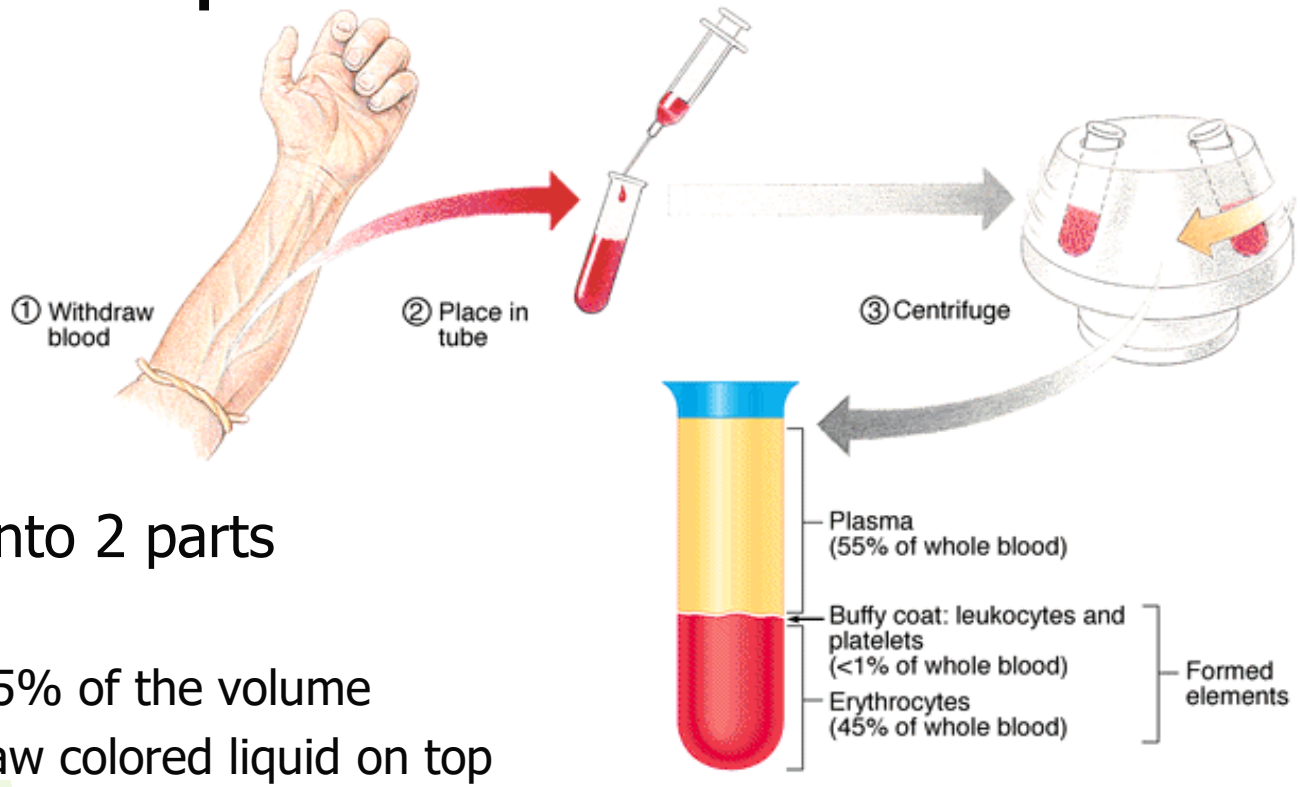
Overview: Composition of Blood

- A liquid connective tissue
- A mixture
  - the **formed elements** - living blood cells & platelets
  - the **plasma** – the fluid matrix
- Denser and more viscous than water
  - due to dissolved ions & organic molecules, especially plasma proteins, and to the blood cells
  - composition and volume regulated by CNS & hormones
- Temp - 38° C
- pH - 7.4 (critical to be between 7.35 and 7.45)
- Volumes differ between sexes, conditional on many factors
  - Females - average 4-5 L
  - Males - average 5-6 L

Functions of Blood

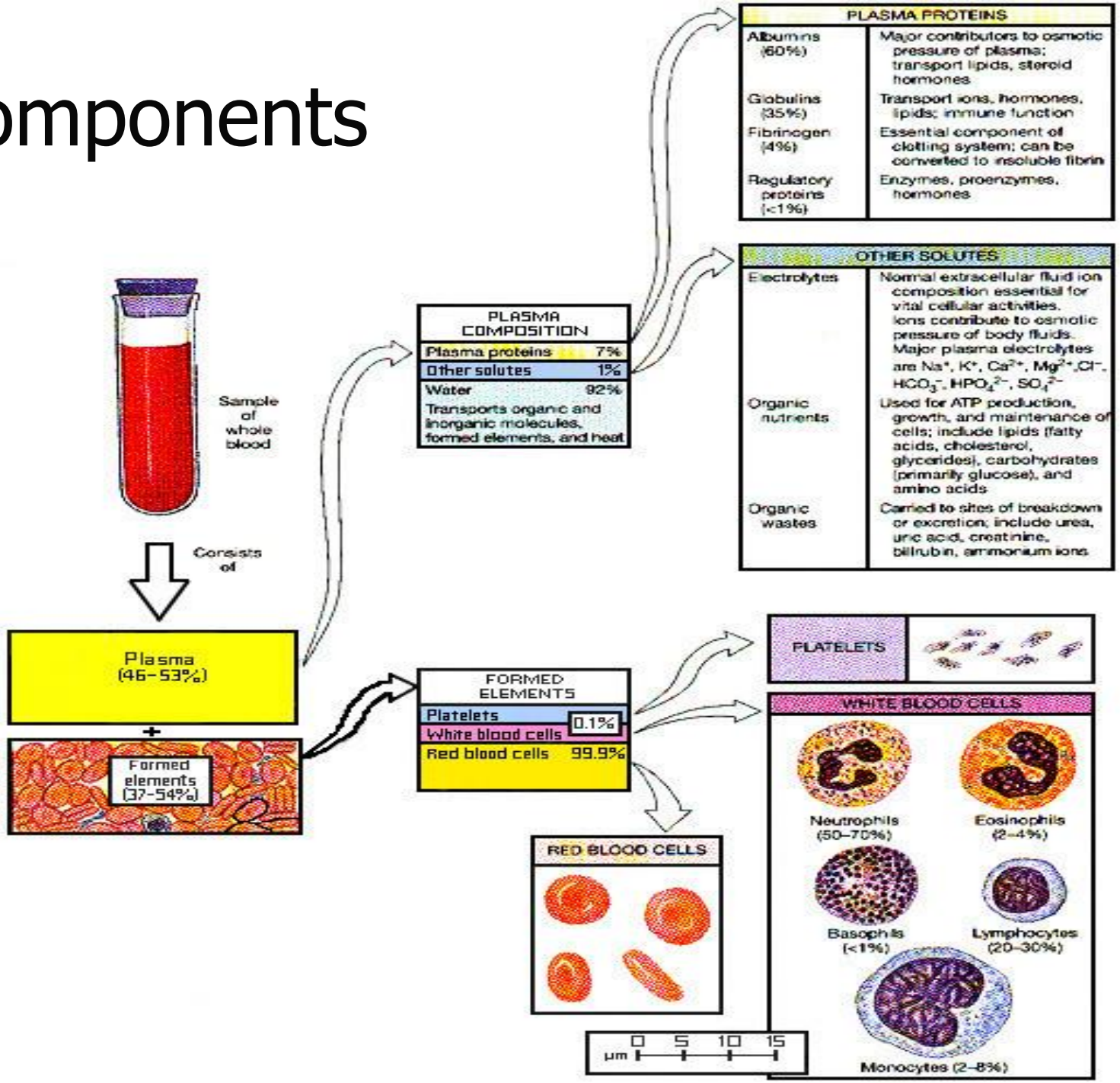
- Transport and Distribution
  - delivery of O_2, nutrients, and hormones
  - removal of CO_2 and metabolic wastes
- Regulation of Internal Homeostasis
  - body temperature
  - pH
  - fluid volume
  - composition of the interstitial fluid/lymph
- Protection
  - necessary for inflammation and repair
  - prevents blood loss by hemostasis (coagulation)
  - prevents infection

Overview: Composition of Blood

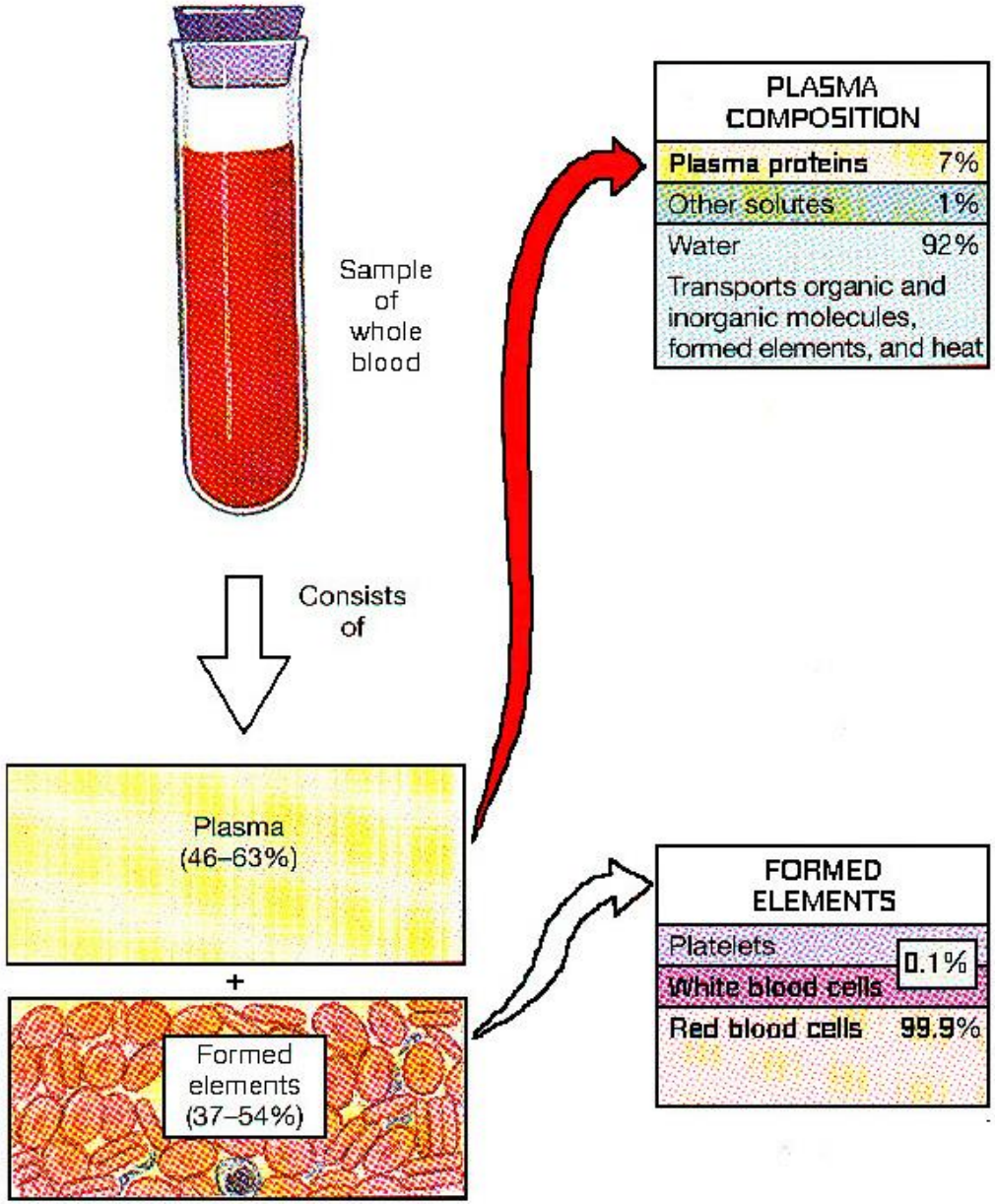


- Blood sample
  - spin it
  - separates into 2 parts
    - plasma
      - ~55% of the volume
      - straw colored liquid on top
    - formed elements - ~45% of the volume
      - red blood cells
      - buffy coat - white blood cells and platelets
  - Hematocrit = "packed cell volume"
    - percentage of formed element measured in a blood sample
    - about 45%

Blood Components

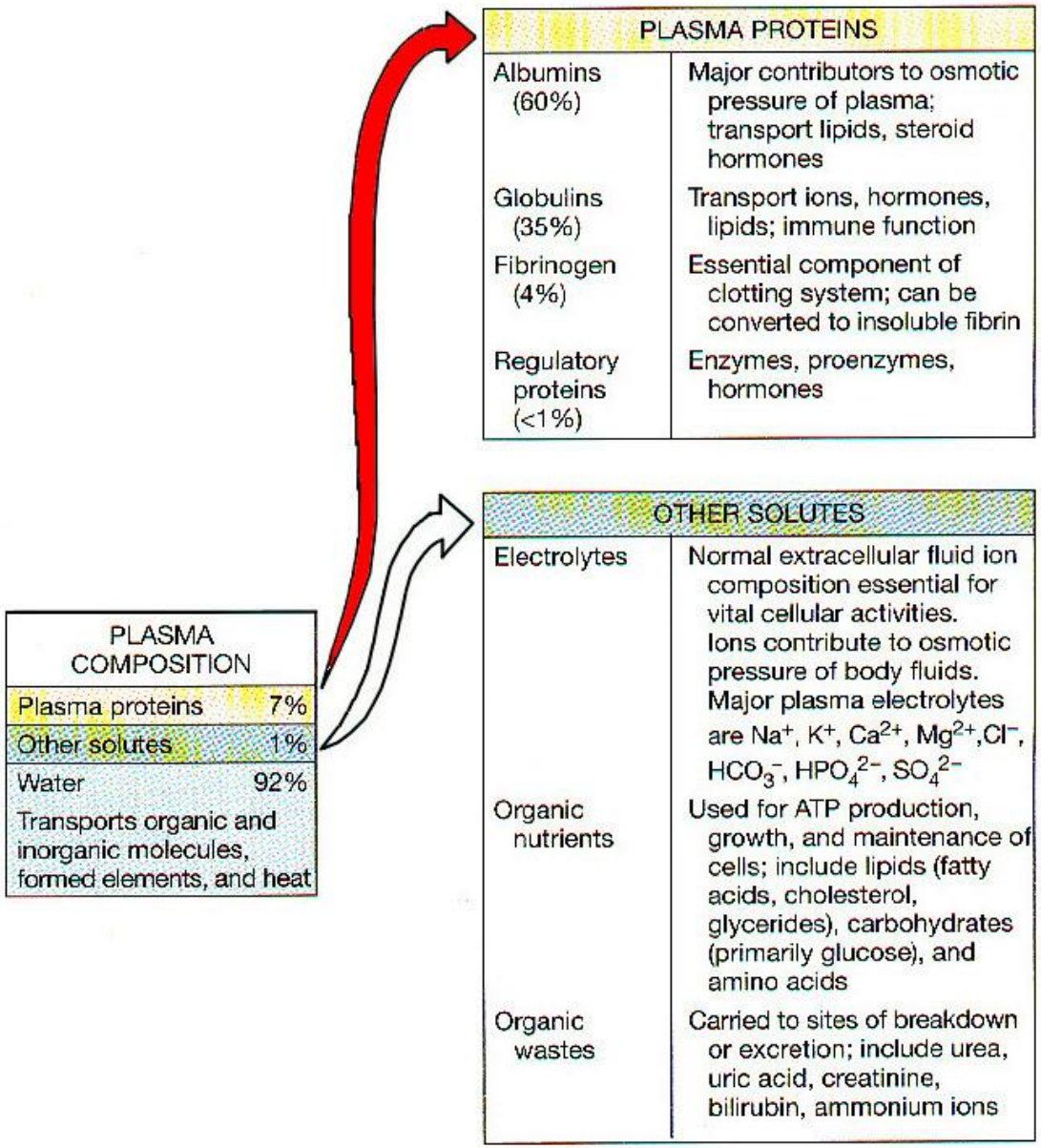


Components of Blood - Plasma



- Plasma
  - 92% water
  - 7% proteins
  - 1% other solutes

Components of Blood - Plasma



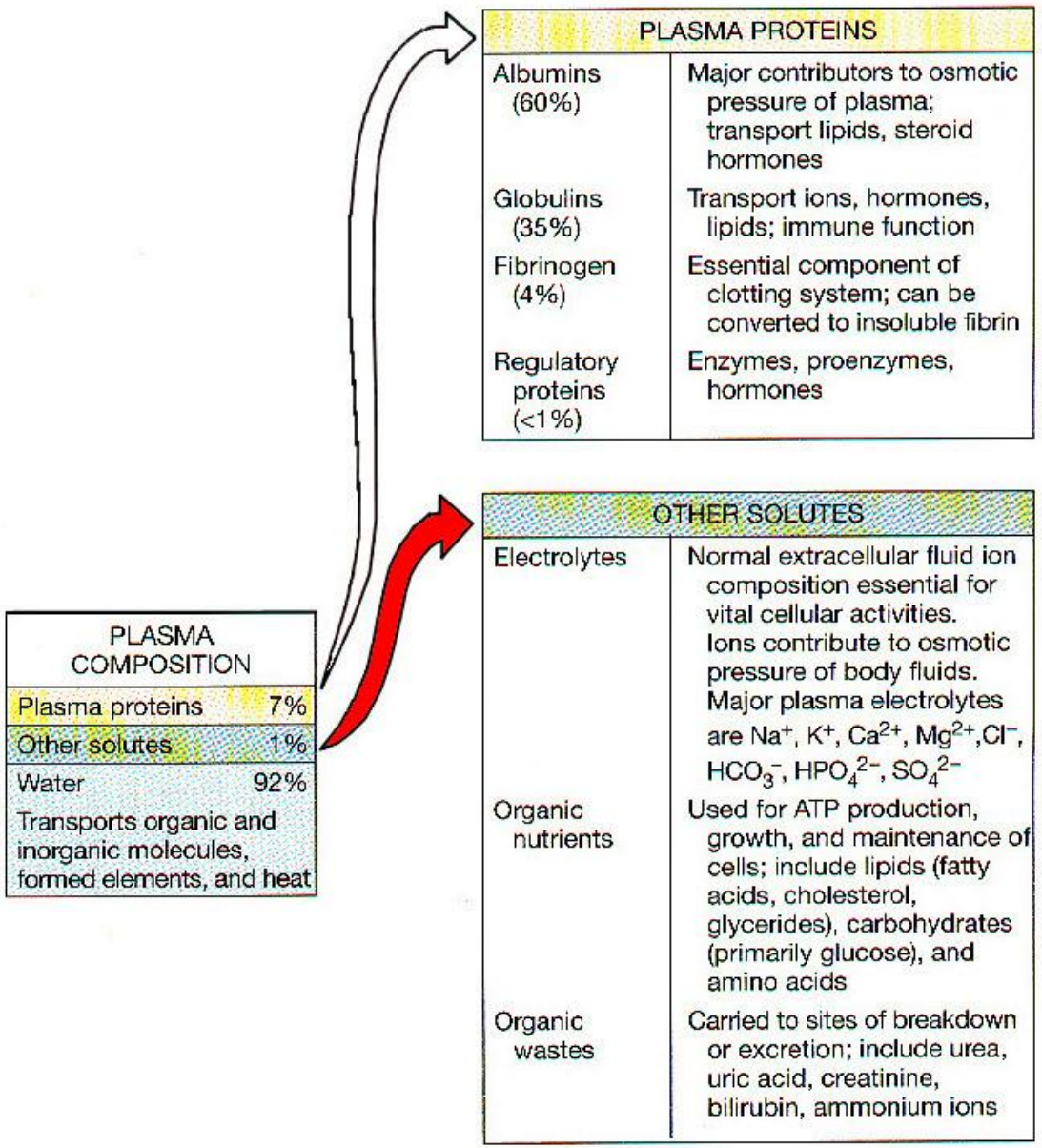
PLASMA COMPOSITION	
Plasma proteins	7%
Other solutes	1%
Water	92%
Transports organic and inorganic molecules, formed elements, and heat	

PLASMA PROTEINS	
Albumins (60%)	Major contributors to osmotic pressure of plasma; transport lipids, steroid hormones
Globulins (35%)	Transport ions, hormones, lipids; immune function
Fibrinogen (4%)	Essential component of clotting system; can be converted to insoluble fibrin
Regulatory proteins (<1%)	Enzymes, proenzymes, hormones

OTHER SOLUTES	
Electrolytes	Normal extracellular fluid ion composition essential for vital cellular activities. Ions contribute to osmotic pressure of body fluids. Major plasma electrolytes are Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, HPO_4^{2-}, SO_4^{2-}
Organic nutrients	Used for ATP production, growth, and maintenance of cells; include lipids (fatty acids, cholesterol, glycerides), carbohydrates (primarily glucose), and amino acids
Organic wastes	Carried to sites of breakdown or excretion; include urea, uric acid, creatinine, bilirubin, ammonium ions

- Proteins important for osmotic balance
  - albumin (60%)
    - transports lipids
    - steroid hormones
  - fibrinogen (4%) - blood clotting
  - globulins (35%) – many different proteins with a wide variety of functions
  - globulin classes α, β, and γ
  - 1% other regulatory proteins

Components of Blood - Plasma



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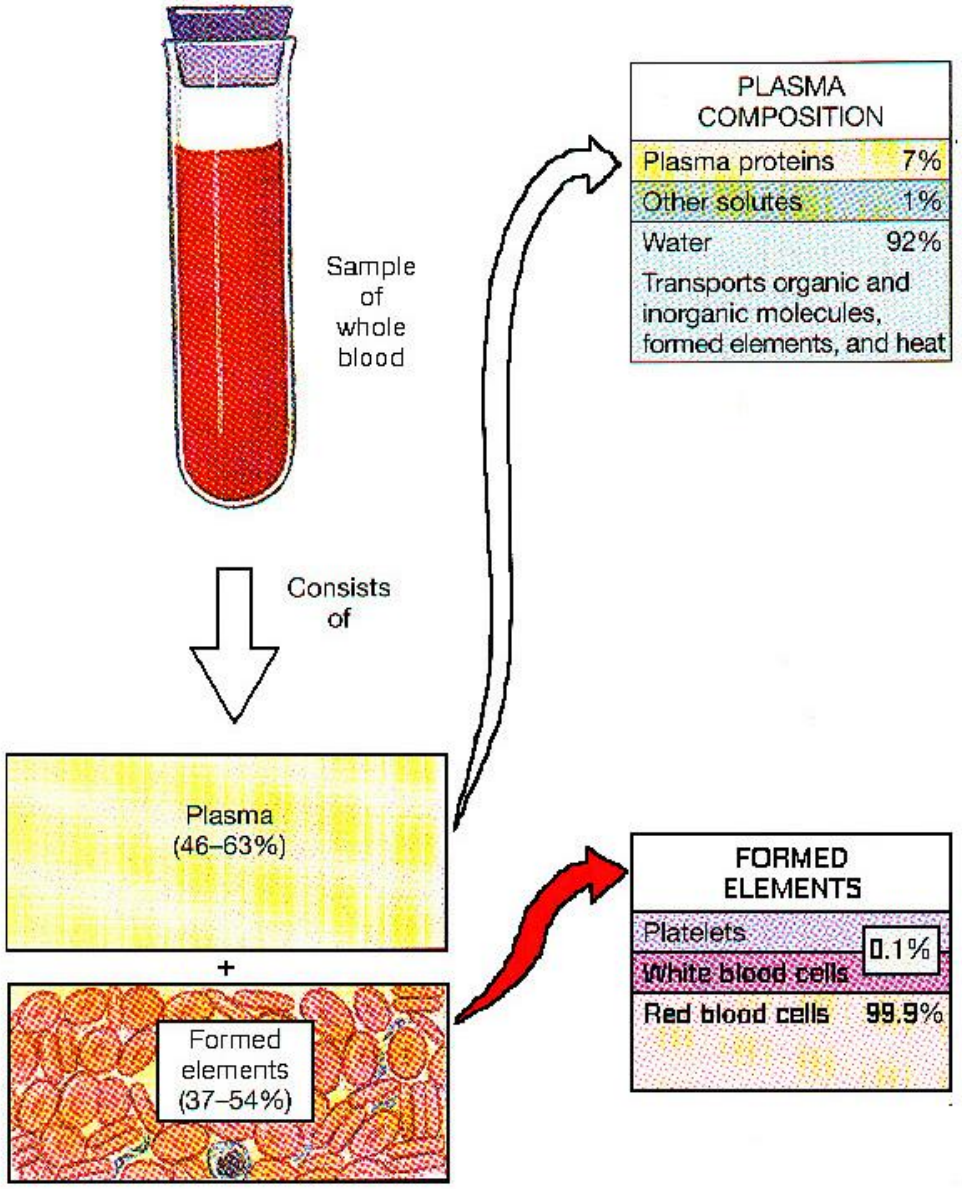
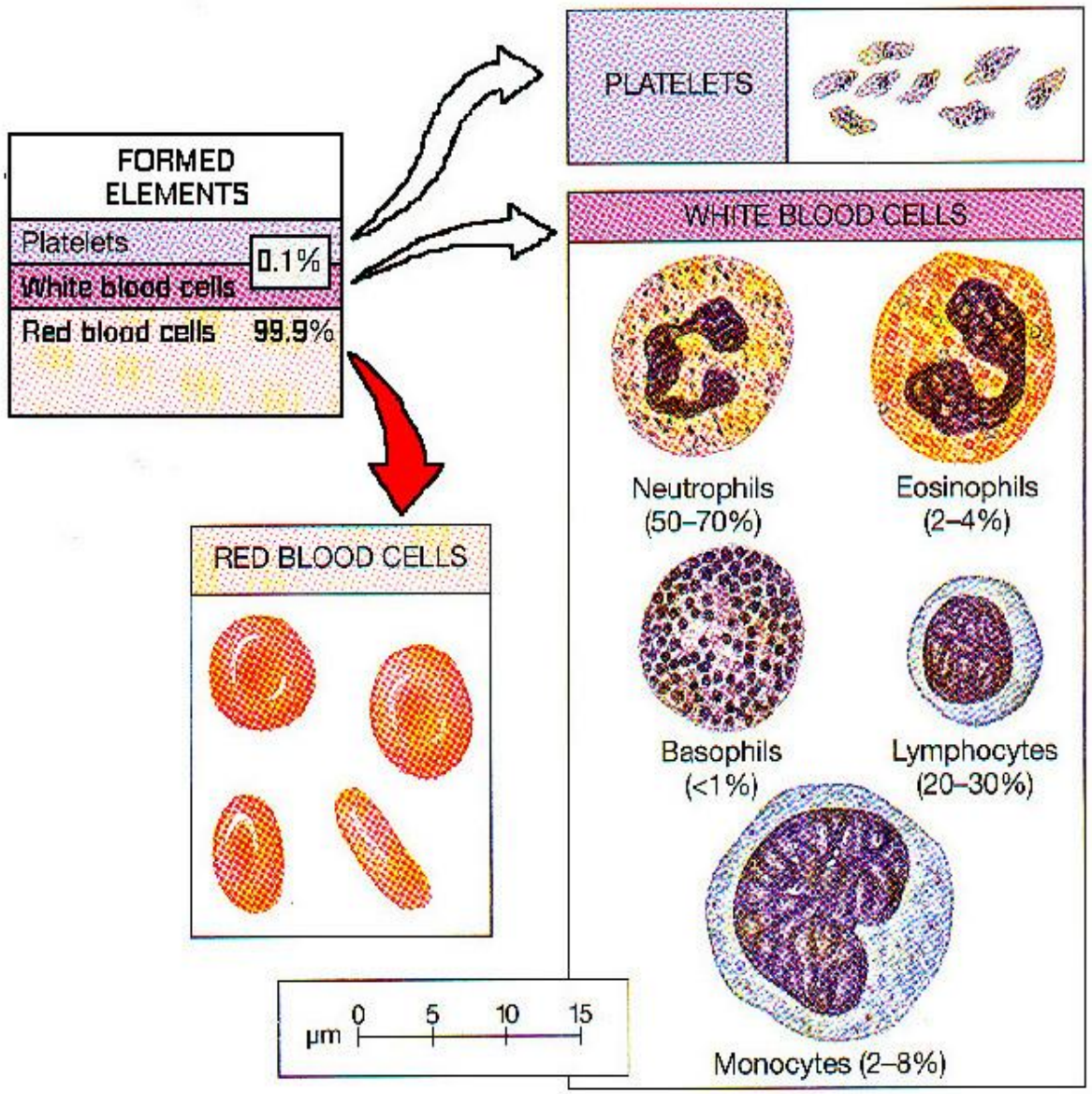
- Other solutes
  - Waste products - carried to various organs for removal
  - Nutrients – glucose and other sugars, amino acids, lipids, vitamins and minerals
  - Electrolytes (ions)
  - Regulatory substances
    - enzymes
    - hormones
  - Gases - O_2, CO_2, N_2

Components of Blood - Formed Elements



- Formed elements
  - >99% red blood cells
  - <1% white blood cells and thrombocytes (platelets)

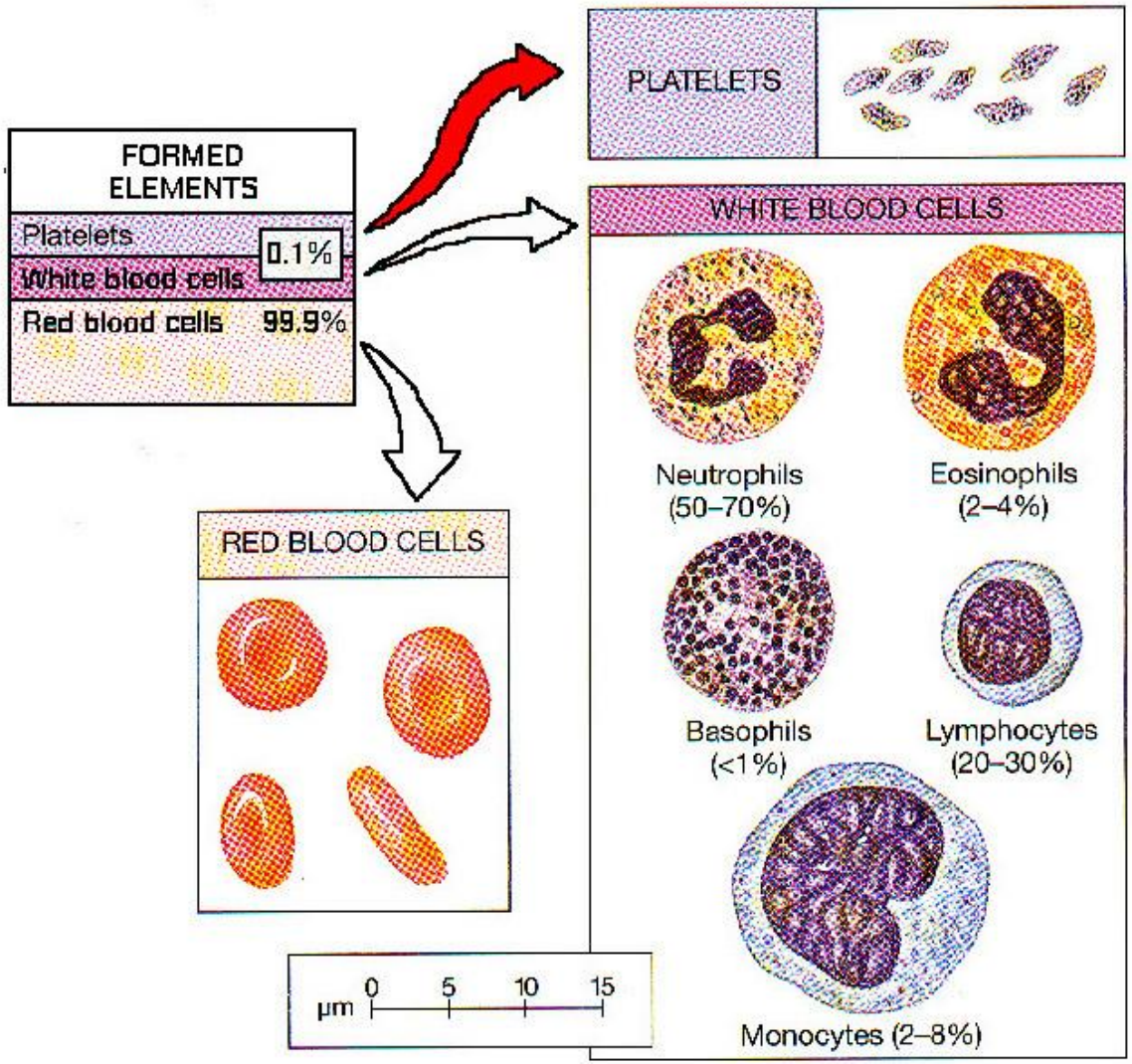
Components of Blood - Formed Elements



- Erythrocytes, or Red Blood Cells (RBC's), for O_2 and CO_2 transport
- RBCs' hemoglobin also helps buffer the blood

IMPORTANT!
Note the differences in relative size and appearance!

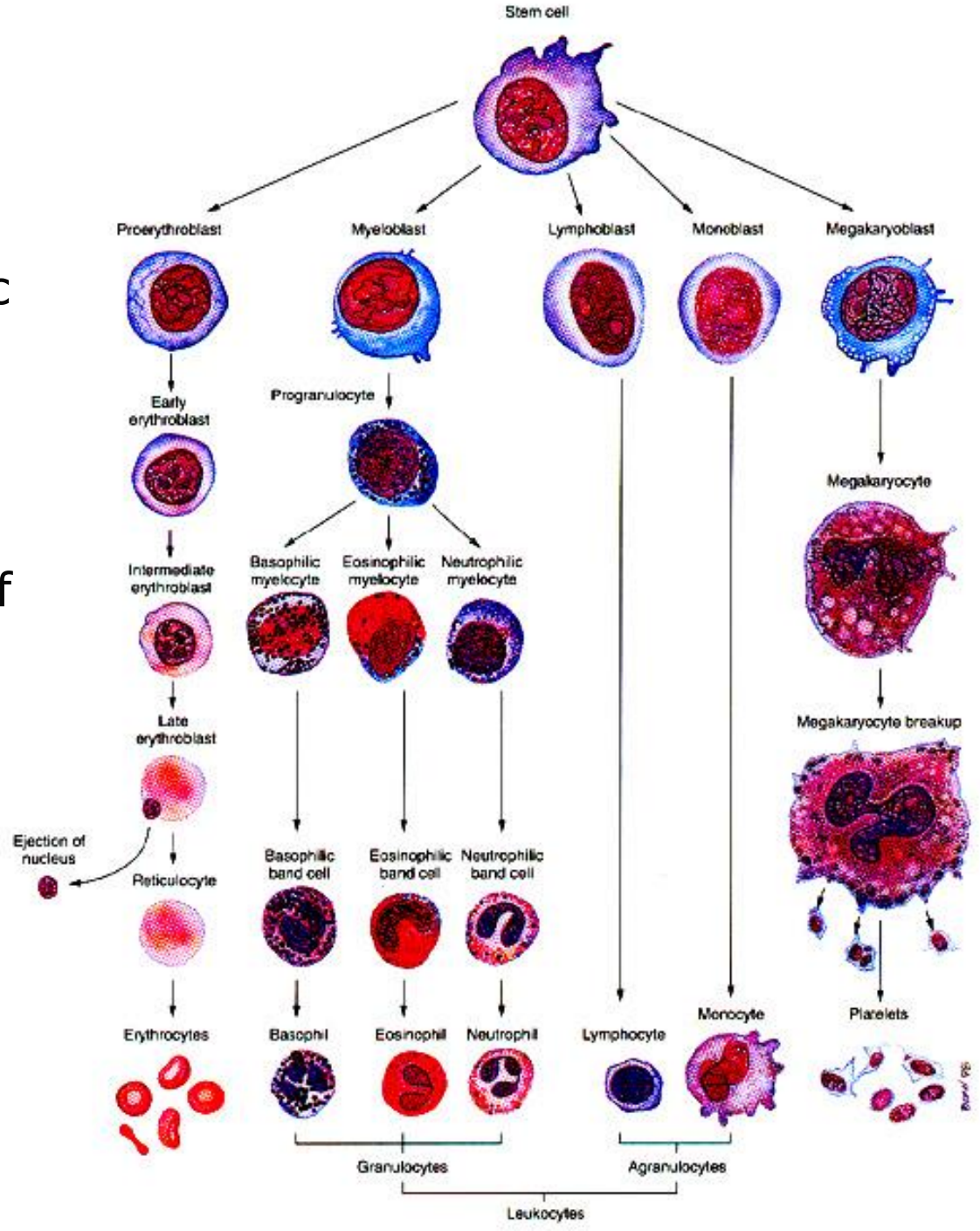
Components of Blood - Formed Elements



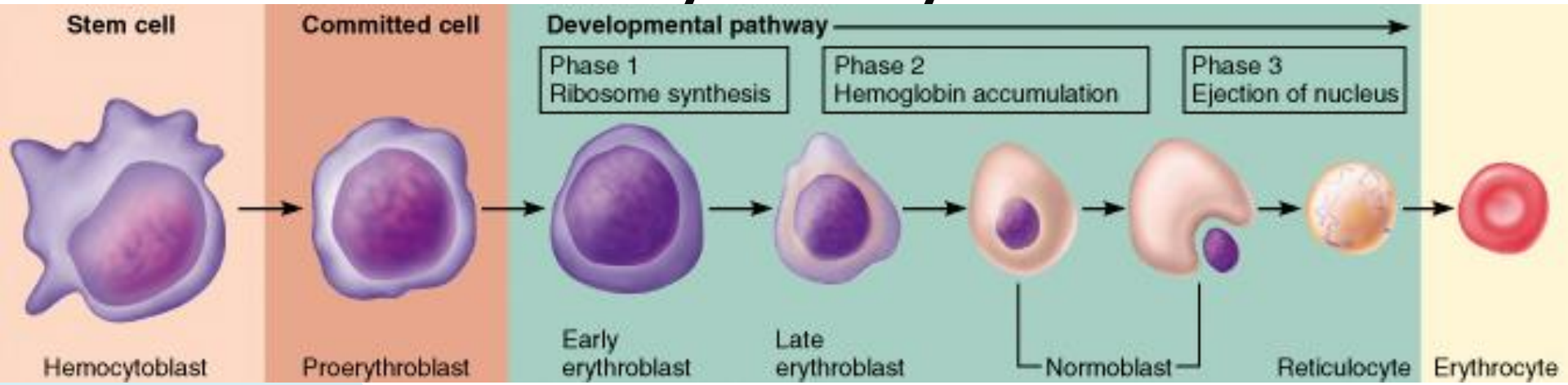
- Leukocytes (White Blood Cells)
  - Granular leukocytes (granulocytes)
    - neutrophils
    - eosinophils
    - basophils
  - Agranular leukocytes (agranulocytes)
    - lymphocytes - T cells, B cells
    - monocytes → tissue macrophages
- Thrombocytes (platelets)

Hematopoiesis

- Blood cell formation
- All blood cells come from pluripotent hematopoietic stem cells (hemocytoblasts)
  - reside in red bone marrow
  - give rise to 5 types of precursor cells
  - precursors develop into RBCs, WBCs and "giant" megakaryocytes which produce platelets by cytoplasmic fragmentation



Production of Erythrocytes

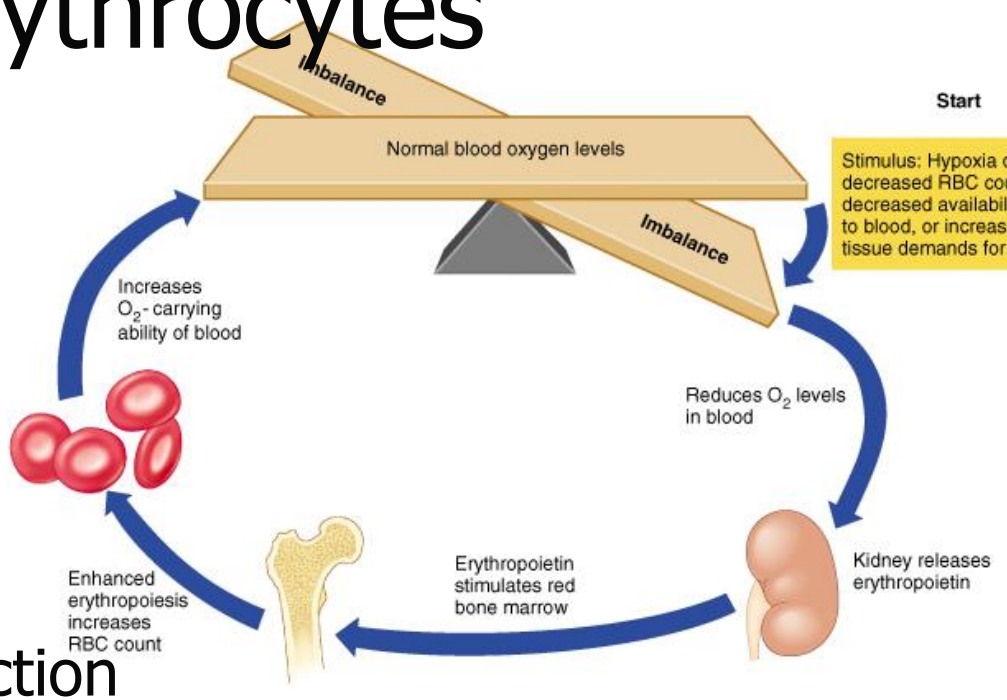


- Erythropoiesis
  - RBC production
  - controlled by hormones, especially erythropoietin (EPO) from the kidney
  - three phases of RBC maturation
    - production of ribosomes
    - synthesis of hemoglobin
    - ejection of the nucleus and reduction in organelles
  - leave bone marrow as reticulocytes → mature in the blood stream to become erythrocytes

RBC Production - Erythropoiesis (cont.)

- Reticulocyte count
  - Reticulocyte
    - final stage before mature RBC
    - released into blood where final maturation occurs
  - Count reticulocytes to evaluate the health of the marrow stem cells or the response of red bone marrow to erythropoietin (EPO)
    - low count - bone marrow not responding
    - high count - replacement production or abnormal circumstances

Production of Erythrocytes

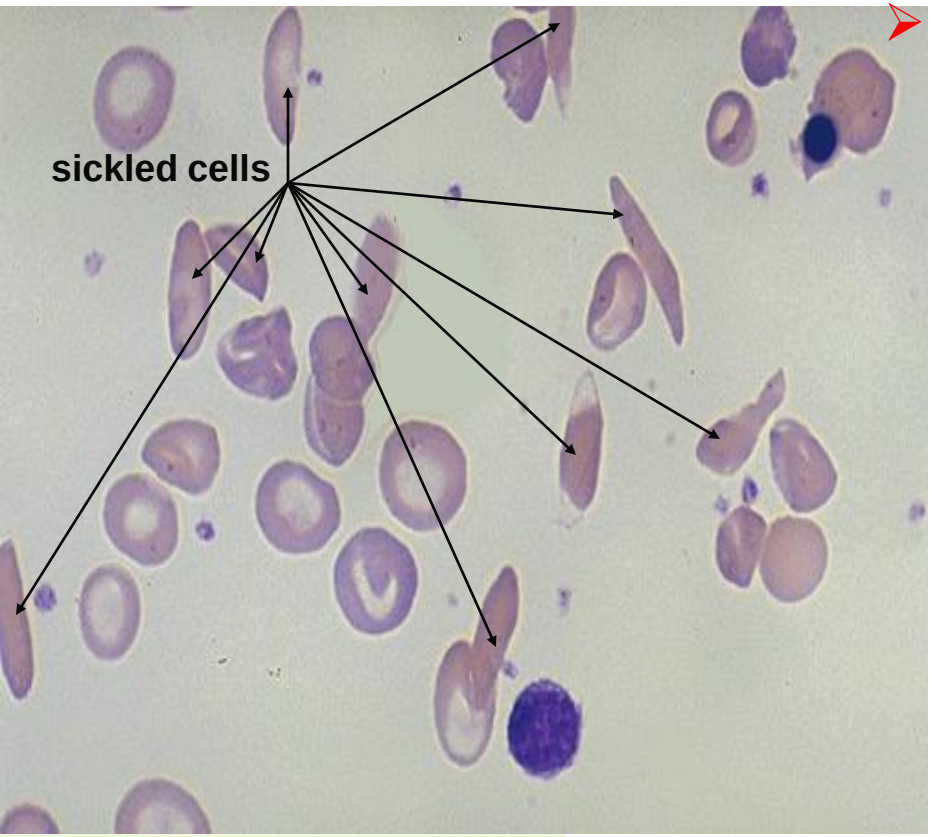


- Regulation of RBC production
  - regulated by negative feedback
    - O_2 levels monitored in kidneys
    - hypoxia increases RBC production
  - production stimulated by erythropoietin (EPO) from kidneys
- Numbers
  - ♂ - 5.4 million RBC's/ml (testosterone stimulates EPO synthesis)
  - ♀ - 4.8 million RBC's/ml
  - 2 million cells released into blood/second

RBC Production - Anemia

- Anemia – symptoms of reduced O_2 carrying capacity of the blood
- Causes
  - Insufficient number of RBC's
    - hemorrhage - loss of RBC's
    - hemolytic anemia - premature RBC destruction due to transfusion reaction, various diseases, or genetic problems
    - aplastic anemia
      - destruction or inhibition of hematopoietic components in bone marrow
      - tumors, toxins, drugs, or irradiation
  - Decreased hemoglobin content in the RBCs
    - iron (heme) deficiency - insufficient iron due to diet or poor absorption
    - pernicious anemia - lack of Vitamin B_{12}
      - Vitamin B_{12}
        - common in the diet
        - needed for developing RBC cell division
      - intrinsic factor needed for proper B_{12} absorption, often deficient and the actual cause of the B_{12} deficiency

RBC Production - Anemia

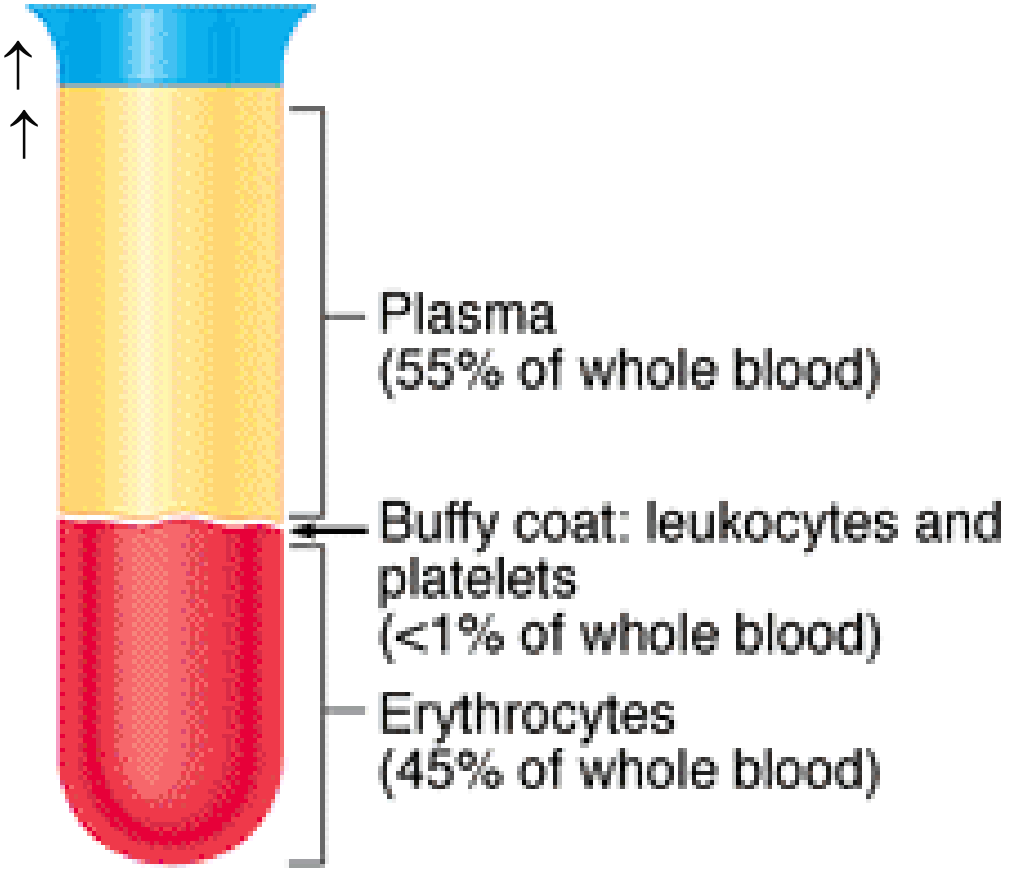


Abnormal Hgb - hereditary

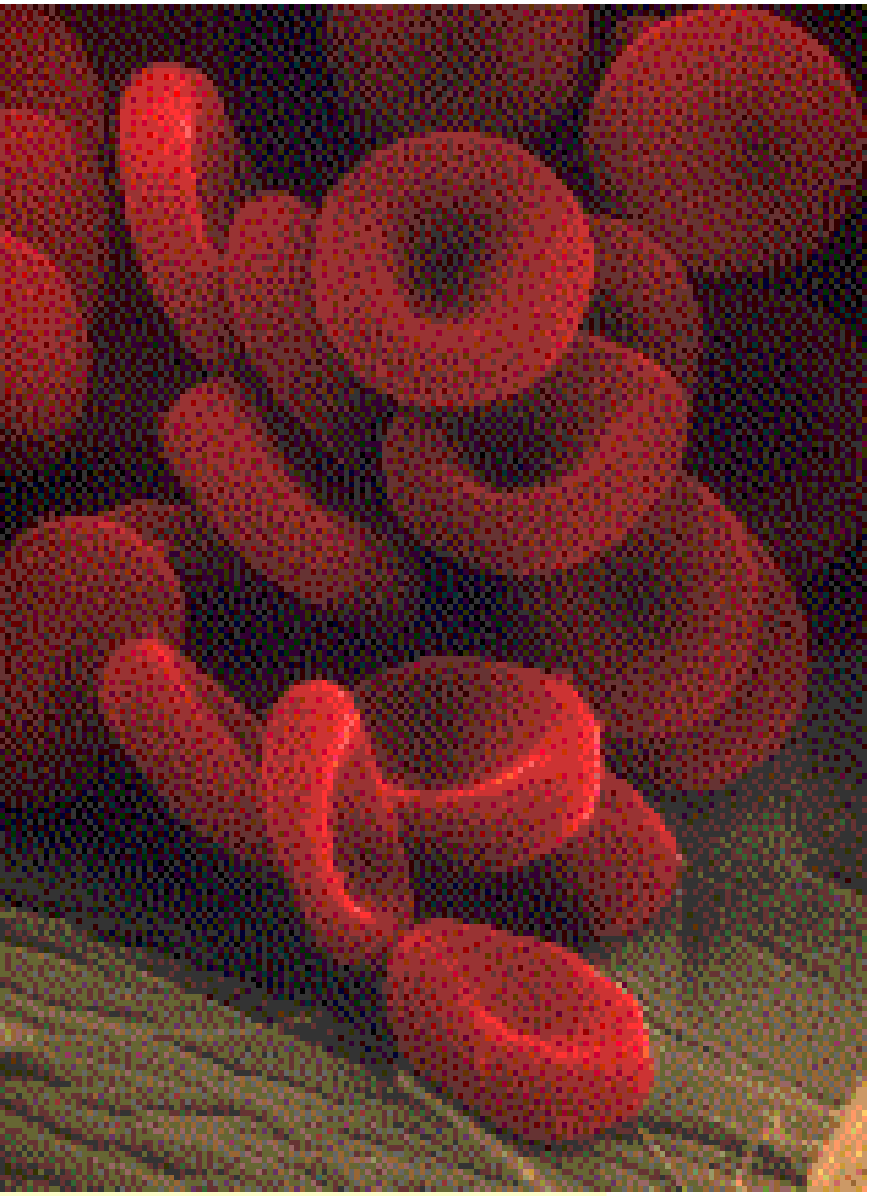
- Thalassemias
  - Greeks, Italians (Mediterraneans)
  - reduced or absent globin synthesis
  - RBC's delicate - may rupture
  - low RBC count
- Sickle Cell Anemia
  - Africans, African-Americans
  - Substitution mutation of 1 AA in the hemoglobin molecule changes the shape, flexibility & lifespan of the RBCs
    - prevents adequate O_2 transport
    - sickled cells lodge in and block capillaries
  - Need two copies of the abnormal recessive gene for Sickle Cell Disease
  - One normal, one abnormal copy: increased resistance to malaria = Sickle Cell Trait

RBC Production - Erythropoiesis (cont.)

- Hematocrit (Hct)
  - % of blood that is RBC's
  - ♂ : 40-54% (47%), ♀: 38-46% (42%), Why?
  - Indicates RBC production and state of hydration
  - Abnormal Hct
    - high altitude – hypoxia ↑
    - athletes - blood doping ↑
    - polycythemia ↑
    - anemias ↓
    - hemorrhage ↓
    - malaria ↓
    - cancer ↓
    - chemotherapy ↓
    - radiation ↓
    - drugs ↓

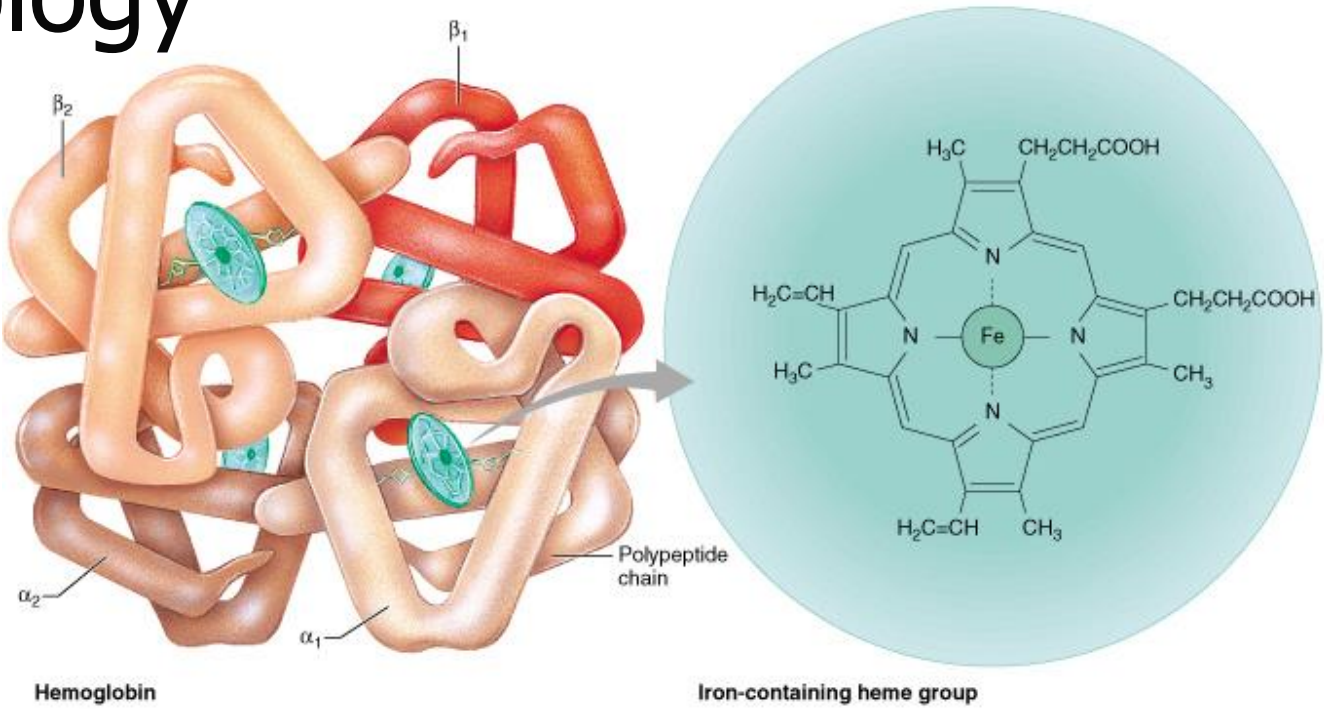


RBC Structure



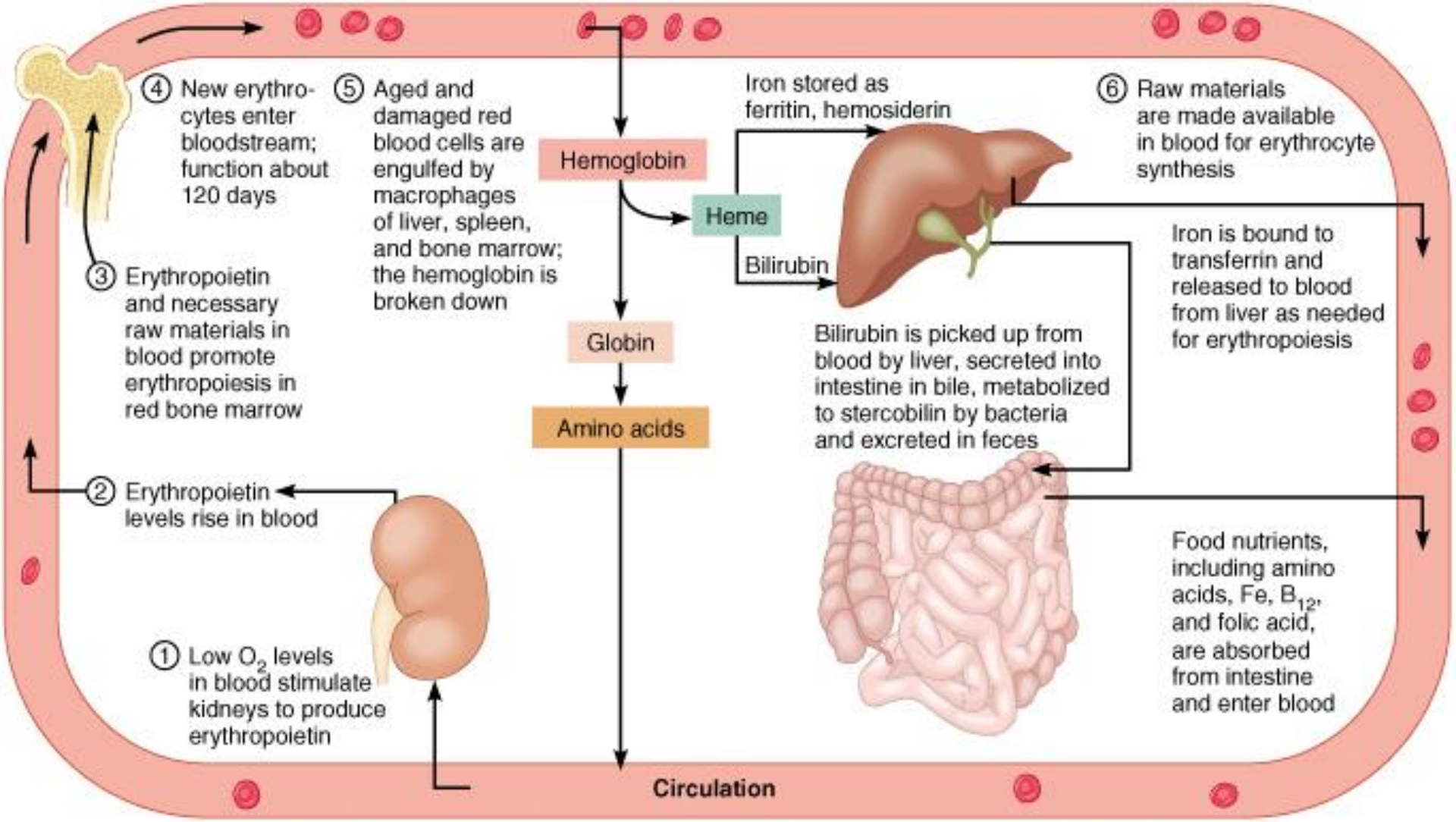
- ~280 million Hgb molecules/cell
- Hgb for O_2 transport
- Bi-Concave shape
  - greater surface area/volume ratio increases gas diffusion
  - flexibility allows passage through narrow capillaries

RBC Physiology

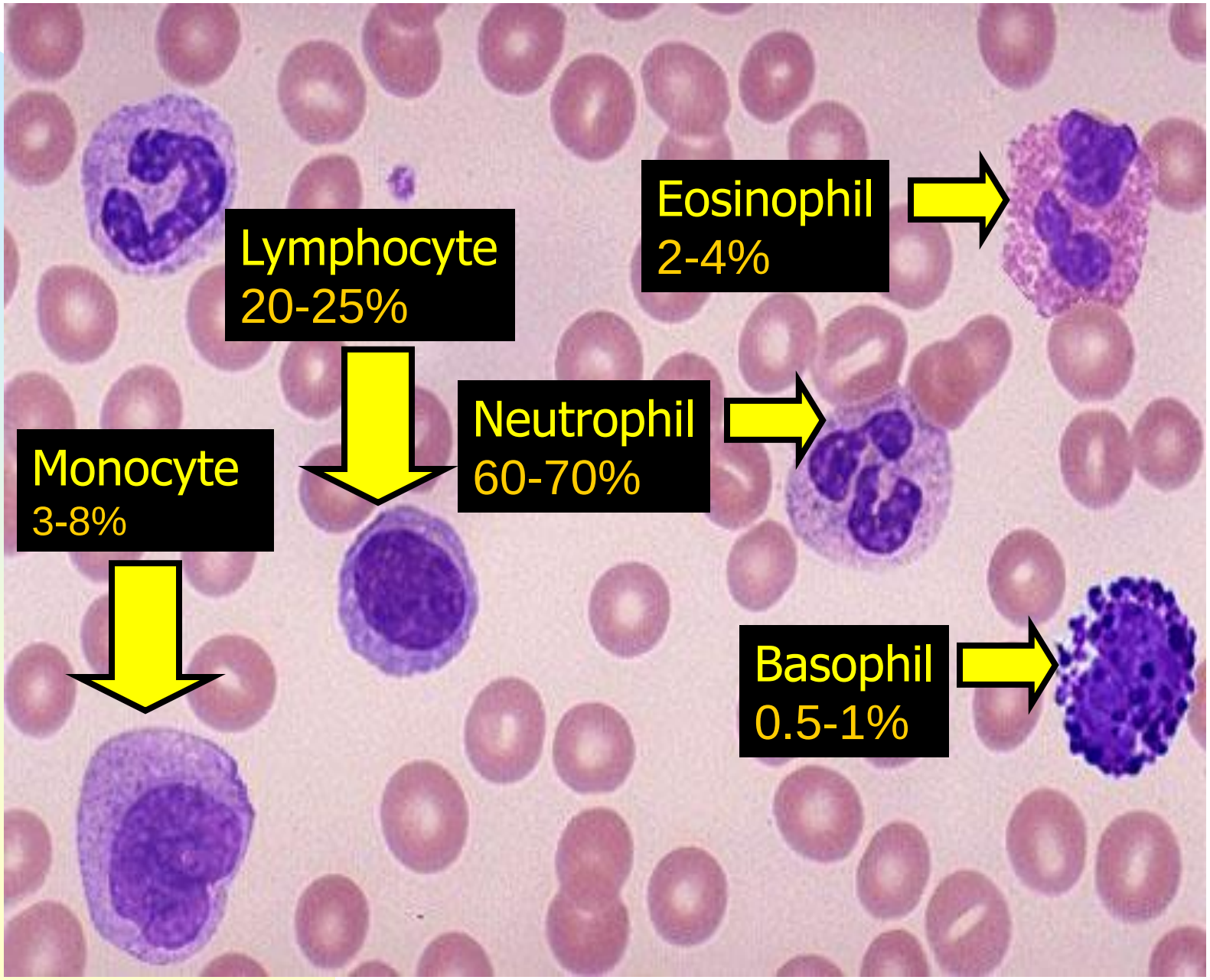


- O_2 combines with Hgb in lungs
- O_2 gas not very soluble in H_2O
- Hemoglobin transports O_2 Hemoglobin
  - 2 α globin chains & 2 β globin chains
  - 4 heme groups (lipid)
  - each heme binds an iron ion (Fe^{2+}) that carries 1 O_2

RBC Life Span



Differential WBC Count



Lymphocytes - Physiology

- Immune response through lymphocytes responding to ***antigen (AG)***

- An antigen is:
  - any chemical substance recognized as foreign when introduced into the body
  - substance (usually proteins) that stimulate immune responses

Lymphocytes - Physiology

- Two main types of lymphocytes
  - B-cells
    - particularly active in attacking bacteria
    - develop into plasma cells to produce ***antibodies (Ab)***
      - bind to antigen to form antibody-antigen (Ag-Ab) complexes
      - complexes prevents Ag from interacting with other body cells or molecules
      - memory B cells – dormant until future exposure to Ag
  - T-cells
    - attack viruses, fungi, transplants, cancer, some bacteria
    - 4 types of cells
      - cytotoxic (killer) T cells - destroy foreign invaders
      - helper T cells - assist B cells and cytotoxic T cells
      - suppressor T cells – help bring immune response to an end
      - memory T cells - dormant until future exposure to Ag

Leukocyte Life Span and Number

- Life span determined by activity
  - Ingesting foreign organisms, toxins, shortens life
  - Healthy WBC's – majority last days, but some last months to years
  - During infection, WBCs may only live hours
    - engorge with ingested organisms, necrotic cells, toxins, Ab-Ag complexes
    - often die and lyse (burst)

Leukocyte Life Span and Number

- 5,000 - 10,000 WBC's/mm^3 blood
  - *RBC/WBC ratio 700/1*

- Differential WBC count (a standard clinical lab report)
  - Neutrophils 60-70%
  - Lymphocytes 20-25%
  - Monocytes 3-8%
  - Eosinophils 2-4%
  - Basophils 0.5-1%

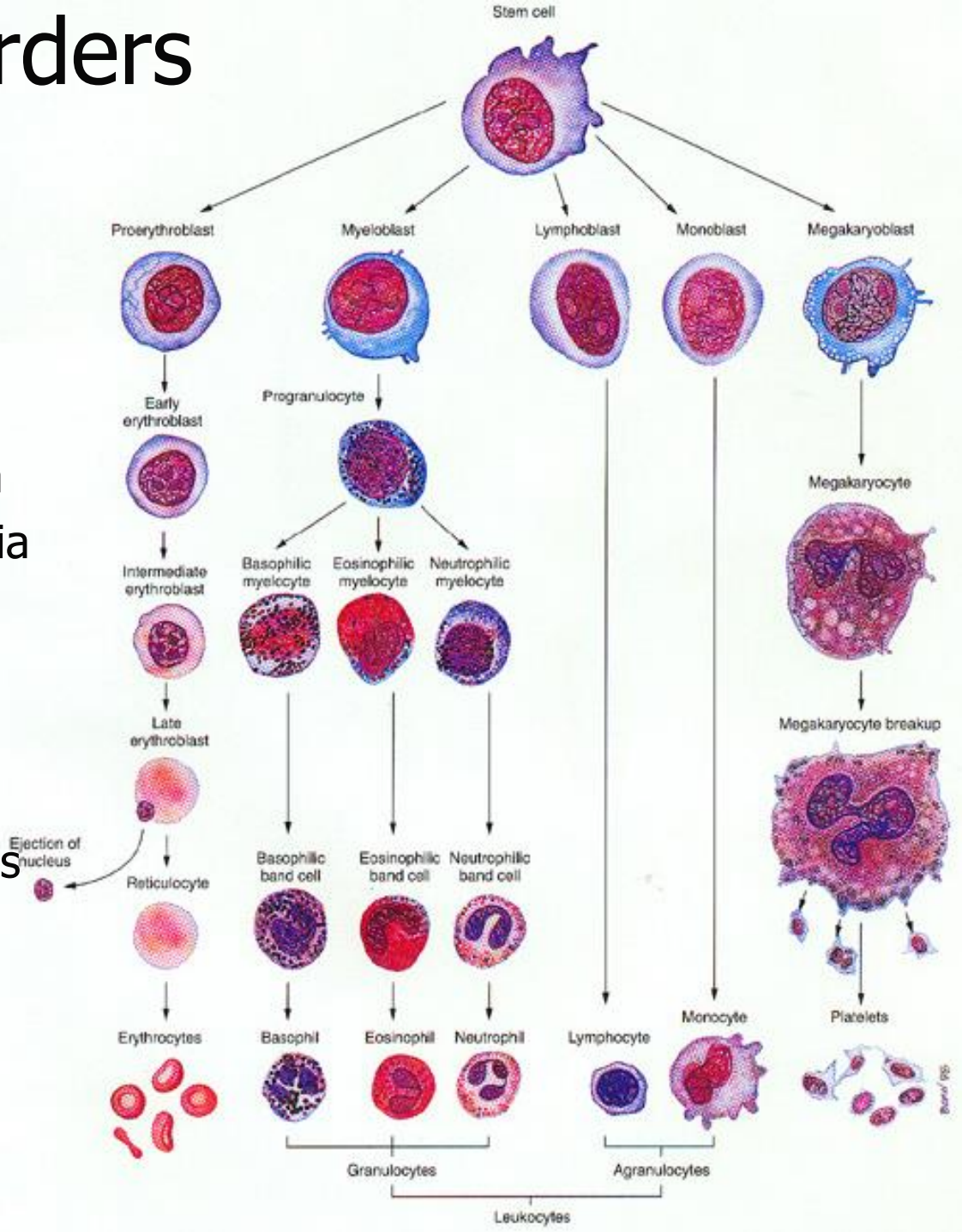
- Abnormal proportions are correlated with different types of disease processes

Leukocyte Number Abnormalities

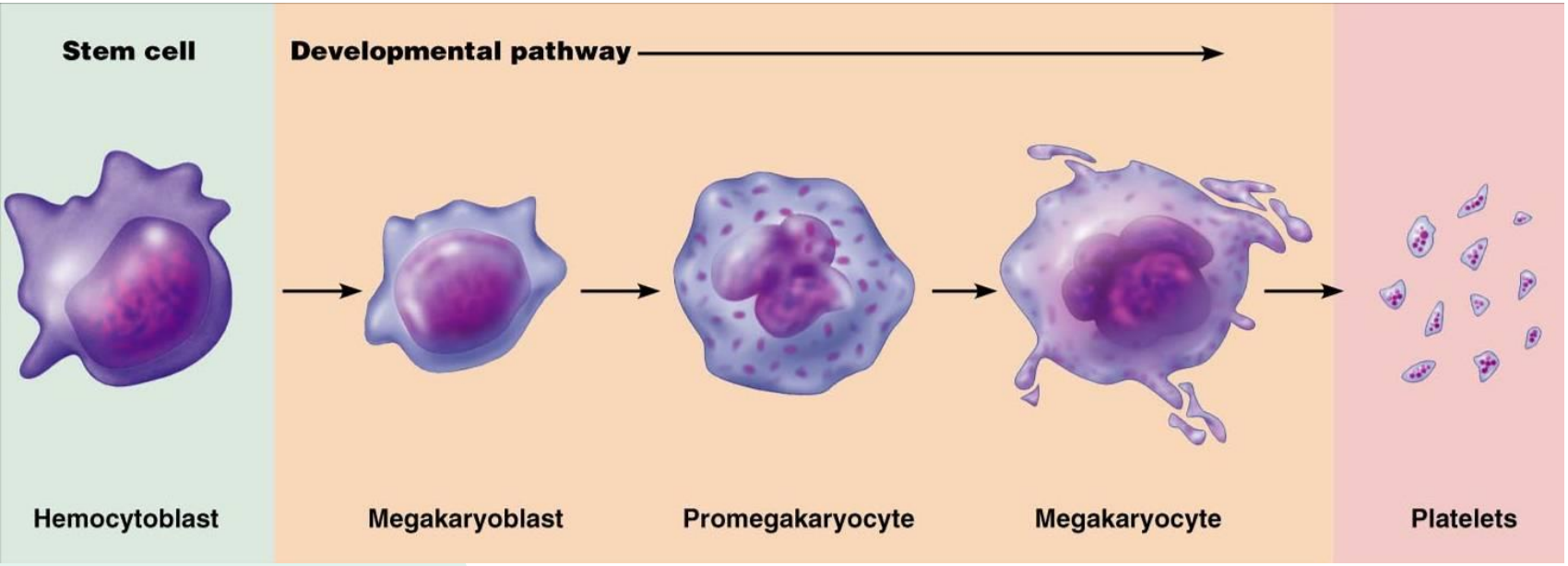
- Leukopenia = decreased numbers
  - malnutrition, chronic disease states
  - drug induced - glucocorticoids, anti-cancer drugs, etc.
- Leukocytosis = increased numbers
  - Normal component of inflammatory response to injuries and infections
- Leukemia, Lymphomas = grossly increased numbers, abnormal forms; many subcategories
  - bone marrow and blood stream (leukemia) or tissue spaces (lymphoma) fill with cancerous (nonfunctional) leukocytes
  - crowds out other cells types
    - anemia
    - bleeding
    - immunodeficiency

Leukocyte Disorders

- Generally a descendent of a single cell
  - different types of cells
    - myelocytic leukemia
    - lymphocytic leukemia
  - under different cancerous conditions
    - acute - if derived from *-blast* type cells
    - chronic - if derived from later stages

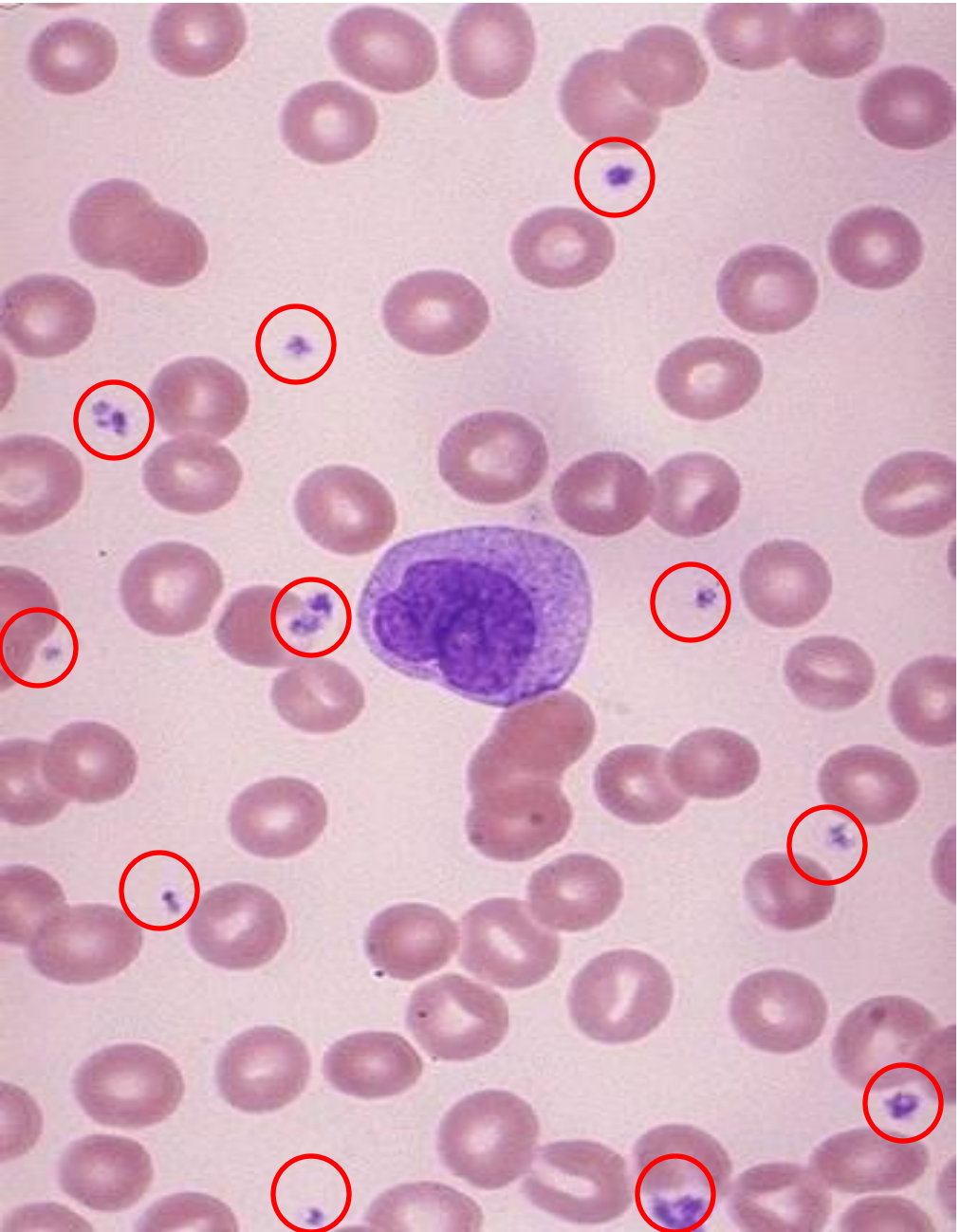


Thrombocytes - Platelets



- Development
  - Megakaryocytes shed small cytoplasmic fragments
  - Each fragment surrounded by plasma membrane
- Anatomy
  - 250,000-400,000/mm^3
  - No nucleus, disc shaped
  - 2-4 µm diameter with many granules

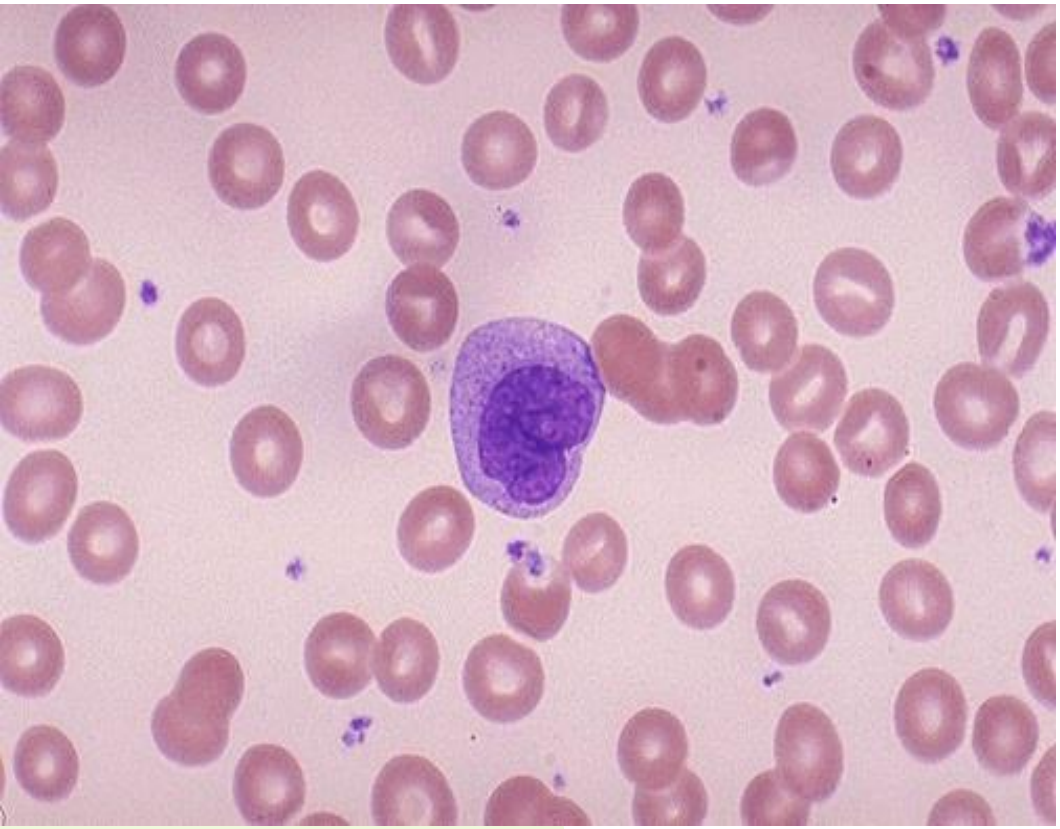
Thrombocytes - Platelets (cont.)



Physiology

- Short life span (5-9 days)
- Help plug small holes in blood vessels
- Granules contain regulatory factors which serve several important functions in:
  - coagulation
  - inflammation
  - immune defenses

Thrombocytes - Platelets (Granules)



- alpha granules
  - clotting factors
  - platelet derived growth factor (PDGF)
- dense granules
  - Ca^{++}, ADP, ATP
  - Thromboxane A_2,
  - vasoconstrictors
  - clot promoting enzymes

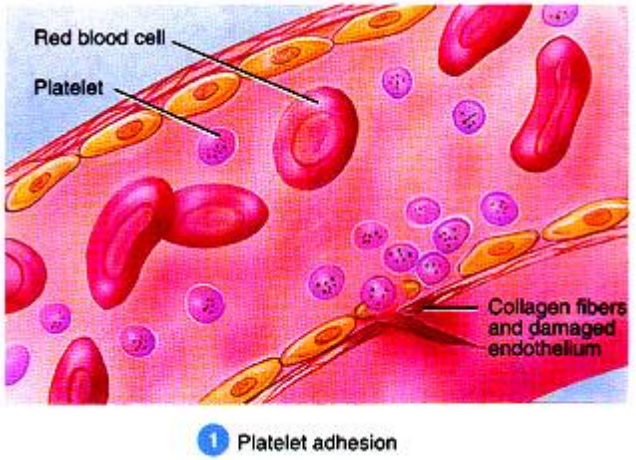
Hemostasis

- 3 mechanisms exist to stop bleeding

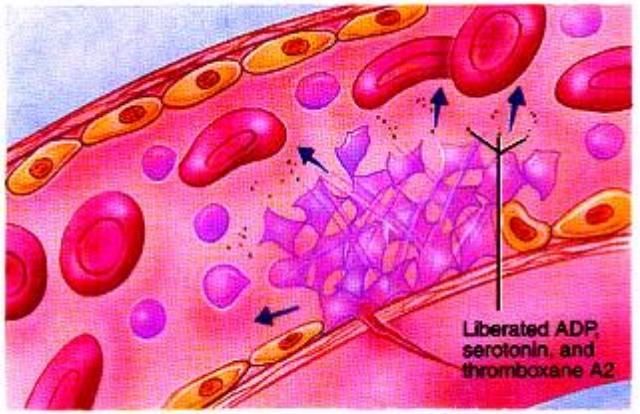
- First - Vascular Spasm
  - Blood vessel constricts when damaged
    - vessel wall smooth muscle contracts immediately
    - blood flow slows through vessel
    - local trigger or autonomic reflex?

Hemostasis (cont.)

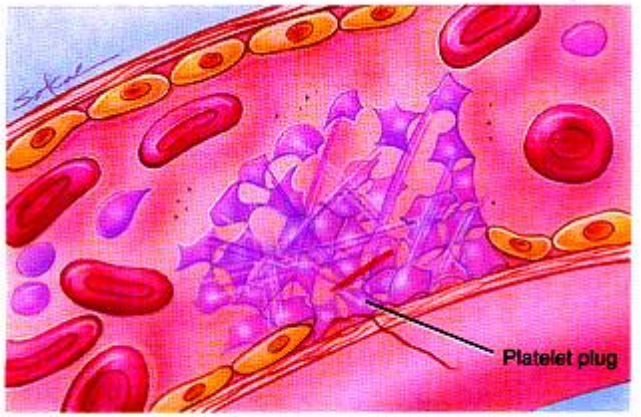
- Second - Platelet Plug Formation
  1) Platelet adhesion
     - platelets stick to exposed collagen
     - tissue factors activate platelets
  2) Platelet release reaction
     - platelets attach to other platelets
     - release granule contents (thromboxane A_2)
     - promote vasoconstriction, platelet activation and aggregation
  3) Platelet aggregation ➲ platelet plug
     - blocks blood loss in small vessels
     - less effective in larger vessels



1 Platelet adhesion



2 Platelet release reaction



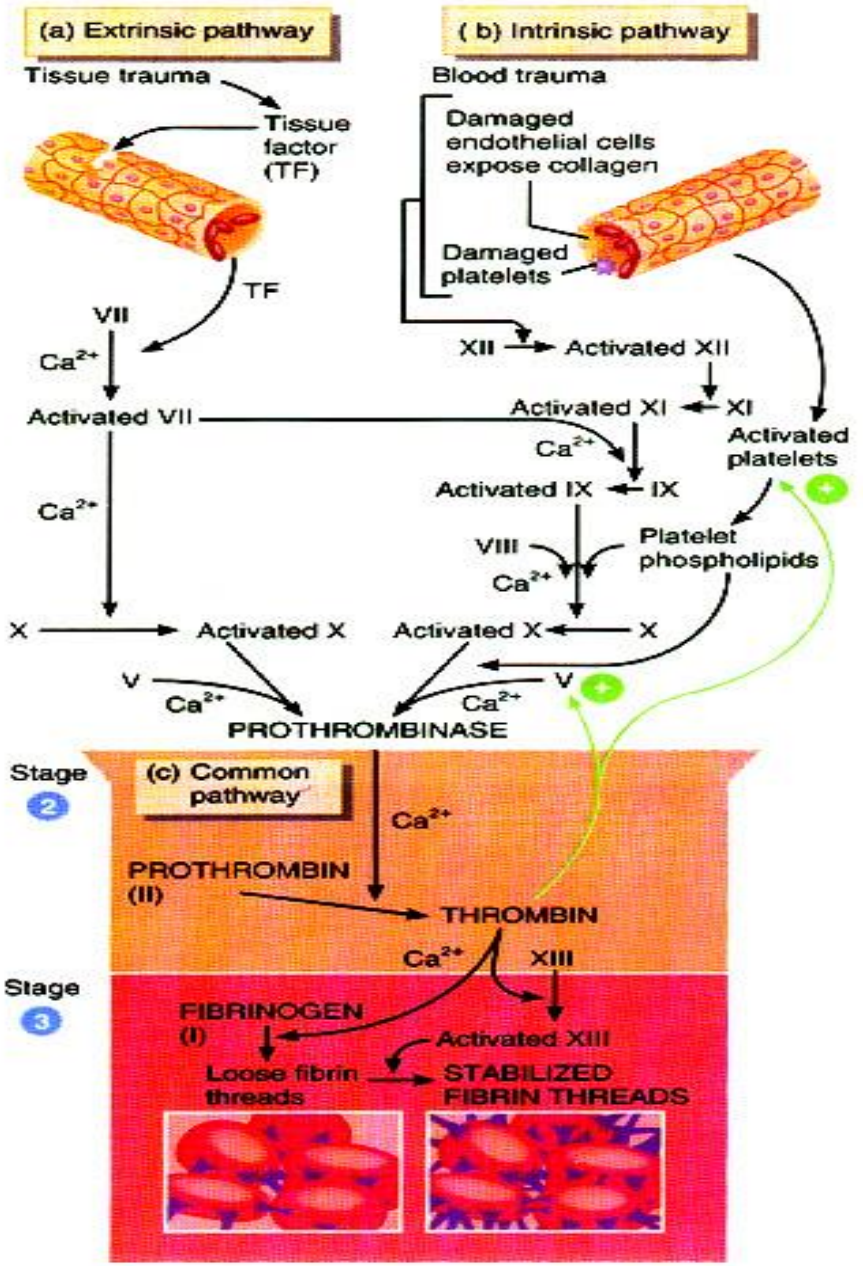
3 Platelet aggregation

Hemostasis (cont.)

- Third - Coagulation
  - Gel formation (clotting) in blood plasma traps the formed elements
  - Thrombosis - clotting in a normal vessel
  - Hemorrhage - slowed clotting may lead to bleeding

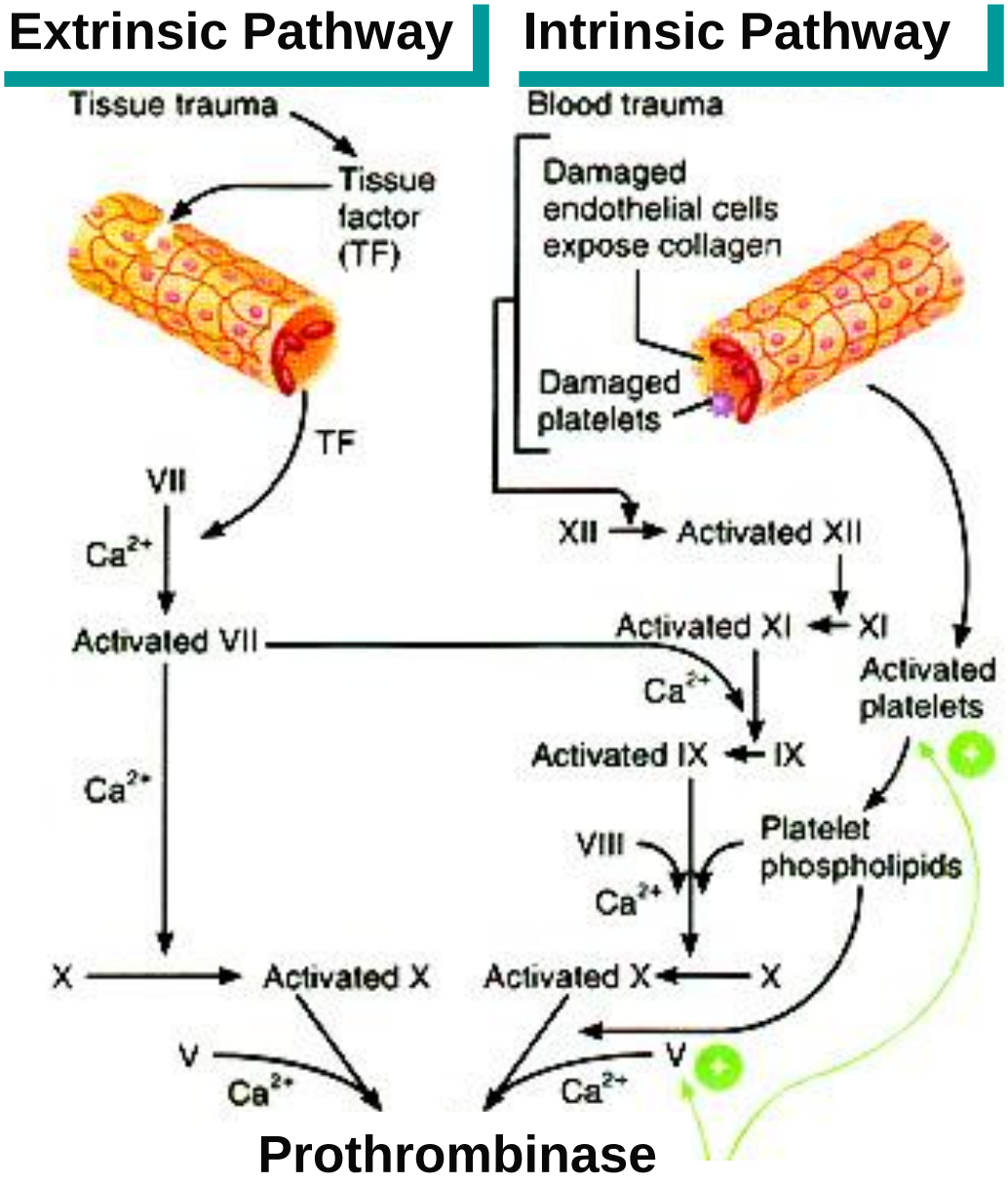
Hemostasis - Coagulation

- A complicated process that functions as a positive feedback cascade
- Fibrinogen → **Fibrin** traps blood cells
- 2 pathways – **extrinsic** & **intrinsic** unite in a common final process
- Pathways involve 12 numbered factors and additional helpers (esp. **Ca^{++}**) in clot formation



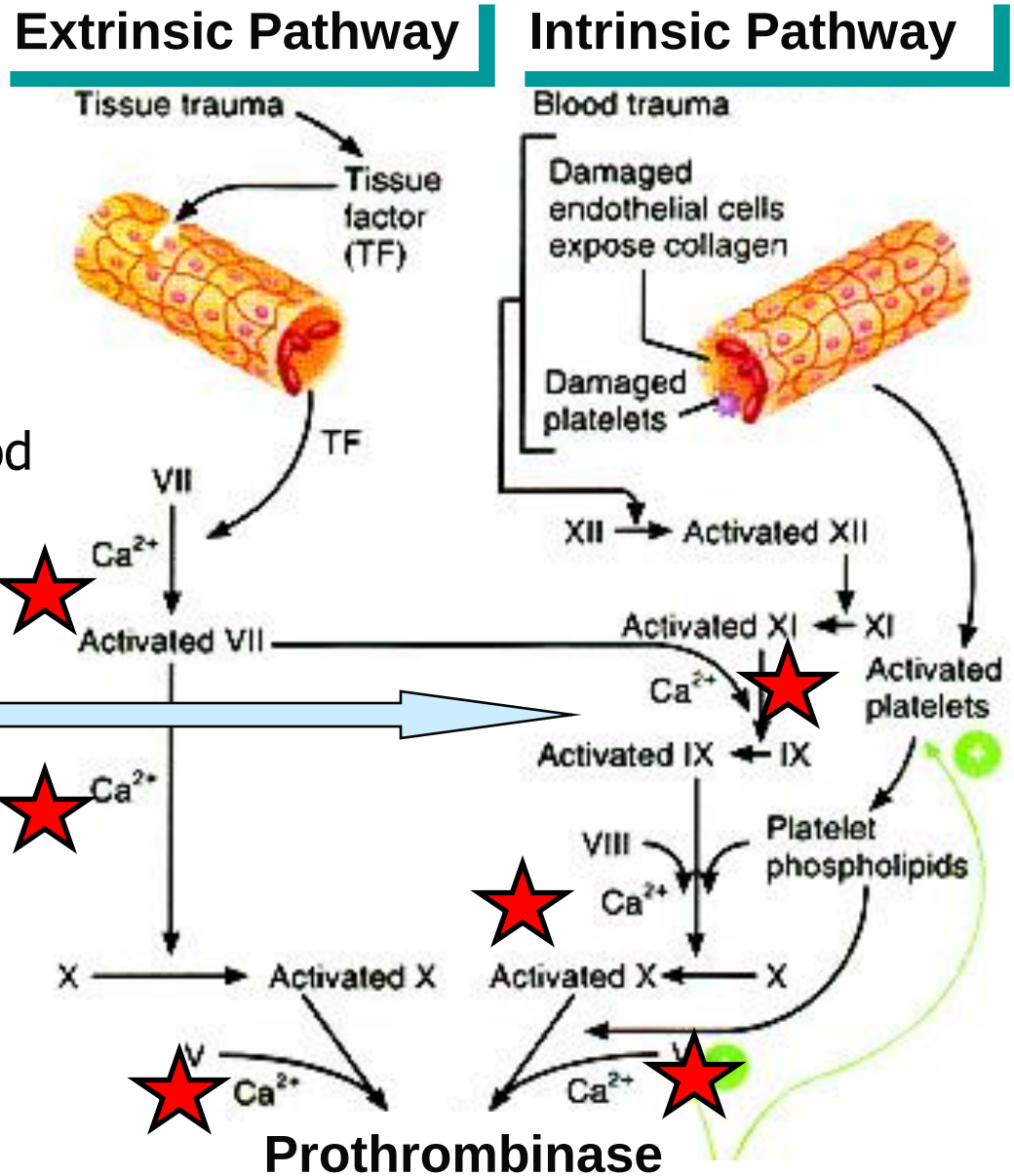
Hemostasis - Coagulation (cont.)

- Stage 1: Prothrombinase formation
  - Prothrombinase catalyzes Prothrombin conversion to Thrombin
  - Stage 1 has 2 parts
    - Part 1: **Extrinsic Pathway**
      - Rapid (seconds)
      - Tissue factor (TF) enters blood from tissue
      - Ultimately activates prothrombinase



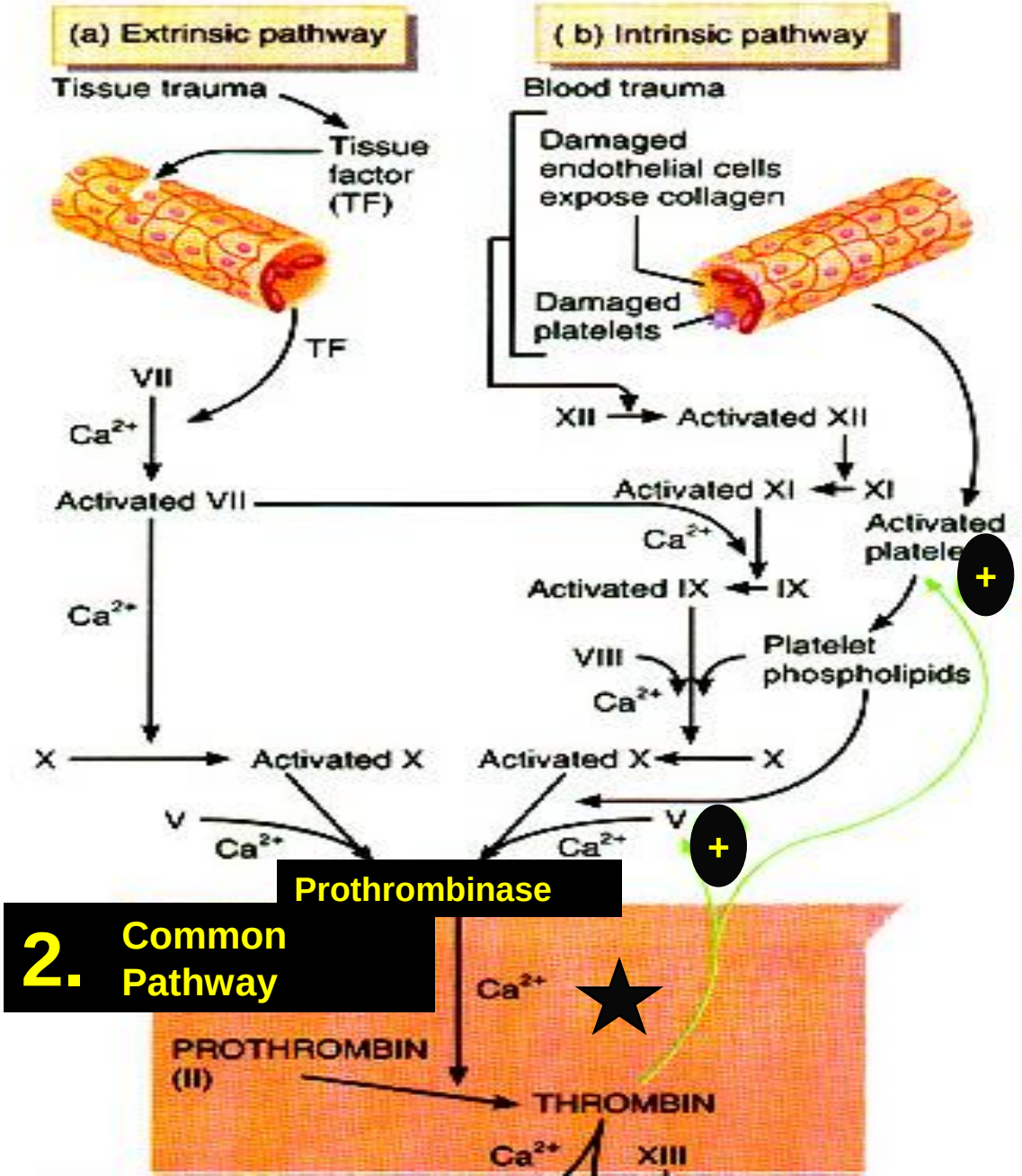
Hemostasis - Coagulation (cont.)

- Stage 1: Prothrombinase formation (cont.)
  - Part 2: **Intrinsic Pathway**
    - Slower (minutes)
    - Activators in blood – from damaged red blood or endothelial cells activate clotting
    - Extrinsic pathway also activates Intrinsic pathway
    - Ultimately activates prothrombinase
- Ca^{2+} is required for activation of both paths!



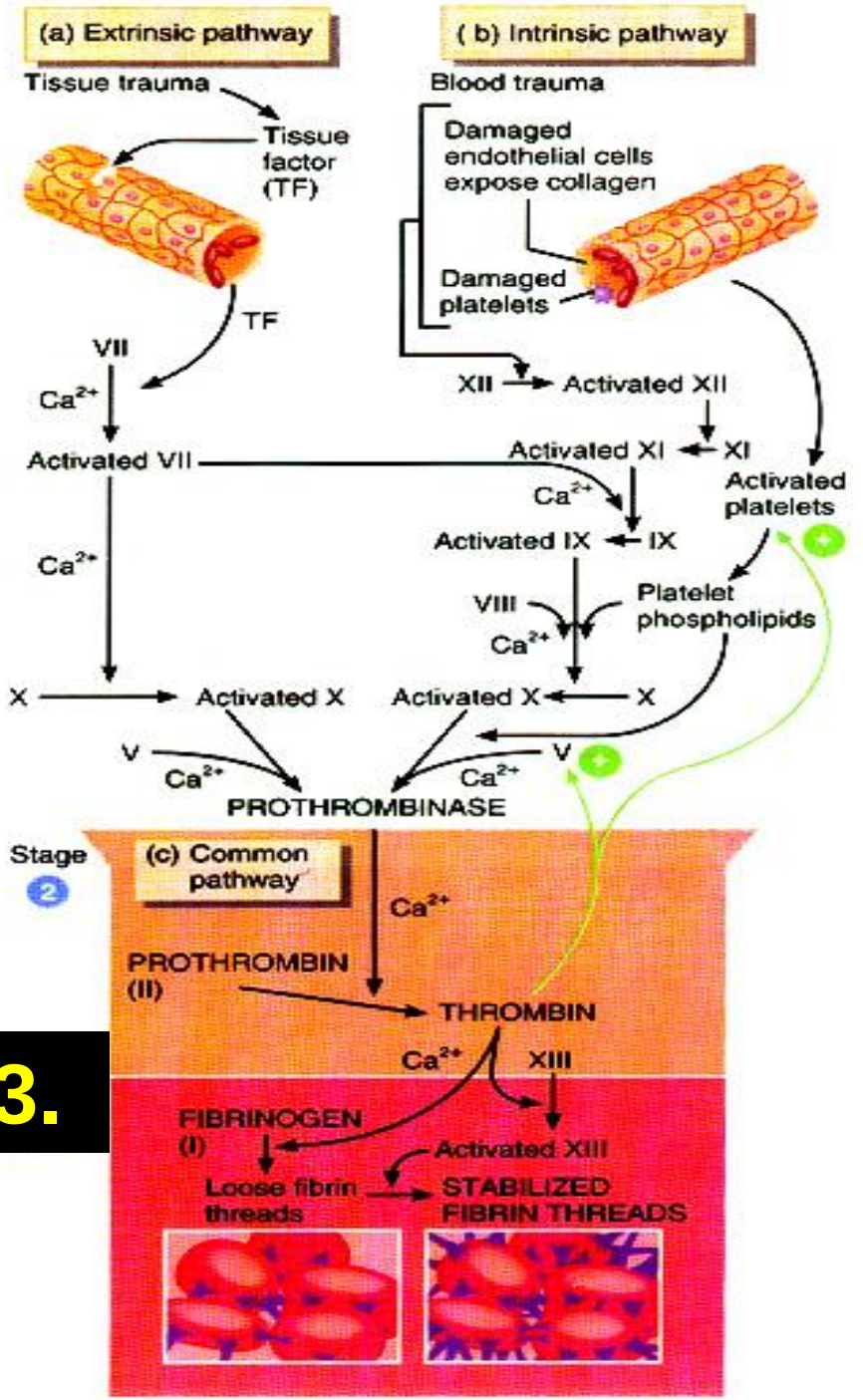
Hemostasis - Coagulation (cont.)

- Stage 2 - Common Pathway
  - Thrombin Formation
    - requires enzyme Prothrombinase & Ca^{++} ions
    - catalyzes prothrombin ⇨ thrombin
  - Thrombin accelerates formation of prothrombinase (positive feedback)
  - Thrombin accelerates platelet activation (positive feedback)



Hemostasis - Coagulation (cont.)

- Stage 3 - Common Pathway
  - Fibrin formation
    - activated enzyme thrombin with Ca^{++} ions catalyzes fibrinogen ⇨ fibrin
      - fibrinogen (soluble)
      - fibrin (insoluble)
- Fibrin
  - Protein threads attach to vessel and tissue surfaces
  - Absorbs & inactivates 90% of thrombin, limits clot formation



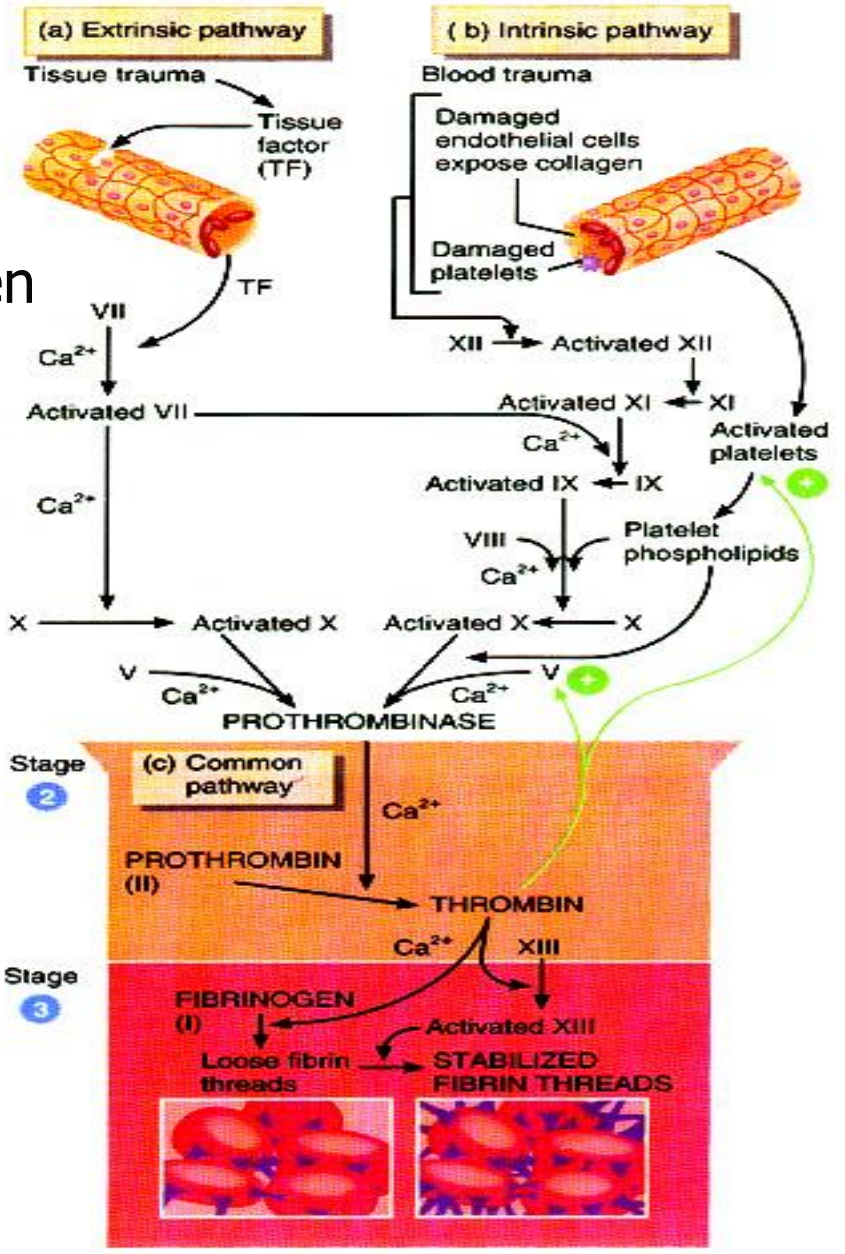
3.

Hemostasis - Coagulation (cont.)

- Clot retraction and repair
  - clot retraction is also known as **syneresis**
  - platelets continue to pull on fibrin threads closing wound
  - formed elements are trapped in fibrin threads, some serum may leak out
- Hemostatic control mechanisms
  - important that clot formation remains local, not systemic
  - several mechanisms work together:
    - fibrin absorbs remaining local thrombin
    - removal of local clotting factors - washed away
    - endothelial cells inhibit platelet aggregation

Hemostasis - Coagulation (cont.)

- Fibrinolysis - dissolution of a clot, begins within 2 days
  - plasminogen trapped in clot
  - many factors convert plasminogen into **plasmin** (**fibrinolysin**)
    - thrombin
    - activated factor XII
    - tissue plasminogen activator (t-PA)
- Plasmin
  - enzymatically digests fibrin threads
  - digests fibrinogen, prothrombin, and several clotting factors



Hemostasis - Coagulation (cont.)

- Thrombolytic (clot-dissolving) agents can be used clinically
  - chemical substances which activate plasminogen
  - streptokinase, tissue plasminogen activator (t-PA), etc.

- Anticoagulant naturally present in blood - heparin
  - produced by mast cells, basophils
  - used clinically to prevent blood clotting in lab blood samples
  - inhibits thrombin and the intrinsic pathway

Hemostasis - Coagulation (cont.)

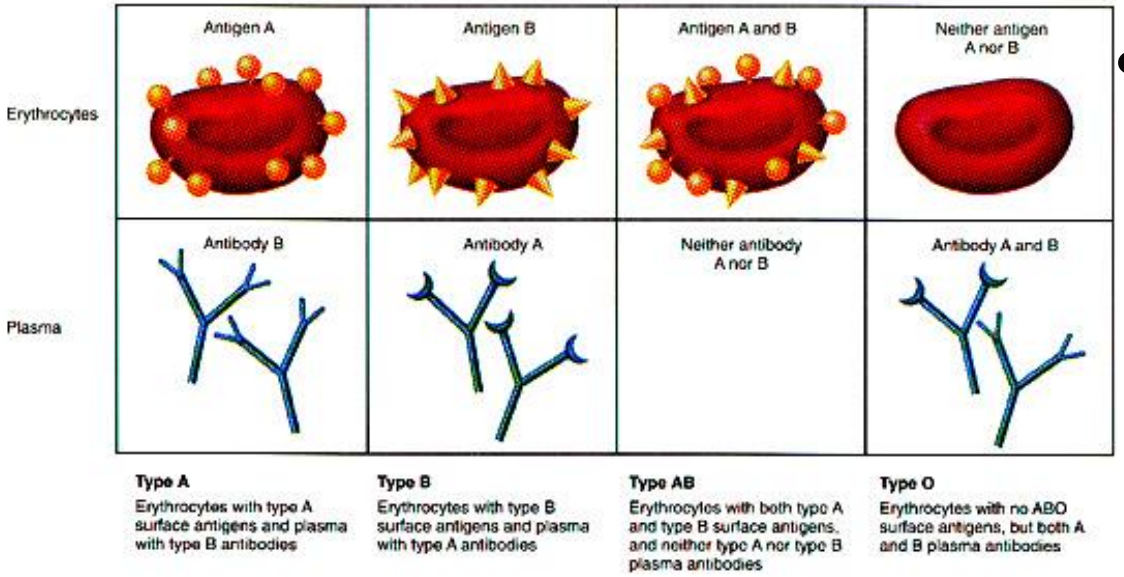
- Other anticoagulants
  - Warfarin (coumadin) - Vitamin K antagonist
    - slow acting, takes days to start and stop its action
    - common ingredient in many rat poisons
    - Vitamin K
      - produced by intestinal normal flora bacteria
      - required for synthesis of factors II (prothrombin), VII, IX, X
  - Aspirin & related NSAIDs
    - blocks platelet aggregation
    - prevents formation of thromboxane A_2
  - CPD (citrate phosphate dextrose)
    - removes Ca^{2+} by chelation
    - used for blood collected in blood banks for transfusion

Hemostasis - Coagulation (cont.)

- Intravascular Clotting
  - Roughened endothelium (atherosclerosis, trauma, infection) or slow blood flow may result in spontaneous clot (thrombus) formation, **thrombosis**
  - Thrombus released into blood becomes thromboembolus
    - pulmonary embolus – may be immediately fatal
    - other materials include air, amniotic fluid, tumor cells, or trauma debris
- Angioplasty - may trigger thrombus formation or fragmentation and release

Blood Types

- RBC surface has genetically determined antigens, *agglutinogens*

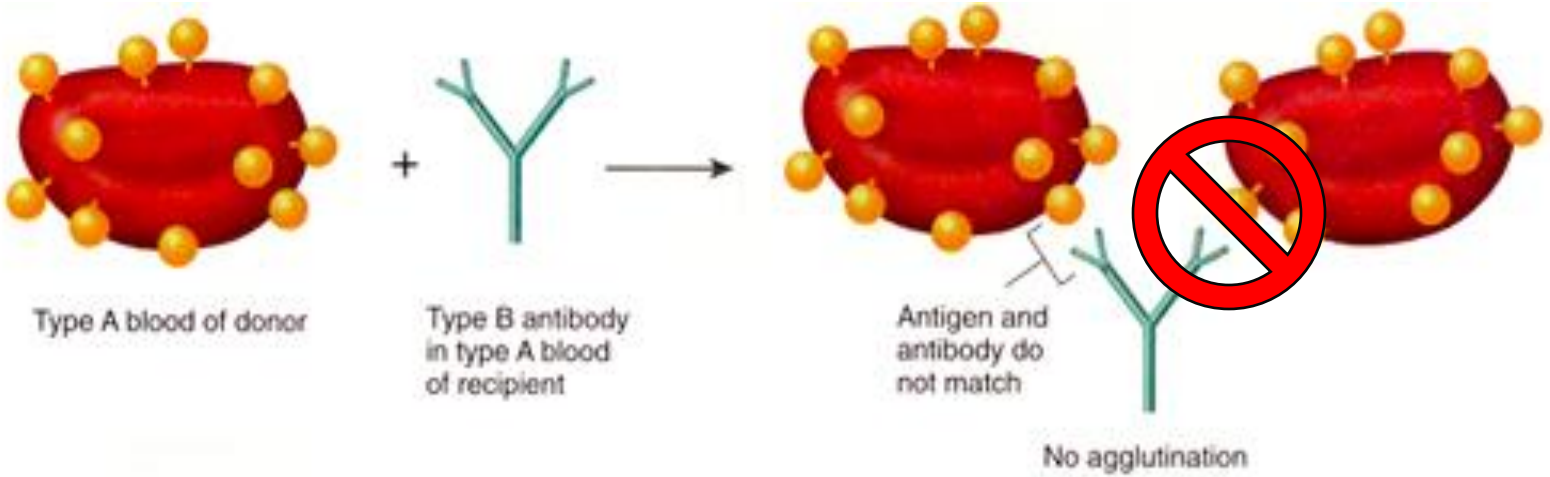


- ABO blood typing
  - 2 glycolipid agglutinogens, A & B
  - one gene from each parent, A, B or O
  - 6 combinations - AA, AB, AO, BB, BO, OO (no agglutinogens)

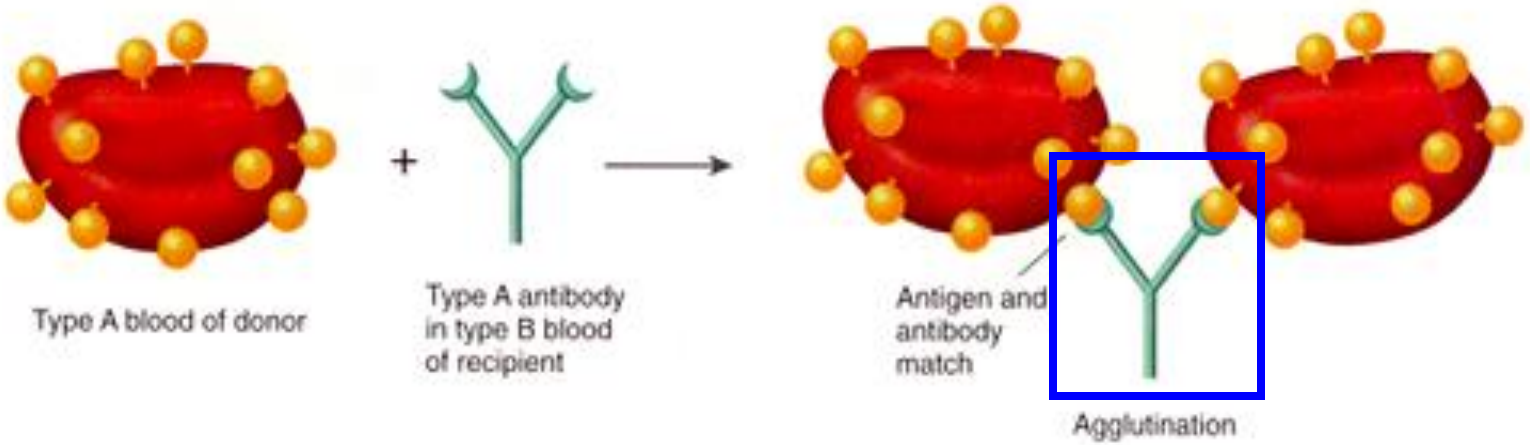
- *Agglutinins*
  - *Naturally occurring antibodies* produced in response to the agglutinogens not present in your blood
  - React in antigen-antibody response to blood not of your type
    - blood type AB = universal recipients
    - blood type O = universal donors

Blood Types (cont.)

Type A blood donated to a type A recipient does not cause an agglutination reaction because the type B antibodies in the recipient do not combine with the type A antigens in the donated blood.



Type A blood donated to a type B recipient causes an agglutination reaction because the type A antibodies in the recipient combine with the type A antigens in the donated blood.



DONOR **RECIPIENT**

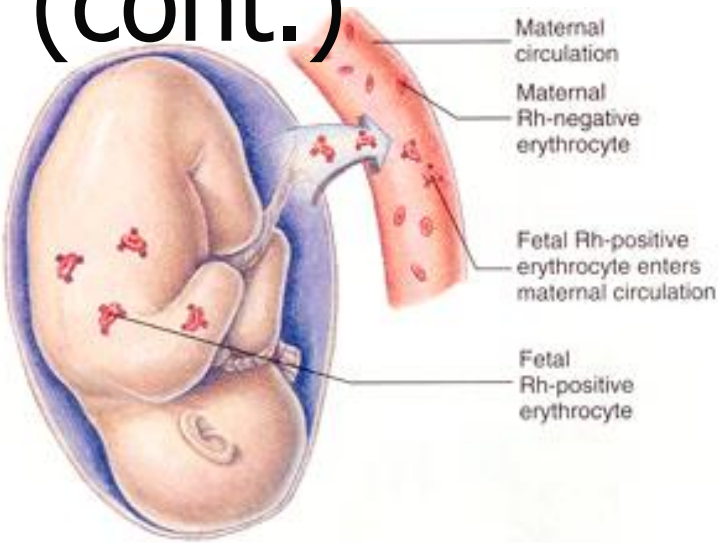
Blood Types (cont.)

- Rh typing – named for the Rhesus monkey Ag
  - those expressing Rh antigens are Rh^+
  - Those without Rh agglutinogens are Rh^-
    - normally, blood does not contain Rh agglutinins
    - immune system only makes agglutinins in response to specific exposure to Rh antigens
    - Rh sensitivity does not occur until second transfusion
    - hemolytic disease of the newborn = erythroblastosis fetalis (many "blue babies" prior to WWII)

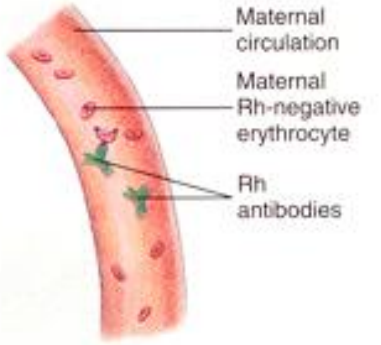
Blood Types (cont.)

- Hemolytic disease of the newborn

Since the 1960s, it has been possible to prevent hemolytic disease of the newborn by administering a therapeutic injection of Rh antibodies into the Rh^- maternal circulation within 72 hours after delivery of an Rh^+ infant.



1. Before or during delivery, Rh-positive erythrocytes from the fetus enter the blood of an Rh-negative woman through a tear in the placenta.



2. The mother is sensitized to the Rh antigen and produces Rh antibodies. Because this usually happens after delivery, there is no effect on the fetus in the first pregnancy.

3. During a subsequent pregnancy with an Rh-positive fetus, Rh-positive erythrocytes cross the placenta, enter the maternal circulation, and stimulate the mother to produce antibodies against the Rh antigen. Antibody production is rapid because the mother has been sensitized to the Rh antigen. The Rh antibodies from the mother cross the placenta, causing agglutination and hemolysis of fetal erythrocytes, and hemolytic disease of the newborn develops.