Chapter 31

Blood as a Circulatory Fluid & the Dynamics of Blood & Lymph Flow

Introduction

The circulatory system supplies inspired O2 as well as substances absorbed from the gastrointestinal tract to the tissues, returns CO2 to the lungs and other products of metabolism to the kidneys, functions in the regulation of body temperature, and distributes hormones and other agents that regulate cell function. The blood, the carrier of these substances, is pumped through a closed system of blood vessels by the heart. The blood flow to each tissue is regulated by local chemical and general neural and humoral mechanisms that dilate or constrict its vessels. Blood is a specialized type of connective tissue, red in color, syrupy fluid which has specific gravity 1.055 and the viscosity 2.5 times that of water. Blood is alkaline (PH=7.4) and appear scarlet red when taken from arteries and purplish from veins. The difference in color is due to its O_2 content . Blood consists of a protein-rich fluid known as plasma, in which are suspended cellular elements: white blood cells, red blood cells, and platelets. The normal total circulating blood volume is about 8% of the body weight (5600 mL in a 70-kg man). About 55% of this volume is plasma. Blood plays a role in maintaining the cellular environment by serving as a transport medium of the body. The various functions of blood result from specialization within the cellular elements or the plasma or the interaction between the two .

BLOOD AS A CIRCULATORY FLUID

Blood consists of a protein-rich fluid known as plasma, in which are suspended cellular elements: white blood cells, red blood cells, and platelets. The normal total

circulating blood volume is about 8% of the body weight (5600 mL in a 70-kg man). About 55% of this volume is plasma.

BONE MARROW

In the adult, red blood cells, many white blood cells, and platelets are formed in the bone marrow. In the fetus, blood cells are also formed in the liver and spleen, and in adults such extramedullary hematopoiesis may occur in diseases in which the bone marrow becomes destroyed or fibrosed. In children, blood cells are actively produced in the marrow cavities of all the bones. By age 20, the marrow in the cavities of the long bones, except for the upper humerus and femur, has become inactive. Active cellular marrow is called red marrow; inactive marrow that is infiltrated with fat is called yellow marrow. The bone marrow is actually one of the largest organs in the body, approaching the size and weight of the liver. It is also one of the most active. Normally, 75% of the cells in the marrow belong to the white blood cell–producing myeloid series and only 25% are maturing red cells, even though there are over 500 times as many red cells in the circulation as there are white cells. This difference in the marrow reflects the fact that the average life span of white cells is short, whereas that of red cells is long.

Hematopoietic stem cells (HSCs) are bone marrow cells that are capable of producing all types of blood cells. They differentiate into one or another type of committed stem cells (progenitor cells). These in turn form the various differentiated types of blood cells. There are separate pools of progenitor cells for megakaryocytes, lymphocytes, erythrocytes, eosinophils, and basophils; neutrophils and monocytes arise from a common precursor. The bone marrow stem cells are also the source of osteoclasts, Kupffer cells mast cells, dendritic cells, and Langerhans cells. The HSCs are few in number but are capable of completely replacing the bone marrow when injected into a patient whose own bone marrow has been entirely destroyed.

WHITE BLOOD CELLS

Normally, human blood contains 4000–11,000 white blood cells per microliter (Table 31–1).

TABLE 31–1 Normal values for the cellular elements in human blood.

Cell	Cells/μL (average)	Approximate Normal Range	Percentage of Total White Cells
Total white blood cells	9000	4000–11,000	…
Granulocytes			
Neutrophils	5400	3000–6000	50–70
Eosinophils	275	150–300	1–4
Basophils	35	0–100	0.4
Lymphocytes	2750	1500–4000	20–40
Monocytes	540	300–600	2–8
Erythrocytes			
Females	4.8×10^6	…	…
Males	5.4×10^6	…	…
Platelets	300,000	200,000–500,000	…

Of these, the granulocytes (polymorphonuclear leukocytes, PMNs) are the most numerous. Young granulocytes have horseshoe-shaped nuclei that become multilobed as the cells grow older (Figure 31–3). Most of them contain neutrophilic granules (neutrophils), but a few contain granules that stain with acidic dyes (eosinophils), and some have basophilic granules (basophils)

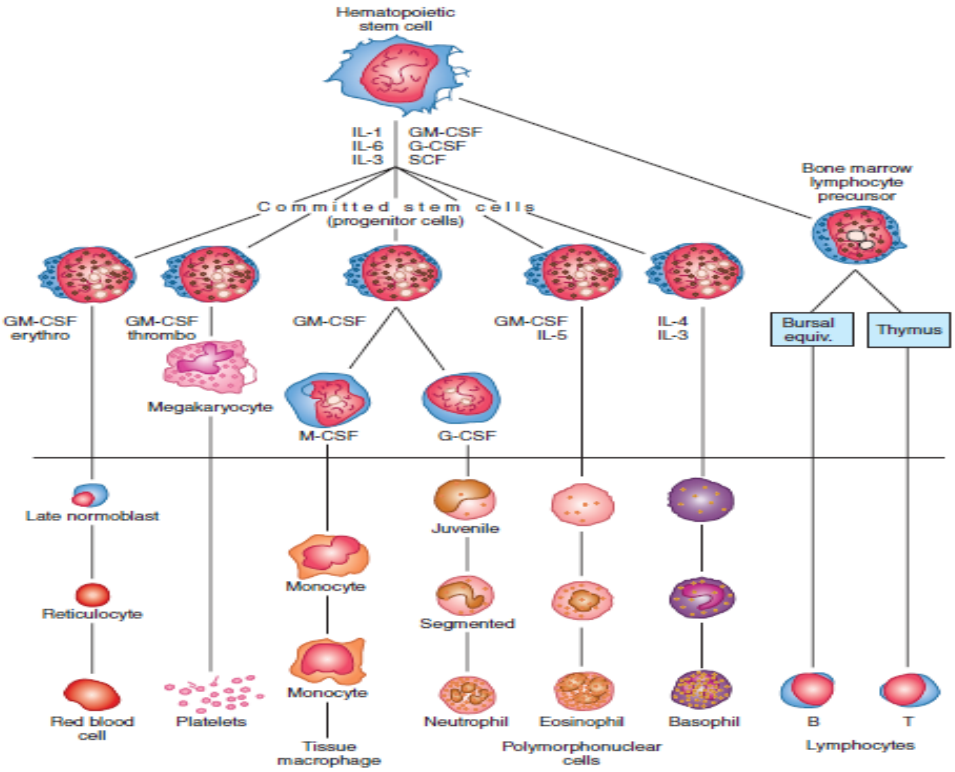

FIGURE 31–3 Development of various formed elements of the blood from bone marrow cells. Cells below the horizontal line are found in normal peripheral blood. The principal sites of action of erythropoietin (erythro) and the various colony-stimulating factors (CSF) that stimulate the differentiation of the components are indicated. G, granulocyte; M, macrophage; IL, interleukin; thrombo, thrombopoietin; erythro, erythropoietin; SCF, stem cell factor.

The other two cell types found normally in peripheral blood are lymphocytes, which have large round nuclei and scanty cytoplasm, and monocytes, which have abundant agranular cytoplasm and kidney-shaped nuclei (Figure 31–3). Acting together, these cells provide the body with the powerful defenses against tumors and viral, bacterial, and parasitic infections .

PLATELETS

Platelets are small, granulated bodies that aggregate at sites of vascular injury. They lack nuclei and are 2–4 μm in diameter). There are about 300,000/μL of circulating blood, and they normally have a half-life of about 4 days. The megakaryocytes, giant cells in the bone marrow, form platelets by pinching off bits of cytoplasm and extruding them into the circulation. Between 60% and 75% of the platelets that have been extruded from the bone marrow are in the circulating blood, and the remainder

are mostly in the spleen. Splenectomy causes an increase in the platelet count (thrombocytosis).

RED BLOOD CELLS

The red blood cells (erythrocytes) carry hemoglobin in the circulation. They are biconcave disks that are manufactured in the bone marrow. In mammals, they lose their nuclei before entering the circulation. In humans, they survive in the circulation for an average of 120 days. The average normal red blood cell count is 5.4 million/μL in men and 4.8 million/μL in women. The number of red cells is also conveniently expressed as the hematocrit, or the percentage of the blood, by volume, that is occupied by erythrocytes. Each human red blood cell is about 7.5 μm in diameter and 2 μm thick, and each contains approximately 29 pg of hemoglobin (Table 31-2).

TABLE 31–2 Characteristics of human red cells.[a]

		Male	Female
Hematocrit (Hct) (%)		47	42
Red blood cells (RBC) (10^6/μL)		5.4	4.8
Hemoglobin (Hb) (g/dL)		16	14
Mean corpuscular volume (MCV) (fL)	$= \frac{\text{Hct} \times 10}{\text{RBC } (10^6/\mu\text{L})}$	87	87
Mean corpuscular hemoglobin (MCH) (pg)	$= \frac{\text{Hb} \times 10}{\text{RBC } (10^6/\mu\text{L})}$	29	29
Mean corpuscular hemoglobin concentration (MCHC) (g/dL)	$= \frac{\text{Hb} \times 100}{\text{Hct}}$	34	34
Mean cell diameter (MCD) (μm)	= Mean diameter of 500 cells in smear	7.5	7.5

[a]Cells with MCVs > 95 fL are called macrocytes; cells with MCVs < 80 fL are called microcytes; cells with MCHCs < 25 g/dL are called hypochromic.

There are thus about 3×10^{13} red blood cells and about 900 g of hemoglobin in the circulating blood of an adult man (Figure 31–5). The feedback control of erythropoiesis by erythropoietin hormone released by renal tissue in presence of low O_2 content in blood .

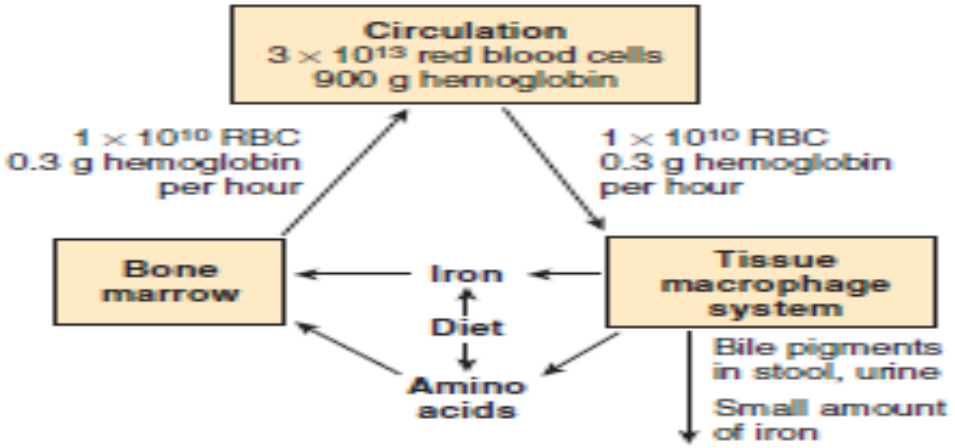

FIGURE 31–5 Red cell formation and destruction. RBC, red blood cells.

HEMOGLOBIN

The red, oxygen-carrying pigment in the red blood cells of vertebrates is hemoglobin, a protein with a molecular weight of 64,450. Hemoglobin is a globular molecule made up of four subunits (Figure 31–6).

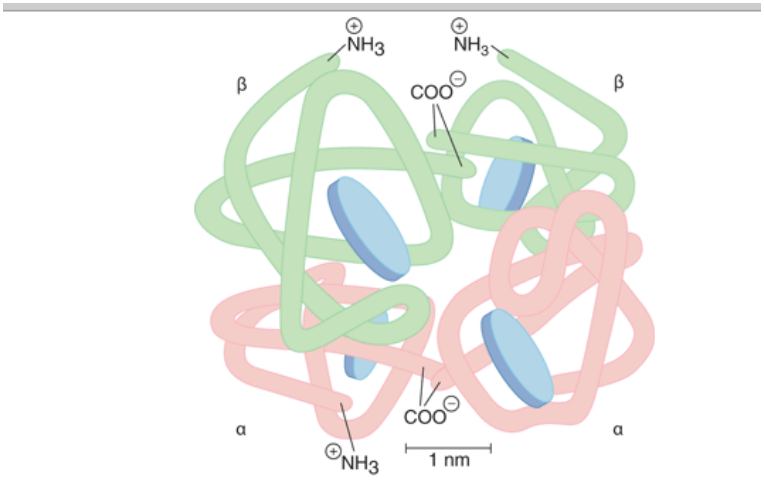

Figure (31-6) Diagrammatic representation of a molecule of hemoglobin A, showing the four subunits.

Each subunit contains a heme moiety conjugated to a polypeptide. Heme is an iron-containing porphyrin derivative. The polypeptides are referred to collectively as the

globin portion of the hemoglobin molecule. There are two pairs of polypeptides in each hemoglobin molecule. In normal adult human hemoglobin (hemoglobin A), the two polypeptides are called α chains and β chains. Thus, hemoglobin A is designated α2β2. Not all the hemoglobin in the blood of normal adults is hemoglobin A. About 2.5% of the hemoglobin is hemoglobin A2, in which β chains are replaced by δ chains (α2δ2). The δ chains contain 10 individual amino acid residues that differ from those in β chains. There are small amounts of hemoglobin A derivatives closely associated with hemoglobin A that represent glycated hemoglobins. HbA_{1a} , HbA_{1b} , HbA_{1c} one of these, hemoglobin A1c (HbA1c), has a glucose attached to the terminal valine in each β chain and is of special interest because it increases in the blood of patients with poorly controlled diabetes mellitus and is measured clinically as a marker of the progression of that disease and/or the effectiveness of treatment.

REACTIONS OF HEMOGLOBIN

O2 binds to the Fe2+ in the heme moiety of hemoglobin to form oxyhemoglobin. The affinity of hemoglobin for O2 is affected by pH, temperature, and the concentration in the red cells of 2,3-bisphosphoglycerate (2,3-BPG). 2,3-BPG λ arise in temperature or fall in PH or an increase in the concentration of 2,3-BPG lower the affinity of hemoglobin for O_2 causing more O_2 to be liberated and H+ compete with O2 for binding to deoxygenated hemoglobin, decreasing the affinity of hemoglobin for O2 by shifting the positions of the four peptide chains (quaternary structure). When blood is exposed to various drugs and other oxidizing agents in vitro or in vivo, the ferrous iron ($Fe^{2+)}$ that is normally present in hemoglobin is converted to ferric iron (Fe^{3+}), forming methemoglobin. Methemoglobin is dark-colored, and when it is present in large quantities in the circulation, it causes a dusky discoloration of the skin resembling cyanosis. Some oxidation of hemoglobin to methemoglobin occurs normally, but an enzyme system in the red cells, the dihydronicotinamide

adenine dinucleotide (NADH)-methemoglobin reductase system, converts methemoglobin back to hemoglobin. Carbon monoxide reacts with hemoglobin to form carbon monoxyhemoglobin (carboxyhemoglobin). The affinity of hemoglobin for O2 is much lower than its affinity for carbon monoxide, which consequently displaces O2 on hemoglobin, reducing the oxygen-carrying capacity of blood .

SYNTHESIS OF HEMOGLOBIN

The average normal hemoglobin content of blood is 16 g/dL in men and 14 g/dL in women, all of it in red cells. In the body of a 70-kg man, there are about 900 g of hemoglobin, and 0.3 g of hemoglobin is destroyed and 0.3 g synthesized every hour (Figure 31–5). The heme portion of the hemoglobin molecule is synthesized from glycine and succinyl-CoA **(Clinical Box 31–2)**

Clinical box 31–2 : Abnormalities of Hemoglobin Production There are two major types of inherited disorders of hemoglobin in humans: the hemoglobinopathies, in which abnormal globin polypeptide chains are produced, and the thalassemias and related disorders, in which the chains are normal in structure but produced in decreased amounts or absent because of defects in the regulatory portion of the globin genes.. In one of the most common examples, hemoglobin S, the α chains are normal but the β chains have a single substitution of a valine residue for one glutamic acid, leading to sickle cell anemia . The cell assume a sickle shape , easily ruptured and the Hb – s loss its ability to carry O_2 he rigid shape of the sickle cell inhibit their movement through the capillaries so they stick forming a pile behind the stuck cells that inhibit O_2 supply to the tissue .

CATABOLISM OF HEMOGLOBIN

When old red blood cells are destroyed by tissue macrophages, the globin portion of the hemoglobin molecule is split off, and the heme is converted to biliverdin. In