BLOOD TRANSFUSION

A CONCEPTUAL APPROACH

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Preface

The transfusion of blood products is an important part of health care practice; however, the principles of transfusion medicine are often less well understood than other aspects of patient care. This book attempts to simplify blood banking practice and to introduce some of the underlying concepts, using illustrations. It is designed to help medical and nursing students, laboratory technologists, physicians and nurses in understanding the principles of transfusion medicine.

This is not meant to be a laboratory manual, and does not provide details of the technological procedures.

"Blood transfusion - A Conceptual Approach" is a companion volume to "Hemostasis and Thrombosis - A Conceptual Approach" by Jack Hirsh and "Fluids and Electrolytes - A Conceptual Approach" by Kinsey Smith. All have been produced in the Faculty of Health Sciences, McMaster University, where they are used in the various undergraduate and postgraduate programs.

October 1983

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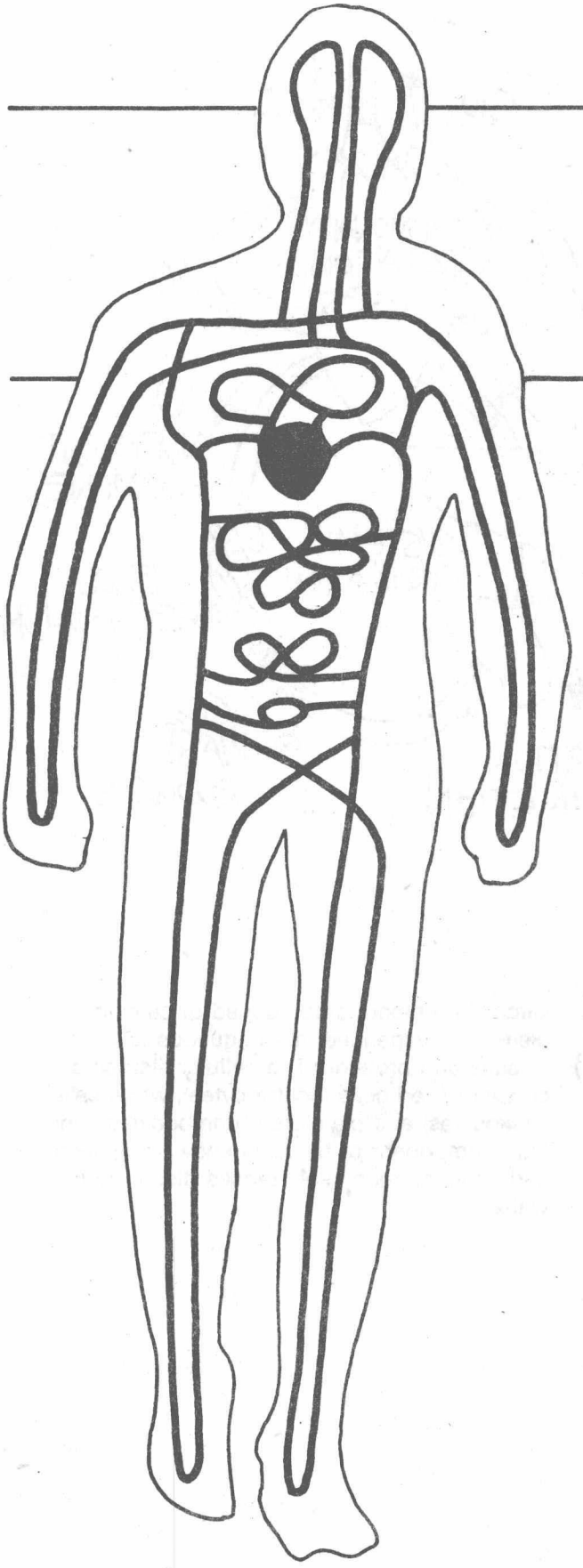


Chapter 1

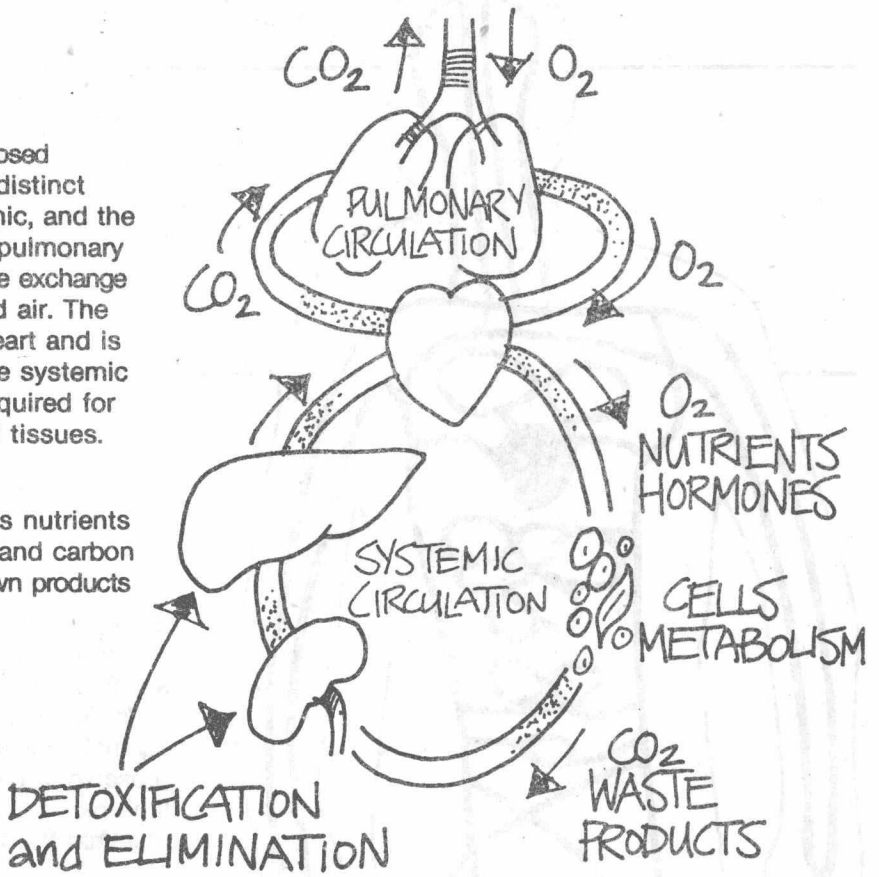
Constituents of Blood

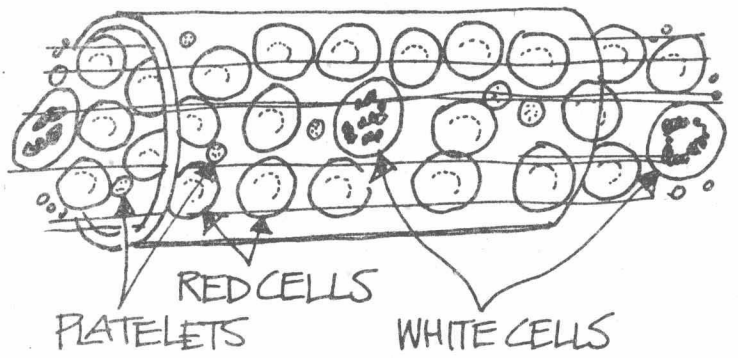
The Function of Blood

Blood is a unique tissue with many properties. It is a transport medium for oxygen and other substances necessary for the metabolism of cells. Some constituents provide protection against invasion by foreign organisms. Others preserve the integrity of healthy blood vessels, limit blood loss from damaged vessels, and maintain the fluidity of the blood.

Blood flows through the body in a closed network of vessels. There are two distinct circulations, pulmonary and systemic, and the heart is the pump for each. In the pulmonary circulation, oxygen and carbon dioxide exchange between the blood and the inspired air. The oxygenated blood returns to the heart and is pumped throughout the body in the systemic circulation providing the oxygen required for the various metabolic processes of tissues.

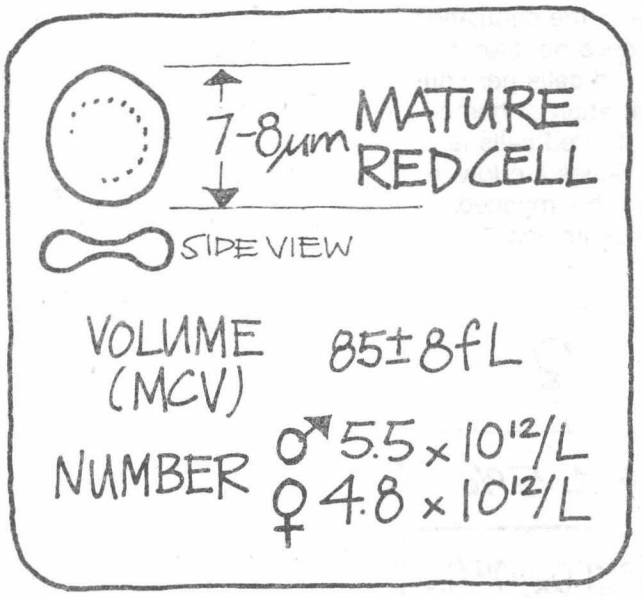
As well as oxygen, blood transports nutrients and hormones to the body's cells, and carbon dioxide and other metabolic breakdown products away from the cells.





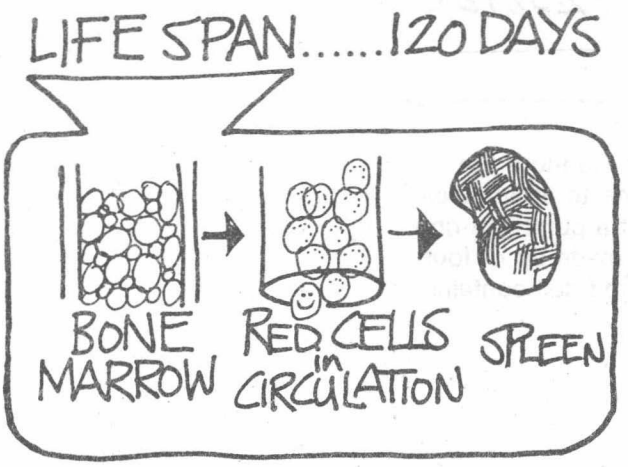
Circulating blood is composed of cellular elements suspended in an aqueous solution of salts and proteins. The cellular elements consist of red cells (erythrocytes), white cells (leukocytes) and platelets (thrombocytes). The fluid component of blood is known as plasma and contains many substances dissolved in water.

Cellular Elements



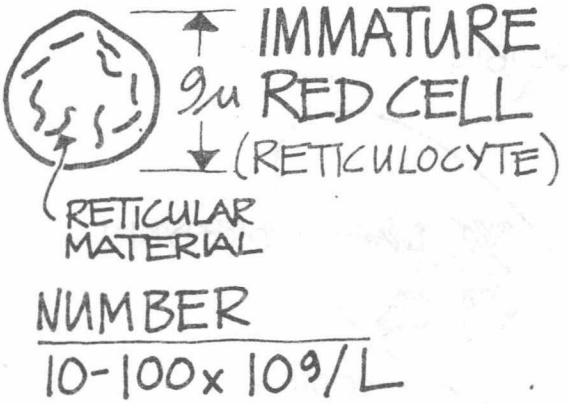
Red Blood Cells (erythrocytes)

Red blood cells are the most numerous cells in the circulation and give blood its characteristic red color. They are produced in the bone marrow and when mature are released into the blood stream as non-nucleated cells. Red cells have more membrane than is required to contain their intracellular material. Consequently, they are flexible and can easily be deformed to squeeze through the small capillaries of the microcirculation. They circulate as biconcave discs.



The number of red blood cells produced and released by the bone marrow is controlled by many factors, including the partial pressure of oxygen, a hormone called erythropoietin and male sex hormones. The influence of male hormones explains why males have more red cells than females.

Red cells survive for approximately four months in the circulation before being cleared by the reticuloendothelial system.

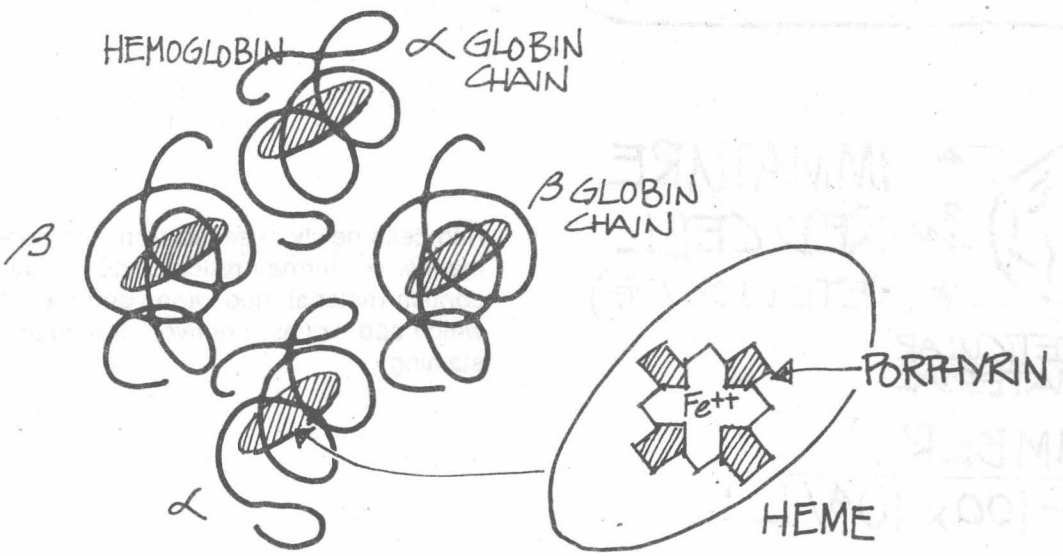


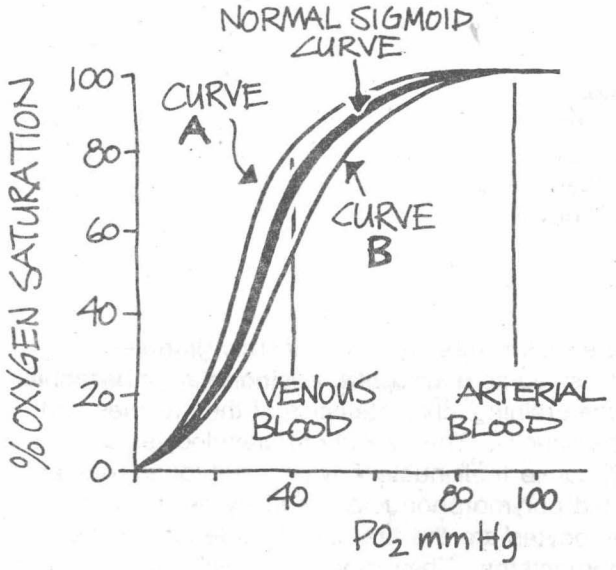
Red cells newly released from the bone marrow are termed reticulocytes because they contain material (ribosomes and mitochondria) which appears as a network (reticulum) after staining.

There is a correlation between the number of red cells in the circulation and their ability to deliver oxygen. The number of red cells per liter of blood is termed the **red cell count.** The percentage of red cells per unit volume of blood is termed the **hematocrit.** The concentration of hemoglobin present in a unit volume of blood after lysis of the red cells is known as the **hemoglobin concentration.** When these values are low, a person is anemic and consequently oxygen delivery can be imparied. The ability of the red cells to transport oxygen can be estimated by measuring the oxygen affinity of hemoglobin.

	♂	♀
HEMATOCRIT	47±7%	42±5%
RED CELL COUNT	$5.5 \pm 1.0 \times 10^{12}$/L	$4.8 \pm 1.0 \times 10^{12}$/L
HEMOGLOBIN CONCENTRATION	15±2.5g/dL	14±2.5g/dL

Red cells transport oxygen from the lungs to tissues throughout the body. Oxygen enters the red cells in the lungs and binds to an intracellular protein called **hemoglobin.** Hemoglobin consists of a porphyrin ring with a central iron atom (heme), and a globular protein made up of four subunits each of which carries one heme group. Each red cell contains many hemoglobin molecules.





	% SATURATION	
	NORMAL	2,3-DPG↓
ARTERIAL BLOOD	97%	97%
VENOUS BLOOD	75%	50%

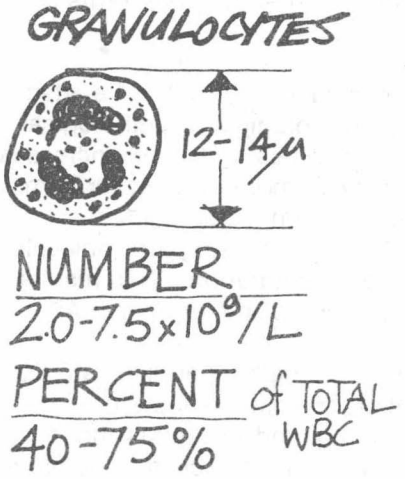
The binding of one molecule of oxygen to heme makes the hemoglobin change its shape, allowing the next oxygen molecule easier access to another binding site. This positive influence results in a characteristic binding pattern between hemoglobin and oxygen. The relationship between oxygen concentration in the blood (the partial pressure of oxygen) and the proportion of oxygen bound to hemoglobin, (the percentage oxygen saturation) forms a sigmoid curve.

The hemoglobin/oxygen affinity can be altered by a number of physiological or pathological events. For example, raising the pH increases this affinity, making it more difficult for hemoglobin to release oxygen. Consequently, hemoglobin holds on to the oxygen molecules maintaining a higher saturation. This results in a shift of the curve to the left (curve A).

Red cells produce 2,3-diphosphoglycerate (2,3-DPG). This substance diminishes the hemoglobin/oxygen affinity and facilitates the release of oxygen from the red cells. Therefore, the oxygen dissociation curve is shifted to the right (curve B). The level of 2,3-DPG progressively decreases as donor blood is stored. Theoretically, this decrease can result in reduced oxygen delivery to the tissues and a shift of the curve to the left. Most transfused patients are unaffected by this change as the 2,3-DPG in donor red cells returns to normal within 24 hours of infusion.

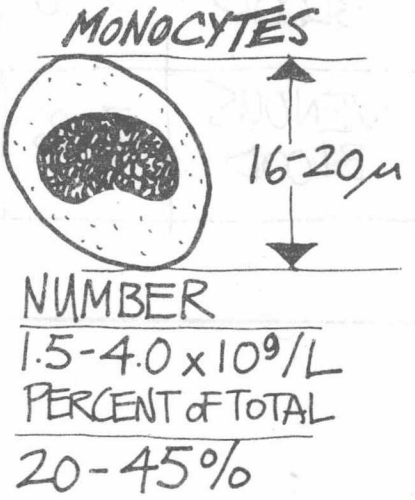
Leukocytes (white blood cells)

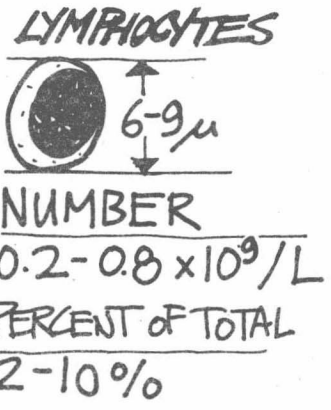
There are three classes of leukocytes called **granulocytes**, **monocytes** and **lymphocytes**. They are all derived from undifferentiated immature bone marrow cells. Leukocytes are particularly important in the defense against infection, their numbers increasing in response to infection. A low leukocyte count predisposes an individual to infection.



Granulocytes are leukocytes with cytoplasmic granules. They can be classified as **neutrophils**, **eosinophils**, or **basophils** depending on the staining characteristics of the granules and the shape of their nuclei. The majority of granulocytes are neutrophils. Because their nuclei have several lobes they are sometimes called polymorphonuclear leukocytes, or polymorphs. Granulocytes are the first line of defense against invading microorganisms. Their motility allows them to move out of the capillary circulation into the tissues, where they ingest microbes or other foreign particles, a process termed **phagocytosis**. Granulocytes remain in the circulation for only a few hours before entering the tissues.

Monocytes are non-granular leukocytes with large kidney-shaped nuclei surrounded by cytoplasm. They are important in the clearance of cells or organisms that have been coated with antibodies. Monocytes remove invading microorganisms or other foreign particles by the process of phagocytosis.





Lymphocytes are non-granular cells with spherical nuclei surrounded by a thin layer of cytoplasm. They are produced by bone marrow cells, but mature in other areas of the body including lymph nodes, thymus and spleen. Lymphocytes are of two different functional types: B-lymphocytes and T-lymphocytes. B-lymphocytes induce antibody production while T-lymphocytes are responsible for cell mediated immunity and play a regulatory role in the immune system.

Platelets

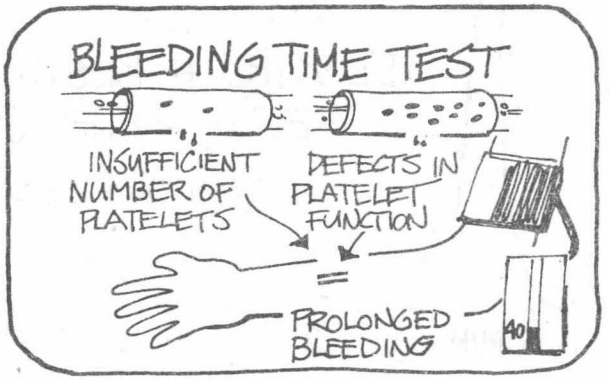
Platelets are small non-nucleated cells produced by the bone marrow. They circulate for approximately 7 days before being cleared from the circulation by the reticuloendothelial system. Platelets play a critical role in hemostasis by forming the hemostatic plug and by interacting with the clotting factors.

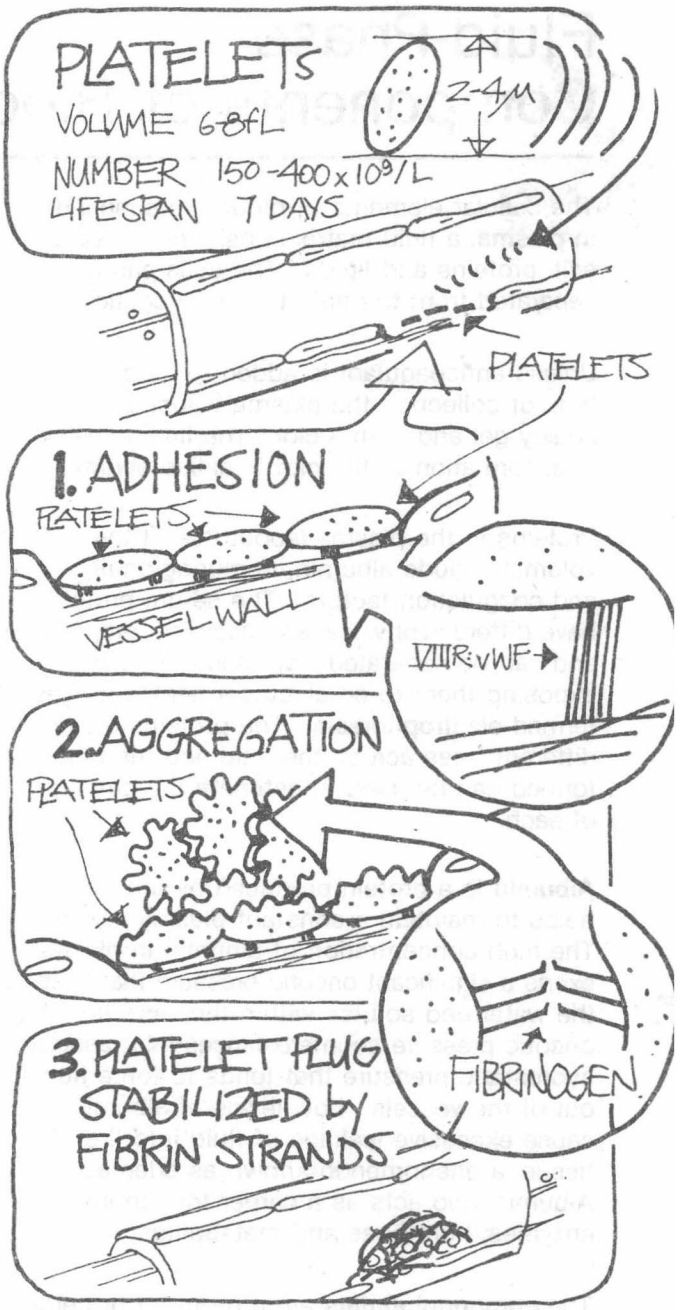
Following a spontaneous or traumatic break in the endothelial lining of a blood vessel, platelets adhere to the subendothelial layers. Adhesion requires the presence of a component of the coagulation factor VIII molecule called the **Von Willebrand factor (VIIIR:vWF)**.

The platelets release a number of substances that cause adjacent platelets to bind to each other and to the adhering platelets, a process termed platelet **aggregation**. This clump of platelets is called the primary platelet plug and unless stabilized it spontaneously falls apart.

Stabilization is accomplished by the sequential activation of serum protein coagulation factors that results in the formation of a fibrin mesh around the platelet plug.

Bleeding can occur when the platelet count is low, or if the platelets present in the circulation do not function normally. The hemostatic effectiveness of circulating platelets is therefore related to both their number and functional ability.





In vivo, platelet function can be measured by the bleeding time test. A standard incision is made in the skin and the time taken for blood flow to stop is estimated. Prolonged bleeding times occur either when the platelet count is low, or when platelets are not functioning normally. Specific **in vitro** tests to measure platelet adhesion and aggregation are also available.

Fluid-Phase Components of Blood

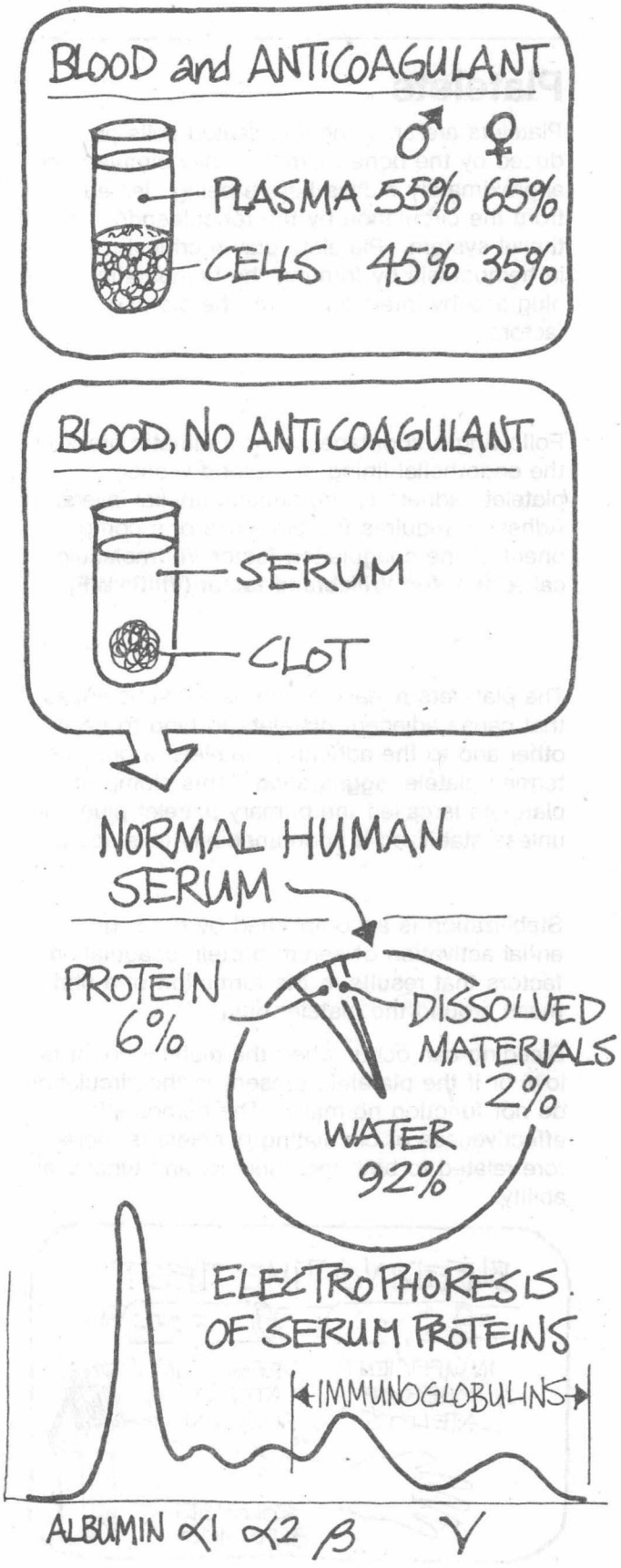
The cellular elements of blood are suspended in **plasma**, a fluid matrix consisting of water, salt, proteins and lipids. The cells can be separated from the fluid by centrifugation.

Unless anticoagulant is added to blood at the time of collection the plasma will spontaneously gel and form a clot. The fluid remaining after formation of the clot is called **serum**.

Proteins in the plasma (about 6% of the volume) include albumin, immunoglobulins and coagulation factors. The serum proteins have different physical and chemical properties, and can be separated from each other by exposing them to an electrical field, a process termed **electrophoresis**. The proteins move at different rates across the field and the pattern formed can be used to estimate the amount of each.

Albumin is a protein produced by the liver. It helps to maintain a constant plasma volume. The high concentration of albumin in plasma exerts a significant oncotic pressure that keeps the water and solutes within the vessels. The oncotic pressure counterbalances intravascular hydrostatic pressure that tends to force fluids out of the vessels. Low levels of albumin cause excessive leakage of fluid into the tissue, a phenomenon known as edema. Albumin also acts as a carrier for various enzymes, hormones and metabolites.

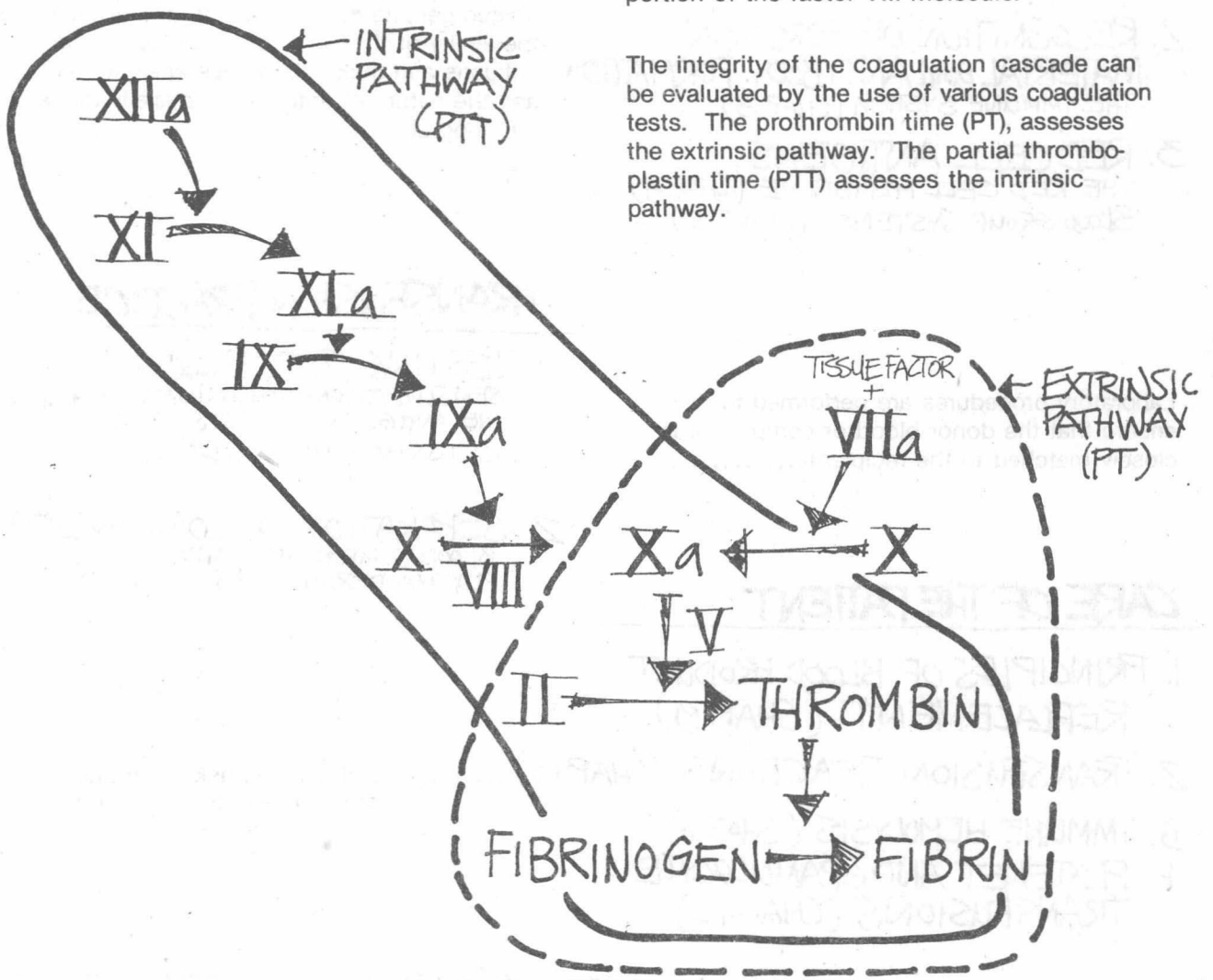
The **immunoglobulins** are a group of proteins produced by B-lymphocytes that protect the individual from infections. Immunoglobulins bind the microorganisms and facilitate their removal by macrophages. Immunoglobulins are found in plasma, in secretions such as saliva or respiratory mucus, and on the surface of certain cells.



The **coagulation proteins** circulate in a nonactive form. Following activation, they sequentially catalyze each other in a cascade that results in the formation of a fibrin clot. All coagulation factors are present in trace amounts except for fibrinogen, which is found in high concentrations. Fibrin formation can occur through two interrelated pathways, the **intrinsic pathway** and the **extrinsic pathway**.

The absence of certain coagulation factors impairs clot formation and can result in abnormal bleeding. For example, a bleeding disorder termed hemophilia is characterized by a decrease in the level of the coagulant portion of the factor VIII molecule.

The integrity of the coagulation cascade can be evaluated by the use of various coagulation tests. The prothrombin time (PT), assesses the extrinsic pathway. The partial thromboplastin time (PTT) assesses the intrinsic pathway.



It is now possible to replace virtually any component of blood by blood transfusion or blood component therapy.

BLOOD AND BLOOD COMPONENTS

DONOR TISSUE ~~REACTIONS~~ HOST DEFENSE

However, when any foreign material is introduced into the body, serious reactions can take place between the donor tissue and the host defenses.

KEY CONCEPTS

1. INDIVIDUALITY
   GENETICS (CHAP. 2)
2. RECOGNITION OF FOREIGN MATERIAL and ANTIBODY FORMATION
   THE IMMUNE SYSTEM (CHAP. 3)
3. RED CELL ANTIGENS
   THE RED CELL MEMBRANE (CHAP. 4)
   BLOOD GROUP SYSTEMS (CHAP. 5)

It is important, therefore, to understand the unique genetic constitution of an individual, the ability of the body to recognize foreign antigens and make antibodies against them, and the nature of antigens, especially those on blood cells.

TRANSFUSION PRACTICE

1. TESTING THE BLOOD
   SENSITIZATION, AGGLUTINATION AND THE ANTIGLOBULIN TESTS (CHAP. 6)
   CROSSMATCHING (CHAP. 7)
2. SEPARATION OF COMPONENTS
   BLOOD COMPONENTS AND PLASMA DERIVATIVES (CHAP. 8)

Laboratory procedures are performed to ensure that the donor blood or component is closely matched to the recipient.....

CARE OF THE PATIENT

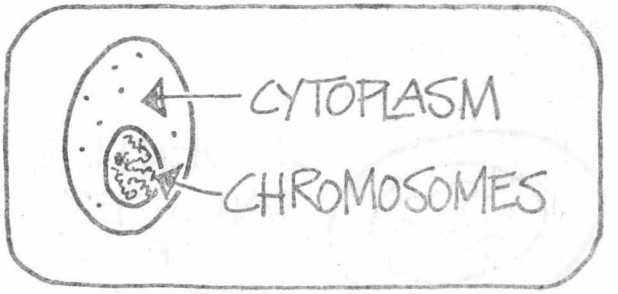
1. PRINCIPLES OF BLOOD PRODUCT REPLACEMENT (CHAP. 9)
2. TRANSFUSION REACTIONS (CHAP. 10)
3. IMMUNE HEMOLYSIS (CHAP. 11)
4. PLATELET AND GRANULOCYTE TRANSFUSIONS (CHAP. 12)

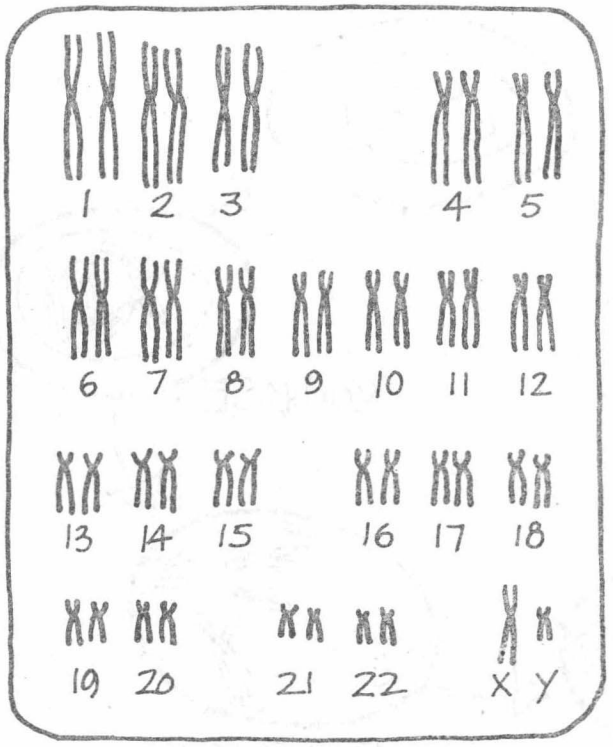
..... and that the risks of transfusion are reduced to a minimum.

Genetics

Genes and Chromosomes

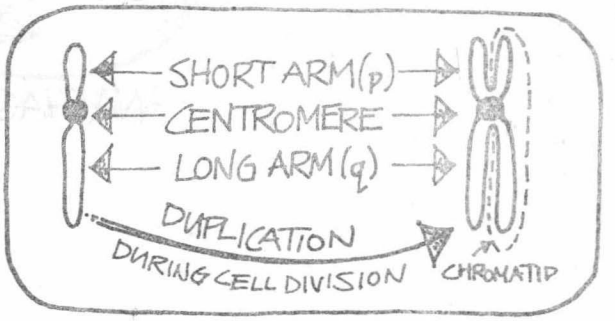
The unique physical features and chemical characteristics of each individual are controlled by genes. Genes represent the genetic information inherited from one's parents. Various genes are located on chromosomes within the cell nuclei.





A chromosome consists of two arms joined by a centromere. If studied during cell division, the chromosome has four arms, because the long and short arms have each duplicated. The chromosome subsequently divides into chromatids during mitosis.

Every human cell, except reproductive cells, contains 46 chromosomes (23 pairs), termed the **diploid** number of chromosomes. The reproductive cells (spermatozoa and ova) contain 23 chromosomes known as the **haploid** number. An embryo is formed by the fusion of a spermatozoon and ovum resulting in a cell containing the complete set of 23 pairs of chromosomes. The embryo contains 22 pairs of homologous chromosomes (autosomes), and one pair of sex chromosomes that determine the gender of the individual. Females have two X chromosomes and males have one X and one Y chromosome.



Cell Division - Mitosis

All cells, except the reproductive cells, divide by **mitosis** producing two genetically identical daughter cells. The process of mitosis can be divided into phases. Before the first step, **prophase**, there is duplication of chromosomes. Prophase is followed by **metaphase** where the chromosomes line up across the equator of the cell. During **anaphase** the **chromatids** migrate to opposite ends of the cell. Finally, in **telophase** the cell divides forming two daughter cells.