Blood cells

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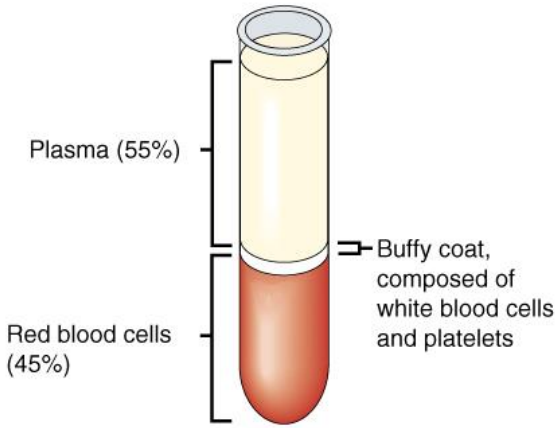
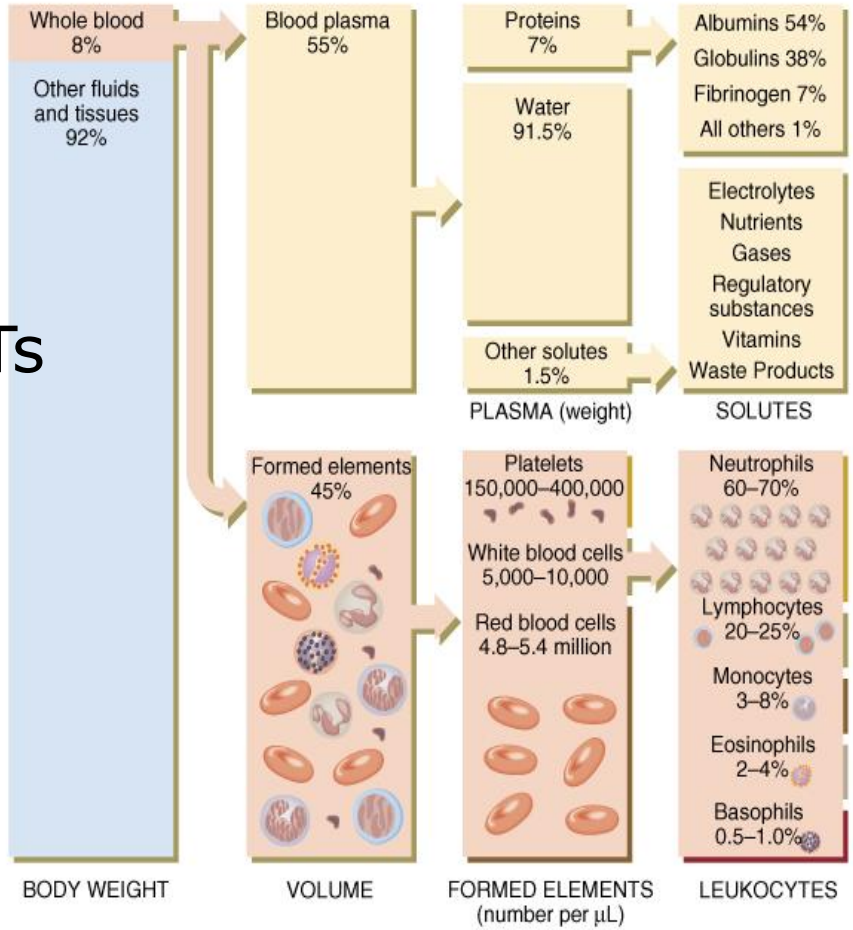
Blood composition

55% plasma
45% cells
(99% RBCs)
< 1% WBCs i PLTs





Composition of the blood

- The blood is a mixture of cells, fluid, proteins and metabolites.
- Blood has four major elements:

- red blood cells (transport oxygen from the lungs to organs and peripheral sites; water-base buffer)

- white blood cells (have a defensive role in destroying invading organisms e.g. bacteria and viruses)

- platelets (the first line of defence against damage to blood vessels)

- plasma (the proteinaceous substance in which the other three elements circulate)

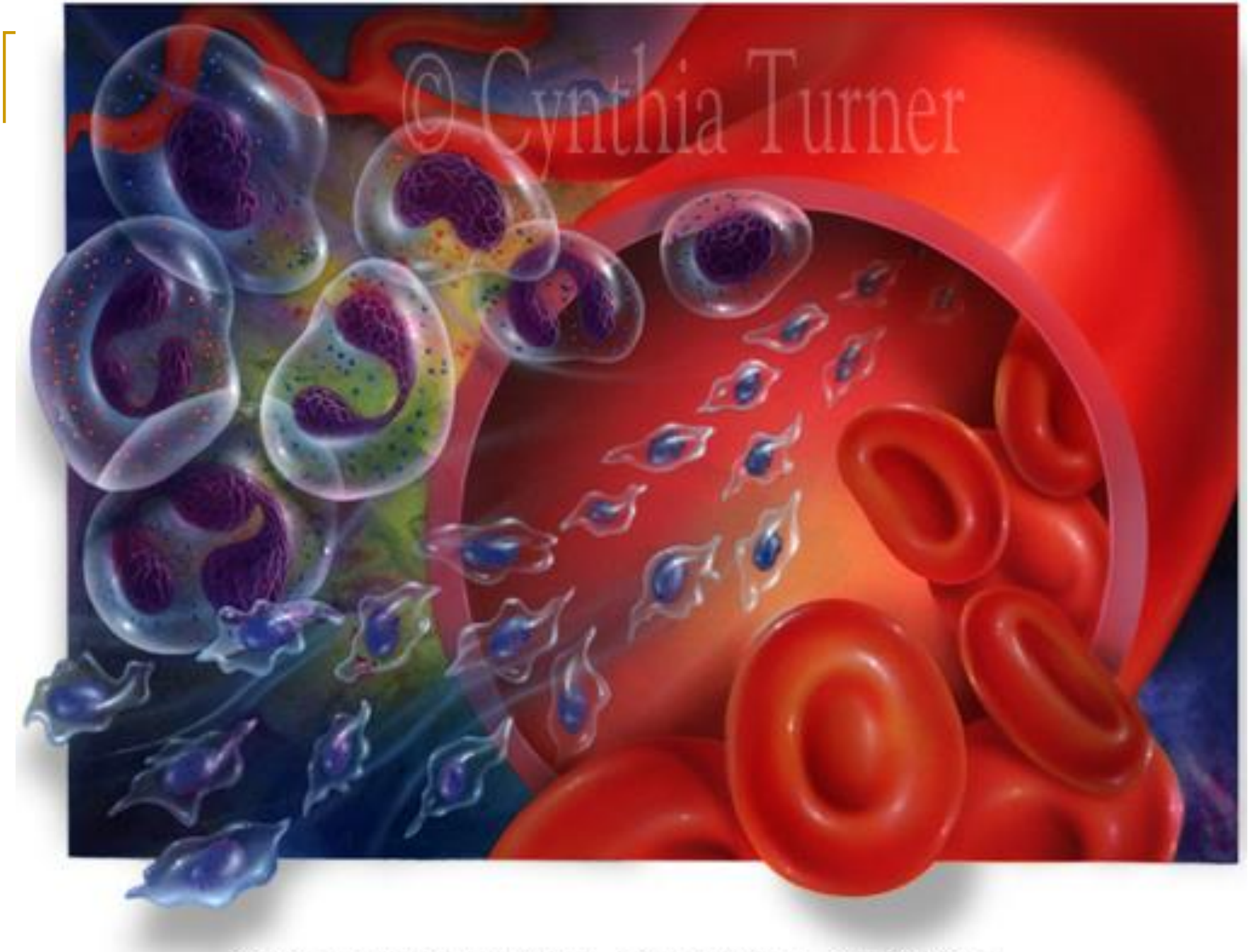
Functions of the blood

- **Delivers nutrients** from the digestive system to all parts of the body
- **Transports oxygen** from the lungs to all parts of the body
- **Transports carbon dioxide** from all parts of the body to the lungs
- **Transports waste products** from cells to the external environment mainly via the kidneys
- **Transports hormones** from the endocrine system to target cells or organs within the body.

Functions of the blood

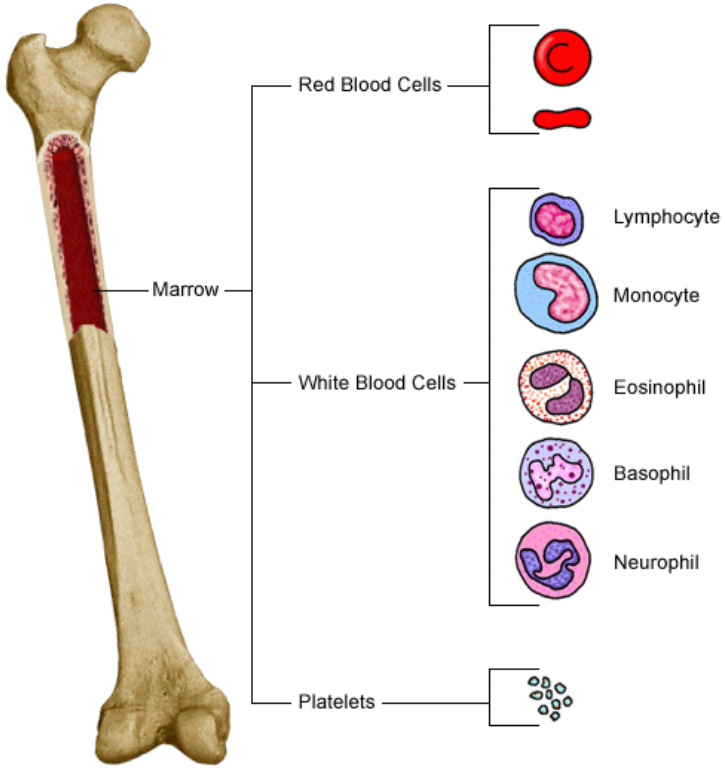
- Through continuous exchange of it's components with tissue fluids promotes **fluid and electrolyte balance**
- Defends the body against attack from foreign organisms via the white blood cells and antibodies
- Defends the body against injury or infection via the **inflammatory response**
- Prevents serious hemorrhage by the **clotting process**
- Maintains the body's **temperature**

  by circulating heat



COMPONENTS OF THE BLOOD

Formation of blood cells



Hemopoiesis

- Hemopoietic cells (those which produce blood) first appear in the yolk sac of the 2-week embryo.
- By 8 weeks, blood making has become established in the liver of the embryo, and

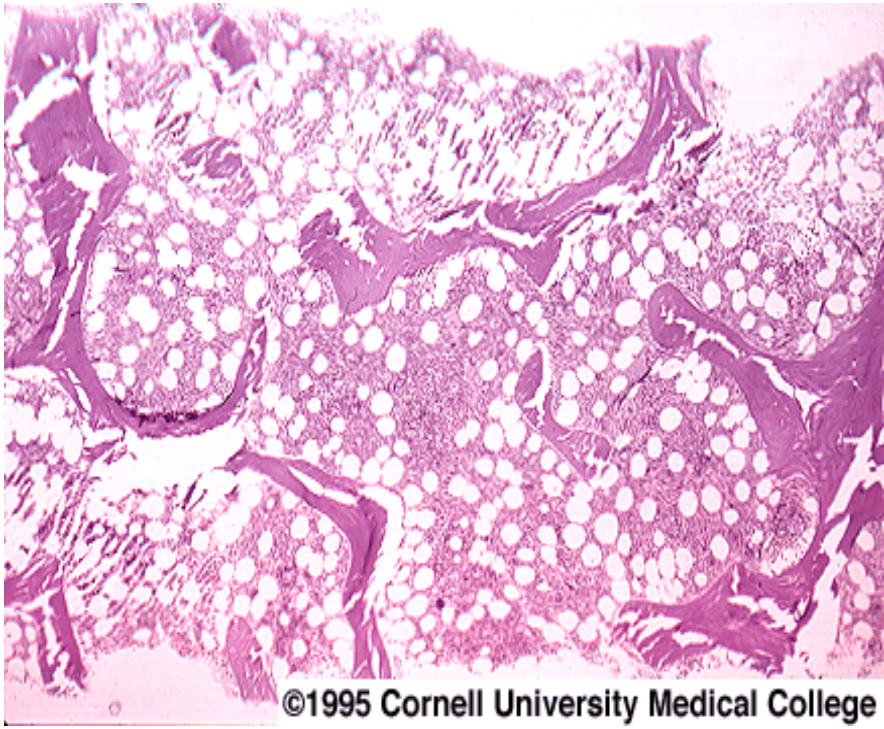
by 12-16 weeks the **liver** is the major site

it remains an active hemopoietic site until a few weeks before birth.

- The spleen is also active during this period, particularly in the production of lymphoid cells, and
- The fetal thymus is a transient site for some lymphocytes.

Development of Marrow

- The highly cellular bone marrow becomes an active blood making site from about 20 weeks gestation and gradually increases its activity until it becomes the major site of production about 10 weeks later.
- At birth, active blood making red marrow occupies the entire capacity of the bones and continues to do so for first 2-3 years after birth



Development of Marrow

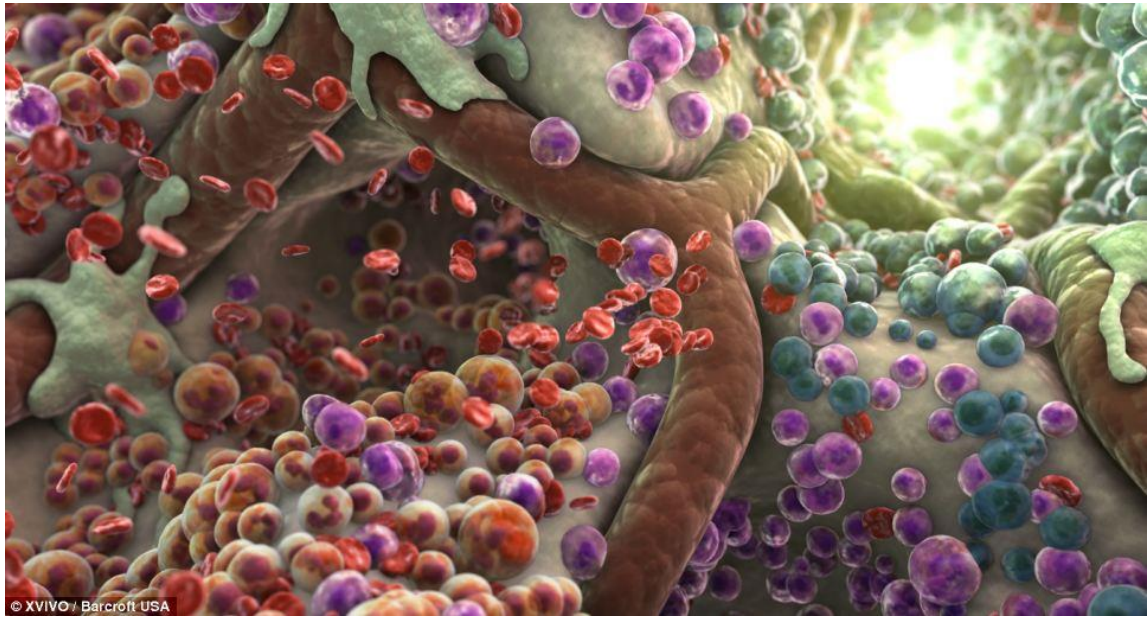
- The red marrow is then very gradually replaced by inactive, fatty, yellow, lymphoid marrow.
- The yellow marrow begins to develop in the shafts of the long bones and continues until (by 20-22 years) red marrow is present only in the upper ends of the femur and humerus and in the flat bones
- total amount of active red marrow is nearly identical in the child and the adult

Bone Marrow

- Bone marrow is composed of 2 compartments:

a. Extravascular

b. Intravascular



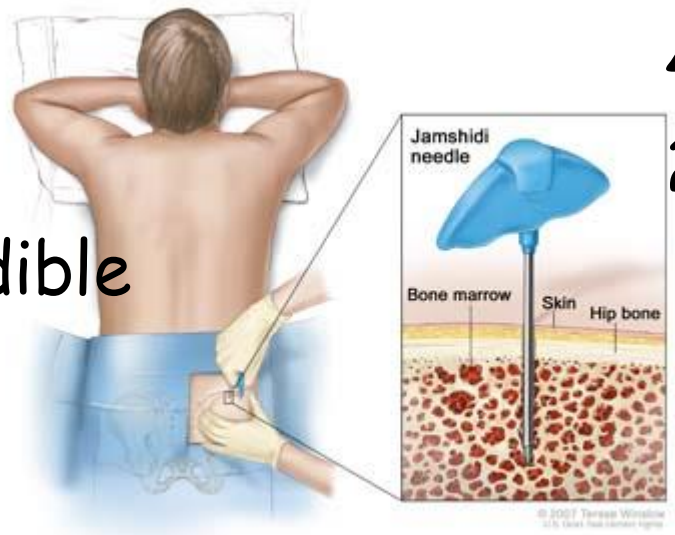
- The central venous sinusoid has a permeable basement membrane
- Red cells squeeze into the sinusoidal lumen, leaving their nuclei behind in the cellular matrix.
- Mature blood cells (from bone marrow) are attracted to the site of migration by chemotactic factors

Red Marrow Function

- About two-thirds of its mass functions in white cell production (leucopoiesis), and one-third in red cell production (erythropoiesis).
- However there are approximately 700 times as many red cells as white cells in peripheral blood.

Distribution of active marrow

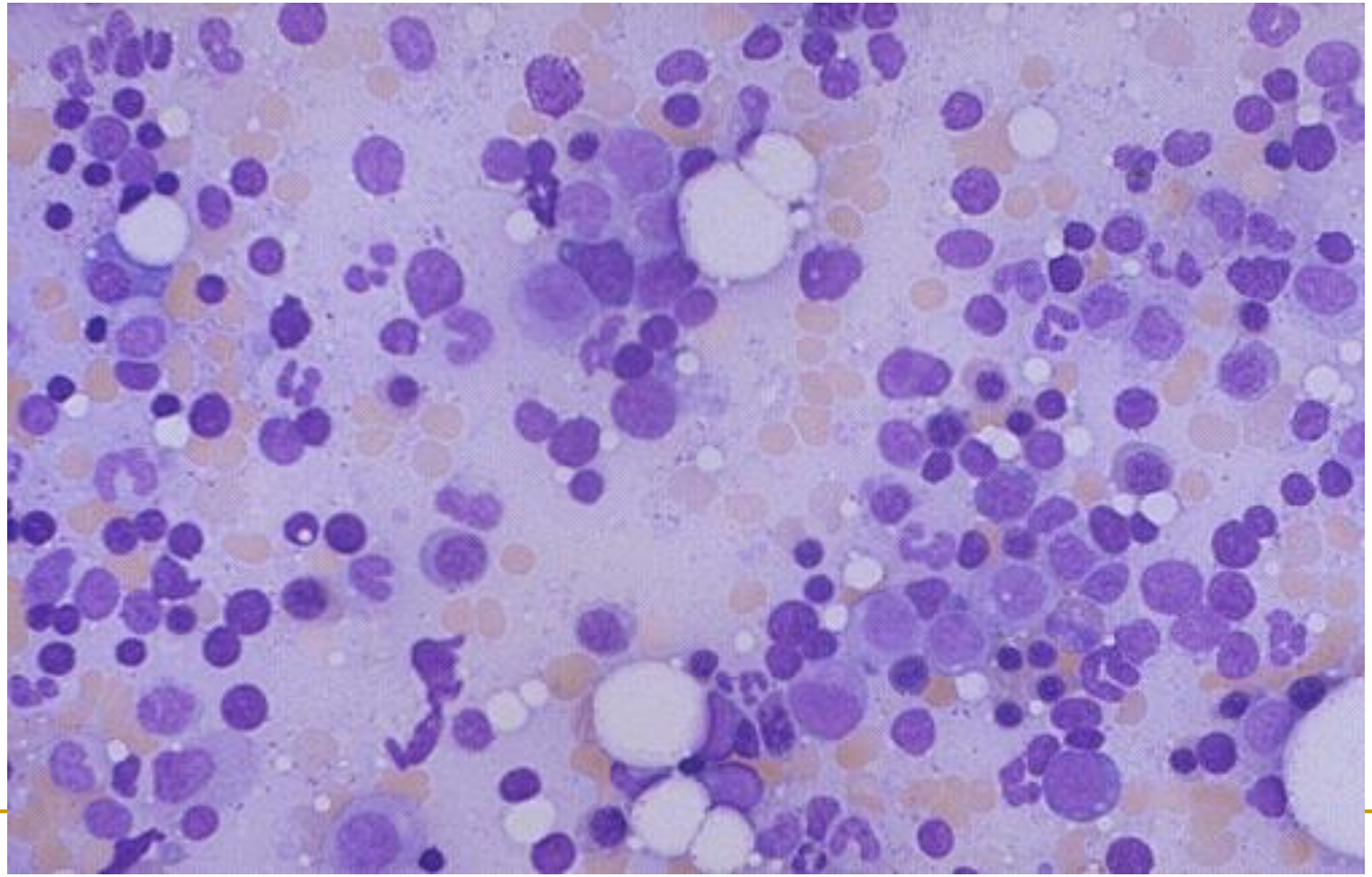
LOCATION	% of TOTAL MARROW
Pelvis	40
Vertebrae	28
Cranium-mandible	13
Ribs	8
Sternum	2
Ends of long bones	8



Bone Marrow

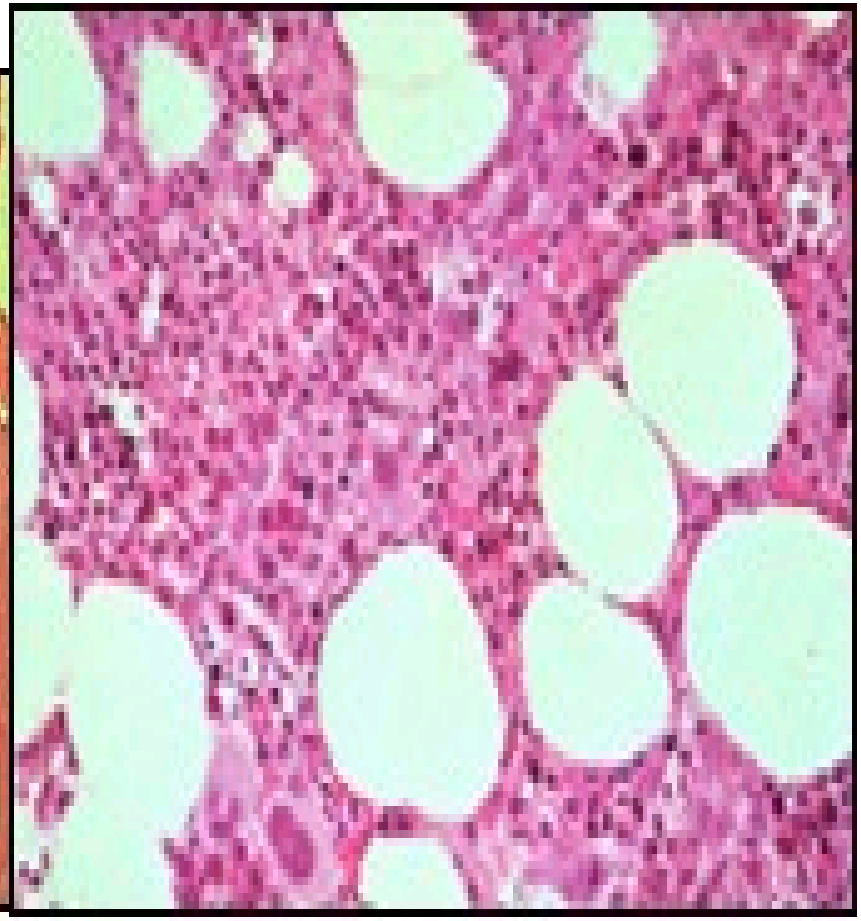
- Examination of the marrow is usually done by needle biopsy of the iliac crest under local anesthesia. (The other possible biopsy site is the anterior superior iliac spine.)
- The procedure involves first aspirating some of the jelly-like marrow substance and smearing it onto a glass slide.

Normal bone marrow smear. Note the presence of erythroid precursors and granulocytic precursors



Aplastic "Empty" Bone Marrow

Normal Bone Marrow

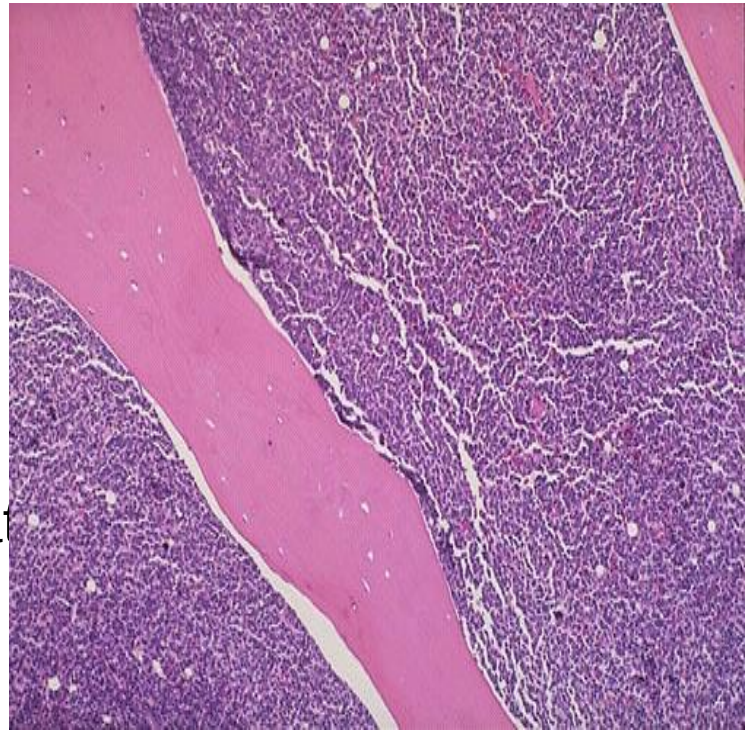


Leukemia

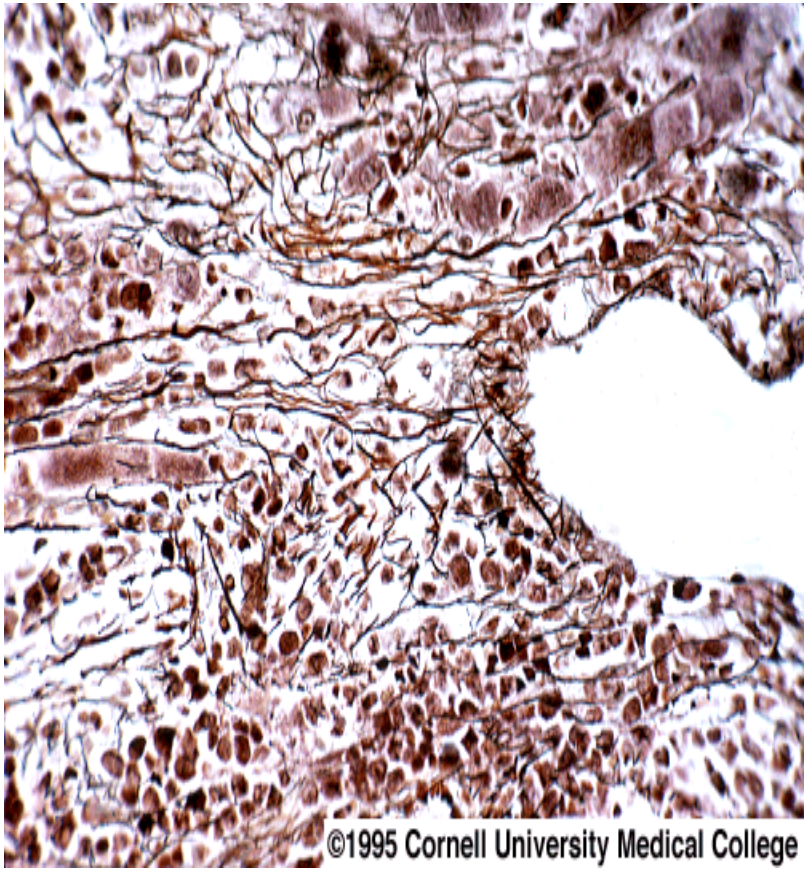
- Leukemia results in a highly cellular marrow. The marrow consists of leukemic cells of acute lymphocytic leukemia (ALL) that have virtually replaced or suppressed normal hemopoiesis.

- Thus, though the marrow is quite cellular, there can be peripheral cytopenias.

- This explains the complications of infection, hemorrhage, and anemia that often appear with leukemia.



Myelofibrosis



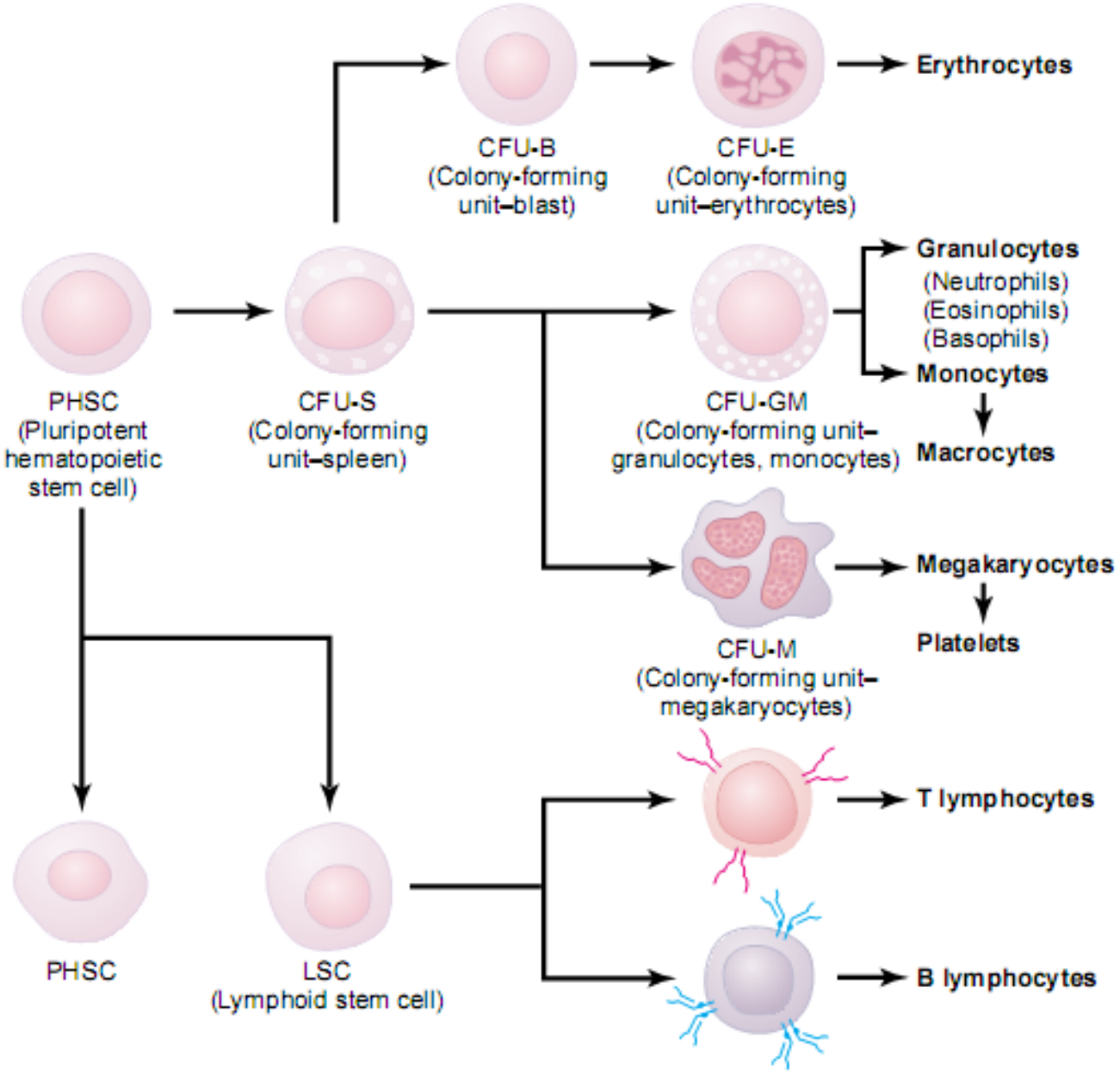
- Myelofibrosis: increased collagen, the type familar as a scar.
- This change is usually irreversible, as with any scar. The marrow cannot be aspirated.

Hematopoietic System

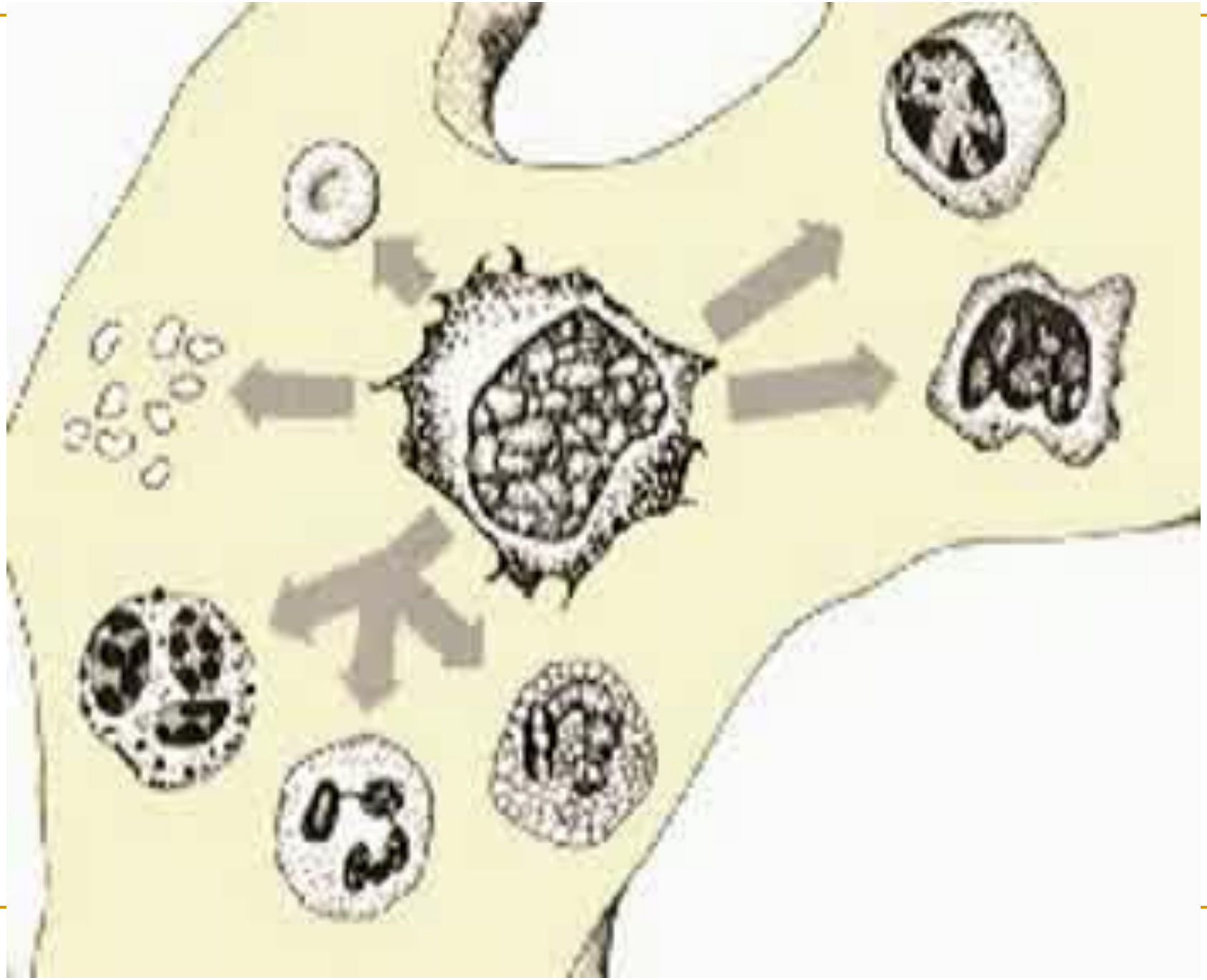
- Number of blood cells in the blood stream depends on three factors:
  - Rate of production
  - Rate of release
  - Length of survival

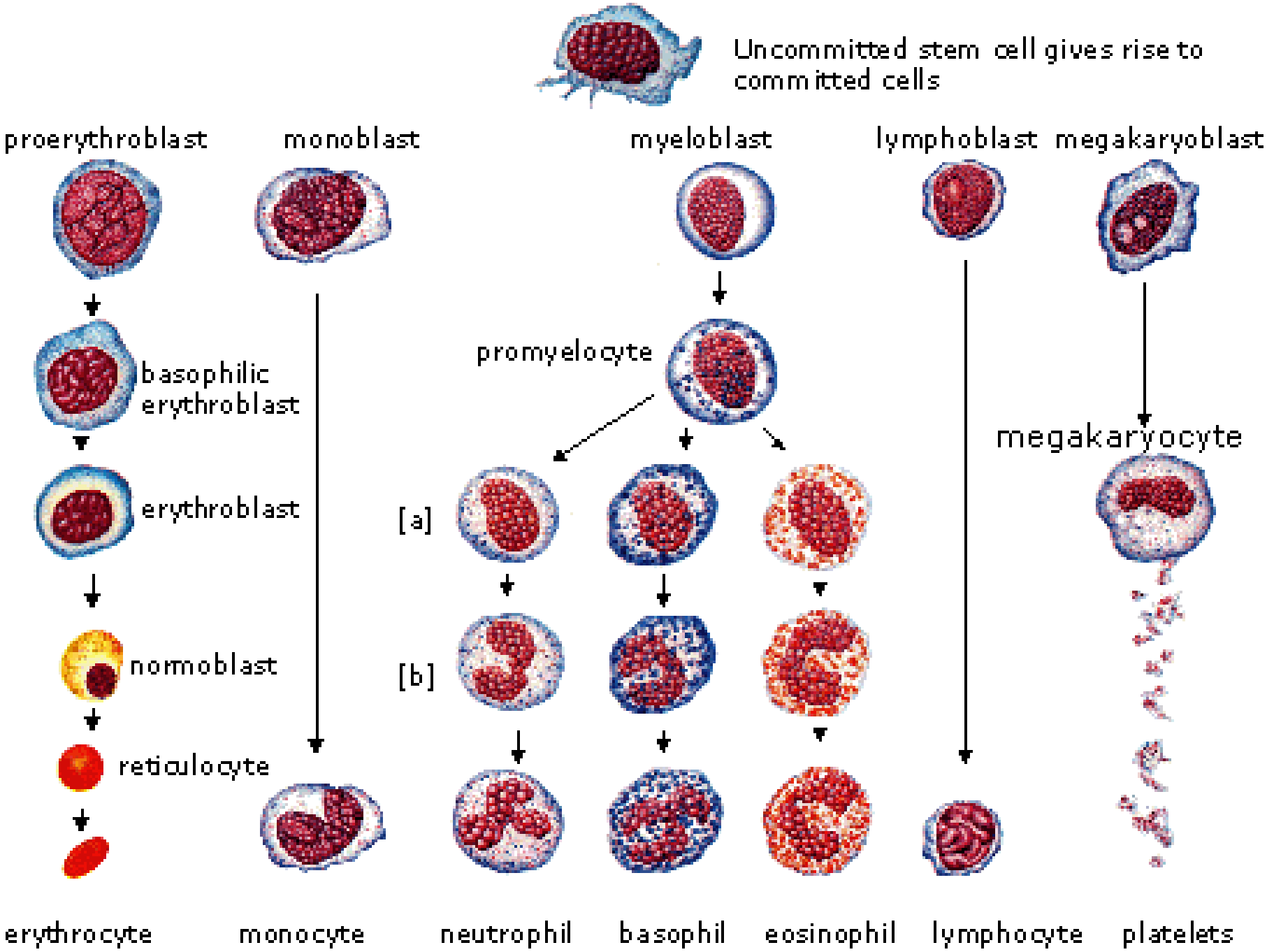
Erythropoiesis

- The pluripotential stem cell is defined as the precursor cell from which all erythrocytes, leukocytes, and megakaryocytes are formed (i.e. all blood cells have a common cell line of origin)
- These stem cells
  - are very rare (only about one in 10,000 bone marrow cells)
- produce, by mitosis, two kinds of progeny:
  - more stem cells
  - cells that begin to differentiate along the paths leading to the various kinds of blood cells


Erythrocytes
CFU-B
(Colony-forming
unit–blast)
CFU-E
(Colony-forming
unit–erythrocytes)
Granulocytes
(Neutrophils)
(Eosinophils)
(Basophils)
Monocytes
Macrocytes
PHSC
(Pluripotent
hematopoietic
stem cell)
CFU-S
(Colony-forming
unit–spleen)
CFU-GM
(Colony-forming unit–
granulocytes, monocytes)
Megakaryocytes
Platelets
CFU-M
(Colony-forming unit–
megakaryocytes)
T lymphocytes
PHSC
LSC
(Lymphoid stem cell)
B lymphocytes

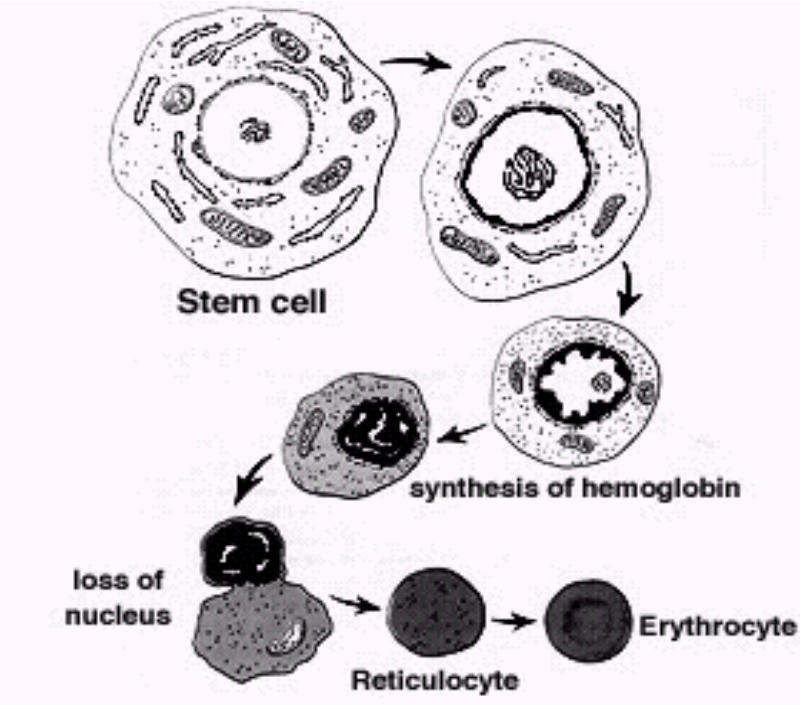
Guyton

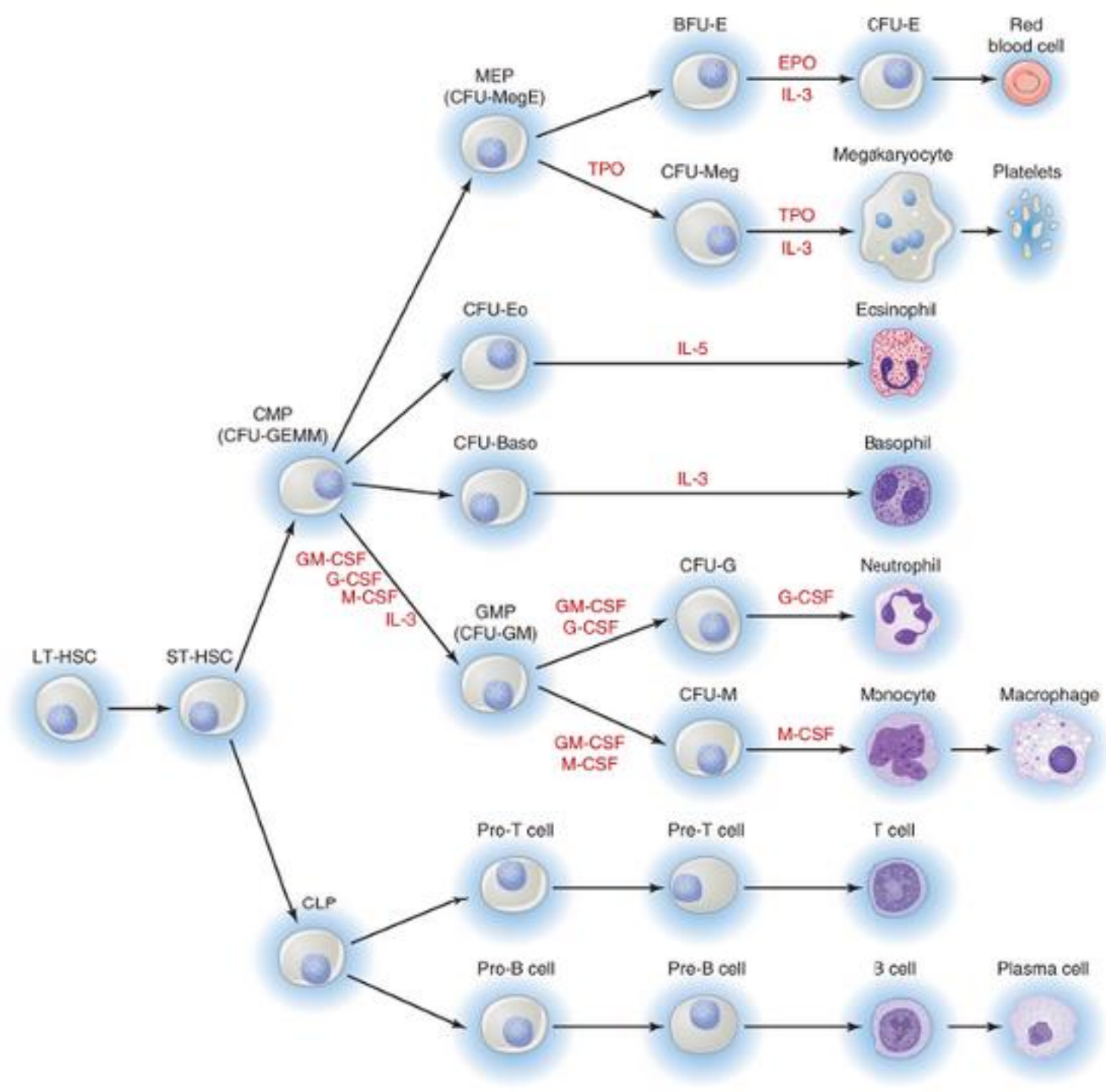



Uncommitted stem cell gives rise to committed cells
proerythroblast
monoblast
myeloblast
lymphoblast
megakaryoblast
basophilic erythroblast
promyelocyte
megakaryocyte
erythroblast
[a]
[b]
normoblast
reticulocyte
erythrocyte
monocyte
neutrophil
basophil
eosinophil
lymphocyte
platelets

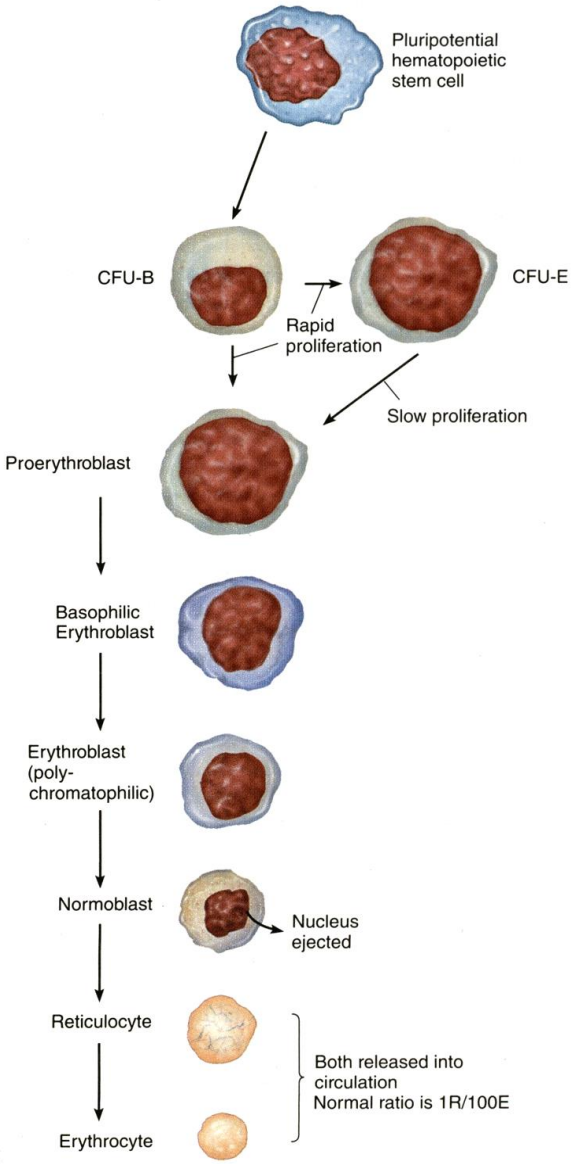
The process of erythrocyte development are characterised by:

- the gradual appearance of hemoglobin and disappearance of ribonucleic acid (RNA) in the cell,
- the progressive degeneration of the cell's nucleus which is eventually extruded from the cell,
- the gradual loss of cytoplasmic organelles, for example mitochondria,
- a gradual reduction in cell size

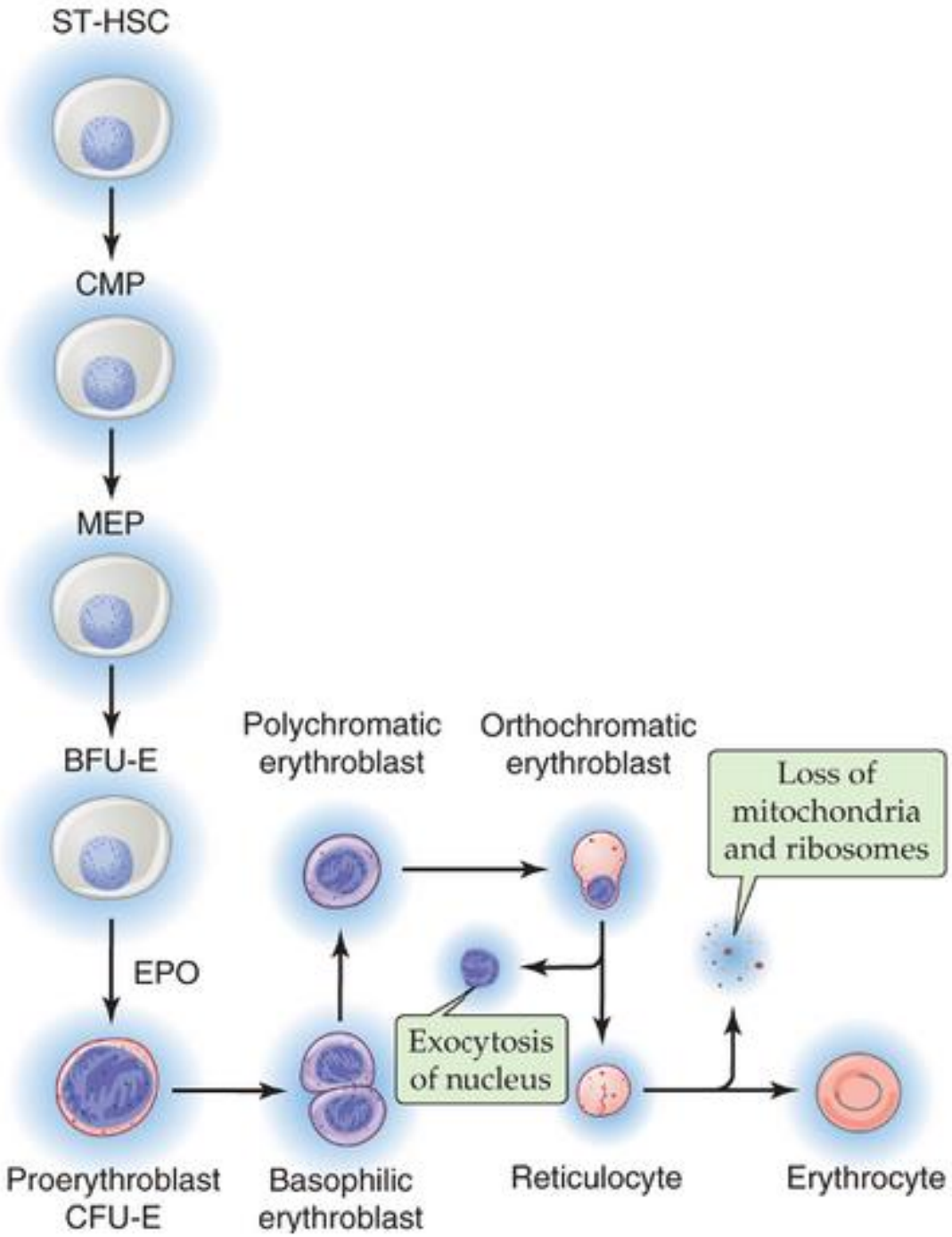



BFU-E
CFU-E
Red blood cell
EPO
IL-3
MEP (CFU-MegE)
TPO
CFU-Meg
Megakaryocyte
Platelets
TPO
IL-3
CFU-Eo
Eosinophil
IL-5
CMP (CFU-GEMM)
CFU-Baso
Basophil
IL-3
GM-CSF
G-CSF
M-CSF
IL-3
CFU-G
Neutrophil
GMP (CFU-GM)
GM-CSF
G-CSF
G-CSF
LT-HSC
ST-HSC
CFU-M
Monocyte
Macrophage
GM-CSF
M-CSF
M-CSF
Pro-T cell
Pro-T cell
T cell
CLP
Pro-B cell
Pro-B cell
B cell
Plasma cell

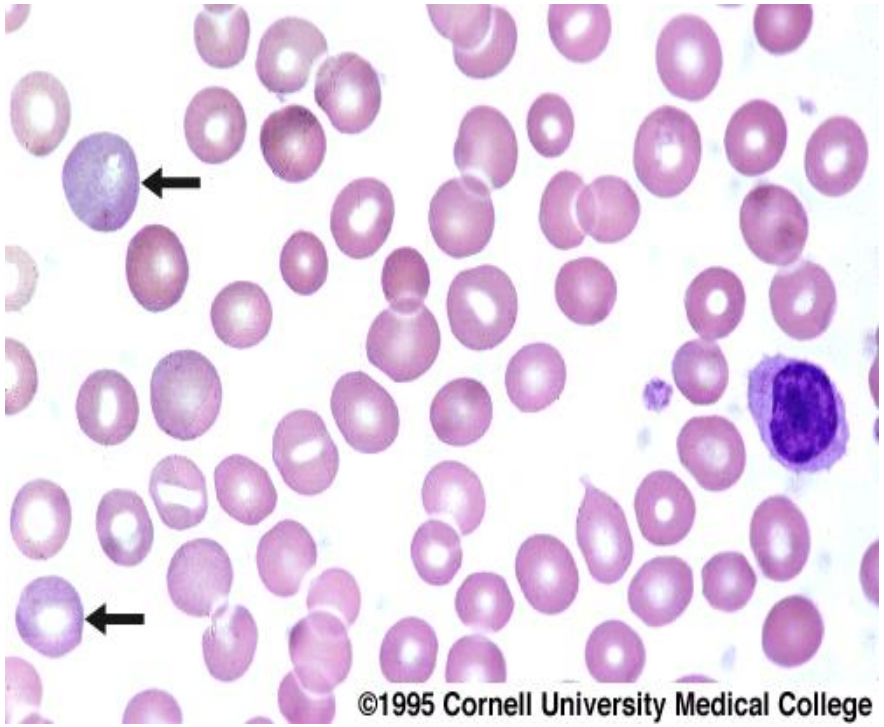
The formation of RBC



- Proerythroblast *(aerobic metabolism, many cytoplasmic organelles)*
- Basophil erythroblast *(beginning of the globin synthesis and Fe incorporation; rich in RNA)*
- Polychromatophil erythroblast *(last proliferative cell; ↑rate of Hb synthesis)*
- Normoblast; acidophil erythroblast *(anaerobic metabolism; pyknotic nucleus)*
- Reticulocyte *(network of ribonucleic acid. As the red cell matures the reticulum disappears)*
- Erythrocyte


ST-HSC
CMP
MEP
BFU-E
EPO
Polychromatic erythroblast
Orthochromatic erythroblast
Loss of mitochondria and ribosomes
Exocytosis of nucleus
Proerythroblast CFU-E
Basophilic erythroblast
Reticulocyte
Erythrocyte

Reticulocytes



- Between 2 and 6% of a new-born baby's circulating red cells are reticulocytes, but this reduces to less than 2% of RBCs in the healthy adult.
- Reticulocyte count increases in conditions in which rapid erythropoiesis occurs
- A reticulocyte normally takes 2-4 days to mature into an erythrocyte.

Normoblstic reaction of bone marrow

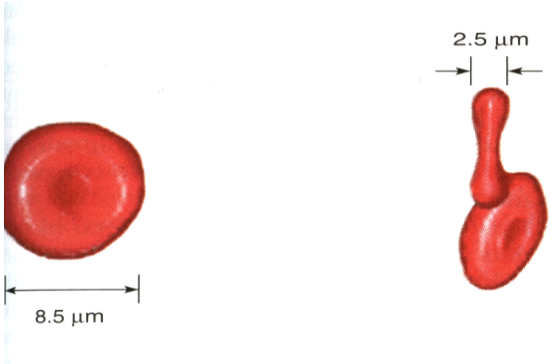
- Normally normoblastic renewal amounts to **12-25%** of all nucleated cells in the bone marrow.

- Percentage of erythroblasts increases with their maturity*(most of normoblasts; less proerythroblasts)*

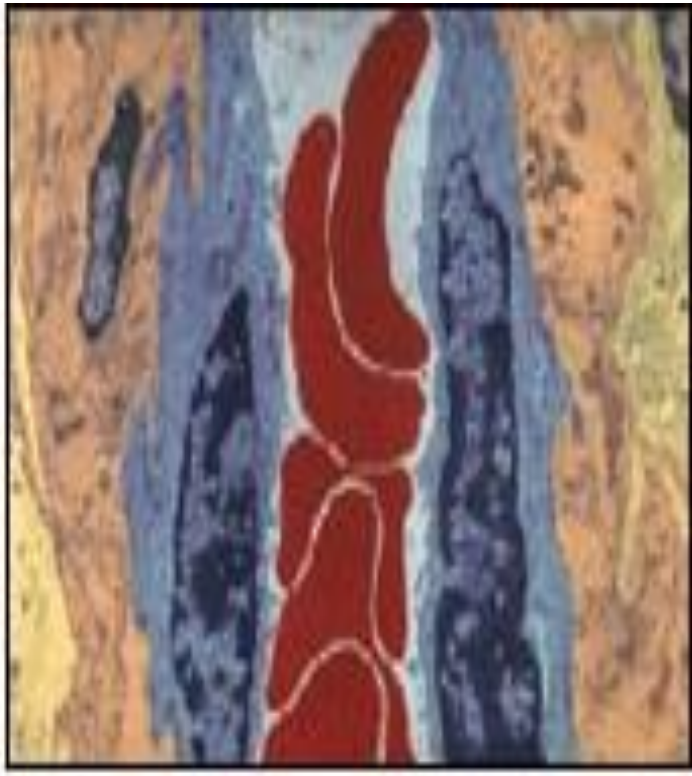
- ↑ requirement – renewal increases to 30%-50%, and even more, there is also increase in percentage of immature cells – normoblastic reaction with shift to the left *(normoblasts in blood stream).*

Red Blood Cells

- the biconcave shape increases the cell's surface area and facilitates diffusion of O_2 and CO_2 into or out of the cell



- the lack of nuclei and organelles contribute to increased Hb content and gas-carrying capacity
- normal erythrocytes must be very flexible. They become deformed when flowing through capillaries and narrow pores (slits) in the spleen



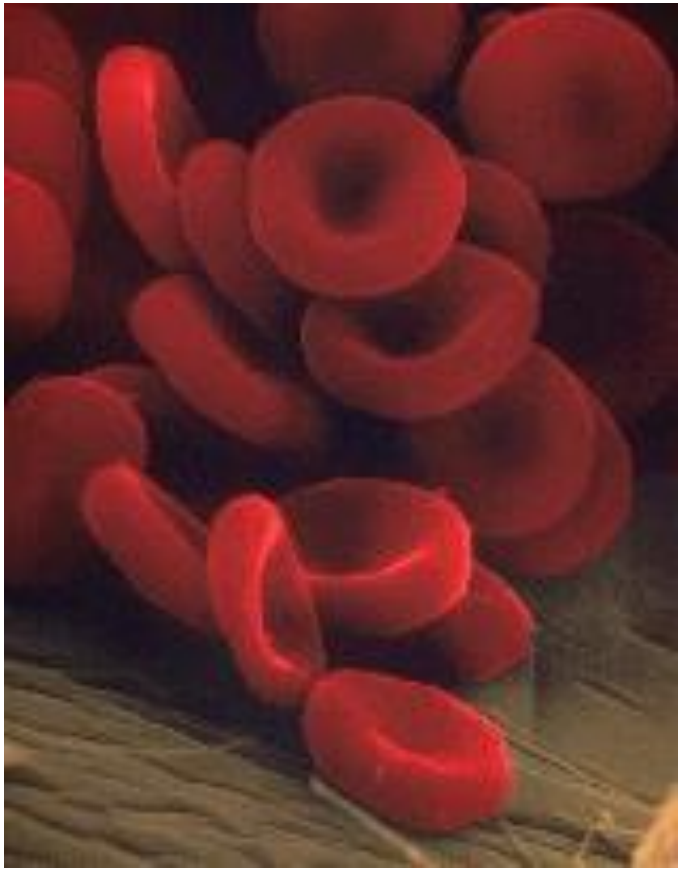
Red blood cell flexibility

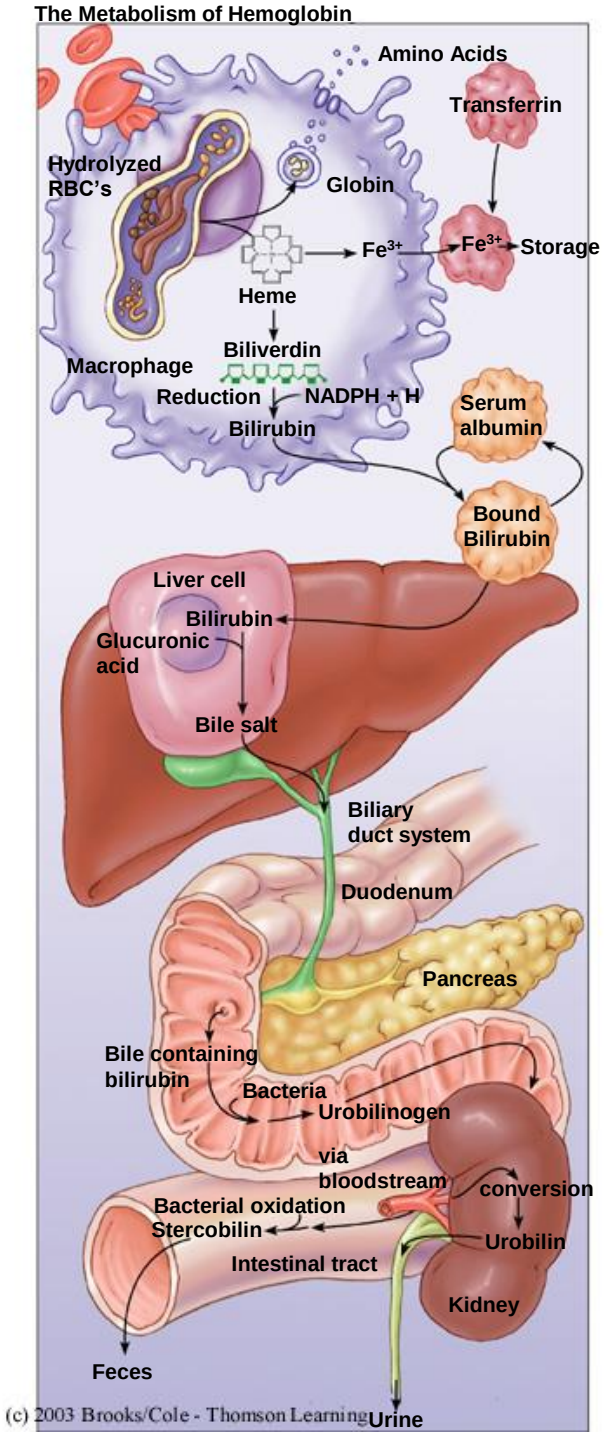
Properties of RBCs

- Glycolysis and pentose shunt
- 2,3DPG (2,3 diphosphoglycerate) – reduces the O2 affinity of Hb
- Gluthatione
- Carbonic anhydrase (CAI and CAII) – rapidly interconvert CO2 and HCO3-
- Cl-HCO3 exchanger AE1
- water channel AQP1

Red Blood Cells

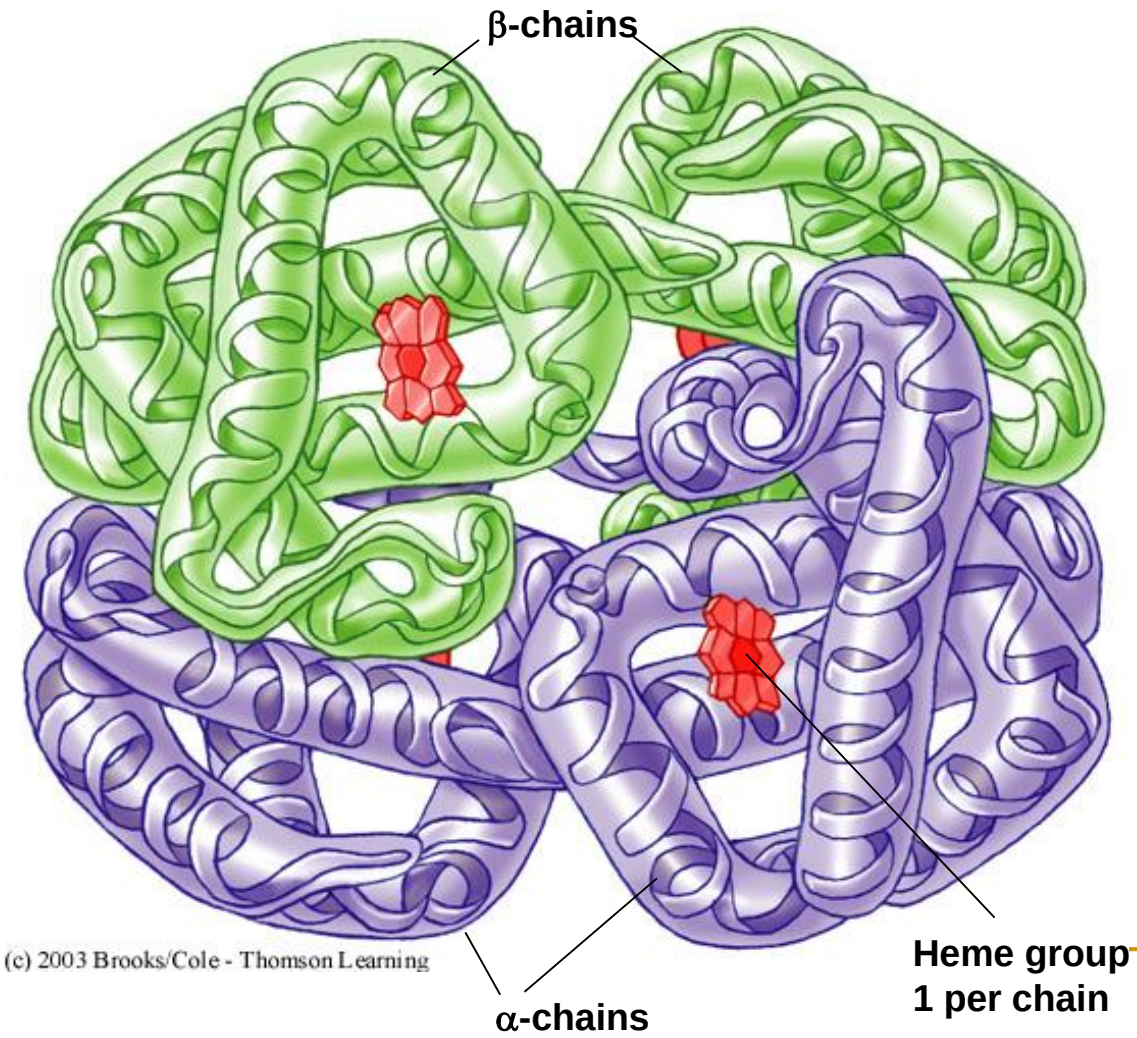
- Normal adult ranges: men 4.5-6.0 T/L; women 3.8-5.2 T/L
- All red blood cells have a limited life span of around 100 to 120 days
- Aged RBC's are removed by the spleen, liver and the bone marrow





- Spleen, liver, and marrow macrophages recognize and ingest old RBCs
- Heme is converted to bilirubin;
- Bound bilirubin is transported to the liver, where it is converted into bile salt
- Small intstine bacteria convert bilirubin into the urobilinogen, most of which is eliminated in the feces in the form of stercobilin
- Some urobilinogen is absorbed from the intestine and excreted with urine, where it becomes oxidized to urobilin

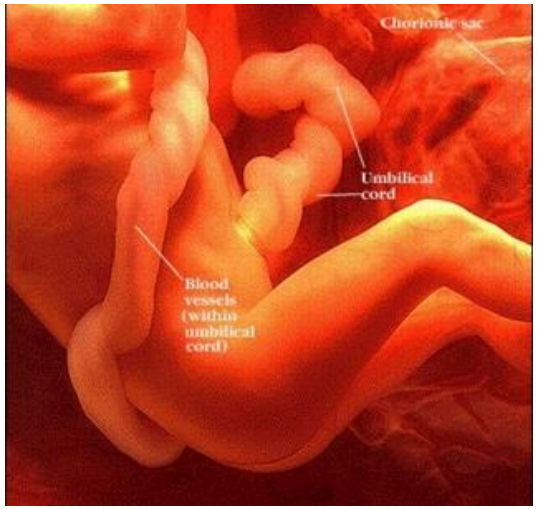
Hemoglobin (Hb) carries O_2, CO_2; is a buffer; reduced Hb binds 4 O_2 → oxyhemoglobin.



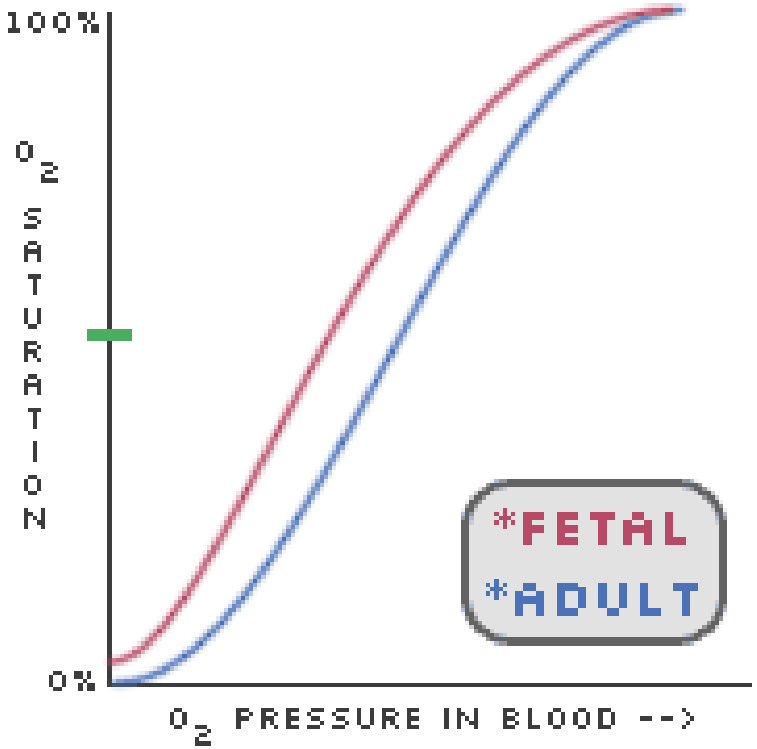
In adults:

- 96% type A1 (2α+2β chains)
- 2% type A2 (2α+2δ chains)
- 2% type F (2α+2γ chains)

Fetal hemoglobin

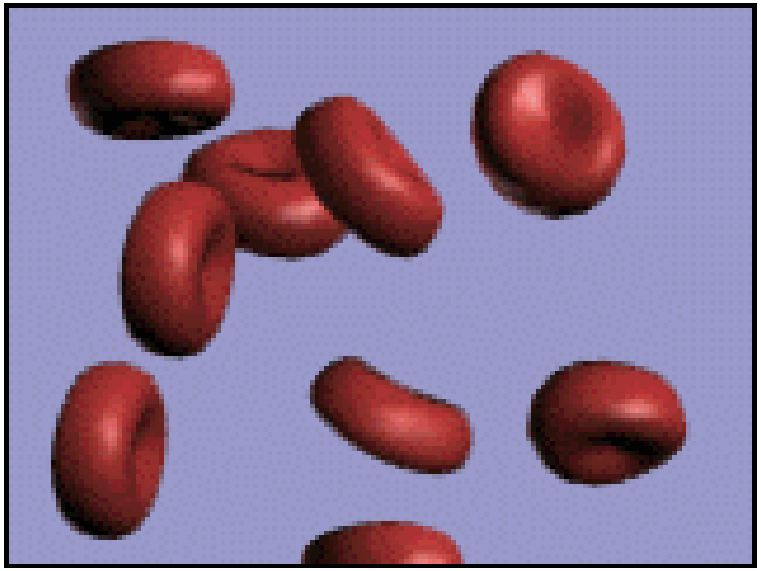


- In fetus: Hb type F (2α+2γ chains) predominates; HbF has greater affinity to O2
- After bitrh repleaced by HbA
-
- By the time the child is 6 months old, the replacement is nearly complete



Hemoglobinopathies

- Minor variations in the amino acid sequence or composition of:
  - α chain e.g. Hemoglobin H disease
  - β chain e.g. Sickle cell disease (Hb type S)



Oxyhemoglobin S, like normal Hb, is soluble in the ICF; however HHb S is insoluble, forming fibrous precipitates of sickle shape. Sickle cells are destroyed faster and may be trapped in capillaries.

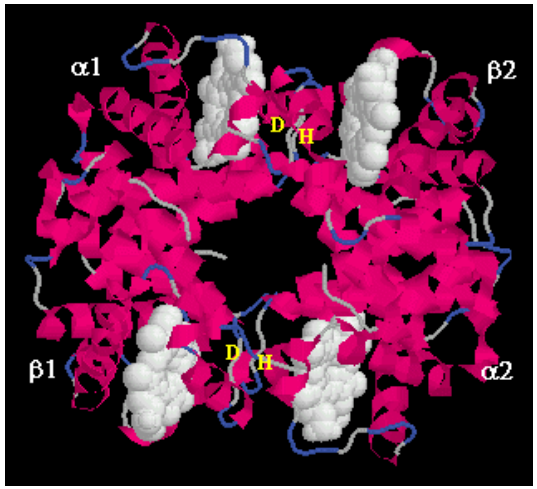
Anemias

- Abnormally low oxygen-carrying capacity of the blood resulting from deficiency in the number of :

  - RBC,

  - Hb,

  - or both



◂ Hb molecule

- Anemia is considered to be present if Hb is less than 12g/dL (norm: men 13-17g/dL, women 12-16 g/dL)

Acute blood loss →

hemorrhagic anemia (normocytic, normochromic).

B12 or/and folate deficiency →

megaloblastic anemia (macrocytic, hyperchromic, immature RBC).

Fe deficiency → microcytic, hypochromic anemia

Hemolytic anemia → increased rate of RBCs destruction (normocytic)

Genetic abnormality/chemical exposure →

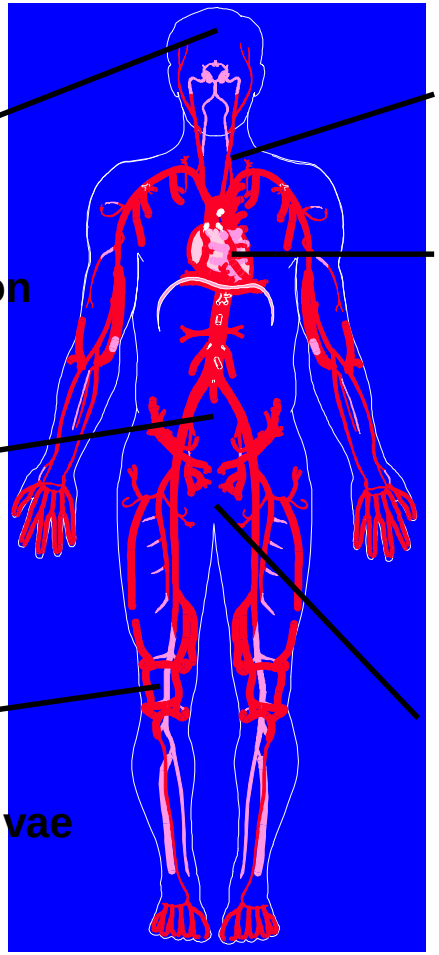
aplastic anemia (lack of RBC production)

Signs and symptoms of anaemia

CNS
- Debilitating fatigue
- Dizziness, vertigo
- Depression
- Impaired cognitive function

Gastro-intestinal system
- Anorexia
- Nausea

Vascular system
- Low skin temperature
- Pallor of skin, mucous membranes and conjunctivae

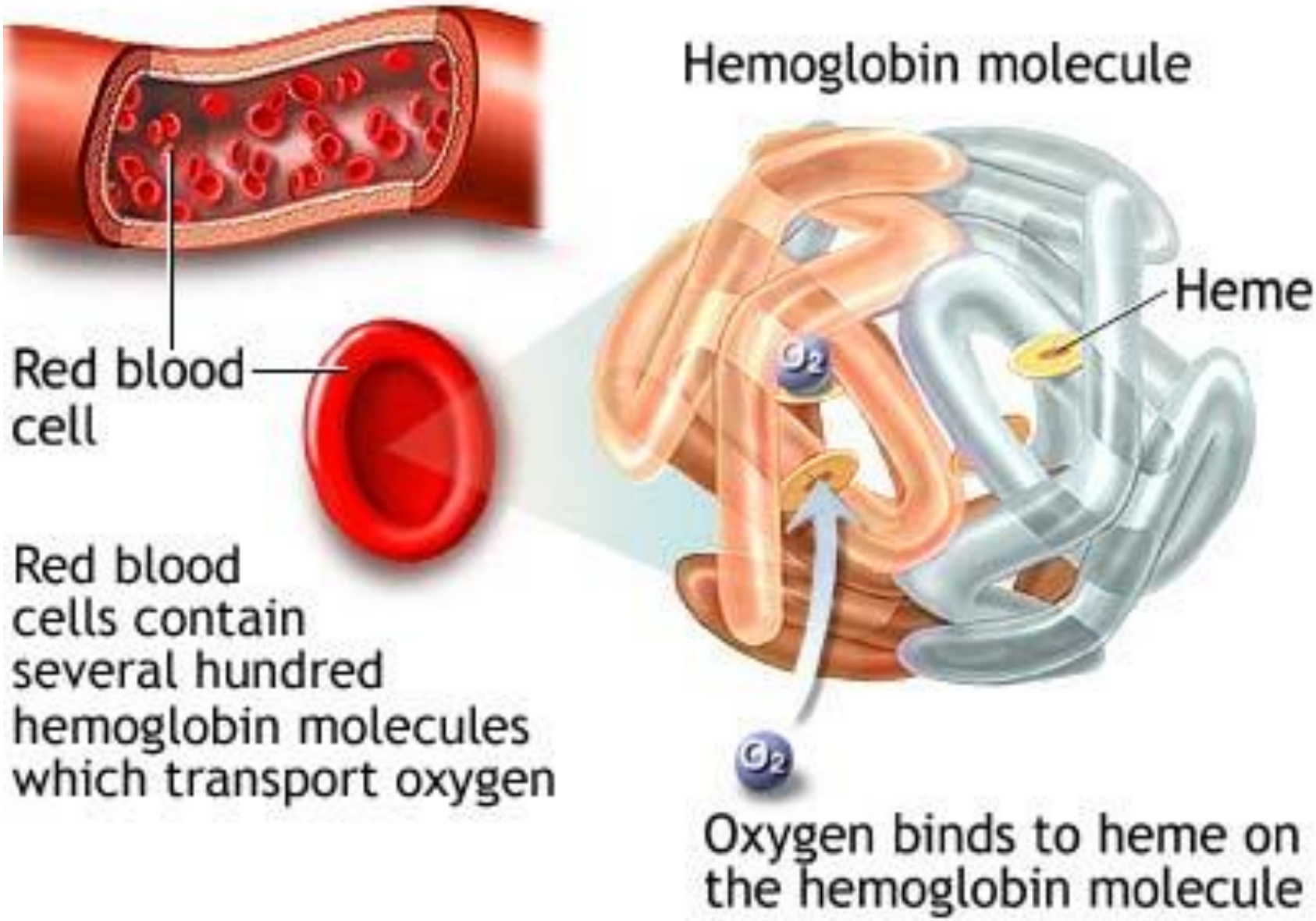


Immune system
- Impaired T cell and macrophage function

Cardiorespiratory system
- Exertional dyspnoea
- Tachycardia, palpitations
- Cardiac enlargement, hypertrophy
- Increased pulse pressure, systolic ejection murmur
- Risk of life-threatening cardiac failure

Genital tract
- Menstrual problems
- Loss of libido

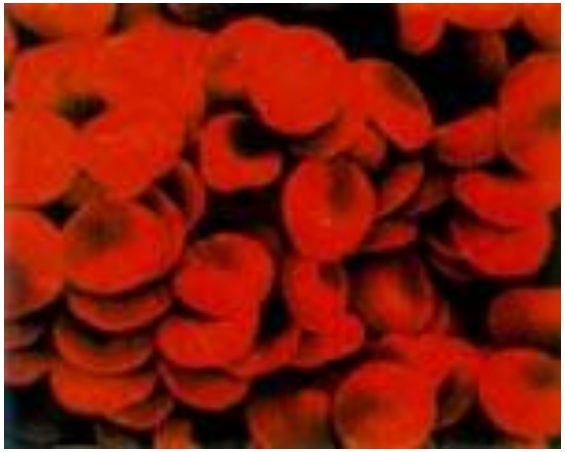
Adapted from Ludwig H, Fritz E. *Semin Oncol.* 1998;25(suppl 7):2-6.


Hemoglobin molecule
Heme
Red blood cell
Red blood cells contain several hundred hemoglobin molecules which transport oxygen
Oxygen binds to heme on the hemoglobin molecule
A.D.A.M.

How many Hb molecules in one RBC?

- More than 250 milion molecules!!!

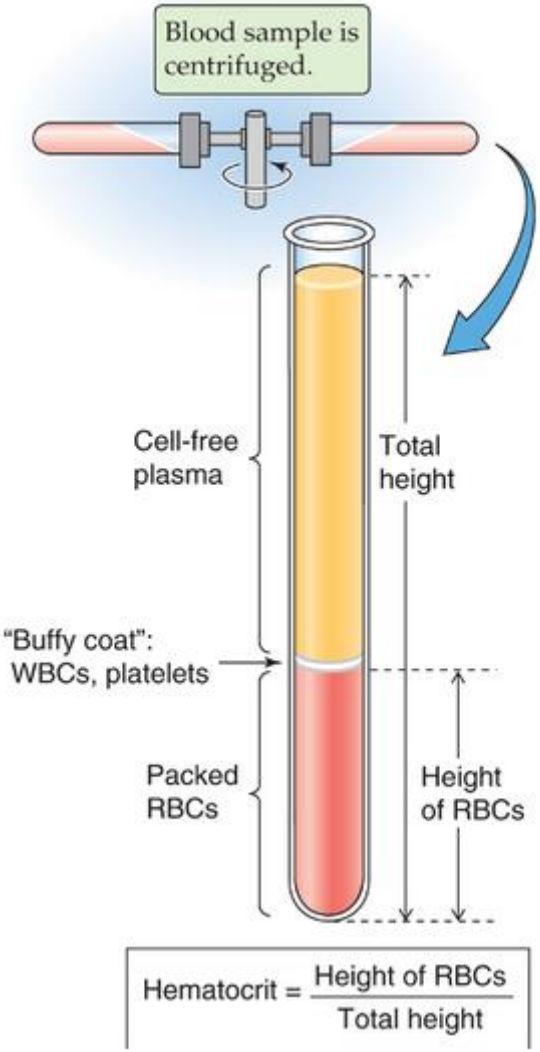
RBC indexes



- MCHC - mean corpuscular hemoglobin concentration (norm: 34%/RBC)
- MCV - mean corpuscular volume (norm: 78-95fL)
- MCH - mean corpuscular hemoglobin index - Hb mass within RBC (norm: 29pg/RBC)

Typical blood cells parameters

Red cell count (10^6/μL blood)	4.0 (female); 4.5 (male)
Hematocrit (%)	40 (female); 45 (male)
Hemoglobin (g/dL blood)	14.0 (female); 15.5 (male)
Mean red cell volume—MCV (fL/cell)	90
Mean red cell hemoglobin—MCH (pg/cell)	30
Mean cell hemoglobin concentration—MCHC (g/dL RBC)	35
Red cell distribution width—RDW (%)	13
White cell count (10^3/μL blood)	8
Platelet count (10^3/μL blood)	300



Evaluation of Microcytosis

MICHELE VAN VRANKEN *Am Fam Physician.* 2010 Nov 1;82(9):1117-1122

Suggested diagnosis				
Test	**Iron deficiency anemia**	**Thalassemia**	**Anemia of chronic disease**	Sideroblastic anemia
Serum ferritin level	Decreased	Increased	Normal to increased	Normal to increased
Serum iron level	Decreased	Normal to increased	Normal to decreased	Normal to increased
Total iron-binding capacity	Increased	Normal	Slightly decreased	Normal
Transferrin saturation	Decreased	Normal to increased	Normal to slightly decreased	Normal to increased

Evaluation of Microcytosis
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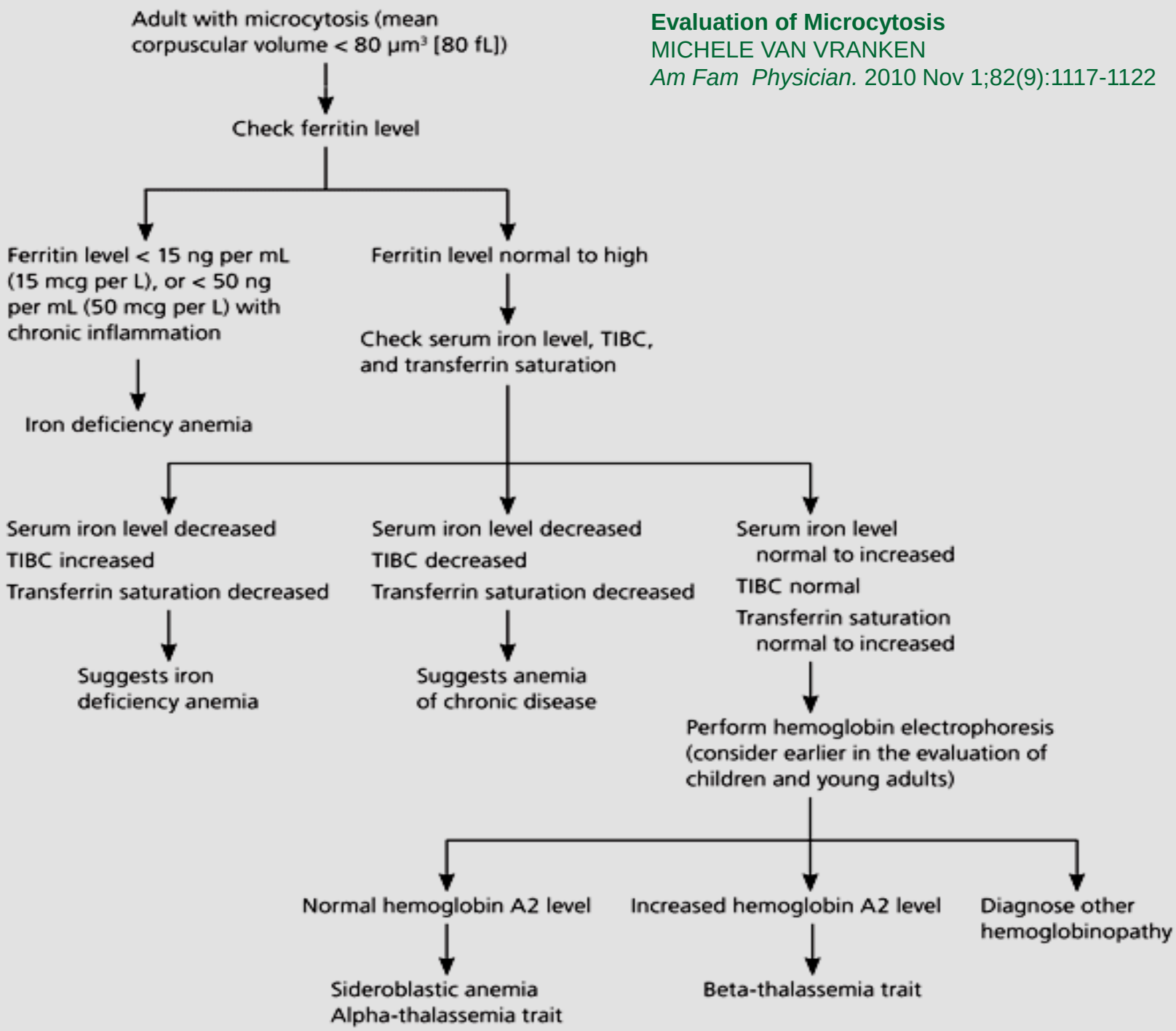
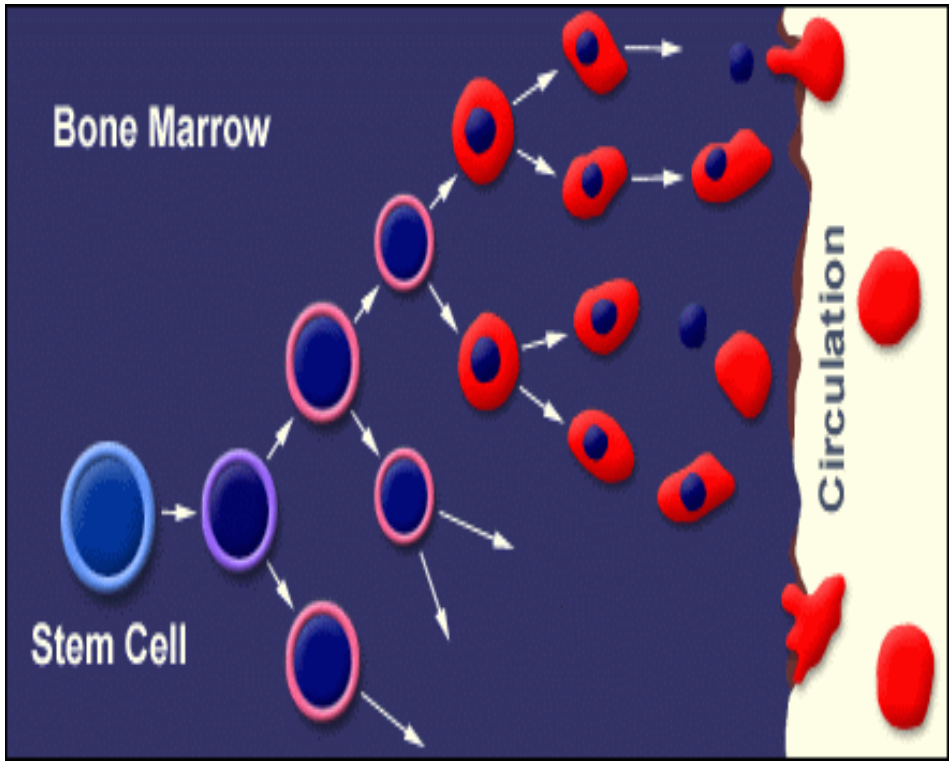


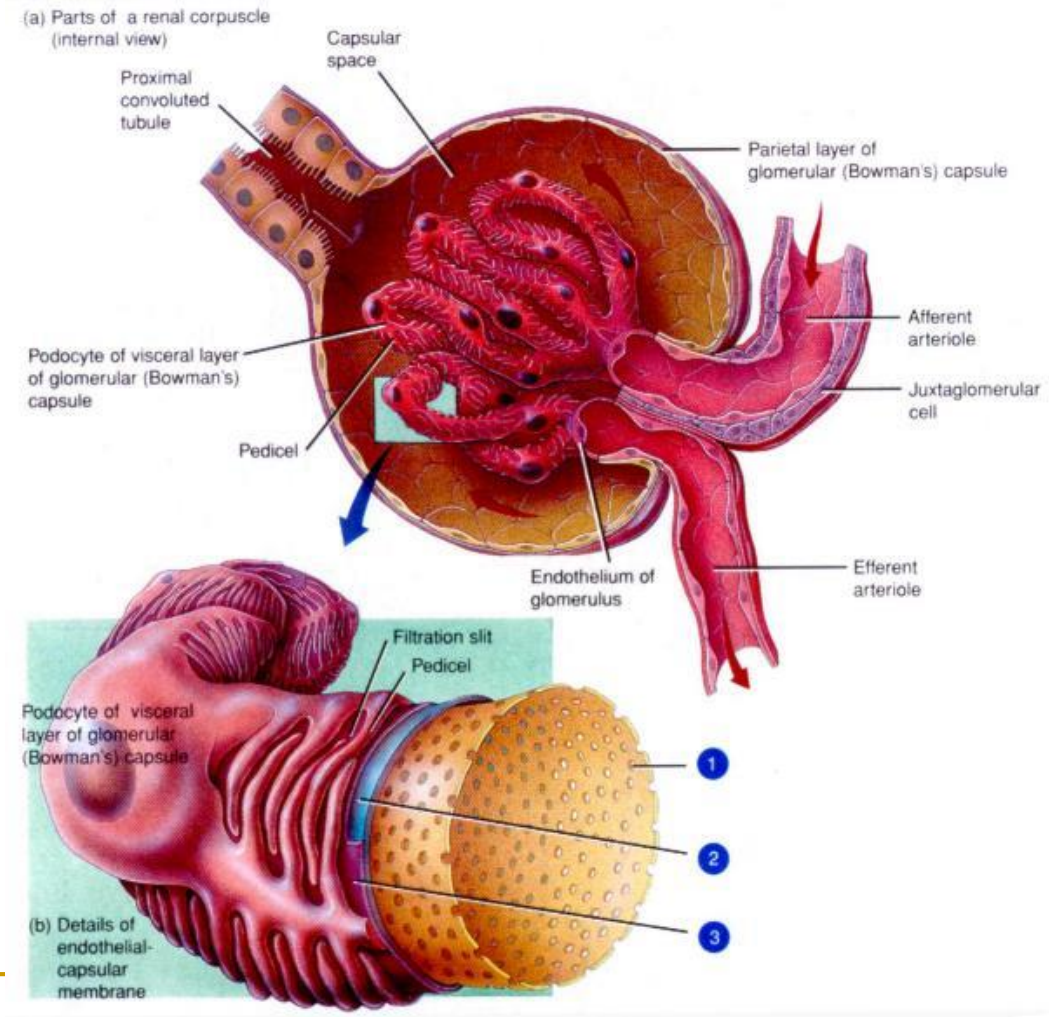
Regulation of erythropoiesis

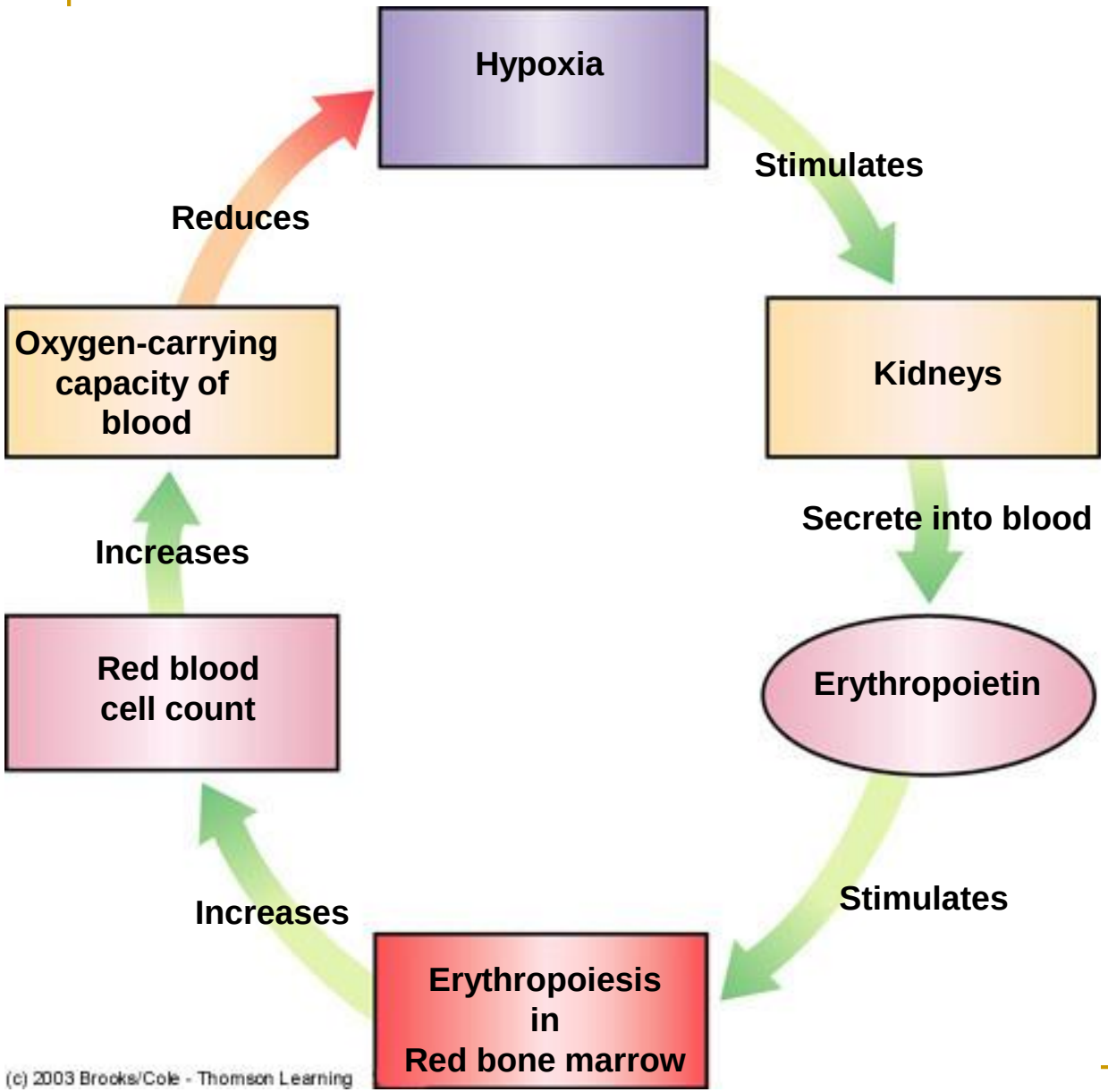
- Hormones and lymphokines (erythropoietin, BPA interleukins, ACTH, TSH, thyroid hormones, glucocorticoids, testosteron etc.)
- vitamins (B12, folic acid, B6)
- metals (Fe, Co, Cu, Mn, Zn)



Erythropoietin (EPO)

- Erythropoietin is synthesized in the fibroblasts of the kidney cortex and is released into the blood in response to hypoxia in the renal arterial blood supply.
- Erythropoietin is a glycoprotein. It is inactivated by the liver and excreted in the urine.
- About 10% of EPO is synthesized in other tissues





Low blood O_2 → kidneys release erythropoietin → increased erythropoiesis

Hormones affecting erythropoiesis

- adrenocorticotrophic hormone (ACTH),
- human growth hormone (GH)
- thyroid-stimulating hormone (TSH),
- thyroid hormones (T3, T4),
- adrenal cortical steroids (cortisol),

all promote erythropoietin formation

Hormones affecting erythropoiesis

- Androgens stimulate and estrogens depress the erythropoietic response.

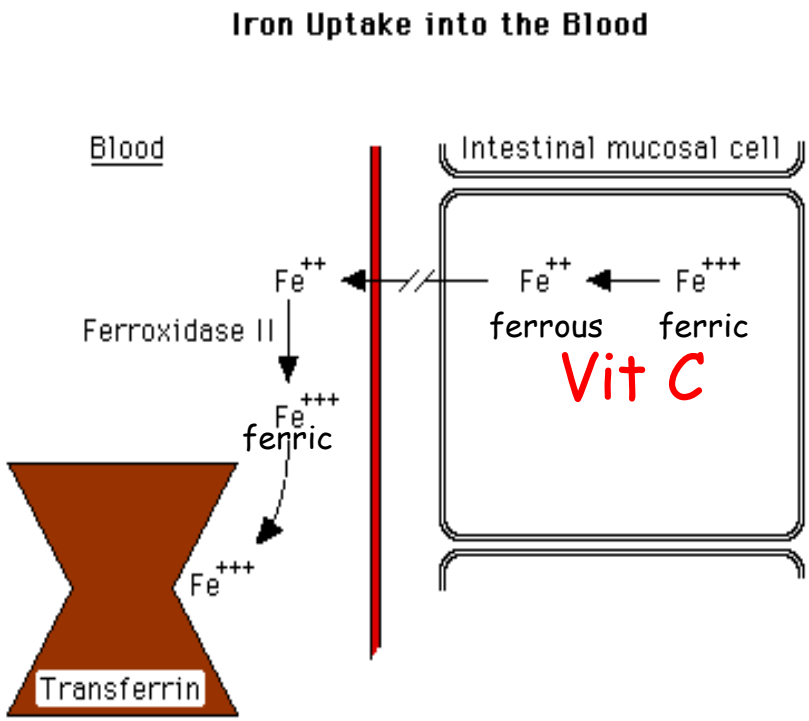
  In addition to the effects of menstrual blood loss, this effect may explain why women tend to have a lower hemoglobin concentration and RBC count than men.

- Erythropoietin is also produced by a variety of tumours of both renal and other tissues.

Dietary requirements for sufficient red blood cell production

Dietary element	Role in red blood cell production
Protein	Required to make red blood cell proteins and also for the globin part of hemoglobin
Vitamin B_6	It plays role in heme synthesis
Vitamin B_{12} and folic acid	Needed for DNA synthesis and are essential in the process of red blood cell formation
Vitamin C	Required for folate metabolism and also facilitates the absorption of iron. Extremely low levels of Vitamin C are needed before any problems occur. Anemia caused by lack of Vitamin C (scurvy) is now extremely rare
Iron	Required for the heme part of hemoglobin
Copper and Cobalt (heme synthesis, EPO)	There are some reports suggesting that these two minerals are essential for the production of red blood cells in other animals but not in humans

Iron Turnover



- Iron absorption is greatest in the duodenum and decreases progressively as one moves distally down the intestine.
- Iron is much more readily absorbed in its ferrous (Fe^{2+}) form than in its ferric (Fe^{3+}) form.
- Vitamin C can increase iron absorption by serving as a reducing agent to maintain iron as Fe^{2+}.

Factors that increase or decrease the absorption of iron

- *Increased Iron Absorption:*

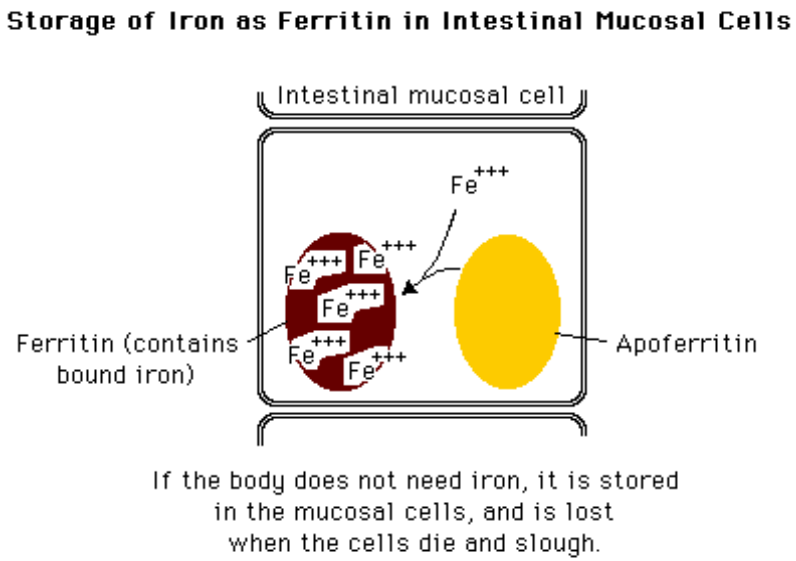
- Anemia
- Iron-deficiency state
- Increased erythropoiesis
- Ascorbic acid
- High altitude

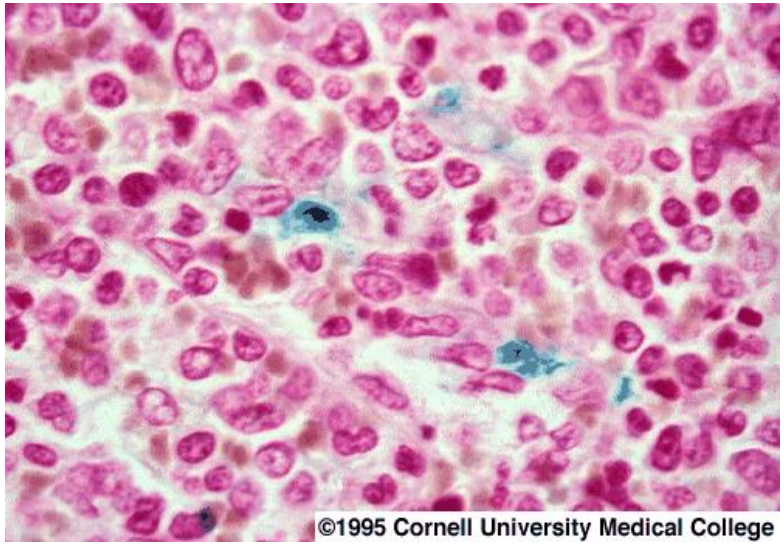
- *Decreased Iron Absorption:*

- Malabsorption diseases
- Transfusion
- Polycythemia
- Increased iron stores
- Fever

Iron in organism

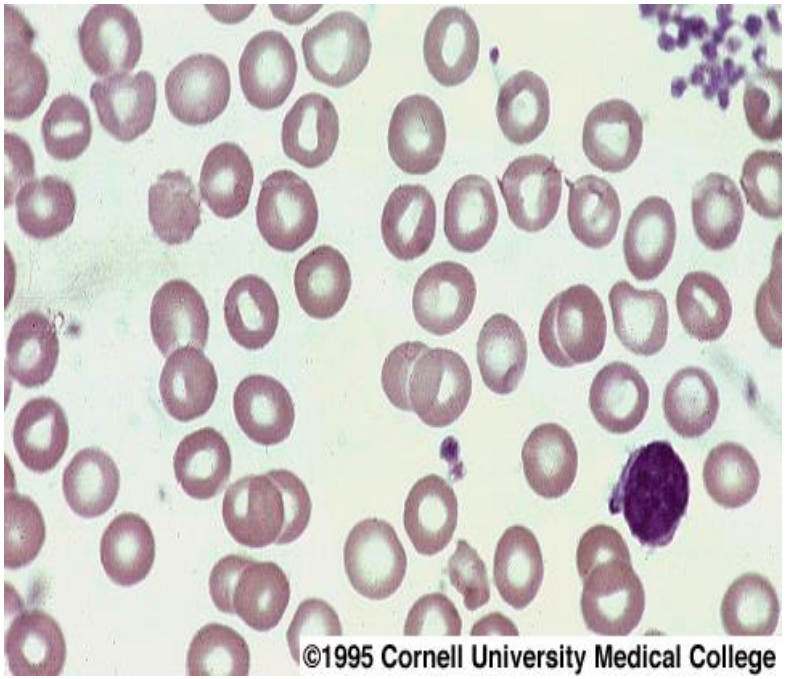
- 65-75% in Hb
- About 13% in ferritin
- About 12 % in hemosiderin
- About 5% in mioglobin
- <1% in enzymes (catalase, cytochromes)
- <1% in transferrin





Spleen, iron in macrophages

Microcytosis due to iron deficiency

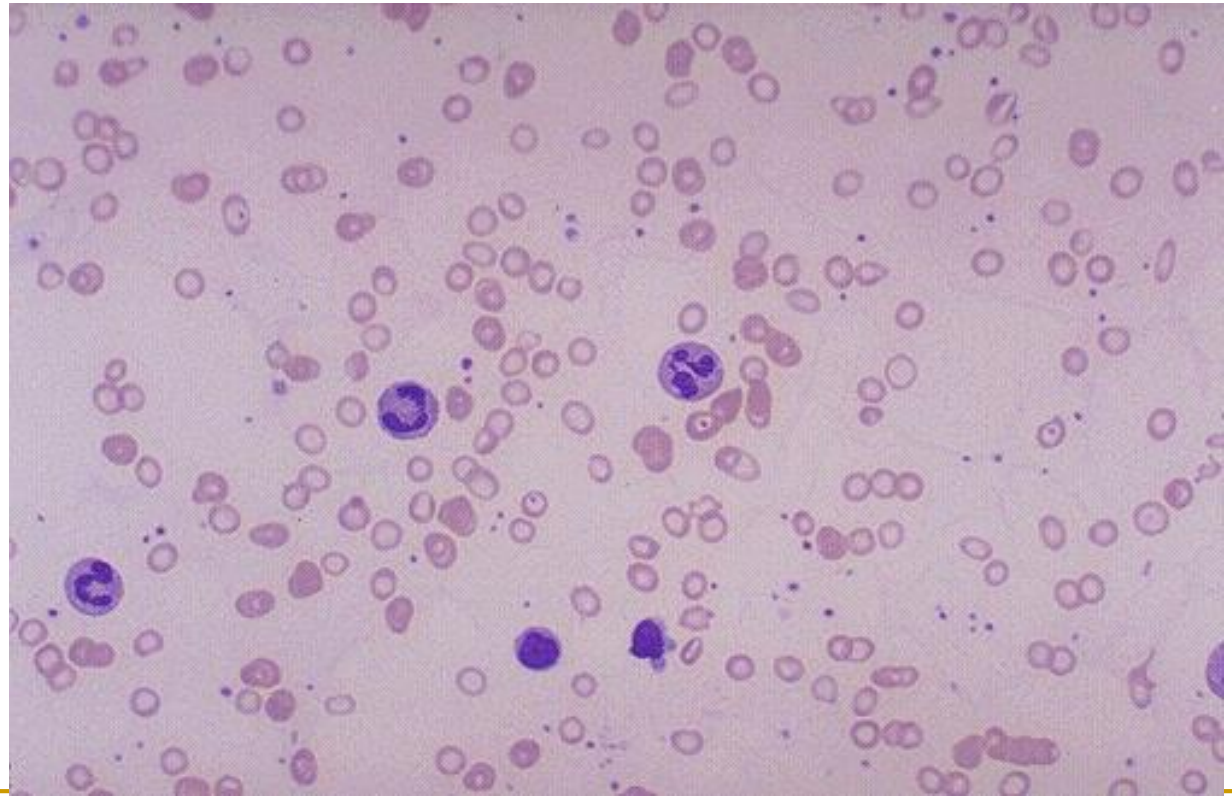


<u>Reasons for iron deficiency:</u>

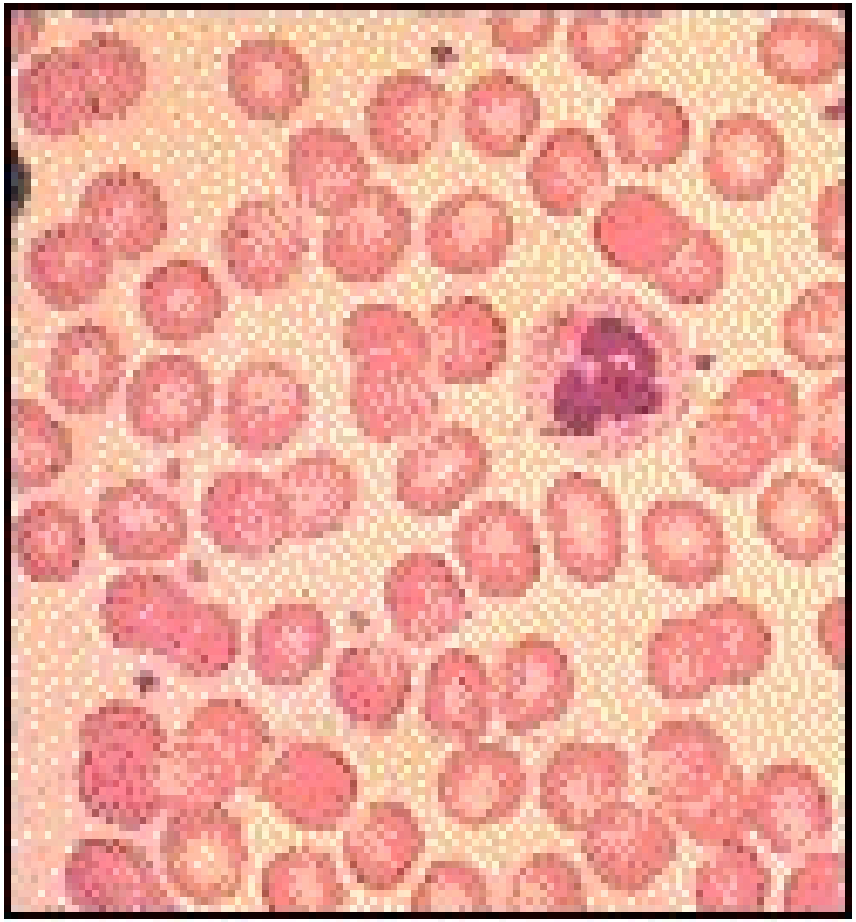
- Chronic blood loss
- Inadequate intake
- Increased need: Growing children and pregnant women (children under 2 are almost always iron deficient)

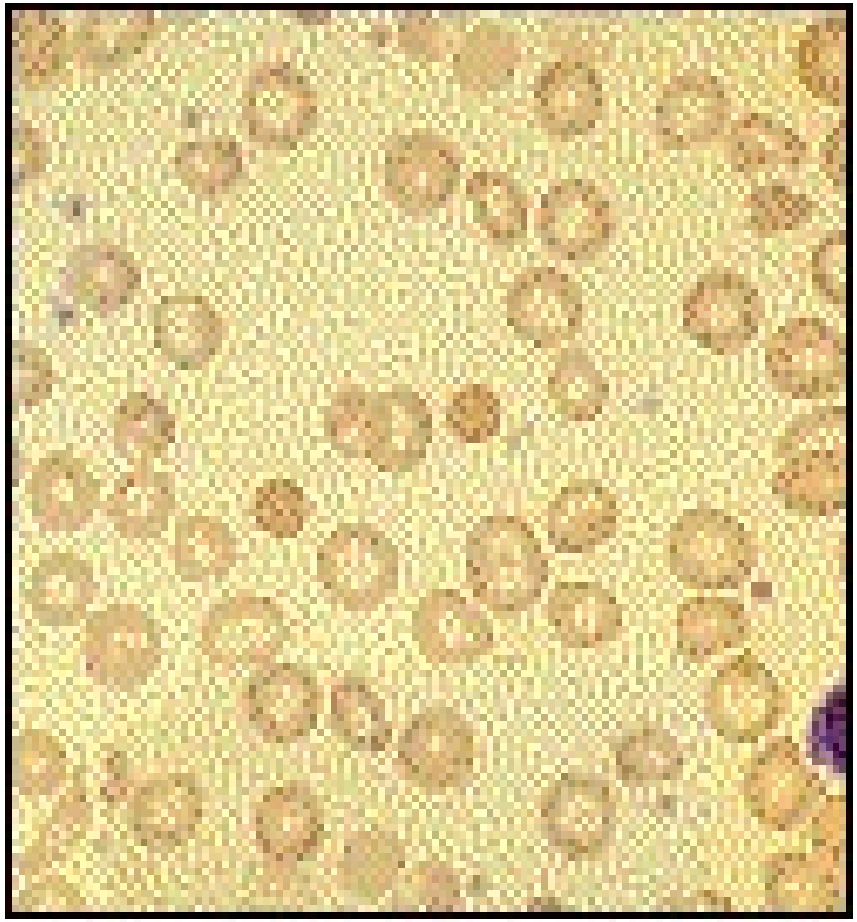
Brittle nails

The RBC's here are smaller than normal and have an increased zone of central pallor. This is indicative of a hypochromic (less hemoglobin in each RBC) microcytic (smaller size of each RBC) anemia. There is also increased anisocytosis (variation in size) and poikilocytosis (variation in shape).

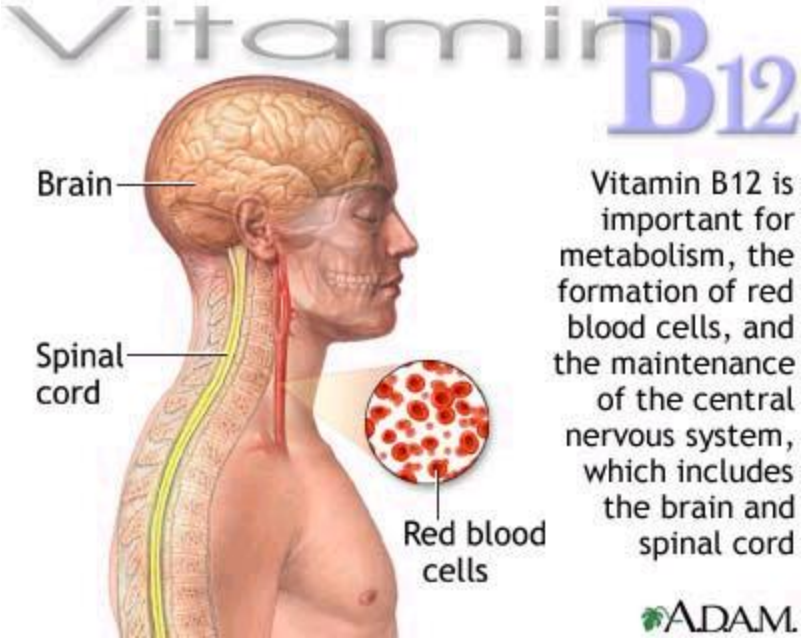


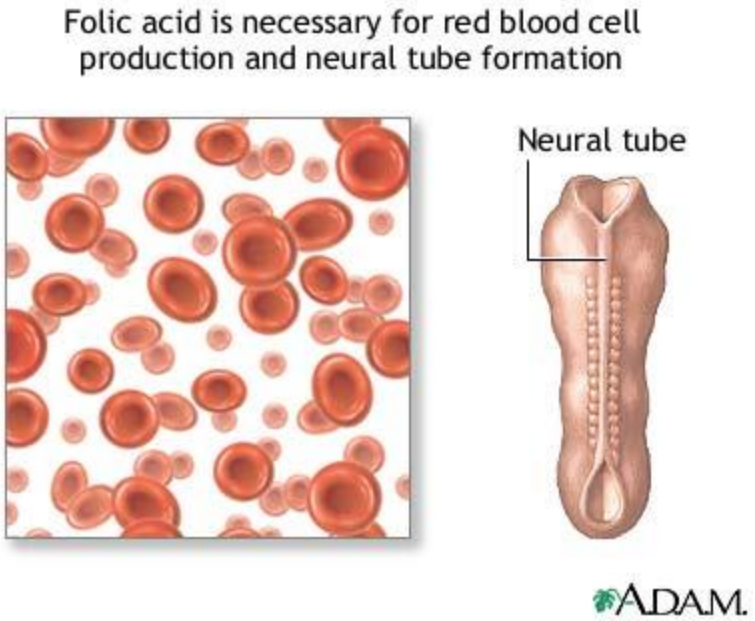
Normal vs. low iron

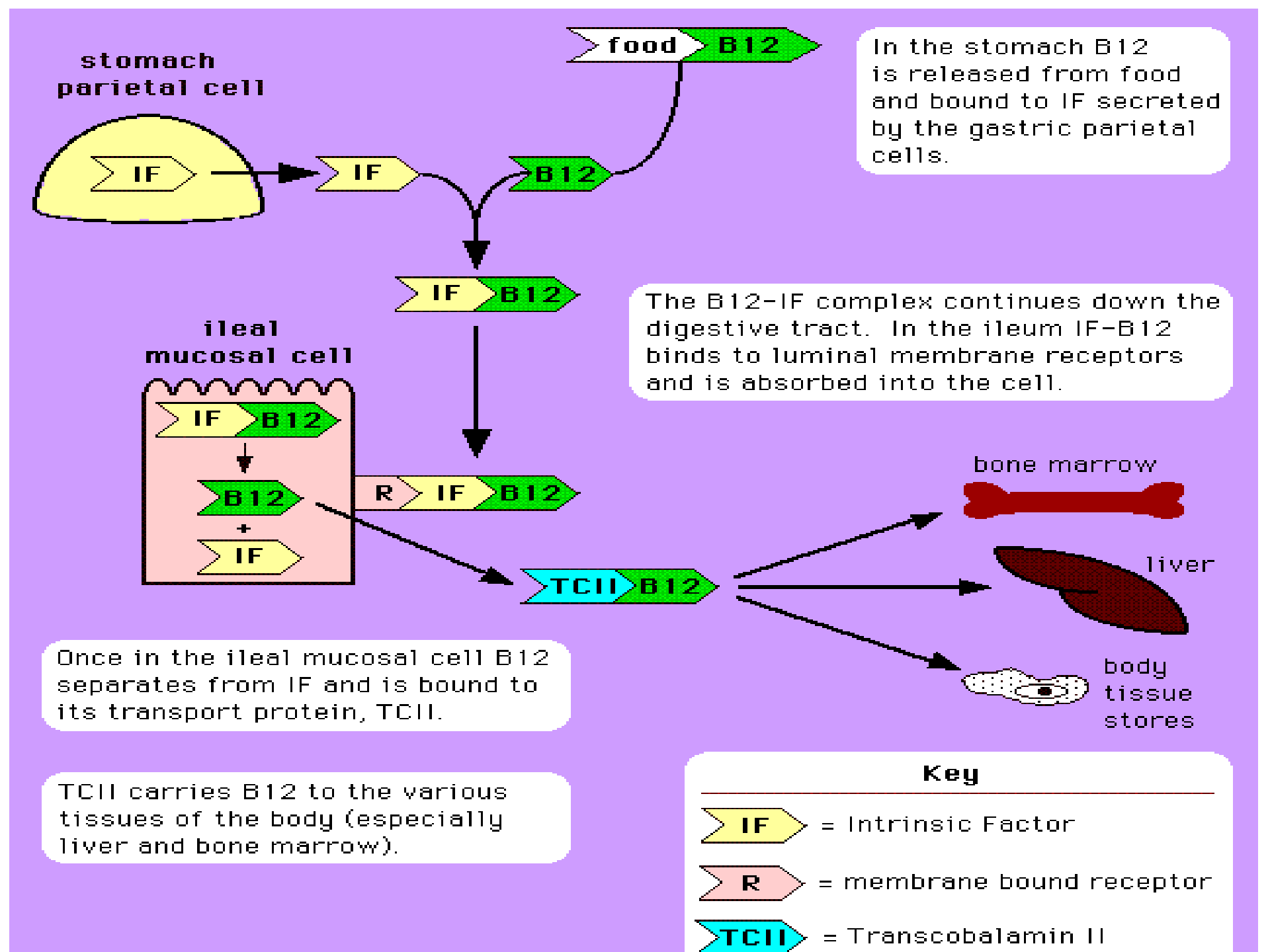




Vitamin B12 and folic acid

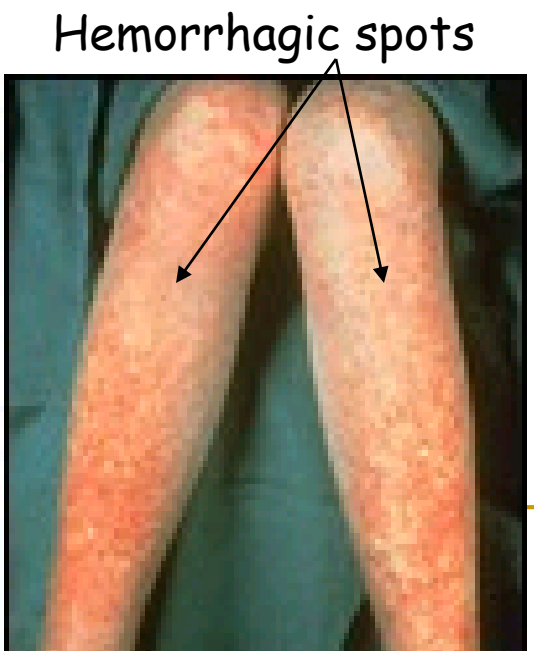


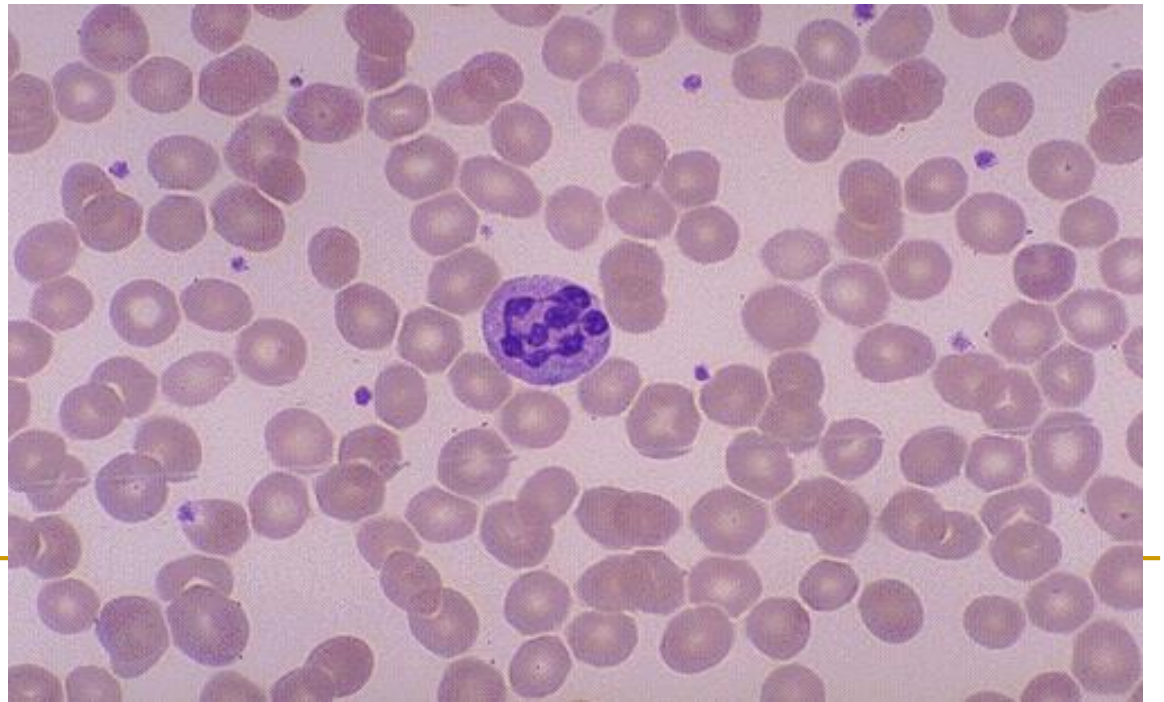



stomach
parietal cell
IF
IF
B12
food
B12
In the stomach B12 is released from food and bound to IF secreted by the gastric parietal cells.
IF
B12
The B12-IF complex continues down the digestive tract. In the ileum IF-B12 binds to luminal membrane receptors and is absorbed into the cell.
ileal
mucosal cell
IF
B12
B12
+
IF
R
IF
B12
TCII
B12
bone marrow
liver
body
tissue
stores
Once in the ileal mucosal cell B12 separates from IF and is bound to its transport protein, TCII.
TCII carries B12 to the various tissues of the body (especially liver and bone marrow).
Key
IF = Intrinsic Factor
R = membrane bound receptor
TCII = Transcobalamin II

Megaloblastic anemias

- When vitamin ***B_{12} or folate*** is deficient, DNA synthesis is interrupted. This leads to megaloblastic changes (macrocytosis). There is often erythroid hyperplasia in the marrow but most of these immature cells die before reaching maturity.
- The lack of DNA synthesis affects the neutrophils leading to nuclear hypersegmentation.
- Often a mild pancytopenia is seen but thrombocytopenia can be severe.

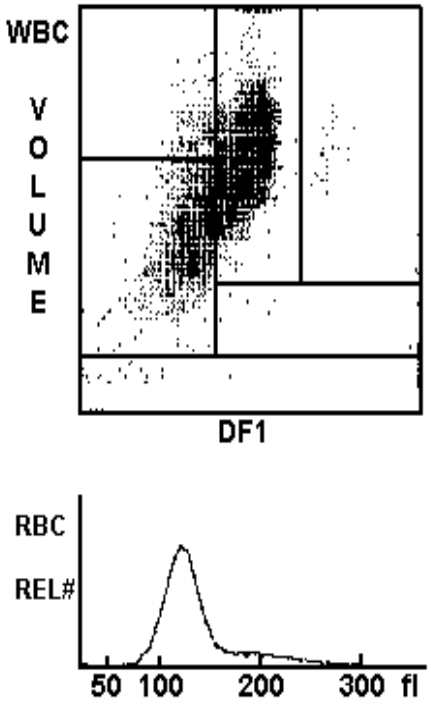




Neurologic symptoms may include:

- Impaired perception of deep touch and vibration
- Present Babinski reflex
- Paresthesias (feeling of "pins and needles")
- Dementia in severe cases

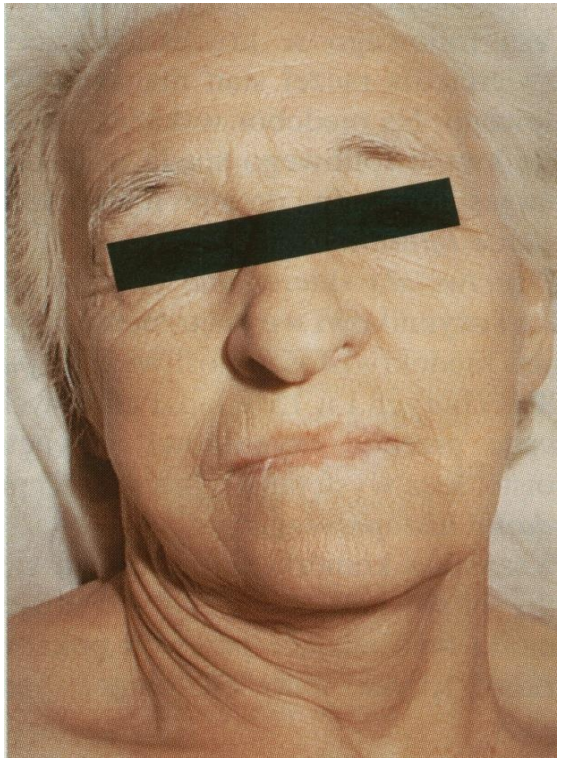
Markedly increased **MCV** *(mean corpuscular volume)* is typical for megaloblastic anemia.



WBC	12.1	H		
	%			
NE	71.[redacted]		[redacted]5	H
LY	15.9		L 1.9	
MO	3.3		0.5	
EO	0.5		L 0.1	
BA	8.7		H 1.1	H
RBC	2.69	L		
HGB	10.6	L		
HCT	31.6	L		
MCV	117.6	H		
MCH	39.6	H		
MCHC	33.7			
RDW	[redacted]			
PLT	578			
MPV	[redacted]			

3.9 Λ

100 Λ



Citric color of skin

Factors responsible for B12 and folic acid deficiency

Factor	Sample
Deficiency of B12:	
Diet	Vegetarianism (rarely), old people
Malabsorption diseases	Crohn disease, resection of ileum, others
Deficiency of folic acid:	
Diet	Alcoholism; old people
Malabsorption diseases	Crohn disease
↑requirement	Pregnancy
pharmacology	Drugs for epileptics

Polycythaemia (excess red blood cell production)

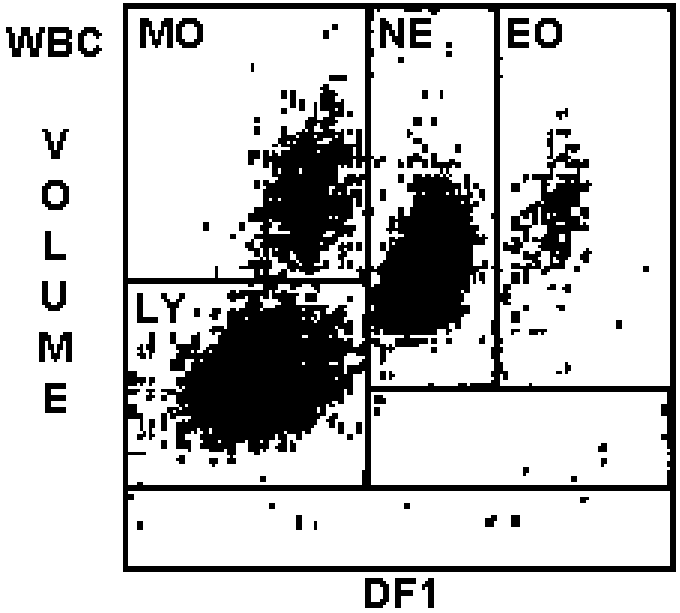
- RBCs > 6.0 T/L, ↑ HCT and HGB
- <u>Reasons:</u>

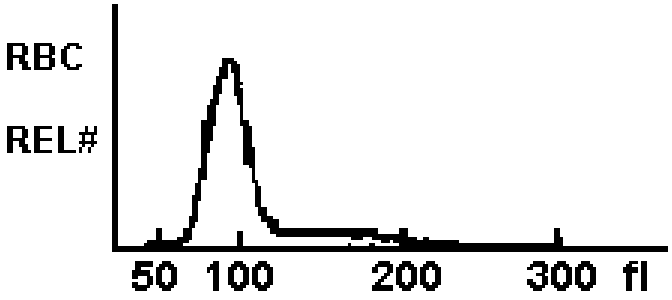
- primary (cancer of myeloid tissue)
- secondary increase in EPO sythesis *(high altitude, chronic lung disease, smoking)*
- pathological increase of EPO *(kidney dieases, liver tumors)*

Normal values of some haematological parameters (CBC – complete blood count)

Parameter		Value
Hemoglobin (HGB)	men women	13-17 g/dL 12-16 g/dL
Red cell count (RBC)	men women	4.5-6.0 T/L 3.8-5.2 T/L
Mean corpuscular volume (MCV)		78-95 fL/RBC
Hematocrit (PCV)	men women	40-52% 37-47%
Reticulocytes		0.2-2.0%
White cells count (WBC)		4-11 G/L
Platelets (PLT)		150-400 G/L

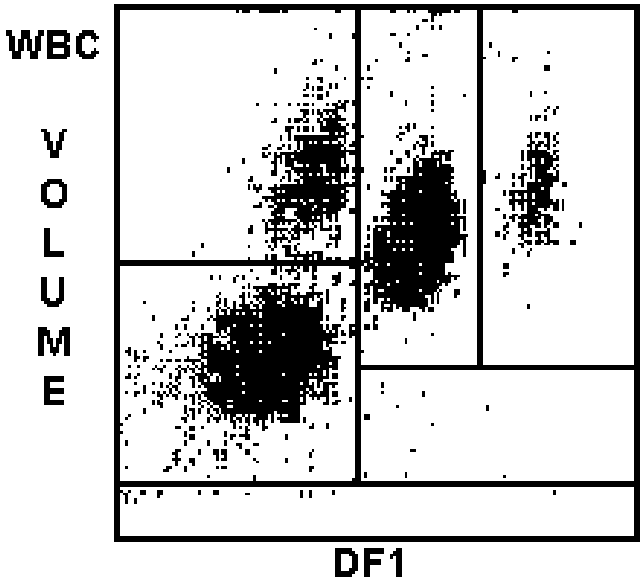
Analyze CBC test results – are they normal?

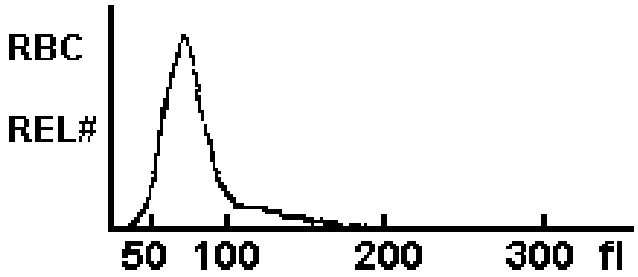




WBC	6.8	
	%	#
NE	52.6	3.6
LY	36.7	2.5
MO	7.8	0.5
EO	2.5	0.2
BA	0.4	0.0
RBC	5.29	
HGB	16.2	
HCT	47.0	
MCV	88.8	
MCH	30.7	
MCHC	34.5	
PLT	179	
MPV	8.4	

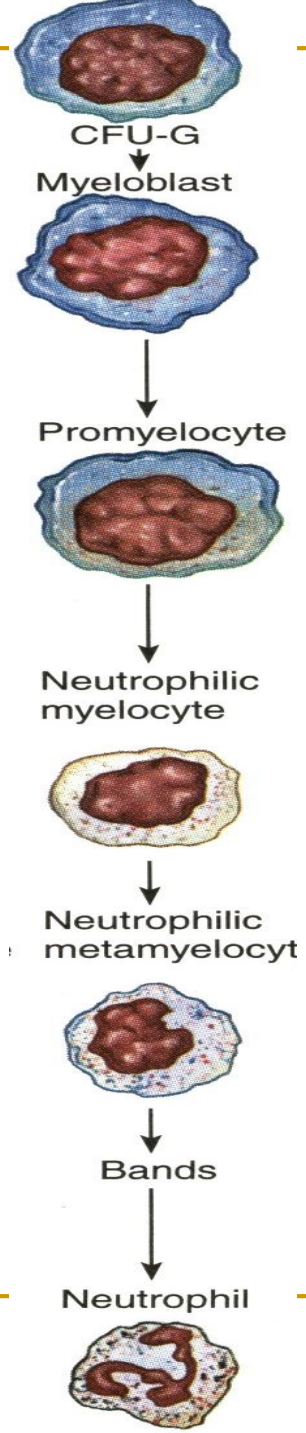
Analyze CBC test results – are they normal?





WBC	5.5		
	%		#
NE	54.7		3.0
LY	34.1		1.9
MO	7.5		0.4
EO	3.0		0.2
BA	0.7		0.0
RBC	4.28	L	
HGB	9.7	L	
HCT	29.9	L	
MCV	69.7	L	
MCH	22.6	L	
MCHC	32.4	L	
PLT	331		
MPV	8.8		

Granulopoiesis



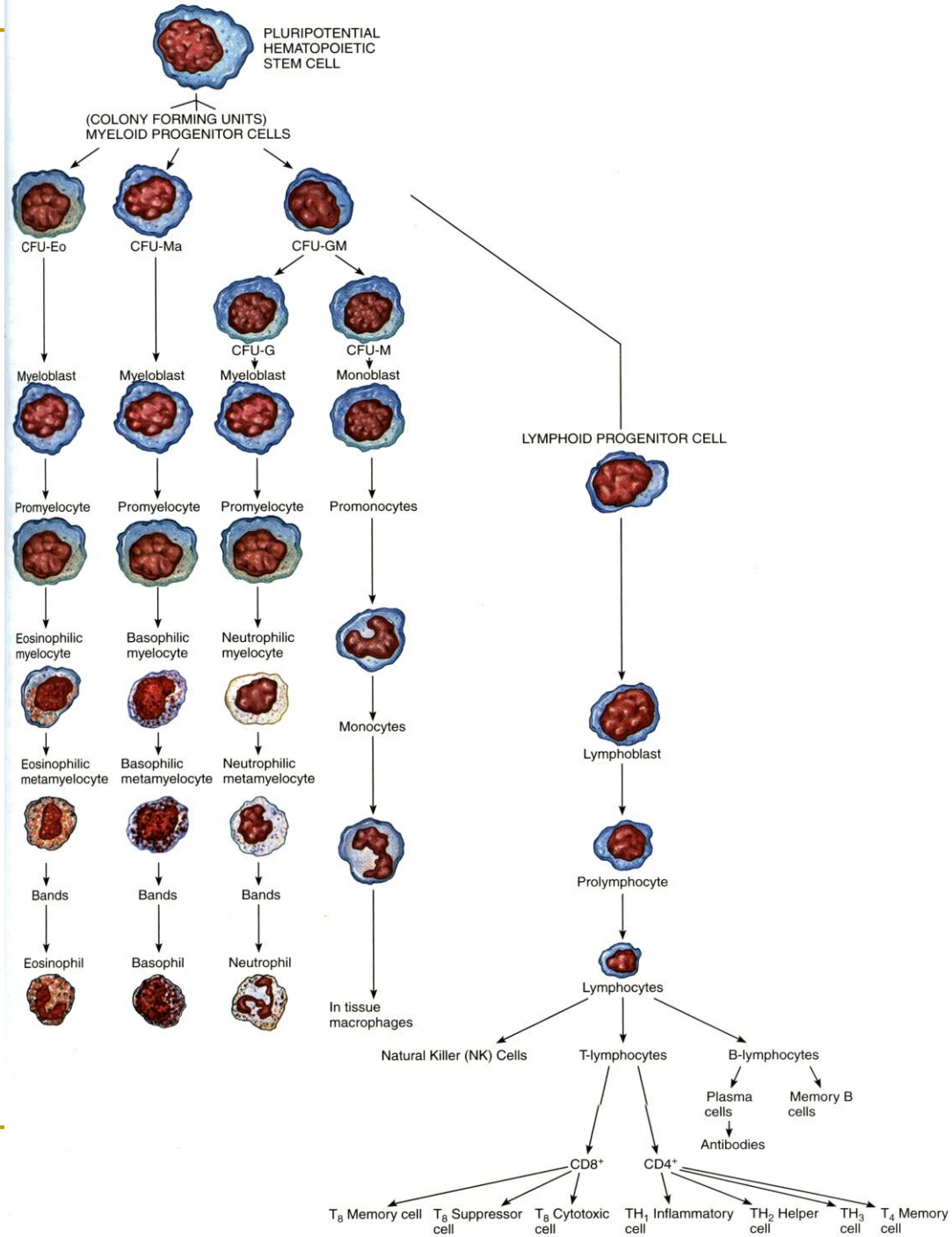
Granulopoiesis

- Granulocytes is the collective name given to three types of WBC. Namely these are: neutrophils, basophils and eosinophils.
- In terms of their formation (granulopoiesis) they all derive from the same type of precursor cells called myeloblasts.
- After birth and into adulthood granulopoiesis occurs in the red marrow.

Granulopoiesis

The process of producing granulocytes is characterised by:

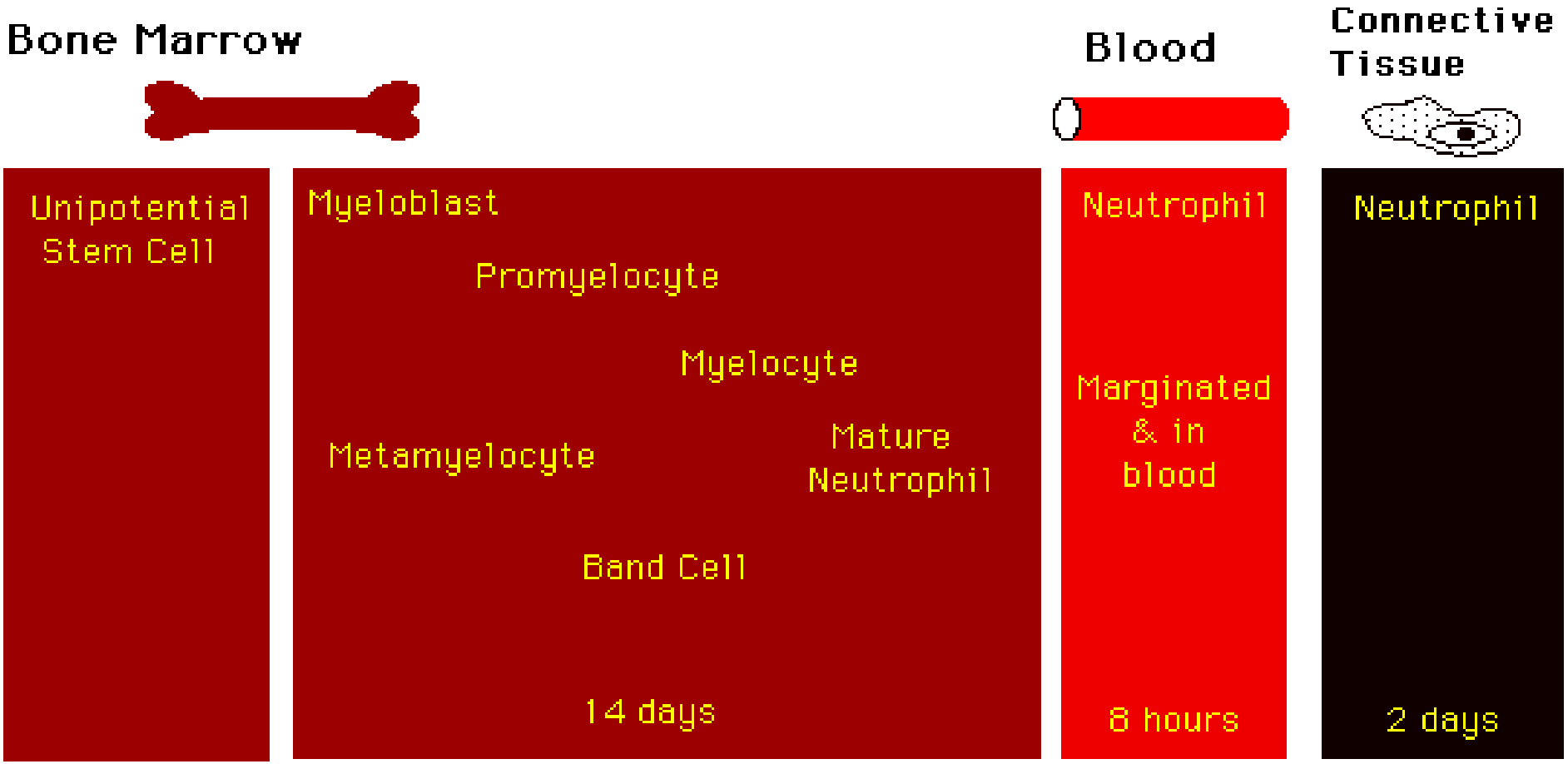
- the progressive condensation and lobulation of the nucleus,
- loss of RNA and other cytoplasmic organelles, for example mitochondria,
- the development of cytoplasmic granules.



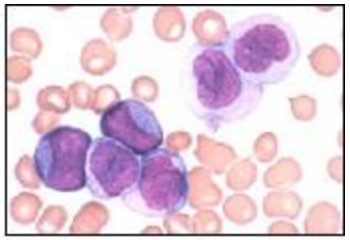
Factors affecting granulopoiesis

- Sympathetic system increases granulopoiesis
- ACTH and glucocorticoids increase count of neutrophils and decrease count of eosinophils, lymphocytes and basophils
- Thyroid hormones, pituitary hormones, adrenal hormones and estrogens – increase granulopoiesis
- Positive feedback – products of WBCs degradation

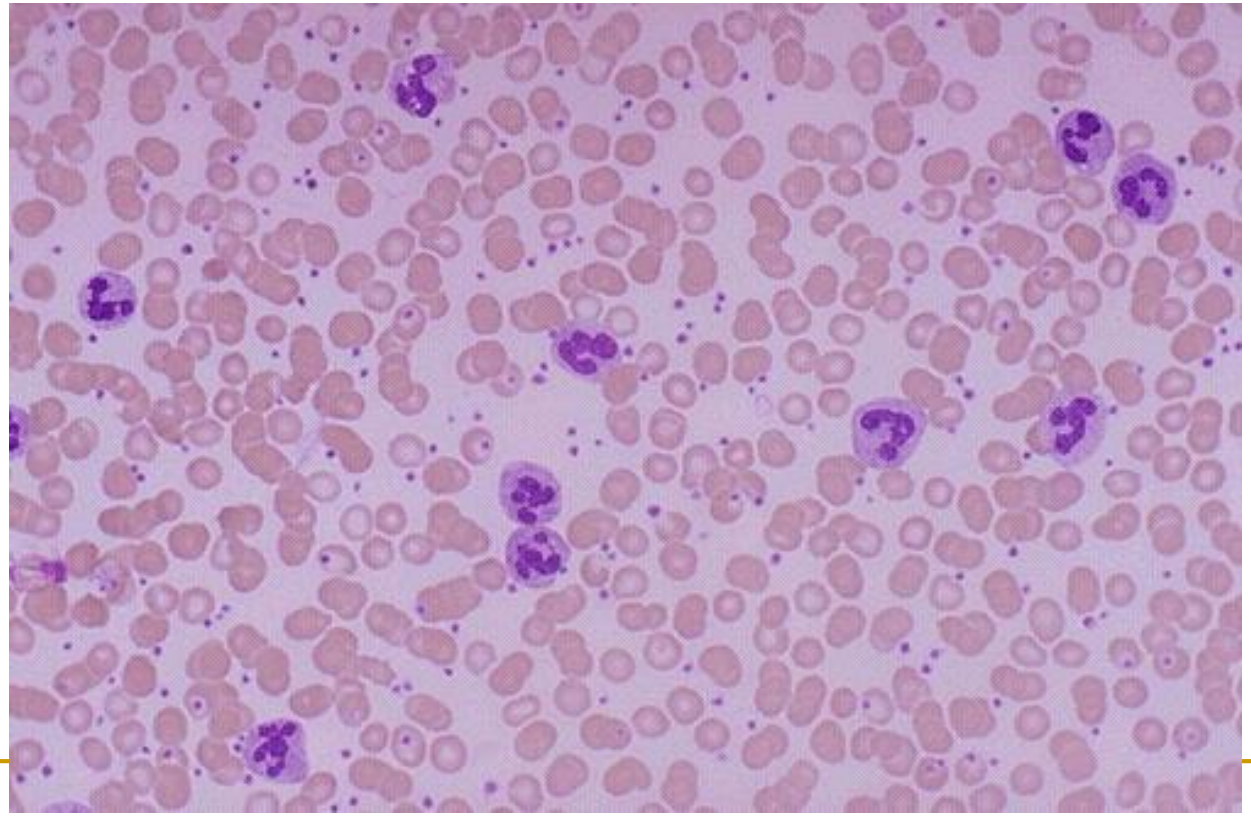
Normal neutrophil renewal in bone marrow amounts to 60-70% of all nucleated cells in the bone marrow. Percentage of neutrophils increases with their maturity*(most of mature neutrophils; less myeloblasts)*



The RBC's in the background appear normal. The important finding here is the presence of many PMN's. An elevated WBC count with mainly neutrophils suggests inflammation or infection. A very high WBC count (>40G/L) that is not a leukemia is known as a *"leukemoid reaction".* This reaction can be distinguished from leukemia by the presence of large amounts of leukocyte alkaline phosphatase (LAP) in the neutrophils.

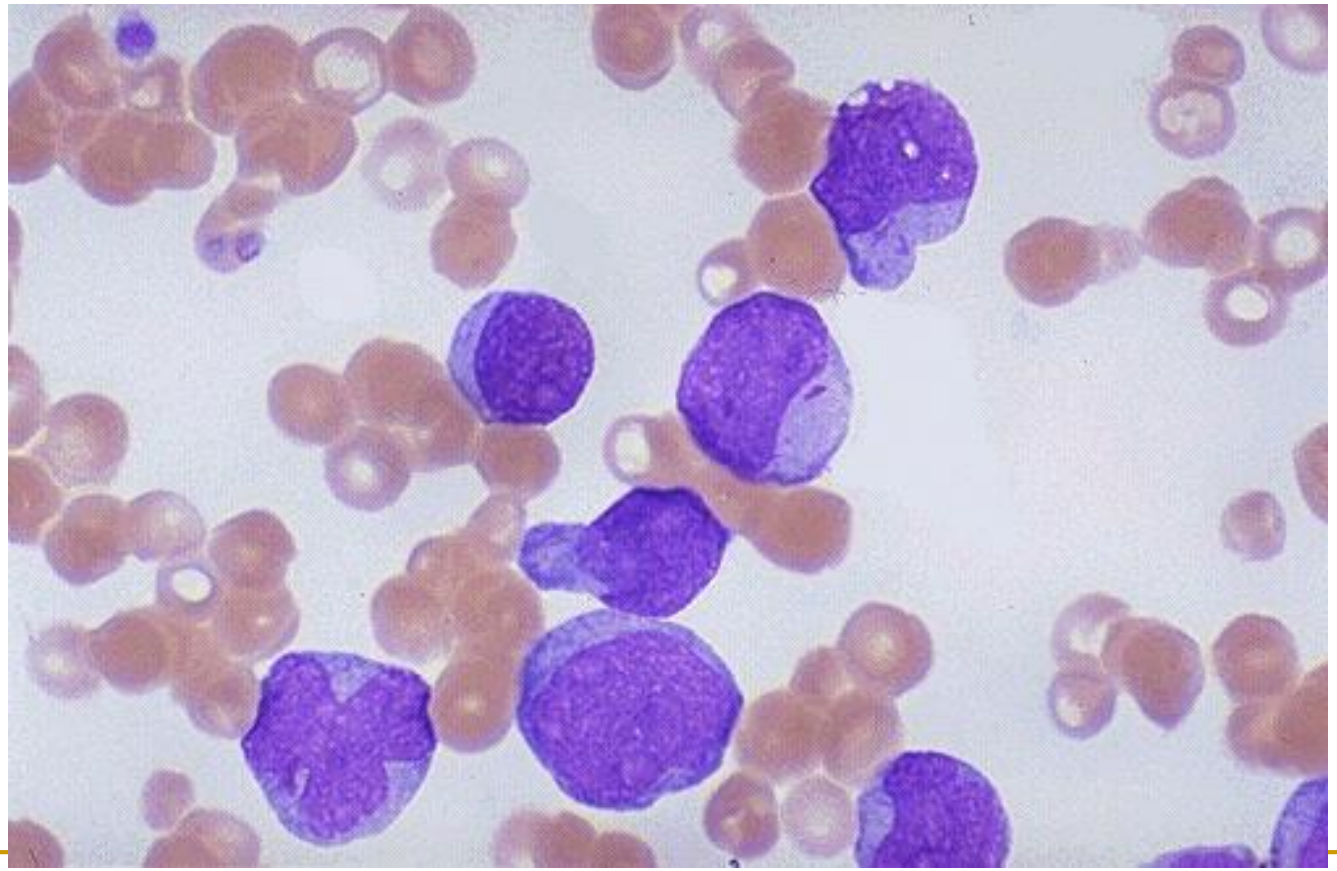


leukemia



Leukemoid reaction

Here are very large, immature myeloblasts typical for acute myelogenous leukemia (AML) that is most prevalent in young adults.

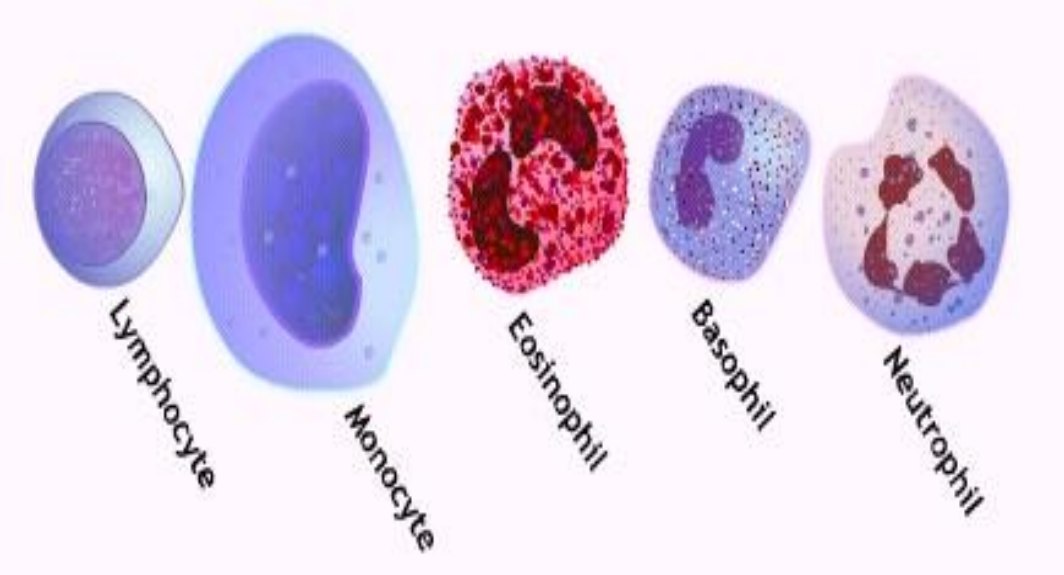


Granulocytes

- In the circulation, about 50% of granulocytes adhere closely to the internal surface of the blood vessels. These are called marginal cells and are not normally included in the white cell count.
- The other half circulate (circulating cells) in the blood and exchange with the marginal population.
- Within hours granulocytes may leave the circulation in response to specific requirements for these cells in the tissues.
- They may survive in the tissues for 4 or 5 days, or less, depending on the conditions they meet.

There are five main types of white blood cells (Schilling's count):

- neutrophils 45-65 %
- eosinophils 1-4 %
- basophils 0.5-1 %
- lymphocytes 20-40 %
- monocytes 3-8 %



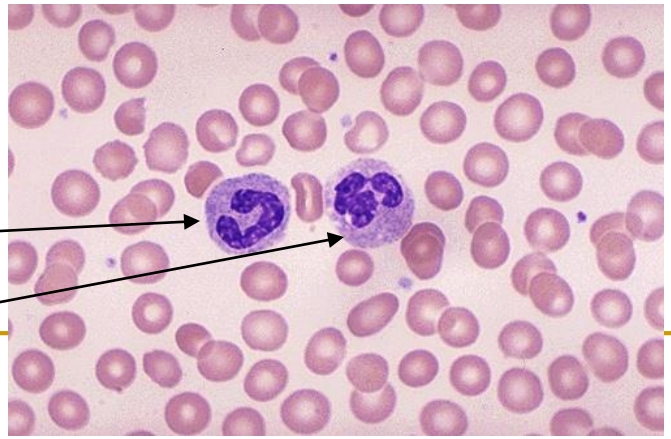
Neutrophils

45-65%

- Neutrophils are the most common granulocytes. They have segmented or rod-shaped nuclei, typically with 2 to 5 lobes („segments", „bands")
- They are motile, can change their shape and are actively phagocytic
- The cytoplasm of neutrophils contains three types of granules

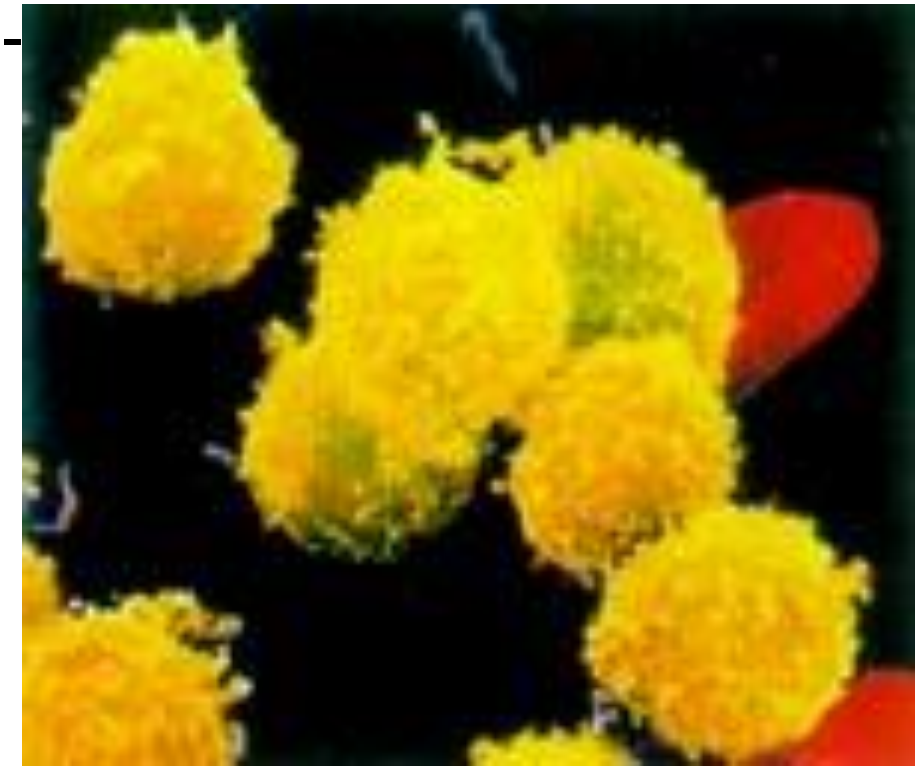
2 neutrophils: with rod-shaped nucleus (band neutrophil)

and segmented nucleus (segment)



Neutrophils

- Primary granules are non-specific and contain lysosomal enzymes, and some lysozyme. The granules are similar to lysosomes.
- The enzymes (MPO) produce hydrogen peroxide



Oxygen-depedent killing

- Respiratory (oxidative) burst
- Molecular oxygen reduced to a range of intermediates:

- superoxide anion
- hydrogen peroxide
- hypochlorite anions
- singlet oxygen
- hydroxyl radicals

$$NADPH + H^+ + 2O_2 \xrightarrow{oxidase} NADP^+ + 2H^+ + 2O_2^-$$

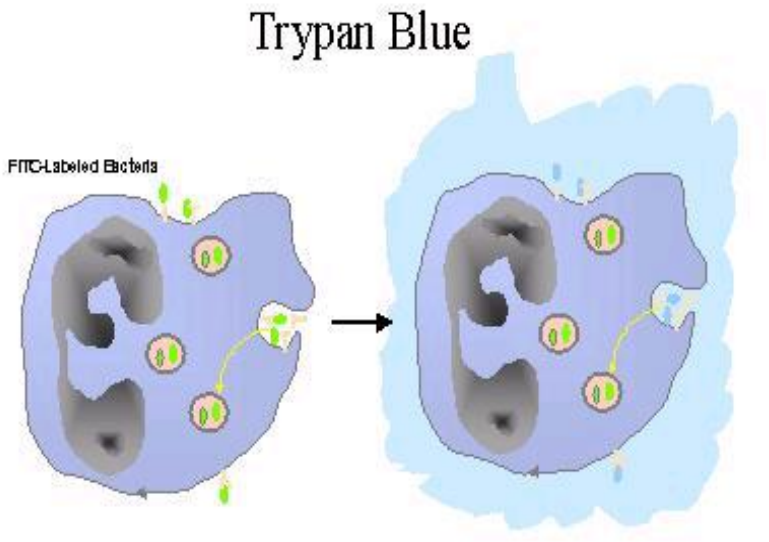
$$O_2^- + O_2^- + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$$

$$Cl^- + H_2O_2 \xrightarrow{MPO} OCl^- + H_2O$$

they are powerful anti-bacterial agents

Oxygen-independent killing

- Lysozyme destroys bacterial cell walls
- Cationic proteins cause pH to fall
- Acid hydrolase enzymes degrade carbochydrates, proteins, lipids, and nucleic acids

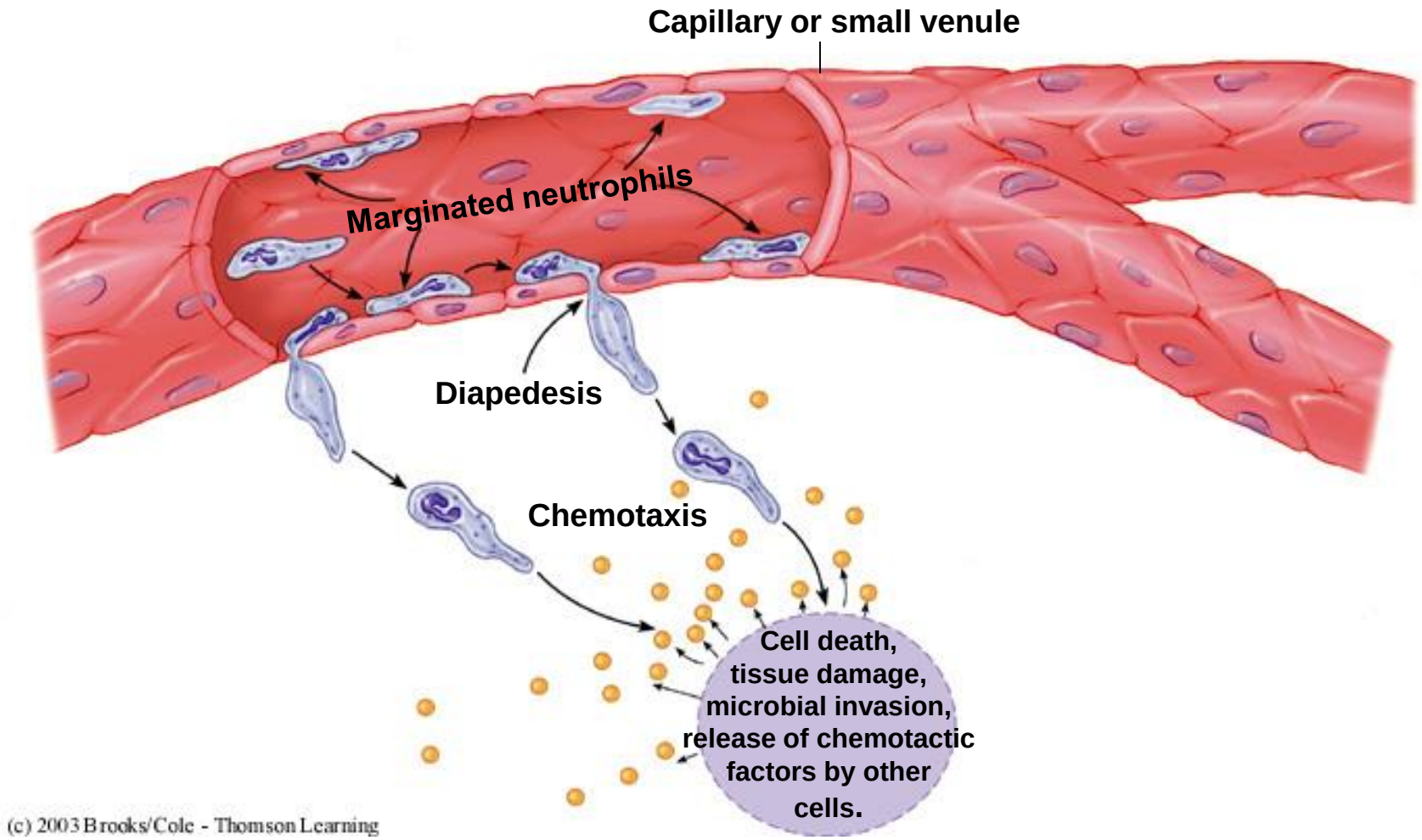


Neutrophils

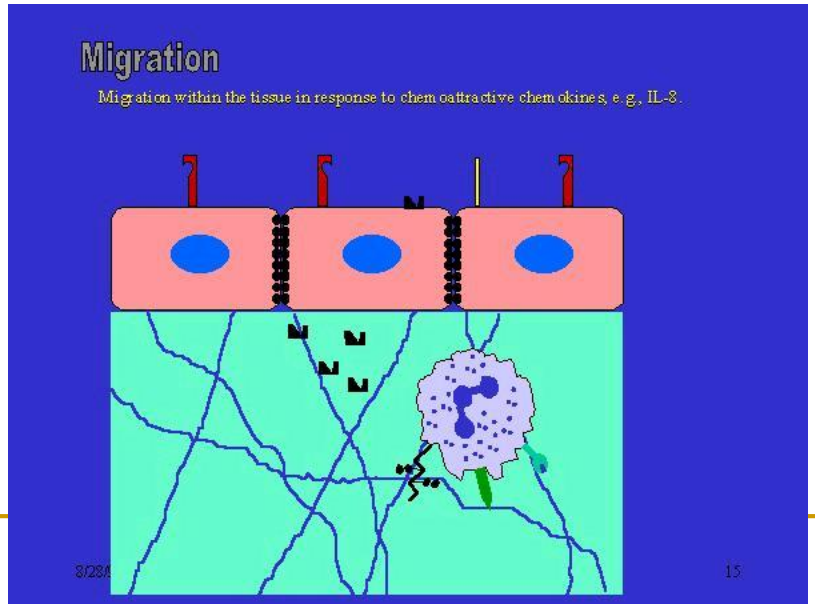
- Secondary granules are specific to neutrophils. They contain collagenase, to help the cell move through connective tissue, and lactoferrin, which is toxic to bacteria and fungi.

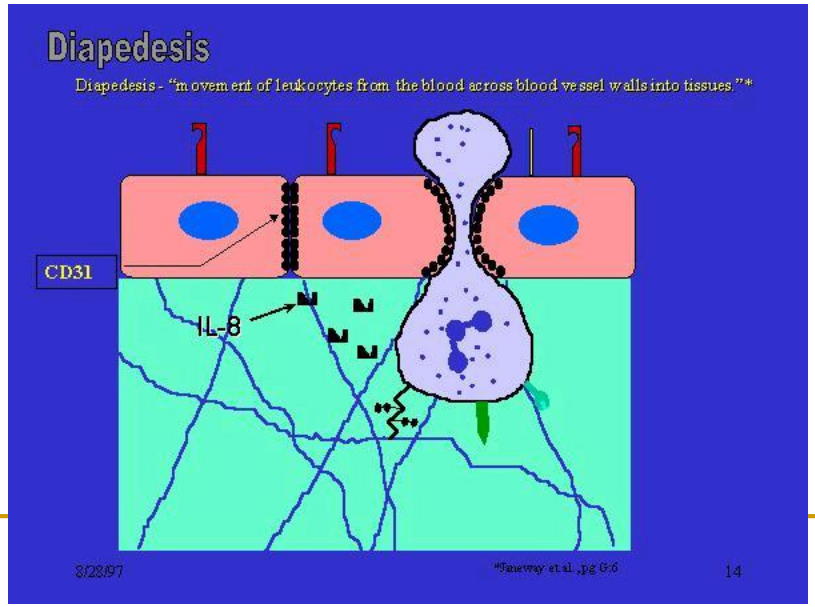
- Tertiary granules may produce proteins which help the neutrophils to stick to other cells.

Neutrophils are phagocytes that can exit the bloodstream (diapedesis) and travel to inflammation.

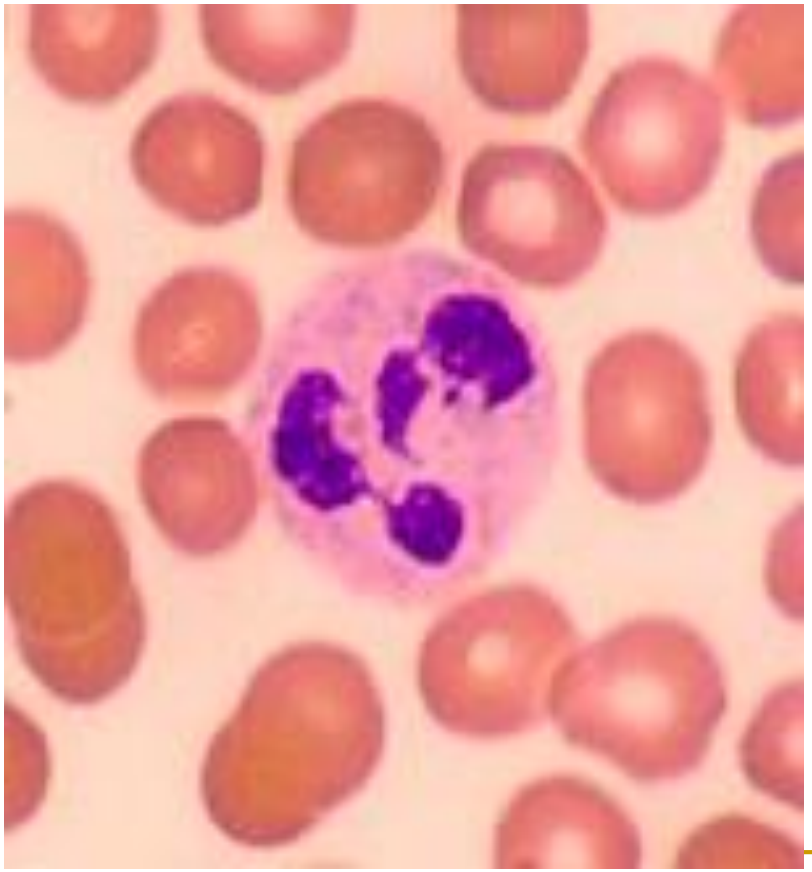


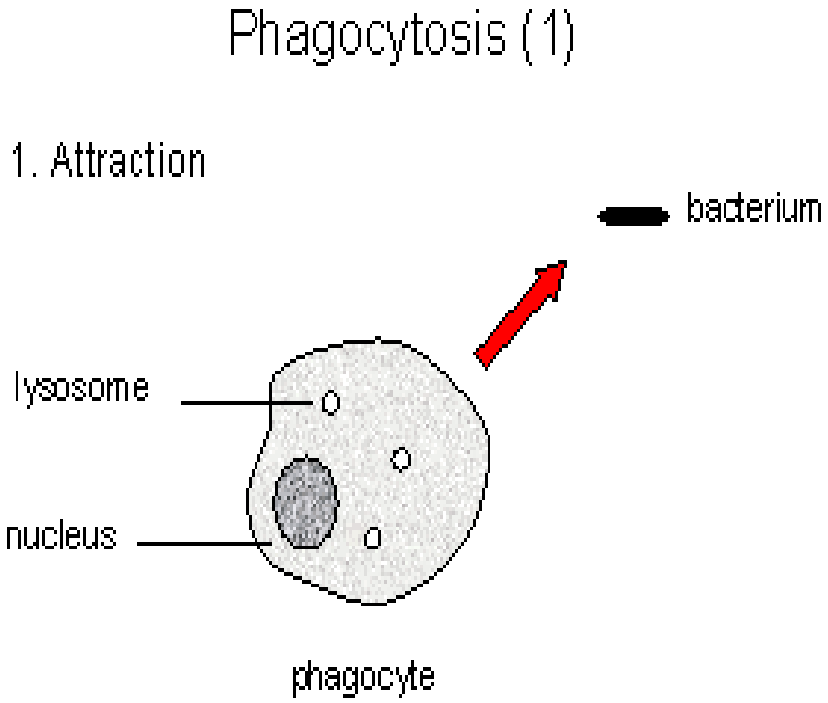
In the area of infection neutrophils respond to chemicals and move towards the area of highest concentration (migration and chemotaxis). Neutrophils respond to chemotactic signals (such as soluble bacterial products, complement components or cytokines) via directional migration to the place of inflammation they undergo activation (preparation for degranulation and release of lysosomal enzymes)





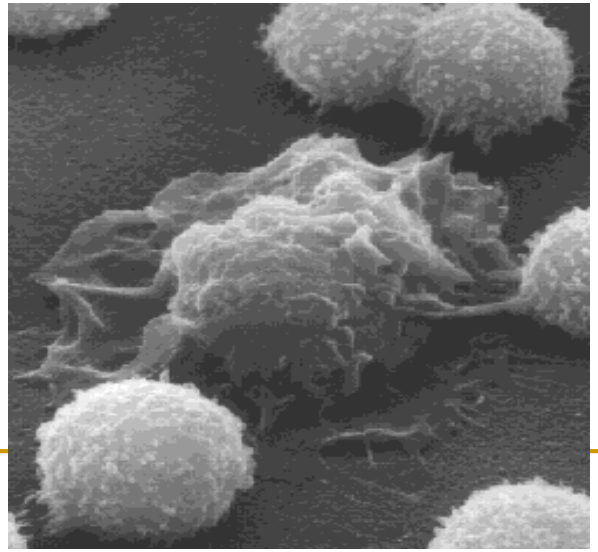
Phagocytosis

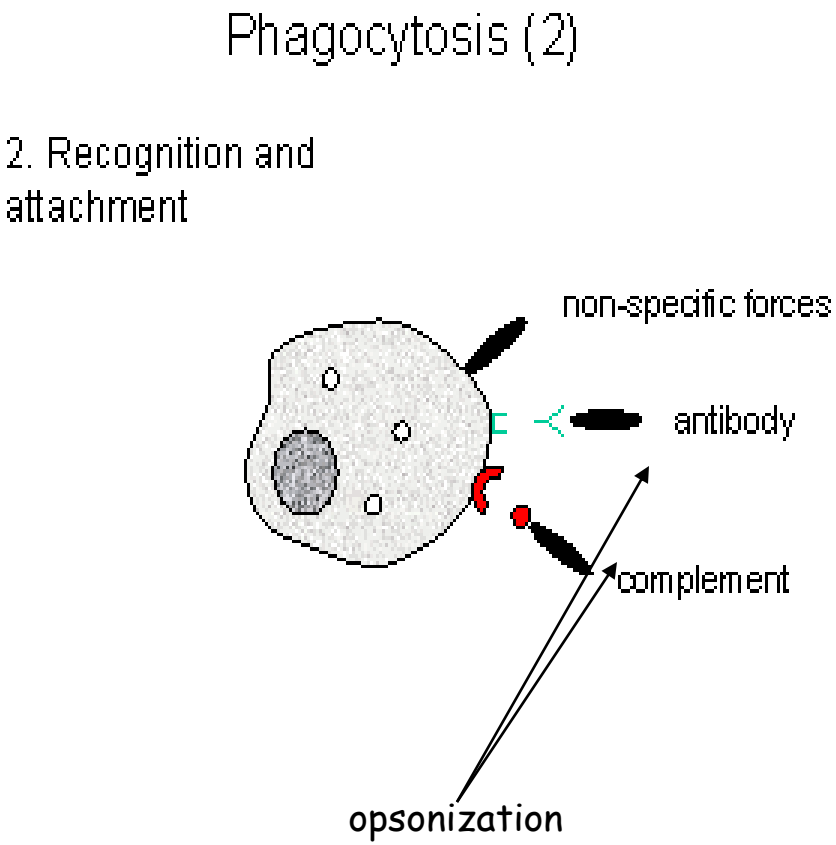




Phagocytosis

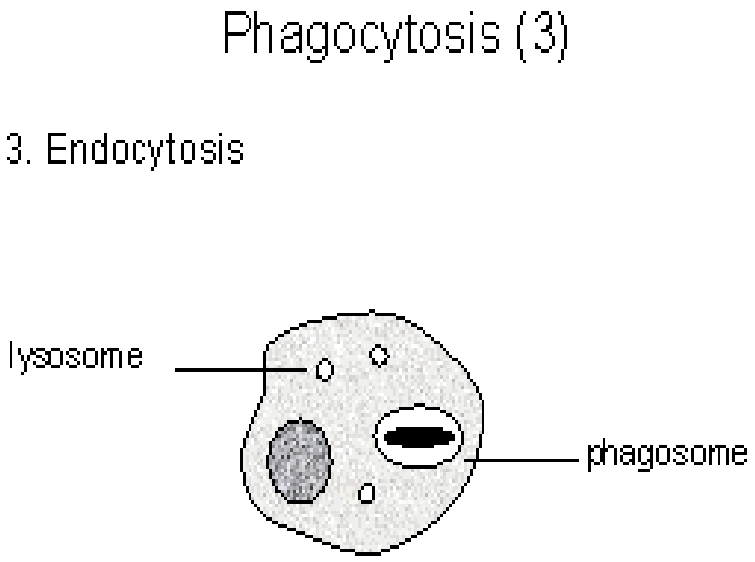
2. Attachment of the bacterium to the long membrane evaginations, called pseudopodia.





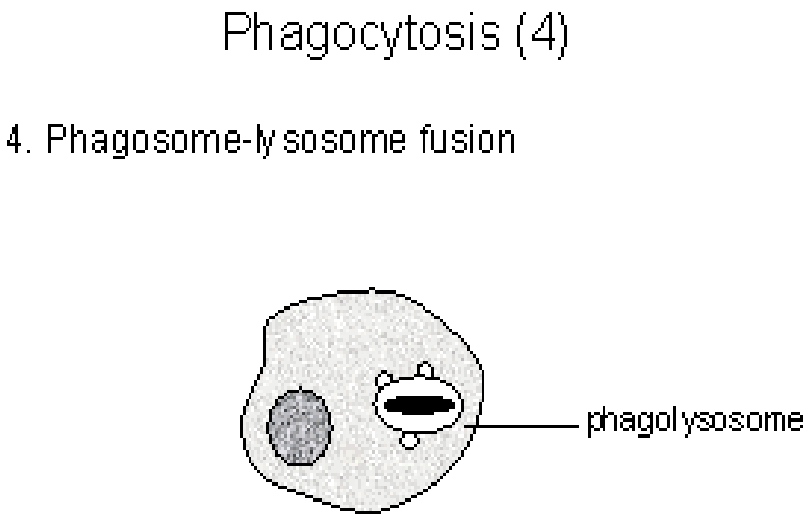
Phagocytosis

3. Ingestion of the bacterium forming a "phagosome," which moves toward the lysosome.



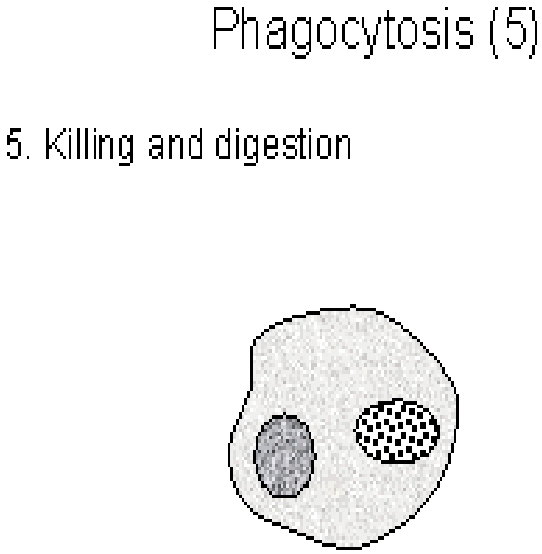
Phagocytosis

4. Fusion of the lysosome and phagosome, releasing lysosomal enzymes into the phagosome.



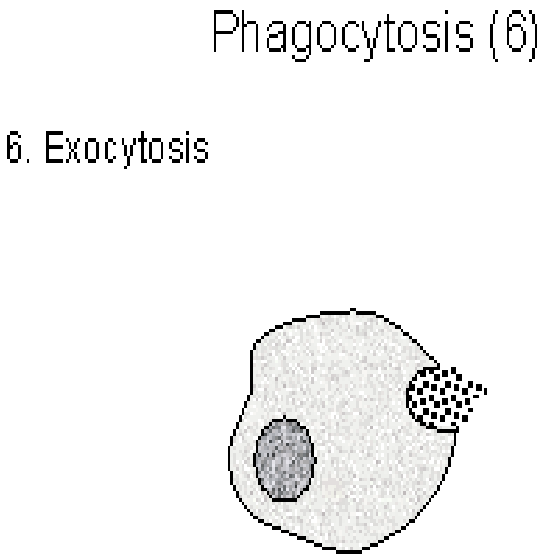
Phagocytosis

5. Digestion of the ingested material.

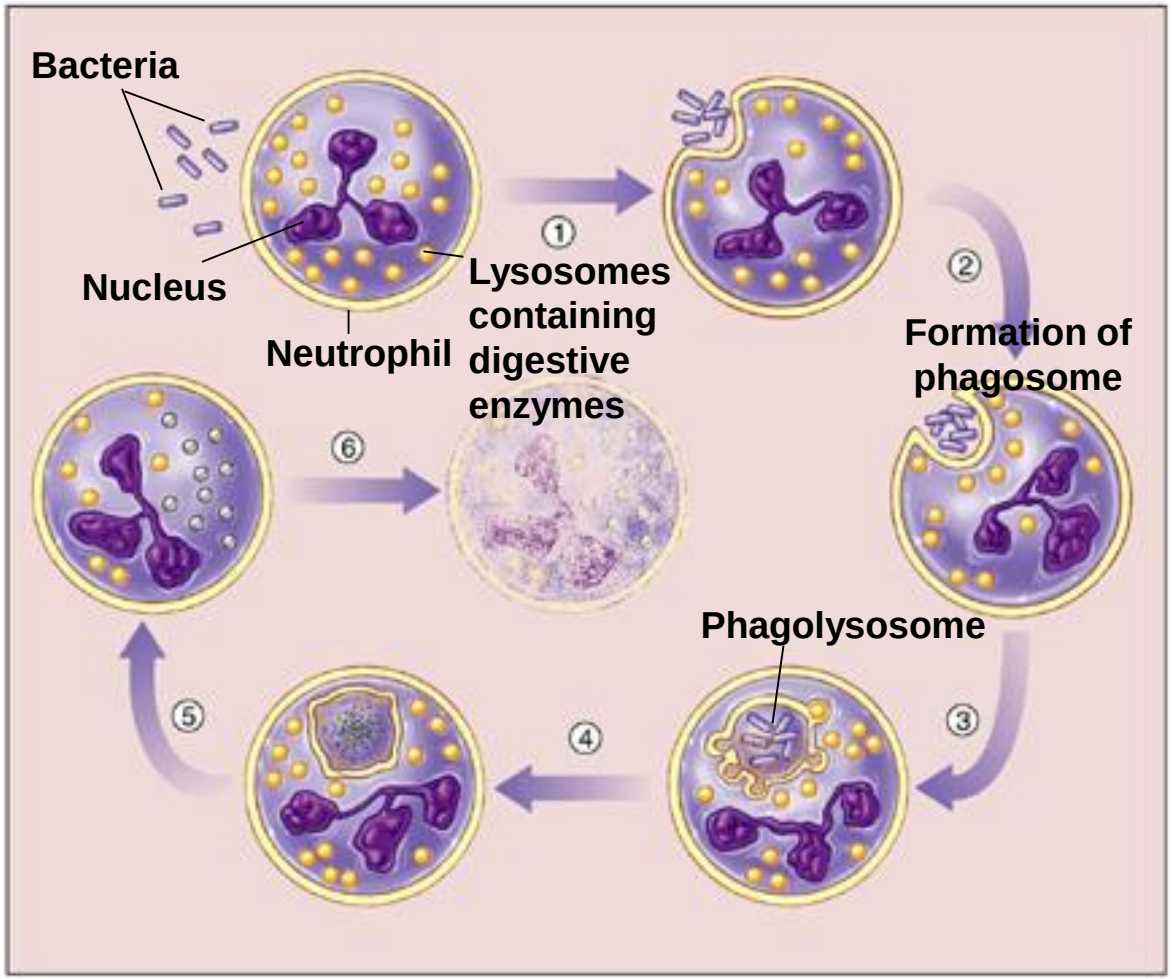


Phagocytosis

6. Release of digestion products from the cell



Neutrophils get to an infection early in large numbers, ingest microbes, die, and damage tissue



(c) 2003 Brooks/Cole - Thomson Learning (a)

1. Ingestion of bacteria by neutrophil.

2. Phagosome forms around bacteria.

3. Degranulation of lysosomes to form digestive vacuole (phagolysosome).

4. Bacterial lysis by digestive enzymes.

5. Dispersement of phagosome in cytosol.

6. Neutrophil lysis.

Types of phagocytic cells

- NEUTROPHILS (polymorfonuclear)

- most common/active
- first to side of injury
- short lived (4-5days)

- EOSINOPHILS

- allergic responses
- parasitic worms

- MONOCYTES

- develop into macrophages

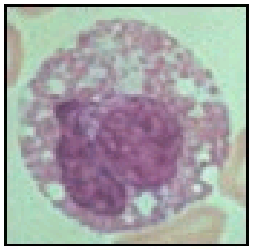
- Wandering MACROPHAGES

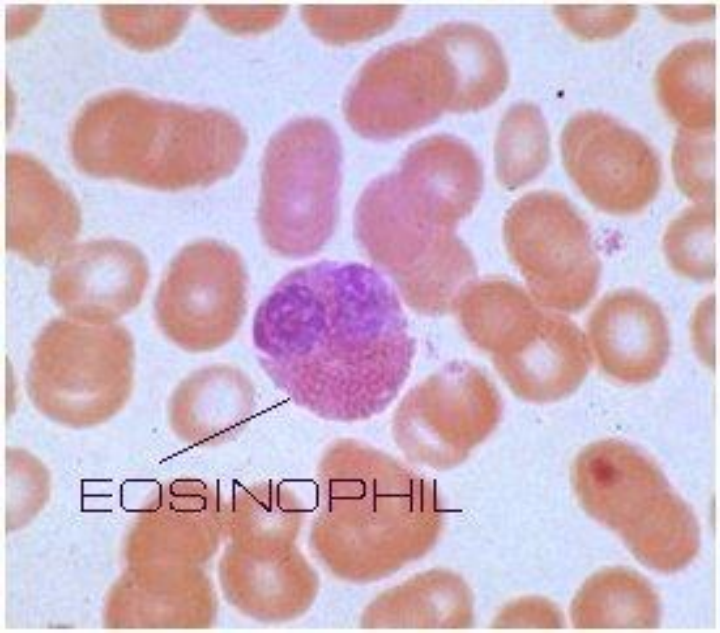
- travel as monocytes
- chemotaxis during inflammation

- Fixed MACROPHAGES

- lymph nodes, spleen, most organs (e.g. skin, brain, liver, kidneys)
- long lived (months to years)

Eosinophils
1-4%





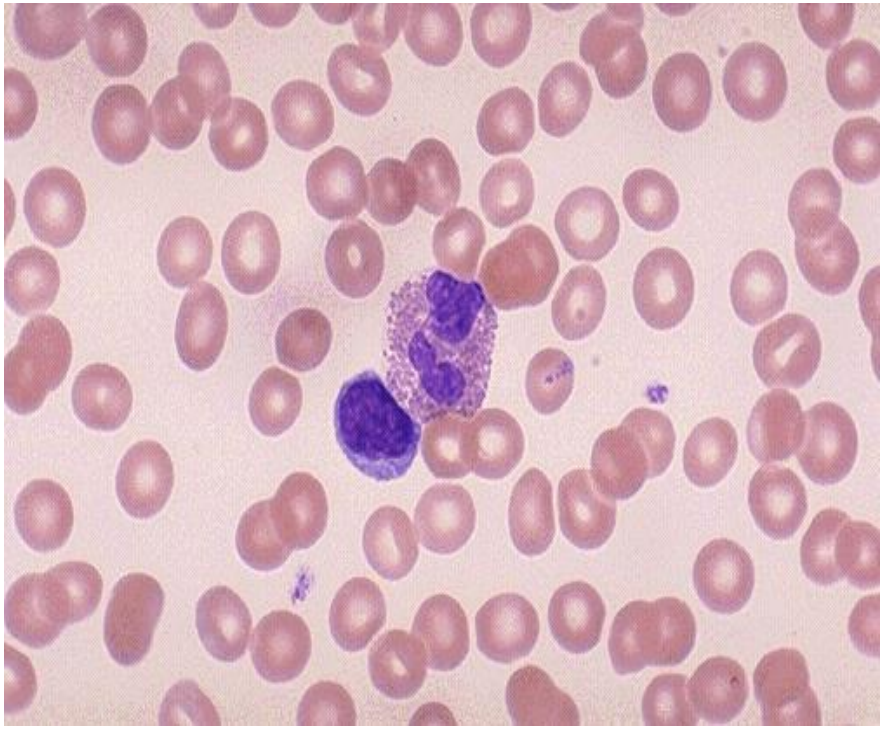
- bi-lobed nucleus
- they increase greatly in many types of parasitic infection and defence against the larvae of parasitic worms and unicellular organisms
- they also increase in number in some allergic states (they neutralise the effect of histamine)

Eosinophils - properties

- The lysosomes contain oxidase, peroxidase and phosphatases
- Eosinophils exhibit chemotaxis;
- They respond to eosinophilic chemotactic factors released by basophils
- Their attraction depends on the presence of antibodies specific to foreign proteins (phagocytosis of Ag-Ab complexes)

Eosinophils

- The granules of eosinophils contain a substance called MBP (major basic protein) which is toxic to many parasitic larvae.
- Eosinophils also have surface receptors for the antibody: immunoglobulin E (IgE).
- These receptors are not found in neutrophils and again this is thought to reflect their role in parasitic infection.

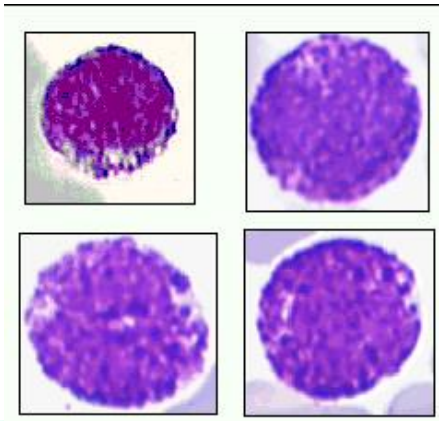


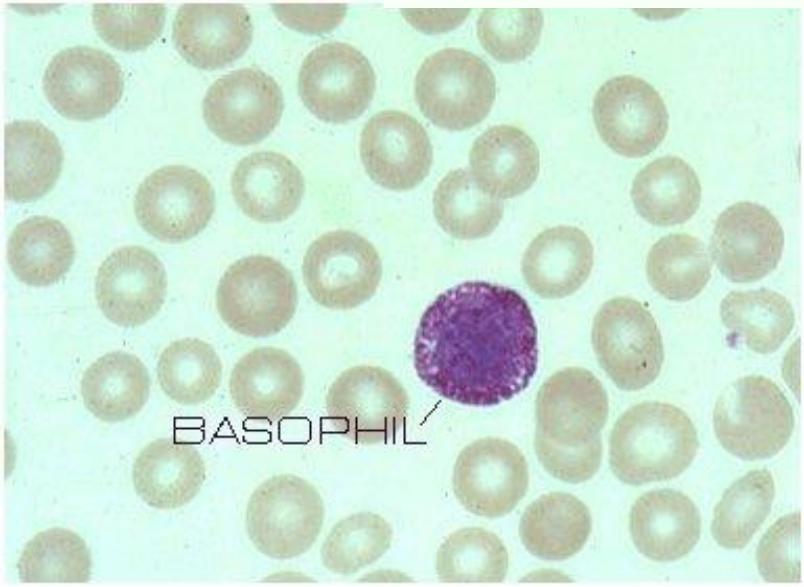
eosinophil with a bilobed nucleus and reddish granules in the cytoplasm. Just underneath it is a small lymphocyte

Function of eosinophils - summary

- they regulate allergic reactions
- they defence against parasitic infections
- they participate in antigen presentation *(for antibodies synthesis)*
- they play role in hemostasis (plasminogen)

Basophils
0-1%

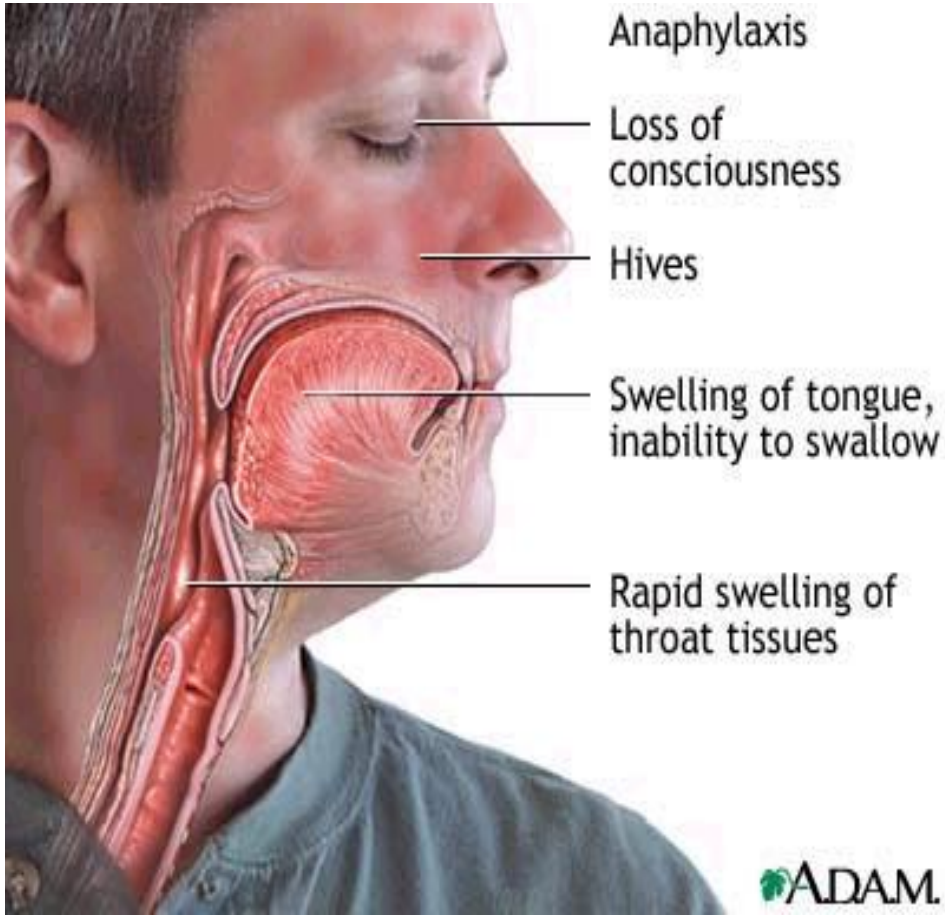




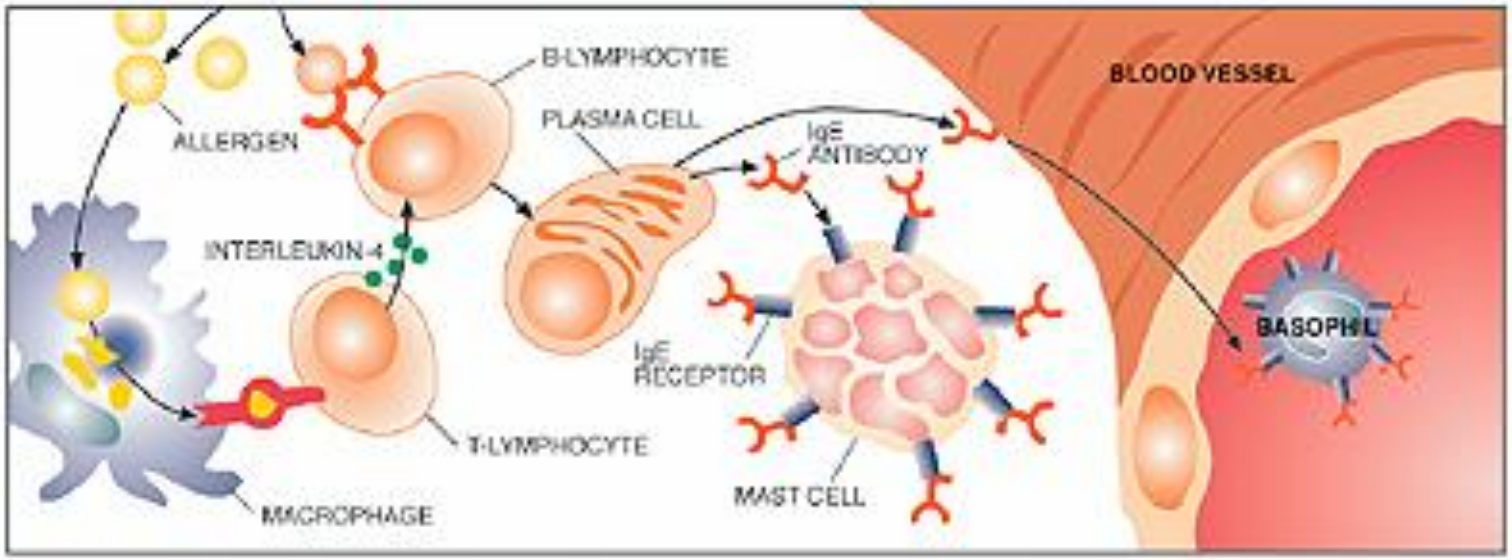
- characterised by their large cytoplasmic granules, and very little cytoplasm
- actually become mast cells on leaving the blood and entering surrounding tissues
- both basophils and mast cells have highly specific receptors for IgE produced in response to various allergens
- basophils are not phagocytic cells !!!

Basophils

- Response to specific allergens is rapid and results degranulation and release of histamine and other agents (among them SRS-A, heparin). The reaction known as immediate hypersensitivity.
- fever, some forms of asthma, urticaria (nettle rash) and most seriously anaphylactic shock.

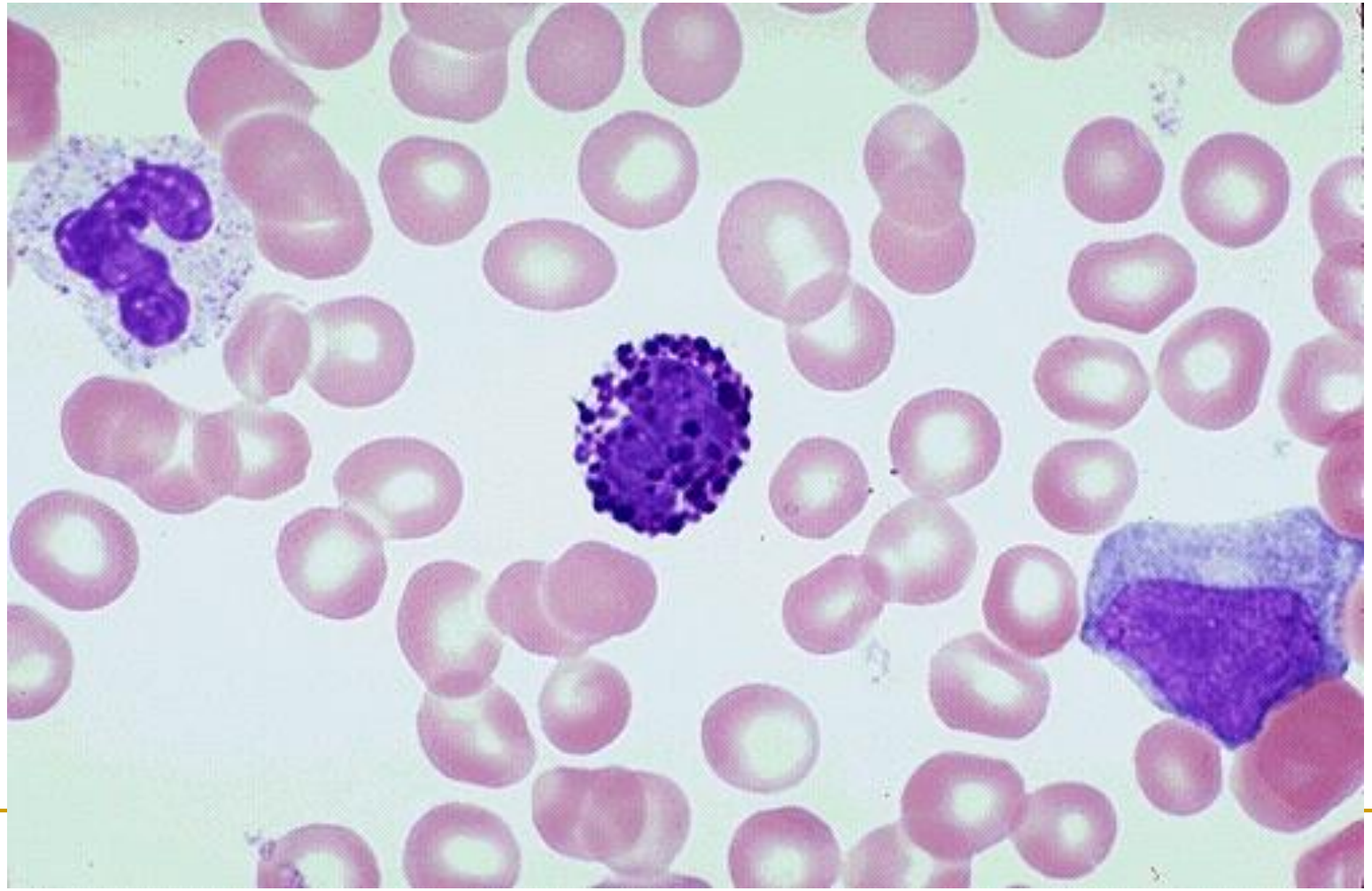


Allergen degradation



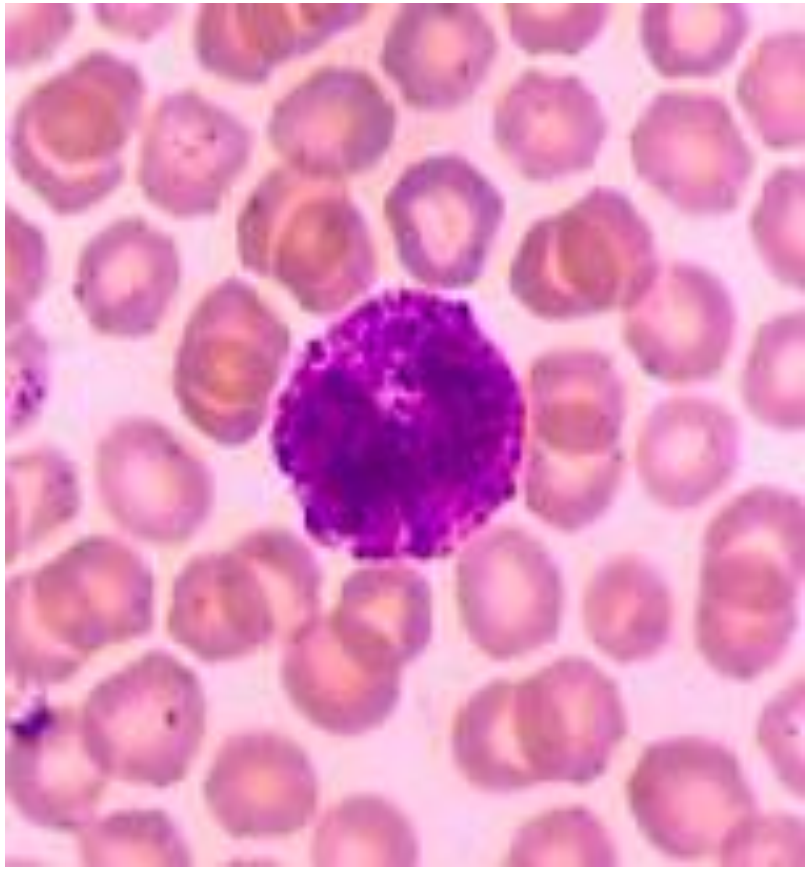
Degradation of allergen by macrophages, presentation to T-cells and B-cells, and production of IgE which causes histamine basophil release

There is a basophil in the center of the field which has a lobed nucleus (like PMN's) and dark blue granules in the cytoplasm. A band neutrophil is seen on the left, and a large, activated lymphocyte on the right.

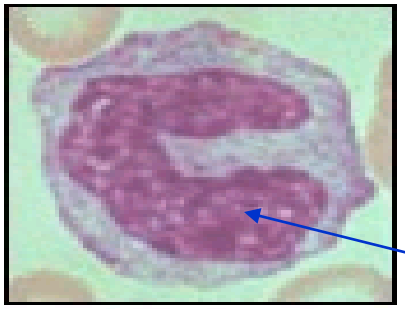


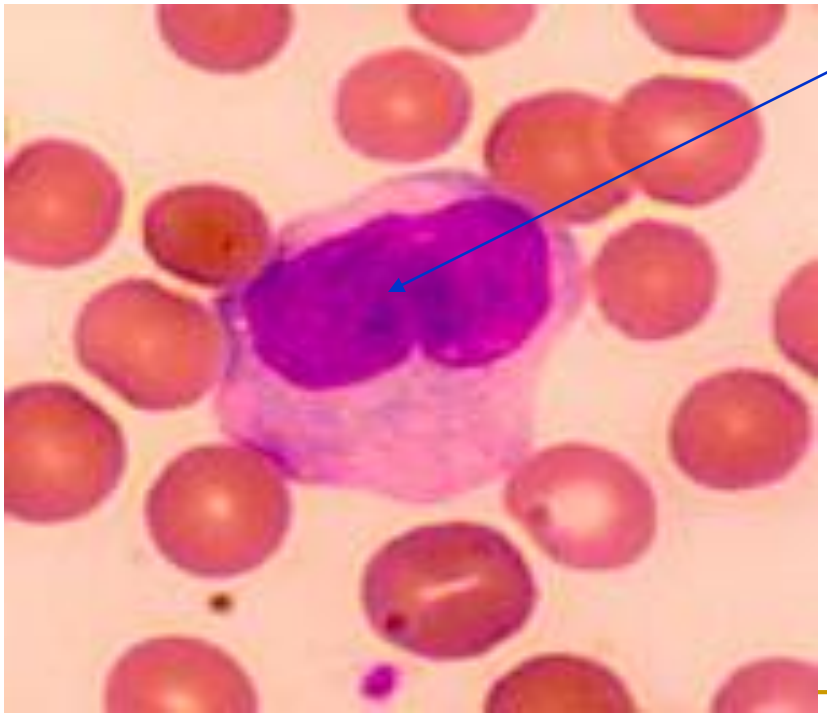
Basophil funtion - summary

- facilitate cell migration to the site of inflammation
- participate in allergic reactions
- modulate blood clotting and lipid profile (via heparin)

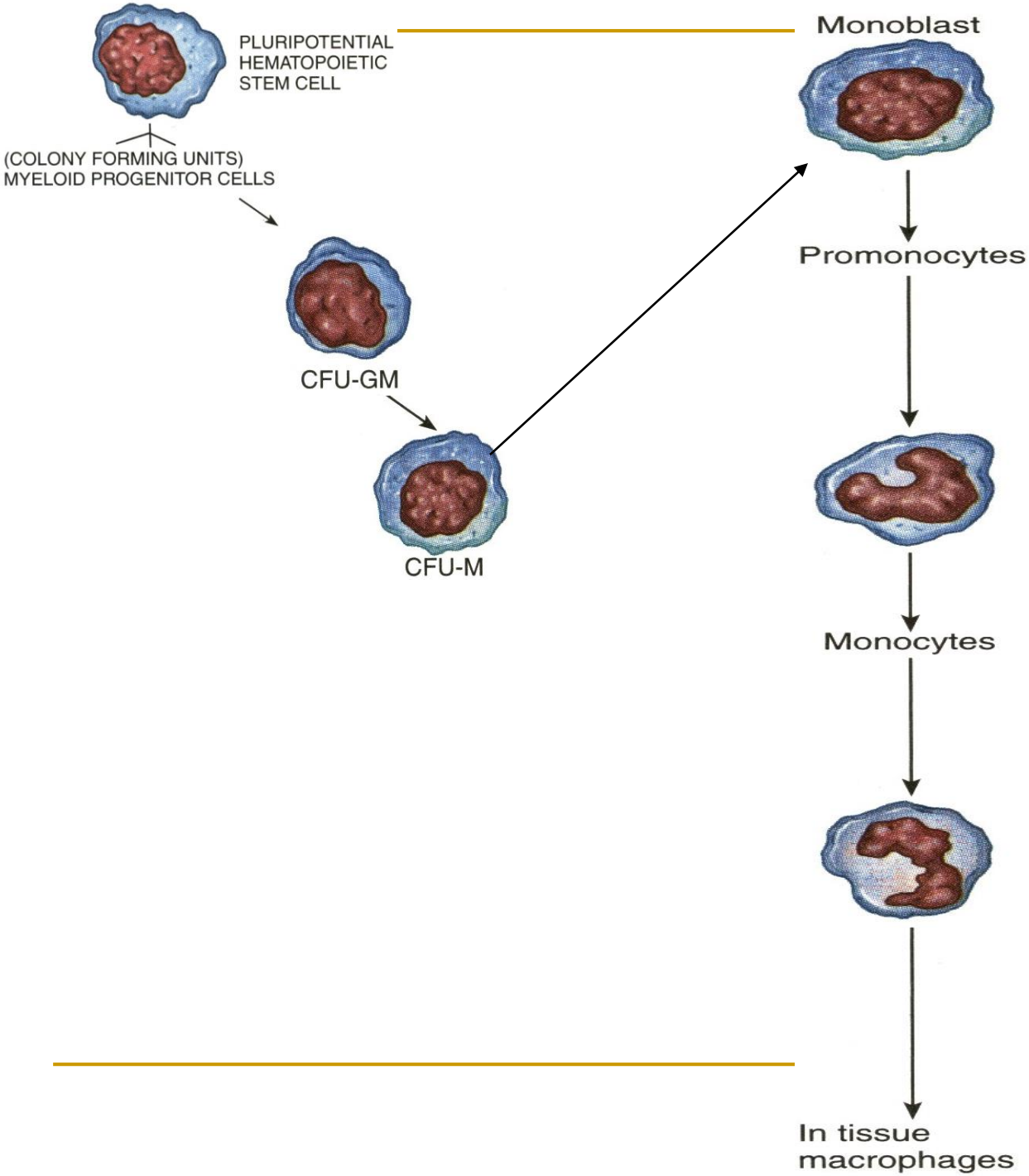


Monocytes
3-8%



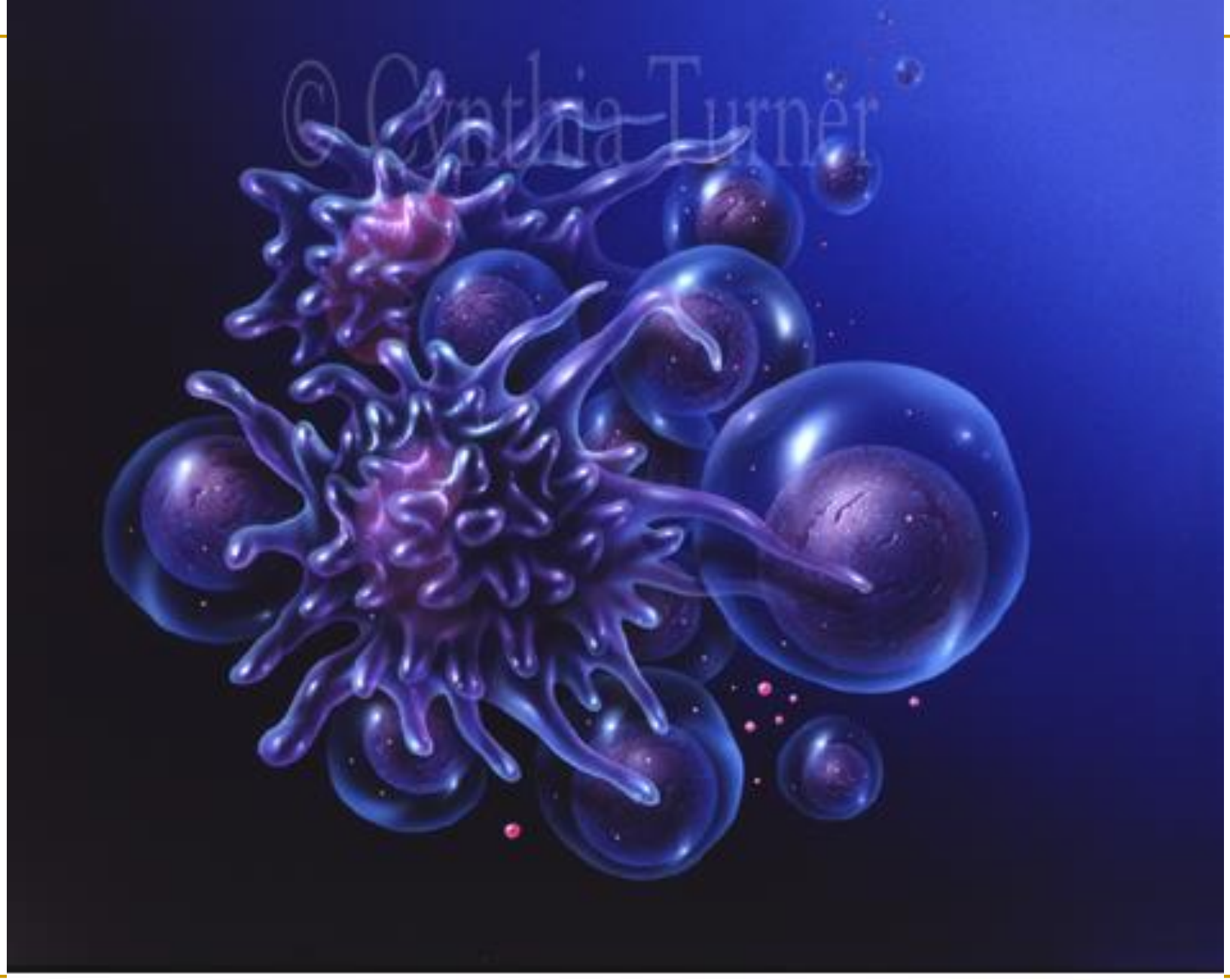


- the largest cell type seen in blood smears
- nuclei are not multilobular like granulocytes, but may be U-shaped or deeply indented (S-shaped)
- Monocytes are actively phagocytic
- Monocytes can migrate out of the bloodstream and become tissue macrophages
- they form part of a cell network known as the monocyte-macrophage system


PLURIPOTENTIAL
HEMATOPOIETIC
STEM CELL
(COLONY FORMING UNITS)
MYELOID PROGENITOR CELLS
CFU-GM
CFU-M
Monoblast
Promonocytes
Monocytes
In tissue
macrophages

Monocytes

- Tissue macrophages (sometimes called histiocytes) respond more slowly than neutrophils to chemotactic stimuli
- They ingest and destroy bacteria, dead cells, iron and foreign matter
- They also function as modulators of the immune response by processing antigen structure and facilitating the concentration of antigen at the lymphocyte's surface (antigen presentation)

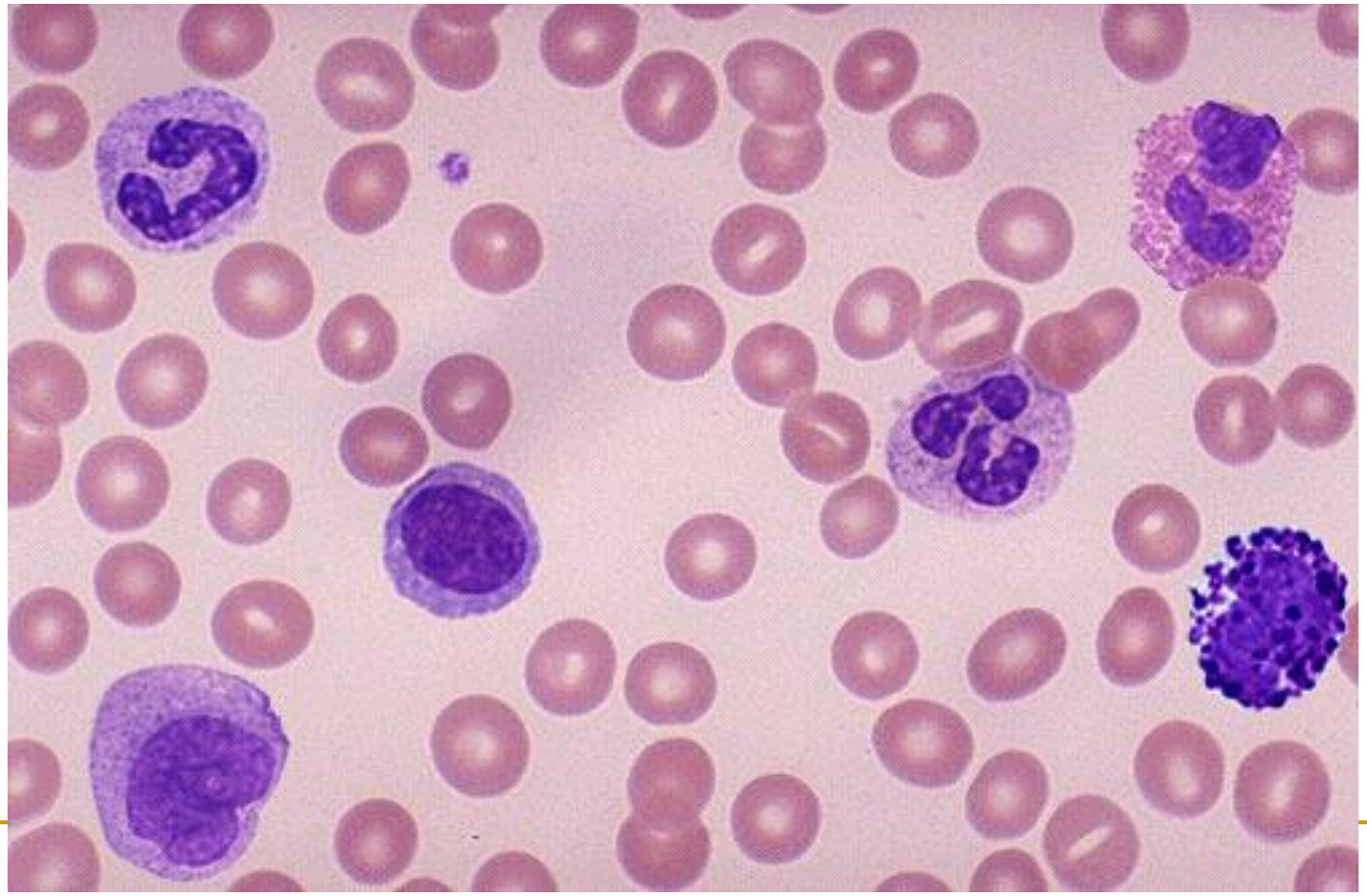


T CELLS & MACROPHAGES

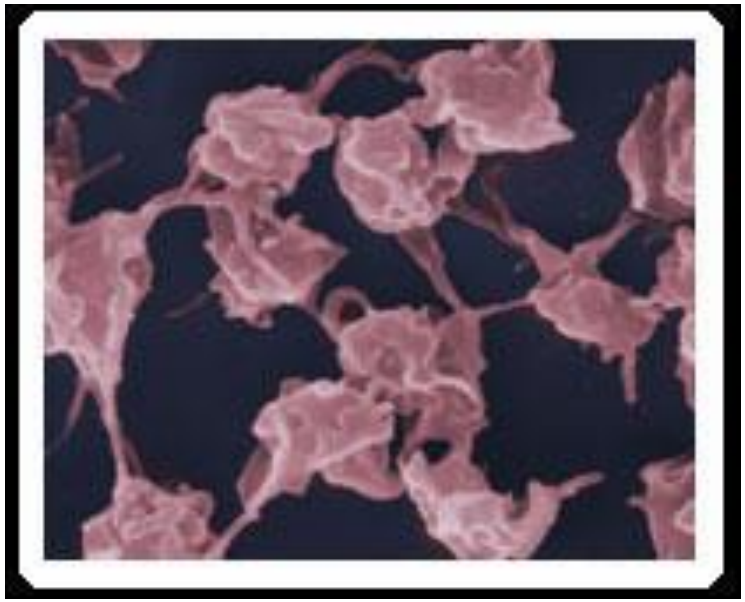
Cells which derive from monocytes include:

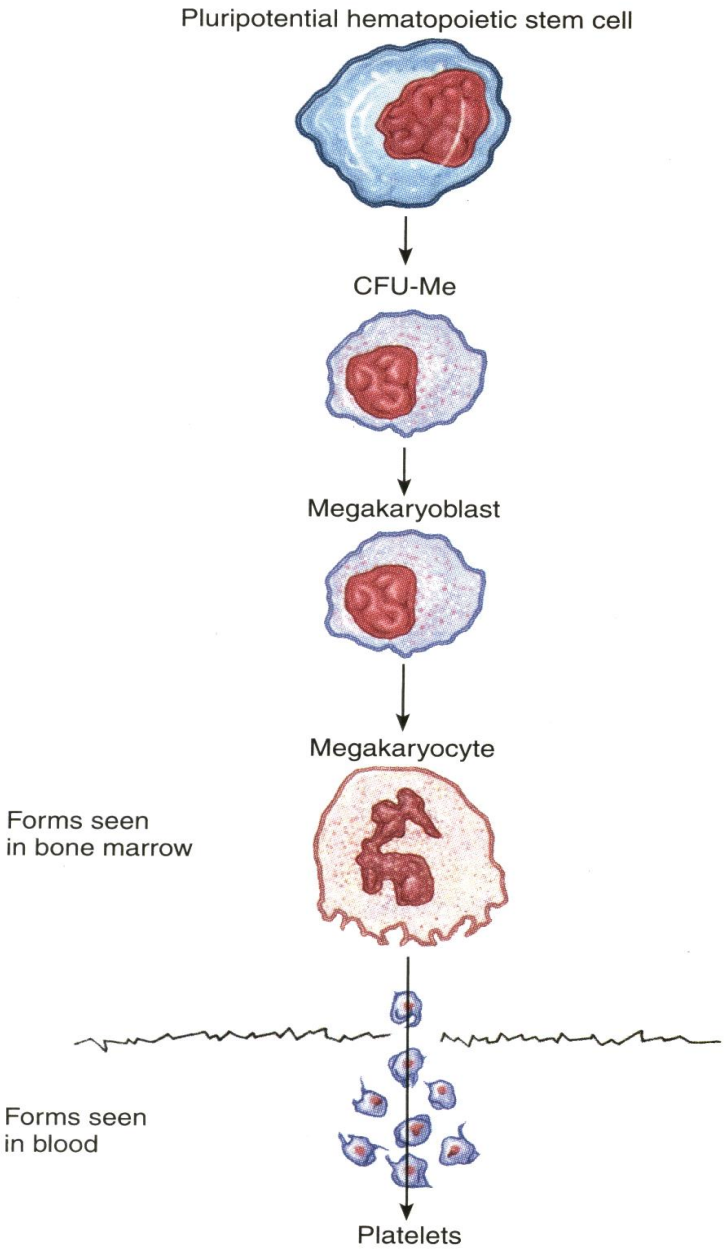
- Kupffer cells of the liver
- sinus lining cells of the spleen and lymph nodes
- pulmonary macrophages
- macrophages in the synovial, pleural and peritoneal fluid
- dendritic antigen presenting cells

Identify the segmented neutrophil, band neutrophil, lymphocyte, monocyte, eosinophil, basophil, and platelet in the image below:



Platelets

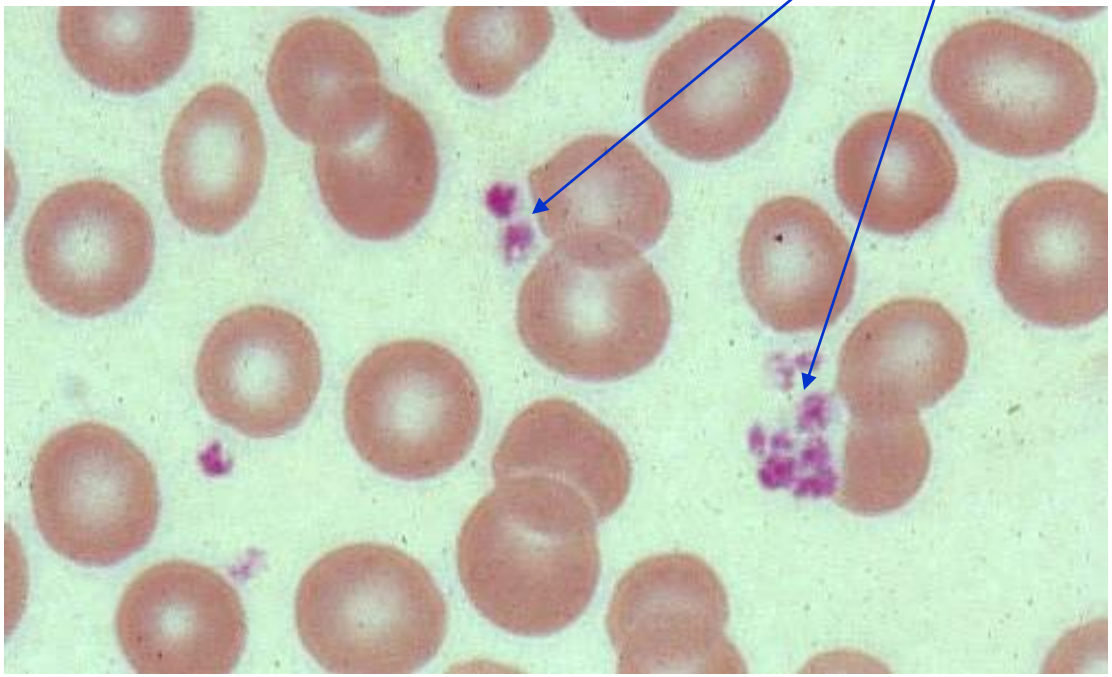


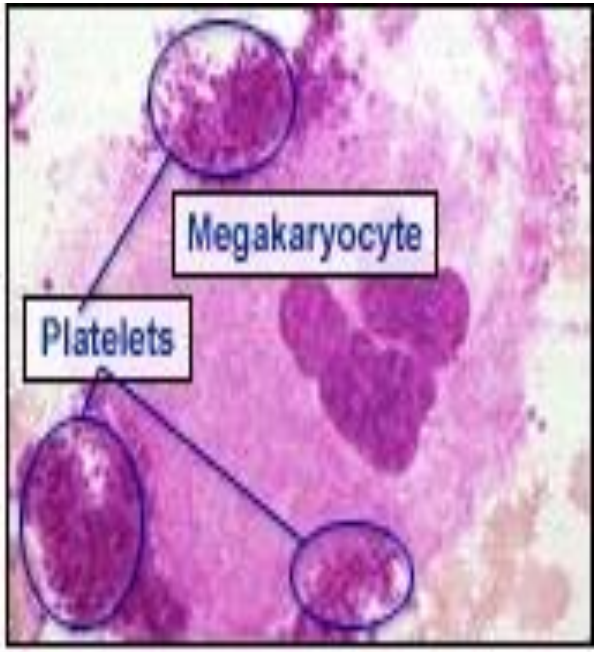


Platelets (thrombocytes)

- thrombocytes, are not true cells, but rather cytoplasmic fragments of a large cell in the bone marrow, the megakaryocyte
- blood normally contains 150,000 to 400,000 per microliter (μl) of platelets

The image shows a number of platelets stained purple associated with some RBC's.





Platelets

- At any one time, about two-thirds of the body's platelets are circulating in the blood and one-third are pooled in the spleen.
- the life span of platelets is between

  1 and 2 weeks
- if not consumed in the process of blood clotting, they are destroyed by macrophages in the liver and spleen