5.2 Plasma and Red Blood Cells

Learning Objectives

- Write the concentrations of the major electrolytes of plasma
- List in order the major proteins of plasma with their functions
- Describe the structure of immunoglobulins
- Describe the shape of erythrocytes
- Calculate mean cell volume and mean corpuscular hemoglobin concentration
- Describe the structure of hemoglobin and list the major variants
- Recognize the structure of heme and the central role of Fe
- Write the negative feedback regulation of erythrocyte formation by erythropoietin
- Describe the destruction of erythrocytes with the life span and metabolic fate of heme
- Describe the handling of Fe in the body
- Explain the basis of blood typing, identifying universal donor and recipient types

PLASMA CONSISTS MAINLY OF WATER, ELECTROLYTES, AND PROTEINS

All of the components of blood are either suspended or dissolved in a watery phase. The dissolved materials include all of the electrolytes, a variety of proteins, nutrients, gases, wastes, and hormones. Some of these are not readily soluble in water and so they are helped along by little "flotation devices"—typically proteins that coat the materials and allow them to be carried in the water phase. Because some of the volume of the plasma is occupied by these materials, **water makes up only 92% of the mass of plasma**. Because these materials occupy volume, water also makes up about 92% of the volume of plasma. Thus, concentrations of dissolved substances when expressed per L of plasma are lower than those expressed per L of plasma water.

Electrolytes are dissolved substances that dissociate into ions and therefore confer electrical conductivity onto the solution. The electrolytes in plasma include Na^+, K^+, Cl^-, HCO_3^-, Ca^{2+}, H^+, Mg^{2+}, and $H_2PO_4^-$, and a variety of other ions. These ions contribute to the overall osmotic pressure of plasma and also determine the concentrations of these ions in the **interstitial fluid**. The equilibrium potential for any ion across the cell membrane depends on the concentrations of the ion in the interstitial fluid and in the cell (see Chapter 3.1). These equilibrium potentials and the conductances to the ions determine the resting potential and the excitability of the cells to external stimuli. The concentrations of ions in normal plasma and in the interstitial fluid are given in Table 5.2.1.

Plasma contains a number of different proteins that can be classified on the basis of their solubility and coagulability, among other characteristics, and each of these classes contain a variety of members. Figure 5.1.1 illustrates the components that make up the plasma proteins.

The serum **albumin** concentration varies from 2.8 to 4.5 g%, where "g%" refers to the g of albumin per 100 mL of plasma. It makes up more than 50% of the total plasma protein but, because it is smaller than other plasma proteins, it makes up a larger fraction of the total molar concentration of protein. Thus, albumin makes up a larger fraction of the plasma osmolarity due to proteins. Albumin is made in the liver and secreted into the blood. Its regions of high hydrophobicity bind a variety of hydrophobic materials including fatty acids, bilirubin, and steroid hormones. This binding allows albumin to transport these materials in the blood.

The **globulins** are the second most abundant class of plasma proteins, accounting for about 3.1 g% of the plasma protein. About 80% of the globulins are synthesized by the liver and secreted into the blood. The rest are synthesized in various parts of the body. The **γ-globulins** are synthesized in the **lymph nodes** and in the **reticuloendothelial cells** that are distributed widely throughout the body, especially in the spleen. The globulins are divided into subclasses based on their separation by electrophoresis (see Figure 5.2.1).

The α_1-globulins include the **high-density lipoproteins** or **HDL**, which are complexes of proteins and lipids that are used to transport lipids through the blood. In this case the lipids are noncovalently bound in large macromolecular assemblies that are coated with proteins called **apolipoproteins**. The apolipoproteins, also called apoproteins, maintain the solubility of the lipoproteins and provide recognition sites for the tissues that metabolize the lipids found in these lipoproteins.

The major α_2-globulin, **macroglobulin**, is present at about 0.2 g%. It has a molecular weight of 842 kDa and

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TABLE 5.2.1 Concentration of Ions in Plasma and Interstitial Fluid

Electrolyte	Plasma C (mEq/L)	ISF C (mEq/L)
Na^+	142	144
K^+	4	4
Ca^{2+}	5	2.4
Mg^{2+}	3	1.5
H^+	3.9×10^{-5}	3.7×10^{-5}
Cl^-	105	114
HCO_3^-	24	25
Phosphates	2.5	2.5
Sulfate	1	1
Organic acids	5	5
Protein	16	4
Total osmolarity	296	296

The concentration is given in units of milliequivalents/L. This unit is related to molarity through the charge per ion, *z*. The concentration in milliequivalents/L is related to the concentration in millimolar by $C_{mEq} = |zC_{mM}|$. The concentrations given are the total concentration and not the free concentrations. In the case of Ca^{2+}, about half of the 5 mEq/L are bound to plasma proteins, so that the *free* plasma $[Ca^{2+}]$ is closer to 2.5 mEq/L or 1.25 mM. The actual concentrations in individuals vary within a range of normal, and typical values are given. Plasma proteins occupy a significant volume, so that the water content of plasma is reduced. The concentrations shown here are expressed per L of plasma, not per L of plasma water.

its major function appears to be inhibition of proteolytic activity. Other α_2-globulins include **prothrombin**, a 62.7 kDa protein that is essential in blood clotting; **angiotensinogen**, a precursor for **angiotensin**, a potent vasoconstrictor; **erythropoietin**, a 34 kDa glycoprotein synthesized and secreted by the kidney that controls the formation of red blood cells.

The major β-globulins are **transferrin**, an 80 kDa protein that binds and transports iron, and the β-lipoproteins. These lipoproteins include the **low-density lipoproteins (LDL)** and the **very low-density lipoproteins** or **VLDL**. As with the HDL described above, these are macromolecular assemblies of insoluble lipid and its apolipoprotein coat that keeps the lipoprotein in suspension and helps tissues bind and absorb the lipid for metabolism.

Specialized cells produce and release **antibodies** into the plasma. These are all members of the γ-globulin class of proteins, of which there are several types. Because they form part of the body's immune defense, these globulins are also called **immunoglobulins**. Antibodies are proteins composed of multiples of heavy and light protein chains that are linked together by disulfide bonds, as shown in Figure 5.2.2.

About 80% of the immunoglobulins in blood are IgG. IgG and IgM provide the major defense against bacteria. The IgM class is polymerized to give $(LH)_{2n}$, where L is the light chain, H is the heavy chain, and $n = 5-6$. Its molecular weight is about 750 kDa. This

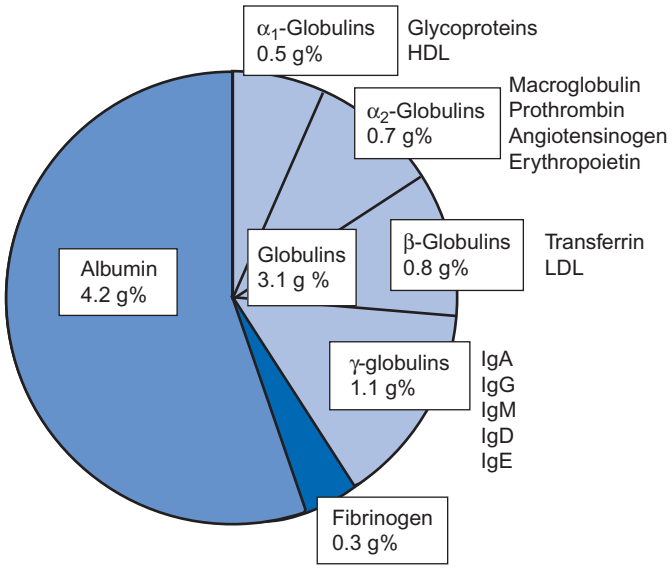

FIGURE 5.2.1 Composition of plasma proteins. "Albumin" refers to a class of proteins that are readily soluble and that coagulate upon heating. Examples are egg ovalbumin and serum albumin. Serum albumin (molecular weight of 66.5 kDa) is the smallest and most abundant of the major plasma proteins. "Globulin" refers to proteins that are insoluble or sparingly soluble in water, but whose solubility is greatly increased by adding salts such as NaCl. These proteins coagulate when heated. The names of the various classes of the globulins derive from how they separate during electrophoresis. The numbers indicate typical values within normal ranges of 2.8–4.5 g% for albumin; 0.4–0.5 g% for α_1-globulins; 0.4–0.9 g% for α_2-globulins; 0.6–1.1 g% for β-globulins.

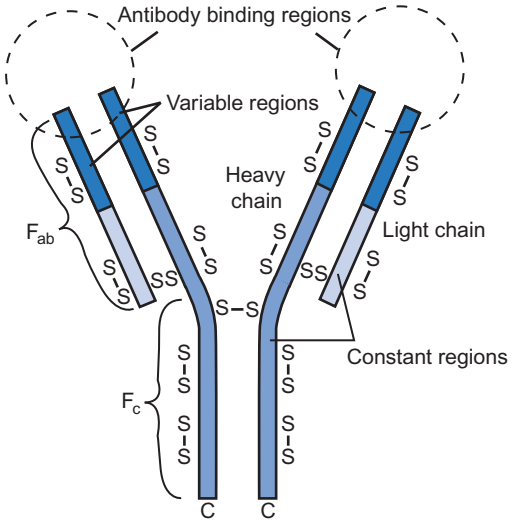

FIGURE 5.2.2 Chemical structure of a γ-globulin. The IgG class shown here has a molecular weight of 150 kDa. It consists of four polypeptide chains. Two heavy chains and two light chains are connected by disulfide bonds and noncovalent interactions. Both heavy and light chains consist of regions that are constant and other regions that vary. These variable regions allow the immunoglobulins to bind to specific **antigens**. The fragment of the immunoglobulin containing the **a**ntigen **b**inding region is called $\mathbf{F_{ab}}$; the fragment containing the **c**onstant region is called $\mathbf{F_c}$. Binding of the antigen by the antibody allows the body to recognize the antigen and "tag" it for destruction.

immunoglobulin is a receptor on special cells of the immune system called **B-lymphocytes**. It is also secreted into the plasma by **plasma cells**, B-lymphocytes to which an antigen has bound and activated the

production and secretion of antibodies. IgA is found in secretions of the gastrointestinal tract, respiratory tract, genitourinary system, milk, and tears. IgE appears to help defend against parasitic worms and be involved in allergic responses such as hay fever, asthma, and hives.

Human plasma contains 0.3 g% of fibrinogen. This large protein (330 kDa) is a precursor to **fibrin**, which forms the blood clot.

PLASMA PROTEINS AND IONS BUFFER CHANGES IN PLASMA pH

Proteins and phosphate groups in plasma provide the first defense against changes in the plasma H^+ by binding or releasing H^+ according to **Le Chatelier's Principle**. Le Chatelier's Principle states that a reaction at equilibrium will react to a disturbance of the equilibrium in the opposite direction to the disturbance. The reactions are:

$$\text{HPr} \rightleftharpoons \text{Pr}^- + \text{H}^+ \qquad \text{H}_2\text{PO}_4^- \rightleftharpoons \text{HPO}_4^{-2} + \text{H}^+ \qquad [5.2.1]$$

where Pr indicates plasma protein. When the $[H^+]$ increases, the available Pr^- and HPO_4^{-2} binds it and ***buffers*** the change in $[H^+]$; conversely, when H^+ ions are being consumed by some process, Pr and $H_2PO_4^{-1}$ can release more H^+ and ***buffer*** decreases in $[H^+]$. These chemical buffers for $[H^+]$ are the first and most immediate response to changes in plasma $[H^+]$ but they do not actively regulate pH. Instead, both the lungs and kidneys participate in the regulation of body $[H^+]$ (see Chapters 6.5 and 7.7). The **buffer capacity** is defined as Δ **acid/** Δ**pH** and for plasma it is about 7.3 mEq L^{-1} per pH unit.

THE *ONCOTIC PRESSURE* OF PLASMA PROTEINS RETAINS CIRCULATORY VOLUME

The total osmotic pressure of plasma is given by the van't Hoff equation:

$$\pi = RT \sum \phi_S C_S \qquad [5.2.2]$$

where π is the osmotic pressure, R is the gas constant ($= 0.082$ L atm mol^{-1} K^{-1}), T is the temperature (in K), C_s is the molar concentration of species s, and φ_s is the osmotic coefficient of the species s. The contributions of the solutes can be divided into two components: (1) the **crystalloids** and (2) the proteins (**colloids**). Because the crystalloids cross the capillary membranes easily, whereas the plasma proteins do not, the osmotic pressure difference between the interstitial fluid and the plasma is due almost entirely to the plasma proteins alone. Therefore, the osmotic pressure due to the proteins alone is given a separate name, the **colloid osmotic pressure** or the **oncotic** pressure. Because the plasma protein concentration exceeds that in the interstitial fluid, there is a net osmotic pressure favoring fluid movement from the interstitial space to the plasma. This movement is necessary to counteract the pressure-driven filtration of fluid out of the capillaries because of the higher hydrostatic pressure within the capillaries. Thus, reduction in plasma protein concentration is associated with **edema**, or swelling of the tissues (see "Clinical Applications: Edema" in Chapter 5.10).

THE *ERYTHROCYTE* IS THE MOST ABUNDANT CELL IN THE BLOOD

Erythrocytes have a distinctive biconcave disk shape that distinguishes them from all other cells. The cells are about 7–8 μm in diameter and about 2 μm thick at the widest, with a depression in the middle. A micrograph of a blood smear is shown in Figure 5.2.3. A cytoskeleton holds the cell in this shape and allows the cell to deform in order to fit through capillaries that are often smaller than the diameter of the red blood cell. Thus, the cell bends to fit through. A cartoon illustrating the possible cytoskeletal attachments of red blood cells is shown in Figure 5.2.4. Each mm^3 of blood contains some $4.5–5.5 \times 10^6$ of these cells. The main function of erythrocytes is to carry oxygen bound to hemoglobin.

ERYTHROCYTES CONTAIN A LOT OF *HEMOGLOBIN*

Hemoglobin is the protein component of blood that gives it its red color. It is named for its two components: a protein or **globin** component, and a **heme** group that contains iron and is responsible for hemoglobin's ability to bind oxygen. The normal hemoglobin concentration in plasma is 14–17 g% for adult males and 12–16 g% for females. This is g of hemoglobin per deciliter (= 0.1 L) of whole blood.

HEMOGLOBIN CONSISTS OF FOUR POLYPEPTIDE CHAINS, EACH WITH A *HEME* GROUP

Hemoglobin is made up of four polypeptide chains. Two of these are α-globin molecules, each containing

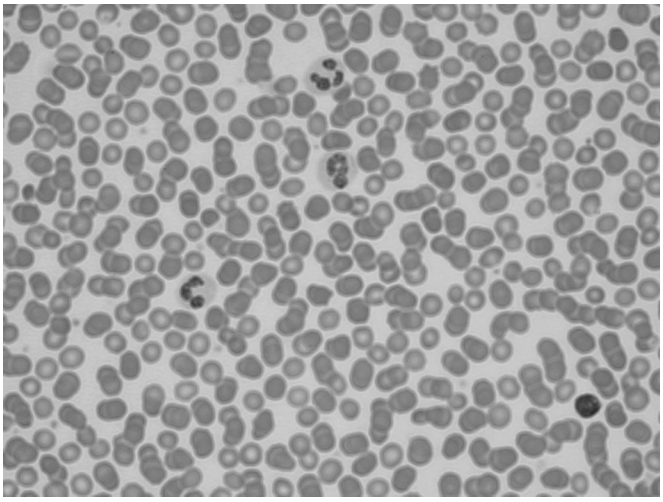

FIGURE 5.2.3 Wright's stain of whole blood. Most of the cells visible in this micrograph are red blood cells, which have no nuclei. White blood cells have nuclei that stain purple with this stain and therefore are easily seen.

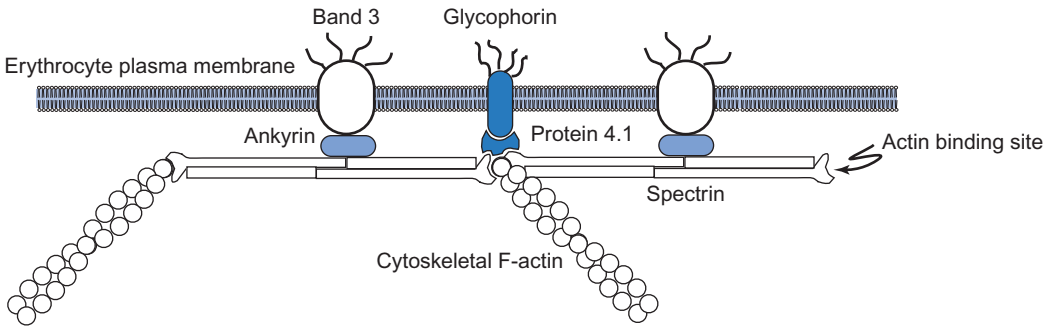

FIGURE 5.2.4 Cytoskeleton of erythrocytes. **Spectrin** consists of four polypeptides, two α and two β chains of 240 and 220 kDa, respectively. The β-chain contains an **actin** binding site at one end, so the assembled tetramer has an actin binding site at each end. The actin–spectrin complex is attached to the membrane through two proteins: **ankyrin** binds to spectrin and to **band 3**, a protein that is inserted in the plasma membrane of the red blood cell. Additional links between the cytoskeleton and the membrane may be provided by other proteins and transmembrane proteins such as **glycophorin**.

141 amino acids, and the other two are globins of another type (β, γ, δ, or ε), each with 146 amino acids. About 98% of adult human hemoglobin is HbA_1, consisting of two α and two β chains, and so it is designated $\alpha_2\beta_2$. Some 2% or so is type HbA_2, with the composition $\alpha_2\delta_2$. The type of hemoglobin changes during embryonic development. Early on during embryogenesis hemoglobin has the composition $\alpha_2\varepsilon_2$, which then switches to the fetal form with the composition $\alpha_2\gamma_2$. These forms are necessary because the fetus must be able to "steal" oxygen from the maternal circulation, and therefore it must bind oxygen more avidly than the maternal hemoglobin. A cartoon of the structure of hemoglobin is shown in Figure 5.2.5.

In addition to its variation during embryogenesis and its heterogeneity in the adult, hemoglobin differs among individuals. The human population makes over 500 different kinds of hemoglobins due to mutations at one or more loci. Most of the changes from the predominant form do not alter hemoglobin's ability to transport oxygen and otherwise do not adversely affect the carrier of the abnormal gene. On the other hand, the abnormal hemoglobin in **sickle cell anemia**, a hereditary disease, arises from a single amino acid substitution (see Clinical Applications Box "Sickle Cell Disease and Malaria").

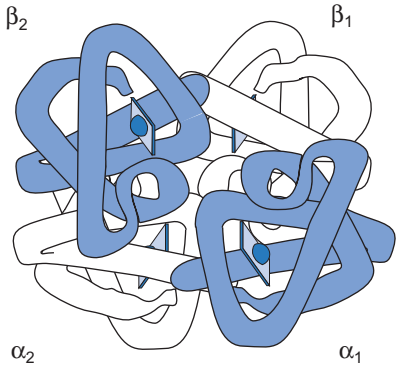

FIGURE 5.2.5 Highly schematic drawing of the structure of hemoglobin. The drawing shows hemoglobin A_1 with the composition $\alpha_2\beta_2$. Each globin protein forms a complex with a heme moiety, which in turn consists of porphyrin complexed with an iron atom. (Source: *Adapted from Dickerson and Geis,* The Structure and Action of Proteins, *Harper and Row, New York, NY, 1969.*)

Each of the four polypeptide chains in hemoglobin contains a heme group that consists of a **porphyrin skeleton** and a central **iron** atom. Its chemical structure is shown in Figure 5.2.6.

EXAMPLE 5.2.1 Mean Cell Volume

The typical hematocrit (Hct) is about 45. If the density of cells is 5×10^6 mm^{-3}, what is the RBC mean cell volume?

As shown in Figure 5.1.4, centrifugation separates plasma from the cellular elements of blood. The red blood cells make up almost all of the cellular elements. Hct is defined as:

$$\text{Hct} = \text{packed cell volume/total blood volume} \times 100$$

The hematocrit can be reported as the **hematocrit ratio**, which is the ratio without multiplying it by 100 to convert it to a percentage. Normal values of Hct are 42–52% for adult males and 37–47% for adult females. **Anemia** occurs when Hct < 25%. If Hct > 75%, the condition is called **polycythemia**, but it can be caused transiently by dehydration.

The mean cell volume is calculated as MCV = Hct ratio/density of cells. For the normal values given above, we calculate

$$\text{MCV} = 0.45/5 \times 10^{12} \text{ cells L}^{-1} = .09 \times 10^{-12} \text{ L cell}^{-1}$$
$$= 90 \times 10^{-15} \text{ L cell}^{-1} = 90 \text{ fL cell}^{-1}$$

The mean cell volume can be used to distinguish among different types of anemias. **Microcytic** and **macrocytic** anemias are those in which erythrocytes are abnormally small or large, respectively.

EXAMPLE 5.2.2 Mean Corpuscular Hemoglobin Concentration

The hematocrit ratio is 0.45 and the hemoglobin concentration is 15 g%. What is the mean corpuscular hemoglobin concentration?

The mean corpuscular hemoglobin concentration is found by dividing the aggregate hemoglobin content of the red blood cells by its aggregate volume. Since both are determined in whole blood, the mean corpuscular hemoglobin concentration can be found by

$$\text{MCHC} = \text{hemoglobin concentration}/\text{hematocrit ratio}$$
$$= 150\ \text{g L}^{-1}/0.45 = 333.3\ \text{g L}^{-1}$$

This can be converted to molarity by dividing by the gram molecular weight of hemoglobin, 64,500 g mol^{-1}:

$$333\ \text{g L}^{-1}/64,500\ \text{g mol}^{-1} = 5.17 \times 10^{-3}\ \text{M}$$

These calculations are useful in describing different kinds of anemias. **Hypochromic** and **normochromic** anemias describe conditions in which the hemoglobin concentration is reduced or normal, respectively.

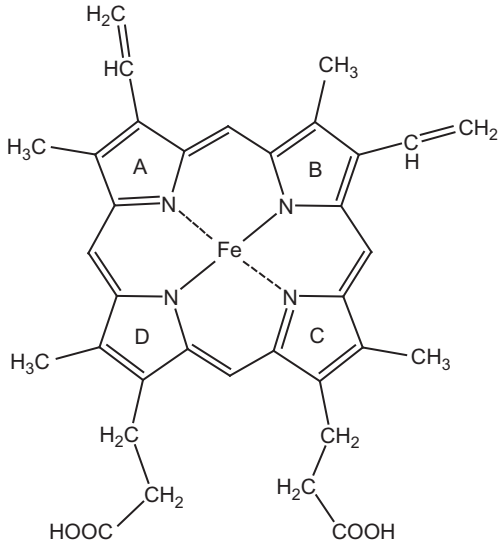

FIGURE 5.2.6 Chemical structure of heme. The porphyrin skeleton consists of the four rings (A–D) and their associated side chains. The Fe atom in the center forms a coordination complex with oxygen. Heme binds oxygen only when iron is in the ferrous (Fe^{2+}) oxidation state: oxidation of Fe to the ferric state (Fe^{3+}) prohibits oxygen binding. Hemoglobin with Fe^{3+} is called **methemoglobin**. Free heme without the protein also does not bind oxygen because some of the coordination bonds of the Fe atom with oxygen are provided by the protein component of hemoglobin.

ERYTHROPOIETIN CONTROLS FORMATION OF ERYTHROCYTES FROM *PLURIPOTENT STEM CELLS* IN BONE MARROW

Erythrocytes and every kind of white blood cell derive from **pluripotent stem cells** that reside in the bone marrow. "Potency" is used by embryologists to define what kinds of cells a precursor cell may become by **differentiation**. A "totipotent" cell, which occurs early during embryogenesis, is capable of becoming any cell in the body. A "pluripotent" cell is already partially differentiated but remains capable of forming a variety of cells. The pluripotent stem cells in the marrow cannot become nerve or muscle cells, but they can give rise to any of the blood cells. Pluripotent stem cells differentiate into **committed stem cells** (those with a set fate) under the influence of **cytokines**. Cytokines are chemical factors released from one cell that affects the growth or activity of another cell. The most important cytokine for **erythropoiesis** (from the Greek "poiesis," meaning "a making") is **erythropoietin**. This glycoprotein hormone is made in the kidney and secreted into the blood in response to **hypoxia**, or low oxygen levels in the tissue. The hypoxia generally results from low oxygen content in the perfusing blood or from low perfusion of the tissue. This system forms a negative feedback loop, in which low oxygen levels stimulate erythropoietin release, which increases erythropoiesis, which in turn raises oxygen delivery to the tissue, which raises oxygen levels, as shown schematically in Figure 5.2.7.

PHAGOCYTES IN THE *RETICULOENDOTHELIAL SYSTEM* DESTROY WORN ERYTHROCYTES

The number of erythrocytes in the circulation results from a balance between their continual synthesis and destruction. Oxidative damage of red blood cell membranes with age makes them increasingly fragile. **Macrophages** in the spleen, liver, and bone marrow consume the worn out red blood cells by engulfing them and then destroying them. These macrophages make up part of the **reticuloendothelial system**, a combination of monocytes, mobile macrophages and fixed tissue macrophages, and a few specialized endothelial cells in the bone marrow, spleen, liver, and lymph nodes. All of these cells are phagocytotic and they form a system for the elimination of foreign materials or worn out body parts. Isotopic experiments show that **the average life span of an erythrocyte is about 126 ± 7 days**.

Macrophages engulf red blood cells and break down all of its components: membrane, cytosolic enzymes, and hemoglobin. The macrophages remove heme from hemoglobin and break the globin part down to its constituent amino acids. The iron is removed from heme and reused to make new heme, and the porphyrin skeleton is broken down first into **biliverdin** and then into **bilirubin**. Bilirubin is sparingly soluble. It is solubilized in the liver by covalently attaching glucuronic acid. The conjugated bilirubin is then excreted into the intestinal tract through

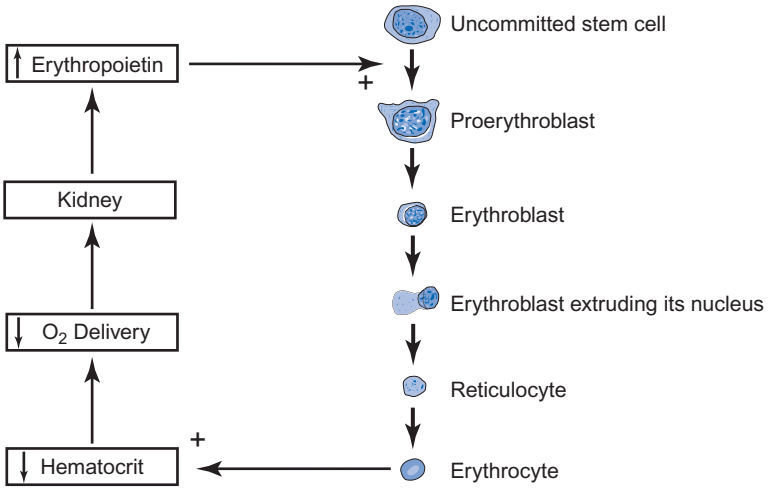

FIGURE 5.2.7 Control of erythropoiesis by erythropoietin. Decreased hematocrit or decreased blood volume will decrease oxygen delivery to the kidney, which decreases oxygen within this tissue, increasing release of erythropoietin, which travels through the blood to the bone marrow where it stimulates differentiation of uncommitted stem cells to begin forming erythrocytes. The formation of erythrocytes takes place in stages, some of which are shown here. Increased formation of erythrocytes completes a negative feedback loop, in which the original signal, a decreased hematocrit or blood volume, is corrected by increased formation of erythrocytes.

the bile (see Chapter 8.4). In the intestine, bacteria deconjugate bilirubin diglucuronide and further convert bilirubin to urobilinogen and stercobilinogen. These are oxidized to **urobilin** and **stercobilin**, respectively, which are excreted in the urine and feces, respectively. These colored materials make significant contributions to the color of urine and feces. **Destruction of 1 g of hemoglobin produces about 35 mg of bilirubin**. Poor liver function leads to a buildup of bilirubin levels in the blood and **jaundice**, the yellow appearance of the skin due to accumulation of bilirubin in the tissues.

IRON RECYCLES INTO NEW HEME

Each day about 20–30 mg of iron is recycled from destroyed red blood cells, which is much more than the daily intake or absorption of iron from the diet. Iron released from hemoglobin is transferred to **transferrin**, a plasma protein of 80 kDa with two iron binding sites per molecule. Its normal plasma concentration is 0.22–0.35 g%, but clinicians monitor its physiological function by measuring the **total iron binding capacity** of serum (**TIBC**), which ranges from 45 to 80 μM (also reported as 250–450 μg dL^{-1}). The serum iron concentration reports the amount of iron that is actually bound to transferrin; its normal values are about 10–30 μM. Thus iron typically occupies some 30% of the available binding sites in serum.

Most cells need iron to form heme groups that are incorporated into proteins of the electron transport chain of mitochondria. Cells import the iron from the blood by binding the Fe–transferrin complex to a **transferrin receptor** located on the cell's plasma membrane. Cells then endocytose the receptor-diferric transferrin complex. The iron is released and incorporated into heme or stored as **ferritin**. Ferritin is the iron complex of a protein, apoferritin, and a ferric hydroxide phosphate. The apoferritin monomer has a molecular weight of about 20 kDa; some 24 monomers associate to form a protein shell with a cavity that holds crystals of FeOOH with some phosphate. Each ferritin complex has the capacity for 4300 iron atoms, but typically they contain about 2000 iron atoms. Figure 5.2.8 shows typical elemental Fe processing per day.

Iron differs from most nutrients in that **there is no excretory pathway for excess iron**. Instead, it accumulates as an insoluble complex of ferritin and iron called **hemosiderin**. The liver can accumulate enough hemosiderin to destroy the organ in a disease called **hemosiderosis**.

HUMAN BLOOD CAN BE CLASSIFIED INTO A SMALL NUMBER OF BLOOD TYPES

The surface of red cell membranes carries two related antigens, called type A and type B. Whether an individual human has these antigens or not depends on their genotype: an individual may have neither of the antigens, or they may have either one, or they may have both. In addition to these antigens, individuals almost always have plasma antibodies that will react with whatever antigen is *not* on their red blood cell membranes. These antibodies are not inherited but develop after birth due to exposure to small quantities of the antigens in the food and air. These antibodies will bind to the antigens and cause the red cells to clump together, or **agglutinate**. Thus, the type A and type B antigens are called **agglutinogens** and the antibodies that react to them are called **agglutinins**. Agglutination occurs because the antibodies have multiple binding sites for the antigens. The IgG class of antibodies has two sites whereas the IgM class has 10 sites per molecule. A single antibody molecule can bind to antigen molecules on two or more different cells, thereby linking them. If this agglutination occurs within the circulatory system, the individual is at great risk of cardiovascular collapse and death.

The blood groups are produced by three alleles at a single location on each of two chromosomes. The three alleles are type O, type A, and type B. These three different alleles allow for six different genotypes, as shown in Table 5.2.2. A single allele of type A or type B is sufficient to express antigen A or B on the surface of the red cell. The blood types, agglutinogens, and agglutinins are also shown in Table 5.2.2.

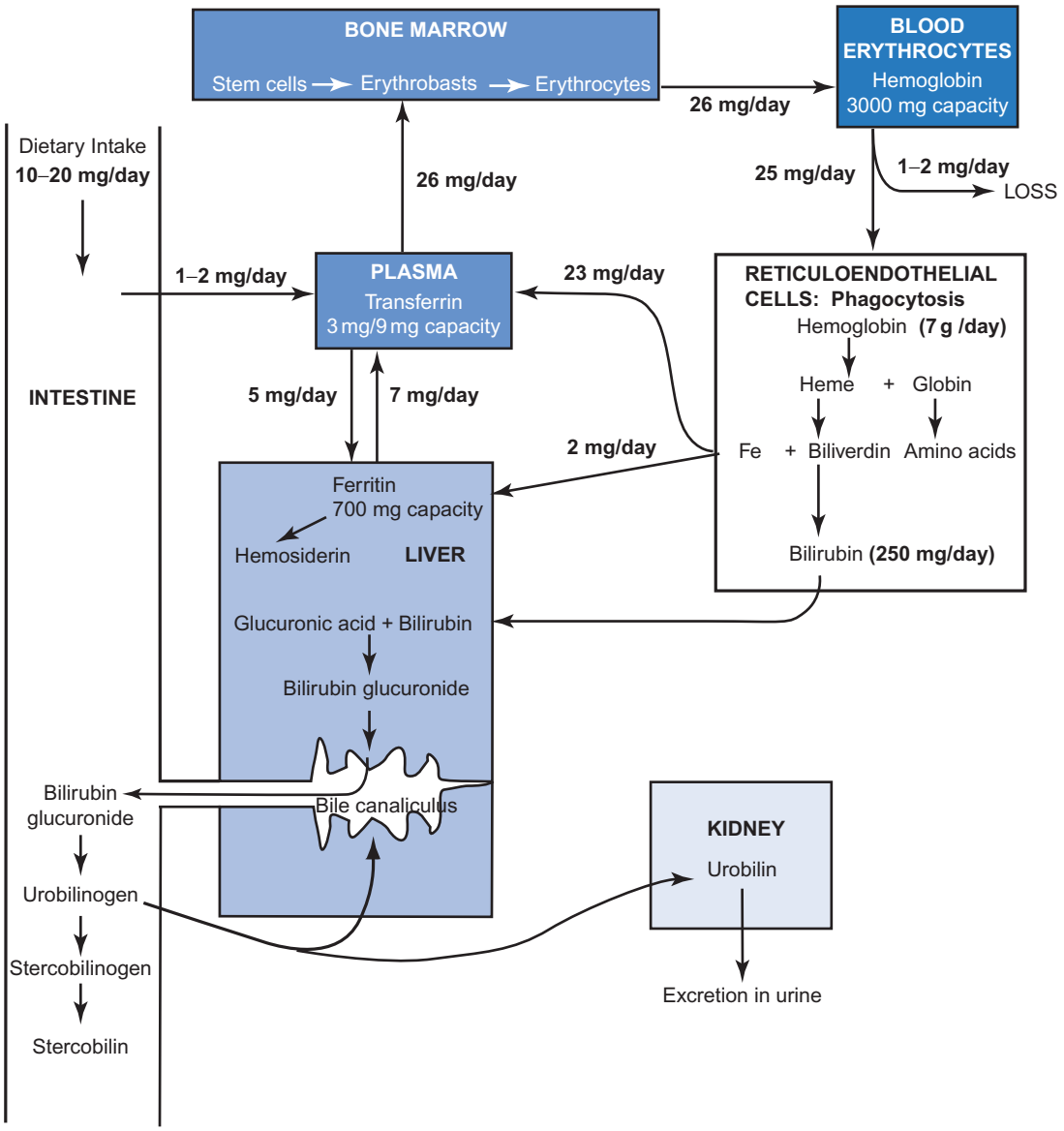

FIGURE 5.2.8 Iron balance and heme degradation pathways. The numbers indicate the amounts of elemental iron that are processed each day. For simplicity, some minor pathways have been omitted. The two numbers in parentheses for hemoglobin breakdown and bilirubin formation refer to the amounts of these materials processed each day.

TABLE 5.2.2 Genotypes, Agglutinogens, and Agglutinins for the Major Blood Groups

Genotypes	Blood Group	Agglutinogens	Agglutinins
OO	O	–	anti-A and anti-B
OA and AA	A	A	anti-B
OB and BB	B	B	anti-A
AB	AB	A and B	–

Cells from a person with Type O blood will not agglutinate when placed in the serum of persons with Type A, Type B, or Type AB blood, because the cells lack the agglutinogen. On the other hand, infusion of Type O blood does not clump the recipient's cells because the agglutinins present in the Type O serum are so diluted that there are insufficient numbers of antibodies to clump the cells. Thus, **Type O blood is a universal donor type**. Persons with Type AB blood do not agglutinate blood originating from Type O, Type A, or Type B blood, because they lack the agglutinins. So people with **Type AB blood are called universal recipients.**

Clinical Applications: Erythroblastosis Fetalis

In addition to the four major blood groups, there are a variety of other factors, including the Rh factor, that influence compatibility of blood. In all cases, blood must be matched to avoid transfusion reactions. The distinction between the Rh factor and the other major blood groups is that agglutinins to the Rh factor do not develop spontaneously as do agglutinins to the Type A or Type B agglutinogens. Instead, people who are Rh− must be exposed directly to Rh+ blood in order to develop the antigens. This occurs when an Rh− mother carries an Rh+ baby. In the first pregnancy, there is usually little contact between the baby's blood and the mother's so that the mother does not develop antibodies to the Rh agglutinogens. During birth, there usually is some contact between placental fetal blood and maternal blood that begins the production of anti-Rh agglutinins in the mother. In the next pregnancy, the anti-Rh agglutinins can penetrate the placenta and cause red cell agglutination in the fetus. The condition is called **erythroblastosis fetalis**, in which the fetal or newborn red cells agglutinate and are subsequently phagocytosed and degraded. The probability of developing the disease increases with each successive pregnancy involving an Rh− mother and Rh+ baby. The baby is at risk due to severe anemia and also due to precipitation of bilirubin in neuronal cells that may result in mental retardation and motor impairment.

SUMMARY

Blood consists of plasma, red blood cells, and white blood cells. The fraction of the blood volume occupied by red blood cells is called the hematocrit ratio, and is typically about 0.37−0.52. It is usually higher for males than females because of the monthly blood loss in the menstrual cycle. The red blood cells are packed with hemoglobin, which binds most of the oxygen that is carried in blood. Hemoglobin consists of four polypeptide chains associated noncovalently. Each chain binds one heme group, which consists of a porphyrin ring and a complexed iron atom. Erythrocytes are made from pluripotent stem cells in the bone marrow in a process called erythropoiesis. Erythropoiesis is stimulated by a hormone, erythropoietin, that is made in the kidney in response to poor oxygenation.

The erythrocyte has a distinctive biconcave disk shape that is maintained by a cytoskeleton. This shape allows it to travel through narrow capillaries. Cells become damaged with age and are degraded by macrophages that comprise the reticuloendothelial system. The average life span of an erythrocyte is about 120 days. The iron in the erythrocyte hemoglobin is recycled, and the porphyrin pigments are degraded and excreted in urine and feces.

Erythrocytes also contain agglutinogen proteins on their surfaces. Persons with type A blood carry the A agglutinogen; persons with type B carry the B agglutinogen; persons with AB contain both; and persons with type O blood carry neither. The plasma contains antibodies directed against the agglutinogens that are not present in the blood. Thus, persons with type O blood have antibodies to both A and B agglutinogens. These agglutinogens form the basis of the blood types.

Plasma contains water and electrolytes, a host of nutrients, and a variety of proteins. The major protein classes include fibrinogen, which is necessary for blood clotting; albumin, which forms a large part of the plasma oncotic pressure and carries many insoluble materials; and the globulins, which are involved in lipid transport and immunological reactions. Plasma is distinct from serum in that serum lacks the clotting proteins.

REVIEW QUESTIONS

1. How do you determine the hematocrit?
2. From the hematocrit and number of red blood cells (obtained by hemacytometry), calculate MCV.
3. What is the oncotic pressure? What protein is mainly responsible for it?
4. What are the three most highly concentrated cations in plasma?
5. What are the three most highly concentrated anions in plasma?
6. What is an antibody? What proteins are antibodies?
7. What protein clots the blood?
8. What controls red blood cell formation? How is it regulated?
9. What major proteins maintain the shape of the erythrocyte?
10. What is hemoglobin? What does it do? Where is it? What is its structure?
11. How long do red blood cells live? Where are they broken down? What happens to the heme?
12. How is Fe from broken heme recycled? What does transferrin do? What does ferritin do? What is hemosiderosis?
13. What causes blood types? What are the major types? Which is the universal donor? Universal recipient?

Clinical Applications: Anemia

Anemia literally means "no blood." It refers to any condition in which the oxygen carrying capacity of blood is diminished due to a reduction in the number or volume of red blood cells, or a reduction in the hemoglobin content of blood. Anemia therefore refers to the concentration of oxygen carrying material and not its total amount in the body. There are a variety of causes of anemia that can broadly be classified according to increased loss of oxygen carrier or decreased production.

(*Continued*)

Clinical Applications: Anemia (Continued)

Increased loss of blood through the stools or internal bleeding can reduce the number of red blood cells per unit volume of blood, while the cells maintain their normal size and hemoglobin content. Such abnormal blood loss can be the result of drugs such as aspirin and other NSAIDs (nonsteroidal anti-inflammatory drugs) that interfere with blood clotting.

Increased destruction of red blood cells can be accelerated when the red cells show an abnormal fragility. Persons with mutations in the red blood cytoskeleton, for example, make spherical red blood cells rather than flattened biconcave disks. These cells rupture more easily when they pass through the circulation and so the lifetime of these cells is shortened. This condition is called **hereditary spherocytosis**. Abnormal hemoglobin, such as occurs in **sickle cell disease**, also shortens the life span of the erythrocytes. Parasitic infections such as malaria rupture red blood cells, thereby increasing the loss of red blood cells.

Decreased ability to form red blood cells can be due to deficiency in the materials needed to make the cells. Thus, insufficient iron leads to an **iron-deficiency anemia** that is characterized by normal numbers of red cells, but with reduced hemoglobin content. These cells are usually smaller than normal (**microcytic**) and they contain less hemoglobin (the cells are **hypochromic**). Formation of red blood cells requires two vitamins: **vitamin B_{12}** (also called cobalamin) and **folic acid**. Both of these are required to make the materials for DNA replication. Proliferation of the stem cells and maturation of the erythrocytes requires DNA production and so deficiencies in these nutrients results in a reduction in the number of red blood cells being produced. Dietary deficiency of vitamin B_{12} is rare. The lack of the vitamin is often associated with a deficiency in the production of **intrinsic factor**, a substance secreted by cells lining the stomach. Intrinsic factor is necessary for the proper absorption of vitamin B_{12} from the ingested food. Lack of intrinsic factor thus translates to a lack of vitamin B_{12}. This condition is called **pernicious anemia**. In addition to anemia, there are central nervous consequences of vitamin B_{12} deficiency that are independent of the anemia.

Aplastic anemia refers to the situation in which the bone marrow fails to produce adequate numbers of red blood cells. Radiation, chemotherapy, or exposure to toxic chemicals can interfere with the erythropoietic capability of the marrow. Failure to produce enough red blood cells can also result from insufficient circulating levels of erythropoietin. This can occur in renal anemia, in which the kidneys no longer produce sufficient erythropoietin.

Clinical Applications: Sickle Cell Disease and Malaria

Sickle cell disease results from a single amino acid substitution in which the amino acid valine replaces glutamic acid at position 6 in the β-chain of hemoglobin. This changes the physical characteristics of hemoglobin so that it polymerizes when it becomes deoxygenated. The polymerized hemoglobin deforms the red blood cells, causing them to resemble a sickle shape, or a crescent moon. The misshapened cells do not bend easily when they pass through the narrow capillaries, causing poor circulation and reducing the life span of the cells. Because erythrocytes are more easily destroyed, sickle cell anemia results.

Darwin's theory of evolution predicts that maladaptive mutations such as sickle cell anemia should be removed from the population because such traits reduce the ability to produce offspring to carry the trait forward. So why does such an inherited disorder persist in the population? The short answer is that although sickle cell disease produces a potentially debilitating anemia, it also provides protection against malarial infections.

Malaria literally means "mala aria" or "bad air." This name reflects the early idea that malaria was spread by bad air. The Italian scientist Giovanni Batista Grassi established in 1898 that this disease results from the parasitic infection of a protozoan of the genus *Plasmodium*, which is transmitted to people through the bite of a mosquito. The life cycle of *Plasmodium falciparum* has three distinct stages. The sporogenic phase occurs in the *Anopheles* mosquito, in which the protozoan migrates to the salivary gland and forms sporozoites. The female Anopheles mosquito injects the sporozoites into the human host when she obtains her blood meal. The second stage occurs in the liver of the human host. The sporozoites penetrate liver cells, reproducing into hundreds of merozoites which are released when the liver cell ruptures. The third stage occurs in the blood when the merozoites penetrate red blood cells to produce hundreds of microgametocytes. About 3 days after initial penetration by the merozoite, the red blood cells rupture to release microgametocytes and more merozoites. These can reinfect other red blood cells or be taken up when another mosquito bites the infected person. The rupture of the red blood cells is accompanied by fever, from which malaria derives its second name, "swamp fever." The disease is characterized by recurrent fevers corresponding to the cycle of microgametocyte and merozoite formation and rupture of red cells.

Malaria for some reasons speeds the sickling process, so that infected red blood cells are rapidly deformed and then destroyed by the spleen rather than producing more merozoites. Thus the infection is curtailed. People who are heterozygous for the sickle trait are partly protected from malaria while the sickle cell anemia is also mild. People who are homozygous for the sickle trait may suffer from sickle cell anemia of variable severity. Because of its advantage against malaria, the sickle cell trait has reached a kind of equilibrium in populations indigenous to areas of natural malaria infestation. In areas of malaria absence, however, the sickle cell trait confers a selective disadvantage.

Malaria most likely originated in Africa and spread to the New World by European slave traders. In the early 1600s, Jesuit missionaries in South America learned that extracts of the bark of the Cinchona tree could cure malaria. Its active ingredient is a toxic plant alkaloid called **quinine**. Quinine has now been synthesized and the synthetic analogue is called mefloquine. Other drugs include chloroquine, a synthetic drug, and Qinghaosu, derived from the sweet wormwood plant in China. There are a variety of types of malaria owing to different species of *Plasmodium* and their sensitivities to these drugs, and their ability to infect man and various animals also varies.