Chapter 17: Blood

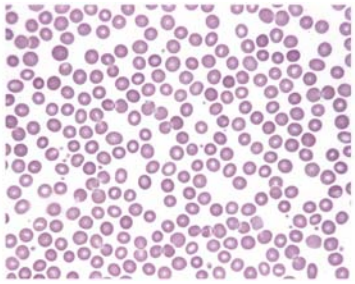
Overview

- Blood functions
- Compostion of whole blood
- Plasma
- RBCs – structure, function, and development
- Blood types
- WBCs
- Platelets
- Hemostasis

The Cardiovascular System

- A circulating transport system composed of:
  - a pump (the heart)
  - a conducting system (blood vessels)
  - a fluid medium (blood)
- Functions to transport:
  - oxygen and carbon dioxide
  - nutrients
  - hormones
  - immune system components
  - waste products

Blood – tissue type?



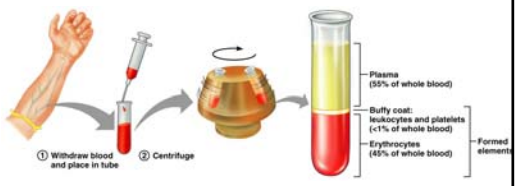
General Characteristics of Blood

- Blood is a sticky, opaque fluid with a metallic taste
- Color varies from scarlet to dark red High viscosity (due to cells)
- Temperature is 38°C
- Normal pH range = 7.35–7.45
- Blood volume (liters) = 7% of body weight (kilograms):
  - adult male: 5 to 6 liters
  - adult female: 4 to 5 liters

Blood - General Functions

- Transport of dissolved gases, nutrients, hormones, and metabolic wastes
- Regulation of pH, body temperature, ion composition of interstitial fluids
- Restriction of fluid loss at the injury site
- Defense against toxins and pathogens

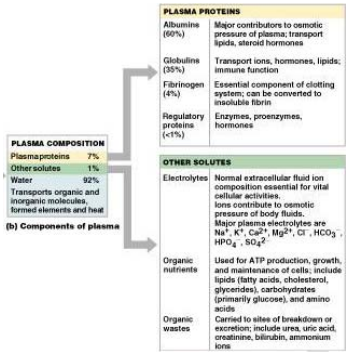
Whole Blood



Whole Blood

- Plasma: Fluid component
  - Water (90%)
  - Dissolved plasma proteins
  - Other solutes
- Formed elements: Cells and fragments
  - RBCs (carry Oxygen)
  - WBCs (immunity)
  - Platelets (cell fragments involved in clotting)

Plasma



Plasma

- Makes up 50–60% of blood volume
- More than 90% of plasma is water
- Other constiuents:
  - Plasma proteins
  - Lactic acid, urea, creatinine
  - Organic nutrients – glucose, carbohydrates, amino acids
  - Electrolytes – sodium, potassium, calcium, chloride, bicarbonate
  - Respiratory gases – oxygen and carbon dioxide

Body Fluids

Extracellular Fluid (ECF) = Interstitial fluid (IF) and plasma plus a few other body fluids such as CSF

- Plasma and IF exchange water, ions, & small solutes across capillary walls

Intracellular Fluid (ICF)=fluid inside cells

ECF and ICF differ in their levels of:

- O_2 and CO_2
- Dissolved proteins: plasma proteins do not pass through capillary walls (too large)

Plasma proteins

- Albumins (60%): major component of osmotic pressure of plasma
  - Transport proteins for fatty acids, thyroid hormones, steroid hormones
- Globulins (35%): antibodies (immunoglobulins) and transport proteins:
  - hormone-binding proteins
  - metalloproteins
  - apolipoproteins (lipoproteins)
  - steroid-binding proteins
- Fibrinogens (4%)
  -functions in blood clotting (form fibrin)
- Others (1%) including hormones

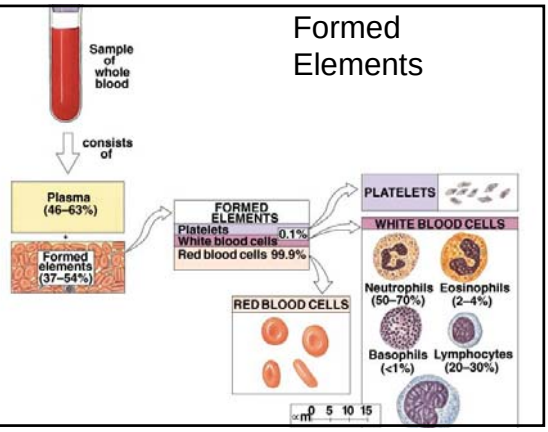
Origins of Plasma Proteins

- 90% made in liver
- Others not made in the liver include:
  - Antibodies made by plasma cells (a special type of WBC)
  - Peptide hormones made by endocrine organs

Serum

- Liquid part of a blood sample in which dissolved fibrinogen has converted to solid fibrin
- Often, this term refers to plasma that has had the clotting proteins removed

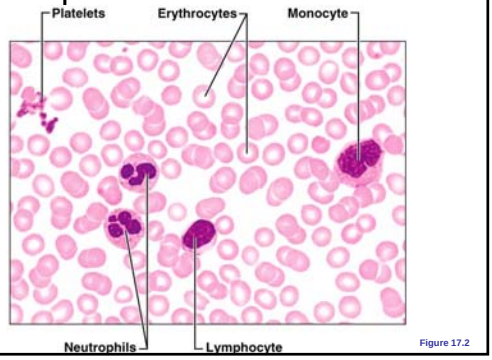
Formed Elements



Formed Elements

- These are the cells (and quasi-cellular) constituents of blood
- Red blood cells (RBCs) make up 99.9% of blood's formed elements
- White blood cells and platelets make up the rest

Components of Whole Blood

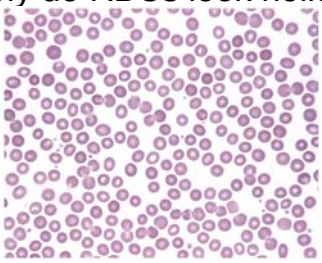


Measuring RBCs

- Red blood cell count: reports the number of RBCs in 1 microliter whole blood
  - Male: 4.5–6.3 million
  - female: 4.2–5.5 million
- Hematocrit (packed cell volume, PCV): percentage of RBCs in centrifuged whole blood
  - male: 40–54 (avg = 46)
  - female: 37–47 (avg = 42)

RBCs make up about 1/3 of all cells in the body!

Why do RBCs look hollow?

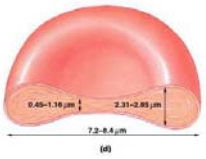


No nucleus

Biconcave structure

RBC Structure

- Small and highly specialized disc
- Thin in middle and thicker at edge



Why this structure?

Importance of RBC Shape and Size

1. High surface-to-volume ratio:
   - Increase surface area for gas exchange
2. Discs form stacks:
   - smoothes flow through narrow blood vessels
3. Discs bend and flex entering small capillaries:
   - 7.8 μm RBC passes through 4 μm capillary

RBC characteristics

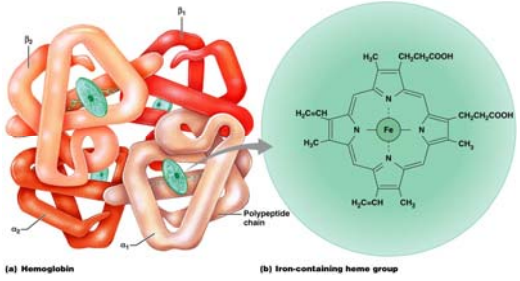
- Shaped like biconcave discs
- Function primarily to carry oxygen -contain hemoglobin (95% of RBC protein)
- Lack a nucleus and contain few organelles (no mitochondria, ribosomes)
- Life span approx. 120 days
- Generate ATP anaerobically (no mitochondria) so they don't consume any of the oxygen that they transport

Hemoglobin (Hb)

- Protein molecule inside RBCs that transports respiratory gases
- Composed of:
  - Four protein chains called globins
    - adults: 2 alpha and 2 beta chains
  - Each of these four chains is bound to a pigment molecules called heme
    - each of which contain one iron ion (red color) and bind one oxygen molecule
- Each RBC ~280 million molecules

Hemoglobin Structure

- Complex quaternary structure



Fetal Hemoglobin (Hb F)

- Made up of 2 alpha and 2 gamma chains
- Has a higher affinity for oxygen than adult hemoglobin, “steals” oxygen from maternal hemoglobin in utero

RBC fate

After 100-120 days:

- 10% hemolyze in the blood
- 90% removed by macrophages in the spleen (especially), the liver and the bone marrow and heme is recycled:
  - heme degraded to biliverdin (green)
  - biliverdin converted to bilirubin (yellowish)
  - Bilirubin leaves Mphage, binds to albumin, tranported to liver for excretion in bile (high levels of bilirubin in jaundice)
- In colon, bacteria convert bilirubin to *urobilinogens* and *stercobilinogens* – colors feces
- Some is absorbed into circulation and eliminated by kidneys in urine – colors urine

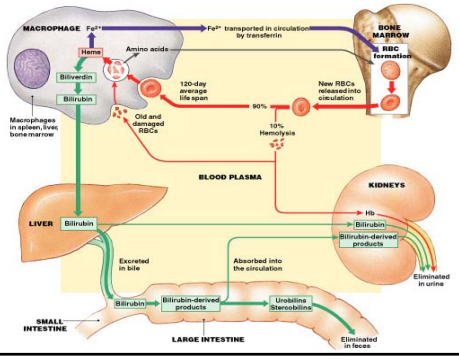
Serum Bilirubin

- Red cells account for 85% of bilirubin formed = Unconjugated
- In liver it is conjugated and secreted into bile to large intestine
- Hemolytic jaundice: elevated levels of unconjugated bilirubin
- Obstructive jaundice: elevated levels of conjugated bilirubin because bile ducts are blocked (bile that can’t be secreted)

Recycling

- Iron
  - Heme iron is removed in spleen (or liver or bone marrow)
  - Binds to plasma protein called transferrin
  - Transferrin is taken up in bone marrow and used to make new heme in developing RBCs
  - Very efficient
- Globin protein
  - Amino acids travel through bloodstream to bone marrow and can be used in erythropoiesis

RBC recycling



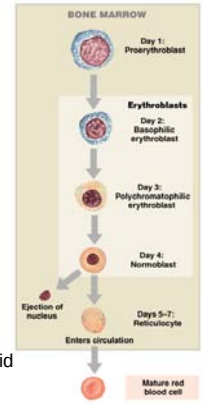
Hematopoiesis

- Development of all the cells of the lymphoid/myeloid lineage
  - Includes: RBCs, all types of WBCs, and platelets
- All start out as hemocytoblasts, a pluripotent stem cell:
  - Myeloid stem cells give rise to RBCs, platelets and some WBCs
  - Lymphoid stem cells give rise to lymphocytes only
- Occurs in red bone marrow (axial and epiphyses)

Erythropoiesis

- Rate of RBC production controlled by erythropoietin - EPO (from where?)
- What is necessary for healthy RBCs?

amino acids
iron
vitamins B_{12}, B_6, and folic acid



Erythropoietin Mechanism

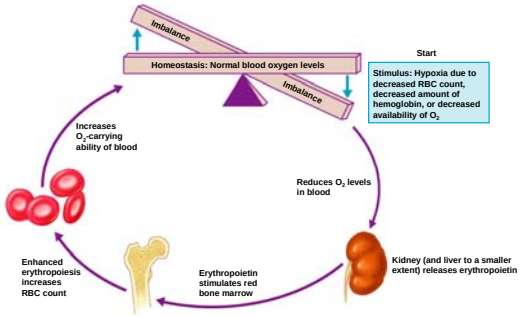


Figure 17.6

RBC Maturation

- Hematocytoblast → myeloid stem cell → proerythroblast → erythroblast → reticulocyte → mature RBC
- Reticulocytes have no nucleus and enter bloodstream still containing ribosomes and mRNA. After a day or so of furious Hb production, lose their organelles and become mature RBCs

Regulation of Erythropoiesis

- Circulating erythrocytes – the number remains constant and reflects a balance between RBC production and destruction
  - Too few RBCs leads to tissue hypoxia
  - Too many RBCs causes undesirable blood viscosity

Blood Types

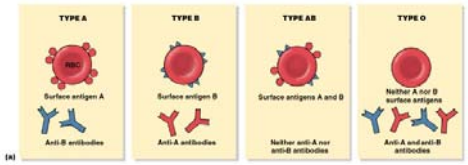
- Genetically determined cell surface markers (antigens) on RBCs, including
  - ABO group – glycolipids on RBC surface
  - Rh factor – membrane protein

4 Basic Blood Types

- A has surface antigen A
- B has surface antigen B
- AB has both antigens A and B
- O has neither A nor B

- A has type B antibodies
- B has type A antibodies
- O has both A and B antibodies
- AB has neither A nor B antibodies

4 Basic Blood Types



- Antigens also called agglutinogens
- Antibodies called agglutinins

ABO Antigens and Antibodies

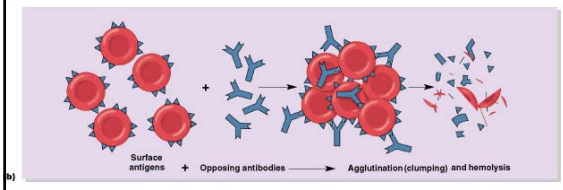
	Surface Antigens	Antibodies
A	A	Anti-B
B	B	Anti-A
AB	A, B	none
O	none	Anti-A Anti-B

The Rh Factor

- Also called D antigen
- Either Rh positive (Rh^+) or Rh negative (Rh^-)
- Only sensitized Rh^- blood has anti-Rh antibodies

	Surface Antigens	Antibo-dies
Rh^+	Rh factor	none
Rh^-	none	none
Rh^- Sens	none	Anti Rh

Cross-Reaction

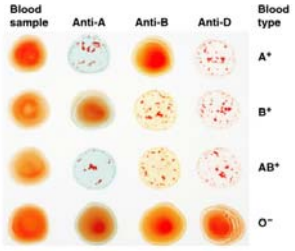


Cross-Reaction

- If donor and recipient blood types not compatible:
  - Plasma antibody meets its specific surface antigen and blood will agglutinate and hemolyze

Blood Type Test

- Determines blood type and compatibility



Cross-Match Test

- Performed on donor and recipient blood for compatibility to blood surface antigens other than ABO and Rh

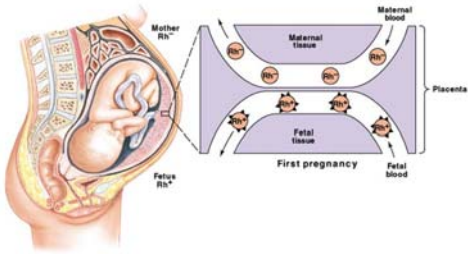
Blood type questions

- Which blood type is the best in emergency settings (hint: which type can be given to anyone?)
- Which blood type is the lucky one that can receive blood from <u>any</u> donor?

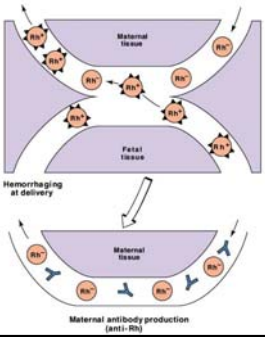
Hemolytic Disease of the Newborn (Erythroblastosis Fetalis)

- Mother is Rh^-
- Father and fetus are Rh^+
- First pregnancy = sensitization at delivery due to hemorrhage
- Second pregnancy = Anti-Rh IgG antibodies can cross placenta to attack fetal RBCs→ hemolysis and excess presence of erythroblasts

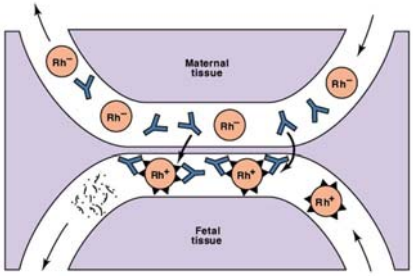
Hemolytic Disease of the Newborn



Rh^+ Fetal cells enter mother's circulation at delivery



Second pregnancy is attacked by maternal antibodies



Treatment?

Transfusions

- Unit whole blood = 500ml
- About half of this is plasma which contains antibodies. There is a slight risk of graft versus host (GVH) reactions, but since the volume in one unit is only about 10% of total plasma volume, usually gets diluted out
- If RBCs are needed, can use packed RBCs instead of whole blood

White Blood Cells (WBCs)

- Leukocytes: the only blood components that are complete cells; have nuclei and other organelles, not involved in oxygen transport.
- Functions:
  - Defend against pathogens
  - Remove toxins and wastes
  - Attack abnormal cells

WBC in blood vs. tissue

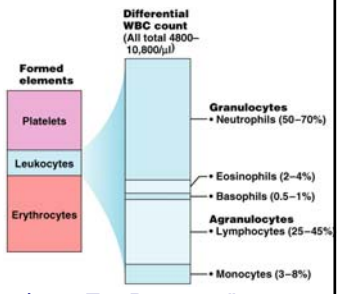
- Very small numbers in blood:
  - 6000 to 9000 per microliter
  - Outnumbered 1000:1 by RBCs
  - But only 1% of WBC are in blood
- Most WBCs are not found in blood but instead in connective tissue proper and in lymphatic system organs
- Can leave capillaries via diapedesis

Circulating WBCs

- WBCs can migrate out of capillaries into tissues via diapedesis
- Have amoeboid movement (using actin)
- Attracted to chemical stimuli (positive chemotaxis)
- Some are phagocytic: neutrophils, eosinophils, and monocytes

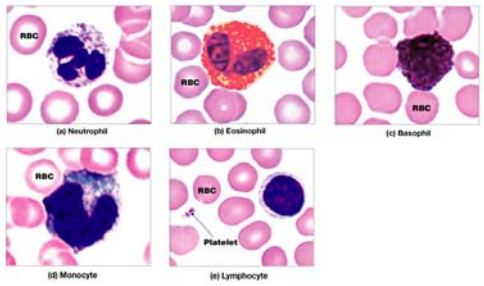
5 Types of WBCs

1. Neutrophils
2. Lymphocytes
3. Monocytes
4. Eosinophils
5. Basophils

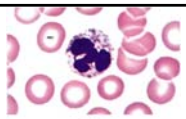


"Never Let Monkeys Eat Bananas"

Types of WBCs

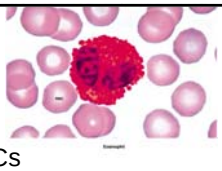


Neutrophils



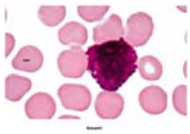
- Also called polymorphonuclear leukocytes
- 50–70% of circulating WBCs
- Pale cytoplasm granules with lysosomal enzymes and bactericides (hydrogen peroxide and superoxide)
- Phagocytes that are the first to attack bacteria, engulf and digest pathogens with defensins
- Release prostaglandins and leukotrienes (inflammation and alarm call)
- Form pus

Eosinophils



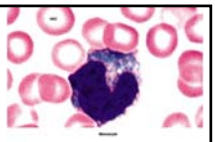
- Also called acidophils
- 2–4% of circulating WBCs
- Attack large parasites by excreting toxic compounds
- Sensitive to allergens
- Control inflammation with enzymes that counteract inflammatory effects of neutrophils and mast cells

Basophils



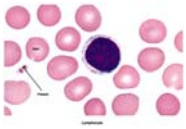
- Less than 1% of circulating WBCs
- Small cells that accumulate in damaged tissue
- Release histamine to dilate blood vessels and heparin prevent blood clotting
- Similar to mast cells (found in the tissues)

Monocytes



- 2–8% of circulating WBCs
- Are large and spherical
- Enter peripheral tissues and become macrophages
- Engulf large particles and pathogens
- Secrete substances that attract immune system cells and fibroblasts to injured area

Lymphocytes



- T cells, B cells and NK cells
- 20–30% of circulating WBCs
- Note the little cytoplasm
- Migrate in and out of blood
- Most of them are in connective tissues and lymphatic organs (spleen, lymph nodes)
- Respond to specific antigens

The Differential Count of Circulating WBCs

- Detects changes in WBC populations during infections, inflammation, and allergic reactions

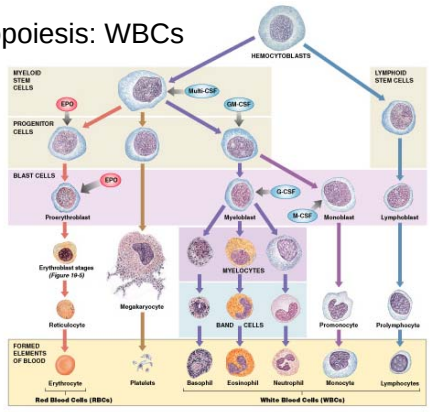
WBC Disorders

- Leukopenia:
  - abnormally low WBC count
- Leukocytosis:
  - high WBC count (normal response to infection)
- Leukemia:
  - extremely high WBC count

Blood disease nomenclature

- -penia (poverty): too little of a cell type in the blood
- -cytosis: too much of a cell type in the blood
- -emia: refering to the presence of something (anything) in the blood

Hematopoiesis: WBCs



WBC classes

- Granulocytes – neutrophils, eosinophils, and basophils
  - Contain cytoplasmic granules that stain specifically (acidic, basic, or both) with Wright's stain
  - Are larger and usually shorter-lived than RBCs
  - Have lobed nuclei
  - Are all phagocytic cells
- Agranulocytes – lymphocytes and monocytes:
  - Lack visible cytoplasmic granules
  - Have spherical (lymphocytes) or kidney-shaped (monocytes) nuclei

WBC Production

- Like RBCs, WBCs originate from hemocytoblasts in the bone marrow
- Hemocytoblasts differentiate into myeloid stem cells and lymphoid stem cells
- Myeloid stem cells become myeloblasts, which give rise to neurophils, basophils, and eosinophils (granulocytes), OR monoblasts, which become monocytes.
- Lymphoid stem cells become lymphoblasts, and give rise to lymphocytes (B, T, and NK cells)
- All complete their development in the bone marrow except T cells, which mature in the thymus

4 Colony-Stimulating Factors (CSFs)

- Hormones that regulate blood cell populations:

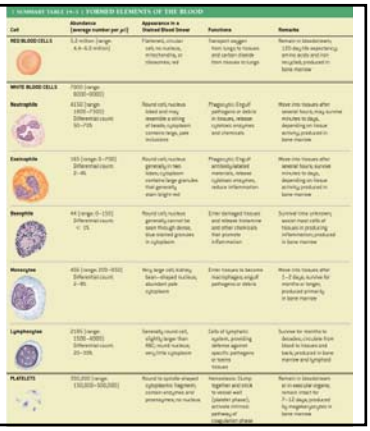
M-CSF:
- stimulates monocyte production

G-CSF:
- stimulates granulocyte production (neutrophils, eosinophils, and basophils)

GM-CSF:
- stimulates granulocyte and monocyte production

Multi-CSF:
- accelerates production of granulocytes, monocytes, platelets, and RBCs (all blood except lymphocytes)

Summary: Formed Elements of Blood



Platelets

- Cell fragments involved in human clotting system (cf. thrombocytes)
- Functions:
  - Release important clotting chemicals
  - Temporarily patch damaged vessel walls
  - Actively contract tissue after clot formation
- Circulate for 9–12 days in blood
- Removed by spleen
- 1/3 are reserved in spleen for emergencies
- Have a central granule containing serotonin, Ca^{2+}, enzymes, ADP, and platelet-derived growth factor (PDGF)

Platelet Counts

- 150,000 to 500,000 per microliter
- Thrombocytopenia:
  - abnormally low platelet count
- Thrombocytosis:
  - abnormally high platelet count

Thrombocytopoiesis

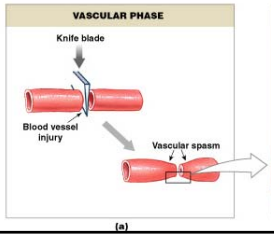
- Like RBCs and WBCs (except lymphocytes), platelets come from myeloid stem cells in bone marrow
- Differentiate into giant cells called Megakaryocytes, which break off membrane bound packets of cytoplasm to form platelets
- Controlled by Thrombopoietin (TPO) from kidneys, Inteleukin-6 (IL-6), & Multi-CSF

Hemostasis

- Cessation of bleeding:
  - vascular phase
  - platelet phase
  - coagulation phase
- Provides framework for repairs

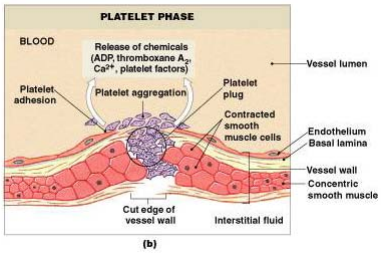
The Vascular Phase

- A cut triggers vascular spasm: smooth muscles in the vessel contract to limit blood loss
- Immediate, 30-minute contraction



The Platelet Phase

- Begins within 15 seconds after injury



The Platelet Phase

- Platelets do not stick to each other or to blood vessel epithelium
- But when epithelium is damaged, platelets can bind to exposed collagen with help of Von Willebrand Factor (VWF)
- Platelet adhesion (attachment):
  - Platelets also become activated and aggregate (stick together) to form a platelet plug that closes small breaks

Activated Platelets

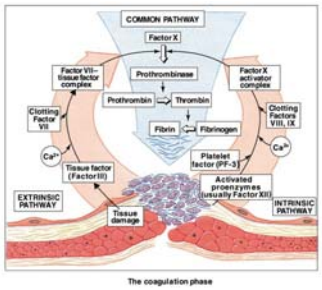
- Become spherical and extend cytoplasmic processes
- Granules break down and release several compounds
  - Serotonin enhances vascular spasm
  - Adenosine diphosphate (ADP) → aggregation
  - Thromboxane A_2 → spasms and aggregation
  - Clotting factors (see later)
- Positive f/b leads to plug formation in 1min

Platelet Plug Size is Restriction to Injury Site

- Prostacyclin:
  - released by intact endothelial cells, inhibits platelet aggregation to the site of injury only
- Inhibitory compounds:
  - released by other white blood cells
- Circulating plasma enzymes:
  - break down ADP
- Negative (inhibitory) feedback:
  - at high concentration, serotonin blocks ADP action
- Development of blood clot:
  - isolates area by sealing it off

The Coagulation Phase

- Begins 30 seconds – 1 min after the injury



The coagulation phase

The Coagulation Phase

- Blood clotting (coagulation):
  - Involves a series of steps that converts circulating fibrinogen into insoluble fibrin and turns liquid blood into a gel
- Blood clot = Fibrin network:
  - Covers platelet plug and cements it
  - Traps blood cells
  - Seals off area

Coagulation

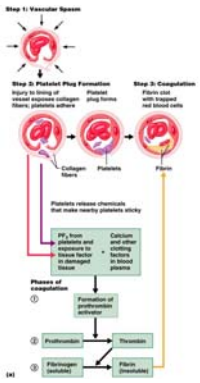


Figure 17.13a

Clotting Factors

- Proteins or ions in plasma required for normal clotting
  - 11 major proteins
  - Calcium ions

3 Coagulation Pathways

- Extrinsic pathway:
  - begins in the vessel wall outside bloodstream
- Intrinsic pathway:
  - begins with circulating proenzymes within bloodstream

Normally, both are activated

- Common pathway:
  - where intrinsic and extrinsic pathways converge

The Extrinsic Pathway

- Damaged cells release tissue factor (TF) also called factor III
- TF + other compounds including Calcium = enzyme complex
- Activates Factor X (ten)

Shorter, faster pathway that bypasses several steps in the intrinsic pathway

The Intrinsic Pathway

- Activation of proenzymes by exposed **collagen**
- Combines with PF–3 from platelets
- Series of reactions involving calcium result in factors VIII and IX combining to activate Factor X

Slower, more productive pathway

Happens in vitro (acivated by glass surfaces)

The Common Pathway

- Activated Factor X leads to enzyme prothrombinase (prothrombin activator)
- This converts prothrombin to thrombin
- Thrombin converts fibrinogen (a ubiquitous plasma protein) to fibrin
- Fibrin polymer covers the platelet plug

Thrombin

- Stimulates formation of tissue factor, which stimulates release of PF-3 by platelets
- This positive feedback loop involves both intrinsic and extrinsic pathways and accelerates clotting

Clotting Area is Restricted

1. Anticoagulants (plasma proteins):
   - antithrombin-III
   - Fibrin itself binds thrombin and prevents it from exerting positive feedback
2. Heparin from endothelium
3. Prostacyclin from endothelium
4. Protein C (activated by thrombomodulin) activates plasmin

Other Factors

- Calcium ions (Ca^{2+}) and vitamin K (from diet and colon bacteria) are both essential to the clotting process

Clot Retraction

- After clot has formed, platelets contract and pull torn area together, squeezing out serum
- Stabilizes injury site, facilitates repair
- Takes 30–60 minutes
- Repair
  - Platelet-derived growth factor (PDGF) stimulates rebuilding of blood vessel wall
  - Fibroblasts form a connective tissue patch
  - Stimulated by vascular endothelial growth factor (VEGF), endothelial cells multiply and restore the endothelial lining

Fibrinolysis

- Slow process of dissolving clot
- thrombin and tissue plasminogen activator (t-PA): activate plasminogen
  - Note that this is the same thrombin that helped activate the fibrin in the first place
- Plasminogen produces plasmin, which digests fibrin strands

Summary

- Blood functions
- Compostion of whole blood
- Plasma
- RBCs – structure, function, and development
- Blood types
- WBCs
- Platelets
- Hemostasis

Blood disorders

Complete Blood Count (CBC)

- The CBC is used as a broad screening test to check for such disorders as anemia, infection, and others. It is actually a panel of tests that examines different parts of the blood and includes the following:
- Red blood cell (RBC) count is a count of the actual number of red blood cells per volume of blood. Both increases and decreases can point to abnormal conditions.
- Hemoglobin measures the amount of oxygen-carrying protein in the blood.
- Hematocrit measures the percentage of blood that is cells (red blood cells).

CBC tests: WBCs and Platelets

- White blood cell (WBC) count is a count of the actual number of white blood cells per volume of blood. Both increases and decreases can be significant.
- White blood cell differential looks at the numbers of the five types of white blood cells present.
- Platelet count is the number of platelets in a given volume of blood. Both increases and decreases can point to abnormal conditions of excess bleeding or clotting.

Blood Volume

- Hypovolemia
- Hypervolemia
- Questions:
  - What might cause each?
  - Symptoms?
  - Which is more common?
  - How does your body prevent these conditions (or correct them when they develop)?

Polycythemia

- Elevated hematocrit with normal blood volume
- Erythrocytosis: excess RBCs.
  - Happens when you travel to altitude (less oxygen can be carried per RBC, need more cells)
  - Occurs in heart failure or lung disease (inadequate tissue oxygenation), can make blood thick
  - Blood doping: Inject EPO or remove packed RBCs and reinfuse just before a race

Hemoglobin Disorders

- Thalassemias: result from inadequate production of either the alpha or beta chain of hemoglobin. Lowers number of mature RBCs in blood. Treatment includes transfusions.
- Sickle-cell anemia: mutation in beta globin gene that does not cause inadequate expression but causes another problem.

Thalassemias

- Alpha-thalassemia
  - We have four copies of alpha globin gene
  - 3 good/1bad: carrier
  - 2good/2bad: *alpha-thalassemia trait*
  - 1good/3bad: microcytic anemia
  - 4bad: die before birth
- Beta-thalassemia
  - We have only two copies of beta globin gene
  - No good copies: *beta-thalassemia major*:
    - Severe microcytic anemia
    - Low hematocrit (below 20)
  - One good copy: *beta-thalassemia trait*
    - Few clinical symptoms

Anemias

- Hematocrit or hemoglobin levels are below normal, caused by several conditions
- Characterized by a decrease in the oxygen carrying capacity of the blood (due to the problems with RBCs or with hemoglobin)
- Can be macrocytic (big RBCs) or microcytic

Sickle-Cell Anemia

- Mutation in beta globin gene resulting in production of HbS
- At low oxygen, cells with HbS become rigid and adopt a "sickle" shape: makes them fragile and can become stuck in small capillaries (last 10 days in blood)
- One bad copy: sickling trait
- Two bad copies: SCA
- Treatments?
  Transfusions, hydroxyurea, butyrate

Pernicious Anemia

- Low RBC production due to lack of vitamin B_{12}
- Vitamin B_{12} absorption requires Intrinsic factor (IF) from cells in the stomach. No IF, no B_{12}.

Iron Deficiency Anemia

- Caused by low dietary iron or blood loss
- RBCs made without enough functional hemoglobin: microcytic
- Low hematocrit
- 12% of menstruating women may have it
- Treatment?

Changes in blood parameters

- Macrocytic anemia caused by vitamin B12 deficiency.
- Microcytic anemia is seen in iron deficiency anemia or thalassemias.

Iron Loading

- Excess iron intake, gets depostied in peripheral tissues notably heart valves
- Very dangerous, leads to heart failure
- Can develop as a result of repeated transfusions of whole blood given to severely anemic patients – they need the functional RBCs, but the RBCs keep getting broken down and the iron is retained

Leukemia

- Blood cancer – no solid tumor (cf. lymphoma)
- Myeloid or lymphoid
- Lymphoid more common in children
- Myeloid more common in adults
- Treatment?

Clotting Disorders: Excessive Clotting

- Embolus
- Thrombus
- Anticoagulant therapies:
  - Heparin: activates antithrombin III
  - Coumadin: blocks Vitamin K action
  - t-PA: activates plasmin
  - Streptokinase/urokinase: also activate plasmin
  - Asprin: inactivates platelet enzymes and prostacyclin production
  - EDTA – Calcium chelator

Clotting Disorders: Inadequate Clotting

- Hemophilia A: Gene for factor VIII is on X chromosome (sex-linked) and so this type of hemophilia is almost exclusively in males
- DIC – disseminated intravascular coagulation: small fibrin clots form throughout the blood, leads to shortage of fibrin when it is needed