endothelium and the exudation of fluid through leaky vessels. This prolongs the red cell transit times, making clinically significant sickling more likely. Sickle red cells also have a greater tendency than normal red cells to adhere to endothelial cells, apparently because membrane damage makes them sticky. In fact, the adhesion of sickle red cells to cultured endothelial cells correlates with clinical severity, presumably because this “stickiness” reflects a greater risk for delays in transit across microvascular beds in vivo.

Two major consequences stem from the sickling of red cells (Fig. 12–4). First, repeated episodes of deoxygenation cause membrane damage and dehydration of red cells, which become rigid and irreversibly sickled. These dysfunctional red cells are recognized and removed by mononuclear phagocyte cells, producing a chronic extravascular hemolytic anemia. Overall, the mean life span of red cells in sickle cell anemia patients averages only 20 days (one-sixth of normal). Second, the sickling of red cells produces widespread microvascular obstructions, which result in ischemic tissue damage and pain crises. Vaso-occlusion does not correlate with the number of irreversibly sickled cells and therefore appears to result from factors, such as infection, inflammation, dehydration, and acidosis, that trigger the sickling of reversibly sickled cells.

**Morphology**

The anatomic alterations in sickle cell anemia stem from the following three aspects of the disease: (1) the severe chronic hemolytic anemia; (2) the increased breakdown of heme pigments, which are processed into bilirubin; and (3) the microvascular obstruction, which provokes tissue ischemia and infarction. In peripheral smears, bizarre elongated, spindled, or boat-shaped irreversibly sickled red cells are evident (see Fig. 12–3). Both the anemia and the vascular stasis lead to fatty changes in the heart, liver, and renal tubules. There is a compensatory hyperplasia of erythroid progenitors in the marrow. The burgeoning marrow often causes bone resorption and secondary new bone formation, resulting in prominent cheekbones and changes in the skull resembling a “crew-cut” in roentgenograms. Extramedullary hematopoiesis can also appear in the spleen and liver.

In children there is moderate splenomegaly (splenic weight as great as 500 gm) caused by congestion of the red pulp, which is stuffed with sickled red cells. However, the chronic splenic erythrostasis results in
progressive hypoxic tissue damage, which eventually reduces the spleen to a functionally useless nubbin of fibrous tissue. This process, referred to as *autosplenectomy*, is complete by adulthood.

**Vascular congestion, thrombosis, and infarction** can affect any organ, including bones, liver, kidney, retina, brain, lung, and skin. The bone marrow is particularly prone to ischemia, because of its relatively sluggish blood flow and high rate of metabolism. Priapism, another common problem, can lead to penile fibrosis and eventual erectile dysfunction. As with the other hemolytic anemias, *hemosiderosis* and *gallstones* are common.

**Clinical Course.** Homozygous sickle cell disease usually becomes apparent after the sixth month of life, since HBF is gradually replaced by HbS. The anemia is severe; most patients have hematocrit values of 18% to 30% (normal range, 35%-45%). The chronic hemolysis is associated with marked reticulocytosis and hyperbilirubinemia. From the time of onset, the process runs an unremitting course, punctuated by sudden crises. The most serious of these are the *vaso-occlusive*, or *pain, crises*. Pain crises can involve many sites but are most common in the bone marrow, where they often progress to infarction and necrosis.

A feared complication is the acute chest syndrome, which can be triggered by pulmonary infections or fat emboli from necrotic marrow that secondarily involve the lung. The blood flow in the inflamed, ischemic lung becomes sluggish and “spleenlike,” leading to sickness within hypoxic pulmonary beds. This exacerbates the underlying pulmonary dysfunction, creating a vicious cycle of worsening pulmonary and systemic hypoxemia, sickling, and vaso-occlusion. Another major complication is *central nervous system stroke*, which sometimes occurs in the setting of the acute chest syndrome. Although virtually any organ can be damaged by ischemic injury in the course of the disease, the acute chest syndrome and stroke are the two leading causes of ischemia-related death.

A second acute event, the aplastic crisis, represents a sudden but usually temporary cessation of erythropoiesis. As in hereditary spherocytosis, these are usually triggered by parvovirus infection of erythroblasts, and, while severe, are self-limited.

In addition to these crises, patients with sickle cell disease are prone to infections. Both children and adults with sickle cell disease are functionally asplenic, making them susceptible to infections caused by encapsulated bacteria, such as pneumococci. In adults the basis for “hyposplenism” is autoinfarction. In the earlier childhood phase of splenic enlargement, congestion caused by trapped sickled red cells apparently interferes with bacterial sequestration and killing; hence, even children with enlarged spleens are at risk for fatal septicemia. Defects in the alternative complement pathway that impair the opsonization of encapsulated bacteria are also observed. For reasons that are not entirely clear, patients with sickle cell disease are particularly predisposed to *Salmonella* osteomyelitis.

In full-blown sickle cell disease, at least some irreversibly sickled red cells can be seen on an ordinary peripheral blood smear. In sickle cell trait, sickling can be induced in vitro by exposing cells to marked hypoxia. Ultimately, the diagnosis depends on the electrophoretic demonstration of HbS. Prenatal diagnosis of sickle cell anemia can be performed by analyzing the DNA in fetal cells obtained by amniocentesis or biopsy of chorionic villi (Chapter 7).

The clinical course of patients with sickle cell anemia is highly variable. As a result of improvements in supportive care, an increasing number of patients are surviving into adulthood and producing offspring. Of particular importance is prophylactic treatment with penicillin to prevent pneumococcal infections. Approximately 50% of patients survive beyond the fifth decade. In contrast, sickle cell trait causes symptoms rarely and only under extreme conditions, such as following vigorous exertion at high altitudes.

Hydroxyurea, a “gentle” inhibitor of DNA synthesis, has been shown to reduce pain crises and lessen the anemia. Hydroxyurea increases the red cell levels of HbF, acts as an anti-inflammatory agent by inhibiting the production of white cells, increases the MCV, and is oxidized by heme groups to produce NO, a potent vasodilator and inhibitor of platelet aggregation. These complementary intracorpussular and extracorpussular effects are believed to work together to lessen microvascular sickling and its attendant signs and symptoms.

**Thalassemia**

The thalassemias are a heterogeneous group of inherited disorders caused by mutations that decrease the rate of synthesis of α- or β-globin chains. As a consequence there is a deficiency of hemoglobin, with additional secondary red cell abnormalities caused by the relative excess of the other unaffected globin chain.

**Molecular Pathogenesis.** A diverse collection of molecular defects underlies the thalassemias, which are inherited as autosomal codominant conditions. Recall that adult hemoglobin, or HbA, is a tetramer composed of two α chains and two β chains. The α chains are encoded by two α-globin genes, which lie in tandem on chromosome 11, while the β chains are encoded by a single β-globin gene located on chromosome 16. The mutations that cause thalassemia are particularly common among Mediterranean, African, and Asian populations. The clinical features vary widely depending on the specific combination of alleles that are inherited by the patient (Table 12–3), as will be described below.

**β-Thalassemia**

The β-globin mutations associated with β-thalassemia fall into two categories: (1) β0, in which no β-globin chains are produced; and (2) β+, in which there is reduced (but detectable) β-globin synthesis. Sequencing of β-thalassemia genes has revealed more than 100 different responsible mutations, the majority of which consist of single-base changes. Individuals inheriting one abnormal allele have *thalassemia minor* or *thalassemia trait*, which
is asymptomatic or mildly symptomatic. Most individu-
als inheriting any two $\beta^0$ and $\beta^+$ alleles have $\beta$-thalassemia
major; occasionally, individuals inheriting two $\beta^+$ alleles
have a milder disease termed $\beta$-thalassemia
intermedia. In contrast to $\alpha$-thalassemias, described later,
gene deletions rarely underlie $\beta$-thalassemias
(Table 12–3).

Most of the mutations in $\beta$-thalassemia fall into one
of three molecular subtypes (Fig. 12–5):

- The promoter region controls the initiation and rate
  of transcription. Some mutations lie within promoter
  regions and typically lead to reduced globin gene tran-
  scription. Because some $\beta$-globin is synthesized, such
  alleles are designated $\beta^+$.
- Mutations in the coding sequences are usually asso-
  ciated with more serious consequences. For example,
in some cases a single-nucleotide change in one of
the exons leads to the formation of a termination, or
“stop” codon, which interrupts translation of $\beta$-globin
messenger RNA (mRNA) and completely prevents the
synthesis of $\beta$-globin. Such alleles are designated $\beta^0$.

- Mutations that lead to aberrant mRNA processing
  are the most common cause of $\beta$-thalassemia. Most of
these affect introns, but some have been located within
exons. If the mutation alters the normal splice junc-
tions, splicing does not occur, and all of the mRNA
formed is abnormal. Unspliced mRNA is degraded
within the nucleus, and no $\beta$-globin is made. However,
some mutations affect the introns at locations away
from the normal intron-exon splice junction. These
mutations create new sites that are substrates for the
action of splicing enzymes at abnormal locations-
within an intron, for example. Because normal splice
sites remain intact, both normal and abnormal splicing
occur, and normal $\beta$-globin mRNA is decreased but not
absent. Thus, depending on their position, splice junc-
tion mutations can create either $\beta^0$ or $\beta^+$ alleles.

Two conditions contribute to the pathogenesis of the
anemia in $\beta$-thalassemia. The reduced synthesis of $\beta$-

Figure 12–5

The $\beta$-globin gene and some sites at which point mutations giving rise to $\beta$-thalassemia have been localized. Asterisks within circles indicate the most common sites of mutations that cause different types of $\beta$-thalassemia. (Modified from Wyngaarden JB, Smith LH, Bennett JC [eds]: Cecil Textbook of Medicine, 19th ed. Philadelphia, WB Saunders, 1992.)
microcytic. Even more important is red cell hemolysis, which results from the unbalanced rates of β-globin and α-globin chain synthesis. Unpaired α chains form insoluble aggregates that precipitate within the red cells and cause membrane damage that is severe enough to provoke extravascular hemolysis (Fig. 12–6). Erythroblasts in the bone marrow are also susceptible to damage through the same mechanism, which in severe β-thalassemia results in the destruction of the majority of erythroid progenitors before their maturation into red cells. This intramedullary destruction of erythroid precursors (ineffective erythropoiesis) has another untoward effect: it is associated with an inappropriate increase in the absorption of dietary iron, which often leads to iron overload.

α-Thalassemia

The molecular basis of α-thalassemia is quite different from that of β-thalassemia. Most of the α-thalassemias are caused by deletions that remove one or more of the α-globin gene loci. The severity of the disease that results from these lesions is directly proportional to the number of α-globin genes that are missing (see Table 12–3). For example, the loss of a single α-globin gene is associated with a silent-carrier state, whereas the deletion of all four α-globin genes is associated with fetal death in

![Figure 12–6](image-url)

Pathogenesis of β-thalassemia major. Note that aggregates of excess α-globin are not visible on routine blood smears. Blood transfusions, on the one hand, correct the anemia and reduce stimulus for erythropoietin secretion and deformities induced by marrow expansion; on the other hand, they add to systemic iron overload.
uter, because the blood has virtually no oxygen-delivering capacity. With loss of three α-globin genes there is a relative excess of β-globin or chains other than α-globin. Excess β-globin (or γ-globin chains early in life) forms relatively stable δ4 and γ4 tetramers known as HbH and Hb Bart, respectively, that cause less membrane damage than do free α-globin chains. Therefore, the hemolytic anemia and ineffective erythropoiesis tend be less severe in α-thalassemia than in β-thalassemia. Unfortunately, both HbH and Hb Bart have an abnormally high affinity for oxygen, which renders them ineffective at delivering oxygen to the tissues.

**Morphology**

Only the morphologic changes in β-thalassemia, which is more common in the United States, will be described. In β-thalassemia minor the abnormalities are confined to the peripheral blood. In smears the red cells appear small (microcytic), pale (hypochromic), and irregular in shape. Target cells are often seen, a feature that results from the relatively large surface area-to-volume ratio, which leads Hb to collect in a central, dark-red “puddle.” In smears from patients with β-thalassemia major the microcytosis and hypochromia are much more pronounced, and there is marked poikilocytosis, anisocytosis, and reticulocytosis. Nucleated red cells (normoblasts) are also seen, which reflect the underlying erythropoietic drive. The anatomic changes in β-thalassemia major are similar to those seen in other hemolytic anemias but more extreme in degree. The combination of ineffective erythropoiesis and hemolysis results in a striking hyperplasia of erythroid progenitors, with a shift toward early forms. The expanded erythropoietic marrow may completely fill the intramedullary space of the skeleton, invade the bony cortex, impair bone growth, and produce skeletal deformities. The extramedullary hematopoiesis and the hyperplasia of the mononuclear phagocytes result in prominent splenomegaly, hepatomegaly, and lymphadenopathy. The ineffective erythropoietic precursors consume nutrients and produce growth retardation and a degree of cachexia reminiscent of that seen in cancer patients. Unless stem cell transplantation is done, patients may die of congestive heart failure. The anemia is generally severe, and patients usually do not require transfusions. Thus, the iron overload that is so common in β-thalassemia major is rarely seen. α-Thalassemia trait (caused by deletion of two α-globin genes) is often an asymptomatic condition associated with microcytic red cells and mild anemia.

**Glucose-6-Phosphate Dehydrogenase Deficiency**

The red cell is vulnerable to injury by endogenous and exogenous oxidants, which are normally inactivated by reduced glutathione (GSH). Abnormalities affecting the enzymes that are required for GSH production reduce the ability of red cells to protect themselves from oxidative injury and lead to hemolytic anemias. The prototype (and most prevalent) of these anemias is that associated with a deficiency of glucose-6-phosphate dehydrogenase (G6PD). The G6PD gene is on the X chromosome. More than 400 G6PD variants have been identified, but only a few are associated with disease. One of the most important is the G6PD A⁻ variant, which is carried by approximately 10% of black males in the United States. G6PD A⁻ has normal enzymatic activity but a decreased half-life. Because red cells lack the capacity for protein synthesis, older G6PD A⁻ red cells become progressively deficient in enzyme activity and more vulnerable to oxidant stress.

G6PD deficiency produces no symptoms until the patient is exposed to an environmental factor (most commonly infectious agents or drugs) that results in increased oxidant stress. The drugs incriminated include antimalarials (e.g., primaquine), sulfonamides, nitrofurantoin, phenacetin, aspirin (in large doses), and vitamin K derivatives. More commonly, episodes of hemolysis are
triggered by infections, which induced phagocytes to produce free radicals as part of the normal host response. These offending agents produce oxidants such as hydrogen peroxide that are sopped up by GSH, which is converted to oxidized glutathione in the process. Because regeneration of GSH is impaired in G6PD-deficient cells, hydrogen peroxide is free to “attack” other red cell components, including globin chains, which have sulfhydryl groups that are susceptible to oxidation. Oxidized Hb denatures and precipitates, forming intracellular inclusions called Heinz bodies, which can damage the cell membrane sufficiently to cause intravascular hemolysis. Other cells that are less severely damaged nevertheless suffer from a loss of deformability, and their cell membranes are further damaged when splenic phagocytes attempt to “pluck out” the Heinz bodies, creating so-called bite cells (Fig. 12–7). All of these changes predispose the red cells to becoming trapped in the splenic sinusoids and destroyed by the phagocytes (extravascular hemolysis).

Drug-induced hemolysis is acute and of variable clinical severity. Typically, patients develop evidence of hemolysis after a lag period of 2 or 3 days. Because the G6PD gene is on the X chromosome, all the red cells of affected males are affected. However, because of random inactivation of one X chromosome in women (Chapter 7), heterozygous females have two distinct populations of red cells, one normal and the other deficient in G6PD activity. Thus, affected males are more vulnerable to oxidant injury, whereas most carrier females are asymptomatic, except those with a very large proportion of deficient red cells (a chance situation known as unfavorable lyonization). In G6PD A−, the enzyme deficiency is most marked in older red cells, which are thus more susceptible to lysis. Since the marrow compensates by producing new (young) resistant red cells, hemolysis tends to abate even if drug exposure continues. In other variants, such as G6PD Mediterranean, found mainly in the Middle East, the enzyme deficiency and the hemolysis that occur upon exposure to oxidants are more severe.

Paroxysmal Nocturnal Hemoglobinuria

A rare disorder of unknown etiology, paroxysmal nocturnal hemoglobinuria (PNH) is mentioned here because it is the only form of hemolytic anemia that results from an acquired membrane defect secondary to a mutation that affects myeloid stem cells. The mutant gene, called PIGA, is required for the synthesis of a specific type of intramembranous glycolipid anchor, phosphatidylinositol glycan (PIG), which is a component of diverse membrane-associated proteins. Without the membrane anchor, these “PIG-tailed” proteins cannot be expressed on the surface of cells. The affected proteins include several that limit the spontaneous activation of complement on the surface of cells. As a result, PIG-deficient precursors give rise to red cells that are inordinately sensitive to the lytic activity of complement. It is believed that the hemolysis is nocturnal because the blood becomes acidic during sleep (because of CO2 retention) and an acid pH may promote hemolysis. It is not known why red cell destruction is paroxysmal. Several other PIG-tailed proteins are deficient from the membranes of granulocytes and platelets, possibly explaining the striking susceptibility of these patients to infections and intravascular thromboses.

PIGA is X-linked, and thus normal cells have only a single active PIGA gene, mutation of which is sufficient to give rise to PIG deficiency. Because all myeloid lineages are affected in PNH, the responsible mutations must occur in a multipotent stem cell. Remarkably, most, if not all, normal individuals harbor small numbers of PIG-deficient bone marrow cells that have mutations identical to those that cause PNH. It is believed that clinically evident PNH occurs only in rare instances in which the PIG-deficient clone has a survival advantage. One is the setting of primary bone marrow failure (aplastic anemia), which appears most often to be caused by immune-mediated destruction or suppression of marrow stem cells. It is hypothesized that in PNH patients, autoreactive T cells specifically recognize PIG-tailed surface antigens on normal bone marrow progenitors. Because PIG-deficient stem cells do not express these targets, they escape immune attack and eventually replace the normal marrow elements. Therapy with an antibody that inhibits the C5–9 complement membrane complex (and thereby red cell hemolysis) is currently under evaluation.

Immunohemolytic Anemias

Antibodies that recognize determinants on red cell membranes cause these uncommon forms of hemolytic anemia. The antibodies may arise spontaneously or be induced by exogenous agents such as drugs or chemicals. Immunohemolytic anemias are classified based on (1) the nature of the antibody and (2) the presence of certain predisposing conditions (summarized in Table 12–4).

Whatever the cause of antibody formation, the diagnosis of immunohemolytic anemias depends on the detec-
tion of antibodies and/or complement on patient red cells. This is done using the direct Coombs antiglobulin test, which measures the capacity of antibodies raised in animals against human immunoglobulins or complement to agglutinate red cells from the patient. The indirect Coombs test, in which patient serum is tested for the ability to agglutinate defined red cells, can then be used to characterize the target of the autoantibody.

Warm Antibody Immunohemolytic Anemias. These are caused by immunoglobulin G (IgG) or, rarely, immunoglobulin A (IgA) antibodies that are active at 37°C. More than 60% of cases are idiopathic (primary), while another 25% are associated with an underlying disease affecting the immune system (e.g., systemic lupus erythematosus [SLE]) or are induced by drugs. The hemolysis usually results from the opsonization of red cells by the autoantibodies, which leads to erythropagocytosis in the spleen and elsewhere. Spheroidal cells resembling those seen in hereditary spherocytosis are often found in the peripheral blood smear. Presumably, cell membrane is removed during attempted phagocytosis of antibody-coated cells. This reduces the surface area-to-volume ratio and leads to the formation of spherocytes, which are rapidly destroyed in the spleen, as described earlier. The clinical severity of immunohemolytic anemia is quite variable. Most patients have chronic mild anemia with moderate splenomegaly and often require no treatment.

The mechanisms of hemolysis induced by drugs are varied and in some cases poorly understood. Drugs such as α-methyldopa induce autoantibodies that are directed against intrinsic red cell antigens, in particular Rh blood group antigens, producing an anemia that is indistinguishable from primary idiopathic immunohemolytic anemia. Presumably, the drug alters native epitopes and thus allows a bypass of T-cell tolerance to the membrane proteins (see Chapter 5). In other cases, drugs such as penicillin act as haptons and induce an antibody response by binding to a red cell membrane protein. Sometimes antibodies bind to a drug in the circulation and form immune complexes, which are then deposited on red cell membranes. Here they may fix complement or act as opsonins, either of which can damage red cells and lead to hemolysis.

Cold Antibody Immunohemolytic Anemias. These anemias are caused by low-affinity immunoglobulin M (IgM) antibodies, which bind to red cell membranes only at temperatures below 30°C, which are commonly experienced in distal parts of the body (e.g., ears, hands, and toes). Although IgM fixes complement well, the later steps of complement fixation occur inefficiently at temperatures below 37°C. As a result, most cells with bound IgM pick up some C3b but are not lysed in the periphery. When these cells travel to warmer areas, the weakly bound IgM antibody is released, but the coating of C3b remains. Because C3b is an opsonin (Chapter 2), the cells are phagocytosed by the mononuclear phagocyte system, especially Kupffer cells; hence, the hemolysis is extravascular. Cold agglutinins sometimes develop transiently during recovery from pneumonia caused by Mycoplasma sp. and infectious mononucleosis, producing a mild anemia of little clinical importance. A chronic cold agglutinin hemolytic anemia occurs in association with lymphoid neoplasms or as an idiopathic condition. In addition to anemia, Raynaud phenomenon often occurs in these patients as a result of the agglutination of red cells in the capillaries of exposed parts of the body.

### Hemolytic Anemias Resulting from Mechanical Trauma to Red Cells

Red cells are disrupted by physical trauma in a variety of circumstances. Clinically important hemolytic anemias are sometimes caused by cardiac valve prostheses or by the narrowing and partial obstruction of the vasculature. Traumatic hemolytic anemia can be seen incidentally following any activity that produces repeated physical blows (e.g., marathon racing and bongo drumming) but is of clinical importance mainly in patients with mechanical heart valves, which can cause sufficiently turbulent blood flow to shear red cells. Microangiopathic hemolytic anemia is observed in a variety of pathologic states in which small vessels become partially obstructed. The most frequent of these conditions is disseminated intravascular coagulation (DIC; see later), in which the narrowing is caused by the intravascular deposition of fibrin. Other causes of microangiopathic hemolytic anemia include malignant hypertension, SLE, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, and disseminated cancer, all of which produce vascular lesions that predispose the circulating red cells to mechanical injury. The morphologic alterations in the injured red cells (schistocytes) are striking and quite characteristic; “burr cells,” “helmet cells,” and “triangle cells” may be seen (Fig. 12–8). While the recognition of microangiopathic hemolysis often provides an important diagnostic clue, in and of itself it is not usually a major clinical problem.

### Malaria

It has been estimated that 200 million persons suffer from this infectious disease, which is one of the most widespread afflictions of humans. Malaria is endemic in Asia and Africa, but with widespread jet travel, cases now occur all over the world. Malaria is caused by one of four types of protozoa. Of these, the most important is Plasmodium falciparum, which causes tertian malaria (falci-
Parasites hybridize to red cell membranes at intervals of approximately 48 hours for \textit{P. vivax}, \textit{P. ovale}, and \textit{P. falciparum}, and 72 hours for \textit{P. malariae}. The clinical spikes of shaking, chills, and fever coincide with this release.

- The parasites destroy large numbers of red cells and thus cause hemolytic anemia.
- A characteristic brown malarial pigment, probably a derivative of Hb that is identical to hematin, is released from the ruptured red cells along with the merozoites, discoloring principally the spleen, but also the liver, lymph nodes, and bone marrow.
- Activation of the phagocytic defense mechanisms of the host leads to marked hyperplasia of the mononuclear phagocyte system throughout the body, reflected in massive splenomegaly. Less frequently, the liver may also be enlarged.

\textit{Falciparum malaria} often involves the brain, a complication known as cerebral malaria. Normally, red cells bear negatively charged surfaces that interact poorly with endothelial cells. Infection of red cells with \textit{P. falciparum} induces the appearance of positively charged surface knobs containing parasite-encoded proteins, which bind to adhesion molecules expressed on activated endothelium. Several endothelial cell adhesion molecules have been proposed to mediate this interaction, including intercellular adhesion molecule 1, which leads to the sequestration of red cells in postcapillary venules. In the brain this process gives rise to engorged cerebral vessels that are full of parasitized red cells and often occluded by microthrombi. Cerebral malaria is rapidly progressive; convulsions, coma, and death usually occur within days to weeks. Fortunately, falciparum malaria more commonly pursues a more chronic course that may be punctuated at any time by a dramatic complication known as blackwater fever. The trigger for this uncommon complication is obscure, but it is associated with massive hemolysis, leading to jaundice, hemoglobinemia, and hemoglobinuria.

With appropriate chemotherapy, the prognosis for patients with most forms of malaria is good; however, treatment of falciparum malaria is becoming more difficult, as a result of the emergence of drug-resistant strains. Because of the potentially serious consequences of this disease, early diagnosis and treatment are particularly important but are sometimes delayed in nonendemic settings. The ultimate solution is an effective vaccine, which is long sought but still elusive.

**SUMMARY**

### Hemolytic Anemias

- **Hereditary Spherocytosis:**

  - Autosomal dominant disorder caused by inherited mutations that affect the red cell membrane skeleton, leading to loss of membrane and eventual conversion of red cells to spherocytes, which are phagocytosed and removed in the spleen.
  - Manifested by anemia, splenomegaly.

- **Sickle Cell Anemia:**

  - Autosomal recessive disorder that results from a mutation in \(\beta\)-globin that causes deoxygenated hemoglobin to self-associate into long polymers that distort (sickle) the red cell.
  - Blockade of vessels by aggregates of sickled cells causes acute pain crises and tissue infarction.
In the following sections some common examples of tumor or inflammatory cells (myelophthisic anemia) or the replacement of the bone marrow by include those associated with bone marrow failure (aplastic anemia) or the replacement of the bone marrow by thrombosis.

Iron Deficiency Anemia

Iron is absorbed in the duodenum, where it must pass through the apical and basolateral membranes of enterocytes (Fig. 12–9). Nonheme iron is carried across each of these two membranes by distinct transporters. After reduction by ferric reductase, the reduced iron is transported by the divalent metal transporter (DMT1) across the apical membrane into the cytoplasm. At least two additional proteins are then required for the basolateral transfer of iron to transferrin in the plasma: ferroportin, which acts as a transporter; and hephaestin, which oxidizes the iron. Both DMT1 and ferroportin are widely distributed in the body and are involved in iron transport in other tissues as well. As depicted in Figure 12–9, only a fraction of the iron that enters the cell is delivered to plasma transferrin by the action of ferroportin. The remainder is bound to ferritin and lost through the exfoliation of mucosal cells.

When the body is replete with iron, most of the iron that enters duodenal cells is bound to ferritin and never transferred to transferrin; in iron deficiency, or when there is ineffective erythropoiesis, transfer to plasma transferrin is enhanced. This balance is regulated by hepcidin, a small hepatic peptide that is synthesized and secreted in an iron-dependent fashion. Plasma hepcidin binds to ferroportin and induces its internalization and degradation; thus, when hepcidin concentrations are high, ferroportin levels fall, and less iron is transferred out of the enterocytes to transferrin. Conversely, when hepcidin levels are low, as occurs in hemochromatosis (Chapter 16), transport of iron from the enterocytes to plasma is increased, resulting eventually in systemic iron overload.

Negative iron balance and consequent anemia can result from a variety of causes:

- Low dietary intake alone is rarely the cause of iron deficiency in the United States, because the average daily dietary intake of 10mg to 20mg is more than
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enough for males and adequate for females. In other parts of the world, however, low intake and poor bioavailability from predominantly vegetarian diets are an important cause of iron deficiency.

• Malabsorption can occur with sprue and celiac disease or after gastrectomy (Chapter 15).
• Increased demands not met by normal dietary intake occur around the world during pregnancy and infancy.
• Chronic blood loss is the most important cause of iron deficiency anemia in the western world; this loss may occur from the gastrointestinal tract (e.g., peptic ulcers, colonic cancer, hemorrhoids, hookworm disease) or the female genital tract (e.g., menorrhagia, metrorrhagia, cancers).

Regardless of the cause, iron deficiency develops insidiously. At first iron stores are depleted, leading to a decline in serum ferritin and the absence of stainable iron in the bone marrow. This is followed by a decrease in serum iron and a rise in the serum iron-binding capacity. Ultimately the capacity to synthesize hemoglobin, myoglobin, and other iron-containing proteins is diminished, leading to anemia, impaired work and cognitive performance, and even reduced immunocompetence.

Clinical Course. In most instances, iron deficiency anemia is asymptomatic. Nonspecific manifestations, such as weakness, listlessness, and pallor, may be present in severe cases. With long-standing severe anemia, thinning, flattening, and eventually “spooning” of the fingernails sometimes appears. A curious but characteristic neurobehavioral complication is pica, the compulsion to consume non-foodstuffs such as dirt or clay.

Diagnostic criteria include anemia, hypochromic and microcytic red cell indices, low serum ferritin and serum iron levels, low transferrin saturation, increased total iron-binding capacity, and, ultimately, response to iron therapy. Persons frequently die with this form of anemia but rarely of it. It is important to remember that in reasonably well-nourished persons, microcytic hypochromic anemia is relatively mild. The red cells are microcytic and hypochromic, reflecting the reductions in MCV and MCHC (Fig. 12–10). For unclear reasons, iron deficiency anemia is often accompanied by an increase in the platelet count. Although erythropoietin levels are increased, the marrow response is blunted by the iron deficiency, and thus the marrow cellularity is usually only slightly increased. Extramedullary hematopoiesis is uncommon.

Morphology

Except in unusual circumstances, iron deficiency anemia is relatively mild. The red cells are microcytic and hypochromic, reflecting the reductions in MCV and MCHC (Fig. 12–10). For unclear reasons, iron deficiency anemia is often accompanied by an increase in the platelet count. Although erythropoietin levels are increased, the marrow response is blunted by the iron deficiency, and thus the marrow cellularity is usually only slightly increased. Extramedullary hematopoiesis is uncommon.

Figure 12–10

Hypochromic microcytic anemia of iron deficiency. Note the small red cells containing a narrow rim of hemoglobin at the periphery. Compare to the scattered, fully hemoglobinized cells derived from a recent blood transfusion given to the patient. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)
Folate deficiency and vitamin B12 deficiency. Both vitamins are required for DNA synthesis, and, hence, their effects on hematopoiesis are quite similar. However, as will be described, the causes and consequences of folate and vitamin B12 deficiency differ in important ways.

**Pathogenesis.** The morphologic hallmark of megaloblastic anemias is an enlargement of erythroid precursors (**megaloblasts**), which gives rise to abnormally large red cells (macrocytes). The other myeloid lineages are also affected. Most notably, granulocyte precursors are enlarged (**giant metamyelocytes**) and yield highly characteristic **hypersegmented neutrophils**. Underlying the cellular gigantism is an impairment of DNA synthesis, which results in a delay in nuclear maturation and cell division. Because the synthesis of RNA and cytoplasmic elements proceeds at a normal rate and thus outpaces that of the nucleus, the hematopoietic precursors show **nuclear-cytoplasmic asynchrony**. This maturational derangement contributes to anemia in several ways. Some megaloblasts are so defective in DNA synthesis that they undergo apoptosis in the marrow (**ineffective hematopoiesis**). Others succeed in maturing into red cells but do so after fewer cell divisions; as a result, the total output from these precursors is diminished. Granulocyte and platelet precursors are similarly affected. As a result, most patients with megaloblastic anemia develop pancytopenia (anemia, thrombocytopenia, and granulocytopenia).

**Anemia of Chronic Disease**

This is the most common form of anemia in hospitalized patients. It superficially resembles the anemia of iron deficiency, but it stems from inflammation-induced sequestration of iron within the cells of the mononuclear phagocyte (reticuloendothelial) system. It occurs in a variety of chronic inflammatory disorders, including the following:

- Chronic microbial infections, such as osteomyelitis, bacterial endocarditis, and lung abscesses
- Chronic immune disorders, such as rheumatoid arthritis and regional enteritis
- Neoplasms, such as Hodgkin lymphoma and carcinomas of the lung and breast

The serum iron levels are usually low, and the red cells can be normocytic and normochromic, or, as in anemia of iron deficiency, hypochromic and microcytic. However, the anemia of chronic disease is associated with **increased storage iron in the bone marrow**, a **high serum ferritin concentration**, and a **reduced total iron-binding capacity**.

The teleologic explanation for iron sequestration in the presence of a wide variety of chronic inflammatory disorders is unclear; it may serve to inhibit the growth of iron-dependent microorganisms or to augment certain aspects of host immunity. Administration of erythropoietin and iron can improve the anemia, but only effective treatment of the underlying condition is curative.

**Megaloblastic Anemias**

There are two principal causes of megaloblastic anemia: folate deficiency and vitamin B12 deficiency. Both vitamins are required for DNA synthesis, and, hence, the effects of their deficiency on hematopoiesis are quite similar. However, as will be described, the causes and consequences of folate and vitamin B12 deficiency differ in important ways.

**Morphology**

Certain morphologic features are common to all forms of megaloblastic anemias. The **bone marrow** is markedly hypercellular, as a result of increased numbers of **megaloblasts**. These cells are larger than normoblasts and have a delicate, finely reticulated nuclear chromatin (**suggestive of nuclear immaturity**) and an abundant, strikingly basophilic cytoplasm (Fig. 12–11). As the megaloblasts differentiate and begin to acquire hemoglobin, the nucleus retains its finely distributed chromatin and fails to undergo the chromatin clumping typical of an orthochromatic normoblast. Similarly, the granulocytic precursors also demonstrate nuclear-cytoplasmic asynchrony, yielding giant metamyelocytes. Megakaryocytes, too, may be abnormally large and have bizarre multilobed nuclei.

In the **peripheral blood** the earliest change is usually the appearance of **hypersegmented neutrophils**, which appear even before the onset of anemia. Normally, neutrophils have three or four nuclear lobes, but in megaloblastic anemias neutrophils often have five or more. The red cells typically include large, egg-shaped macroovalocytes; the **MCV** is often greater than 110fL (normal, 82–92fL). Although macrocytes appear hyperchromic, in reality the **MCHC** is normal. Large, misshapen platelets may also be seen. Morphologic changes in other systems, especially the gastrointestinal tract, also occur, giving rise to some of the clinical features.

*Figure 12–11*

Comparison of normoblasts (**left**) and megaloblasts (**right**). The megaloblasts are larger, have relatively immature nuclei with finely reticulated chromatin, and have an abundant basophilic cytoplasm. (Courtesy of Dr. José Hernandez, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)
**Folate (Folic Acid) Deficiency Anemia**

Megaloblastic anemia secondary to folate deficiency is not common, but marginal folate stores occur with surprising frequency even in apparently healthy individuals. The risk of clinically significant folate deficiency is high in those with a poor diet (the economically deprived, the indigent, and the elderly) or increased metabolic needs (pregnant women and patients with chronic hemolytic anemias).

Ironically, folate is widely prevalent in nearly all foods but is readily destroyed by 10 to 15 minutes of cooking. Thus, the best sources of folate are fresh uncooked vegetables and fruits. Food folates are predominantly in polyglutamate form and must be split into monoglutamates for absorption, a conversion that is hampered by acidic foods and substances found in beans and other legumes. Phenytoin (Dilantin) and a few other drugs also inhibit folate absorption, while others, such as methotrexate, inhibit folate metabolism. The principal site of intestinal absorption is the upper third of the small intestine; thus, malabsorptive disorders that affect this level of the gut, such as celiac disease and tropical sprue, can impair folate uptake.

The metabolism and physiologic functions of folate are complex. Here, it is sufficient to note that, after absorption, folate is transported in the blood mainly as polyglutamate and must be split into monoglutamate form in the liver and other cells of the body. Vitamin B12 is absorbed, the body handles it very efficiently. As a result, deficiencies due to diet are rare and are virtually confined to strict vegans. Once vitamin B12 is absorbed, the body handles it very efficiently. It is stored in the liver, which normally contains reserves that are sufficient to support bodily needs for 5 to 20 years.

Until proved otherwise, a deficiency of vitamin B12 in the western world is caused by pernicious anemia. This disease seems to stem from an autoimmune reaction against parietal cells and intrinsic factor itself, which produces gastric mucosal atrophy (Chapter 15). Several associations favor an autoimmune basis:

- Autoantibodies are present in the serum and gastric juice of most patients with pernicious anemia. Three types of antibodies have been found: parietal canalicular antibodies, which bind to the mucosal parietal cells; blocking antibodies, which block the binding of vitamin B12 to intrinsic factor; and binding antibodies that react with intrinsic factor-B12 complex and prevent it from binding to the ileal receptor.
- An occurrence of pernicious anemia with other autoimmune diseases such as Hashimoto thyroiditis, Addison disease, and type I diabetes mellitus is well documented.
- The frequency of serum antibodies to intrinsic factor is increased in patients with other autoimmune diseases.

Chronic vitamin B12 malabsorption is also seen following gastrectomy (which leads to loss of cells producing intrinsic factor) or resection of ileum (which prevents absorption of intrinsic factor-B12 complex), and in disorders that involve the distal ileum (such as Crohn disease, tropical sprue, and Whipple disease). In individu-
anemia responds dramatically to parenteral vitamin B12, position sense, particularly in the toes. Although the or hands, followed by unsteadiness of gait and loss of with symmetric numbness, tingling, and burning in feet folate deficiency are seen. The spinal cord disease begins dice. Gastrointestinal symptoms similar to those seen in tion of erythroid progenitors may give rise to mild jaun-

is pallor, easy fatigability, and, in severe cases, dyspnea

leukopenia with hypersegmented granulocytes, and (6) a

dramatic reticulocytic response (within 2–3 days) to par-

or with overt megaloblastic anemia.

Clinical Features. Manifestations of vitamin B12 defi-

ciency are nonspecific. As with any other anemia, there

is pallor, easy fatigability, and, in severe cases, dyspnea

and even congestive heart failure. The increased destruct-

dion of erythroid progenitors may give rise to mild jaun-
dice. Gastrointestinal symptoms similar to those seen in

folate deficiency are seen. The spinal cord disease begins

with symmetric numbness, tingling, and burning in feet

or hands, followed by unsteadiness of gait and loss of

position sense, particularly in the toes. Although the

anemia responds dramatically to parenteral vitamin B12,

the neurologic manifestations often fail to resolve. As dis-

cussed in Chapter 15, patients with pernicious anemia

have an increased risk of gastric carcinoma.

The diagnostic features of pernicious anemia include

(1) low serum vitamin B12 levels, (2) normal or elevated

serum folate levels, (3) serum antibodies to intrinsic

factor, (4) moderate to severe megaloblastic anemia, (5)

leukopenia with hypersegmented granulocytes, and (6) a

dramatic reticulocytic response (within 2–3 days) to par-

enteral administration of vitamin B12.

Aplastic Anemia

Aplastic anemia is a disorder in which multipotent myeloid stem cells are suppressed, leading to marrow failure and pancytopenia. Notwithstanding its name, aplastic anemia should not be confused with selective suppression of erythroid stem cells (pure red cell aplasia), in which anemia is the only manifestation.

Etiology and Pathogenesis. In more than half of cases, aplastic anemia is idiopathic. In the remainder, an exposure to known myelotoxic agents, such as drugs or chemicals, can be identified. With some agents, the marrow damage is predictable, dose related, and usually reversible. Included in this category are antineoplastic drugs (e.g., alkylating agents, antimetabolites), benzene, and chloramphenicol. In other instances marrow toxicity occurs as an apparent “idiosyncratic” or hypersensitivity

reaction to small doses of known myelotoxic drugs (e.g., chloramphenicol) or to drugs such as sulfaamides, which are not myelotoxic in other persons.

Aplastic anemia sometimes arises after certain viral infections, most often community-acquired viral hepatitis. The specific virus responsible is not known; hepatitis viruses A, B, and C are apparently not the culprits. Marrow aplasia develops insidiously several months after recovery from the hepatitis and follows a relentless course.

The pathogenetic events leading to marrow failure remain vague, but it seems that autoreactive T cells may play an important role. This is supported by a variety of experimental data and clinical experience, which has shown that in 70% to 80% of cases aplastic anemia responds to immunosuppressive therapy aimed at T cells. Much less clear are the events that trigger the T-cell attack on marrow stem cells; perhaps viral antigens, drug-derived haptons, and/or genetic damage create neoantigens within stem cells that serve as targets for the immune system.

Rare but interesting genetic conditions are also associated with marrow failure. Of note, a small fraction of patients with “acquired” aplastic anemia have inherited defects in telomerase, which you will recall is needed for the maintenance and stability of chromosomes. In these settings intrinsic defects lead directly to damage and senescence of hematopoietic stem cells.

Morphology

The bone marrow in aplastic anemia typically is markedly hypocellular, with greater than 90% of the intertrabecular space being occupied by fat. The limited cellularity often consists of only lymphocytes and plasma cells. These changes are better appreciated in bone marrow biopsy specimens than in marrow aspirates, which often yield a “dry tap.” A number of secondary changes often accompany marrow failure. Anemia may cause fatty change in the liver, and thrombocytopenia and granulocytopenia may result in hemorhages and bacterial infections, respectively. The requirement for transfusions may eventually cause hemosiderosis.

Clinical Course. Aplastic anemia affects persons of all ages and both sexes. The slowly progressive anemia causes the insidious development of weakness, pallor, and dyspnea. Thrombocytopenia often presents with petechiae and ecchymoses. Granulocytopenia may be manifested only by frequent and persistent minor infections or by the sudden onset of chills, fever, and prostration. It is important to distinguish aplastic anemia from anemias caused by marrow infiltration (myelophthisic anemia), “aleukemic leukemia,” and granulomatous diseases. Because pancytopenia is common to these conditions, their clinical manifestations may be indistinguishable, but they are easily distinguished by examination of the bone marrow. Splenomegaly is characteristically absent in aplastic anemia; if it is present, the
diagnosis of aplastic anemia should be seriously questioned. Typically, the red cells are normocytic and normochromic, although slight macrocytosis is occasionally present; reticulocytes are reduced in number.

The prognosis of marrow aplasia is quite unpredictable. As mentioned earlier, withdrawal of toxic drugs may lead to recovery in some cases. The idiopathic form has a poor prognosis if left untreated. Bone marrow transplantation is an extremely effective form of therapy, especially if performed in nontransfused patients younger than 40 years of age. It is proposed that transfusions sensitize patients to alloantigens, producing a high engraftment failure rate following bone marrow transplantation. As mentioned earlier, patients who are poor transplant candidates may benefit from immunosuppressive therapy.

**Myelophthisic Anemia**

This form of anemia is caused by the extensive replacement of the marrow by tumors or other lesions. It is most commonly associated with metastatic breast, lung, or prostate cancer, but other cancers, advanced tuberculosis, lipid storage disorders, and osteosclerosis can produce a similar clinical picture. The principal manifestations of marrow infiltration include anemia and thrombocytopenia; in general, the white cell series is less affected. Characteristically, misshapen red cells, some resembling teardrops, are seen in the peripheral blood. Immature granulocytic and erythrocytic precursors may also be seen (leukoerythroblastosis), along with a slightly elevated white cell count. Treatment is focused on the management of the underlying condition.

**SUMMARY**

**Anemias of Diminished Erythropoiesis**

- **Iron Deficiency Anemia:**
  - Inadequate intake of iron results in insufficient hemoglobin synthesis and hypochromic and microcytic red cells.
- **Anemia of Chronic Disease:**
  - Caused by production of inflammatory cytokines, which cause iron to be sequestered in macrophages, resulting in an anemia that is usually normochromic and normocytic.
- **Megaloblastic Anemia:**
  - Caused by deficiencies of folate or vitamin B₁₂, which lead to inadequate synthesis of thymidine and defective DNA replication.
  - Results in enlarged abnormal hematopoietic precursors (megaloblasts) in the bone marrow, ineffective erythropoiesis, and (in most cases) pancytopenia.
- **Aplastic Anemia:**
  - Caused by bone marrow failure (hypocellularity) due to diverse causes, including exposures to toxins and radiation, idiosyncratic reactions to drugs and viruses, and inherited defects in DNA repair and the enzyme telomerase.

- **Myelophthisic Anemia:**
  - Caused by replacement of the bone marrow by infiltrative processes such as metastatic carcinoma and granulomatous disease.
  - Leads to the release of early erythroid and granulocytic precursors (leukoerythroblastosis) and the appearance of tear-drop red cells in the peripheral blood.

**Laboratory Diagnosis of Anemias**

The diagnosis of anemia is established by a decrease in the hemoglobin and the hematocrit to levels that are below normal. Based on the red cell hemoglobin content and size, anemias can be placed into three major subgroups: normocytic normochromic, microcytic hypochromic, and macrocytic. The presence of red cells with a particular morphology, such as spherocytes, sickled cells, and fragmented cells, provide additional etiologic clues. The specialized tests cited below are particularly important in establishing the diagnosis of certain classes of anemia:

- Gel electrophoresis: used to detect abnormal hemoglobins, such as HbS
- Coombs test: used to diagnose immunohemolytic anemias
- Reticulocyte counts: used to distinguish between anemias caused by red cell destruction (hemolysis) and decreased production (marrow failure)
- Iron indices (serum iron, serum iron-binding capacity, transferrin saturation, and serum ferritin concentrations): used to distinguish between hypochromic microcytic anemias caused by iron deficiency, anemia of chronic disease, and thalassemia minor
- Serum and red cell folate and vitamin B₁₂ concentrations: used to identify the cause of megaloblastic anemia
- Plasma unconjugated bilirubin and haptoglobin concentrations: used to support the diagnosis of hemolytic anemia

In isolated anemia, tests performed on the peripheral blood usually suffice to establish a cause. In contrast, when anemia occurs in combination with thrombocytopenia and/or granulocytopenia, it is much more likely to be associated with marrow aplasia or infiltration; in these instances, a marrow examination is often critical for diagnosis.

**POLYCYTHEMIA**

Polycythemia, or **erythrocytosis**, as it is sometimes referred to, denotes an increase in the blood concentration of red cells, which usually correlates with an increase in the hemoglobin concentration. Polycythemia may be **relative**, when there is hemococoncentration caused by a decrease in plasma volume, or **absolute**, when there is an
Relative polycythemia results from any cause of dehydration, such as water deprivation, prolonged vomiting, diarrhea, or the excessive use of diuretics. Absolute polycythemia is said to be primary when the increase in red cell mass results from an autonomous proliferation of the myeloid stem cells, and secondary when the red cell progenitors are proliferating in response to an increase in erythropoietin. Primary polycythemia (polycythemia vera [PCV]) is a clonal, neoplastic proliferation of myeloid progenitors, which is considered later in this chapter with the other myeloproliferative disorders. The increases in erythropoietin that are seen in secondary polycythemias have a variety of causes (Table 12–5).

**Table 12–5  Pathophysiologic Classification of Polycythemia**

<table>
<thead>
<tr>
<th>Relative</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced plasma volume (hemoconcentration)</td>
<td>Primary: Abnormal proliferation of myeloid stem cells, normal or low erythropoietin levels (polycythemia vera); inherited activating mutations in the erythropoietin receptor (rare)</td>
</tr>
<tr>
<td></td>
<td>Secondary: Increased erythropoietin levels</td>
</tr>
<tr>
<td></td>
<td>Appropriate: lung disease, high-altitude living, cyanotic heart disease</td>
</tr>
<tr>
<td></td>
<td>Inappropriate: erythropoietin-secreting tumors (e.g., renal cell carcinoma, hepatoma, cerebellar hemangioblastoma); surreptitious erythropoietin use (e.g., in endurance athletes)</td>
</tr>
</tbody>
</table>

**WHITE CELL DISORDERS**

Disorders of white cells include deficiencies (leukopenias) and proliferations, which may be reactive or neoplastic. Reactive proliferation in response to an underlying primary, often microbial, disease is fairly common. Neoplastic disorders, though less common, are more ominous; they cause approximately 9% of all cancer deaths in adults and a staggering 40% in children younger than 15 years. In the following discussion we first describe some non-neoplastic conditions and then consider in some detail the malignant proliferations of white cells.

**NON-NEOPLASTIC DISORDERS OF WHITE CELLS**

**Leukopenia**

Leukopenia results most commonly from a decrease in granulocytes, which are the most prevalent circulating white cells. Lymphopenias are much less common; they are associated with congenital immunodeficiency diseases or are acquired in association with specific clinical states, such as advanced human immunodeficiency virus (HIV) infection or treatment with corticosteroids. Only the more common leukopenias that affect granulocytes are discussed here.

**Neutropenia/Agranulocytosis**

A reduction in the number of granulocytes in blood is known as *neutropenia* or sometimes, when severe, as *agranulocytosis*. Characteristically, the total white cell count is reduced to 1000 cells/μL and in some instances to as few as 200 to 300 cells/μL. Affected persons are extremely susceptible to bacterial and fungal infections, which can be severe enough to cause death.

**Etiology and Pathogenesis.** The mechanisms that cause neutropenia can be broadly divided into two categories:

- **Inadequate or ineffective granulopoiesis.** Reduced granulopoiesis is a manifestation of generalized marrow failure, which occurs in aplastic anemia and a variety of leukemias. Cancer chemotherapy agents also produce neutropenia by inducing transient marrow aplasia. Alternatively, some neutropenias are isolated, with only the differentiation of committed granulocytic precursors being affected. These forms of neutropenia are most often caused by certain drugs or, more uncommonly, by neoplastic proliferations of cytotoxic T cells and natural killer (NK) cells.

- **Accelerated removal or destruction of neutrophils.** This can be encountered with immune-mediated injury to neutrophils (triggered in some cases by drugs), or it may be idiopathic. Increased peripheral utilization can occur in overwhelming bacterial, fungal, or rickettsial infections. An enlarged spleen can also lead to sequestration and accelerated removal of neutrophils.

**Morphology**

The anatomic alterations in the bone marrow depend on the underlying basis of the neutropenia. **Marrow hypercellularity** is seen when the neutropenia results from excessive destruction of the mature neutrophils or from ineffective granulopoiesis, such as occurs in megaloblastic anemia. In contrast, agents such as drugs that suppress granulocytopenia are associated with a marked decrease in maturing granulocytic precursors in the marrow. Erythropoiesis and megakaryopoiesis can be normal if the responsible agent specifically affects the granulocytes, but with most myelotoxic drugs all marrow elements are affected.
Clinical Course. The initial symptoms are often malaise, chills, and fever, with subsequent marked weakness and fatigability. Infections constitute the major problem. They commonly take the form of ulcerating, necrotizing lesions of the gingiva, floor of the mouth, buccal mucosa, pharynx, or other sites within the oral cavity (agranulocytic angina). These lesions often show a massive growth of microorganisms, due to the inability to mount a leukocyte response. In addition to removal of the offending drug and control of infections, treatment efforts may also include the administration of granulocyte colony-stimulating factor, which stimulates neutrophil production by the bone marrow.

Reactive Leukocytosis

An increase in the number of white cells is common in a variety of reactive inflammatory states caused by microbial and nonmicrobial stimuli. Leukocytoses are relatively nonspecific and can be classified on the basis of the particular white cell series affected (Table 12–6). As will be discussed later, in some cases reactive leukocytosis may mimic leukemia. Such leukemoid reactions must be distinguished from true malignancies of the white cells. Infectious mononucleosis, a form of lymphocytosis caused by Epstein-Barr virus (EBV) infection, merits separate consideration because it gives rise to a distinctive syndrome.

### Table 12-6 Causes of Leukocytosis

<table>
<thead>
<tr>
<th>Neutrophilic Leukocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial infections, especially those caused by pyogenic organisms; sterile inflammation caused by, for example, tissue necrosis (myocardial infarction, burns)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eosinophilic Leukocytosis (Eosinophilia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic disorders such as asthma, hay fever, allergic skin diseases (e.g., pemphigus, dermatitis herpetiformis); parasitic infestations; drug reactions; certain malignances (e.g., Hodgkin disease and some non-Hodgkin lymphomas); collagen vascular disorders and some vasculitides; atheroembolic disease (transient)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basophilic Leukocytosis (Basophilia)</th>
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</thead>
<tbody>
<tr>
<td>Rare, often indicative of a myeloproliferative disease (e.g., chronic myelogenous leukemia)</td>
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</table>

<table>
<thead>
<tr>
<th>Monocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic infections (e.g., tuberculosis), bacterial endocarditis, rickettsiosis, and malaria; collagen vascular diseases (e.g., systemic lupus erythematosus); and inflammatory bowel diseases (e.g., ulcerative colitis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymphocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accompanies monocytosis in many disorders associated with chronic immunologic stimulation (e.g., tuberculosis, brucellosis); viral infections (e.g., hepatitis A, cytomegalovirus, Epstein-Barr virus); Bordetella pertussis infection</td>
</tr>
</tbody>
</table>

### Infectious Mononucleosis

In the Western world, infectious mononucleosis is an acute, self-limited disease of adolescents and young adults that is caused by B lymphocytotropic EBV, a member of the herpesvirus family. The infection is characterized by (1) fever, sore throat, and generalized lymphadenitis; (2) an increase of lymphocytes in blood, many of which have an atypical morphology; and (3) an antibody and T cell response to EBV. It should be noted that cytomegalovirus infection induces a similar syndrome, which can be differentiated only by serologic methods.

#### Epidemiology and Immunology

EBV is ubiquitous in all human populations. Where economic deprivation results in inadequate living standards, EBV infection early in life is nearly universal. At this age, symptomatic disease is uncommon, and, even though infected hosts develop an immune response (described later), more than half continue to shed virus. In contrast, in developed countries that enjoy better standards of hygiene, infection is usually delayed until adolescence or young adulthood. For reasons that are not clear, only about 20% of healthy seropositive persons in developed countries shed the virus, and only about 50% of those who are exposed to the virus acquire the infection. Transmission to a seronegative “kissing cousin” usually involves direct oral contact. It is hypothesized (but not proven) that the virus initially infects oropharyngeal epithelial cells and then spreads to underlying lymphoid tissue (tonsils and adenoids), where B lymphocytes, which have receptors for EBV, are infected. The infection of B cells takes one of two forms. In a minority of cells, the infection leads to viral replication and eventual cell lysis accompanied by the release of virions. In most cells, however, the infection is nonproductive, and the virus persists in latent form as an extrachromosomal episome. B cells that are latently infected with EBV undergo polyclonal activation and proliferation, as a result of the action of several EBV proteins (Chapter 6). These cells disseminate in the circulation and secrete antibodies with several specificities, including the well-known heterophil anti-sheep red cell antibodies that are recognized in diagnostic tests for mononucleosis. During this early acute infection, EBV is shed in the saliva; it is not known if the source of these virions is oropharyngeal epithelial cells or B cells.

A normal immune response is extremely important in controlling the proliferation of EBV-infected B cells and spread of virus. Early in the course of the infection, IgM, and, later, IgG, antibodies are formed against viral capsid antigens. The latter persist for life. More important in the control of polyclonal B-cell proliferation are cytotoxic CD8+ T cells and NK cells. Virus-specific cytotoxic T cells appear as atypical lymphocytes in the circulation, a finding that is characteristic of acute mononucleosis. In otherwise healthy persons, the fully developed humoral and cellular responses to EBV act as brakes on viral shedding, limiting the number of infected B cells rather than eliminating them. Latent EBV remains in a few B cells and possibly oropharyngeal epithelial cells as well. As will be seen, impaired immunity in the host can have disastrous consequences.
Morphology

The major alterations involve the blood, lymph nodes, spleen, liver, central nervous system, and, occasionally, other organs. There is peripheral blood leukocytosis, with a white cell count that is usually between 12,000 and 18,000 cells/μL. Typically more than half of these cells are large, atypical lymphocytes, 12 to 16 μm in diameter, with an abundant cytoplasm that often contains azurophilic granules and an oval, indented, or folded nucleus (Fig. 12–12). These atypical lymphocytes, which are sufficiently distinctive to suggest the diagnosis, are mainly cytotoxic CD8+ T cells.

The lymph nodes are enlarged throughout the body, including the posterior cervical, axillary, and groin regions. Histologically, the enlarged nodes are flooded by atypical lymphocytes, which occupy the paracortical (T-cell) areas. Occasionally, cells resembling Reed-Sternberg cells, the hallmark of Hodgkin lymphoma, are present. Because of these atypical features, special tests are sometimes needed to distinguish the reactive changes of mononucleosis from malignant lymphoma.

The spleen is enlarged in most cases, weighing between 300 and 500 gm. The histologic changes are analogous to those of the lymph nodes, showing a heavy infiltration of atypical lymphocytes. As a result of the increase in splenic size and the infiltration of the trabeculae and capsule by the lymphocytes, such spleens are fragile and prone to rupture after even minor trauma.

Liver function is almost always transiently impaired to some degree. Histologically, atypical lymphocytes are seen in the portal areas and sinusoids, and scattered, isolated cells or foci of parenchymal necrosis filled with lymphocytes may be present. This histologic picture can be difficult to distinguish from other forms of viral hepatitis.

Clinical Course. Although mononucleosis classically presents as fever, sore throat, lymphadenitis, and the other features mentioned earlier, atypical presentations are not unusual. It can appear with little or no fever and only malaise, fatigue, and lymphadenopathy, raising the specter of lymphoma; as a fever of unknown origin, unassociated with significant lymphadenopathy or other localized findings; as hepatitis that is difficult to differentiate from one of the hepatotropic viral syndromes (Chapter 16); or as a febrile rash resembling rubella. Ultimately, the diagnosis depends on the following findings, in increasing order of specificity: (1) lymphocytosis with the characteristic atypical lymphocytes in the peripheral blood, (2) a positive heterophil reaction (monospot test), and (3) a rising titer of antibodies specific for EBV antigens (viral capsid antigens, early antigens, or Epstein-Barr nuclear antigen). In most patients, mononucleosis resolves within 4 to 6 weeks, but sometimes the fatigue lasts longer. Occasionally, one or more complications supervene. Perhaps the most common of these is hepatic dysfunction, associated with jaundice, elevated hepatic enzyme levels, disturbed appetite, and, rarely, even liver failure. Other complications involve the nervous system, kidneys, bone marrow, lungs, eyes, heart, and spleen (including fatal splenic rupture).

EBV is a potent transforming virus that plays a role in a number of human malignancies, including several types of B-cell lymphoma (Chapter 6). A serious complication in those lacking T-cell immunity (particularly organ and bone marrow transplant recipients) is that the EBV-driven B-cell proliferation can run amok, leading to death. This process can be initiated by an acute infection or the reactivation of a latent B-cell infection and generally begins as a polyclonal proliferation that progresses to overt monoclonal B-cell lymphoma over time. Reconstitution of immunity (e.g., by cessation of immunosuppressive therapy) is sometimes sufficient to cause complete regression of the B-cell proliferation, which is uniformly fatal if left untreated.

The importance of T cells and NK cells in the control of EBV infection is driven home by X-linked lymphoproliferative syndrome, a rare inherited immunodeficiency characterized by inability to mount an immune response against EBV. Most affected boys have a mutation in the SH2D1A gene, which encodes a signaling protein that is important in the activation of T cells and NK cells. On exposure to EBV, more than 50% of these boys develop an overwhelming infection that is usually fatal. Of the remainder, some develop lymphoma or hypogammaglobulinemia, the basis of which is not understood.

Reactive Lymphadenitis

Infections and nonmicrobial inflammatory stimuli not only cause leukocytosis but also involve the lymph nodes, which act as defensive barriers. Any immune response against foreign antigens is often associated with lymph node enlargement (lymphadenopathy). The infections that cause lymphadenitis are numerous and varied and may be acute or chronic. In most instances, the histologic appearance of the nodes is entirely nonspecific. A somewhat distinctive form of lymphadenitis that occurs with cat scratch disease will be described separately.
Acute Nonspecific Lymphadenitis

This form of lymphadenitis may be confined to a local group of nodes draining a focal infection, or be generalized in systemic bacterial or viral infections.

**Morphology**

Macroscopically, inflamed nodes in acute nonspecific lymphadenitis are swollen, gray-red, and engorged. Histologically, there are large germinal centers containing numerous mitotic figures. When the cause is a pyogenic organism, a neutrophilic infiltrate is seen about the follicles and within the lymphoid sinuses. With severe infections, the centers of follicles can undergo necrosis, resulting in the formation of an abscess.

Affected nodes are tender and, when abscess formation is extensive, become fluctuant. The overlying skin is frequently red, and penetration of the infection to the skin can produce draining sinuses. With control of the infection, the lymph nodes can revert to their normal appearance or, if damaged by the immune response, undergo scarring.

**Sinus Histiocytosis.** This reactive pattern is characterized by distention and prominence of the lymphatic sinusoids, owing to a marked hypertrophy of lining endothelial cells and an infiltrate of macrophages (histiocytes). Sinus histiocytosis is often encountered in lymph nodes draining cancers and may represent an immune response to the tumor or its products.

Chronic Nonspecific Lymphadenitis

This condition can assume one of three patterns, depending on the causative agent: follicular hyperplasia, paracortical hyperplasia, or sinus histiocytosis.

**Morphology**

Follicular Hyperplasia. This pattern is associated with infections or inflammatory processes that activate B cells, which enter into B-cell follicles and create the follicular (or germinal center) reaction. The cells in the reactive follicles include the activated B cells, scattered phagocytic macrophages containing nuclear debris (tingible body macrophages), and an inconspicuous meshwork of follicular dendritic cells that function in antigen display to the B cells. Causes of follicular hyperplasia include rheumatoid arthritis, toxoplasmosis, and the early stages of HIV infection. This form of lymphadenitis can be confused morphologically with follicular lymphomas (discussed later). Findings that favor a diagnosis of follicular hyperplasia are (1) the preservation of the lymph node architecture, with normal lymphoid tissue between germinal centers; (2) variation in the shape and size of the lymphoid nodules; (3) a mixed population of lymphocytes at various stages of differentiation; and (4) prominent phagocytic and mitotic activity in germinal centers.

Paracortical Hyperplasia. This pattern is characterized by reactive changes within the T-cell regions of the lymph node. On immune activation parafollicular T cells transform into large proliferating immunoblasts that can efface the B-cell follicles. Paracortical hyperplasia is encountered in viral infections (such as EBV), following certain vaccinations (e.g., smallpox), and in immune reactions induced by certain drugs (especially phenytoin).

Sinus Histiocytosis. This reactive pattern is characterized by distention and prominence of the lymphatic sinusoids, owing to a marked hypertrophy of lining endothelial cells and an infiltrate of macrophages (histiocytes). Sinus histiocytosis is often encountered in lymph nodes draining cancers and may represent an immune response to the tumor or its products.

Cat Scratch Disease

Cat scratch disease is a self-limited lymphadenitis caused by the bacterium *Bartonella henselae*. It is primarily a disease of childhood; 90% of the patients are younger than 18 years of age. It presents as regional lymphadenopathy, most frequently in the axilla and neck. The nodal enlargement appears approximately 2 weeks after a feline scratch or, uncommonly, after a splinter or thorn injury. A raised, inflammatory nodule, vesicle, or eschar is sometimes visible at the site of skin injury. In most patients the lymph node enlargement regresses over the next 2 to 4 months. Rarely, patients develop encephalitis, osteomyelitis, or thrombocytopenia.

**Morphology**

The anatomic changes in the lymph node in cat scratch disease are quite characteristic. Initially, sarcoid-like granulomas are formed, but these then undergo central necrosis associated with the accumulation of neutrophils. These irregular stellate necrotizing granulomas are similar in appearance to those seen in certain other infections, such as lymhogranuloma venereum. The microbe is extracellular and can be visualized only with silver stains or electron microscopy. The diagnosis is based on a history of exposure to cats, the clinical findings, a positive skin test to the microbial antigen, and the distinctive morphologic changes in the lymph nodes.

**NEOPLASTIC PROLIFERATIONS OF WHITE CELLS**

Tumors represent the most important of the white cell disorders. They can be divided into three broad categories based on the origin of the tumor cells:

- **Lymphoid neoplasms**, which include non-Hodgkin lymphomas (NHLs), Hodgkin lymphomas, lymphocytic leukemias, and plasma cell dyscrasias and related disorders. In many instances these tumors are composed of cells that resemble normal stages of lymphocyte differentiation, a feature that serves as one of the bases for their classification.
- **Myeloid neoplasms** arise from stem cells that normally give rise to the formed elements of the blood: granulocytes, red cells, and platelets. The myeloid neoplasms fall into three fairly distinct subcategories: acute myelogenous leukemias, in which immature progeni-
tor cells accumulate in the bone marrow; chronic myeloproliferative disorders, in which inappropriately increased production of formed blood elements leads to elevated blood cell counts; and myelodysplastic syndromes, which are characteristically associated with ineffective hematopoiesis and cytopenias. • Histiocytic neoplasms represent proliferative lesions of histiocytes. Of special interest is a spectrum of proliferations comprising Langerhans cells (the Langerhans cell histiocytoses).

Lymphoid Neoplasms

The lymphoid neoplasms encompass a group of entities that vary widely in their clinical presentation and behavior, thus presenting challenges to students and clinicians alike. Some of these neoplasms characteristically appear as leukemias, tumors that primarily involve the bone marrow with spillage of neoplastic cells into the peripheral blood. Others tend to present as lymphomas, tumors that produce masses in involved lymph nodes or other tissues. Plasma cell tumors, the plasma cell dyscrasias, usually present within the bones as discrete masses and cause systemic symptoms related to the production of a complete or partial monoclonal immunoglobulin. Despite these tendencies, all lymphoid neoplasms have the potential to spread to lymph nodes and various tissues throughout the body, especially the liver, spleen, and bone marrow. In some cases lymphomas or plasma cell tumors spill over into the peripheral blood, creating a leukemia-like picture. Conversely, leukemias of lymphoid cells, originating in the bone marrow, can infiltrate lymph nodes and other tissues, creating the histologic picture of lymphoma. Because of the overlap in clinical presentations, the various lymphoid neoplasms can only be distinguished based on the appearance and molecular characteristics of the tumor cells. Stated another way, for purposes of diagnosis and prognostication, it is most helpful to focus on what the tumor cell is, not where it resides in the patient.

Two groups of lymphomas are recognized: Hodgkin lymphoma and non-Hodgkin lymphomas. Although both arise most commonly in lymphoid tissues, Hodgkin lymphoma is set apart by the presence of distinctive neoplastic Reed-Sternberg giant cells (see below), which in involved nodes are usually greatly outnumbered by non-neoplastic inflammatory cells. The biologic behavior and clinical treatment of Hodgkin lymphoma are also different from those of most NHLs, making the distinction of practical importance.

Historically, few areas of pathology have evoked as much controversy and confusion as the classification of lymphoid neoplasms, which is perhaps inevitable given the intrinsic complexity of the immune system from which they arise. Great progress has been made over the last decade in this area, however, and an international working group of pathologists, molecular biologists, and clinicians working on behalf of the World Health Organization (WHO) has formulated a widely accepted classification scheme that relies on a combination of morphologic, phenotypic, genotypic, and clinical features. Before we delve into the classification of lymphoid neoplasms, certain important relevant principles should be emphasized:

• B- and T-cell tumors are often composed of cells that are arrested or derived from specific stages of their normal differentiation pathways (Fig. 12–13). The diagnosis and classification of these tumors relies heavily on tests (either immunohistochemistry or flow cytometry) that detect lineage-specific antigens (e.g., B-cell, T-cell, and NK-cell markers) and markers of maturity. As will become evident, many such markers are identified according to their cluster of differentiation (CD) number.

• The most common lymphomas of adults are derived from follicular center or post-follicular center B cells. This conclusion is drawn from molecular analyses, which have shown that most B-cell lymphomas have undergone somatic hypermutation, an activity that is confined to follicular center B cells. Follicular center B cells also undergo immunoglobulin class switching, and together with somatic hypermutation, these forms of regulated genomic instability seem to place B cells at a relatively high risk for mutations that can lead to transformation. In fact, many recurrent chromosomal translocations that are commonly seen in mature B-cell malignancies involve the immunoglobulin (Ig) loci and seem to stem from mistakes that are made during attempted recombination events involving Ig genes. In this regard, it is interesting that mature T cells (which are genomically stable) give rise to lymphomas much less frequently and very rarely have chromosomal translocations involving the T-cell receptor loci.

• All lymphoid neoplasms are derived from a single transformed cell and are therefore monoclonal. As will be recalled from Chapter 5, during the differentiation of precursor B and T cells there is a somatic rearrangement of their antigen receptor genes. This process ensures that each lymphocyte makes a single, unique antigen receptor. Because antigen receptor gene rearrangement precedes transformation, the daughter cells derived from a given malignant progenitor share the same antigen receptor gene configuration and synthesize identical antigen receptor proteins (either immunoglobulins or T-cell receptors). For this reason, analysis of antigen receptor genes and their protein products is frequently used to differentiate monoclonal neoplasms from polyclonal, reactive processes.

• As tumors of the immune system, lymphoid neoplasms often disrupt normal immune regulatory mechanisms. Both immunodeficiency (as evidenced by susceptibility to infection) and autoimmunity can be seen, sometimes in the same patient. Ironically, patients with inherited or acquired immunodeficiency are themselves at high risk of developing certain lymphoid neoplasms, particularly those associated with EBV infection.

• Although NHLs often present at a particular tissue site, sensitive molecular assays usually show that the tumor is widely disseminated at the time of diagnosis. As a result, with few exceptions, only systemic therapies are curative. In contrast, Hodgkin lymphoma often presents at a single site and spreads in a pre-
dictable fashion to contiguous lymph node groups. For this reason, early in its course, local therapy may be indicated.

The WHO classification of lymphoid neoplasms considers the morphology, cell of origin (determined in practice by immunophenotyping), clinical features, and genotype (e.g., karyotype, presence of viral genomes) of each entity. It includes all lymphoid neoplasms, including leukemias and multiple myeloma, and segregates them on the basis of origin into three major categories: (1) tumors of B cells, (2) tumors of T cells and NK cells, and (3) Hodgkin lymphoma.

An updated version of the WHO classification of lymphoid neoplasms is presented in Table 12–7. As can be seen, the diagnostic entities are numerous. Our focus will be on the subset of neoplasms listed below, which together constitute more than 90% of the lymphoid neoplasms seen in the United States:

- Precursor B- and T-cell lymphoblastic leukemia/lymphoma (commonly called acute lymphoblastic leukemia, or ALL)
- Small lymphocytic lymphoma/chronic lymphocytic leukemia
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphomas
- Burkitt lymphoma
- Multiple myeloma and related plasma cell dyscrasias
- Hodgkin lymphoma

The salient features of the more common lymphoid neoplasms are summarized in Table 12–8. We will also touch on a few of the uncommon entities that have distinctive clinicopathologic features.

Precursor B- and T-Cell Lymphoblastic Leukemia/Lymphoma

These are aggressive tumors, composed of immature lymphocytes (lymphoblasts), which occur predominantly in children and young adults. The various lymphoblastic tumors are morphologically indistinguishable and often cause similar signs and symptoms. Because precursor B- and T-cell neoplasms have overlapping features, we will consider them together.

Just as B-cell precursors normally develop within the bone marrow, pre-B-lymphoblastic tumors characteristically appear in bone marrow and peripheral blood as leukemias. Similarly, pre-T-lymphoblastic tumors commonly present as masses involving the thymus, which is the
Leukemias are rapidly growing tumors, normal bone marrow progenitors grow at an even more rapid rate. The principal pathogenetic problem in acute leukemia is a block in differentiation. This leads to the accumulation of immature leukemic blasts in the bone marrow, which suppress the function of normal hematopoietic stem cells by physical displacement and other poorly understood mechanisms. Eventually bone marrow failure results, which accounts for the major clinical manifestations of acute leukemia. Thus, the therapeutic goal is to reduce the leukemic clone sufficiently to allow normal hematopoiesis to resume.

Clinical Features of Acute Leukemias. The acute leukemias have the following characteristics:

- **Abrupt stormy onset.** Most patients present within 3 months of the onset of symptoms.
- **Symptoms related to depression of normal marrow function.** These include fatigue (due mainly to anemia), fever (reflecting infections resulting from the absence of mature leukocytes), and bleeding (petechiae, ecchymoses, epistaxis, gum bleeding) secondary to thrombocytopenia.
- **Bone pain and tenderness.** These result from marrow expansion and infiltration of the subperiosteum.
- **Generalized lymphadenopathy, splenomegaly, and hepatomegaly.** These reflect dissemination of the leukemic cells, and are more pronounced in ALL than in AML.
- **Central nervous system manifestations.** These include headache, vomiting, and nerve palsies resulting from meningeal spread; these features are more common in children than in adults and are more common in ALL than AML.

Laboratory Findings of Acute Leukemias. The diagnosis of acute leukemia rests on the identification of blast forms in the peripheral blood and the bone marrow. The white cell count is variable; it is sometimes elevated to more than 100,000 cells/μL, but in about 50% of patients it is less than 10,000 cells/μL. Anemia is almost always present, and the platelet count is usually below 100,000 platelets/μL. Neutropenia is also a common finding in the peripheral blood. Uncommonly the peripheral blood examination shows pancytopenia but no blasts (aleukemic leukemia); here, the diagnosis can only be established by examining the bone marrow.

**Morphology**

**Because of different responses to therapy, it is of great practical importance to distinguish ALL from AML.** By definition, in ALL, blasts compose more than 25% of the marrow cellularity. The nuclei of lymphoblasts in Wright-Giemsa-stained preparations have somewhat coarse and clumped chromatin and one or two nucleoli (Fig. 12-14A); myeloblasts tend to have finer chromatin and more cytoplasm, which may contain granules (Fig. 12-14B). The cytoplasm of lymphoblasts often contains large aggregates of periodic acid–Schiff-positive material, whereas myeloblasts are often peroxidase positive.
### Table 12-8  Summary of the More Common Lymphoid Neoplasms

<table>
<thead>
<tr>
<th>Entity</th>
<th>Frequency</th>
<th>Salient Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor B-cell lymphoblastic</td>
<td>85% of childhood acute leukemia/lymphoma</td>
<td>Lymphoblasts with irregular nuclear contours, condensed chromatin, small nucleoli, and scant agranular cytoplasm</td>
</tr>
<tr>
<td>leukemia/lymphoma</td>
<td>15% of childhood acute leukemia; 40% of childhood lymphomas</td>
<td>Identical to precursor B-cell lymphoblastic leukemia/lymphoma</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma/chronic</td>
<td>3% to 4% of adult lymphomas; 30% of all leukemias</td>
<td>Small resting lymphocytes mixed with variable numbers of large activated cells; lymph nodes diffusely effaced</td>
</tr>
<tr>
<td>lymphocytic leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>40% of adult lymphomas</td>
<td>Frequent small “cleaved” cells mixed with large cells; growth pattern is usually nodular (follicular)</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>3% to 4% of adult lymphomas</td>
<td>Small to intermediate-sized irregular lymphocytes growing in a diffuse pattern</td>
</tr>
<tr>
<td>Extranodal marginal zone lymphoma</td>
<td>∼5% of adult lymphomas</td>
<td>Variable cell size and differentiation; 40% show plasmacytic differentiation; B cells home to epithelium, creating “lymphoepithelial lesions”</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>40% to 50% of adult lymphomas</td>
<td>Variable; most resemble large germinal center B cells; diffuse growth pattern</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>&lt;1% of lymphomas in the United States</td>
<td>Intermediate-sized round lymphoid cells with several nucleoli; diffuse tissue involvement associated with apoptosis produces a “starry-sky” appearance</td>
</tr>
<tr>
<td>Plasmacytoma/plasma cell myeloma</td>
<td>Most common lymphoid neoplasm in older adults</td>
<td>Plasma cells in sheets, sometimes with prominent nucleoli or inclusions containing Ig</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>Most common cutaneous lymphoid malignancy</td>
<td>In most cases, small lymphoid cells with markedly convoluted nuclei; cells often infiltrate the epidermis (Pautrier microabscesses)</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, not</td>
<td>Most common adult T-cell lymphoma</td>
<td>Variable; usually a spectrum of small to large lymphoid cells with irregular nuclear contours</td>
</tr>
<tr>
<td>otherwise specified (NOS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma, nodular sclerosis</td>
<td>Most common type of Hodgkin lymphoma</td>
<td>Lacunar Reed-Sternberg cell variants in a mixed inflammatory background; broad sclerotic bands of collagen usually also present</td>
</tr>
<tr>
<td>type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma, mixed cellularity</td>
<td>Second most common form of Hodgkin lymphoma</td>
<td>Frequent classic Reed-Sternberg cells in a mixed inflammatory background</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; Ig, immunoglobulin.
## Immunophenotype

<table>
<thead>
<tr>
<th>Immunophenotype</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TdT+ immature B cells (CD19+, variable expression of other B-cell markers)</td>
<td>Usually presents as acute leukemia; less common in adults; prognosis is predicted by karyotype</td>
</tr>
<tr>
<td>TdT+ immature T cells (CD2+, CD7+, variable expression of other T-cell markers)</td>
<td>Most common in adolescent males; often presents as a mediastinal mass due to thymic involvement; highly associated with mutations in NOTCH1</td>
</tr>
<tr>
<td>CD5+ B-cell expressing surface Ig</td>
<td>Occurs in older adults; usually involves nodes, marrow, and spleen; most patients have peripheral blood involvement; indolent</td>
</tr>
<tr>
<td>CD10+ BCL2+ mature B cells that express surface Ig</td>
<td>Occurs in older adults; usually involves nodes, marrow, and spleen; associated with t(14;18); indolent</td>
</tr>
<tr>
<td>CD5+ mature B cells that express cyclin D1 and have surface Ig</td>
<td>Occurs mainly in older males; usually involves nodes, marrow, and spleen; GI tract also commonly affected; t(11;14) is characteristic; moderately aggressive</td>
</tr>
<tr>
<td>CD5- CD10- mature B cells with surface Ig</td>
<td>Frequently occurs at extranodal sites involved by chronic inflammation; very indolent; may be cured by local excision</td>
</tr>
<tr>
<td>Mature B cells with variable expression of CD10 and surface Ig</td>
<td>Occurs in all ages, but most common in older adults; often arise at extranodal sites; aggressive</td>
</tr>
<tr>
<td>Mature CD10+ B cells expressing surface Ig</td>
<td>Endemic in Africa, sporadic elsewhere; increased frequency in immunosuppressed patients; predominantly affects children; often presents with visceral involvement; highly aggressive</td>
</tr>
<tr>
<td>Terminally differentiated plasma cells containing cytoplasmic Ig</td>
<td>Myeloma presents as disseminated bone disease, often with destructive lytic lesions. Hypercalcemia, renal insufficiency, and bacterial infections are common</td>
</tr>
<tr>
<td>CD4+ mature T cells</td>
<td>Presents with localized or more generalized skin involvement; generally indolent. Sézary syndrome, a more aggressive variant, is characterized by diffuse skin erythema and peripheral blood involvement</td>
</tr>
<tr>
<td>Mature T-cell phenotype (CD3+)</td>
<td>Probably spans a diverse collection of rare tumors. Often disseminated, generally aggressive</td>
</tr>
<tr>
<td>CD15+, CD30+ Reed-Sternberg cells</td>
<td>Most common in young adults, often arises in the mediastinum or cervical lymph nodes</td>
</tr>
<tr>
<td>CD15+, CD30+ Reed-Sternberg cells</td>
<td>Most common in men, more likely to present at advanced stages than the nodular sclerosis type EBV+ in 70% of cases</td>
</tr>
</tbody>
</table>

Having completed our “short course” in acute leukemia, we will return to lymphoblastic leukemia/lymphoma; the AMLs are discussed later.

**Immunophenotyping.** Immunophenotyping is very useful in subtyping lymphoblastic tumors and distinguishing them from AML. Terminal deoxytransferase, an enzyme that is specifically expressed in pre-B and pre-T cells, is present in more than 95% of cases. Further subtyping of ALL into pre-B- and pre-T-cell types relies on stains for lineage-specific markers, such as CD19 (B cell) and CD3 (T cell). Although immunophenotyping has historically proven somewhat useful in predicting clinical outcome, the tumor karyotype provides more robust and specific prognostic information.

**Karyotypic Changes.** Approximately 90% of patients with lymphoblastic leukemia/lymphoma have nonrandom karyotypic abnormalities. Most common in pre-B-cell tumors is hyperdiploidy (>50 chromosomes/cell), which is associated with the presence of a cryptic (12;21) chromosomal translocation involving the **TEL1** and **AML1** genes. The presence of these aberrations correlates with a good outcome. Poor outcomes are observed with pre-B-cell tumors that have translocations involving the **MLL** gene on chromosome 11q23 or the Philadelphia (Ph) chromosome. Pre-T-cell tumors are associated with a group of chromosomal rearrangements that are completely different than those found in pre-B-cell tumors, but none is predictive of outcome.

**Activating Mutations in NOTCH1.** NOTCH1 is a transmembrane receptor whose activity is essential for normal T-cell development. NOTCH1 signals promote the proliferation and survival of pre-T cells and are capable of causing stem cells to differentiate into pre-T cells outside of the thymus. Interestingly, 55% to 60% of pre-T-cell tumors have activating point mutations in NOTCH1, indicating that the NOTCH1 signaling pathway plays a central role in the development of many pre-T ALLs. The ability of NOTCH1 to promote T-cell development outside the thymus may explain why some patients with pre-T-cell tumors have bone marrow disease and no thymic involvement.
Prognosis. Treatment of lymphoblastic tumors of childhood represents one of the great success stories in oncology. Children 2 to 10 years of age have the best prognosis; most can be cured. Other groups of patients do less well. Variables correlated with worse outcomes include male gender, age younger than 2 or older than 10 years, and a high leukocyte count at diagnosis. Age-dependent differences in the frequencies of various karyotypic abnormalities are likely to explain the relationship of age to outcome. Tumors with rearrangements of MLL or the Ph chromosome (both associated with a poor outcome) are most common in children younger than age 2 and adults, respectively, whereas tumors with “good prognosis” chromosomal aberrations (such as the t[12;21] and hyperdiploidy) are common in the 2- to 10-year age group.

Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia

These two disorders are morphologically, phenotypically, and genotypically identical, differing only in the extent of peripheral blood involvement. Arbitrarily, if the peripheral blood lymphocytosis exceeds 4000 cells/mm³, the patient is diagnosed with chronic lymphocytic leukemia (CLL); if not, a diagnosis of small lymphocytic lymphoma (SLL) is made. Most patients fit the criteria for CLL, which is the most common leukemia of adults in the western world. In contrast, SLL constitutes only 4% of NHLs. For unclear reasons, both CLL and SLL are much less common in Asia.

Pathophysiology. The neoplastic B cells, through mechanisms that are not understood, suppress normal B-cell function, often resulting in hypogammaglobulinemia. Paradoxically, approximately 15% of patients have autoantibodies against autologous red cells; other autoantibodies can also be detected. When present, these autoantibodies are made by nontumor B cells, indicating that there is a general breakdown in immune regulation. As time passes the tumor cells tend to displace the normal marrow elements, leading to anemia, neutropenia, and eventual thrombocytopenia.

Immunophenotype, Karyotype, and Molecular Features. CLL/SLL is a neoplasm of mature B cells expressing the pan-B-cell markers CD19, CD20, and CD23 and surface immunoglobulin heavy and light chains. The tumor cells also express CD5, a tendency that is shared (among the B-cell neoplasms) only by mantle cell lymphoma. Approximately 50% of patients have karyotypic abnormalities, the most common of which are trisomy 12 and deletions of chromosomes 11 and 12. Unlike other lymphoid neoplasms, chromosomal translocations are rare. Of interest, most CLL/SLLs have undergone somatic hypermutation of their immunoglobulin segments, a finding that is consistent with an origin from a post–follicular center B cell (possibly a memory cell). Less commonly these tumors are derived from naive B cells that have not undergone a follicular center reaction; such tumors appear to have a substantially worse prognosis.

Clinical Features. CLL/SLL is often asymptomatic at presentation. The most common symptoms are nonspecific and include easy fatigability, weight loss, and anorexia. Generalized lymphadenopathy and hepat-
**Morphology**

Lymph nodes are effaced by proliferations that usually have a distinctly nodular appearance (Fig. 12–16A). The tumor cells resemble normal follicular center B cells. Most commonly, the predominant neoplastic cells are “centrocyte-like” cells slightly larger than resting lymphocytes that have angular “cleaved” nuclear contours with prominent indentations and linear infoldings (see Fig. 12–16B). The nuclear chromatin is coarse and condensed, and nucleoli are indistinct. These small, cleaved cells are mixed with variable numbers of larger “centroblast-like” cells that have vesicular chromatin, several nucleoli, and modest amounts of cytoplasm. In most tumors, centroblast-like cells are a minor component of the overall cellularity, mitoses are infrequent, and single necrotic cells (cells undergoing apoptosis) are not seen. These findings help to distinguish neoplastic follicles from reactive follicles, in which mitoses and apoptosis are prominent. Uncommonly, centroblast-like cells predominate, a histology that correlates with a more aggressive clinical behavior.

**Immunophenotype and Molecular Features.** These tumors express the pan-B-cell markers CD19 and CD20, CD10, and BCL6, a transcription factor that is required for follicular center formation. In addition, the neoplastic cells characteristically express BCL2, a protein that is absent from normal follicular B cells. As would be expected of a B cell–derived tumor, the immunoglobulin genes show evidence of somatic hypermutation.

**Karyotype.** The majority of tumors have a characteristic t(14;18) translocation. This translocation fuses the BCL2 gene on chromosome 18q21 to the IgH locus on chromosome 14 and leads to the inappropriate expression of BCL2 protein, which functions to prevent apoptosis (Chapter 6).

**Clinical Features.** Follicular lymphoma occurs predominantly in older persons (rarely before age 20 years) and affects males and females equally. It usually presents as painless lymphadenopathy, which is frequently generalized. Involvement of visceral sites is uncommon, but the bone marrow almost always contains lymphoma at the time of diagnosis. The natural history is prolonged (median survival, 7–9 years), but follicular lymphoma is not easily curable, a feature that is common to most of the indolent lymphoid malignancies. Their incurability may be related in part to the elevated levels of BCL2, which may protect tumor cells from the effects of chemotherapeutic agents. In about 40% of patients, follicular lymphoma progresses to a diffuse large B-cell lymphoma, with or without treatment. This is an ominous transition, because tumors arising from such conversions are much less curable than de novo diffuse large B-cell lymphomas, described later.

**Figure 12–16**

Follicular lymphoma, involving a lymph node. **A,** Nodular aggregates of lymphoma cells are present throughout. **B,** At high magnification, small lymphoid cells with condensed chromatin and irregular or cleaved nuclear outlines (centrocytes) are mixed with a population of larger cells with nucleoli (centroblasts). (**A,** Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)
Mantle Cell Lymphoma

Mantle cell lymphomas are composed of B cells that resemble cells in the mantle zone of normal lymphoid follicles. They constitute approximately 4% of all NHLs and occur mainly in older males.

**Morphology**

Mantle cell lymphomas involve lymph nodes in a diffuse or vaguely nodular pattern. The tumor cells are usually slightly larger than normal lymphocytes and have an irregular nucleus and inconspicuous nucleoli. Less commonly, the cells are larger and morphologically resemble lymphoblasts. The bone marrow is involved in the majority of cases, and about 20% of patients have peripheral blood involvement. One unexplained but characteristic tendency is the frequent involvement of the gastrointestinal tract, sometimes in the form of multifocal submucosal nodules that grossly resemble polyps (lymphomatoid polyposis).

**Immunophenotype.** The tumor cells usually coexpress surface IgM and IgD, the pan–B-cell antigens CD19 and CD20, and (like CLL/SLL) CD5. Mantle cell lymphoma is distinguished from CLL/SLL by the absence of proliferation centers and the presence of cyclin D1 protein.

**Karyotype and Molecular Features.** Most (and possibly all) tumors have a t(11;14) translocation that fuses the cyclin D1 gene on chromosome 11 to the IgH locus on chromosome 14. This translocation dysregulates the expression of cyclin D1, a cell cycle regulator (Chapter 6), and explains the characteristically increased cyclin D1 protein levels. The immunoglobulin loci have not undergone somatic hypermutation, consistent with an origin from a naive B cell.

**Clinical Features.** Most patients present with fatigue and lymphadenopathy and are found to have generalized disease involving the bone marrow, spleen, liver, and (often) the gastrointestinal tract. These tumors are aggressive and incurable, and are associated with a median survival of 3 to 5 years.

Diffuse Large B-Cell Lymphoma

This diagnostic category includes several forms of NHL that share certain features, including a B-cell phenotype, a diffuse growth pattern, and an aggressive clinical history. As a group, this is the most important type of lymphoma in adults, as it accounts for approximately 50% of adult NHL.

**Morphology**

The nuclei of the neoplastic B cells are large (at least three to four times the size of resting lymphocytes) and can take a variety of forms. In many tumors, cells with round, irregular, or cleaved nuclear contours, dispersed chromatin, several distinct nucleoli, and modest amounts of pale cytoplasm predominate (Fig. 12–17). Such cells resemble “centroblasts,” the large cells that are seen in reactive lymphoid follicles. In other tumors, the cells have a large round or multilobulated vesicular nucleus, one or two centrally placed prominent nucleoli, and abundant cytoplasm that can be either pale or intensely staining. These cells resemble an “immunoblast,” a type of antigen-activated lymphocyte that is normally found in the paracortex of lymph nodes.

**Immunophenotype and Molecular Features.** These are mature B-cell tumors that express pan–B-cell antigens, such as CD19 and CD20. Many also express surface IgM and/or IgG. Other antigens (e.g., CD10) are variably expressed. These tumors uniformly demonstrate somatic hypermutation of immunoglobulin genes, consistent with an origin from a follicular or post-follicular center B cell.

**Karyotype.** Approximately 30% of tumors have a t(14;18) translocation involving the BCL2 gene. Such tumors may represent “transformed” follicular lymphomas. About one-third have rearrangements of the BCL6 gene, located on 3q27, and mutations in BCL6 are seen in an even higher fraction of tumors. Both the translocations and the mutations seem to cause inappropriate increases in BCL6 protein levels.

**Distinct Subtypes.** Several distinctive clinicopathologic subtypes are included in the general category of diffuse large B-cell lymphoma. EBV is implicated in the pathogenesis of diffuse large B-cell lymphomas that arise in the setting of the acquired immunodeficiency syndrome (AIDS) and iatrogenic immunosuppression (e.g., in transplant patients). In the post-transplant setting, these tumors often begin as EBV-driven polyclonal B-cell proliferations that may regress if immune function is restored. Otherwise, with time, progression to mono-
clonal large B-cell lymphoma is observed. Kaposi sarcoma herpesvirus (KSHV), also called human herpesvirus type 8 (HHV-8) is associated with a rare group of tumors that present as primary effusion lymphomas within the pleura, pericardium, or peritoneum. The tumor cells are latently infected with KSHV, which encodes proteins homologous to several known oncoproteins, including cyclin D1. Patients with these primary effusion lymphomas are usually immunosuppressed. Note that this virus is also associated with Kaposi sarcoma in AIDS patients (Chapter 5). Mediastinal large B-cell lymphoma usually presents in young females and shows a predilection for spread to abdominal viscera and the central nervous system.

Clinical Features. Although the median age at presentation is about 60 years, diffuse large B-cell lymphomas can arise at any age; they constitute about 15% of childhood lymphomas. Patients typically present with a rapidly enlarging, often symptomatic mass at one or several sites. Extramedullary presentations are common. Although the gastrointestinal tract and the brain are among the more frequent extranodal sites, these tumors can arise in virtually any organ or tissue. Unlike the more indolent lymphomas (e.g., follicular lymphoma), involvement of the liver, spleen, and bone marrow is not common at the time of diagnosis.

Diffuse large cell B-cell lymphomas are aggressive tumors that are rapidly fatal if untreated. With intensive combination chemotherapy, however, complete remission can be achieved in 60% to 80% of the patients; of these, approximately 50% remain free of disease for several years and are often cured. For those not cured with conventional therapy, other more aggressive treatments (e.g., high-dose therapy and bone marrow transplantation) offer some hope. Microarray-based molecular profiling of these tumors may improve the ability to predict the response to current therapies and perhaps even identify targets for new therapeutic approaches (Chapter 6).

Burkitt Lymphoma

Burkitt lymphoma is endemic in some parts of Africa and sporadic in other areas, including the United States. Histologically, the African and nonendemic diseases are identical, although there are clinical and virologic differences. The relationship of these disorders to EBV is discussed in Chapter 6.

**Morphology**

The tumor cells are uniform and intermediate in size and have round or oval nuclei containing two to five prominent nucleoli (Fig. 12–18). The nuclear size approximates that of benign macrophages within the tumor. There is a moderate amount of basophilic or amphophilic cytoplasm, which on smears is often seen to contain small, lipid-filled vacuoles. A high mitotic rate is very characteristic of this tumor, as is cell death, accounting for the presence of numerous tissue macrophages containing ingested nuclear debris. Because these benign macrophages are often surrounded by a clear space, they create a “starry sky” pattern.

**Immunophenotype and Molecular Features.** These B-cell tumors express surface IgM, κ or λ light chain, the pan–B-cell markers CD19 and CD20, and CD10. The immunoglobulin genes are somatically hypermutated, consistent with an origin from a follicular center B cell.

**Karyotype.** Burkitt lymphoma is always associated with translocations involving the MYC gene on chromosome 8. Most translocations fuse MYC with the IgH gene on chromosome 14, but variant translocations involving the κ or λ light chain loci on chromosomes 2 and 22, respectively, are also observed. The net result of each is the dysregulation and overexpression of the MYC protein. The role of Myc in transformation was discussed in Chapter 6.

Clinical Features. Both the endemic and nonendemic forms affect mainly children and young adults. Burkitt lymphoma accounts for approximately 30% of childhood NHLs in the United States. In both forms, the disease usually arises at extranodal sites. In African patients, involvement of the maxilla or mandible is the common mode of presentation, whereas abdominal tumors involving the bowel, retroperitoneum, and ovaries are more common in North America. Leukemic presentations are uncommon, especially in the endemic form, but do occur and must be distinguished from acute lymphoblastic leukemias, which respond to different drug regimens. Burkitt lymphoma is a high-grade tumor that is among the fastest growing human neoplasms; however, with very aggressive chemotherapy regimens, the majority of patients can be cured.

**Multiple Myeloma and Related Plasma Cell Disorders**

The common feature that is shared among multiple myeloma and the plasma cell dyscrasias is that all originate from a clone of B cells that differentiates into
plasma cells and secretes a single complete or partial immunoglobulin. Because the serum usually contains excessive amounts of immunoglobulins, these disorders have also been called monoclonal gammopathies, and the associated immunoglobulin is often referred to as an M component. Although the presence of an M component may be indicative of an overt B-cell malignancy, M components are fairly common in otherwise normal elderly persons, a condition known as monoclonal gammopathy of undetermined significance. Collectively, these disorders account for about 15% of deaths from tumors of white blood cells; they are most common in middle-aged and elderly persons.

The plasma cell dyscrasias can be divided into six major variants: (1) multiple myeloma, (2) localized plasmacytoma (solitary myeloma), (3) lymphoplasmacytic lymphoma, (4) heavy-chain disease, (5) primary or immunocyte-associated amyloidosis, and (6) monoclonal gammopathy of undetermined significance. In all forms, the immunoglobulin genes are somatically hypermutated, consistent with an origin from a post-follicular center B cell. Each of these disorders will be briefly described, and then the morphologic features of the more common forms will be presented.

Multiple Myeloma. Multiple myeloma, by far the most common of the malignant plasma cell dyscrasias, is a clonal proliferation of neoplastic plasma cells in the bone marrow that is usually associated with multifocal lytic lesions throughout the skeletal system. The proliferation of neoplastic plasma cells, also called myeloma cells, is supported by the cytokine interleukin 6 (IL-6), which is produced by fibroblasts and macrophages in the bone marrow stroma. As is true of other B-cell malignancies, it has been appreciated recently that many myelomas have chromosomal translocations involving the IgH locus on chromosome 14. The identified fusion partners include the cyclin D1, fibroblast growth factor receptor 3, and cyclin D3 genes; late in the course, translocations involving MYC are sometimes observed. As might be surmised by the list of genes involved by chromosomal translocations, dysregulation of D cyclins seems to be of general importance in multiple myeloma.

The most common M component is IgG (60%), followed by IgA (20% to 25%); only rarely is it IgM, IgD, or IgE. In the remaining 15% to 20% of cases, the plasma cells produce only κ or λ light chains. Because of their low molecular weight, the free light chains are rapidly excreted in the urine, where they are termed Bence-Jones proteins. Even more commonly, malignant plasma cells secrete complete immunoglobulin molecules and free light chains and thus produce both serum M components and Bence-Jones proteins. As will be seen, the excess light chains have untoward effects on renal function and are an important aspect of the pathophysiology of multiple myeloma.

Localized Plasmacytoma. These are solitary lesions involving the skeleton or the soft tissues. Skeletal plasmacytomas tend to occur in the same locations as multiple myeloma, whereas extraneous lesions occur mainly in the upper respiratory tract (sinuses, nasopharynx, larynx). Modestly elevated M proteins are demonstrable in some of these patients. Those with solitary skeletal plasmacytomas usually have occult disease elsewhere, and most develop full-blown multiple myeloma over a period of 5 to 10 years. Extraneous (soft tissue) plasmacytomas spread less commonly and are often cured by local resection.

Lymphoplasmacytic Lymphoma. This tumor is composed of a mixed proliferation of B cells that range from small round lymphocytes to plasmacytic lymphocytes to plasma cells. It behaves like an indolent B-cell lymphoma and commonly involves multiple lymph nodes, the bone marrow, and the spleen at the time of presentation. It is included in the plasma cell dyscrasias because the tumor produces an M component, but, unlike multiple myeloma, it consists in most cases of IgM. Often, the large amount of IgM causes the blood to become viscous, producing a syndrome called Waldenström macroglobulinemia, described below. Other symptoms are related to the infiltration of various tissues, particularly the bone marrow, by tumor cells. The synthesis of immunoglobulin heavy and light chains is balanced, so free light chains and Bence-Jones proteinuria are not seen. Unlike myeloma, this disease does not produce lytic bone lesions.

Heavy-Chain Disease. This is not a specific entity but a group of proliferations in which only heavy chains are produced, most commonly IgA. IgA heavy-chain disease shows a predilection for the lymphoid tissues where IgA is normally produced, such as the small intestine and respiratory tract, and may represent a variant of MALT lymphoma (discussed later). The less common IgG heavy-chain disease often presents as diffuse lymphadenopathy and hepatosplenomegaly and histologically resembles lymphoplasmacytic lymphoma.

Primary or Immunocyte-Associated Amyloidosis. It may be recalled that a monoclonal proliferation of plasma cells that secrete free light chains underlies this form of amyloidosis (Chapter 5). The amyloid deposits (of AL type) consist of partially degraded light chains.

Monoclonal Gammapathy of Undetermined Significance. Monoclonal gammapathy of undetermined significance (MGUS) is the term applied to monoclonal gammapathies that are detected in asymptomatic individuals. M proteins are found in the serum of 1% to 3% of asymptomatic healthy persons older than age 50 years, making this the most common plasma cell dyscrasia. Despite the name, it is increasingly apparent that MGUS is a precursor lesion that should be considered a form of neoplasia. Patients with MGUS develop a well-defined plasma cell dyscrasia (myeloma, lymphoplasmacytic lymphoma, or amyloidosis) at a rate of 1% per year. Moreover, MGUS cells often contain the same chromosomal translocations that are found in full-blown multiple myeloma. Thus, the diagnosis of MGUS should be made with caution and only after careful exclusion of all other forms of monoclonal gammapathies, particularly multiple myeloma. In general, patients with MGUS have less than 3 gm/dL of monoclonal protein in the serum and no Bence-Jones proteinuria.
Morphology

Multiple myeloma presents most often as multifocal destructive bone lesions throughout the skeletal system. Although any bone can be affected, the following distribution was found in a large series of cases: vertebral column, 66%; ribs, 44%; skull, 41%; pelvis, 28%; femur, 24%; clavicle, 10%; and scapula, 10%. These focal lesions generally begin in the medullary cavity, erode the cancellous bone, and progressively destroy the cortical bone. The bone resorption results from the secretion of certain cytokines (e.g., IL-1β, tumor necrosis factor, IL-6) by myeloma cells. These cytokines stimulate production of another cytokine called RANK-ligand, which promotes the differentiation and activation of osteoclasts (Chapter 21). Plasma cell lesions often lead to pathologic fractures, which occur most frequently in the vertebral column. The bone lesions usually appear radiographically as punched-out defects of 1 to 4 cm in diameter (Fig. 12–19A), but in some cases diffuse skeletal demineralization is evident. Microscopic examination of the marrow reveals an increased number of plasma cells, which constitute 10% to 90% of the cellularity. The neoplastic cells can resemble normal mature plasma cells, but they more often show abnormal features, such as prominent nucleoli or abnormal cytoplasmic inclusions containing immunoglobulin (Fig. 12–19B). With progressive disease, plasma cell infiltrations of soft tissues can be encountered in the spleen, liver, kidneys, lungs, and lymph nodes, or they may be more widely distributed. Terminally, a leukemic picture may emerge.

Renal involvement, generally called myeloma nephrosis, is a distinctive feature of multiple myeloma. Proteinaceous casts are prominent in the distal convoluted tubules and collecting ducts. Most of these casts are made up of Bence-Jones proteins, but they may also contain complete immunoglobulins, Tamm-Horsfall protein, and albumin. Some casts have tintorial properties of amyloid. This is not surprising, in that AL amyloid is derived from Bence-Jones proteins (Chapter 5). Multinucleate giant cells created by the fusion of infiltrating macrophages usually surround the casts. Very often the epithelial cells lining the cast-filled tubules become necrotic or atrophic because of the toxic actions of the Bence-Jones proteins. Metastatic calcification stemming from bone resorption and hypercalcemia may be encountered. When complicated by systemic amyloidosis, nodular glomerular lesions are present. Pyelonephritis can also occur as a result of the increased susceptibility to bacterial infections. Less commonly, interstitial infiltrates of abnormal plasma cells are seen.

In contrast to multiple myeloma, lymphoplasmacytic lymphoma is not associated with lytic skeletal lesions. Instead, the neoplastic cells diffusely infiltrate the bone marrow, lymph nodes, spleen, and sometimes the liver. Infiltrations of other organs also occur, particularly with disease progression. The cellular infiltrate consists of lymphocytes, plasma cells, and plasmacytoid lymphocytes of intermediate differentiation. The remaining forms of plasma cell dyscrasias have either already been described (e.g., primary amyloidosis; Chapter 5) or are too rare for further description.

Clinical Course. The clinical manifestations of the plasma cell dyscrasias are varied. They result from the destructive or otherwise damaging effect of the infiltrating neoplastic cells in various tissues and the abnormal immunoglobulins secreted by the tumors. In multiple myeloma the pathologic effects of plasma cell tumors predominate, whereas in lymphoplasmacytic lymphoma most of the signs and symptoms result from the IgM macroglobulins in the serum.

The peak age of incidence of multiple myeloma is between 50 and 60 years. The major clinicopathologic features of this disease can be summarized as follows:

- Bone pain, resulting from infiltration by neoplastic plasma cells, is extremely common. Pathologic fractures and hypercalcemia occur, with focal bone destruc-
the bulins greatly increase blood viscosity. This gives rise to macroglobulin. Because of their size, the macroglobulin can be traced to the presence of large amounts of IgMseventh decades. Most clinical symptoms of this disease with the peak incidence being between the sixth and examinations of the bone marrow is used to find macroglobulinemia, which is characterized by the following features:

- Renal insufficiency occurs in as many as 50% of patients. It results from multiple conditions, such as recurrent bacterial infections and hypercalcinemia, but most importantly from the toxic effects of Bence-Jones proteins on cells lining the tubules.
- Amyloidosis develops in 5% to 10% of patients.

The diagnosis of multiple myeloma can be strongly suspected when the characteristic focal, punched-out radiologic defects in the bone are present—especially when located in the vertebrae or calvarium. Electrophoresis of the serum and urine is an important diagnostic tool. In 99% of cases a monoclonal spike of complete immunoglobulin or immunoglobulin light chain light chain can be detected in the serum, in the urine, or in both. In the remaining 1% of cases, monoclonal immunoglobulins can be found within the plasma cells but not in the serum or urine. Such cases are sometimes called nonsecretory myelomas. Examination of the bone marrow is used to confirm the presence of a plasma cell proliferation.

Lymphoplasmacytic lymphoma affects older persons, with the peak incidence being between the sixth and seventh decades. Most clinical symptoms of this disease can be traced to the presence of large amounts of IgM (macroglobulin). Because of their size, the macroglobulins greatly increase blood viscosity. This gives rise to the hyperviscosity syndrome known as Waldenström macroglobulinemia, which is characterized by the following features:

- Visual impairment, related to the striking tortuosity and distention of retinal veins; retinal hemorrhages and exudates can also contribute to the visual problems
- Neurologic problems such as headaches, dizziness, tinnitus, deafness, and stupor, stemming from sluggish blood flow and sludging
- Bleeding, related to the formation of complexes between macroglobulins and clotting factors as well as interference with platelet functions
- Cryoglobulinemia, related to precipitation of macroglobulins at low temperatures and producing symptoms such as Raynaud phenomenon and cold urticaria.

Multiple myeloma is a progressive disease, with median survival ranging from 4 to 5 years. The median survival in lymphoplasmacytic lymphoma is somewhat longer, in the range of 4 to 5 years. Although aggressive therapies are being tried in both, neither disease is presently curable.

Hodgkin Lymphoma

Hodgkin lymphoma encompasses a distinctive group of neoplasms that arise almost invariably in a single lymph node or chain of lymph nodes and spread characteristically in a stepwise fashion to the anatomically contiguous nodes. It is separated from the non-Hodgkin lymphomas for several reasons. First, it is characterized morphologically by the presence of distinctive neoplastic giant cells called Reed-Sternberg (RS) cells, which are admixed with reactive, nonmalignant inflammatory cells. Second, it is often associated with somewhat distinctive clinical features, including systemic manifestations such as fever. Third, its stereotypical pattern of spread allows it to be treated differently than most other lymphoid neoplasms. Despite these distinguishing features, molecular studies have shown that it is a tumor of B-cell origin.

Classification. Five subtypes of Hodgkin lymphoma are recognized: (1) nodular sclerosis, (2) mixed cellularity, (3) lymphocyte predominance, (4) lymphocyte rich, and (5) lymphocyte depletion. The latter two subtypes are uncommon and will not be mentioned further. Before delineating the remaining three, however, we should describe the common denominator among all—RS cells and variants thereof—and the staging system used to characterize the extent of the disease in an individual.

Morphology

The sine qua non for Hodgkin lymphoma is the Reed-Sternberg (RS) cell (Fig. 12–20). This is a large cell (15–45μm in diameter) with an enlarged multilobated nucleus, exceptionally prominent nucleoli, and abundant, usually slightly eosinophilic, cytoplasm. Particularly characteristic are cells with two mirror-image nuclei or nuclear lobes, each containing a large (inclusion-like) acidophilic nucleolus surrounded by a distinctive clear zone; together they impart an owl-eye appearance. The nuclear membrane is distinct. As we will see, such “classic” RS cells are common in the mixed-cellularity subtype, uncommon in the nodular sclerosis subtype, and rare in the lymphocyte-predominance subtype; in these latter two subtypes, other characteristic RS cell variants predominate.

The staging of Hodgkin lymphoma (Table 12–9) is of clinical importance, because the course, choice of therapy, and prognosis are all intimately related to the distribution of the disease. With this background we can turn to the morphologic classification of Hodgkin lymphoma into its subgroups and point out some of the salient clinical features of each. Later the manifestations common to all will be presented. The essential features that serve to differentiate the major subgroups (lymphocyte predominance, nodular sclerosis, and mixed cellularity) are the morphology, immunophenotype, and frequency of the neoplastic elements (RS cells) and the nature of the tissue response.
CHAPTER 12 — The Hematopoietic and Lymphoid Systems

Figure 12–20
Hodgkin lymphoma. A binucleate Reed-Sternberg cell with large, inclusion-like nucleoli and abundant cytoplasm is surrounded by lymphocytes, and an eosinophil can be seen below. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Figure 12–21
Hodgkin lymphoma, nodular sclerosis type. A distinctive “lacunar cell” with multilobed nucleus containing many small nucleoli is seen lying within a clear space created by retraction of its cytoplasm. It is surrounded by lymphocytes. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Nodular Sclerosis Hodgkin Lymphoma. This is the most common form. It is equally frequent in men and women and has a striking propensity to involve the lower cervical, supraclavicular, and mediastinal lymph nodes. Most of the patients are adolescents or young adults, and the overall prognosis is excellent. It is characterized morphologically by:

• The presence of a particular variant of the RS cell, the lacunar cell (Fig. 12–21). This cell is large and has a single multilobate nucleus with multiple small nucleoli and an abundant, pale-staining cytoplasm. In formalin-fixed tissue, the cytoplasm often retracts, giving rise to the appearance of cells lying in empty spaces, or lacunae.

Table 12–9 Clinical Staging of Hodgkin and Non-Hodgkin Lymphomas (Ann Arbor Classification) *

<table>
<thead>
<tr>
<th>Stage</th>
<th>Distribution of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or tissue (I&lt;sub&gt;A&lt;/sub&gt;)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited contiguous extralymphatic organs or tissue (II&lt;sub&gt;A&lt;/sub&gt;)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (III&lt;sub&gt;A&lt;/sub&gt;), limited contiguous extralymphatic organ or site (III&lt;sub&gt;B&lt;/sub&gt;), or both (III&lt;sub&gt;A&lt;/sub&gt;B)</td>
</tr>
<tr>
<td>IV</td>
<td>Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with or without lymphatic involvement</td>
</tr>
</tbody>
</table>

* All stages are further divided on the basis of the absence (A) or presence (B) of the following systemic symptoms: significant fever, night sweats, unexplained loss of more than 10% of normal body weight.


Mixed-Cellularity Hodgkin Lymphoma. This is the most common form of Hodgkin lymphoma in patients older than the age of 50 and overall comprises about 25% of

Figure 12–22
Hodgkin lymphoma, nodular sclerosis type. A low-power view shows well-defined bands of pink, acellular collagen that have subdivided the tumor cells into nodules. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)
Etiology and Pathogenesis. Determining the origin of the neoplastic RS cells of Hodgkin lymphoma has proved daunting, in part because these cells are rare compared with the surrounding reactive inflammatory infiltrate. It has been recognized for some time that the L&H variants of RS cells found in nodular lymphocyte-predominance Hodgkin lymphoma express B-cell markers, supporting a B-cell origin. By contrast, the RS cells in other forms of Hodgkin lymphoma have been enigmatic, in that they generally do not express lineage-specific lymphoid markers. This uncertainty was finally resolved by elegant studies performed on single microdissected RS cells obtained from cases of mixed-cellularity and nodular-sclerosis Hodgkin lymphoma. Sequence analysis of DNA amplified from such cells has shown that each RS cell from any given case possesses the same immunoglobulin gene rearrangements as its neighbor and that the rearranged immunoglobulin genes have undergone somatic hypermutation. As a result, it is now agreed that Hodgkin lymphoma is a neoplasm arising from germinal center B cells.

This said, many puzzles remain to be answered. RS cells are aneuploid but lack the chromosomal translocations that are common in other germinal center B-cell lymphomas and have patterns of gene expression that bear little resemblance to normal B cells. The events that transform these cells and alter their appearance and gene expression programs are still unknown. One clue stems from the involvement of EBV. The EBV genome is present...
activates eosinophils), transforming growth factor secreted by RS cells, including IL-5 (which attracts and infiltrate seems to result from a number of cytokines vival of RS cells.

If EBV is playing a causative role, are there common oncogenic signals in EBV-positive and EBV-negative tumors? A possible lead stems from the observation that the RS cells in classical forms of Hodgkin lymphoma, regardless of their EBV status, contain high levels of activated NF-κB, a transcription factor that normally stimulates B-cell proliferation and protects B cells from pro-apoptotic signals. Several EBV proteins that are known to activate NF-κB are expressed in EBV-positive RS cells. Somatic mutations that abolish the function of IκB, an important inhibitor of NF-κB, have been found in EBV-negative RS cells. Thus, hyperactivation of NF-κB may be a central event in the genesis, growth, and survival of RS cells.

The characteristic non-neoplastic, inflammatory-cell infiltrate seems to result from a number of cytokines secreted by RS cells, including IL-5 (which attracts and activates eosinophils), transforming growth factor β (a fibrogenic factor), and IL-13 (which may stimulate RS cells through an autocrine mechanism). Conversely, the responding inflammatory cells, rather than being innocent bystanders, produce factors (such as CD30 ligand) that can aid the growth and survival of RS cells, and contribute further to the tissue reaction.

Clinical Course. Hodgkin lymphomas, like NHLs, usually present as a painless enlargement of the lymph nodes. Although a definitive distinction from NHL can be made only by examination of a lymph node biopsy specimen, several clinical features favor the diagnosis of Hodgkin lymphoma (Table 12–10). Younger patients with the more favorable histologic types tend to present in clinical stages I or II and are usually free of systemic manifestations. Patients with disseminated disease (stages III and IV) are more likely to have systemic complaints such as fever, unexplained weight loss, pruritus, and anemia. As mentioned earlier, these patients generally have the histologically less favorable variants. The outlook after aggressive radiotherapy and chemotherapy for patients with this disease, including those with disseminated disease, is generally very good. With current modalities of therapy, the clinical stage is the most important prognostic indicator. The 5-year survival rate of patients with stage I-A or II-A disease is close to 100%. Even with advanced disease (stage IV-A or IV-B), the overall 5-year disease-free survival rate is around 50%. However, therapeutic successes have also brought problems. Long-term survivors of radiotherapy protocols are at much higher risk of developing certain malignancies, including lung cancer, melanoma, and breast cancer. As a result, current efforts are aimed at developing less genotoxic therapeutic regimens that decrease therapy-related complications while preserving a high cure rate.

### Miscellaneous Lymphoid Neoplasms

Of the many remaining forms of lymphoid neoplasia within the WHO classification, several with distinctive or clinically important features merit brief discussion.

**Extranodal Marginal Zone Lymphoma.** This is a special category of low-grade mature B-cell tumors that arise most commonly in mucosal-associated lymphoid tissue (MALT), such as salivary glands, small and large bowel, and lungs, and some nonmucosal sites such as the orbit and breast. Extranodal marginal zone lymphomas tend to develop in the setting of autoimmune disorders (such as Sjögren syndrome and Hashimoto thyroiditis) or chronic infections with such organisms as *Helicobacter pylori* and *Campylobacter jejuni*, suggesting that sustained antigenic stimulation contributes to lymphomagenesis. In the case of *H. pylori*-associated gastric MALT lymphoma, eradication of the organism with antibiotic therapy often leads to regression of the tumor cells, which seem to depend on cytokines secreted by *H. pylori*-specific T cells for their growth and survival (Chapter 6). When arising at other sites, MALT tumors can often be cured by local excision or radiotherapy. Two recurrent cytogenetic abnormalities are recognized: t(1;14), involving the *BCL10* and *IγH* genes; and t(11;18), involving the MALT1 and IAP2 genes.

**Hairy Cell Leukemia.** This uncommon, indolent B-cell neoplasm is distinguished by the presence of leukemic cells that have fine, hairlike cytoplasmic projections. The tumor cells express pan-B-cell markers, including CD19 and CD20, surface immunoglobulin, and, characteristically, CD11c and CD103; these two antigens are not present on most other B-cell tumors, making them diagnostically useful.

This tumor occurs mainly in older males, and its manifestations result largely from infiltration of bone marrow
composed of neoplastic CD4+ T cells that home to the skin; as a result, they are often referred to as cutaneous T-cell lymphomas. Mycosis fungoides usually presents as a nonspecific erythrodermic rash, which over time tends to progress through a plaque phase to a tumor phase. Histologically, there is infiltration of the epidermis and upper dermis by neoplastic T cells, which often have a cerebriform nucleus characterized by marked infolding of the nuclear membrane. With progressive disease, both nodal and visceral dissemination appear. Sézary syndrome is a clinical variant characterized by the presence of (1) a generalized exfoliative erythroderma and (2) tumor cells (Sézary cells) in the peripheral blood. Circulating tumor cells are also present in as many as 25% of cases of plaque- or tumor-phase mycosis fungoides. Patients with erythrodermic-phase mycosis fungoides often survive for many years, whereas survival is generally 1 to 3 years for patients with tumor-phase disease, visceral disease, or Sézary syndrome.

Adult T-Cell Leukemia/Lymphoma. This T-cell neoplasm is caused by a retrovirus, human T-cell leukemia virus type 1 (HTLV-1). It is endemic in southern Japan, the Caribbean basin, and West Africa and occurs sporadically elsewhere, including in the southeastern United States. The pathogenesis of this tumor is discussed in Chapter 6. In addition to causing lymphoid malignancies, HTLV-1 infection can also give rise to transverse myelitis, a progressive demyelinating disease that affects the central nervous system and the spinal cord. Adult T-cell leukemia/lymphoma is characterized by skin lesions, generalized lymphadenopathy, hepatosplenomegaly, hypercalcemia, and variable numbers of malignant CD4+ lymphocytes in the peripheral blood. The leukemic cells express high levels of CD25, the IL-2 receptor α chain. In most cases this is an extremely aggressive disease, with a median survival time of about 8 months. In 15% to 20% of patients the course of the disease is chronic; their disease is clinically indistinguishable from cutaneous T-cell lymphoma.

Peripheral T-Cell Lymphomas. This is a heterogeneous group of tumors that together make up about 15% of adult NHLs. Although several rare distinctive subtypes fall under this heading, most tumors in this group are unclassifiable. In general, they present as disseminated disease, are aggressive, and respond poorly to therapy.

**SUMMARY**

**Lymphoid Neoplasms**

- **Classified based on cell of origin and stage of differentiation**
- **Most common types in children are acute lymphoblastic leukemias and lymphomas, which are derived from B- and T-cell precursors.**
  - Highly aggressive tumors that present with symptoms of bone marrow failure, or as rapidly growing masses.
  - Tumor cells contain genetic lesions that block differentiation, leading to the accumulation of immature blasts that cannot function as immune cells.
- **Most common types in adults are non-Hodgkin lymphomas derived from germinal center B cells.**
  - May be indolent (e.g., follicular lymphoma) or aggressive (e.g., diffuse large B-cell lymphoma).
  - Sometimes interfere with the immune system by dysregulating the function of normal B and T cells (e.g., chronic lymphocytic leukemia, multiple myeloma).
  - Often contain chromosomal translocations or mutations involving genes (such as BCL2 and BCL6) that regulate normal mature B-cell development and survival.
- **Precursor B- and T-Cell Lymphoblastic Leukemia/Lymphoma:**
  - Aggressive tumors of pre-B or pre-T cells that are most common in childhood and young adults, but which occur throughout life.
  - Most patients present with bone marrow failure caused by extensive marrow replacement by leukemic cells, resulting in pancytopenia.
- **Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia:**
  - Tumor of mature B cells that usually presents with involvement of the bone marrow and the lymph nodes.
  - Follows an indolent course, commonly associated with immune abnormalities, including an increased susceptibility to infection and autoimmune disorders.
- **Follicular Lymphoma:**
  - Tumor cells recapitulate the growth pattern of normal germinal center B cells; more than 80% of cases are associated with a t(14;18) translocation that results in the over-expression of the anti-apoptotic protein BCL2.
- **Mantle Cell Lymphoma:**
  - Tumor of mature B cells that usually presents with advanced disease involving lymph nodes,
bone marrow, and extranodal sites such as the gut.

- Highly associated with a t(11;14) translocation that results in over-expression of cyclin D1, a regulator of cell cycle progression.
- **Diffuse Large B-Cell Lymphoma:**
  - Heterogeneous group of mature B cell tumors that share a similar large-cell morphology and aggressive clinical behavior; the most common type of lymphoma.
  - Highly associated with rearrangements or mutations of BCL6 gene; one-third arise from follicular lymphomas and carry a t(14;18) translocation.
- **Burkitt Lymphoma:**
  - Very aggressive tumor of mature B cells that usually arises at extranodal sites, is uniformly associated with translocations involving the c-MYC proto-oncogene, and is often associated with latent infection by Epstein-Barr virus (EBV).
- **Multiple Myeloma:**
  - Plasma cell tumor that usually presents as multiple lytic bone lesions with pathologic fractures and hypercalcemia.
  - Neoplastic plasma cells may suppress normal humoral immunity and secrete paratrabecular immunoglobulins that are often nephrotoxic.
- **Hodgkin Lymphoma:**
  - Unusual tumor mostly comprised of reactive lymphocytes, macrophages, and stromal cells; the malignant cell, the Reed-Sternberg cell (which is derived from B cells), typically makes up a minor fraction of the tumor mass.

See also Table 2–8 for features of different tumors.

**Myeloid Neoplasms**

Myeloid neoplasms arise from hematopoietic stem cells and typically give rise to monoclonal proliferations that replace normal bone marrow cells. There are three general categories of myeloid neoplasia. In the AMLs, the neoplastic cells are blocked at some early stage of myeloid cell development. Immature myeloid cells (blasts), which can exhibit evidence of granulocytic, erythroid, monocytic, or megakaryocytic differentiation, accumulate in the marrow, replacing normal elements, and frequently circulate in the peripheral blood. In the chronic myeloproliferative disorders, the neoplastic clone retains the capacity to undergo terminal differentiation but exhibits increased or dysregulated growth. Commonly there is an increase in one or more of the formed elements (red cells, platelets, and/or granulocytes) in the peripheral blood. In the myelodysplastic syndromes, terminal differentiation occurs but in a disordered and ineffective fashion, leading to the appearance of dysplastic marrow precursors and peripheral blood cytopenias.

Although these three categories provide a useful starting point when considering the myeloid neoplasms, the divisions between them sometimes blur. Both myelodysplastic syndromes and myeloproliferative disorders often transform to a picture identical to acute myelogenous leukemia, and some patients present with disorders that have features of both myelodysplastic and myeloproliferative disorders. Given that all arise from hematopoietic stem cells, the close relationship among these disorders is not surprising.

**Acute Myelogenous Leukemia**

AML primarily affects older adults, with the median age being 50 years. It is an extremely heterogeneous disorder, as will be discussed below. The clinical signs and symptoms, which closely resemble those produced by ALL, are usually related to marrow failure caused by the replacement of normal marrow elements by leukemic blasts. Fatigue and pallor, abnormal bleeding, and infections are common in newly diagnosed patients, who typically present within a few weeks of the onset of symptoms. Splenomegaly and lymphadenopathy are in general less prominent than in ALL, but, rarely, AML presents as a discrete tissue mass (a so-called granulocytic sarcoma). Ideally the diagnosis and classification of AML are based on the results of morphologic, histochemical, immunophenotypic, and karyotypic studies. Of these tests, karyotyping is most predictive of outcome.

**Pathophysiology.** Most AMLs are associated with acquired mutations in transcription factors that inhibit normal myeloid differentiation, leading to the accumulation of cells at earlier stages of development. Of particular interest is the t(15;17) translocation in acute promyelocytic leukemia. This translocation results in the fusion of the retinoic acid receptor α (RARA) gene on chromosome 17 with the PML gene on chromosome 15. The chimeric gene(s) produce abnormal PML/RARA fusion proteins that block myeloid differentiation at the promyelocytic stage, probably by inhibiting the function of normal RARA receptors. Remarkably, pharmacologic doses of retinoic acid (Chapter 8), a vitamin A analogue, overcome this block and cause the neoplastic promyelocytes to terminally differentiate in neutrophils and die. Because neutrophils live, on average, for 6 hours, the result is the rapid clearance of tumor cells and remission in a high fraction of patients. The effect is very specific; AMLs without translocations involving RARA do not respond to retinoic acid. Sufferers relapse if treated with retinoic acid alone, possibly because the neoplastic progenitor that gives rise to the promyelocytes is resistant to the pro-differentiative effects of retinoic acid. However, when combined with chemotherapy, the prognosis is excellent. Nonetheless, this is an important example of an effective therapy that is targeted at a tumor-specific molecular defect.

Other work using transgenic or gene knock-in mice has generally suggested that the mutated transcription factors found in AML are not sufficient, in and of themselves, to cause the disease. Complementary mutations.
have been described in a number of genes that have no effect on maturation but instead promote enhanced proliferation and survival. One example is gain-of-function mutations in FLT3 (a surface receptor with tyrosine kinase activity), which are seen in a number of AML subtypes, including acute promyelocytic leukemia.

**Morphology**

By definition, in AML myeloid blasts or promyelocytes make up more than 20% of the bone marrow cellularity. Myeloblasts (precursors of granulocytes) have delicate nuclear chromatin; three to five nucleoli; and fine, azurophilic granules in the cytoplasm (see Fig. 12–14B). Distinctive red-staining rodlike structures (Auer rods) may be present in myeloblasts or more differentiated cells; they are particularly prevalent in the progranulocytes found in acute promyelocytic leukemia (Fig. 12–25). Auer rods are found only in neoplastic myeloblasts and are thus a helpful diagnostic clue when present. In other subtypes of AML, monoblasts, erythroblasts, or megakaryoblasts predominate.

**Classification.** AMLs are diverse in terms of genetics, the predominant line of differentiation, and the maturity of cells. The latter two features serve as the basis for the Revised French-American-British (FAB) classification (Table 12–11A), which is still used widely. However, experience has shown that the FAB classification has limited prognostic value, whereas certain recurrent chromosomal abnormalities, prior drug exposure, and a history of myelodysplastic syndrome are predictive of outcome. As a result, a new WHO classification has been proposed that takes these variables into account (Table 12–11B). The FAB categories are used within the WHO classification for tumors that lack these strong prognostic factors.

**Histochemistry.** Cases with granulocytic differentiation are typically positive for the enzyme myeloperoxidase, which is detected by incubation of cells with peroxidase substrates. Auer rods are intensely peroxidase positive, which can help bring out their presence when they are rare. Monocytic differentiation is demonstrated by staining for lysosomal nonspecific esterases.

**Immunophenotype.** The expression of immunologic markers is heterogeneous in AML. Most express some combination of myeloid-associated antigens, such as CD13, CD14, CD15, CD64, or CD117 (cKIT). CD33 is expressed on pluripotent stem cells but is retained on myeloid progenitor cells. Such markers are helpful in distinguishing AML from ALL (as shown in Fig. 12–14) and identifying primitive AMLs (e.g., the M0 subtype). In addition, monoclonal antibodies reactive with platelet-associated antigens are very helpful in the diagnosis of the M7 subtype, acute megakaryocytic leukemia.

**Prognosis.** AML is a devastating disease. Tumors with “good-risk” karyotypic aberrations (t[8;21], inv[16]) are associated with a 50% chance of long-term disease-free survival, but the overall long-term disease-free survival is only 15% to 30% with conventional chemotherapy. An increasing number of patients with AML are being treated with more aggressive approaches, such as allogeneic bone marrow transplantation.

**Myelodysplastic Syndromes**

In patients with these disorders, the bone marrow is partly or wholly replaced by the clonal progeny of a transformed multipotent stem cell that retains the capacity to differentiate into red cells, granulocytes, and platelets, but in a manner that is both ineffective and disordered. As a result the bone marrow is usually hypercellular or normocellular, but the peripheral blood shows one or more cytopenias. The abnormal stem cell clone in the bone marrow is genetically unstable, which leads to acquisition of additional mutations and the eventual transformation to AML. Most cases are idiopathic, but some develop after chemotherapy with alkylating agents or exposure to ionizing radiation therapy.

Cytogenetic studies reveal that a chromosomally abnormal clone of cells is present in the marrow of as many as 70% of individuals with this disease. Some common karyotypic abnormalities include loss of chromosomes 5 or 7, or deletions of 5q or 7q. Morphologically, the marrow is populated by abnormal-appearing hematopoietic precursors. Some of the more common abnormalities include megakaryoblastoid erythroid precursors resembling those seen in the megaloblastic anemias, erythroid forms with iron deposits within their mitochondria (ringed sideroblasts), granulocyte precursors with abnormal granules or nuclear maturation, and small megakaryocytes with single small nuclei.

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**Myelodysplastic Syndromes**

In patients with these disorders, the bone marrow is partly or wholly replaced by the clonal progeny of a transformed multipotent stem cell that retains the capacity to differentiate into red cells, granulocytes, and platelets, but in a manner that is both ineffective and disordered. As a result the bone marrow is usually hypercellular or normocellular, but the peripheral blood shows one or more cytopenias. The abnormal stem cell clone in the bone marrow is genetically unstable, which leads to acquisition of additional mutations and the eventual transformation to AML. Most cases are idiopathic, but some develop after chemotherapy with alkylating agents or exposure to ionizing radiation therapy.

Cytogenetic studies reveal that a chromosomally abnormal clone of cells is present in the marrow of as many as 70% of individuals with this disease. Some common karyotypic abnormalities include loss of chromosomes 5 or 7, or deletions of 5q or 7q. Morphologically, the marrow is populated by abnormal-appearing hematopoietic precursors. Some of the more common abnormalities include megakaryoblastoid erythroid precursors resembling those seen in the megaloblastic anemias, erythroid forms with iron deposits within their mitochondria (ringed sideroblasts), granulocyte precursors with abnormal granules or nuclear maturation, and small megakaryocytes with single small nuclei.
Most individuals with this disease are between 50 and 70 years of age. AML develops in 10% to 40%. The others suffer from infections, anemia, and hemorrhages, as a result of the defective bone marrow function. The response to chemotherapy is usually poor, lending support to the idea that myelodysplasia arises in a background of stem cell failure. It is of interest in this regard that some patients with aplastic anemia eventually develop a myelodysplastic syndrome, and a significant minority of patients with myelodysplasia respond to T-cell immunosuppressants. In this subset of patients, it is possible that the malignant clone “grows out” because normal stem cells are under attack by T cells. As discussed earlier, a similar mechanism seems to underlie paroxysmal nocturnal hemoglobinuria. The prognosis is variable; the median survival time varies from 9 to 29 months and is worse in those with increased marrow blasts or cytogenetic abnormalities at the time of diagnosis.

**Chronic Myeloproliferative Disorders**

These disorders are marked by the hyperproliferation of neoplastic myeloid progenitors that retain the capacity for terminal differentiation; as a result, there is an increase in one or more formed elements of the peripheral blood. The neoplastic progenitors tend to seed secondary hematopoietic organs (the spleen, liver, and

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**Table 12–11A  Revised FAB Classification of Acute Myelogenous Leukemias (AML)**

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Incidence (% of AML)</th>
<th>Morphology/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Minimally differentiated AML</td>
<td>2–3</td>
<td>Blasts lack Auer rods and myeloperoxidase but express myeloid lineage surface markers.</td>
</tr>
<tr>
<td>M1</td>
<td>AML without maturation</td>
<td>20</td>
<td>Some blasts (≥23%) are myeloperoxidase positive; few granules or Auer rods and very little maturation beyond the myeloblast stage of differentiation.</td>
</tr>
<tr>
<td>M2</td>
<td>AML with maturation</td>
<td>30–40</td>
<td>&gt;20% of marrow cells are myeloblasts, but many cells are seen at later stages of granulocyte differentiation; Auer rods are usually present; often associated with t(8;21).</td>
</tr>
<tr>
<td>M3</td>
<td>Acute promyelocytic leukemia</td>
<td>5–10</td>
<td>Most cells are abnormal promyelocytes, often containing many Auer rods per cell; patients are younger on average (median age 35–40yr); high incidence of DIC; strongly associated with t(15;17).</td>
</tr>
<tr>
<td>M4</td>
<td>Acute myelomonocytic leukemia</td>
<td>15–20</td>
<td>Myelocytic and monocytic differentiation evident by cytochemical stains; monoblasts are positive for nonspecific esterase; myeloid cells show a range of maturation; variable numbers of Auer rods; subset associated with inv(16).</td>
</tr>
<tr>
<td>M5</td>
<td>Acute monocytic leukemia</td>
<td>10</td>
<td>Monoblasts and immature monocytic cells (myeloperoxidase negative, nonspecific esterase positive) predominate; Auer rods are usually absent; older patients; more likely to be associated with organomegaly, lymphadenopathy, and tissue infiltration; the M5b subtype is defined by the predominance of mature-appearing monocytes in the peripheral blood, whereas only immature cells are seen in the M5a subtype.</td>
</tr>
<tr>
<td>M6</td>
<td>Acute erythroleukemia</td>
<td>5</td>
<td>Most commonly associated with abundant dysplastic erythroid progenitors; &gt;20% of cells of the marrow nonerythroid cells are myeloblasts, which may contain Auer rods; usually occurs in advanced age or following exposure to mutagens (e.g., chemotherapy).</td>
</tr>
<tr>
<td>M7</td>
<td>Acute megakaryocytic leukemia</td>
<td>1</td>
<td>Blasts of megakaryocytic lineage predominate, as judged by expression of platelet-specific antigens; myelofibrosis or increased marrow reticulin often present; Auer rods are absent.</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation.

**Table 12–11B  Proposed WHO Classification of Acute Myelogenous Leukemia (AML)**

<table>
<thead>
<tr>
<th>Class</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. AML with Recurrent Chromosomal Translocations</td>
<td></td>
</tr>
<tr>
<td>AML with t(8;21)(q22;q22); CBFA2/ETO fusion gene</td>
<td>Favorable</td>
</tr>
<tr>
<td>AML with inv(16)(p13;q22); CBFb/MYH11 fusion gene</td>
<td>Favorable</td>
</tr>
<tr>
<td>AML with t(15;17)(q22;q11.2); PML/RARa</td>
<td>Favorable</td>
</tr>
<tr>
<td>AML with t(11q23;variant)</td>
<td>Poor</td>
</tr>
<tr>
<td>II. AML with Multilineage Dysplasia</td>
<td></td>
</tr>
<tr>
<td>With prior myelodysplastic syndrome</td>
<td>Very poor</td>
</tr>
<tr>
<td>Without prior myelodysplastic syndrome</td>
<td>Poor</td>
</tr>
<tr>
<td>III. AML, Therapy-Related</td>
<td></td>
</tr>
<tr>
<td>Alkylating agent related</td>
<td>Very poor</td>
</tr>
<tr>
<td>Epipodophyllotoxin related</td>
<td>Very poor</td>
</tr>
<tr>
<td>IV. AML, Not Otherwise Classified</td>
<td></td>
</tr>
<tr>
<td>Subclasses defined by extent and type of differentiation (M0–M7)</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>
lymph nodes), resulting in hepatosplenomegaly (caused by neoplastic extramedullary hematopoiesis) and mild lymphadenopathy. A common theme is the association of these disorders with mutated tyrosine kinases, which generate high-intensity constitutive signals that mimic those that regulate the growth and survival of normal myeloid cells. This insight provides a satisfying explanation for the observed overproduction of myeloid cells and is important therapeutically because of the availability of tyrosine kinase inhibitors.

Most patients with this disease subgroup fall into one of four diagnostic entities: chronic myelogenous leukemia (CML), polycythemia vera (PCV), primary myelofibrosis, and essential thrombocytopenia. CML is clearly separated from the other disorders by being associated with a characteristic abnormality, the presence of a BCR-ABL fusion gene. In contrast, the other myeloproliferative disorders show considerable overlap clinically and genetically. Mutations of the JAK2 kinase are the single most common genetic abnormality in this group. It is seen in &gt;90% of cases of polycythemia vera, 50% of primary myelofibrosis, and 30% of essential thrombocytopenias. Additional rarer types of myeloproliferative disorders are associated with activating mutations in still other tyrosine kinases, such as platelet derived growth factor receptor alpha and beta. Thus, an evolving theme is that most, if not all, myeloproliferative disorders are associated with an abnormal increase in the activity of one or another tyrosine kinase, which appears to stimulate the same signaling pathways that are normally activated by hematopoietic growth factors. Only CML, PCV, and primary myelofibrosis are presented here. Essential thrombocytopenia and other myeloproliferative disorders occur too infrequently to merit discussion.

**Chronic Myelogenous Leukemia**

CML principally affects adults between 25 and 60 years of age and accounts for 15% to 20% of all cases of leukemia. The peak incidence is in the fourth and fifth decades of life.

**Pathophysiology.** CML is uniformly associated with the presence of an acquired genetic abnormality, a BCR-ABL fusion gene. In about 95% of cases the BCR-ABL fusion gene is the product of a (9;22) translocation that moves the ABL gene from chromosome 9 to a position on chromosome 22 adjacent to the BCR gene. The derivative chromosome 22 is often referred to as the Philadelphia (Ph) chromosome, because it was discovered in Philadelphia. In the remaining 5% of patients, the BCR-ABL fusion gene is created by rearrangements that are cytogenetically cryptic or obscured by the involvement of more than two chromosomes. In individuals with CML the BCR-ABL fusion gene is present in granulocytic, erythrocytic, megakaryocytic, and B-cell precursors, and in some cases T-cell precursors as well. This finding is firm evidence for the origin of CML from a pluripotent stem cell. As you recall from Chapter 6, the BCR-ABL gene encodes a fusion protein consisting of portions of BCR and the tyrosine kinase domain of ABL that is critical for neoplastic transformation. Although the Ph chromosome is highly characteristic of CML, it should be remembered that it is also present in 25% of adults with ALL and rare cases of adults with AML.

Normal myeloid progenitors depend on signals generated by growth factors and their receptors for growth and survival, but CML progenitors have much decreased requirements. This altered growth-factor dependence is due to the presence of the BCR-ABL tyrosine kinase, which generates constitutive signals that mimic the effects of growth-factor receptor activation. Although the BCR-ABL fusion gene is present in multiple lineages, for unclear reasons the granulocyte precursors are most affected. As is evident from the markedly elevated number of granulocytes in the bone marrow and peripheral blood, the proliferating CML progenitors retain the capacity for terminal differentiation.

### Morphology

The peripheral blood findings are highly characteristic. The leukocyte count is elevated, often exceeding 100,000 cells/μL. The circulating cells are predominantly neutrophils, metamyelocytes, and myelocytes (Fig. 12-26), but basophils and eosinophils are also prominent. A small proportion of myeloblasts, usually less than 5%, can be seen in the peripheral blood. An increased number of platelets (thrombocytosis) is also typical. The bone marrow is hypercellular as a result of a hyperplasia of granulocytic and megakaryocytic precursors. Myeloblasts are usually only slightly increased, and there is frequently an increase in the number of phagocytes. The red pulp of the enlarged spleen has an appearance that resembles bone marrow because of the extensive extramedullary hematopoiesis. This burgeoning mass of hematopoietic cells often compromises the local blood supply, leading to splenic infarcts.

**Clinical Features.** The onset of CML is usually slow, and the initial symptoms are often nonspecific (e.g., easy fatigability, weakness, and weight loss). Sometimes the first

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**Figure 12-26**

Chronic myelogenous leukemia. Peripheral blood smear shows many mature neutrophils, some metamyelocytes, and a myelocyte. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)
symptom is a dragging sensation in the abdomen, caused by the extreme splenomegaly that is characteristic of this condition. On occasion it may be necessary to distinguish CML from a “leukemoid reaction,” a dramatic elevation of the granulocyte count in response to infection, stress, chronic inflammation, and certain neoplasms. The presence of the Ph chromosome is the most definitive way of distinguishing CML from leukemoid reactions (and the other chronic myeloproliferative disorders). Measurement of leukocyte alkaline phosphatase can also be helpful, because the granulocytes in CML are almost completely devoid of this enzyme, whereas it is increased in leukemoid reactions and other myeloproliferative disorders (such as PCV).

The course of CML is one of slow progression. Even without treatment, the median survival is 3 years. After a variable (and unpredictable) period, approximately 50% of individuals with CML enter an accelerated phase, during which there is a gradual failure in the response to treatment; increasing anemia and new thrombocytopenia; the appearance of additional cytogenetic abnormalities; and, finally, transformation into a picture resembling acute leukemia (i.e., blast crisis). In the remaining 50% blast crisis occurs abruptly, without an intermediate accelerated phase. Notably, in 30% of patients, the blast crisis is of a pre–B-cell type, further attesting to the origin of CML from a pluripotent stem cell. In the remaining 70% of patients, the blast crisis resembles AML. Less commonly, CML progresses to a phase of extensive bone marrow fibrosis resembling that seen in other myeloproliferative disorders, most notably myeloid metaplasia with myelofibrosis.

Treatment of CML is evolving rapidly. Most patients were formerly treated with palliative “gentle” chemotherapy, which unfortunately did not prevent the development of blast crisis. Bone marrow transplantation was (and remains) a definitive form of therapy, being curative in 70% of patients, but it carries a high risk of death in patients without a matched donor and in the aged. An inhibitor of the BCR-ABL tyrosine kinase, Gleevec (imatinib mesylate), induces complete remission in a high fraction of individuals with stable-phase CML with little of the toxicity associated with nonspecific chemotherapeutic agents. When CML suffers on imatinib mesylate relapse, they often have new mutations in the active site of BCR-ABL that prevent the binding of imatinib mesylate; this proves that the drug is working by “hitting the target.” Further work is needed to determine whether imatinib mesylate is curative, but it is an excellent therapy for persons who cannot undergo bone marrow transplantation and has stimulated great interest in the development of other targeted cancer therapies.

Polycythemia Vera

The hallmark of PCV is the excessive neoplastic proliferation and maturation of erythroid, granulocytic, and megakaryocytic elements, producing a panmyelosis. Although platelet and granulocyte numbers are increased, the most obvious clinical signs and symptoms are related to the absolute increase in red cell mass. This must be distinguished from relative polycythemia, which results from hemoconcentration. Unlike reactive forms of absolute polycythemia, PCV is associated with low levels of erythropoietin in the serum, which is a reflection of the hypersensitivity of the neoplastic clone to erythropoietin and other growth factors. Recently it was observed that in nearly all cases, PCV cells carry a particular mutation in JAK2, a tyrosine kinase that acts in the signaling pathways downstream of the erythropoietin receptor and other growth factor receptors. This mutation, which results in a valine-to-phenylalanine substitution at residue 617, is sufficient to render cells expressing the erythropoietin receptor hypersensitive to erythropoietin, suggesting that it is probably an important part of the pathogenesis of PCV.

Morphology

The major anatomic changes in PCV stem from the increase in blood volume and viscosity brought about by the polycythemia. Plenothoracic congestion of all tissues and organs is characteristic. The liver is enlarged and frequently contains foci of extramedullary hematopoiesis. The spleen is slightly enlarged (250–300 gm) in about 75% of patients, because of the vascular congestion. As a result of the increased viscosity and vascular stasis, thromboses and infarctions are common, particularly in the heart, spleen, and kidneys. Hemorrhages occur in about a third of these individuals, probably as a result of excessive distention of blood vessels and abnormal platelet function. They usually affect the gastrointestinal tract, oropharynx, or brain. Although these hemorrhages may occasionally be spontaneous, they more often follow some minor trauma or surgical procedure. Platelets produced from the neoplastic clone are often dysfunctional. Depending on their nature, the platelet defects can either exacerbate the tendency for thrombosis or lead to abnormal bleeding. As in CML, the peripheral blood often shows increased basophils.

The bone marrow is hypercellular due to the hyperplasia of erythroid, myeloid, and megakaryocytic forms. In addition, some degree of marrow fibrosis is present in 10% of patients at the time of diagnosis. In a subset of patients, the disease progresses to myelofibrosis, where the marrow space is largely replaced by fibroblasts and collagen.

Clinical Course. PCV appears insidiously, usually in late middle age. Patients are pellagoidic and often somewhat cyanotic. Histamine release from the neoplastic basophils may contribute to pruritus, which can be intense. Excessive histamine release may also account for the peptic ulceration seen in these individuals. Other complaints are referable to the thrombotic and hemorrhagic tendencies and to hypertension. Headache, dizziness, gastrointestinal symptoms, hematemesis, and melena are common. Because of the high rate of cell turnover, symptomatic gout is seen in 5% to 10% of cases, and many more patients have asymptomatic hyperuricemia.

The diagnosis is usually made in the laboratory. Red cell counts range from 6 to 10 million per microliter, and the hematocrit often approaches 60%. The other myeloid lineages are also hyperproliferative: the granulocyte...
count can be as high as 50,000 cells/mm³, and the platelet count is often greater than 400,000 cells/mm³. The basophil count is also frequently elevated. The platelets are functionally abnormal in most cases, and giant forms and megakaryocyte fragments are seen in the blood. About 30% of patients develop thrombotic complications, usually affecting the brain or heart. Hepatic vein thrombosis, giving rise to the Budd-Chiari syndrome (Chapter 16), is an uncommon but grave complication. Minor hemorrhages (e.g., epistaxis and bleeding from gums) are common, and life-threatening hemorrhages occur in 5% to 10% of patients. In those receiving no treatment, death occurs from vascular complications within months after diagnosis; however, if the red cell mass is maintained at near normal levels by phlebotomies, the median survival is around 10 years.

Prolonged survival with treatment has revealed that PCV tends to evolve to a “spent phase,” during which the clinical and anatomic features of primary myelofibrosis develop. After an average interval of 10 years, 15% to 20% of tumors undergo such a transformation. This transition is marked by creeping fibrosis in the bone marrow and a shift of hematopoiesis to the spleen, which enlarges markedly. Transformation to a “blast crisis” identical to AML also occurs but much less frequently than in CML. Targeted molecular therapy with JAK2 inhibitors is presently under consideration.

Myeloid Metaplasia with Primary Myelofibrosis

In this chronic myeloproliferative disorder, a “spent phase” of marrow fibrosis supervenes early in the disease course, often following a brief period in which the peripheral blood white cell and platelet counts are elevated. As hematopoiesis shifts from the fibrotic marrow to the spleen, liver, and lymph nodes, extreme splenomegaly and hepatomegaly develop. Hematopoiesis in these extramedullary sites tends to be disordered and inefficient and, together with the marrow fibrosis, leads to moderate-to-severe anemia and thrombocytopenia in most patients.

Although marrow fibrosis is characteristic, the fibroblasts that lay down the collagen are not clonal descendants of the transformed stem cells. Instead, marrow fibrosis is secondary to derangements confined to the hematopoietic cells, particularly the megakaryocytes. It is believed that 

\[ \text{megakaryocytes are stimulated to proliferate by platelet-derived growth factor and transforming growth factor} \beta \text{ released from neoplastic megakaryocytes. These two growth factors are known to be mitogenic for fibroblasts.} \]

By the time patients come to clinical attention, marrow fibrosis and marked extramedullary hematopoiesis are usually evident. More uncommonly, marrow fibrosis is less advanced at diagnosis, and the clinical picture resembles that seen in other “hyperproliferative” myeloproliferative disorders.

It is of pathogenic and possibly therapeutic importance that the same JAK2 mutation that is found in PCV (a valine-to-phenylalanine mutation at amino residue 617) is present in around half of the cases of primary myelofibrosis (as well as in a similar proportion of individuals with essential thrombocytosis), findings that emphasize the extent of the overlap between these entities. It is not yet known why tumors with the same mutation have such varied clinical pictures. Perhaps the JAK2 mutation occurs in a different stem cell population in primary myelofibrosis, or the unknown mutations that promote progression to the spent phase occur much earlier in some individuals by chance.

**Morphology**

The principal site of the extramedullary hematopoiesis in myeloid metaplasia with primary myelofibrosis is the spleen, which is usually markedly enlarged, sometimes weighing as much as 4000 gm. As is always true when splenomegaly is massive, multiple subcapsular infarcts are often present. Histologically the spleen contains normoblasts, granulocyte precursors, and megakaryocytes, which are often prominent in terms of their numbers and bizarre morphology. Sometimes disproportional activity of any one of the three major cell lines is seen.

The liver is often moderately enlarged, with foci of extramedullary hematopoiesis. Microscopically, the lymph nodes also contain foci of extramedullary hematopoiesis, but these are insufficient to cause appreciable enlargement.

The bone marrow in a typical case is hypocellular and diffusely fibrotic. However, early in the course the marrow can be hypercellular, with equal representation of the three major cell lines. Both early and late in the disease, megakaryocytes are often prominent and are usually dysplastic.

**Clinical Course.** Primary myelofibrosis can begin with a blood picture suggestive of PCV or CML, but it more commonly has progressed to marrow fibrosis by the time it comes to clinical attention. Most patients have moderate-to-severe anemia. The white cell count can be normal, reduced, or markedly elevated. Early in the disease course, the platelet count is normal or elevated, but eventually patients develop thrombocytopenia. The peripheral blood smear appears markedly abnormal (Fig. 12–27). Red cell abnormalities include bizarre shapes (poikilocytes, teardrop cells). Nucleated erythroid precursors are often found in the peripheral blood as well. Immature white cells (myelocytes and metamyelocytes) are also seen, and basophils are sometimes increased as well. The presence of nucleated red cell precursors and immature white cells is referred to as leukoerythroblastosis. Platelets are often abnormal in size and shape and defective in function. In some cases the clinical and blood picture resembles CML, but the Ph chromosome is absent. Because of a high rate of cell turnover, hyperuricemia and gout may also complicate the picture.

The outcome of this disease is variable, but the median survival time is 4 to 5 years. There is a constant threat of infections, as well as thrombotic and hemorrhagic episodes stemming from platelet abnormalities. Splenic infarctions are common. In 5% to 15% of individuals, there is eventually a blast crisis resembling AML.
Myelofibrosis with myeloid metaplasia (peripheral blood smear). Two nucleated erythroid precursors and several teardrop-shaped red cells (dacryocytes) are evident. Immature myeloid cells were present in other fields. An identical picture can be seen in other diseases producing marrow distortion and fibrosis.

**SUMMARY**

**Myeloid Neoplasms**

Myeloid tumors are mainly tumors of adults that fall into three groups.

- **Acute Myelogenous Leukemias (AML):**
  - Collection of aggressive tumors that are comprised of immature myeloid lineage cells (myeloblasts), which replace the marrow and suppress normal hematopoiesis.
  - AML cells contain diverse genetic lesions that often lead to the expression of abnormal transcription factors that block myeloid cell differentiation.

- **Chronic Myeloproliferative Disorders:**
  - Indolent tumors in which production of cells is initially increased, leading to high blood counts and extramedullary hematopoiesis.
  - Commonly associated with acquired genetic lesions that lead to constitutive activation of tyrosine kinases, which mimic signals from normal growth factors; treated with kinase inhibitors.
  - Two main types are:
    - **Chronic Myelogenous Leukemia (CML):** myeloid tumor arising from a pluripotent stem cell; associated with chromosome rearrangements that cause the formation of a BCR-ABL fusion gene, which encodes a constitutively active tyrosine kinase; causes increased hematopoiesis, particularly in the granulocytic and thrombocytic lineages; if untreated, inevitably progresses to a blast crisis phase that can resemble either AML or lymphoblastic leukemia.
    - **Polycythemia Vera:** myeloid tumor associated with point mutations that activate JAK2, a tyrosine kinase; causes increased hematopoiesis with high white cell, platelet, and red cell counts; the latter is responsible for most of the clinical symptoms.
  - **Myelodysplastic Syndromes:** group of myeloid tumors characterized by disordered and ineffective hematopoiesis. Most patients present with pancytopenia, and many progress to a disease state that is identical to AML.
    - **Myeloid Metaplasia with Myelofibrosis** is the most common myelodysplastic syndrome. It is a myeloid tumor in which abnormal megakaryocytes release growth factors that stimulate reactive marrow fibroblasts to deposit collagen, and the resulting fibrosis slowly replaces the marrow space, leading to pancytopenia and extramedullary hematopoiesis, which can produce massive splenomegaly.

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**Histiocytic Neoplasms**

**Langerhans Cell Histiocytoses**

The term histiocytosis is an “umbrella” designation for a variety of proliferative disorders of histiocytes, or macrophages. Some, such as very rare histiocytic lymphomas, are clearly malignant neoplasms. Others, such as most histiocytic proliferations in lymph nodes, are completely benign and reactive. Between these two extremes lies a group of relatively rare tumors, the Langerhans cell histiocytoses, which are derived from Langerhans cells. You will recall that the Langerhans cell is an immature dendritic cell that is found normally in many organs, most prominently the skin (Chapter 5).

These proliferations take on different clinical forms, but all are believed to be variations of the same basic disorder. The proliferating Langerhans cells are human leukocyte antigen DR (HLA-DR) positive and express the CD1 antigen. Characteristically, these cells have HX bodies (Birbeck granules) in their cytoplasm. Under the electron microscope these are seen to have a pentalaminar, rodlike, tubular structure, with characteristic periodicity and sometimes a dilated terminal end (“tennis racket” appearance). Under the light microscope the proliferating Langerhans cells in these disorders do not resemble their normal dendritic counterparts. Instead, they have abundant, often vacuolated, cytoplasm with vesicular nuclei. This appearance is more akin to that of tissue histiocytes (macrophages), hence the term Langerhans cell histiocytosis.

Acute disseminated Langerhans cell histiocytosis (Letterer-Siwe disease) usually occurs in children younger than 2 years of age but may occasionally be seen in adults. The dominant clinical feature is the development of multifocal cutaneous lesions composed of Langerhans cells that grossly resemble seborrheic skin eruptions. Most of those affected have concurrent hepatosplenomegaly, lymphadenopathy, pulmonary lesions, and, eventually, destructive osteolytic bone lesions. Extensive infiltration of the marrow often leads to anemia, throm-
bleeding disorders are as follows: various tests used in the initial evaluation of patients with tests used in the evaluation of a bleeding diathesis. The review normal hemostasis and the common laboratory on a discussion of disorders of coagulation, we should first rated blood by using an electronic particle counter. Counts outside this range must be confirmed by a preres with the intrinsic pathway. PT is measured in seconds and requires fresh plasma. It is abnormal when there is a defect in platelet numbers or function. Bleeding time. This represents the time taken for a standardized skin puncture to stop bleeding. Measured in minutes, this procedure provides an in vivo assessment of platelet response to limited vascular injury. The reference range depends on the actual method used and varies from 2 to 9 minutes. It is abnormal when there is a defect in platelet numbers or function. Bleeding time is fraught with variability and poor reproducibility. Hence, new instrument-based assays that provide quantitative measures of platelet function are being introduced. Platelet counts. These are obtained on anticoagulated blood by using an electronic particle counter. The reference range is 150 x 10^3 to 450 x 10^3 cells/mm^3. Counts outside this range must be confirmed by a visual inspection of a peripheral blood smear. Prothrombin time (PT). This procedure tests the adequacy of the extrinsic and common coagulation pathways. It represents the time needed for plasma to clot in the presence of an exogenously added source of tissue thromboplastin (e.g., brain extract) and Ca^{2+}.

Unifocal lesions usually affect the skeletal system. They may be asymptomatic or cause pain and tenderness and, in some instances, pathologic fractures. This is an indolent disorder that may heal spontaneously or be cured by local excision or irradiation. Multifocal Langerhans cell histiocytosis usually affects children, who present with fever; diffuse eruptions, particularly on the scalp and in the ear canals; and frequent bouts of otitis media, mastoiditis, and upper respiratory tract infections. The proliferation may sometimes cause mild lymphadenopathy, hepatomegaly, and splenomegaly. In about 50% of patients, involvement of the posterior pituitary stalk of the hypothalamus leads to diabetes insipidus. The combination of calvarial bone defects, diabetes insipidus, and exophtalmos is referred to as the Hand-Schüller-Christian triad. Many patients experience spontaneous regressions; others are treated effectively with chemotherapy.

BLEEDING DISORDERS

These disorders are characterized clinically by abnormal bleeding, which can either be spontaneous or become evident after some inciting event (e.g., trauma or surgery). It should be recalled from the discussion in Chapter 4 that the normal hemostatic response involves the blood vessel wall, the platelets, and the clotting cascade, and abnormalities in any of these three components can be associated with clinically significant bleeding. Before embarking on a discussion of disorders of coagulation, we should first review normal hemostasis and the common laboratory tests used in the evaluation of a bleeding diathesis. The various tests used in the initial evaluation of patients with bleeding disorders are as follows:

- **Bleeding time.** This represents the time taken for a standardized skin puncture to stop bleeding. Measured in minutes, this procedure provides an in vivo assessment of platelet response to limited vascular injury. The reference range depends on the actual method used and varies from 2 to 9 minutes. It is abnormal when there is a defect in platelet numbers or function. Bleeding time is fraught with variability and poor reproducibility. Hence, new instrument-based assays that provide quantitative measures of platelet function are being introduced.
- **Platelet counts.** These are obtained on anticoagulated blood by using an electronic particle counter. The reference range is 150 x 10^3 to 450 x 10^3 cells/mm^3. Counts outside this range must be confirmed by a visual inspection of a peripheral blood smear.
- **Prothrombin time (PT).** This procedure tests the adequacy of the extrinsic and common coagulation pathways. It represents the time needed for plasma to clot in the presence of an exogenously added source of tissue thromboplastin (e.g., brain extract) and Ca^{2+}.

Additional, more specialized tests are available that measure the levels of specific clotting factors, fibrinogen, and fibrin split products; assess the presence of circulating anticoagulants; and evaluate platelet function. With this overview we can return to the three important categories of bleeding disorders.

Abnormalities of vessels can contribute to bleeding in several ways. Increased fragility of the vessels is associated with severe vitamin C deficiency (scurvy) (Chapter 8), systemic amyloidosis (Chapter 5), chronic glucocorticoid use, rare inherited conditions affecting the connective tissues, and a large number of infectious and hypersensitivity vasculitides. The latter include meningococcemia, infective endocarditis, the rickettsial diseases, typhoid, and Henoch-Schönlein purpura. Some of these conditions are discussed in other chapters; others are beyond the scope of this book. A hemorrhagic diathesis that is purely the result of vascular fragility is characterized by the apparently spontaneous appearance of petechiae and ecchymoses in the skin and mucous membranes (probably resulting from minor trauma). In most instances, the
Bleeding can also be triggered by systemic conditions that activate or damage endothelial cells. If severe enough, such insults convert the vascular lining to a prothrombotic surface that activates coagulation throughout the circulatory system. Paradoxically, in such consumptive coagulopathies platelets and coagulation factors are used up faster than they can be replaced, and the resulting deficiencies (which are readily identified in laboratory tests of coagulation) often lead to severe bleeding.

Deficiencies of platelets (thrombocytopenia) are important causes of hemorrhage. They can occur in a variety of clinical settings that are discussed later. Other disorders are characterized by qualitative defects in platelet function. These include defects that are acquired, as in uremia, after aspirin ingestion, and in certain myeloproliferative disorders, or inherited, as in von Willebrand disease and other rare congenital disorders. The clinical signs of inadequate platelet function include easy bruising, nosebleeds, excessive bleeding from minor trauma, and menorrhagia. The PT and PTT are normal, but the bleeding time is prolonged.

Bleeding diatheses based purely on a derangement of blood clotting differ in several respects from those resulting from defects in the vessel walls or in platelets. The PT, PTT, or both, are prolonged, whereas the bleeding time is normal. Petechiae and other evidence of bleeding from very minor surface trauma are usually absent. However, massive hemorrhage can occur subsequent to operative or dental procedures or severe trauma. Moreover, hemorrhages into areas of the body subject to trauma, such as the joints of the lower extremities, are characteristic. This category includes the hemophilia, an important group of inherited coagulopathies.

Disseminated intravascular coagulation, one of the most common consumptive coagulopathies, presents with laboratory and clinical features related to both thrombocytopenia and coagulation factor deficiencies. Von Willebrand disease is a fairly common inherited disorder in which both platelet and (to a lesser degree) coagulation factor function are abnormal. With this as an overview, we will now turn to specific bleeding disorders.

**DISSEMINATED INTRAVASCULAR COAGULATION**

An acute, subacute, or chronic thrombohemorrhagic disorder, disseminated intravascular coagulation (DIC) occurs as a secondary complication in a variety of diseases. It is caused by the systemic activation of the coagulation pathways, leading to the formation of thrombi throughout the microcirculation. As a consequence of the widespread thromboses, there is consumption of platelets and coagulation factors and, secondarily, activation of fibrinolysis. Thus, DIC can give rise to either tissue hypoxia and microinfarcts caused by myriad microthrombi or to a bleeding disorder related to pathologic activation of fibrinolysis and the depletion of the elements required for hemostasis (hence the term consumptive coagulopathy). This entity is probably a more common cause of bleeding than all of the congenital coagulopathy disorders combined.

**Etiology and Pathogenesis.** Before presenting the specific disorders associated with DIC, we will discuss in a general way the pathogenetic mechanisms by which intravascular clotting can occur. Reference to earlier comments on normal blood coagulation (Chapter 4) may be helpful at this point. It suffices here to recall that clotting can be initiated by either of two pathways: the extrinsic pathway, which is triggered by the release of tissue factor (tissue thromboplastin), or the intrinsic pathway, which involves the activation of factor XII by surface contact, collagen, or other negatively charged substances. Both pathways lead to the generation of thrombin. Clot-inhibiting influences include the rapid clearance of activated clotting factors by the mononuclear phagocytic system or by the liver, activation of endogenous anticoagulants (e.g., protein C), and activation of fibrinolysis.

Two major mechanisms can trigger DIC: (1) the release of tissue factor or thromboplastic substances into the circulation, and (2) widespread endothelial cell damage (Fig. 12–28). Thromboplastic substances can be released into the circulation from a variety of sources—for example, the placenta in obstetric complications, the cytoplasmic granules of acute promyelocytic leukemia cells, or mucin-secreting adenocarcinoma cells. Carcinomas can also release other procoagulant substances, such as proteolytic enzymes, and other still-undefined tumor products. Some tumors express tissue factor on the cell membrane. In gram-negative and gram-positive sepsis (important causes of DIC), endotoxins or exotoxins cause increased synthesis, surface expression, and release of tissue factor from monocytes. Furthermore, activated monocytes release IL-1 and tumor necrosis factor, both of which increase the expression of tissue factor on endothelial cells and simultaneously decrease the expression of thrombomodulin. The latter, you may recall, activates protein C, an anticoagulant (Chapter 4). The net result is the enhanced activation of the extrinsic clotting system and the blunting of inhibitory pathways that tend to prevent coagulation.

Severe endothelial cell injury can initiate DIC by causing the release of tissue factor and by exposing subendothelial collagen and von Willebrand factor (vWF), which act together to promote platelet aggregation and the activation of the intrinsic coagulation cascade. Even subtle endothelial damage can unleash procoagulant activity by stimulating the increased expression of tissue factor on endothelial cell surfaces. Widespread endothelial injury can be produced by the deposition of antigen-antibody complexes (e.g., in SLE), by temperature extremes (e.g., following heat stroke or burns), or by infections (e.g., meningococci and rickettsiae). As discussed in Chapter 4, endothelial injury is an important consequence of endotoxemia, and, not surprisingly, DIC is a frequent complication of gram-negative sepsis.

Several additional disorders associated with DIC are listed in Table 12–12. Of these, DIC is most likely to occur after sepsis, obstetric complications, malignancy, and major trauma (especially trauma to the brain), the initiating events in these conditions are multiple and often
interrelated. For example, in obstetric conditions, tissue factor derived from the placenta, retained dead fetus, or amniotic fluid enters the circulation; however, shock, hypoxia, and acidosis often coexist and can lead to widespread endothelial injury. Trauma to the brain releases fat and phospholipids, which can act as contact factors and thereby activate the intrinsic arm of the coagulation cascade.

Whatever the pathogenetic mechanism, DIC has two consequences. First, there is widespread fibrin deposition within the microcirculation. This leads to ischemia in the more severely affected or vulnerable organs and to hemolysis as red cells are traumatized while passing through vessels narrowed by fibrin thrombi (microangiopathic hemolytic anemia). Second, a bleeding diathesis results from the depletion of platelets and clotting factors and the secondary release of plasminogen activators. Plasmin cleaves not only fibrin (fibrinolysis) but also factors V and VIII, thereby reducing their concentration further. In addition, fibrinolysis creates fibrin degradation products, which inhibit platelet aggregation, have antithrombin activity, and impair fibrin polymerization, all of which contribute to the hemostatic failure (see Fig. 12–28).

<table>
<thead>
<tr>
<th>Table 12–12</th>
<th>Major Disorders Associated with Disseminated Intravascular Coagulation</th>
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<tbody>
<tr>
<td>Obstetric Complications</td>
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<tr>
<td>Abruptio placentae</td>
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<td>Retained dead fetus</td>
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<td>Septic abortion</td>
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<td>Amniotic fluid embolism</td>
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<td>Toxemia</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Sepsis (gram-negative and gram-positive)</td>
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<tr>
<td>Meningococcemia</td>
<td></td>
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<tr>
<td>Rocky Mountain spotted fever</td>
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<tr>
<td>Histoplasmosis</td>
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<tr>
<td>Aspergillosis</td>
<td></td>
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<tr>
<td>Malaria</td>
<td></td>
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<tr>
<td>Neoplasms</td>
<td></td>
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<tr>
<td>Carcinomas of pancreas, prostate, lung, and stomach</td>
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<tr>
<td>Acute promyelocytic leukemia</td>
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<tr>
<td>Massive Tissue Injury</td>
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<tr>
<td>Trauma</td>
<td></td>
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<tr>
<td>Burns</td>
<td></td>
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<tr>
<td>Extensive surgery</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Acute intravascular hemolysis, snakebite, giant hemangioma, shock, heat stroke, vasculitis, aortic aneurysm, liver disease</td>
<td></td>
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</table>

**Morphology**

In DIC microthrombi are found principally in the arterioles and capillaries of the kidneys, adrenals, brain, and heart, but no organ is spared, and the lungs, liver, and gastrointestinal mucosa can be prominently involved. The glomeruli contain small fibrin thrombi. These may be associated with only a subtle, reactive swelling of the endothelial cells, or varying degrees of focal glomerulitis. The microvascular occlusions lead to small infarcts in the renal cortex. In severe cases, the ischemia can destroy the entire cortex and cause bilateral renal cortical necrosis. Involvement of the adrenal glands can produce the Waterhouse-Friderichsen syndrome.
Platelet counts in the range of 20,000 to 50,000 cells/μL generally considered to constitute thrombocytopenia. There are also conditions associated with an increased risk of post-traumatic bleeding, and spontaneous bleeding becomes evident when counts fall below 20,000 cells/μL. Most bleeding tends to occur from small, superficial blood vessels and produces petechiae or large ecchymoses in the skin, the mucous membranes of the gastrointestinal and urinary tracts, and other sites. Larger hemorrhages into the central nervous system are a major hazard in patients with markedly depressed platelet counts.

The major causes of thrombocytopenia are listed in Table 12–13. Clinically important thrombocytopenias are confined to those disorders in which there is reduced production or increased destruction of platelets. In most cases in which the cause is accelerated destruction, the bone marrow reveals a compensatory increase in the number of megakaryoblasts and syncytial megakaryoblasts that characterizes this condition.

The bleeding tendency associated with DIC is manifested not only by larger than expected hemorrhages near foci of infarction but also by diffuse petechiae and ecchymoses, which can be found on the skin, serosal linings of the body cavities, epicardium, endocardium, lungs, and mucosal lining of the urinary tract.

**Clinical Course.** As might be imagined, depending on the balance between clotting and bleeding tendencies, the range of possible clinical manifestations is enormous. In general, acute DIC (e.g., that associated with obstetric complications) is dominated by a bleeding diathesis, whereas chronic DIC (e.g., as occurs in an individual with cancer) tends to present with symptoms related to thrombosis. Typically, the abnormal clotting occurs only in the microcirculation, although large vessels are involved occasionally. The manifestations may be minimal, or there may be shock, with acute renal failure, dyspnea, cyanosis, convulsions, and coma. Most often, attention is called to the presence of DIC by prolonged and copious postpartum bleeding or by the presence of petechiae and ecchymoses on the skin. These may be the only manifestations, or there may be severe hemorrhage into the gut or urinary tract. Laboratory evaluation reveals thrombocytopenia and prolongation of PT and PTT (resulting from depletion of platelets, clotting factors, and fibrinogen). Fibrin split products are increased in the plasma.

The prognosis for patients with DIC is highly variable, and depends on the nature of the underlying disorder and the severity of the intravascular clotting and fibrinolysis. In some acute cases it can be life-threatening and must be treated aggressively with anticoagulants such as heparin or the coagulants contained in fresh-frozen plasma. Conversely, in more chronic forms DIC is sometimes identified as a laboratory abnormality. In either circumstance, definitive treatment must be directed at the cause of the DIC, not at its hematostatic consequences.

**Immune Thrombocytopenic Purpura**

Immune thrombocytopenic purpura (ITP), also called idiopathic thrombocytopenic purpura, can occur in the setting of a variety of conditions and exposures (secondary ITP) or in the absence of any known risk factors (primary or idiopathic ITP). There are two clinical sub-

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**Table 12–13 Causes of Thrombocytopenia**

<table>
<thead>
<tr>
<th>Decreased Production of Platelets</th>
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<tr>
<td>Generalized disease of bone marrow</td>
</tr>
<tr>
<td>Aplastic anemia: congenital and acquired</td>
</tr>
<tr>
<td>Marrow infiltration: leukemia, disseminated cancer</td>
</tr>
</tbody>
</table>

| Selective impairment of platelet production |
| Drug-induced: alcohol, thiazides, cytotoxic drugs |
| Infections: measles, HIV infection |

| Ineffective megakaryopoiesis |
| Megaloblastic anemia |
| Paroxysmal nocturnal hemoglobinuria |

| Decreased Platelet Survival |
| Immunologic destruction |
| Autoimmune: immune thrombocytopenic purpura, systemic lupus erythematosus |
| Isoimmune: post-transfusion and neonatal |
| Drug-associated: quinidine, heparin, sulfa compounds |
| Infections: infectious mononucleosis, HIV infection, cytomegalovirus infection |

| Nonimmunologic destruction |
| Disseminated intravascular coagulation |
| Thrombotic thrombocytopenic purpura |
| Giant hemangiomas |
| Microangiopathic hemolytic anemias |

| Sequestration |
| Hypersplenism |

| Dilutional |
| HIV, human immunodeficiency virus. |
types of primary ITP: chronic primary ITP, a relatively common disorder that tends to affect adult females between the ages of 20 and 40 years; and acute ITP, a self-limited form that is most commonly seen in children subsequent to viral infections.

Antiplatelet immunoglobulins directed against platelet membrane glycoproteins IIb/IIa or Ib/IX complexes can be identified in 80% of patients with chronic ITP. The spleen is an important site of antiplatelet antibody production and the major site of destruction of the IgG-coated platelets. It is usually normal in size and shows only subtle evidence of increased platelet destruction; thus, splenic enlargement or lymphadenopathy should lead one to consider other possible diagnoses. Nonetheless, the importance of the spleen in this disorder is confirmed by the clinical benefits produced by splenectomy, which normalizes the platelet count and induces a complete remission in more than two-thirds of patients. The bone marrow usually contains increased numbers of megakaryocytes, a finding that is common to all forms of thrombocytopenia that are caused by accelerated platelet destruction. A marrow examination can be helpful in excluding marrow failure as a cause of the thrombocytopenia.

The onset of chronic ITP is insidious. Common findings include petechiae, easy bruising, epistaxis, gum bleeding, and hemorrhages after minor trauma. Fortunately, more serious intracerebral or subarachnoid hemorrhages occur much less commonly. The diagnosis rests on the clinical features, the presence of thrombocytopenia, examination of the marrow, and the exclusion of secondary ITP. Reliable clinical tests for antiplatelet antibodies are not widely available.

**Heparin-Induced Thrombocytopenia**

This special type of drug-induced thrombocytopenia merits brief mention because of its clinical importance. Moderate to severe thrombocytopenia develops in 3% to 5% of individuals treated with unfractionated heparin after 1 to 2 weeks of therapy. The disorder is caused by IgG antibodies that bind to platelet factor IV on platelet surfaces in a heparin-dependent fashion. This activates platelets and induces their aggregation, thus exacerbating the condition that heparin is used to treat—thrombosis. Both venous and arterial thromboses occur, even in the setting of marked thrombocytopenia, and can cause severe morbidity (e.g., loss of limbs because of vascular insufficiency) and death. Cessation of heparin therapy breaks the cycle of platelet activation and consumption.

**Thrombotic Microangiopathies: Thrombotic Thrombocytopenic Purpura and Hemolytic-Uremic Syndrome**

The term thrombotic microangiopathies encompasses a spectrum of clinical syndromes that include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS). As originally defined, TTP is associated with the pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, and renal failure. HUS is also associated with microangiopathic hemolytic anemia and thrombocytopenia but is distinguished from TTP by the absence of neurologic symptoms, the dominance of acute renal failure, and an onset in childhood (Chapter 14). Clinical experience has blurred these distinctions, because many adults with TTP lack one or more of the five criteria, and some patients with HUS have fever and neurologic dysfunction. Fundamental to both of these conditions is the widespread formation of hyaline thrombi in the microcirculation that are composed primarily of dense aggregates of platelets surrounded by fibrin. The consumption of platelets leads to thrombocytopenia, and the narrowing of blood vessels by the platelet-rich thrombi results in a microangiopathic hemolytic anemia.

For many years the pathogenesis of TTP was enigmatic, although treatment with plasma exchange (initiated in the early 1970s) converted it from a disease that was almost uniformly fatal to one that is successfully treated in more than 80% of individuals. Recently, the underlying cause of most cases of TTP has been elucidated. In brief, symptomatic patients are deficient in a metalloprotease called ADAMTS13. This enzyme degrades very-high-molecular-weight multimer of vWF, and hence the absence of ADAMTS13 activity allows multimers of vWF to accumulate in plasma. Under some circumstances, these colossal vWF multimers promote platelet microaggregate formation throughout the circulation. The superimposition of an endothelial cell injury (caused by some other condition) can further promote microaggregate formation, thus initiating or exacerbating clinically evident TTP.

The deficiency of ADAMTS13 activity can be an inherited condition, but it is more commonly caused by an acquired autoantibody that binds and inhibits the metalloprotease. TTP must be considered in any individual who presents with unexplained thrombocytopenia and microangiopathic hemolytic anemia, because the failure to make an early diagnosis can be fatal.

Although clinically similar to TTP, HUS has a different basis, because ADAMTS13 levels are normal in this disorder. HUS in children and the elderly usually occurs subsequent to infectious gastroenteritis caused by E. coli strain O157:H7. This organism elaborates a Shiga-like toxin that damages endothelial cells, which initiates platelet activation and aggregation. Affected individuals often present with bloody diarrhea, which is followed a few days later by HUS. With supportive care and plasma exchange, recovery is possible, but irreversible renal damage and death can occur in more severe cases. About 10% of cases in children are not preceded by infection with Shiga toxin-producing bacteria. Some of these patients have mutations in the gene encoding complement regulatory proteins, notably factor H. Deficiency of this protein leads to uncontrolled complement activation after minor endothelial injury, resulting in thrombosis. HUS can also be seen after exposures to other factors (e.g., certain drugs, radiation therapy) that damage endothelial cells. Here the prognosis is more guarded, in part because the underlying conditions are often chronic or life-threatening.

Although DIC and the thrombotic microangiopathies share features such as microvascular occlusion and microangiopathic hemolytic anemia, they are pathogenetically distinct. In TTP and HUS, unlike in DIC,
activation of the coagulation cascade is not of primary importance, and thus the laboratory tests of coagulation (such as the PT and the PTT) are usually normal.

**COAGULATION DISORDERS**

These disorders result from either congenital or acquired deficiencies of clotting factors. Most common are the acquired coagulation factor deficiencies, which typically affect many factors simultaneously. As was discussed in Chapter 8, vitamin K is essential for the synthesis of prothrombin and clotting factors VII, IX, and X, and its deficiency causes a severe coagulation defect. The liver is the site of both the synthesis of several coagulation factors and the removal of many activated coagulation factors; thus, parenchymal diseases of the liver are common causes of complex hemorrhagic diatheses.

Hereditary deficiencies have been identified for each of the coagulation factors. These deficiencies characteristically occur singly. Hemophilia A, resulting from deficiency of factor VIII, and hemophilia B (Christmas disease), resulting from deficiency of factor IX, are transmitted as X-linked recessive disorders, whereas most others are autosomal disorders. These inherited deficiencies are rare; only von Willebrand disease, hemophilia A, and hemophilia B are sufficiently common to warrant further consideration here.

**Deficiencies of Factor VIII–vWF Complex**

Hemophilia A and von Willebrand disease, two of the most common inherited disorders of bleeding, are caused by qualitative or quantitative defects involving the factor VIII–vWF complex. Before we can discuss these disorders, it is useful to review the structure and function of these proteins.

**Plasma factor VIII–vWF complex is made up of two proteins** (Fig. 12–29). One, which is required for the activation of factor X in the intrinsic coagulation pathway, is called factor VIII procoagulant protein, or factor VIII. Deficiency of factor VIII gives rise to hemophilia A. Factor VIII is associated noncovalently with a much larger protein, vWF, that forms high-molecular-weight multimers of sizes that range as high as 20 megadaltons. vWF is found normally in the plasma (in association with factor VIII), in platelet granules, in endothelial cells in unusual cytoplasmic vesicles called Weibel-Palade bodies, and in the subendothelium, where it binds to collagen.

When endothelial cells are stripped away by trauma or injury, subendothelial vWF becomes exposed and binds to platelets through the receptors glycoproteins Ib and IIb/IIIa (see Fig. 12–29). The most important function of vWF is to facilitate the adhesion of platelets to damaged blood vessel walls, which is a crucial early event in the formation of a hemostatic plug. It is this activity that is believed to be deficient in von Willebrand disease. In addition to its function in platelet adhesion, vWF also serves as a carrier for factor VIII.

The various forms of von Willebrand disease can be characterized by immunologic techniques and the so-called ristocetin agglutination test. Ristocetin (developed as an antibiotic) binds platelets and promotes the interaction between vWF and platelet membrane glycoprotein Ib. The binding of vWF creates interplatelet “bridges” that lead to the formation of platelet clumps (agglutination), an event that can be measured easily. Thus, ristocetin-dependent platelet agglutination serves as a useful bioassay for vWF.

The two components of the factor VIII–vWF complex are encoded by separate genes and are synthesized by different cells. vWF is produced by both megakaryocytes and endothelial cells. The latter are the major source of

**Figure 12–29**

Structure and function of factor VIII–von Willebrand factor (vWF) complex. Factor VIII and vWF are synthesized in the liver and in endothelial cells, respectively. The two circulate as a complex in the circulation. vWF is also present in the subendothelial matrix of normal blood vessels. Factor VIII takes part in the coagulation cascade by activating factor X. vWF causes adhesion of platelets to subendothelial collagen, primarily through the glycoprotein Ib (GpIb) platelet receptor. Ristocetin activates GpIb receptors in vitro and causes platelet aggregation if vWF is present.
plasma vWF, whereas most factor VIII is synthesized in the liver. To summarize, the two components of factor VIII–vWF complex, synthesized separately, come together and circulate in the plasma as a unit that serves to promote clotting as well as the platelet-vessel wall interactions necessary to ensure hemostasis.

With this background we can turn to the discussion of diseases resulting from deficiencies of factor VIII–vWF complex.

**von Willebrand Disease**

von Willebrand disease is marked by spontaneous bleeding from mucous membranes, excessive bleeding from wounds, menorrhagia, and a prolonged bleeding time in the presence of a normal platelet count. In most cases it is transmitted as an autosomal dominant disorder. Its precise incidence is difficult to estimate, because in many instances the clinical manifestations are mild and the diagnosis requires sophisticated tests; it may well be the most common inherited bleeding disorder.

Individuals with von Willebrand disease have a compound defect involving platelet function and the coagulation pathway. The amounts of factor VIII are only moderately depressed, and it is the defect in platelet function that dominates the clinical picture. Except for rare homozygous patients with type III von Willebrand disease, the effects of factor VIII deficiency that characterize hemophilia are not seen.

The classic and most common variant of von Willebrand disease (type I) is an autosomal dominant disorder characterized by a reduced quantity of circulating vWF. Because vWF stabilizes factor VIII by binding to it, its deficiency causes a secondary decrease in factor VIII levels, but not to levels that are clinically significant. The other, less common, varieties of von Willebrand disease tend to show both qualitative and quantitative defects in vWF. Type II is divided into several subtypes that are all characterized by a selective loss of high-molecular-weight multimers of vWF. Because these multimers are the most active form, there is a functional deficiency of vWF. In type IIA, the high-molecular-weight multimers are not synthesized, leading to a true deficiency. In type IIB, functionally abnormal high-molecular-weight multimers are synthesized that are rapidly removed from the circulation. These high-molecular-weight multimers cause spontaneous platelet aggregation (a situation reminiscent of the very-high-molecular-weight multimer aggregates that are seen in TTP), and indeed some individuals with type IIB von Willebrand disease have chronic mild thrombocytopenia that is presumably caused by platelet consumption.

**Factor VIII Deficiency (Hemophilia A, Classic Hemophilia)**

Hemophilia A is the most common hereditary disease associated with serious bleeding. It is an X-linked recessive disorder that is caused by reduction in factor VIII activity. It primarily affects males, but much less commonly excessive bleeding also occurs in heterozygous females, presumably as a result of extremely unfavorable lyonization (inactivation of the normal X chromosome in most of the cells). Approximately 30% of cases are caused by new mutations; in the remainder, there is a positive family history. Severe hemophilia A is observed in individuals with a marked degree of factor VIII deficiency (activity levels of <1% of normal). Milder deficiencies may only become apparent when a major hemodynamic stress supervenes, such as trauma. The varying degrees of factor VIII deficiency are for the most part explained by the existence of many different causative mutations. As in the thalassemias, several types of genetic lesions (e.g., deletions, splice junction mutations, nonsense mutations) have been identified. In about 10% of patients, the factor VIII concentration is normal by immunoassay, but the coagulant activity detected by bioassay is low because of a mutation that causes the synthesis of functionally abnormal protein.

In all symptomatic cases there is a tendency toward easy bruising and massive hemorrhage after trauma or operative procedures. In addition, “spontaneous” hemorrhages are frequently encountered in regions of the body that are normally subject to trauma, particularly the joints, where recurrent bleeds into the joints (hemarthroses) lead to progressive deformities that can be crippling. Petechiae are characteristically absent. Typically, patients with hemophilia A have a prolonged PTT that is corrected by mixing the patient’s plasma with normal plasma. In approximately 15% of the most severely affected patients, replacement therapy is complicated by the development of neutralizing antibodies against factor VIII, perhaps because factor VIII is seen as foreign in severely deficient individuals. In these persons the PTT fails to correct in mixing studies. Specific factor VIII assays are required to confirm the diagnosis on hemophilia A.

Treatment involves infusion of factor VIII. Historically, factor VIII was prepared from human plasma, carrying with it the risk of transmission of viral diseases. As was mentioned in Chapter 5, before 1985 thousands of hemophiliacs received factor VIII preparations contaminated with HIV. Subsequently, many became seropositive and developed AIDS. The availability and widespread use of recombinant factor VIII and more highly purified factor VIII concentrates has now eliminated the infectious risk of factor VIII replacement therapy.

**Factor IX Deficiency (Hemophilia B, Christmas Disease)**

Severe factor IX deficiency is an X-linked disorder that is indistinguishable clinically from hemophilia A but is much less common. The PTT is prolonged, and the bleeding time is normal. The diagnosis of Christmas disease (named after the first patient with this condition) is made with specific assays of factor IX. It is treated by infusion of recombinant factor IX.
SPLENOMEGALY

The spleen is frequently secondarily involved in a wide variety of systemic diseases. In virtually all instances, the response of the spleen causes its enlargement (splenomegaly), which produces a set of stereotypical signs and symptoms. Evaluation of splenomegaly is a common clinical problem that is aided considerably by knowledge of the usual limits of the splenic enlargement that is seen in the context of specific disorders. It would be erroneous to attribute enlargement of the spleen into the pelvis to vitamin B12 deficiency, or to entertain a diagnosis of CML in the absence of significant splenomegaly. As an aid to diagnosis, then, we present the following list of disorders, classified according to the degree of splenomegaly that is characteristically produced:

A. Massive splenomegaly (weight more than 1000gm)
   1. Chronic myeloproliferative disorders (chronic myeloid leukemia, myeloid metaplasia with myelofibrosis)
   2. Chronic lymphocytic leukemia
   3. Hairy cell leukemia

B. Moderate splenomegaly (weight 500–1000gm)
   1. Chronic congestive splenomegaly (portal hypertension or splenic vein obstruction)
   2. Acute leukemias (inconstant)
   3. Hereditary spherocytosis
   4. Thalassemia major
   5. Autoimmune hemolytic anemia
   6. Thalassemia
   7. Niemann-Pick disease
   8. Langerhans histiocytosis
   9. Chronic splenitis (especially with infective endocarditis)
   10. Tuberculosis, sarcoidosis, typhoid
   11. Metastatic carcinoma or sarcoma

C. Mild splenomegaly (weight <500gm)
   1. Acute splenitis
   2. Acute splenic congestion
   3. Infectious mononucleosis

SUMMARY

Bleeding Disorders

- **Disseminated Intravascular Coagulation:**
  - Syndrome in which systemic activation of the coagulation cascade by various stimuli, including sepsis, massive tissue injury, and release of procoagulant factors from tumor cells, leads to consumption of coagulation factors and platelets.
  - The clinical picture can be dominated by bleeding, vascular occlusion and tissue hypoxemia, or both. Common stimuli include sepsis, major trauma, certain cancers, and obstetric complications.

- **Immune Thrombocytopenia Purpura (ITP):**
  - Caused by autoantibodies against platelet antigens; may be triggered by drugs, infections, or lymphomas, or be idiopathic.

- **Thrombotic Thrombocytopenia Purpura (TTP):**
  - Caused most commonly by acquired or inherited deficiencies of ADAMTS13, a plasma metalloprotease that normally prevents the accumulation of very high molecular weight multimers of von Willebrand factor (vWF). Deficiency of ADAMTS13 results in abnormally large vWF multimers, which lead to the formation of platelet-rich thrombi, particularly in the kidney and the central nervous system.

Hemolytic Uremic Syndrome resembles TTP clinically, but is caused by deficiencies of complement regulatory protein factor H, or agents that damage endothelial cells, such as a Shiga-like toxin elaborated by E. coli strain O157:H7. The endothelial injury initiates platelet activation, platelet aggregation, and microvascular thrombosis.

- **von Willebrand Disease:**
  - Autosomal dominant disorder caused by mutations in vWF, which normally functions as a bridging molecule between platelets and subendothelial collagen.
  - Typically causes a mild to moderate bleeding disorder that mimics that caused by thrombocytopenia.

- **Hemophilia A** is an X-linked disorder caused by mutations in coagulation factor VIII. Affected males typically present with severe bleeding into soft tissues and joints, and have a prolonged partial thromboplastin time (PTT).

- **Hemophilia B** is an X-linked disorder caused by mutations in coagulation factor IX; clinically, it is identical to hemophilia A.
4. Miscellaneous acute febrile disorders, including septicemia, SLE, and intra-abdominal infections

The microscopic changes associated with these diseases need not be described here, because they have been discussed in the relevant sections of this and other chapters.

An enlarged spleen often removes excessive numbers of one or more of the formed elements of blood, resulting in anemia, leukopenia, or thrombocytopenia. This is referred to as hypersplenism, a state that can be associated with many of the diseases affecting the spleen listed previously. In addition, platelets are particularly susceptible to sequestration in the interstices of the red pulp; as a result, thrombocytopenia is more prevalent and severe in individuals with splenomegaly than are anemia or neutropenia.

**DISORDERS OF THE THYMUS**

As is well known, the thymus is a central lymphoid organ that has a crucial role in T-cell differentiation. It is not surprising, therefore, that the thymus can be involved by lymphomas, particularly those of T-cell lineage, which were discussed earlier in this chapter. Here we will focus on the two most frequent (albeit uncommon) disorders of the thymus: thymic hyperplasia and thymoma.

**Thymic Hyperplasia**

Hyperplasia of the thymus is often associated with the appearance of lymphoid follicles, or germinal centers, within the medulla. These germinal centers contain reactive B cells, which are normally present in only low numbers in the thymus. Thymic follicular hyperplasia is present in most patients with myasthenia gravis and is sometimes also found in other autoimmune diseases, such as SLE and rheumatoid arthritis. The relationship between the thymus and myasthenia gravis is discussed in Chapter 21. Significantly, removal of the hyperplastic thymus is often beneficial early in the disease.

**Thymoma**

The term thymoma is restricted to tumors in which epithelial cells constitute the neoplastic element. Scant or abundant precursor T cells (thymocytes) are present in these tumors, but these are non-neoplastic. Several classification systems for thymoma have been proposed on the basis of cytologic and biologic criteria. One simple and clinically useful classification is as follows:

- Benign or encapsulated thymoma: cytologically and biologically benign
- Malignant thymoma
  - Type I: cytologically benign but biologically aggressive and capable of local invasion and, rarely, distant spread
  - Type II, also called thymic carcinoma: cytologically malignant with all of the features of cancer and comparable behavior

**Morphology**

Macroscopically, thymomas are lobulated, firm, gray-white masses up to 15 to 20 cm in longest dimension. Most appear encapsulated, but in 20% to 25% there is apparent penetration of the capsule and infiltration of perithymic tissues and structures.

Microscopically, virtually all thymomas are made up of a mixture of epithelial cells and a variable infiltrate of non-neoplastic thymocytes. The relative proportions of the epithelial and lymphocytic components are of little significance. In benign thymomas the epithelial cells are spindled or elongated and resemble those that normally populate the medulla. As a result, these are sometimes referred to as medullary thymomas. In other tumors there is an admixture of the plumper, rounder, cortical-type epithelial cells; this pattern is sometimes referred to as a mixed thymoma. The medullary and mixed patterns account for 60% to 70% of all thymomas.

**Malignant thymoma type I** is a tumor that is cytologically bland but locally invasive. These tumors occasionally (and unpredictably) metastasize and account for 20% to 25% of all thymomas. They are composed of varying proportions of epithelial cells and reactive thymocytes; the epithelial cells usually resemble those that are normally found in the cortex, in that they have abundant cytoplasm and rounded vesicular nuclei. The neoplastic epithelial cells often form palisades around blood vessels. Sometimes spindled epithelial cells are present as well. The critical distinguishing feature is the penetration of the capsule and the invasion of surrounding structures.

**Malignant thymoma type II** is perhaps better thought of as a form of thymic carcinoma. These represent about 5% of thymomas and, in contrast to the type I malignant thymomas, are malignant cytologically. Macroscopically, they are usually fleshy, obviously invasive masses sometimes accompanied by metastases to such sites as the lungs. Most resemble either poorly or well-differentiated squamous cell carcinomas. The next most common malignant pattern is lymphoepithelioma-like carcinoma, which is composed of anaplastic cortical-type epithelial cells mixed with large numbers of benign thymocytes. Tumors of this type are more common in Asian populations and sometimes contain the EBV genome.

**Clinical Features.** All thymomas are rarities, the malignant more so than the benign. They may arise at any age but typically occur in middle adult life. In a large series, about 30% were asymptomatic; 30% to 40% produced local manifestations such as a mass demonstrable on computed tomography in the anterosuperior mediastinum associated with cough, dyspnea, and superior vena cava syndrome; and the remainder were associated with some systemic disease, principally myasthenia gravis. Fifteen to 20% of patients with this disorder have a thymoma. Removal of the tumor often leads to improvement in the neuromuscular disorder. Additional associations with thymomas include hypogammaglobulinemia, SLE, pure red cell aplasia, and nonthymic cancers.
BIBLIOGRAPHY

**Red Cell Disorders**


[Bib entry for an overview of hemolytic anemias.]


[An update on the causes of aplastic anemia.]


[A review on the role of cytokines in cerebral malaria.]


[Recent insights into the pathogenesis of sickle-cell disease.]


[A recent overview of the anemia of chronic disease.]


[Discussion of the dual role of somatic mutation and autoimmunity in PNH.]

**White Cell Disorders**


[A progress report on the WHO classification of lymphoid neoplasms.]


[A proposed updated classification system for acute myelogenous leukemias, myeloproliferative disorders, and myelodysplastic syndromes.]


[An example of how understanding the molecular biology of CML has led to improved treatment.]


[A timely and thorough review on the increasing number of mutations that activate tyrosine kinases in cancer, many of which occur in acute leukemia and myeloproliferative disorders.]


[Current concise review on the molecular pathogenesis, diagnosis, and treatment of ALL.]


[An article on the role of current treatment in Hodgkin lymphoma pathogenesis and therapy.]


[An article on the role of current therapy in understanding acute myeloid leukemia.]

**Coagulation Disorders**


[An excellent review on ADAMTS13 deficiency in TTP.]


[A clinically oriented review on the causes, pathogenesis, and treatment of DIC.]


[An article on the role of autoantibodies against platelet factor 4 and heparin in heparin-induced thrombocytopenia.]


[An update on the diagnosis of von Willebrand disease.]


[An article on the clinical relevance of the hemolytic-uremic syndrome.]

**Disorders That Affect the Spleen and Thymus**


[An article on the role of current therapy in understanding thymic epithelial tumors.]

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