The chapters in Part 2 focus on the pathologic anatomy and pathophysiology of diseases that originate in, or exert their primary effects on, particular organ systems.

**Chapter 11 Diseases of Blood Cells and Blood Coagulation**
Reviews the composition of normal blood and normal blood cell formation. Discusses anemia, leukemia, lymphoma, and coagulation dysfunction, as well as other disorders.

**Chapter 12 Diseases of Blood Vessels**
Reviews normal vascular anatomy and blood flow and discusses atherosclerosis, hypertension, and other vascular diseases.

**Chapter 13 Diseases of the Heart**
Reviews normal cardiac anatomy and cardiopulmonary blood flow, and discusses coronary artery disease, valvular disease, congestive heart failure, congenital heart disease, and other disorders.

**Chapter 14 Diseases of the Respiratory System**
Reviews normal pulmonary anatomy, ventilation, and gas exchange, and discusses asthma, cigarette smoking, chronic bronchitis, and emphysema. Also covers pulmonary edema and thromboembolism, pneumonia, tuberculosis, lung cancer, and other disorders.

**Chapter 15 Diseases of the Gastrointestinal Tract**
Reviews normal gastrointestinal anatomy and digestion. Discusses intestinal bleeding and obstruction; gastritis and peptic ulcers; diarrhea, parasitic disease, and malabsorption syndromes; ulcerative colitis and Crohn disease; benign and malignant gastrointestinal tumors; and other disorders.

**Chapter 16 Diseases of the Liver and Biliary Tract**
Reviews the normal anatomy and physiology of the liver and biliary tract. Discusses cirrhosis, hepatitis, and alcoholic and metabolic liver disease; gallstones and other gallbladder disease; cancers of the liver and biliary tract; and other disorders.

**Chapter 17 Diseases of the Pancreas**
Reviews the normal anatomy and physiology of the digestive and endocrine functions of the pancreas. Discusses diabetes, pancreaticitis, pancreatic cancer, and other disorders.

**Chapter 18 Diseases of Endocrine Glands**
Reviews the normal anatomy and physiology of the pituitary, thyroid, parathyroid, and adrenal glands, their interrelationships, and their role in homeostasis, as well as the importance of negative feedback loops. Discusses overactivity and underactivity of the endocrine glands, as well as tumors and other disorders of each.

**Chapter 19 Diseases of the Kidney**
Reviews the normal gross anatomy of the urinary tract, the microscopic anatomy of the glomerulus and renal tubules, the formation and flow of urine, the regulation salt and water balance, and normal urination. Discusses glomerulonephritis and other inflammatory disease, the role of the kidney in hypertension, cancers of the kidney and bladder, and other disorders.

**Chapter 20 Diseases of the Lower Urinary Tract and Male Genitalia**
Reviews the normal anatomy and physiology of the lower urinary tract and male genitalia. Discusses cystitis, urethritis, epididymitis, and other inflammations; erectile dysfunction and infertility; syphilis and other sexually transmitted diseases; prostate enlargement; cancers of the penis, prostate and bladder; and other disorders.

**Chapter 21 Diseases of the Female Genital Tract and Breast**
Reviews the normal anatomy and physiology of the female genitalia and breast, including ovulation, fertilization, menstruation, pregnancy, lactation, and menopause. Discusses sexually transmitted disease, ectopic pregnancy, abortion, infertility, endometriosis, placental disease, dysplasia and cancer of the cervix, cancers and other tumors of the ovary, and other disorders.

**Chapter 22 Diseases of Bones, Joints, and Skeletal Muscle**
Reviews the normal anatomy and physiology of bone and muscle types, muscle and muscle types, and ligaments and tendons. Discusses bone infection and infarction, osteoporosis and fractures, arthritis and joint injury, tumors and tumor-like conditions of bone and muscle, and other disorders.

**Chapter 23 Diseases of the Nervous System**
Reviews the normal anatomy and physiology of the brain, spinal cord, peripheral nerves, and autonomic nervous system, their interconnections, and their connections to other cells. Discusses increased intracranial pressure, stroke, brain trauma, and brain hemorrhage; encephalitis and meningitis; degenerative diseases and brain toxins; benign and malignant tumors of nerve cells; and other disorders.

**Chapter 24 Diseases of the Skin**
Reviews the peculiar language of skin disease, the normal physiology and microscopic anatomy of skin, and the role of skin in body defense against the environment. Discusses selected skin conditions, including the effects of systemic disease, sunlight, and pregnancy. Also covers hair loss, eczema, acne, allergies, autoimmune disease, infections and other inflammations, premalignant and malignant lesions including malignant melanoma, and other diseases.

**Chapter 25 Diseases of the Eye and Ear**
Reviews the normal anatomy of the eye and the optics and physiology of vision. Discusses refractive disorders, infections, cataract, glaucoma, choriorretinitis, and other inflammations; neoplasms of the eye; and other disorders. Also reviews the normal anatomy of the ear and the physiology of hearing and balance. Discusses acute otitis media, deafness, vertigo, and other disorders.
CHAPTER 11

Diseases of Blood Cells and Blood Coagulation

This chapter begins with a review of the composition of normal blood and normal blood cell formation. Later sections discuss anemia, leukemia, lymphoma, coagulation dysfunction, and other disorders.

Section 1: Diseases of Blood Cells

BACK TO BASICS
- Normal Blood Production (Hematopoiesis)
- Cell Compartments and Life Span
- Laboratory Assessment of Blood Cells

TOO LITTLE HEMOGLOBIN (ANEMIA)
- The Anemia of Hemorrhage
- Anemia of Red Cell Destruction (Hemolytic Anemia)
- Anemia of Insufficient Red Cell Production

TOO MANY RED CELLS—POLYCYTHEMIA

TOO FEW WHITE CELLS—LEUKOPENIA AND AGRANULOCYTOSIS

TOO MANY WHITE CELLS—BENIGN AND MALIGNANT DISORDERS OF LEUKOCYTES
- Peripheral Leukocyte Responses to Infection or Injury
- Lymph Node Response to Injury or Infection
- Lymphoid Neoplasms
- Myeloid Neoplasms

DISORDERS OF THE SPLEEN AND THYMUS

Section 2: Bleeding Disorders

BACK TO BASICS
BLEEDING DISORDERS
- Vascular or Platelet Deficiency
- Coagulation Factor Deficiency
- Disseminated Intravascular Coagulation (DIC)

THROMBOTIC DISORDERS

Learning Objectives

After studying this chapter you should be able to:

1. Give a reasonable estimate of the life span of blood cells and platelets
2. Explain what is meant by red cell indices, and understand how to calculate them
3. Define anemia, and list the major types of anemia
4. Regarding sickle cell anemia, explain the cause and discuss what happens to red cells
5. Explain blood and bone marrow ferritin, iron, transferrin, and iron binding capacity in iron deficiency anemia
6. Explain the difference between relative and absolute erythrocytosis
7. Explain the significance of a left shift in the white cell differential count in peripheral blood
8. Name the two major groups of bone marrow malignancies, and list some of the diseases associated with each
9. Explain the difference between acute and chronic leukemia
10. Distinguish between leukemia and lymphoma
11. Explain why patients with plasma cell proliferation have abnormal blood proteins
12. Name the two major types of lymphoma
13. Name the two types of non-Hodgkin lymphoma according to microscopic patterns, and explain why this distinction is important
14. Define hypersplenism
15. Name the elements of normal hemostasis
16. Characterize bleeding associated with platelet disease
17. Briefly characterize classic hemophilia (hemophilia A)
18. Explain why patients with disseminated intravascular coagulation have bleeding problems
Chapter 11 • Diseases of Blood Cells and Blood Coagulation

Key Terms and Concepts

**BACK TO BASICS**
- myeloid
- lymphoid
- hemoglobin
- hematocrit
- red cell indices
- mean cell volume
- macrocytic
- normocytic
- microcytic
- normochromic
- hypochromic
- reticulocyte

**TOO LITTLE HEMOGLOBIN (ANEMIA)**
- anemia
- hemolysis
- hemoglobinopathy
- megaloblastic anemia

**TOO MANY RED CELLS—POLYCYTHERIA**
- polycythemia vera

**TOO FEW WHITE CELLS—LEUKOPENIA AND AGRANULOCYTOSIS**
- leukopenia

**TOO MANY WHITE CELLS—BENIGN AND MALIGNANT DISORDERS OF LEUKOCYTES**
- leukemia
- lymphoma
- multiple myeloma
- Hodgkin lymphoma
- non-Hodgkin lymphomas (NHL)
- follicular lymphoma
- diffuse lymphoma
- chronic myeloproliferative disorders

**NORMAL HEMOSTASIS, COAGULATION, AND LABORATORY TESTING**
- hemostasis
- coagulation
- extrinsic coagulation pathway
- intrinsic coagulation pathway

**BLEEDING DISORDERS**
- hemorrhagic diathesis
- disseminated intravascular coagulation (DIC)

Blood is thicker than water.

The sentiment of this proverb—that family ties are the closest of all relationships—is as old as writing. In about 1800 BC, the Sumerians, inventors of writing who lived in what is modern-day Iraq, wrote it this way: “Friendship lasts a day, kinship is forever.”

Section 1: Diseases of Blood Cells

**BACK TO BASICS**

Blood is liquid tissue; a mixture of cells and water. The water contains protein, glucose, cholesterol, calcium, hormones, metabolic waste, and hundreds of other substances. **Plasma** is the liquid part of blood; the term refers to blood circulating *in vivo* and to *anticoagulated* blood *in vitro* (in a laboratory tube, for example). **Serum**, the fluid remaining after blood clots, differs from plasma in that serum contains no fibrinogen, which was consumed in formation of the clot. When blood clots it forms a gelatinous mass that traps cells in a mesh of fibrin (Chapter 5). The clot shrinks and after an hour is about half its original size. Serum is the remaining fluid, which was squeezed from the clot. Serum contains no fibrinogen and cannot clot again, and for this reason is widely used for laboratory analyses because clots can interfere with the operation of delicate laboratory equipment. However, sometimes tests are done on *anticoagulated* whole blood or plasma. When referring to concentrations of substances, the words “blood,” “serum,” and “plasma” are often used interchangeably; as for example, when referring to blood or serum or plasma glucose. The composition of normal blood is detailed in Table 11-1 and Figure 11-1.
NORMAL BLOOD PRODUCTION (HEMATOPOIESIS)

The cells in blood are red cells (erythrocytes), white cells (leukocytes), and platelets (cytoplasmic fragments of bone marrow platelet-producing cells, megakaryocytes). In the fetus, production of blood cells takes place in the liver, but by birth most blood cell production has shifted to the bone marrow.

As is depicted in Figure 11-2, all blood cells arise from a common ancestor, the totipotent stem cell. This primitive stem cell gives rise to two other stem cells: a myeloid stem cell that in turn gives rise to red cells, megakaryocytes, monocytes and macrophages, and granulocytes (neutrophils, basophils, eosinophils), and a lymphoid stem cell that give rise to lymphocytes.

Bone marrow red cell production is stimulated by erythropoietin, a hormone synthesized by the kidney. Erythropoietin production is stimulated by low delivery of oxygen to the kidney. Mild general hypoxia occurs in people living at high altitude. Their bone marrow makes extra red cells to compensate, and they have higher red blood cell counts than do people living at lower altitudes. General hypoxia also occurs in patients with chronic lung disease; they, too, have high red cell counts. Local kidney hypoxia can also stimulate erythropoietin production; for example, impaired renal blood flow (ischemia) owing to renal vascular disease can cause increased erythropoietin and very high red cell counts.

Production of white blood cells and platelets is controlled by other hormones and factors.

Red cells have no nucleus and no need for one. Their role is to carry oxygen, and a nucleus would take up unnecessary room. Leukocytes have a nucleus. There are three kinds of leukocytes: granulocytes, lymphocytes, and monocytes. Monocytes are phagocytic: they ingest and digest foreign antigen and present it for action to immune cells for immune response. Lymphocytes are the main cells of the immune system: their task is to react to foreign antigen. Granulocytes have cytoplasmic granules of digestive enzymes and other substances that play an important role in inflammation (Chapter 3). The three granulocytes are: neutrophils, eosinophils, and basophils. Neutrophils are the most abundant granulocyte. Their task is to react to acute injury and infection by ingesting (phagocytosis) and digesting foreign agents, especially bacteria, and by cleaning up inflammatory debris. Basophils and eosinophils are the inflammatory cells of allergic reactions (Chapter 8) and reactions to parasites. Platelets are small fragments of megakaryocyte cytoplasm and have no nucleus. Their task is to stop bleeding by sticking together at points of vascular injury to obstruct hemorrhage, and to initiate the clotting process at the site of bleeding.

CELL COMPARTMENTS AND LIFE SPAN

Blood cells exist in several body compartments (blood, bone marrow, spleen, lymph nodes and, to a great extent in the fetus and a lesser extent in adults, the thymus), and there is constant cell trafficking among them.

How long cells live (and circulate) is critical. Compared to cells in most other tissues, the life span of

<table>
<thead>
<tr>
<th>Value</th>
<th>Units</th>
<th>RED CELLS</th>
<th>WHITE CELLS</th>
<th>PLATELETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (HGB)</td>
<td>mg/dL</td>
<td>13.5–17.1</td>
<td>4.5–10.5</td>
<td>150–350</td>
</tr>
<tr>
<td>Hematocrit (HCT)</td>
<td>%</td>
<td>39–49</td>
<td>4.3–5.9</td>
<td>1.6–4.9</td>
</tr>
<tr>
<td>Red cell count (RBC)</td>
<td>10⁶ cells/ cu mm</td>
<td>4.3–5.9</td>
<td>20–25</td>
<td>3–8</td>
</tr>
<tr>
<td>Red cell MCV</td>
<td>fL</td>
<td>76–100</td>
<td>&lt;5</td>
<td>150–350</td>
</tr>
<tr>
<td>Red cell MCH</td>
<td>g/dL</td>
<td>33–37</td>
<td>0–1</td>
<td>150–350</td>
</tr>
<tr>
<td>Red cell MCH</td>
<td>pg</td>
<td>27–33</td>
<td>0–1</td>
<td>150–350</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>%</td>
<td>0.5–2.0</td>
<td>0.5–2.0</td>
<td>150–350</td>
</tr>
</tbody>
</table>

Table 11-1: Normal (Reference) Ranges for Blood Cells*

*Ranges vary slightly from laboratory to laboratory. Most normal ranges are established by statistical technique to include 95% of healthy persons; therefore 5% of healthy persons have abnormally high or low values.
blood cells is short; therefore, cell turnover is rapid. Red cells have the longest life span of blood cells: about 120 days. Neutrophils, basophils, and eosinophils live about 4 days; lymphocytes and monocytes, a week or two; platelets, a day or two. Old (senescent) blood cells and platelets are removed from circulation by the spleen. This rapid turnover means that it is critical that new cells be produced at a rate that equals the rate at which cells are dying. Many diseases of blood cells are caused by production failure or early cell death or destruction; that is to say, by shortened cell life span. Anemia (too little hemoglobin) is usually attributable to too few red blood cells (anemia can also occur with normal numbers of red cells that do not contain enough hemoglobin). Some patients have low red blood cell count because bone marrow fails to produce enough red blood cells (RBC); in other cases of anemia, RBC life span is short because RBCs are destroyed (hemolysis). The same holds true for platelets and white blood cells—some conditions are attributable to failed cell or platelet production, others to early destruction or death.

**Hemoglobin** is the compound in RBCs to which oxygen attaches for transport from lungs to tissues, therefore the amount of hemoglobin in blood is critical. Hemoglobin cannot be synthesized without iron, vitamin B_{12}, vitamin B_{6}, and folic acid. The character if hemoglobin is important. There are many types of abnormal hemoglobin, most of them stemming from genetic defects of hemoglobin synthesis.

**LABORATORY ASSESSMENT OF BLOOD CELLS**

Laboratory assessment of blood cells is usually performed on a sample of blood collected from an arm vein. Such a blood sample is typically referred to as “peripheral blood” to distinguish it from the pool of blood in large vessels and the viscera, which is slightly more dilute than peripheral blood. Cellular elements typically are measured in anticoagulated whole blood. Conversely, chemical elements, such as glucose, are typically measured in the liquid part of blood, usually serum obtained from a tube containing clotted blood.

The most common standard laboratory study of blood is referred to as a **complete blood count (CBC)**. In modern laboratories the process is automated and consists of a determination of white blood cells (white
Figure 11-2 Hematopoiesis. There are two main groups of blood cells: myeloid and lymphoid, each derived from a primitive stem cell.
blood cell count), red blood cells (red blood cell count), the percentage of white cells that are neutrophils, eosinophils, or basophils (the white cell differential count), the amount of hemoglobin, and the hematocrit. The hematocrit is the percent of blood volume occupied by red blood cells (RBC). It is measured by centrifuging whole blood to compact red blood cells and observing the percentage of whole blood volume occupied by red blood cells. The number of white cells and platelets is so small that their volume is negligible.

Also important in a complete blood count is determination of the red cell indices, which are measures of the size and hemoglobin content of the average RBC. The average size of an RBC is the mean cell volume (MCV); the average amount of hemoglobin in an average RBC is the mean cell hemoglobin (MCH); and the average concentration of hemoglobin per unit of volume in an average RBC is the mean cell hemoglobin concentration (MCHC). As is indicated in Figure 11-3, each of the indices can be calculated using hemoglobin, hematocrit, and red blood cell count. Red cell indices are important in the diagnosis of diseases of red blood cells—in anemia red blood cells may be too large (macrocytic), normal size (normocytic) or too small (microcytic). Additionally, diseased RBCs may have a normal amount of hemoglobin per cell (normochromic) or too little hemoglobin (hypochromic). There is no such thing as a red cell with too much hemoglobin.

Visual examination of blood cells is an important tool, but it is ordinarily not necessary unless there are significant abnormalities in the measurements obtained on a complete blood count. Every laboratory has criteria defining when visual examination is necessary. For example, visual examination may be required if the hemoglobin is below 10 gm/dL, or the WBC count is above 15,000 cells/cu mm. Additionally, the clinician may know of signs and symptoms that indicate need for visual examination of blood cells and can request visual examination. Among the important things detectable by visual examination are the presence of malignant white cells in leukemia, abnormally shaped RBCs, malaria parasites in RBC, RBCs with nuclei, and giant platelets.

Laboratories also seek to identify normal red cell blood antigens for blood group typing, as discussed in Chapter 8, or antibodies attached to the red cell membrane that might account for red cell destruction (hemolysis). Additionally, tests are performed to determine the percentage of new (young) red cells (reticulocytes), which are elevated when red cell production increases as the bone marrow compensates for anemia, red cell destruction, or short red cell life span. Additionally, laboratories can determine the type of hemoglobin in red cells. Normal hemoglobin is hemoglobin A. Hundreds of types of abnormal hemoglobin have been described. Among the most common abnormal hemoglobin is hemoglobin S, the hemoglobin of sickle cell disease.
Too Little Hemoglobin (Anemia)

Anemia is abnormally low hemoglobin in blood and is caused by decreased numbers of red blood cells, decreased amount of hemoglobin in red cells, or both. Usually laboratory measures of hemoglobin, red cell count, and hematocrit move up and down together. Anemia demands thorough investigation because it is always a sign of some underlying condition. Some patients present with signs or symptoms of the primary disease and are found upon investigation to be anemic. For example, a slowly bleeding intestinal cancer may not be detected until it produces intestinal obstruction; and the patient is then found to be anemic from chronic blood loss. Other patients present with symptoms caused directly by the anemia: chronic fatigue and shortness of breath because of lack of oxygen; and pallor of the skin and the oral and conjunctival mucosae.

The first step in the diagnosis of anemia is a complete blood count and determination of red cell indices, because the different types of anemia are typically characterized by red cell of a certain size (mean cell volume, MCV) and hemoglobin content (mean corpuscular hemoglobin concentration, MCHC). For example, small (microcytic, low MCV) RBCs can occur with iron deficiency. A deficiency of iron impairs hemoglobin synthesis, so iron-deficient RBCs contain less hemoglobin than normal and are pale (hypochromic, low MCHC). Few diseases other than iron deficiency produce small, pale RBCs. Knowing the red cell indices dramatically narrows the number of diseases to be considered in the differential diagnosis.

The second step in the diagnostic routine for anemia is to determine if the anemia is associated with blood loss, red cell destruction, or failed bone marrow production of red cells. In this regard it helps to think of the intravascular space (blood) as a tank into which red blood cells are pumped from the bone marrow. They enter the intravascular space and survive an average of 120 days before they die a natural death (apoptosis) and are filtered out by the spleen. Figure 11-4 illustrates the production, circulation, and destruction of RBCs. Anemia occurs 1) if production fails (either not enough cells are added to the circulation to replace the daily natural loss, or red cells do not contain enough hemoglobin); 2) if blood leaks (hemorrhages) from the circulation tank; or 3) if cell lifespan is shortened (hemolysis), and cells die quicker than they can be replaced by the bone marrow.

The Anemia of Hemorrhage

Hemorrhagic blood loss creates two problems: 1) loss of oxygen-carrying capacity when red cells are lost; and 2) loss of iron (80% of body iron is in hemoglobin). If bleeding is limited, lost red cells can be replaced in a few weeks or months by normal bone marrow; however, lost iron is not easily or quickly replaced. If bleeding continues for a long time (as from, for example, an undetected colon cancer), the patient may become iron deficient. Iron deficiency, in turn, hinders the ability of the bone marrow to make hemoglobin, and iron deficiency anemia is the result. By far the most common cause of iron deficiency anemia is chronic blood loss; other causes, such as dietary iron deficiency or defective intestinal absorption of iron, are uncommon.

The main threat of acute blood loss is shock or death, not anemia. If the patient survives an acute hemorrhage, the volume of lost red cells is initially replaced by ingested water and albumin synthesis the liver, and the patient develops a temporary dilutional anemia until the marrow can replace the lost red blood cells. Dilutional anemia features healthy red cells, which have normal size and hemoglobin content; that is, the red cells are normochromic, normocytic (normal MCV and MCHC).

Chronic blood loss usually occurs with one of two conditions: 1) abnormal menstrual bleeding in women during their reproductive years; or 2) intestinal bleeding in either sex, especially from undetected colon can-
cer (see Case Study 11.1 at the end of this chapter). If bleeding is very slow, lost red cells are replaced by new cells from the bone marrow, and the patient does not develop a dilutional anemia. If, however, the rate of red cell loss is greater than the marrow can produce, the lack of red cells in the vascular space is made up by fluid and the patient initially develops a dilutional anemia until the bleeding stops. However, in chronic bleeding the intestinal absorption of dietary iron usually cannot make up for iron lost by hemorrhage, and the patient eventually becomes iron deficient. In iron deficiency the bone marrow has the capacity to produce red cells, but it cannot produce enough hemoglobin for each new cell, and the patient develops iron deficiency anemia, in which red blood cells are small (low MCV) and pale (low MCHC). Therefore, iron deficiency anemia in a man or in a post-menopausal woman is to be considered bleeding from gastrointestinal cancer until proven otherwise. This does not mean that cancer is the most common cause. It is not. Other gastrointestinal diseases are often the cause of the bleeding, but cancer cure depends so heavily on early detection that a search for intestinal malignancy is always the first priority.

**ANEMIA OF RED CELL DESTRUCTION (HEMOLYTIC ANEMIA)**

Premature destruction of red blood cells is called hemolysis, which shortens red cell lifespan. Hemolytic anemia is associated with:

- **An active, hypercellular, bone marrow**, which must work overtime to replace dying cells.
- **Blood that contains a high count of new red blood cells (reticulocytes)**. These new red cells are easy for laboratory technicians to identify on conventional microscopic examination because they have a bluish cast; they can be revealed even more clearly by special stains.
- **Increased blood lactic dehydrogenase (LDH)**. Red blood cells are packed with LDH, an enzyme that is released from dying red cells and rises to high levels in hemolysis.
Part 2 • Diseases of Organ Systems

- **Low blood haptoglobin.** Haptoglobin is a protein that binds hemoglobin liberated from dead RBC and carries it away for disposal, which destroys haptoglobin and decreases its concentration in blood. Low plasma haptoglobin is a key diagnostic indicator of hemolysis.

- **Increased blood bilirubin.** Patients with especially high rates of red cell destruction may have abnormally high levels of blood bilirubin, a product of hemoglobin metabolism. In most patients, however, the liver is able to excrete bilirubin rapidly enough that abnormally high bilirubin does not develop.

There are four main causes of hemolytic anemia: genetic red cell defects, immune and mechanical destruction of red cells, and malarial destruction of red cells.

**Hemolytic Diseases Caused by Genetic Defect**

**Hereditary spherocytosis** is a genetic disorder of structural protein in the red cell membrane that renders cells spherical rather than biconcave and therefore less able to pass through the spleen. The result is a splenic hemolysis. Splenectomy is effective, but it does not, of course, remedy the genetic defect.

**Glucose-6-phosphate dehydrogenase (G6PD) deficiency** is an X-linked genetic disorder that causes deficiency of G6PD in red cells. The gene is present in 10% of African American men, rendering them subject to acute hemolytic episodes upon exposure to certain oxidizing drugs, toxins, or infections.

The **hemoglobinopathies** are genetic disorders of hemoglobin synthesis. More than 300 genetically flawed hemoglobins have been identified. They are molecularly defective and are unstable, causing early red cell death (hemolysis). Normal, molecularly correct hemoglobin is hemoglobin A; abnormal hemoglobins have other names. Most notable among these is hemoglobin S, the cause of **sickle cell anemia**. Additionally, there are hemoglobins C, E, and many others, most very rare. The **thalassemias** are an important group of hemoglobinopathies that differ from the molecularly imperfect hemoglobins—the hemoglobin of thalassemia is molecularly correct but is not produced in sufficient volume because the production mechanism is genetically faulty.

**Sickle Cell Anemia (Hemoglobin S Disease)**

About 8% of African Americans and 30% of African blacks are carriers of the **hemoglobin S** genetic mutation. The higher rate in Africa is Darwinian: hemoglobin S gene conveys resistance to *P. falciparum* malaria, the most severe form of malaria, and provides an advantage in the battle to survive.

The sickle cell defect is a mutation in the gene that codes for globin, the protein molecule of hemoglobin, and is inherited according to the Mendelian model (the genetic defect and its inheritance is discussed in Chapter 7). The gene defect is a recessive trait, requiring inheritance of a defective gene from both mother and father. When the patient inherits the defective gene from both parents (genotype: SS), hemoglobin S is produced, and **sickle cell disease** (phenotype: sickle cell anemia) is the result. If the patient has a defective gene from only one parent (genotype: SA), the condition is called **sickle cell trait** (phenotype: normal; normal hemoglobin A is produced). The patient is a carrier, and no disease is present.

Even in normal physiologic conditions hemoglobin S tends to crystallize (sickle), deforming red cells into a crescent (sickle) shape and subjecting red cells to destruction by the spleen (splenic hemolysis). These deformed cells also have difficulty passing through small blood vessels, which obstructs small blood vessels and causes ischemia and infarcts (Chapter 5). Sickling can be precipitated in carriers (SA) or patients with sickle cell disease (SS) by low oxygen tension (local or general hypoxia), infections, dehydration, and acidosis. For example, the low oxygen tension at high altitudes can induce sickling. A simple laboratory test for the presence of sickle hemoglobin (SA or SS) consists of adding a chemical to bind all oxygen in a drop of blood and then inspecting the specimen for sickled cells. The microscopic appearance of sickled red cells in smears of untreated patient blood is also diagnostic (Fig. 11-5).
Sickle cell disease usually becomes evident shortly after birth, presenting as a severe anemia with chronic hemolysis. The clinical and pathologic findings in sickle cell disease are depicted in Figure 11-6. These findings result from:

- **Obstruction of small blood vessels**, which causes ischemia and infarction of various organs, or gangrene of fingers and toes
- **Anemia**, which causes high-output cardiomegaly and heart failure, bone marrow hyperplasia, and bone deformities induced by the overactive bone marrow
- **Hemolysis**, which produces pigment gallstones (Chapter 16) caused by bilirubin overload on the liver and biliary system
- **Infections**, caused by infarct-associated loss of splenic immune function; or by pathogens that find their way into necrotic bone, lung, and other tissues

About half of patients with sickle cell disease (SS) reach mid-life, but others succumb to a variety of infections—such as *Salmonella* bone infections or pneumococcal sepsis—or to bone marrow failure (aplastic crisis), which is triggered by parvovirus infection of red cell precursors in the bone marrow.

On the other hand, patients who are carriers (sickle cell trait, SA) remain asymptomatic unless the patient's blood oxygen content falls, as happens in ascent to high altitude, severe lung disease, or other condition.

**Thalassemia**

The **thalassemias** are a group of recessive genetic disorders inherited in Mendelian fashion (Chapter 7) in which hemoglobin is molecularly perfect, but the defect causes a decreased amount of hemoglobin production. There are several varieties of thalassemia, which vary from mild to severe depending on the particular genetic defect.

Detailed discussion of the classification of the many types of thalassemia is beyond the scope of this textbook. The most severe form of thalassemia (thalassemia major) appears in childhood; many patients die before age 20. Less severe forms of thalassemia (thalassemia minor) cause anemia but are not associated with decreased life expectancy.

The most common type of thalassemia presents as a severe microcytic hypochromic anemia with small, pale red cells similar to the red cells seen in iron deficiency anemia. In addition to anemia from inadequate production of hemoglobin, the anemia is compounded by a hemolytic component, some of which takes place in the bone marrow before the red cells mature (intramedullary hemolysis). This ineffective red cell production stimulates increased iron absorption from the gastrointestinal tract. This often leads to iron overload (hemochromatosis, Chapter 16) because the body cannot easily excrete iron. Excess amounts of iron are present in blood and bone marrow, which offers an easy way to distinguish thalassemia from iron deficiency: both thalassemia and iron deficiency are characterized by small, pale (low MCV and MCHC) red cells; however, patients with iron deficiency have no iron stores and patients with thalassemia are flooded with iron. As with sickle cell anemia (SS), patients with thalassemia can have skeletal abnormalities because chronically hyperactive bone marrow has a deforming effect. Additionally, the liver and spleen may enlarge markedly as some of their cells transform into bone marrow cells (myeloid metaplasia) in an effort to make up for bone marrow deficiency. The liver is naturally inclined to undergo myeloid metaplasia: recall that in the fetus the liver, not the bone marrow, produces most blood cells. The cause of splenic myeloid metaplasia is not clear.

Patients with mild disease are mildly anemic for life and need no treatment. Patients with severe disease need regular transfusions; and bone marrow transplant may be effective.

**Non-genetic Hemolytic Anemia**

**Immune** hemolytic anemia is caused by antibodies directed against antigens on the red cell membrane. Red cells become coated by antibody, which renders them susceptible to premature removal by the spleen. These antibodies may be detected on red cells or in plasma by a laboratory test (Coombs test, Chapter 8). Immune hemolytic disease often occurs in association with autoimmune disease (especially systemic lupus erythematosus), malignancies of white blood cells (lymphoma and leukemia), infectious mononucleosis, and *Mycoplasma pneumoniae* pneumonia (Chapter 14), and as a reaction to certain drugs.

**Mechanical** hemolytic anemia is caused by physical shredding of red cells as they pass through mechanical devices, such as artificial heart valves. A similar mechanical effect may occur as red cells squeeze through swollen, inflamed small blood vessels affected by autoimmune disease (autoimmune vasculitis, Chapter 12), or as red cells pass through blood vessels partially blocked by intravascular blood clotting (disseminated intravascular coagulation).

Hemolytic disease is also associated with *malaria*, a parasitic disease that infects red cells. Malaria is one of the most widespread diseases in the world and is very common in the tropical areas of Africa and Asia. The word “malaria” is derived from Italian, *mala aria*, for “bad air.” Before science understood that malaria is
Cerebral infarcts (strokes)

Retinal infarcts (retinopathy)

Pulmonary infarcts

Pneumonia

Renal infarcts

Hematuria

Anemia, increased cardiac output

Cardiomegaly

High-output congestive heart failure

Gallstones

Early splenomegaly

Late splenic atrophy (infarcts)

Bone marrow hyperplasia

Bone deformities

Bone infarct (aseptic necrosis)

Infection (osteomyelitis)

Vascular occlusions

Skin ulcers

Gangrene of toes or fingers

Infarcts of fingers

Figure 11-6 Clinical and pathologic findings in sickle cell anemia.
caused by a parasite transmitted by mosquito bites, it was believed the disease to be a product of the “bad air” in swampy, tropical zones.

As is illustrated in Figure 11-7, malaria is caused by four varieties of tiny amoebae smaller than a red blood cell, the *Plasmodium* species, which are transmitted by mosquitoes from infected to non-infected persons. No immunity develops and reinfection may occur.

Clinically, malaria parasites infect and destroy red cells, causing episodes of hemolysis, fever, and jaundice that occur every 48–72 hours as new generations of parasite are reproduced. *Plasmodium falciparum* malaria is especially dangerous because it has a high fatality rate caused by its effect on the brain. Antimalaria drug prophylaxis is effective for all types, but some drug resistant strains now exist.

**ANEMIA OF INSUFFICIENT RED CELL PRODUCTION**

*Inadequate bone marrow red cell production* is another cause of anemia. Inadequate supply of some essential substance necessary for red cell production, such as iron, folic acid, or vitamin B₁₂, can cause anemia. Marrow cell output may fail, associated with adverse effect of drugs, toxin, or radiation or some other, unknown, cause. Destruction or replacement of the marrow by scar tissue or tumor can also result in a decrease in the production of red cells, with consequent anemia.

**Iron Deficiency Anemia**

The body is stingy with iron—natural losses from shedding skin and cells of the GI tract are on the order of 0.1% of total body iron per day. The average diet contains more than enough iron for men, but barely enough for menstruating women, who normally have low iron reserves. Iron balance is maintained largely by intestinal absorption of dietary iron. About 80% of total body iron is in the hemoglobin of red cells; the remaining 20% is stored as ferritin and hemosiderin. *Ferritin* is an iron-protein complex found in the bone marrow, liver, spleen, and skeletal muscle. Plasma ferritin levels vary directly with the amount of ferritin stored in bone marrow; therefore, the level of plasma ferritin is a good indicator of the amount of body iron stores.

Iron is transported from one place to another bound to a special blood protein, *transferrin*, made by the liver. Total transferrin is measured by testing the ability of plasma protein to bind to iron and is expressed as *total iron binding capacity* (TIBC). The degree to which this potential transporting capacity is occupied by actual plasma iron is referred to as the percent saturation of TIBC and is calculated by dividing plasma iron by TIBC. When patients are iron deficient, the liver increases plasma transferrin in an effort to deliver more iron to the bone marrow. Therefore, in *iron deficiency*:

- plasma transferrin (total iron binding capacity) is high
- plasma iron is low
- the percent saturation of transferrin by iron is low

Most iron deficiency can be attributed to blood loss. Other, less common causes include intestinal absorption, owing to intestinal disease, or increased need for iron. For example, infants are at risk of iron deficiency because milk contains little iron, and the rapid growth of children demands iron for expansion of blood volume and other tissues.

**Iron deficiency is the most common of all nutritional deficiencies, affecting perhaps 5% of the population of developed nations and many times more in developing ones.**

When patients lose more iron than they absorb intestinally, iron stores gradually become depleted. Iron stores must be completely exhausted before red cell production is affected, and, therefore, patients become *iron-deficient before they become anemic*, and they become anemic only if iron deficiency persists. This pre-anemic stage is characterized by normal levels of plasma iron and transferrin (expressed as total iron binding capacity, TIBC), but levels of plasma ferritin are low, reflecting low marrow iron stores. As negative iron balance persists, plasma iron levels fall and ferritin (TIBC) levels rise. Finally, *iron deficiency anemia* develops as red cell
production becomes impaired owing to lack of iron. The bone marrow, lacking sufficient iron to make hemoglobin, produces red blood cells that are small (microcytic, low MCV) and pale (hypochromic, low MCHC), illustrated in Figure 11-8.

Iron deficiency anemia is common but rarely fatal. By far the most common cause is chronic blood loss; low dietary intake of iron is rarely the case. The most common causes of chronic blood loss are menstrual abnormalities and gastrointestinal bleeding. The diagnosis of menstrual loss is usually easy to establish; however, loss from gastrointestinal bleeding is much more sinister—it is difficult to document and is often associated with intestinal malignancy, especially carcinoma of the colon. Therefore, it is a good rule to assume that, until proven otherwise, the source of iron deficiency anemia in adult men or postmenopausal women is occult (undetected) bleeding from a gastrointestinal carcinoma.

Think of iron deficiency anemia as a symptom, not a disease; there is always some other, underlying, condition. Oral iron supplementation can rebuild iron stores, but the underlying condition must also be found and treated.

Iron deficiency anemia in an adult man or postmenopausal woman is to be considered to be caused by bleeding from a gastrointestinal cancer until proven otherwise.

Vitamin B₁₂ and Folic Acid Deficiency

Anemia associated with deficiency of either vitamin B₁₂ (cobalamin) or folic acid is characterized by enlarged (macrocytic) red cells, depicted in Figure 11-9. Together these are known as the megaloblastic or macrocytic anemia. “Megalo” and “macro” mean large, and in these anemias the red cells and their bone marrow precursors (blasts) are unusually large.

Vitamin B₁₂ and folic acid are necessary for DNA synthesis. If nuclear DNA cannot be produced, cells cannot be made, hence a deficiency of either B₁₂ or folic acid results in decreased production of red cells, white cells, and platelets (because megakaryocytes are affected as well). Both of these deficiencies result in macrocytic red cells (high MCV), low white blood cell count (leukopenia), and low platelet count (thrombocytopenia). Bone marrow studies in each reveal a hypercellular, active bone marrow filled with enlarged (megaloblastic) red and white cell precursors. The marrow is overly cellular because it is striving ineffectively to produce red and white cells.

Inadequate diet or deficient intestinal absorption may cause deficiency of either B₁₂ or folic acid. Megaloblastic anemia associated with folic acid (folate) deficiency is uncommon because folate is abundant in raw vegetables (however, it is largely destroyed by cooking). Nevertheless, depressed folic acid levels may be found in anyone with a poor diet; chronic alcoholics are especially prone to folic acid deficiency.

Dietary vitamin B₁₂ deficiency is rare—B₁₂ is abundant in meat, eggs, and dairy products, and multiyear reserves are stored in the liver. It is almost impossible to devise a diet deficient in B₁₂ except by observing an unusually strict vegetarian diet over a decade. The most
common cause of B₁₂ deficiency is defective intestinal absorption. B₁₂ absorption requires **intrinsic factor (IF)**, a protein secreted by the gastric mucosa. IF binds to B₁₂ and travels to the lower end of the small bowel (ileum), where absorption takes place. B₁₂ cannot be absorbed by the ileum unless it is bound to IF. Causes of insufficient B₁₂ absorption include gastrectomy (which limits IF production), surgical resection of the ileum (which removes the absorbing site), inflammatory bowel disease (Chapter 15), and other diseases affecting the distal ileum, all of which interfere with absorption of the B₁₂-IF complex.

An additional cause of B₁₂ deficiency that deserves special mention is **pernicious anemia**, an autoimmune disease featuring autoantibodies against gastric mucosal cells and IF. Without treatment, the disease can cause a destructive disease of the spinal cord and is usually fatal, thus the name “pernicious,” meaning deadly, evil, or destructive.

The primary pathologic abnormality in pernicious anemia is **chronic atrophic gastritis**, discussed in detail in Chapter 15. In pernicious anemia atrophic gastric mucosa does not secrete enough intrinsic factor to allow normal B₁₂ absorption in the intestine.

**Anemia of Chronic Disease**

Low output of RBC by the bone marrow can lead to anemia in patients with chronic diseases. The reasons are not clear. The chronic diseases usually involved are malignant neoplasms, chronic infections, and chronic autoimmune disorders. Red cells are normal size (normocytic, normal MCV) and have a normal amount of hemoglobin (normochromic, normal MCHC).

The anemia of chronic disease may look somewhat like iron deficiency because plasma iron is often low and patients are anemic. Plasma iron is usually low because plasma proteins, including transferrin, are reduced secondary to the wasting usually associated with chronic diseases, not because the patient is iron deficient. The distinguishing point between the two is that patients with iron deficiency have small, pale (microcytic, hypochromic) red cells. Furthermore, patients with anemia of chronic disease have normal or high plasma ferritin because iron stores are plentiful and abundant iron is found on bone marrow exam.

**Primary Bone Marrow Failure (Aplastic Anemia)**

Primary bone marrow failure is called **aplastic anemia**. The name, however, is a misnomer: the disease is not just a failure to produce red blood cells, it is a primary failure of **all** marrow elements—red cells, white cells, and megakaryocytes. However, anemia is usually the presenting problem. In fatal cases the cause of death is usually **hemorrhage**, because of low platelet count, or **infection**, secondary to low WBC count. The cause of aplastic anemia is unknown (idiopathic) in most cases. When the cause is known, drugs and chemicals are usually responsible because they exert a toxic effect on bone marrow cells. In some cases the toxic effect is dose-related, as is the case with chemotherapy drugs given to patients with a malignancy. In others, the reaction is termed **idiosyncratic**; that is, the toxic effect is far out of proportion to the dose.

In addition to the fatigue and pallor of anemia, patients with aplastic anemia have low platelet counts (thrombocytopenia), resulting in hemorrhages (skin petechiae and ecchymoses, or internal bleeding), and low white blood cell counts (granulocytopenia), resulting in bacterial infections. Bone marrow biopsy reveals a hypocellular (mostly fat, few hematopoietic cells) bone marrow, as is depicted in Figure 11-10.

**Anemia Caused by Bone Marrow Replacement or Destruction (Myelophthisis)**

In some situations the bone marrow is replaced by malignancy or fibrosis (myelophthisis). Some cancers—notably prostate, lung, breast, and thyroid—metastasize to bone and occupy so much marrow space that there is no room for hematopoietic elements. Radiation, lymphoma, leukemia, and multiple myeloma may have a similar effect. Bone marrow fibrosis warrants special mention. In the absence of known cause, such as radia-
tion damage, marrow fibrosis is usually a manifestation one of several primary malignant disorders of the bone marrow, the chronic myeloproliferative syndromes, discussed later in this chapter.

**Too Many Red Cells—Polycythemia**

Polycythemia (erythrocytosis) is an excess number of red cells in blood. The most common cause of apparent polycythemia is low plasma volume (relative polycythemia). For example, in dehydration, loss of fluid causes blood to become concentrated, but the absolute number of red cells in the body is unaffected. Dehydrated patients, therefore, have relative polycythemia; the absolute number of RBC is not increased. Among the most common causes of negative polycythemia is a poorly understood condition called “stress polycythemia,” which is usually seen in obese, anxious (stressed), hypertensive patients. For reasons that are not well understood, these patients have low plasma volume. Although the total number of red cells in the body does not change, the decreased plasma volume produces a relatively higher than normal number of red cells per unit of blood volume, which increases hematocrit and red cell count.

Other patients have an increased red cell count because there is an actual increase in the total number of RBCs in the body; these patients have absolute polycythemia. Absolute polycythemia can be primary or secondary. Secondary absolute polycythemia is caused by conditions outside the bone marrow that stimulate the marrow to produce red cells. For example, hypoxia, as in a patient with chronic lung disease, stimulates the kidney to produce erythropoietin, a hormone whose release is stimulated by low oxygen levels and whose function is to increase marrow production of red blood cells. For the same reason, people living at high altitudes have secondary polycythemia as compared to those living at lower altitudes. Secondary polycythemia can also be caused by renal tumors (Chapter 19) that secrete erythropoietin.

**Primary** absolute polycythemia occurs with a bone marrow malignancy called polycythemia vera (literally, true polycythemia), a proliferation of primitive bone marrow red cell precursors that is related to myeloid leukemia and related myeloid neoplasms, discussed later in this chapter.

Most of the time an abnormally high red cell count is accompanied by increased hematocrit and hemoglobin and can be explained by conditions other than polycythemia vera. For example, patients who smoke more than just an occasional cigarette damage their lungs enough to reduce oxygen uptake, which stimulates red cell production and a secondary increase of red blood cells. Determining whether or not patients have an absolute or relative increase of red cells can be very difficult because red cell count in peripheral blood is significantly higher than the relatively dilute central pool of blood in viscera and large blood vessels. The accompanying Lab Tools box explains how to distinguish

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**LAB TOOLS**

**Measurement of Total Red Cell Mass**

Determining red cell mass requires a special procedure because the concentration of red cells in blood is higher in peripheral blood than it is in the central pool in the viscera, heart, and lungs, where it is more dilute. For example, a male patient might have a peripheral blood hematocrit of 53% (normal: 39–49), but blood from his heart might have a hematocrit of 44%. Hematocrit levels in the peripheral blood are always the higher than hematocrit levels in the central pool because peripheral blood is a bit “sludgy” and concentrated.

Determining the total amount of red cells in the body is relatively easy. The test is simple and is much like measuring the amount of water in a large tank by dumping into it a known volume, say one gallon, of red dye of known concentration, say 100% pure. After mixing tank water and dye, remove some water and measure the concentration a second time. If the concentration is 1% dye and 99% water, it is easy to see that the tank holds 100 gallons of water because the original one gallon of pure dye has been diluted 100 times.

To measure total red cell mass the method is similar. A known volume, say 10 ml, of patient red cells is tagged with radioactive chromium-51, and a radioactive count of the specimen is taken. Let’s say it is 10,000 counts per minute. The tagged cells are injected back into the patient and circulate to become diluted in the patient’s untagged red cell mass. A second 10 ml specimen is collected and counted. Let’s say the count is 40 counts per minute, or 1/250th of the original. It is easy to see that the patient’s red cell mass is 250 x 10 ml (2500 ml). This result is compared to tables of normal ranges for men and women of various weights to determine if it is normal or high.
between absolute and relative polycythemia by determining total body red cell mass.

**Too Few White Cells—Leukopenia and Agranulocytosis**

*Leukopenia* is low blood white cell count. It is usually caused by a decrease of granulocyte numbers, especially neutrophils, a condition called *neutropenia*. Low numbers of lymphocytes (*lymphopenia*) is uncommon and is usually associated with immune deficiency diseases (Chapter 8), AIDS most notably, or steroid therapy.

Neutropenia may result from accelerated destruction of neutrophils or from a failure of production. Among the causes of increased destruction are increased filtering of neutrophils from blood by the spleen (hypersplenism), autoimmune disease, and overwhelming sepsis. Leukopenia also can be caused by failing bone marrow white cell production, which can be caused by drugs or toxins or when bone marrow is replaced by neoplasm.

When neutropenia is severe it is called *agranulocytosis*. Most agranulocytosis is caused by drugs. In most instances the degree of white cell decline is dose related, and the drugs are those administered as cancer chemotherapy. However, many drugs are known to cause a rare, idiosyncratic (not dose-related) agranulocytosis. The major clinical problem resulting from agranulocytosis is bacterial or fungal infection, either of which may prove fatal, but white cell counts must be profoundly depressed for severe infection to occur.

**Too Many White Cells—Benign and Malignant Disorders of Leukocytes**

*Leukocytosis* is an increase of white blood cells in the peripheral blood. It may be benign (reactive) or malignant (leukemia). *Leukemia* is a malignant proliferation of white cells, either *lymphoid cells* (lymphocytes) or *myeloid cells* (granulocytes or monocytes), in which the malignant cells appear in the peripheral blood. Leukemia is related to *lymphoma*, which is a malignant neoplasm of lymphocytes in lymph nodes and organs that grows as nodular masses. However, in lymphoma no malignant cells are detectable in blood.

Review of normal blood cell production helps understand the relationship of lymphoma to leukemia and to leukemia-related bone marrow neoplasms. As is illustrated in Figure 11-11, all blood cells, and all blood cell malignancies, originate from primitive stem cells: lymphoid stem cells differentiate into lymphocytes, which in turn may develop into lymphocytic leukemia, lymphoma, or plasma cell disorders; and myeloid stem cells differentiate into red blood cells, granulocytes, monocytes, and megakaryocytes, which in turn develop into myeloid malignancies.

Modern laboratory tools allow precise classification of malignant diseases of white cells into dozens of types according to the type of DNA defect present and the precise type of white cell involved, a topic far beyond the scope of this discussion. Our approach is simpler: we will discuss malignancies of white blood cells according to the basic cell type involved, lymphoid or myeloid, and their clinical behavior, either acute or chronic leukemia.

Leukemia of cells in the lymphoid line is called *lymphocytic leukemia*. Leukemia of cells in the myeloid line is called *myelocytic leukemia*. Clinically leukemias are called acute or chronic, according to the maturity of the malignant cells seen in the peripheral blood. When the malignant cells are immature (blasts) the disease is *acute leukemia*, which is aggressive and runs a short course. When the malignant cells are mature the disease is *chronic leukemia*, which is less aggressive and runs a longer course. In everyday practice leukemias are usually designated as a combination of these terms; for example, acute myelocytic or chronic lymphocytic.

*Acute leukemia* is characterized by:

- Abrupt onset, which often presents as acute infection or hemorrhage
- Symptoms related to a decrease in the numbers of normal marrow cells, such as might be seen in anemia, infection, or bleeding from thrombocytopenia
- Bone pain and tenderness when bone marrow becomes packed with cells
- Enlarged lymph nodes, spleen, and liver because of accumulations of malignant cells
- Nervous system symptoms such as headache, vomiting, or nerve palsies from malignant cells infiltrating the meninges

In acute leukemia, peripheral blood WBC counts often are very high; sometimes >100,000 cells/cu mm, but about half the cases have total WBC counts near normal. It is the microscopic appearance of the cells in bone marrow and peripheral blood that is diagnostic—both contain many immature WBC (blasts).

By contrast, the onset of *chronic leukemia* is insidious—patients present with fatigue or pallor from anemia, night sweats, low-grade fever, secondary infection, or enlarged spleen or liver. The clinical course is less rocky and the prognosis is better than for acute
leukemia, although ultimately the cause of death is similar in both acute and chronic leukemia: hemorrhage as a result of low platelet count, or infection because leukemic white blood cells are not effective at fighting infection.

An important shortcoming of this simple classification is that it does not account for the very important fact that leukemias, whether of lymphoid or myeloid origin, can be understood in greater detail and treated more effectively by identifying other characteristics, such as whether malignant lymphocytes are B cells or T cells. However, we will avoid a more precise description of leukemias because these classifications are complex and beyond the scope of this discussion.

PERIPHERAL LEUKOCYTE RESPONSES TO INFECTION OR INJURY

Most leukocytosis is secondary (reactive), resulting from bacterial infection or inflammation associated with tissue necrosis. Most leukocytosis occurs owing to

Figure 11-11 The origin of bone marrow malignancies. Arrows indicate the ways in which an initial malignancy may evolve into a related, but different, malignancy.
increased numbers of granulocytes (granulocytosis), most of which are neutrophils (neutrophilia). The normal WBC count is usually <10,000 cells per microliter (10,000/cu mm). In most instances of infection the WBC count does not rise above 20,000/cu mm. However, sometimes very high reactive white counts occur that may appear alarming, especially in uncommon cases when it rises to over 50,000/cu mm. Such a high reactive WBC count is termed leukemoid reaction (literally, “like leukemia”).

Viral infection usually causes lymphocytosis, an increase in the number of lymphocytes in blood. Eosinophilic leukocytosis is uncommon and when present is almost always associated with allergic reactions or parasitic infection.

Parasitic infections, such as intestinal worms, cause eosinophilia, an increase in the number of blood eosinophils. Allergic reactions (Chapter 8), such as hay fever or allergic asthma, also produce eosinophilia.

Sometimes bacterial infection or other injury causes such demand for neutrophils from the bone marrow that an excess number of immature granulocytes is released into blood. The least mature WBC normally found in the peripheral blood is the band neutrophil (normally <5% of WBC count), which has a banana-shaped nucleus. Release of immature cells is commonly referred to clinically as a “left shift” because the point of release is further to the left in the neutrophil maturation scheme depicted in Figure 11-2. Immature lymphocytes cells do not normally appear in the peripheral blood unless leukemia is present.

Infectious mononucleosis is an acute, self-limited (self-curing) infectious disease associated with lymphocytosis, occurring most often in adolescents and young adults. It is caused by the Epstein-Barr virus (EBV), which infects B lymphocytes and in typical cases causes fever, sore throat, enlarged neck and jaw lymph nodes, and increased lymphocytes in the peripheral blood, many of which are large “atypical” lymphocytes, depicted in Figure 11-12. Immature lymphocytes do not normally appear in the peripheral blood unless leukemia is present.

Figure 11-12 The blood in infectious mononucleosis. The large “atypical” lymphocyte is characteristic.

called the “monospot” test, is positive in over 90% of patients with infectious mononucleosis.

EBV infection may be severe or fatal in immunocompromised patients, such as those with AIDS. EBV infection is also the cause of some lymphomas.

LYMPH NODE RESPONSE TO INJURY OR INFECTION

Lymph nodes are involved in the most common diseases: infection, malignancy, immune reactions, and autoimmune disease. The lymphatic system filters bacteria, cancer cells and other alien substances from tissues. Lymph node lymphocytes are involved in immune reactions, and most lymphomas arise in lymph nodes. Therefore, most lymph nodes involved in a disease process are enlarged (lymphadenopathy).

In the absence of apparent infection or injury enlarged lymph nodes are worrisome and deserve investigation, primarily because they may contain malignant cells, either metastatic from a nearby cancer or a lymphoma that may involve the node. Enlarged, tender nodes are not so worrisome because the cause is almost always infectious even if the specific cause cannot be demonstrated. However, enlarged nontender nodes raise the possibility of malignancy.

Lymphadenitis is infection of a lymph node, usually resulting from the spread of organisms into nodes draining an infected site. If the node is reacting to the infection but is not actually infected, the condition often called reactive hyperplasia or reactive lymphadenitis. Acute lymphadenitis is characterized by enlarged, tender nodes. It is usually seen in cervical (neck) nodes in
association with dental infections or sore throat, or in the axillae or inguinal regions in association with genital infections or infections of the arms or legs. Systemic bacterial or viral infections in children may produce generalized acute nonspecific lymphadenitis. *Chronic lymphadenitis* occurs in two varieties: 1) associated with a specific disease such as tuberculosis and 2) *chronic non-specific lymphadenitis* for which no etiology can be discovered. Patients with chronic, non-specific lymphadenitis usually have large, non-tender lymph nodes, a clinical finding similar to lymph nodes involved by malignancy. On microscopic study pathologic findings vary but evidence of malignancy is absent.

*Catscratch disease* is an acute lymphadenitis caused by a rickettsia-like microorganism, *Bartonella henselae*. It is an acute syndrome of axillary or neck lymphadenitis in children and adolescents that arises about two weeks after a cat scratch (or, rarely, thorn or splinter injury). Lymph node biopsy demonstrates a characteristic granulomatous inflammatory reaction.

**LYMPHOID NEOPLASMS**

Figure 11-11 illustrates the important point that there are two major categories of white blood cells: lymphoid cells and myeloid cells. Lymphoid neoplasms are lymphocytic leukemia, lymphoma, and plasma cell proliferations.

**Lymphocytic Leukemia**

Acute lymphocytic leukemia (ALL) is an uncommon malignant proliferation of immature lymphocytes, usually B cells, that most often occurs in children and young adults. Onset is typically abrupt and accompanied by widespread malignant cell infiltration of bones, lymph nodes, liver and spleen, which cause bone pain, lymphadenopathy, and hepatosplenomegaly. Infiltration of the meninges often occurs, producing headaches, nerve paralysis, and pain. Blood and bone marrow (Fig. 11-13) are overrun by malignant cells; red cell, granulocyte, and platelet counts fall; and anemia, infection, and hemorrhage follow. Chemotherapy induces remission in most patients, and about half of patients are ultimately cured.

Chronic lymphocytic leukemia is a malignant proliferation of B cells that accounts for about a third of all leukemias and is indistinguishable from small cell lymphocytic lymphoma, discussed below, except that small cell lymphocytic lymphoma has few malignant cells in the peripheral blood. The malignant cells in both conditions have a gene defect that stops lymphocyte apoptosis (normal cell death), so that “immortal” lymphocytes overpopulate the blood, lymph nodes, and bone marrow. As malignant B cells proliferate, normal B cells are in short supply. Because B cells produce immunoglobulins (antibodies) to fight infection, little immunoglobulin is made, and patients are predisposed to developing infections.

Chronic lymphocytic leukemia, the most sluggish of all leukemias, occurs primarily in mature adults, as a slowly developing disease that may initially cause only fatigue, weight loss, and poor appetite. Malignant cells multiply in blood, lymph nodes, and spleen, causing lymphocytosis, lymphadenopathy (Fig. 11-14), and splenomegaly. In all cases, however, there is moderate blood lymphocytosis, which sometimes is discovered incidentally in patients under care for other reasons. Chemotherapy is the main form of therapy. Some early, indolent cases require no therapy. Average survival is nearly ten years, and some cases extend for much longer.

**Plasma Cell Proliferations**

Plasma cells are B lymphocytes that are actively making antibodies (immunoglobulins, Chapter 8). In some circumstances, a clone of plasma cells (a group of identical cells derived from a single ancestor cell) proliferates abnormally. These proliferations are referred to as plasma cell dyscrasia. *Dyscrasia* is an old but useful term that essentially means disease. Most plasma cell dyscrasias are malignant, but some are benign. The proliferating clone of plasma cells makes too much of its particular antibody (immunoglobulin), and the result is a very large amount of homogeneous (uniform) immune pro-
tein circulating in blood. This protein appears as a dense band in the gamma globulin region when plasma protein components are separated by protein electrophoresis, illustrated in Figure 11-15. The abnormal protein is called a monoclonal spike, M-spike, M-protein, or monoclonal gammopathy. About 1% of people over 50 have an M-protein in their plasma. Most are not associated with an identifiable abnormal proliferation of plasma cells and are considered benign, but some later prove to have a plasma cell malignancy or develop plasma cell malignancy over the years. Because of this uncertainty, these patients are said to have a monoclonal gammopathy of uncertain significance.

Normal immunoglobulins and abnormal M-proteins are made of two components, heavy chain proteins and light chain proteins (Chapter 8). Sometimes the plasma cell proliferation makes only heavy chains or light chains, in which case the diseases are called heavy chain disease and light chain disease. Light chains are also liberated by the metabolic breakdown of M-proteins. Whatever the cause, light chains are small enough to pass through the glomerulus and into urine, where they are known as Bence Jones protein.

**Multiple Myeloma**

Multiple myeloma is a malignant proliferation of plasma cells. The malignant plasma cells do not circulate in blood but appear as nodular masses in bone marrow (Fig. 11-16). These nodules destroy bone and produce solitary, “punched out” bone defects, especially in the spine and skull (Fig. 11-17), which are so distinctive radiographically that the appearance is diagnostic.

As the clone of malignant plasma cells grows, it replaces normal plasma cells, causing a decline in the production of normal immunoglobulin and normal antibodies. The result is low levels of gamma globulin (hypogammaglobulinemia) and subsequent susceptibility to infections.

Multiple myeloma occurs most frequently in elderly adults. Bone pain, hypercalcemia (as a result of bone destruction), and anemia (because of bone marrow replacement) are common complaints. Low gamma globulin levels cause recurrent infections, and about half of MM patients develop renal failure because of the toxic effect of Bence Jones protein on the renal tubules.

The diagnosis of multiple myeloma can be made by finding characteristic “punched out” bone lesions on radiographs or by finding monoclonal proteins in plasma or urine. Chemotherapy is usually not effective. Average survival is short, about three years.

**Waldenström Macroglobulinemia**

Waldenström macroglobulinemia can be conceived of as a cross between multiple myeloma and small cell
**Figure 11-15** Protein electrophoresis in plasma cell disease. Serum or urine is placed at one end of a strip of gel, across which an electrical current is applied. Most proteins have a negative charge and migrate toward the positive pole at various speeds according to their molecular weight and charge. The serum on the left shows a narrow band in the gamma globulin region. Serum protein has spilled into urine, which demonstrates a matching band. In the scan of patient serum on the right, the height of the tracing is proportional to the amount of protein stained in each band. Monoclonal protein appears as a tall, narrow (monoclonal) “M-protein.”

**Figure 11-16** Multiple myeloma. In this autopsy study of vertebrae, nodules of malignant plasma cells are visible.

**Figure 11-17** Multiple myeloma. In this radiograph of the skull in multiple myeloma, the “punched out” radiolucent lesions are the result of destruction by nodules of plasma cells. (Reprinted with permission from Rubin E. Pathology. 4th ed. Philadelphia. Lippincott Williams and Wilkins, 2005.)
lymphocytic lymphoma. The malignant cells look like lymphocytes, but they produce a particular type of M-protein—IgM, the largest and heaviest of the immunoglobulin molecules, hence the name macroglobulinemia.

Waldenström macroglobulinemia mainly affects adults over 60. In most patients the symptoms are similar to multiple myeloma: anemia, weight loss, fatigue, weakness, lymphadenopathy, and splenomegaly. Waldenström macroglobulinemia differs from multiple myeloma in that the IgM is thick and syrupy (highly viscous) and causes sluggish blood flow. Impaired blood flow to the brain causes dizziness, headache, confusion, and stroke, and poor flow to the eyes causes visual symptoms. Patients may also suffer from hemorrhages because increased levels of IgM interfere with the clotting process. Average survival is a few years, similar to multiple myeloma.

Lymphoma

Lymphomas are malignant neoplasms of lymphocytes or lymphoblasts that grow as nodular masses, usually in lymph nodes (Fig. 11-18) but sometimes in organs. In contrast to leukemic cells, lymphoma cells are not detectable in peripheral blood.

There are two broad types of lymphoma: Hodgkin lymphoma, and all the rest, which are designated non-Hodgkin lymphoma (NHL).

Hodgkin Lymphoma

The malignant cell of Hodgkin lymphoma is a lymphoid cell known as the Reed-Sternberg (RS) cell, but the exact nature of the cell remains a mystery. However, there is substantial evidence that it becomes malignant because of infection by the Epstein-Barr virus (EBV).

Hodgkin lymphoma is the most common malignant neoplasm of Americans between ages 10–30 years. Among Americans it is a bit more common in men than women and occurs almost twice as frequently in Whites than in Blacks.

Immunity is important in Hodgkin lymphoma. Immunocompromised patients have a tendency to develop Hodgkin lymphoma; and patients with Hodgkin lymphoma often have poor T-cell (cellular, delayed) immunity and develop infections as a result.

Hodgkin lymphoma differs from non-Hodgkin lymphomas (NHL) in three important respects:

- Hodgkin lymphoma arises in a single lymph node or chain of nodes and spreads in an orderly, predictable manner to adjacent nodes, rather than spreading widely, like non-Hodgkin lymphoma does
- Hodgkin lymphoma rarely involves structures other than lymph nodes
- All types of Hodgkin lymphoma are associated with defective cell-mediated (T-cell) immunity that is manifest by infections.

Based on microscopic characteristics, several types of Hodgkin disease are recognized. The most important of these is nodular sclerosis Hodgkin lymphoma, which accounts for about 70% of cases. Nodular sclerosis Hodgkin lymphoma differs from other types of Hodgkin lymphoma on several counts:

- It is the only variety of Hodgkin lymphoma that is more common in women than men
- It has a conspicuous tendency to involve neck, upper chest, and mediastinal lymph nodes (Fig. 11-19)
- It is the least aggressive

The first manifestation of Hodgkin lymphoma usually is painless, non-tender enlargement of lymph nodes, often in the neck. As tumor mass grows, however, patients may lose weight and develop night sweats, fever, and fatigue. If T-cell function becomes impaired infections may occur. For reasons unknown, in about 10% of patients with Hodgkin lymphoma the consumption of alcohol causes pain in affected areas.

Radiotherapy and chemotherapy secure permanent remission in most patients with Hodgkin lymphoma, but survival rates vary inversely with the extent of disease at the time of original diagnosis and to a lesser extent with the histologic subtype. Five-year survival for early stage patients is about 90%, and about three fourths can be considered cured. Survival with modern
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chemotherapy and radiation is in the 60–70% range for those with one of the more aggressive subtypes or with clinically advanced disease.

Therapeutic success, however, presents other problems—long-term survivors are at increased risk for other malignancies, especially myeloid bone marrow neoplasms and lung cancer, which can be attributed to failure of immune surveillance (Chapter 8) by the immune system. Risk for breast cancer is also high in young women treated with chest irradiation for mediastinal nodular sclerosis Hodgkin lymphoma.

Non-Hodgkin Lymphoma

Most non-Hodgkin lymphomas are malignant tumors of B lymphocytes. These lymphomas are similar to Hodgkin lymphoma in that both are tumors of lymphocytes, both usually present as a painless enlargement of lymph nodes, and both are associated with immune deficiency and infections.

However, non-Hodgkin lymphomas differ from Hodgkin lymphomas in important ways. On average they are more aggressive and are in a more advanced clinical stage at time of diagnosis, and their microscopic appearance and behavior vary greatly from one type to the next and from one case to the next. One third of non-Hodgkin lymphomas arise not in lymph nodes but in other organs, such as brain, bone, or bowel, whereas Hodgkin lymphoma rarely arises in tissues other than lymph node. Non-Hodgkin lymphomas tend to spread widely from the original site into other lymph nodes, spleen, liver, and bone marrow, and at time of diagnosis most patients are presumed to have widespread disease; therefore, clinical staging is not as important as in Hodgkin disease.

The pathologic classification of non-Hodgkin lymphomas is complex—the World Health Organization classification lists dozens of types. A simpler but useful method classifies non-Hodgkin lymphomas into two main groups: those that with a follicular microscopic appearance are called follicular lymphoma, and the rest are called diffuse lymphoma. Follicular lymphoma, depicted in Figure 11-20B, is so-named because its growth pattern is similar to the lymphoid follicles of normal lymph nodes (Fig. 11-20A). Of all non-Hodgkin lymphomas, about half have a follicular microscopic appearance and half diffuse.

**Follicular lymphomas are less aggressive and have a better prognosis than do diffuse lymphomas.** Follicular lymphomas arise, mainly in adults, as painless, enlarged lymph nodes. Median survival is nearly ten years. Despite this sluggish behavior they do not respond well to chemotherapy.

About half of non-Hodgkin lymphomas are diffuse lymphoma, which grow in a uniform microscopic pattern without follicles. They occur mainly in people over 60 years old, but there are two notable age exceptions: childhood lymphomas and the lymphomas associated with AIDS. Most appear quickly, grow rapidly, and are lethal unless treated. After chemotherapy about 30% of patients experience a permanent remission and can be considered cured. Most of the others undergo temporary complete remissions, but the disease recurs in a few years.

One non-Hodgkin lymphoma variant worth of special mention is small cell lymphocytic lymphoma, an especially low-grade diffuse lymphoma discussed above in connection with chronic lymphocytic leukemia. These are essentially the same disease except that in chronic lymphocytic leukemia the peripheral blood lymphocyte count is high, and in small cell lymphocytic lymphoma it is not.

Prognosis and therapy are guided by the microscopic type (follicular pattern or not, nuclear size), immunotype (B cell or T cell), and clinical stage (extranodal or organ involvement).

The clinical features of non-Hodgkin lymphoma include 1) enlarged, non-tender lymph nodes; 2) an increased metabolic rate that is responsible for constitutional symptoms such as fever, weight loss, malaise, and sweating; and 3) autoimmune phenomena or immunodeficiency problems such as infection.
MYELOID NEOPLASMS

Figure 11-2 illustrates that there are two groups of white blood cells: lymphoid cells and myeloid cells. Lymphoid stem cells give rise to B and T lymphocytes. Myeloid stem cells give rise to granulocytes, monocytes, red blood cells, and megakaryocytes. Under this heading we will discuss neoplasms of each of these types of myeloid cells.

Acute Myeloid Leukemia

Figure 11-11 illustrates that malignancies arising from myeloid stem cells can differentiate into malignant granulocytes, red cells, monocytes, or megakaryocytes. If the malignant proliferation is of immature granulocyte precursor cells, the disease is called acute myelocytic leukemia.

Acute myelocytic leukemia is a malignant proliferation of immature granulocyte precursor cells (myeloblasts) that do not mature enough to develop neutrophilic, eosinophilic, or basophilic granules. All leukemic cells in acute myelocytic leukemia have gene mutations that prevent cells from maturing, and as a result immature myeloid cells overrun blood (Fig. 11-21) and bone marrow.

Acute myelocytic leukemia is a disease primarily of middle-aged and older adults. As malignant cells crowd out normal bone marrow, granulocytes, red cells, and megakaryocytes fail to develop. Onset is typically sudden, and symptoms of marrow failure appear rapidly as the bone marrow becomes packed with malignant cells. Red cell, granulocyte, and platelet counts fall, and anemia, infection, and hemorrhage occur. Symptoms in include bone pain, lymphadenopathy, enlarged spleen and liver, and neurologic defects from leukemic infiltrates in brain and peripheral nerves.

Chemotherapy causes remission in about two thirds of younger patients, but only half of those survive five years. In older patients only about 10% survive five years.

Chronic Myeloproliferative Disorders

As is illustrated in Figure 11-11, the chronic myeloproliferative disorders are related neoplastic diseases, all of which arise from myeloid stem cells and can be considered one condition with various expressions. Each has a tendency to evolve toward acute myelocytic leukemia as a final, fatal phase.

Four disorders are recognized, according to the manner in which the stem cells differentiate, but there is considerable overlap among them.

- Polycythemia vera, malignant red cells predominate
- Chronic myelogenous leukemia, malignant granulocytes predominate
• Malignant thrombocytosis, malignant megakaryocytes predominate
• Myeloid metaplasia with myelofibrosis, malignant cells differentiate toward fibrous tissue

Two features occur to some degree in each of these disorders: myelofibrosis and extramedullary hematopoiesis.

Myelofibrosis is replacement of normal bone marrow by fibrous tissue that grows as a result of fibrogenic factors released by neoplastic megakaryocytes. Marrow fibrosis tends to appear as a final, fatal phase in any of the chronic myeloproliferative syndromes. As is illustrated in Figure 11-22, bone marrow biopsy reveals fibrosis and varying numbers of megakaryocytes but few WBC or RBC. Severe anemia, thrombocytopenia, and leukopenia result in hypoxia, bleeding, and infection.

Extramedullary hematopoiesis is the production of blood cells (hematopoiesis) in organs other than the bone marrow. Most occurs in the spleen and liver. Red cells made outside the bone marrow tend to be deformed and are released into the circulation before los-

![Image](https://example.com/image1)

**Figure 11-21** Acute myelocytic (myeloid) leukemia. A. Normal blood showing normal neutrophil and lymphocyte. B. Acute myelocytic (myeloid) leukemia showing immature myeloid cells (malignant myeloblasts).

![Image](https://example.com/image2)

**Figure 11-22** Myeloid metaplasia with myelofibrosis. This high-power microscopic view reveals that the marrow is completely replaced by malignant fibrous tissue. No normal marrow elements remain.
Polycythemia vera usually appears slowly in middle-aged adults as vague constitutional symptoms. Other manifestations include intestinal bleeding, gout (Chapter 22) caused by joint deposits of uric acid crystals metabolized from the DNA of bone marrow RBC precursors, hypertension because of expanded intravascular volume, intense pruritus (itching) of unknown cause, and a flushed complexion. Hematocrit is usually above 60%, and red cell count and hemoglobin levels are increased correspondingly. The white cell count may be as high as 50,000/cu mm; the platelet count is also high, with counts are often near 500,000/cu mm. Giant platelets and nucleated red cells are seen on microscopic study of blood cells. Some patients have tendency toward deep vein thrombophlebitis; others have problems with hemorrhages. The natural history of polycythemia vera is to evolve over about a decade to a burned-out state with most of the features of myelofibrosis with myeloid metaplasia.

Conclusive diagnosis usually requires determination of total red cell mass, as is discussed in the Lab Tools box earlier in this chapter.

Malignant Thrombocythemia

Malignant thrombocythemia (essential thrombocythemia) is a rare, chronic myeloproliferative disorder in which the predominant malignant cell is the megakaryocyte. Platelet counts can be 500,000/cu mm or higher, but high platelet counts are common in all chronic myeloproliferative syndromes, so the diagnosis is one of exclusion. Circulating giant platelets are common. Bone marrow exam reveals an increase of megakaryocytes, some of them quite large. Myelofibrosis is absent. Thrombosis and hemorrhage are the most common clinical problems. It is a sluggish disorder with periods of quiet; average survival is about 10–15 years.

Myeloid Metaplasia with Myelofibrosis

Myeloid metaplasia with myelofibrosis is a myeloproliferative disorder in which marrow fibrosis predominates. It is caused by a release of fibrogenic factors from neoplastic megakaryocytes. It usually occurs in older adults, most of whom have very large spleens because there is splenic growth of bone marrow cells (extramedullary hematopoiesis, myeloid metaplasia). Red cells made outside the marrow tend to be deformed and retain their nuclei, so the peripheral blood contains many odd-shaped and nucleated red cells. Other blood findings include giant platelets, increased basophil count, and increased uric acid owing to metabolism of malignant cell DNA. Patients also suffer hemorrhagic or thrombotic problems associated with platelet defects. Typically the bone marrow is hypocellular or fibrotic, as is depicted in Figure 11-22. The final phase in some cases is a “blast crisis” that occurs as the case evolves rapidly into acute myeloid leukemia. Chronic myeloid
leukemia and polycythemia vera may evolve ("burn out") into myeloid metaplasia with myelofibrosis. Average survival is a few years.

**Myelodysplasia**

Myelodysplasia is a group of bone marrow stem cell proliferations characterized by ineffective RBC production and a tendency to evolve into acute myelocytic leukemia. Cases occur spontaneously in older adults or as a result of prior chemotherapy or radiation, usually a few years after treatment. Myelodysplasia is also referred to as preleukemia or smoldering leukemia; both terms conveying a correct sense of the disease. The marrow typically is hypercellular and contains many dysplastic red and white cells. Because hematopoiesis is ineffective, patients may come to attention initially because of fatigue (low red cell count), bleeding (thrombocytopenia), or infection (leukopenia). Sometimes one cell type is more affected than others are. For example, red cell production may be especially impaired, giving rise to a syndrome called refractory anemia. Average survival is a few years.

**Disorders of the Spleen and Thymus**

The spleen filters unwanted microbes and substances from blood, the same as lymph nodes do from lymphatic fluid—splenic macrophages trap bacteria, foreign material, and antigens for elimination or presentation to the immune system. The spleen also removes from the circulation old blood cells and platelets, or blood cells to which antibody is attached. For example, in immune hemolytic anemia red cells coated with antibody are trapped and hemolyzed by the spleen. Overactivity of splenic function (hypersplenism) can cause decreased numbers of red cells, white cells, or platelets.

The catalog of conditions that affect the spleen is too long to list in its entirety, but among the most common are viral infections, chronic autoimmune disease, malaria, lymphoma and leukemia, chronic passive congestion owing to right heart failure, and portal hypertension (usually associated with cirrhosis). In almost every instance the result is an enlarged spleen (splenomegaly). Regardless of cause, an enlarged spleen may become overactive and remove more cells from blood than it normally should, destroying normal blood cells and platelets.

The thymus sits behind the upper end of the sternum and is critical to the development of the T lymphocytes of the immune system. It features a cortex of lymphocytes and a medulla of thymocytes (thymic epithelial cells). Relative to body size, it is largest at birth, but in absolute terms it becomes largest at puberty and shrinks to a few grams in adults.

Underdevelopment of the thymus causes serious immune deficiency, discussed in Chapter 8.

Hyperplasia of thymic lymphocytes or epithelial cells is associated with a variety of endocrine and autoimmune disease but is most commonly found in association with myasthenia gravis (Chapter 22), a rare, acquired autoimmune disease in which antibodies block transmission of nerve signals across the neuromuscular synapse—about half of cases have thymic hyperplasia or thymoma.

Thymoma is a tumor of thymic epithelial cells. They are very rare and may be either benign or malignant. Most are discovered in association with myasthenia gravis.

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**Section 2: Bleeding Disorders**

*Don’t worry; the bleeding always stops.*

**ADVICE FROM OLDER SURGEONS TO WORRIED YOUNGER ONES.**

**BACK TO BASICS**

Hemostasis (Fig. 11-23) is a natural reaction, the purpose of which is to stop bleeding. It depends upon the interplay of blood vessels, platelets, and coagulation (clotting). After injury, damaged vessels undergo temporary constriction (vasospasm), and platelets begin to accumulate at the edges of the vascular defect to obstruct blood flow and to release factors to stimulate coagulation. At the same time, escaping blood is exposed to extravascular tissue factors that also stimulate coagulation, resulting ultimately in the weaving of a web of fibrin (a clot) to trap red cells and obstruct further escape of red cells from the vascular defect.

Coagulation begins when blood or platelets contact something they should not: extravascular tissue or a foreign surface. Coagulation is the result of interactions...
Chapter 11 • Diseases of Blood Cells and Blood Coagulation

**Figure 11-23** Normal hemostasis. 

A. Injury occurs.  
B. Temporary vasoconstriction occurs.  
C. Blood contacts tissue, platelets accumulate, and coagulation begins.  
D. Further platelet aggregation occurs, and coagulation produces a web of fibrin in the wound.  
E. Hemorrhage stops as fibrin traps red cells and blocks further bleeding.
among blood coagulation proteins (coagulation factors), which are made by the liver and are denoted by names and Roman numerals. For example, hemophilia factor is factor VIII. Coagulation factors interact with one another in a “falling dominoes” cascade, diagramed in Figure 11-23. The end result is a fibrin clot.

Traditionally, the coagulation cascade is divided into two pathways—the extrinsic coagulation pathway if the process is initiated by contact with tissue, or the intrinsic coagulation pathway if blood comes into contact with a foreign surface such as glass, plastic, or metal. This division is an artifact of laboratory testing; both pathways are active in hemostasis. The nearby Lab Tools box diagrams coagulation process and explains use of the most important laboratory tests.

**LAB TOOLS**

**Lab Tests in Bleeding Disorders**

Hemostasis is assessed by performing laboratory tests to assess platelet action and coagulation. There is no good test to assess blood vessel factors. The accompanying figure outlines a simplified outline of coagulation pathways, coagulation factors, and laboratory tests.

Coagulation is assessed by prothrombin time and partial thromboplastin time. Each is performed by adding reagent to anticoagulated plasma and timed to see how long it takes for a clot to form.

- **Prothrombin time (PT)** is the time it takes for a sample of patient plasma to clot after the addition of a tissue extract that mimics contact of blood with tissue. This initiates coagulation via the extrinsic pathway and, therefore, the result is abnormal if there are defects in the extrinsic or common pathways.

- **Partial thromboplastin time (PTT)** is the time it takes for a sample of patient plasma to clot after addition of compounds that mimic contact of blood with an artificial surface. This initiates coagulation via the intrinsic pathway and, therefore, the result is abnormal if there are defects in the intrinsic or common pathways.

Platelets are assessed by performing a platelet count and platelet function analysis or bleeding time:

Pathways:
- Intrinsic
- Extrinsic
- Common

Blood contact with foreign surface

Coagulation factors VIII, IX, XI, XII

Partial thromboplastin time

Prothrombin time

Tissue trauma

Tissue factors

Coagulation factor VII

Factor V

Factor X

Factor VIII

Prothrombin (II)

Fibrinogen (I)

No good test

Platelet count, bleeding time

Vascular factors

Fibrin formation

Platelets

HEMOSTASIS

Hemostasis and hemostasis tests. Vascular factors, coagulation, and platelets each play a role in maintaining hemostasis and stopping hemorrhage.
Bleeding Disorders

**MAJOR DETERMINANTS OF DISEASE**

- Excessive bleeding is always associated with at least one of three factors:
  - fragile blood vessels
  - low platelet count or defective platelet function
  - decreased coagulation factor activity
- Bleeding related to platelet disorders usually occurs from capillary-sized blood vessels.
- Bleeding related to coagulation factors usually occurs from larger vessels.
- Most coagulation factors are proteins made by the liver, and severe liver disease is often accompanied by excessive bleeding.
- Intravascular clotting is always abnormal and secondary to another disease.

Bleeding is usually the result of vascular injury. Excessive bleeding (hemorrhagic diathesis) is bleeding beyond the expected amount for a certain injury, or bleeding without obvious injury. Excessive bleeding is caused by one of three factors:

1. Fragile small blood vessels
2. Decreased platelet count or ineffective platelet function
3. Decreased coagulation factor activity

Hemorrhage occurs either from capillaries or from larger blood vessels. Patients with platelet problems or fragile small blood vessels usually bleed from capillary-size blood vessels, and the bleeding usually presents as tiny skin or mucosal hemorrhages (petechiae), nose-bleed, hematuria, or excessive menses. On the other hand, patients with coagulation factor deficiency bleed from larger vessels and usually bleed into deep tissues, joints, and body spaces.
**VASCULAR OR PLATELET DEFICIENCY**

Other than trauma, few bleeding problems result solely from fragile small blood vessels. Some people, especially the elderly, do bruise easily, but the reasons are not clear and may relate to weakening of supporting connective tissue. Other causes include autoimmune vasculitis and vitamin C deficiency (scurvy), which weakens the intercellular cement that holds together small blood vessels.

Low platelet count (thrombocytopenia) occurs in a great variety of disorders and is usually characterized by tiny hemorrhages (petechiae, Chapter 5) in skin or mucosa. The normal range for platelet counts in most laboratories is about 130,000–400,000/cu mm. Because of this wide range, most practitioners do not grow concerned unless the platelet count falls below 100,000/cu mm. Even so, excessive bleeding after trauma rarely occurs until the count falls below 50,000/cu mm, and spontaneous hemorrhage usually does not occur until counts fall to about 20,000/cu mm. However, with severe thrombocytopenia, hemorrhage may occur at any site. CNS hemorrhage is a particular hazard for patients with very low platelet counts. In addition to a low platelet count, patients with thrombocytopenia have an abnormal bleeding time (see the related Lab Tools box).

Thrombocytopenia also may also occur when platelet production is low, associated with primary bone marrow disorders, with toxic effects of drugs or chemicals such as thiazide diuretics, or with ineffective platelet production, as in the case of folate or B₁₂ deficiency. The spleen normally filters old platelets out of circulation and may be the cause of low platelet counts. In such cases, the spleen normally filters old platelets out of the blood after about 12 days, so an overactive spleen (hypersplenism) may cause thrombocytopenia.

A much more common cause of low platelet count is immune thrombocytopenic purpura (ITP), in which the body’s immune system destroys its own platelets. ITP usually occurs as an isolated disease, but can be seen in association with other autoimmune disorders, or it rarely may occur as a complication of acute pediatric viral illnesses. Platelets become coated with anti-platelet autoantibodies and are quickly removed by the spleen. Onset of ITP is insidious and may be first noticed by an astute clinician who detects subungual (beneath a fingernail) or conjunctival petechiae. More commonly, however, thrombocytopenia first shows itself as easy bruising, epistaxis (nosebleed), bleeding gums, or unusual bleeding after minor trauma. Treatment with steroids is effective, and splenectomy is curative in most cases.

**COAGULATION FACTOR DEFICIENCY**

The liver produces most coagulation factors, and liver disease is an important cause of coagulation disorders. For example, patients with cirrhosis (Chapter 16), usually have bleeding tendencies because of coagulation defects.

On the other hand, many coagulation defects are inherited and involve single coagulation protein deficiencies, which are inherited in Mendelian fashion (Chapter 7). For example, classic hemophilia is a factor VIII deficiency. Vitamin K is essential for the production of factors VII, IX, and X and prothrombin. Coagulation defects resulting from vitamin K deficiency are most often seen with lengthy antibiotic therapy that eliminates vitamin K-producing bacteria from the intestine.

**von Willebrand disease** stems from a deficiency of von Willebrand factor (vWF), a coagulation factor made in endothelial cells and megakaryocytes. von Willebrand disease is one of the most common inherited coagulation disorders and is characterized by spontaneous bleeding from mouth, nose, and other mucous membranes and by excessive wound bleeding, and excessive menstrual bleeding. Bleeding time is prolonged despite normal platelet count because lack of vWF interferes with platelet adhesion to endothelium.

Classic **hemophilia** (hemophilia A or factor VIII deficiency) is the most common serious inherited coagulation disorder. An X-linked gene defect impairs factor VIII production and therefore this disorder occurs almost exclusively in males; however, about one third of cases are new mutations without positive family history. Spontaneous hemorrhage occurs only in severe deficiency (factor VIII levels about 1% of normal). Lesser deficiencies show varying amounts of post-traumatic bleeding. Intracapsular joint hemorrhage (hemarthrosis, especially in the knee) is a particular problem in patients with severe deficiencies. Repeated episodes may produce crippling joint strictures and immobility (ankylosis). Patients with hemophilia characteristically have a normal bleeding time and platelet count because neither platelets nor vascular factors are at fault. Patients with hemophilia have a normal prothrombin time because the extrinsic and common pathways do not require factor VIII; however, PTT is prolonged because factor VIII is in the intrinsic pathway (see the related Lab Tools box). For those with severe deficiency periodic transfusion with factor VIII is effective. The accompanying History of Medicine box offers a glimpse into the interesting story of hemophilia.

Severe **Christmas disease** (hemophilia B, factor IX deficiency) is clinically similar to classic hemophilia but
is much less common. (It is named for the first patient in whom the disease was identified, not for the annual holiday season.) Like classic hemophilia it is caused by an X-linked recessive gene defect, and it has test abnormalities similar to classic hemophilia (see the related Lab Tools box). Christmas disease may or may not be associated with significant bleeding problems. Diagnosis requires highly specialized testing specifically for factor IX deficiency.

**DISSEMINATED INTRAVASCULAR COAGULATION (DIC)**

Blood is not intended to clot inside the vascular space; blood normally clots only when it comes into contact with tissues outside the vascular space. A major function of the vascular endothelium is to prevent blood from contacting extravascular tissue, thereby preventing coagulation. If the vascular wall is disrupted, bleeding occurs.

DIC is a condition in which clotting occurs inside the vascular space. One consequence is obstruction of small vessels by clots. However, a somewhat surprising aspect of DIC is that patients eventually have a bleeding tendency because clotting factors consumed by the clotting process no longer exist in high enough concentration to prevent abnormal bleeding. Therefore, DIC is said to be a consumptive coagulopathy.

DIC is never a primary disease; it is a complication of other diseases. For example, it may occur in bacterial septicemia when coagulogenic products released by bacteria activate the coagulation cascade.

DIC may be initiated by variety of conditions, which can be grouped into several major categories:

- *Obstetrical complications:* toxemia, premature separation of the placenta (abruptio placenta), amniotic fluid embolism, retained dead fetus
- *Infections:* Gram-negative sepsis, meningococcal meningitis, malaria
- *Neoplasms:* carcinoma of stomach, pancreas, lung, and prostate and acute promyelocytic leukemia
- *Massive tissue trauma:* crush injury, burns
- *Others:* snakebite, heat stroke, acute hemolysis, and vasculitis

Regardless of cause, DIC is usually characterized by hemolytic anemia (as RBCs are shredded by passing through intravascular fibrin webs), thromboses, and hemorrhage as coagulation components are consumed by the clotting process.

**HISTORY OF MEDICINE**

**‘THE ROYAL DISEASE’**

The oldest recognition of hemophilia (deficiency of coagulation factor VIII) is an indirect reference in the Talmud, a collection of Jewish religious writings from the 2nd Century AD, which notes that male infants did not have to be circumcised if two brothers had died from the procedure.

In the 12th Century AD an Arab physician, Albucasis, wrote of a family whose males died of bleeding after minor injuries.

In 1803, the year Lewis and Clark began their epic voyage up the Missouri River, John Otto, a Philadelphia physician, wrote an account of “a hemorrhagic disposition affecting certain families” and recognized that it was hereditary and affected males only.

Hemophilia has been called “The Royal Disease” because it afflicted the royal families of Europe during the reign of Queen Victoria, who ruled England from 1837 to 1901. Hemophilia is a sex-linked, autosomal recessive gene defect (Chapter 7), and the Queen was a carrier who passed the trait on to her daughters, who in turn passed it on to German, Spanish, and Russian royalty in the nineteenth century.

A case can be made that hemophilia dramatically altered the course of history. In 1894, Queen Victoria’s granddaughter, Alexandra, a carrier of the gene for hemophilia, married Nicholas, Tsar of Russia. Their son, Alexei, heir to the throne, was born in 1904 and suffered from severe hemophilia. During the crisis years leading up to the Bolshevik (communist) revolution in 1917, Nicholas and Alexandra’s preoccupation with Alexei’s health led them to an unusual, and eventually fatal, reliance on the advice of the mad monk Gregory Rasputin, the only person who seemed to be able to help the suffering boy. The illness of the heir to the Russian throne, the strain it placed on the Royal family, and the influence of the crazed monk were important factors that led to the bloody overthrow of the Tsar and the installation of a communist state in Russia.
Thrombotic Disorders

In most instances, venous thrombosis is caused by local factors such as turbulent blood flow or local endothelial injury (Chapter 5). However, two conditions exist in which venous thrombosis is promoted by abnormalities of blood coagulation proteins. These disorders do not promote arterial thrombosis (stroke or myocardial infarction), however.

**Lupus anticoagulant** (also called *anti-phospholipid antibody*) is an autoantibody that occurs in about 10% of patients with systemic lupus erythematosus (Chapter 8) and gets its name from the fact that it interferes with laboratory tests of blood coagulation, causing the tests to suggest that coagulation is deficient when, in fact, the opposite is true: lupus anticoagulant promotes venous thrombosis.

Patients with lupus anticoagulant are at increased risk for recurrent venous thrombosis, pulmonary thromboembolism, and recurrent spontaneous abortions. However, most patients with lupus anticoagulant do not have systemic lupus erythematosus or other clinical disease. Lupus anticoagulant also should also be suspected in patients who have abnormal laboratory tests of blood coagulation (prolonged prothrombin or partial thromboplastin time; see the related Lab Tools box) but who do not have clinical evidence of a bleeding disorder.

**Factor V Leiden** is an abnormal form of coagulation factor V produced by a defective gene. Factor V Leiden promotes a generalized tendency to form venous thrombi. The abnormal gene is an autosomal recessive defect (Chapter 7) that is surprisingly common—it is present in about 5% of Caucasians and 1% of African Americans. The heterozygous state is associated with an approximate five-fold increased risk for venous thrombosis; the risk for the homozygous state is much higher. Oral contraceptive use further increases the risk. Factor V Leiden should be suspected in patients with venous thrombosis of any type, pulmonary thromboembolism, or recurrent spontaneous abortions. Laboratory tests are necessary to confirm the diagnosis.

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**CASE STUDY 11.1 “I'M TIRED AND SHORT OF BREATH ALL THE TIME”**

**TOPICS**
- Intestinal bleeding
- Iron deficiency anemia
- Colon cancer

**THE CASE**

**Setting:** You practice with a primary care physician in an office in a large city. Your principal duty is to see new patients before they see the physician.

**Clinical history:** Janice K is a 52-year-old female new patient. When you ask about her main complaint she says, “I’m tired and short of breath all the time.” In the last year she has given up walking for exercise and has to stop to catch her breath when climbing the stairs at home. She has never smoked and has never been hospitalized except for pregnancy. Her only physician visits over the last ten years have been for occasional gynecologic exams and pap smears, the most recent one three years ago. Routine questions about diseases in various organ systems reveal no significant problems.

**Physical examination and other data:** Vital signs are unremarkable except that her resting heart rate is 82/min. She is pale, with fair skin and graying red hair. She is of medium height and average weight. Her conjunctivae are pale. Her chest is clear, and her abdomen is soft and without palpable masses. There are no palpable lymph nodes. Vaginal exam is unremarkable. Digital rectal exam reveals no masses. Stool on the exam glove tests positive for blood. Laboratory studies reveal:
Clinical course: You review her CBC results and conclude that she almost certainly has iron deficiency anemia, probably because of chronic intestinal bleeding. After consulting with the physician, you order a reticulocyte count, plasma iron level, and a barium enema radiograph of her colon. The radiographs reveal a mass in the transverse colon, which the radiologist says is “suspicious for malignancy.” The patient is referred to a colon and rectal surgeon, who performs a colonoscopy and biopsy, which reveals that the suspicious mass is a carcinoma of the colon. A few days later a partial colectomy is performed. The tumor is found to deeply invade the colon wall, and evidence of spread is found in nearby lymph nodes; no liver metastases are found.

Six weeks later she is discharged from the surgeon’s care and returns to your office. The surgeon has instructed her to take oral iron tablets, and you advise her to follow his instructions and come back in six weeks for follow-up laboratory studies, at which time her reticulocyte count is 6%, indicating a brisk outpouring of new RBCs. Plasma iron levels have risen into the normal ranges, and hemoglobin, hematocrit, and red cell count have improved substantially.

DISCUSSION
This patient presented with fatigue and shortness of breath. Coupled with rapid resting heart rate and pallor, the findings strongly suggested anemia. Lab studies confirmed your conclusion and revealed that the anemia was microcytic (low MCV) and hypochromic (low MCHC). Follow-up reticulocyte count and plasma iron confirmed the diagnosis of iron deficiency anemia: plasma iron was low, as it is in iron deficiency anemia, and the reticulocyte count was low, indicating that few new RBCs were being made by the bone marrow because there was not enough iron to form the necessary hemoglobin.

By far the most common cause of iron deficiency anemia in patients over 50 is intestinal bleeding, which is strongly suggested in this case by the fact that the patient’s stool is positive for blood. The most serious common cause of intestinal bleeding in men and women over 50 is colon cancer, which was found by barium enema radiograph and proved by biopsy.

After the tumor was removed and the patient was put on oral iron, a brisk reticulocytosis was exhibited. Removal of the tumor stopped the bleeding, and the supplemental iron allowed new red cells to be produced.

Almost every colon cancer arises from pre-existing benign polyps, which take many years to become fully malignant. Regular stool tests for occult blood and periodic colon exams for all patients over age 50 detect almost all colon cancers before they metastasize.

This patient had not had a test for stool blood in at least ten years, perhaps longer. With regular physical exams, lab studies, and stool exams, her cancer probably could have been detected years earlier, and her prognosis would be better.

Colon cancer is the third leading cause of cancer death in women, behind lung cancer and breast cancer, and it is third behind lung and prostate cancer in men. When statistics for men and women are lumped together, colon cancer is the number two cancer killer after lung cancer.

POINTS TO REMEMBER
• Cancer of the colon is almost entirely preventable with regular stool blood tests and periodic colon examinations.
• Iron deficiency anemia in an adult man or post-menopausal woman should be considered to be caused by an intestinal malignancy until proven otherwise.
1. Give a reasonable estimate of the life span of blood cells and platelets: Blood cells are produced in the bone marrow, circulate for a number of days, and are removed, mainly by the spleen. Red cells have a life span of about 120 days; neutrophils, basophils, and eosinophils about 4 days; lymphocytes and monocytes, a week or two; platelets, a day or two.

2. Explain what is meant by red cell indices, and understand how to calculate them: Red cell indices are measures of red cell size and hemoglobin content. They are calculated ratios among red cell count, hemoglobin, and hematocrit.

3. Define anemia, and list the major types of anemia: Anemia is lower than normal blood hemoglobin or hematocrit levels or red cell counts. Anemia can be caused by 1) decreased production of red cells; 2) increased destruction of red cell; or 3) loss of red cells (hemorrhage).

4. Regarding sickle cell anemia, explain the cause and discuss what happens to red cells: Sickle cell anemia occurs when there is a genetic defect in hemoglobin formation. The altered hemoglobin causes red cells to be deformed into a sickle (crescent) shape. Malformed (sickled) RBCs clog capillaries and impair blood flow. They are prematurely destroyed or removed from circulation after circulating for less than the normal 120 days.

5. Explain blood and bone marrow ferritin, iron, transferrin, and iron binding capacity in iron deficiency anemia: Blood iron and ferritin and marrow ferritin are low because body iron stores are depleted. Blood iron binding capacity is increased as a reflection of increased blood transferrin, a protein made by the liver, which is increased in order to attempt to transport more iron to tissues.

6. Explain the difference between relative and absolute erythrocytosis: Relative erythrocytosis is increased peripheral red cell count that is not associated with increased total body red cell mass. Absolute erythrocytosis is associated with increased total body red cell mass.

7. Explain the significance of a left shift in the white cell differential count in peripheral blood: A “left shift” is caused by release of immature granulocytes from bone marrow into peripheral blood. It occurs most often when the marrow is under stress, as when responding to acute infection.

8. Name the two major groups of bone marrow malignancies, and list some of the diseases associated with each: There are two major groups of bone marrow malignancies: myeloid and lymphoid. Myeloid neoplasms are a very varied group and consist of acute and chronic myeloid leukemia, and a family of related malignancies known as the chronic myeloproliferative syndromes. Lymphoid neoplasms consist of acute and chronic lymphocytic leukemia, lymphomas, and plasma cell proliferations.

9. Distinguish between leukemia and lymphoma: Both are malignancies of leukocytes. In leukemia malignant cells are present throughout the bone marrow are found in high numbers in peripheral blood. In lymphoma malignant cells occur as nodular masses in lymph nodes and other organs; the bone marrow and blood are not much involved.

10. Explain why patients with plasma cell proliferation have abnormal blood proteins: Plasma cell proliferations include benign and malignant growths of plasma cells that produce an excess of immunoglobulin.


12. Name the two types of non-Hodgkin lymphoma according to microscopic patterns, and explain why this distinction is important: The two types are follicular and diffuse. The distinction is important because they behave much differently: follicular lymphomas are less aggressive and have a better prognosis than diffuse ones.

13. Define hypersplenism: Overactivity of the spleen that consumes more than the normal amount of WBC, RBC, or platelets. Hypersplenism is associated with enlarged spleen.

14. Name the elements of normal hemostasis: Hemostasis depends upon the interplay of 1) coagulation, 2) blood vessel factors, and 3) platelets.

15. Characterize bleeding caused by platelet disease: Bleeding is usually the result of low platelet count; bleeding because of platelet malfunction is uncommon. The bleeding is usually from small, capillary-size blood vessels and appears as petechiae or other small hemorrhages.

16. Briefly characterize classic hemophilia (hemophilia A): It is an X-linked genetic deficiency of coagulation factor VIII that occurs in males; mild deficiencies may cause excess post-traumatic bleeding; severe deficiency may cause spontaneous bleeding, especially in joints.

17. Explain why patients with disseminated intravascular coagulation have bleeding problems: Disseminated intravascular coagulation consumes clotting proteins (factors), leaving insufficient clotting proteins to support normal clotting. The result is a tendency toward hemorrhage.
Typical Test Questions

1. Mean cell volume (MCV) is calculated using which of the following:
   A. Hemoglobin and hematocrit
   B. Red cell count and hemoglobin
   C. Red cell count and hematocrit

2. Red cells, granulocytes, and platelets arise from which one of the following?
   A. Monocyte stem cells
   B. Myeloid stem cells
   C. Lymphoid stem cells

3. Hemoglobinopathies are characterized by which one of the following?
   A. Bone marrow red cell aplasia
   B. Autoimmune hemoglobin precipitation
   C. Defective hemoglobin synthesis
   D. Excess hemoglobin

4. Follicular lymphoma is characterized by which one of the following?
   A. Growth in large, nodular masses in the chest and neck
   B. Myelofibrosis with myeloid metaplasia
   C. Very aggressive growth
   D. Microscopic pattern resembling normal lymphoid follicles

5. Which of the following statements is true?
   A. Blood normally clots only in the extravascular space
   B. Most coagulation factors are made in the spleen
   C. Platelet-related bleeding usually occurs from large blood vessels
   D. Most coagulation factors are immunoproteins

6. True or false? Most of plasma volume is protein.

7. True or false? Intrinsic factor is secreted by the gastric mucosa.

8. True or false? Small cell lymphocytic lymphoma is very aggressive.

9. True or false? Nodular sclerosis type is the most common type of Hodgkin lymphoma

10. True or false? Chronic leukemia is characterized by mature white cells in the blood.