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

CHAPTER 31

OBJECTIVES

After studying this chapter, you should be able to:

- Describe the components of blood and lymph, their origins, and the role of hemoglobin in transporting oxygen in red blood cells.
- Understand the molecular basis of blood groups and the reasons for transfusion reactions.
- Delineate the process of hemostasis that restricts blood loss when vessels are damaged, and the adverse consequences of intravascular thrombosis.
- Identify the types of blood and lymphatic vessels that make up the circulatory system and the regulation and function of their primary constituent cell types.
- Describe how physical principles dictate the flow of blood and lymph around the body.
- Understand the basis of methods used to measure blood flow and blood pressure in various vascular segments.
- Understand the basis of disease states where components of the blood and vasculature are abnormal, dysregulated, or both.

Physiology

2nd stage

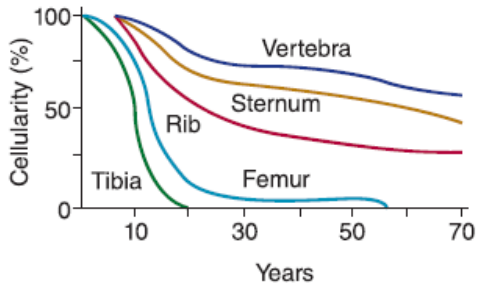
Reference: Ganong's review of medical physiology 25th edition 2015

Chapter 31 blood as a circulatory fluid and dynamic of blood and lymph flow	• blood as circulatory fluids ✓ • bone marrow ✓ • white blood cells ✓ • platelets ✓ • red blood cells ✓ • blood types • plasma • hemostasis • lymph • structural feature of circulation

Blood = **Plasma** (55%) + **cellular elements** (45%)
Plasma = proteins + minerals + water
Cellular elements = RBCs, WBCs & Platelets
Normal blood volume = 8% of body weight
= 5.6L (in 70kg man)
70 x 8/100 = 5.6L

Plasma = 5.6L x 0.55= 3.08L
Cellular elements = 5.6L x 0.45 = 2.52L

Age	Organ	Bone
Fetal life	BM, liver, Spleen	
Childhood (until 5Y)	Red BM	All bones
Adolescence (healthy) 5-20Y	Red BM	Femur; Humerus. Other long bones BM become inactive (yellow marrow)
Adulthood		Vertebrae; Ribs; ilium, sternum
Adult (destroyed or fibrosed BM)	Liver, Spleen	



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 (Figure 31–2). 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

BM is large organ and most active
BM size ~ liver size
BM weight ~ liver weight

BM stem cells = 75% WBCs myeloid + 25% maturing RBCs
RBCs 5 M = WBCs 10000
Blood RBCs number > 500times Blood WBCs number (5M/10000 = 500)
Life span of RBCs = 120days
Life span of WBCs = hours

BM stem cells (HSCs) – undifferentiated HSCs → committed into a type progenitor
Progenitor → differentiated into specific blood cell

Progenitor	Blood cell
Erythrocyte	RBCs
Megakaryocyte	Platelets
Lymphoid	T and B lymphocytes
Granulocyte	Eosinophils, Basophils,
Granulocyte-Monocyte	Neutrophils, Monocytes

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 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 (see Chapter 21), Kupffer cells (see Chapter 28), 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.

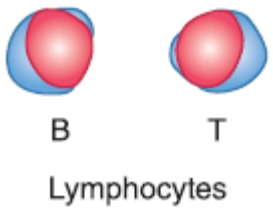
BM transplant

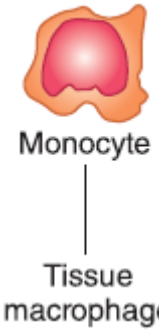
Monocytes → tissue macrophages (Kupffer cells, osteoclasts, mast cells, dendritic cells, Langerhans cells)

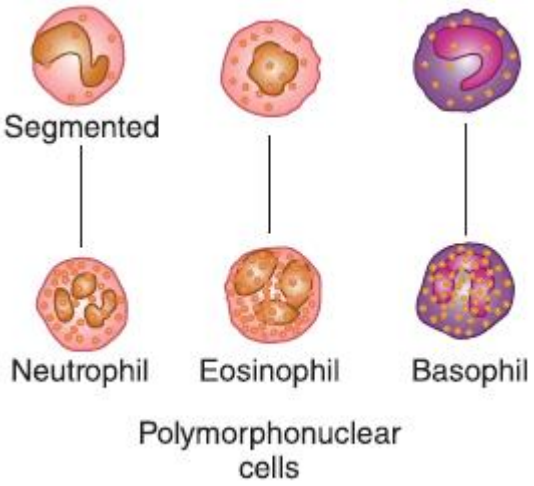
WHITE BLOOD CELLS

Cell	Cells/μL (average)	Approximate Normal Range	Percentage of Total White Cells
Total white blood cells	9000	4000–11,000	…
Granulocytes	5710		
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	…

Normally, human blood contains 4000–11,000 white blood cells per microliter (Table 31–1). 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)**. 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 that were discussed in Chapter 3.

Function: role in blood coagulation
Count: 300,000/uL (circulate in blood)
Life-span: 4days

Megakaryocytes → **fragmented** (cytoplasm pinching off) into platelets

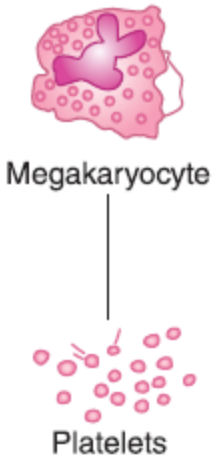
BM platelets:

- 60-70% in blood
- 30-40% in spleen

Why splenectomy increases platelet count?

PLATELETS

Platelets are small, granulated bodies that aggregate at sites of vascular injury. They lack nuclei and are 2–4 μm in diameter (Figure 31–3). 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).**



RBCs = Erythrocytes
Carry **Hb** in circulation
(note: Hb is very small molecule that can filtered through capillaries)
Shape: biconcave disks
Manufactured: in red MB
Nucleus:
Immature RBCs have nucleus (in BM)
Mature RBCs lose nucleus (in blood)
Life-span: 120days
Normal **Count**:
5.4 M/uL in Man
4.8 M/uL in woman
Hematocrit = volume of blood occupied by RBCs
Diameter: 7.5um
Thickness: 2um
Hb content: 29pg/RBC
Total Hb: 900g in blood
Kidney release erythropoietin (ErP)
ErP stimulate BM stem cells differentiation into erythrocytes

RED BLOOD CELLS

The red blood cells (**erythrocytes**) carry hemoglobin in the circulation. They are biconcave disks (Figure 31–4) 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). 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).

1L = 1000,000 uL

Blood 5.6L = 5,600,000 uL ; RBCs = 5,400,000 cell/ uL
Total RBCs = 5,400,000 cell/ uL x 5,600,000 uL
$= 3.02 \times 10^{13}$ cells

1g = 10^{12} pg

Total Hb = 29pg x 3.02×10^{13} = 8.77×10^{14}pg
= $8.77 \times 10^{14} \times 10^{-12} = 8.77 \times 10^{2}$ = 877g

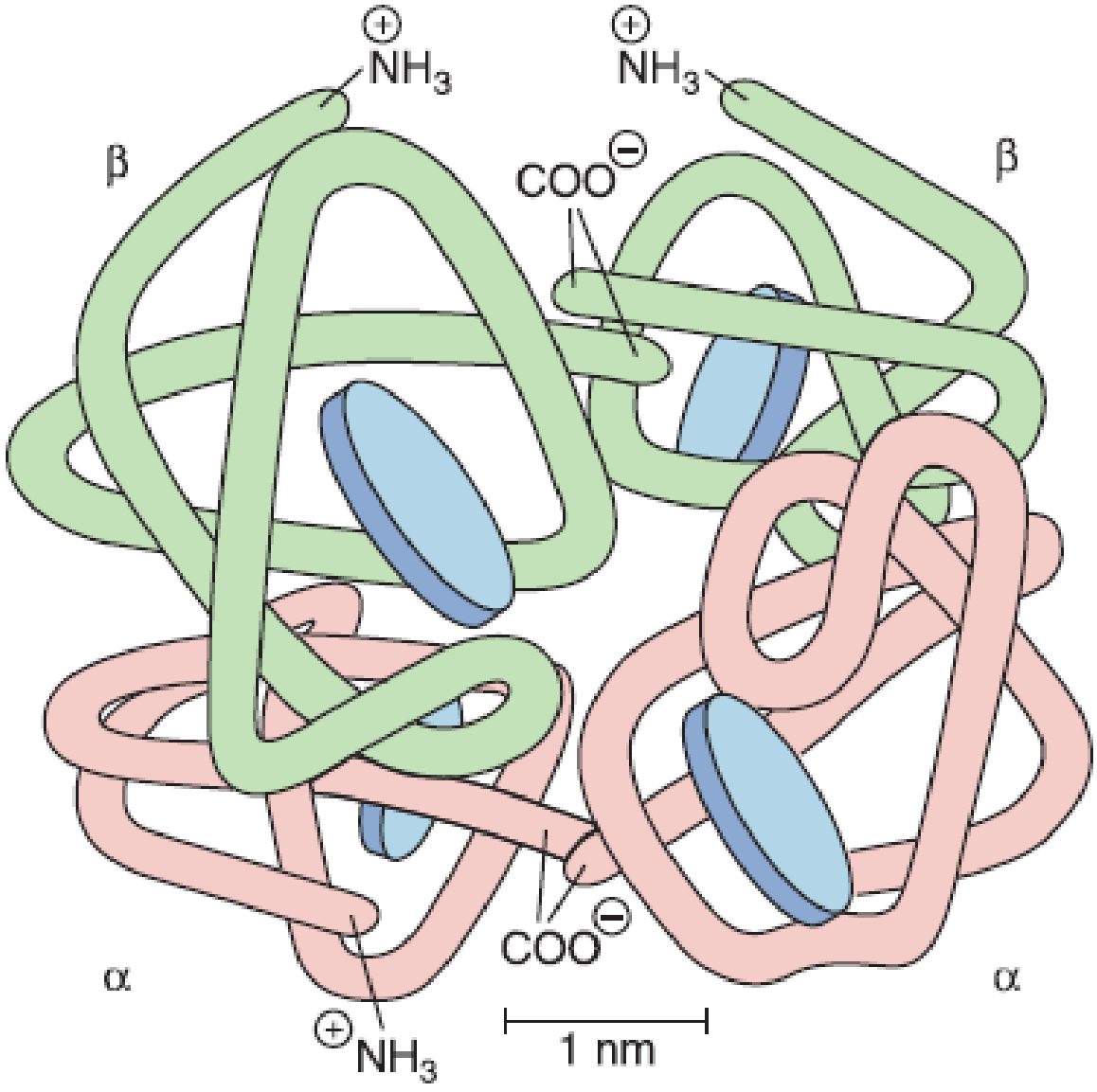
Color: Red pigment
Function: carry O2
Mwt: 6445D (very small)
Structure: 4 subunits
each subunit = heme + a polypeptide
heme = **iron** (Fe^{+2}) + **porphyrin** derivative
Polypeptide= alpha(α), beta(β), gamma(γ) or delta(δ) **globulin**
Adult Hb is 97.5% of type **A** ($\alpha_2\ \beta_2$). The 2.5% is of type A2 ($\alpha_2\ \delta_2$).
δ chain have 10 amino acids differ from that in β chain

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). Each subunit contains a **heme** moiety conjugated to a polypeptide. Heme is an iron-containing porphyrin derivative (Figure 31–7). 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 $\alpha_2\beta_2$. Not all the hemoglobin in the blood of normal adults is hemoglobin A. About 2.5% of the hemoglobin is hemoglobin A_2, in which β chains are replaced by δ chains ($\alpha_2\delta_2$). The δ chains contain 10 individual amino acid residues that differ from those in β chains.

HbA1c - **Glycated Hb**
Glucose attached to terminal valine in β chain. Increase in **poorly controlled DM** (marker of disease progression and/or effective treatment)

There are small amounts of hemoglobin A derivatives closely associated with hemoglobin A that represent glycated hemoglobins. One of these, hemoglobin A_{1c} (HbA_{1c}), 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 (see Chapter 24), and is measured clinically as a marker of the progression of that disease and/or the effectiveness of treatment.


⊕ NH3
⊕ NH3
β
β
COO⊖
COO⊖
α
α
⊕ NH3
1 nm

Oxyhemoglobin = Hb bind O2
Hb affinty to O2 depends on

- **pH (H+ conc.)**
- **Temp.**
- **RBC conc. of DPG "also called BPG"**

H+ & DPG compete with O2 for binding to deoxy Hb

Nitrites "in blood" oxidize Fe^{+2} in Hb into Fe^{+3} → Methemoglobin (metHb)
Methemoglobin:

- **Oxidized form of Hb**
- **Dark-color: When become in excess → dusky skin "cyanosis"**
- **Occurs normally in small percent**
- **Normally NADH-metHb reductase system converts metHb to Hb**
- **Congenital absence of this system → hereditary methemoglobinemia**

Carboxyhemoglobin = Hb binds CO
Hb affinity to O2 << affinity to CO
CO displaces O2 from Hb
CO reduce O2 carrying capacity of blood

REACTIONS OF HEMOGLOBIN

O_2 binds to the Fe^{2+} in the heme moiety of hemoglobin to form **oxyhemoglobin.** The affinity of hemoglobin for O_2 is affected by pH, temperature, and the concentration in the red cells of 2,3-bisphosphoglycerate (2,3-BPG). 2,3-BPG and H^+ compete with O_2 for binding to deoxygenated hemoglobin, decreasing the affinity of hemoglobin for O_2 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 (see Chapter 35). 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. Congenital absence of this system is one cause of hereditary methemoglobinemia.

Carbon monoxide reacts with hemoglobin to form **carbon monoxyhemoglobin (carboxyhemoglobin).** The affinity of hemoglobin for O_2 is much lower than its affinity for carbon monoxide, which consequently displaces O_2 on hemoglobin, reducing the oxygen-carrying capacity of blood (see Chapter 35).

Normal Hb in blood:

- 16g/dL (16g/100ml) in men
- 14g/dL (14g/100ml) in women

In 70kg man; Total blood Hb = 900g and in every hour there is:

- 0.3g Hb destroyed
- 0.3g Hb synthesized

- Heme is synthesized in early stages from glycine and succinyl CoA in mitochondria

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).

Hemoglobinopathies (abnormal globin polypeptide)

- **HbS** : normal α chain but glutamic acid in β chain is replaced by valine → sickle cell anemia
- HbS polymerized at low O_2 tensions → sickle-shaped RBC that **hemolyzed** and form aggregates that block blood vessels
- **Inherent disease** - More prevalent in Africa
- **Treatment**:
  - Hydroxyurea that stimulate production of Hb
  - BM transplantation
  - Antibiotics

Thalassemias – normal polypeptide chains but either produced in decreased amount or absent

- Thalassemia **major** (β thalassemia): gene for β chain is missing
- Thalassemia **minor** (α thalassemia): gene for α chain is missing
- Thalassemias cause **sever anemia**
- Treatment:
  - Repeated blood transfusion with such treatment there is a risk of iron overload that require iron chelating drugs
  - BM transplant

- Old RBCs destroyed by **macrophages** in **spleen**
- The **globin** portion split off → **amino acid** → refresh blood amino acid pool
- **Heme** is converted to **biliverdin + CO** by heme oxygenase (CO act as intracellular messenger)
- Most of biliverdin is converted into **bilirubin** and excreted in bile
- The liver **conjugate** bilirubin with glucuronic acid before excretion into bile
- Heme **iron** is bind to transferrin and transported to liver for **storing** and BM for **reuse** in Hb synthesis

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.** The enzyme involved is a subtype of heme oxygenase (see Figure 28–4), and CO is formed in the process. CO is an intercellular messenger, like NO (see Chapters 2 and 3). In humans, most of the biliverdin is converted to **bilirubin** and excreted in the bile (see Chapter 28). The iron from the heme is reused for hemoglobin synthesis.

Exposure of the skin to white light converts bilirubin to lumirubin, which has a shorter half-life than bilirubin. **Phototherapy** (exposure to light) is of value in treating infants with jaundice due to hemolysis.

Iron is essential for hemoglobin synthesis; if blood is lost from the body and the iron deficiency is not corrected, **iron deficiency anemia** results.