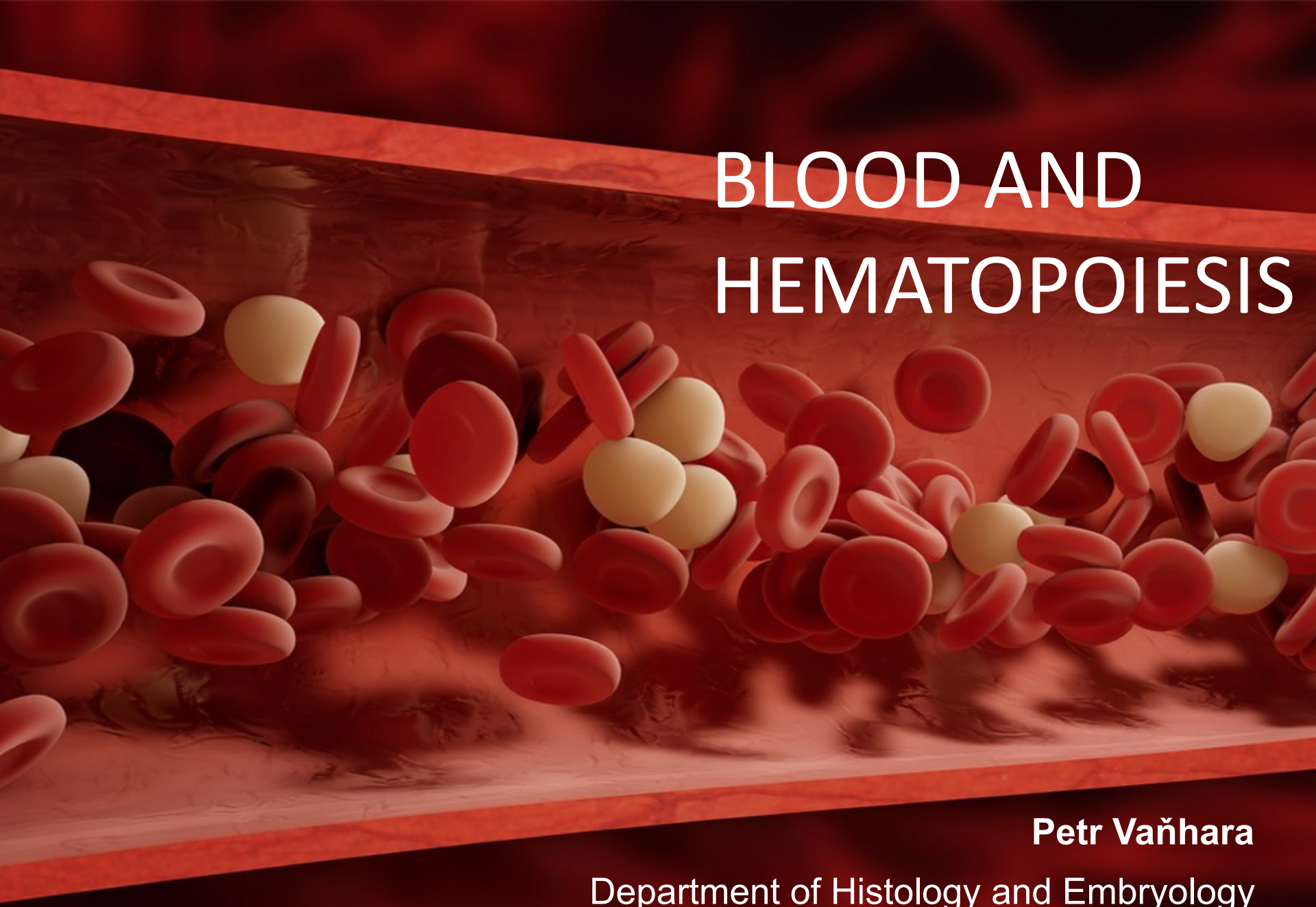
BLOOD AND HEMATOPOIESIS



Petr Vaňhara

Department of Histology and Embryology
LF MU

https://static.wixstatic.com/media/f7d5d5_556b193d57884373904c39dff4f187d6~mv2.jpg/v1/fill/w_646,h_363,al_c,q_80,usm_0.66_1.00_0.01/f7d5d5_556b193d57884373904c39dff4f187d6~mv2.webp

BLOOD

Blood is body fluid

- transport medium (O_2, CO_2, metabolites, hormones, nutrients...)
- homeostasis of inner body environment (thermoregulation, acidobasic equilibrium, oncotic pressure)
- integrity of cardiovascular system (clotting cascade)
- immune reactions

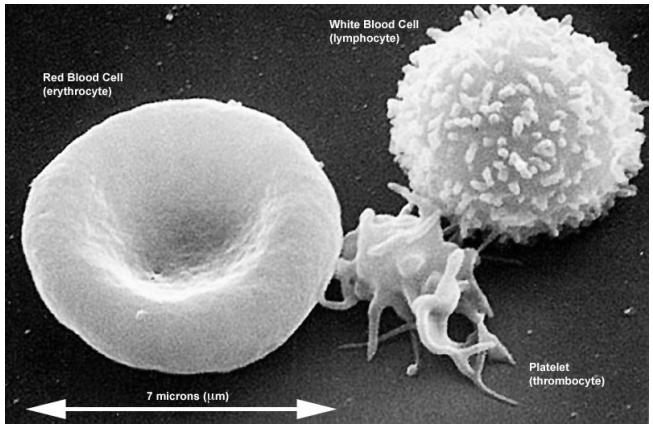
plasma

- ions, proteins, low mass organic compounds
- fluid ECM

Blood can be considered as a specialized connective tissue

formed blood elements

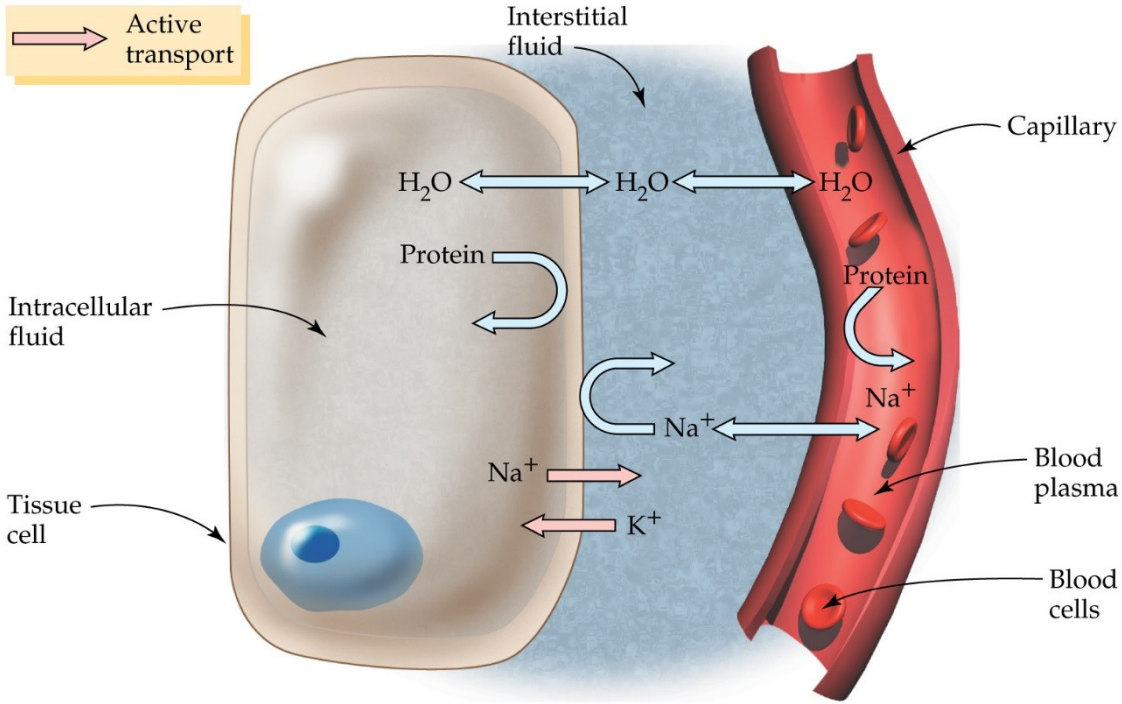
- erythrocytes
- leukocytes
- thrombocytes

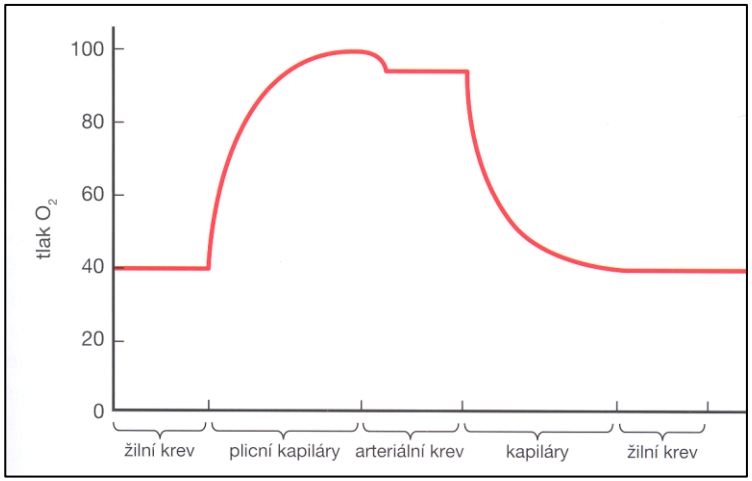


BLOOD PLAMA AND TISSUE FLUID

plasma

- 2,8-3,5 l
- pH 7.4 (± 0.05)
- ~ 92% **water**
- ~ 1% **ions** (Na^+, K^+, Ca^+, Mg^+, Cl^-, HCO_3^-), **low mass organic compounds** (glucose, aminoacids, cholesterol, lipids, waste products of metabolism), **respiration gases**
- ~ 7% **proteins** (albumins, globulins, fibrinogen)





Venous blood

Lung capillaries

Arterial blood

Capillaries

Venous blood

IONS AND LOW MASS MOLECULES OF BLOOD PLSAMA (~1%)

- ~ 1% **ions** (Na^+, K^+, Ca^+, Mg^+, Cl^-, HCO_3^-), **low mass organic compounds** (glucose, aminoacids, cholesterol, lipids, waste products of metabolism), **respiration gases**

Cations	Sodium	136–148 mmol/l	Osmotic pressure, volume, pH
	Potassium	3,7–5,0 mmol/l	Membrane potential of cells (nerve, muscle)
	Calcium	2,15–2,61 mmol/l	Permeability of membranes, blood clotting, neuromuscular junctions
	Magnesium	0,66–0,94 mmol/l	Cofactor of enzymes, neuronal conduction
	Iron ♂ Iron ♀	12–27 µmol/l 10–24 µmol/l	Cofactor of enzymes, in hem of hemoglobin
	Copper	12–22 µmol/l	Cofactor of enzymes
Anions	Chlorides	95–110 mmol/l	Osmotic pressure, volume, pH
	Bicarbonates $[HCO_3]^-$	22–26 mmol/l	Transport of CO_2, buffer - pH
	P_i	0,6–1,4 mmol/l	Buffer - pH
	Iodide	276–630 µmol/l	Hormones of thyroid gland

IONS AND LOW MASS MOLECULES OF BLOOD PLSAMA (~1%)

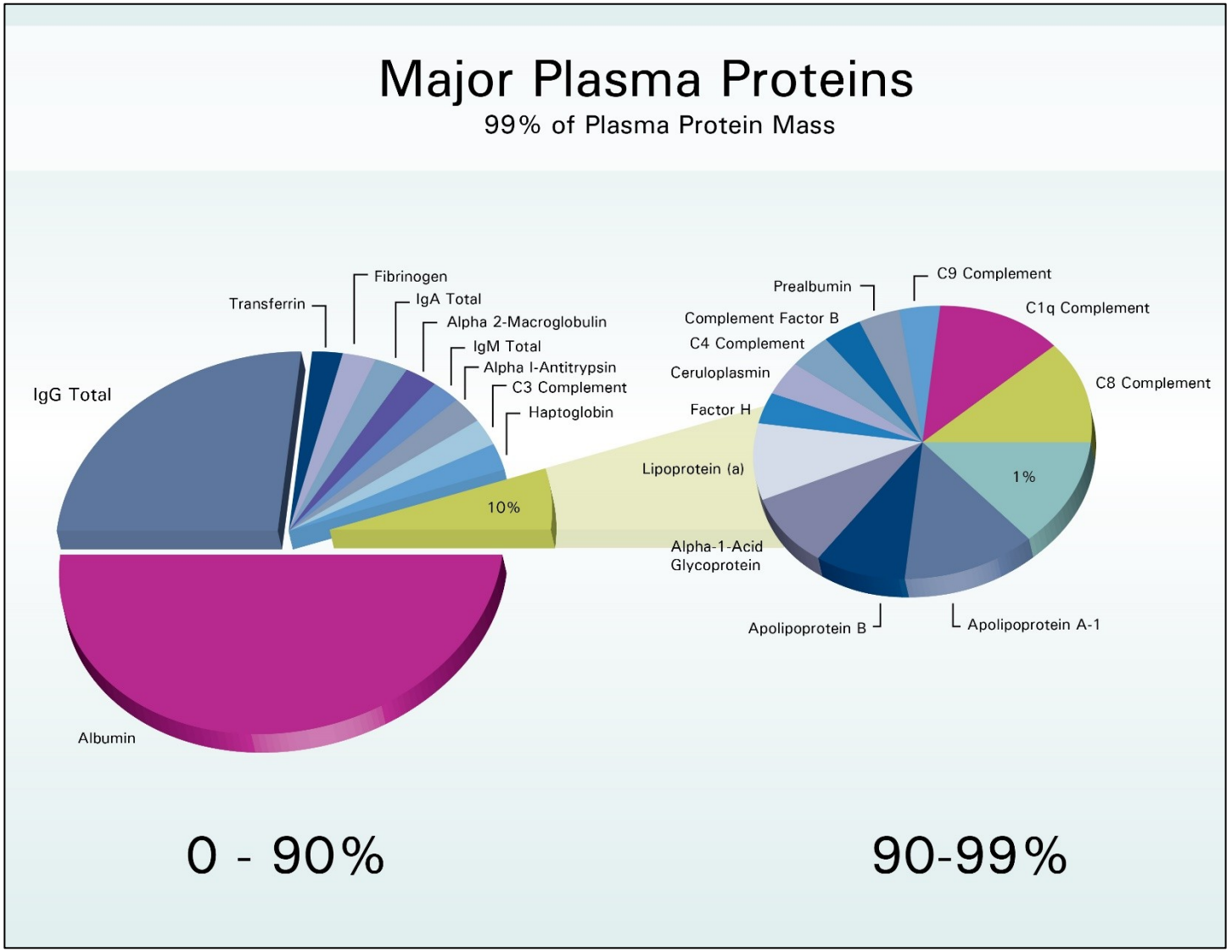
- ~ 1% **ions** (Na^+, K^+, Ca^+, Mg^+, Cl^-, HCO_3^-), **low mass organic compounds** (glucose, aminoacids, cholesterol, lipids, waste products of metabolism), **respiration gases**

Glucose	3,3–6,1 mmol/l
Aminoacids	2,3–3,9 mmol/l
Urea	3,0–7,6 mmol/l
Lipids	4–9 g/l
Triacylglycerols	0,5–1,8 mmol/l
Phospholipids	1,8–2,5 g/l
Creatinine	55–110 µmol/l
Cholesterol (total)	3,5–5,2 mmol/l
Bilirubin	3,3–18,0 µmol/l
Lactate	0,55–2,22 mmol/l

COMPOSITION OF BLOOD PLASMA IS CONSTANT
regulated in narrow range→ essential for clinical medicine

PROTEINS OF BLOOD PLASMA (7%)

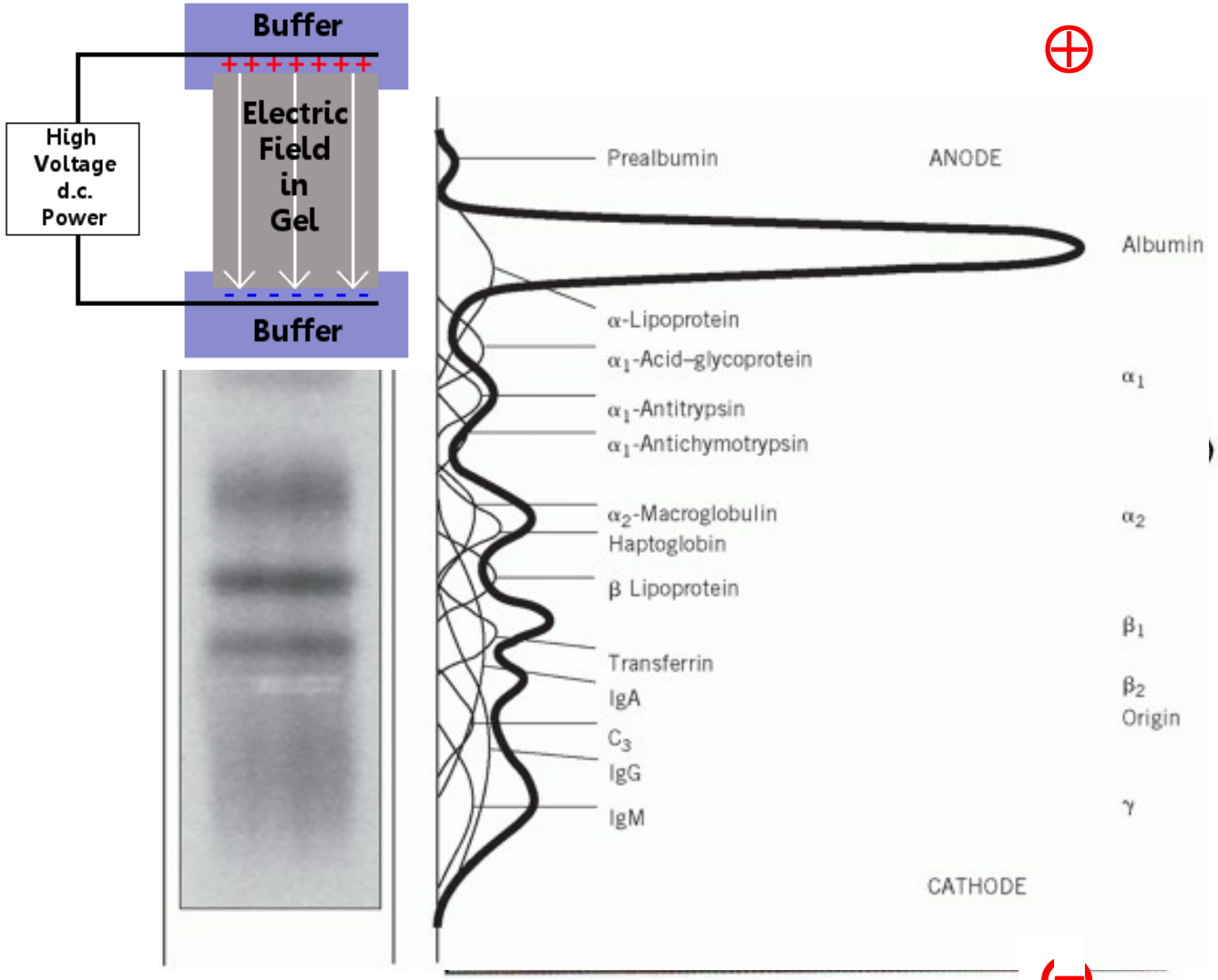
- oncotic blood pressure
- transport
- coagulation
- immune response
- regulatory proteins



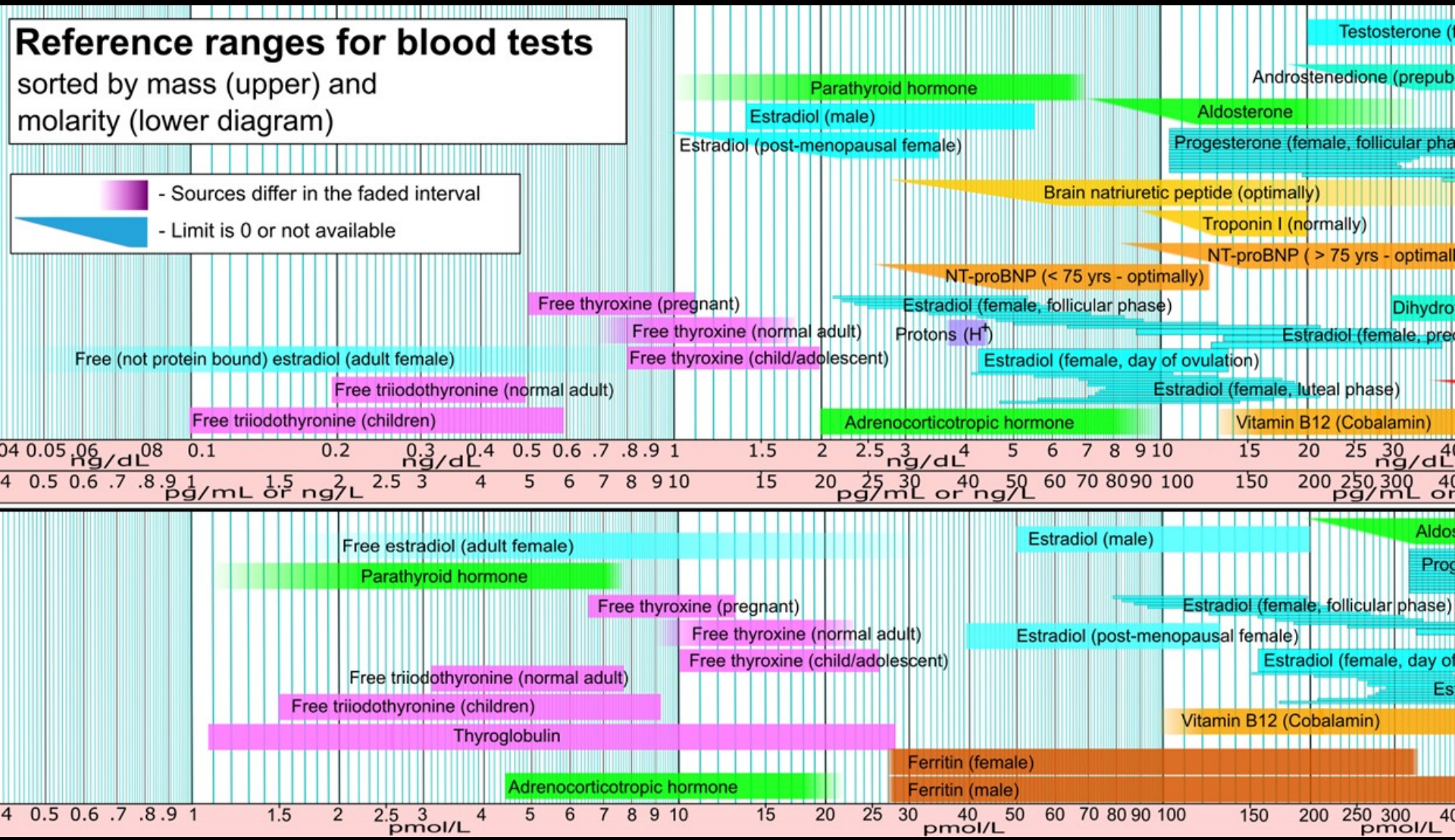
https://pharmaceuticalintelligence.files.wordpress.com/2014/06/major_plasma_proteins2.jpg

PROTEINS OF BLOOD PLASMA (7%)

- **prealbumin**
  - transport
- **albumin**
  - 68kDa
  - transport
  - osmotic pressure
- **α1 region**
  - α1 lipoprotein (HDL)
  - α1 acid glycoprotein
  - α1 antitrypsin
  - (α1 fetoprotein)
- **α2 region**
  - α2 macroglobulin
  - haptoglobin
- **β1 region**
  - transferrin
  - hemopexin
  - β lipoprotein (LDL)
  - C4 (complement)
- **β2 region**
  - CRP
  - fibrinogen
  - β2 microglobuin
  - C3 (complement)
- **γ region**
  - IgA, IgG, IgM



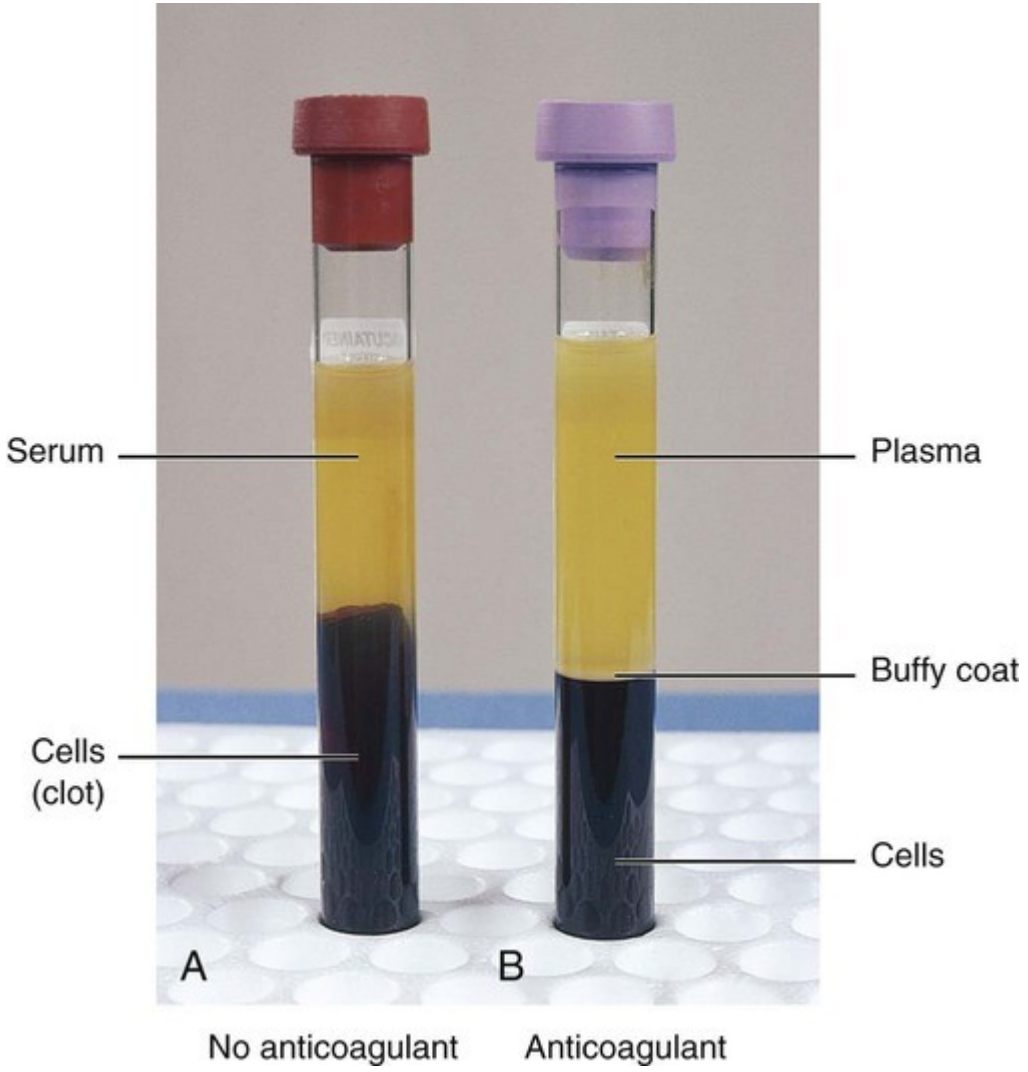
. Electrophoretic separation of se m proteins
A. Electrophoretogram of normal serum on cellulose acetate strip
B. Densitometric scanning from cellulose acetate strip converts bands to characteristic peaks of albumin, α_1-globulin, α_2-globulin, β-globulin and γ-globulin



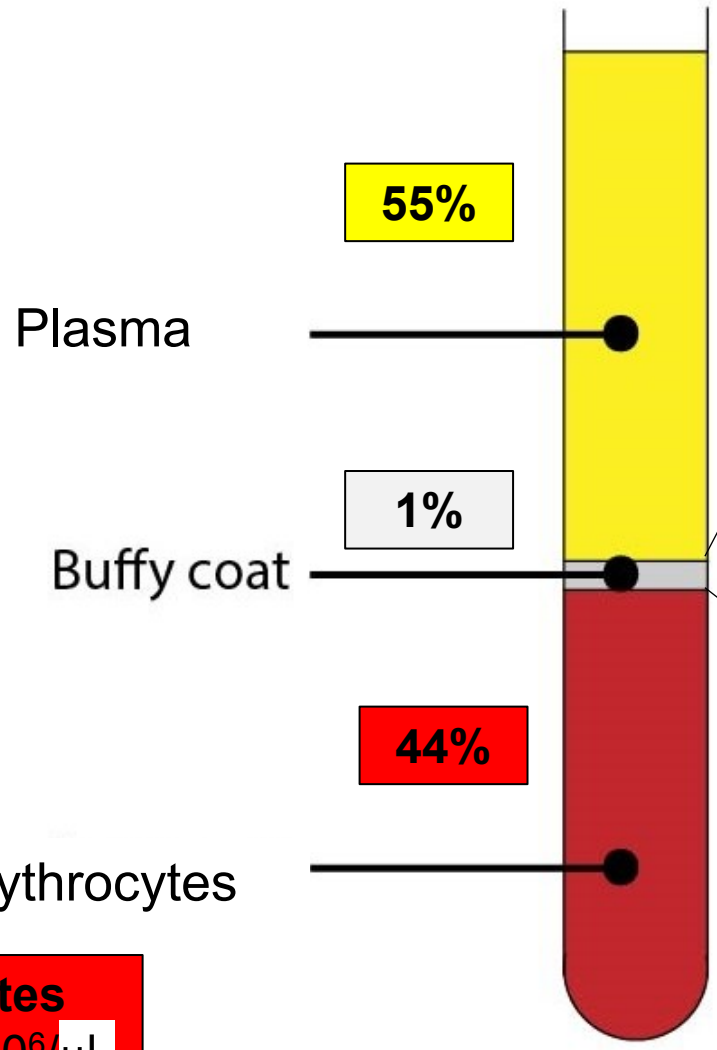
https://en.wikipedia.org/wiki/Reference_ranges_for_blood_tests

BLOOD PLASMA AND SERUM

- **serum ≠ plasma**



FORMED BLOOD ELEMENTS



Leukocytes
4.5-11 × $10^3/\mu l$

neutrophils	71%
eosinophils	3%
bazophils	1%
monocytes	5%
lymfocytes	20%

Thrombocytes
150-450 × $10^3/\mu l$

Erythrocytes
4.2-6.2 × $10^6/\mu l$

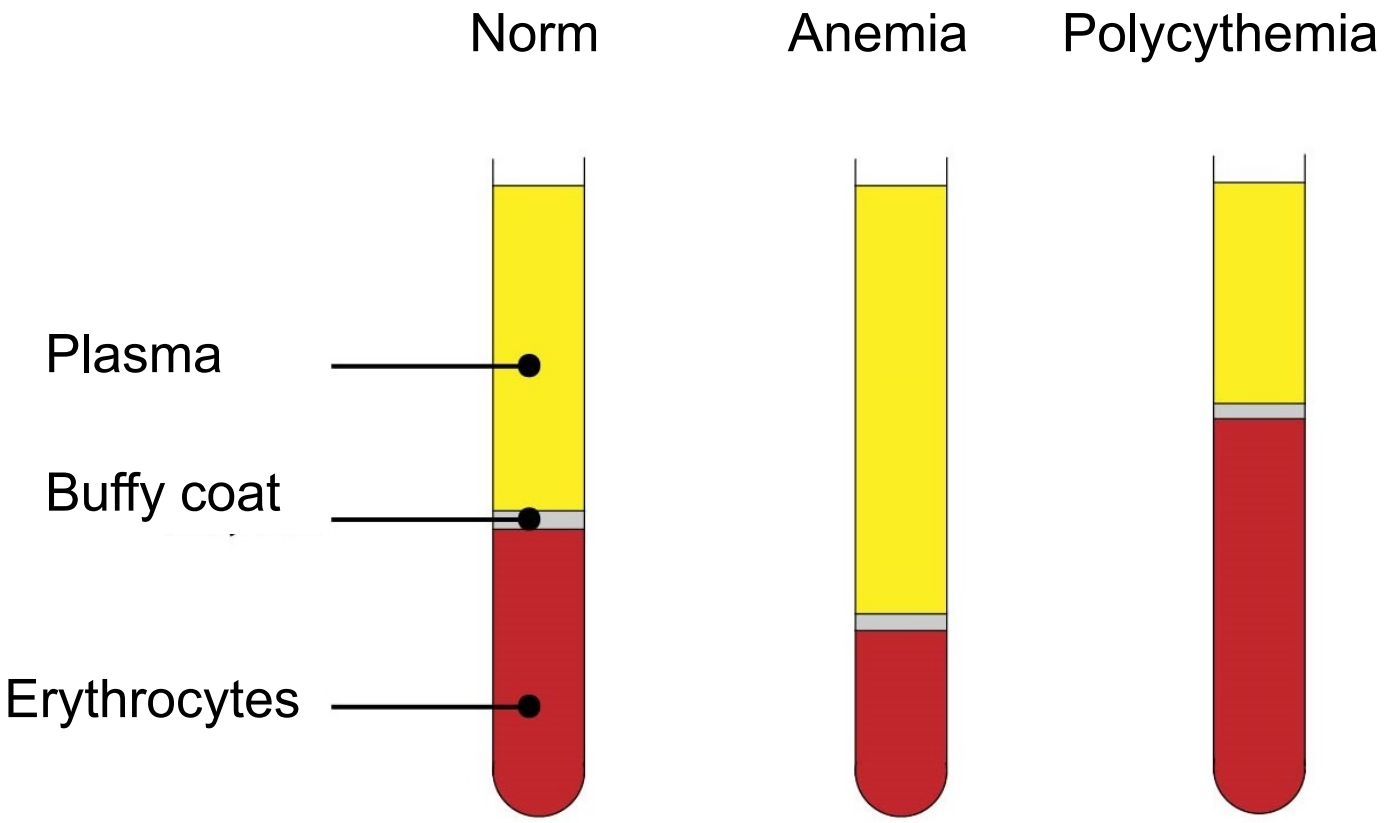
Ratio of erythrocyte mass volume to volume of full blood

Erythrocytes
$4.2\text{-}6.2 \times 10^6/\mu l$

HEMATOCRIT

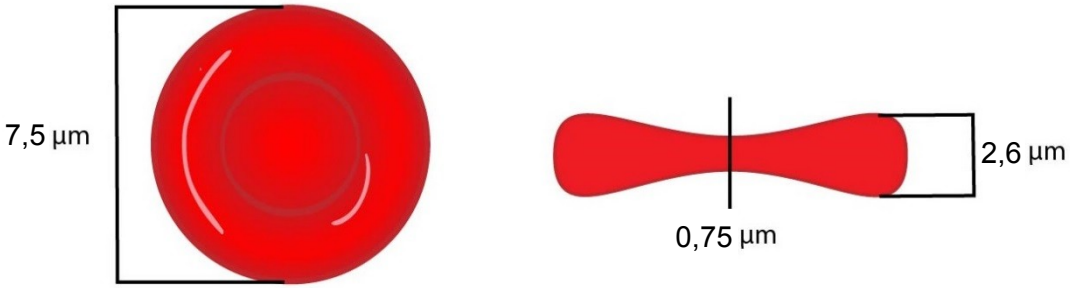
47±5%

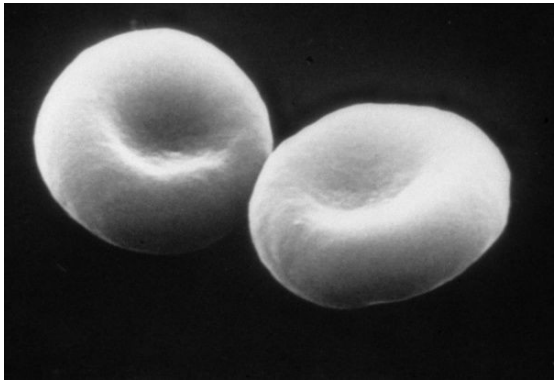
42±4%

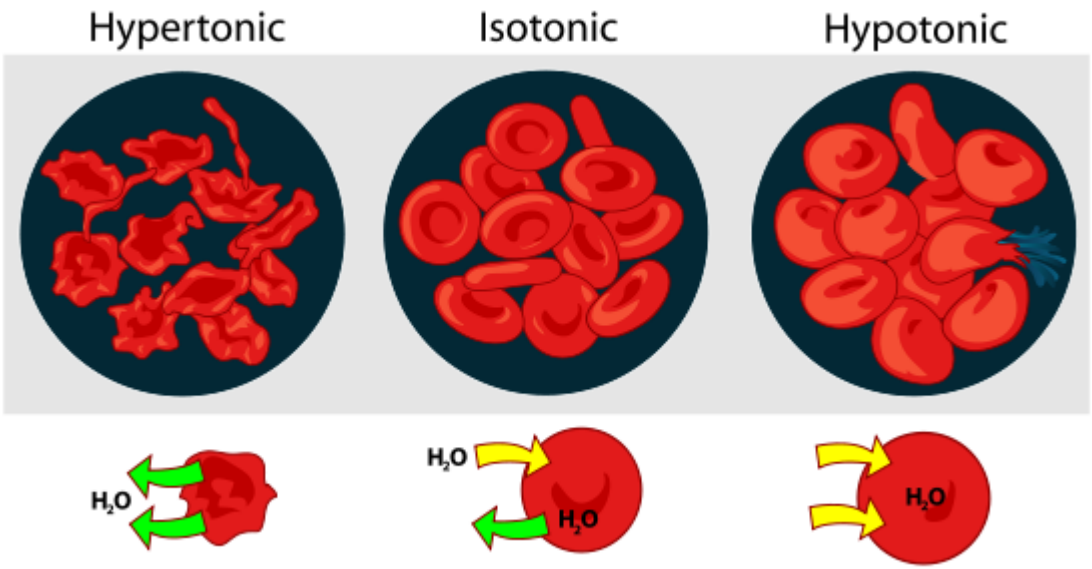


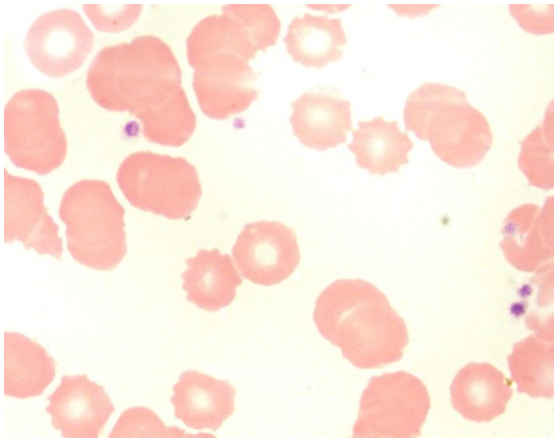
ERYTHROCYTES

Size depends on osmotic pressure of environment





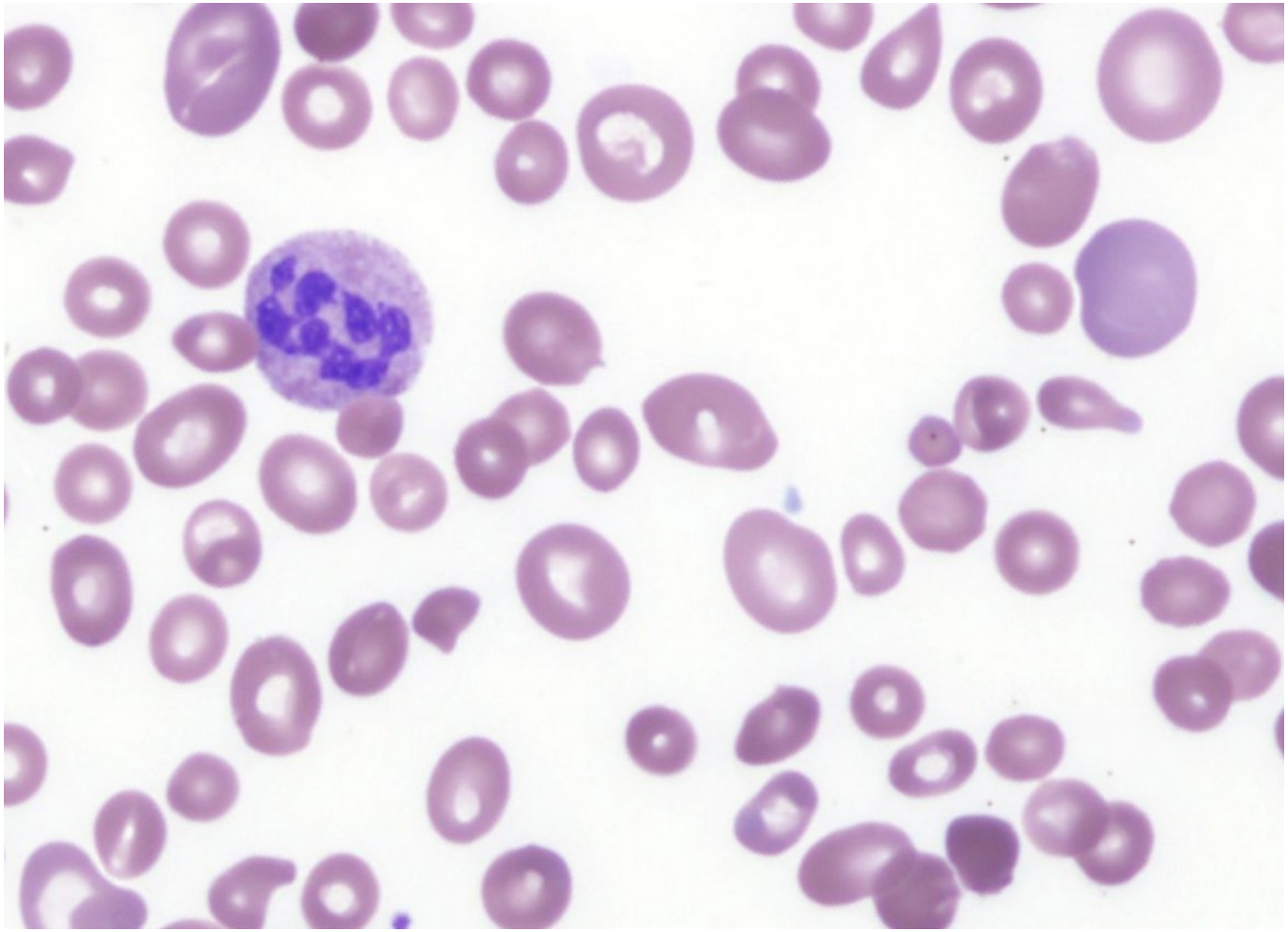




ERYTHROCYTES

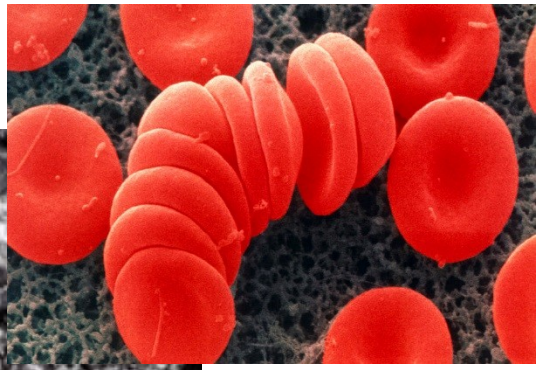
Deviations from normal size

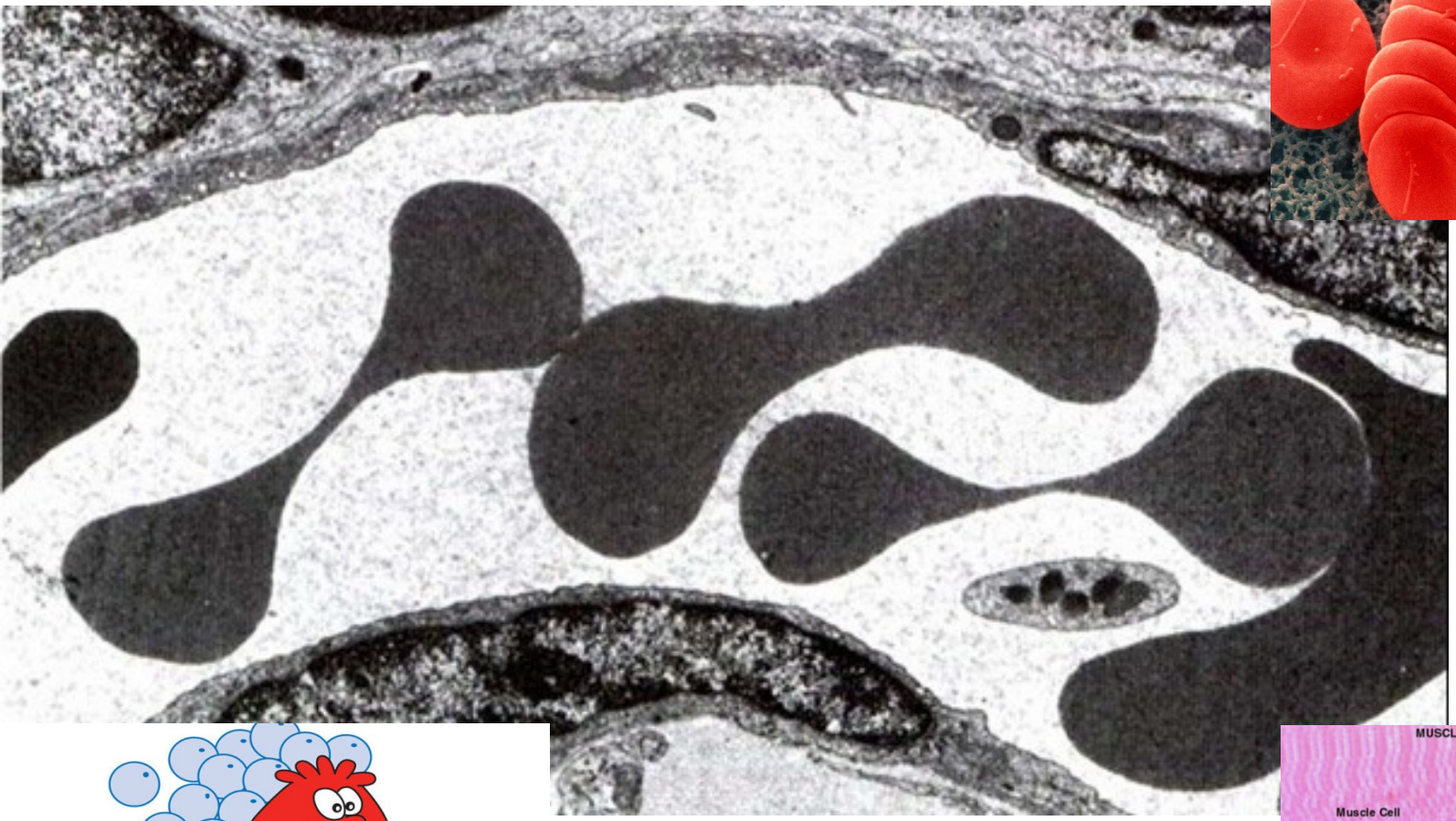
- **anisocytosis**
- macrocytes (>9 μm)
- microcytes (<6 μm)

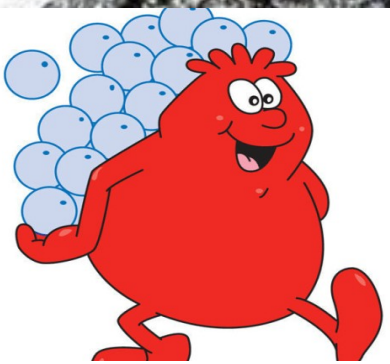


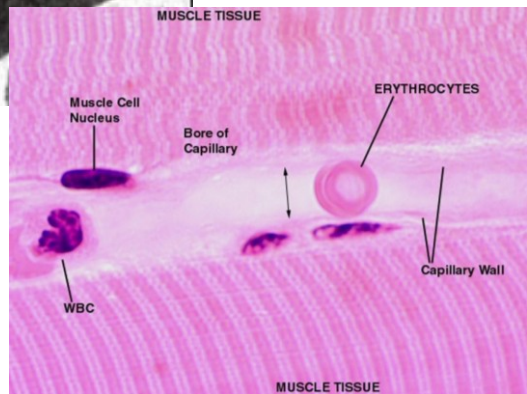
ERYTHROCYTES

Erythrocyte is amazingly flexible cell









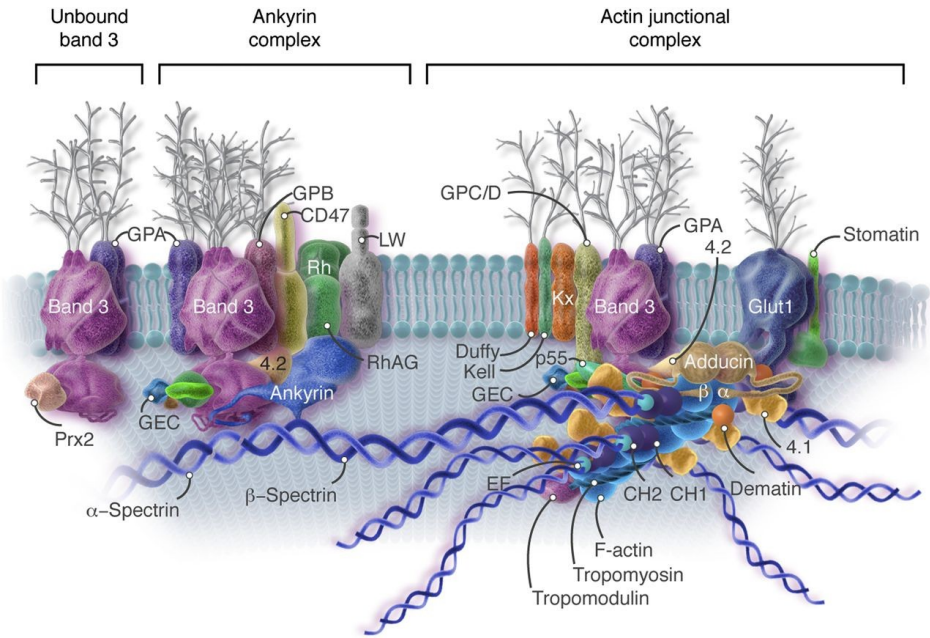
ERYTHROCYTES

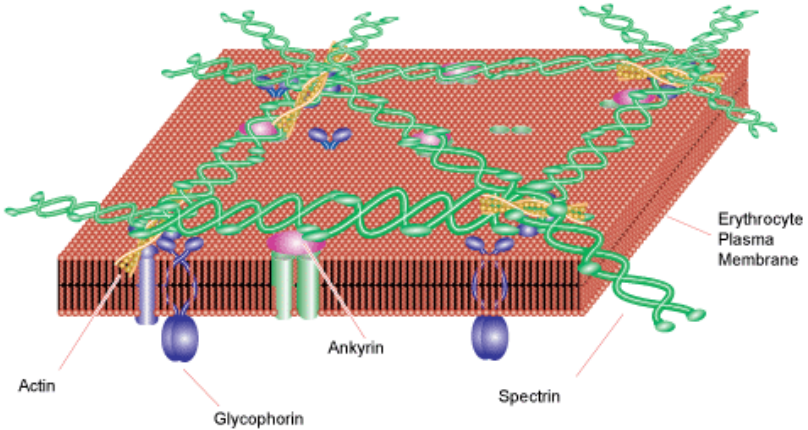
Shape of erythrocytes

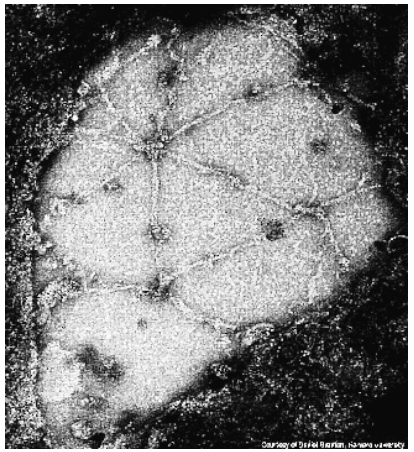
- **integral proteins**
- band 3, glycoprotein A (ion transporters)
- **spectrin**
- **ankyrin**

- **aktin a s aktinem asociované proteiny**
- tropomodulin, tropomyosin

- **hemoglobin**





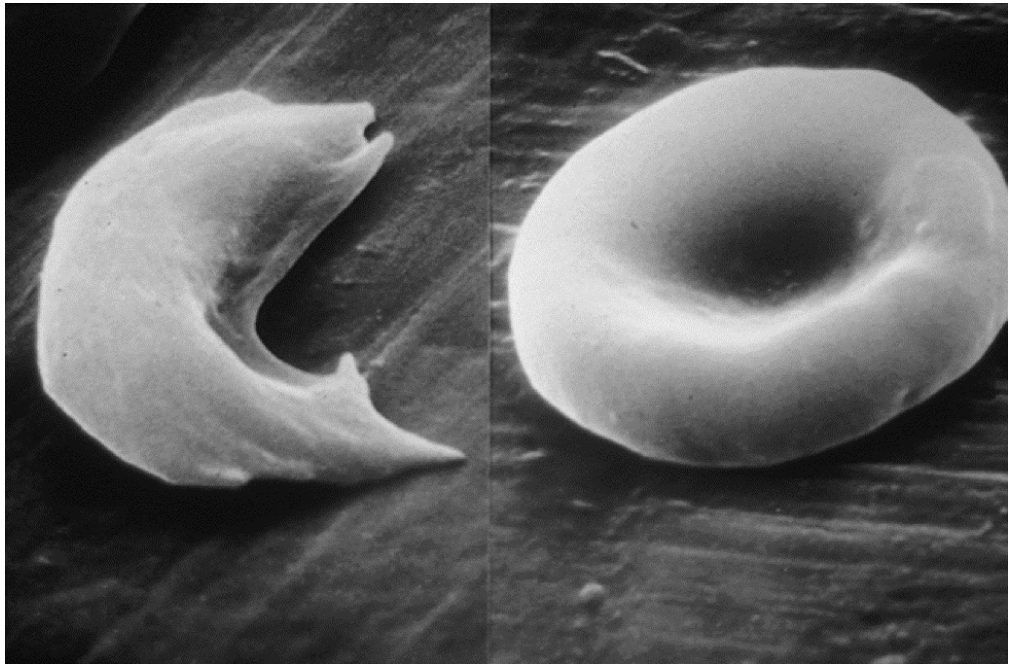


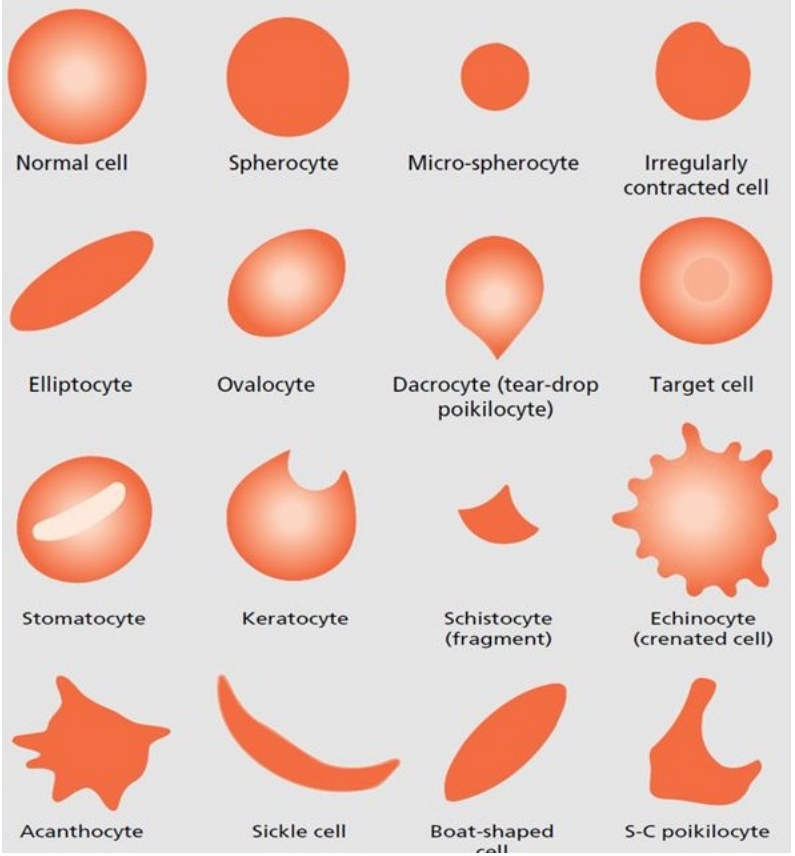
ERYTHROCYTES

Deviations from biconcave shape

- **poikilocytosis**

- **acantocytes** (irregular spikes)
- **codocytes** („tyre “)
- **echinocytes** (spiked membrane)
- **eliptocytes** (elliptic)
- **spherocytes** (spheroidal)
- **stomatocytes** (some parts missing or other irregularities)
- **drepanocytes** (sickle)
- **dacrocytes** (tear drop)

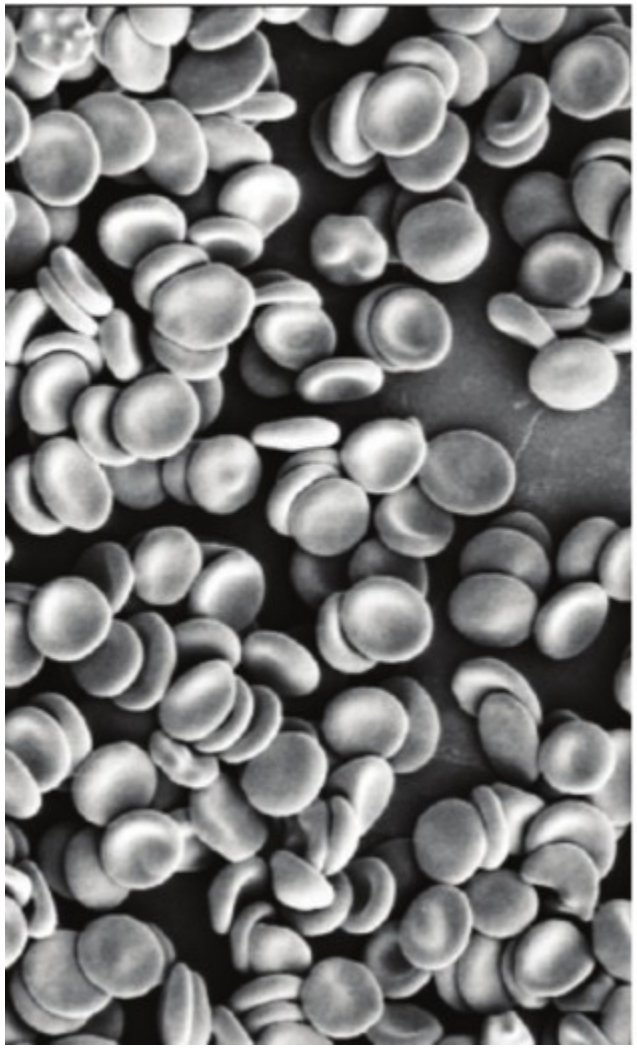




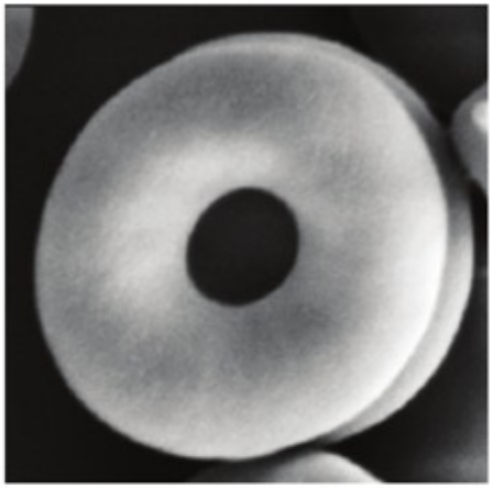
ERYTHROCYTES

Deviations from biconcave shape

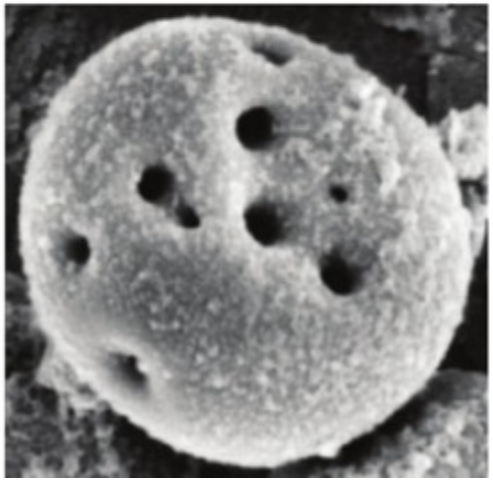
Normal



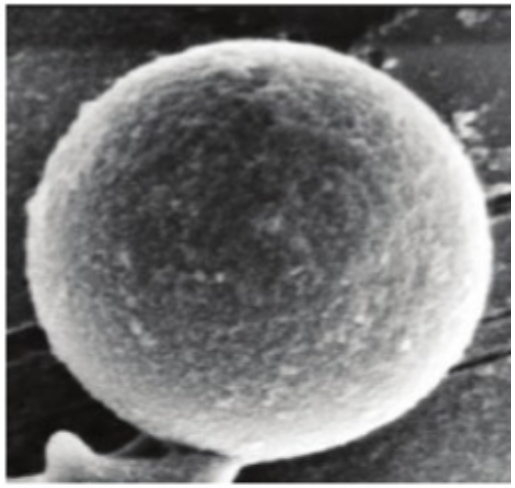
Codocyte



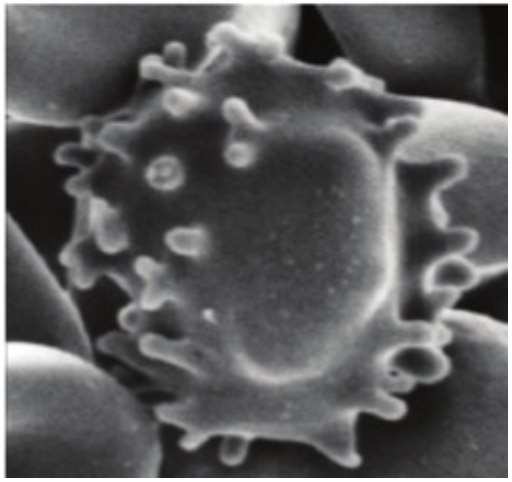
(b)



Spherocyte



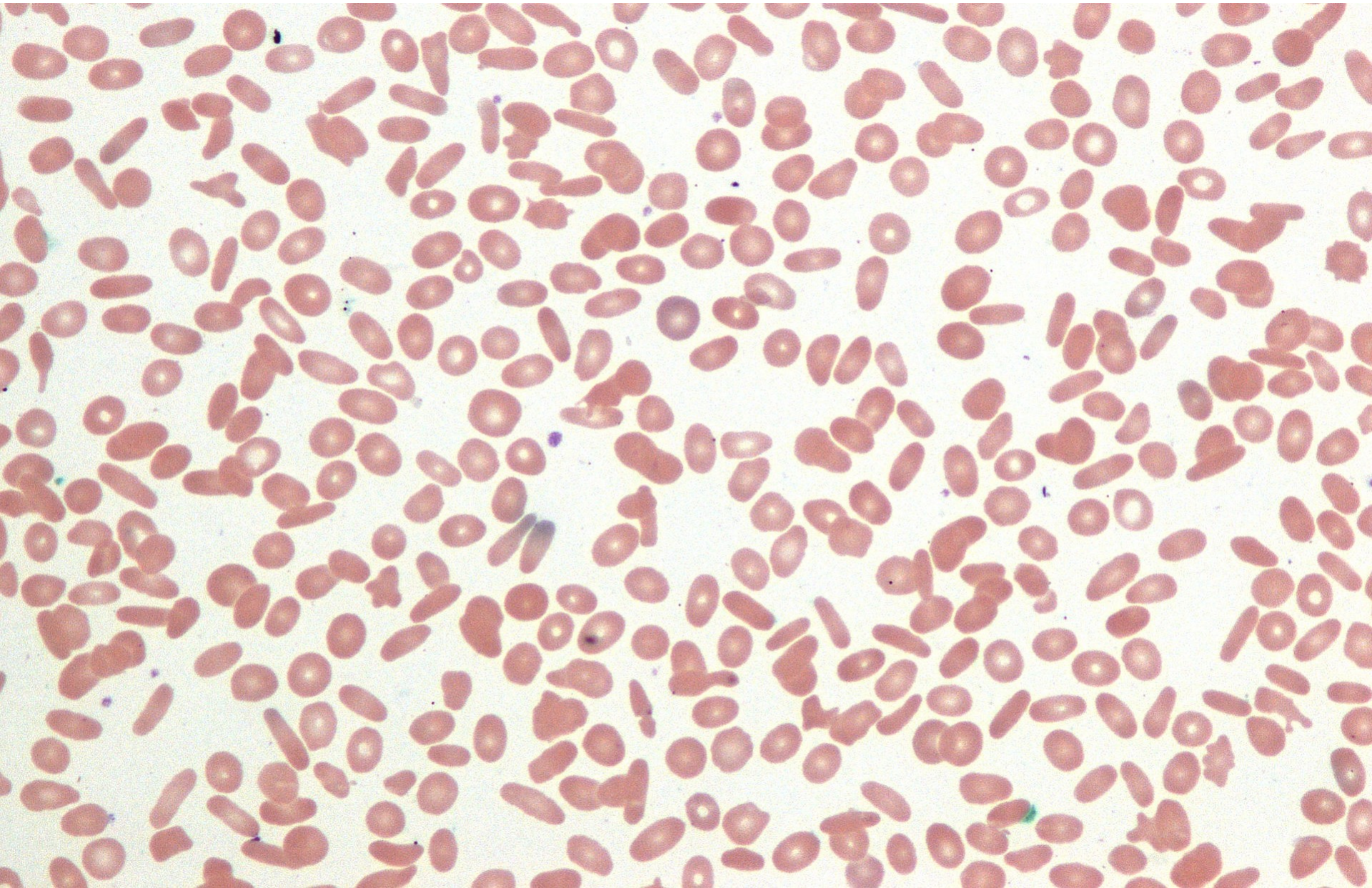
(d)



Echinocyte

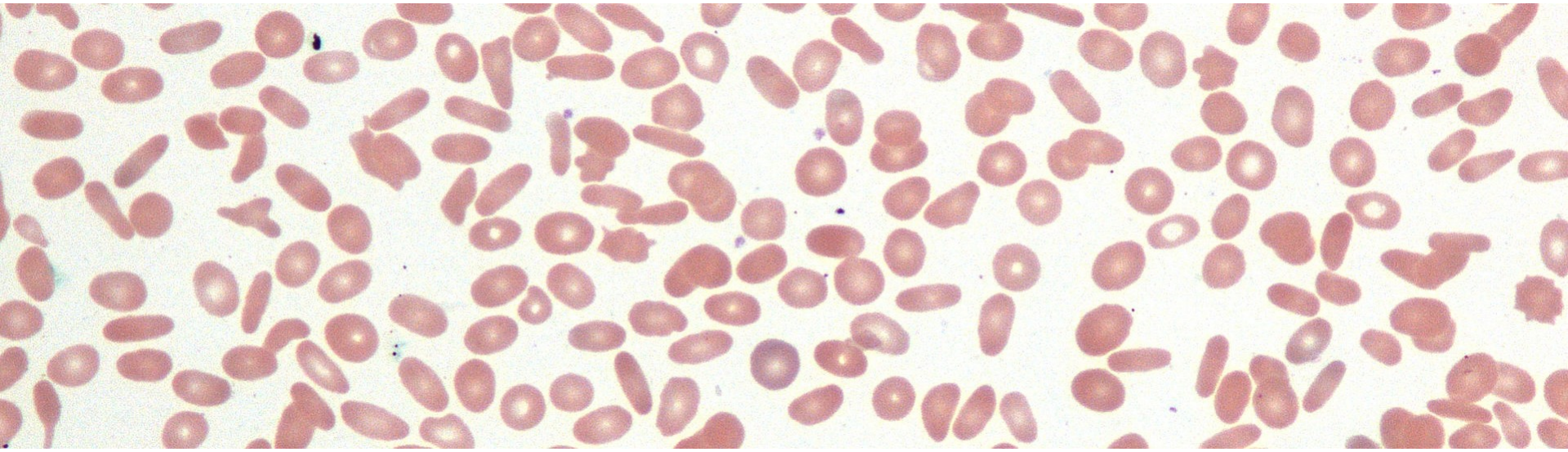
ERYTHROCYTES

Hereditary eliptocytosis

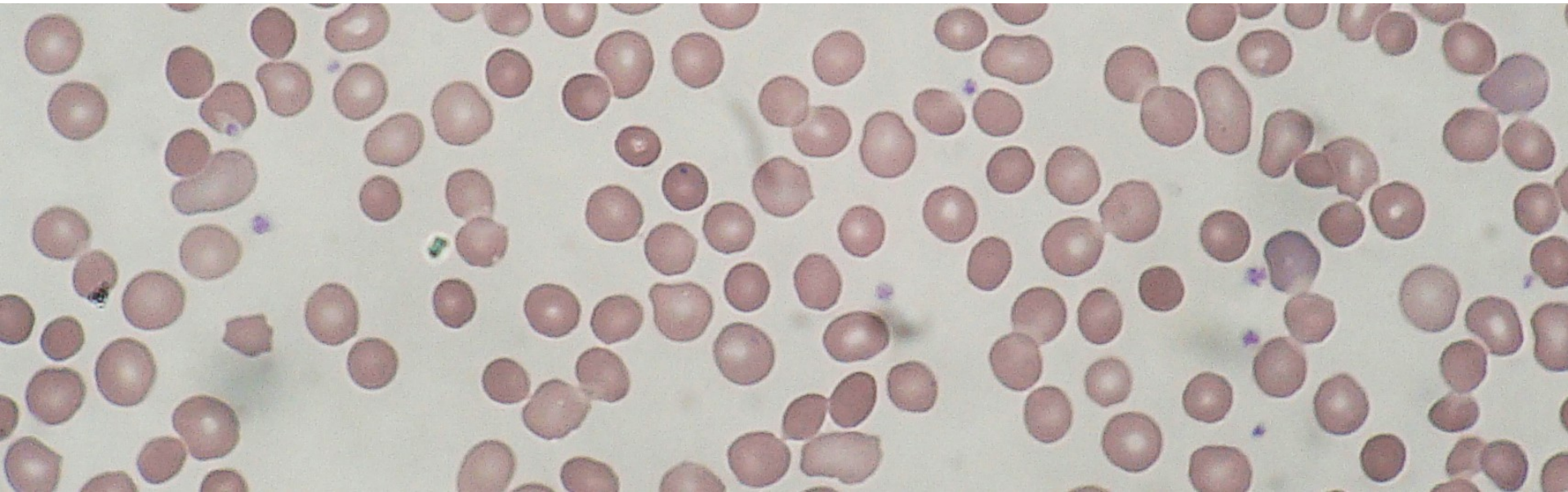


ERYTHROCYTES

Hereditary eliptocytosis

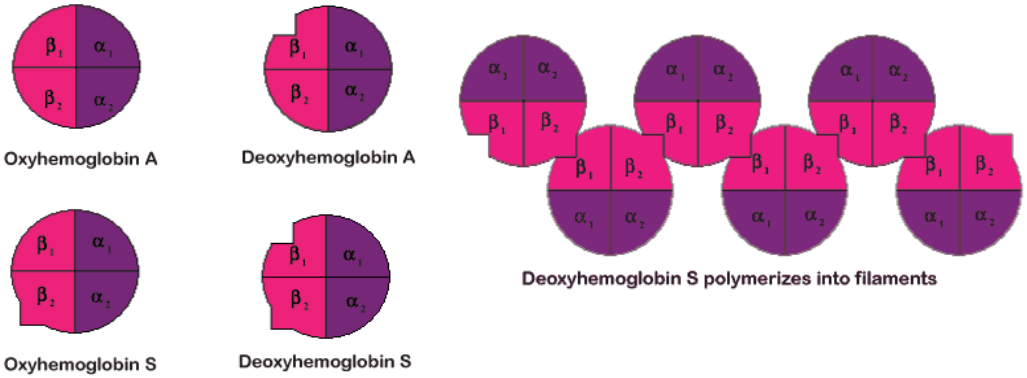


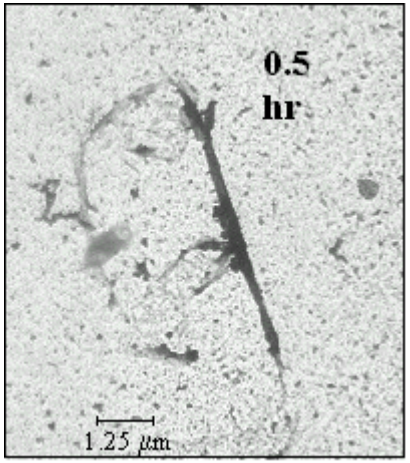
Hereditary spherocytosis

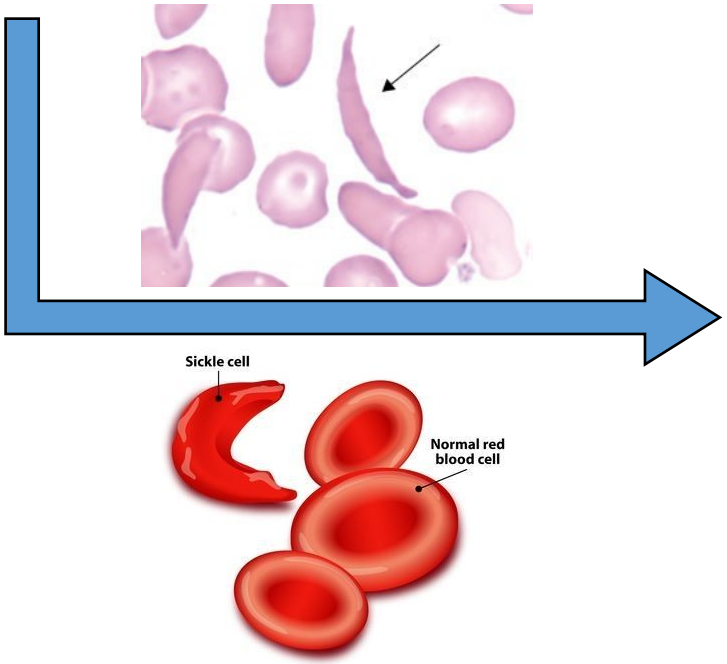


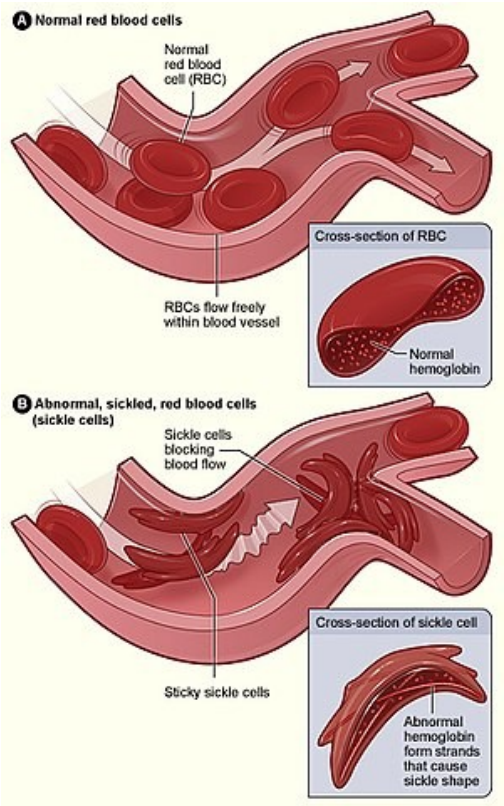
Sickle cell anemia

- Abnormal hemoglobin (hemoglobin S)





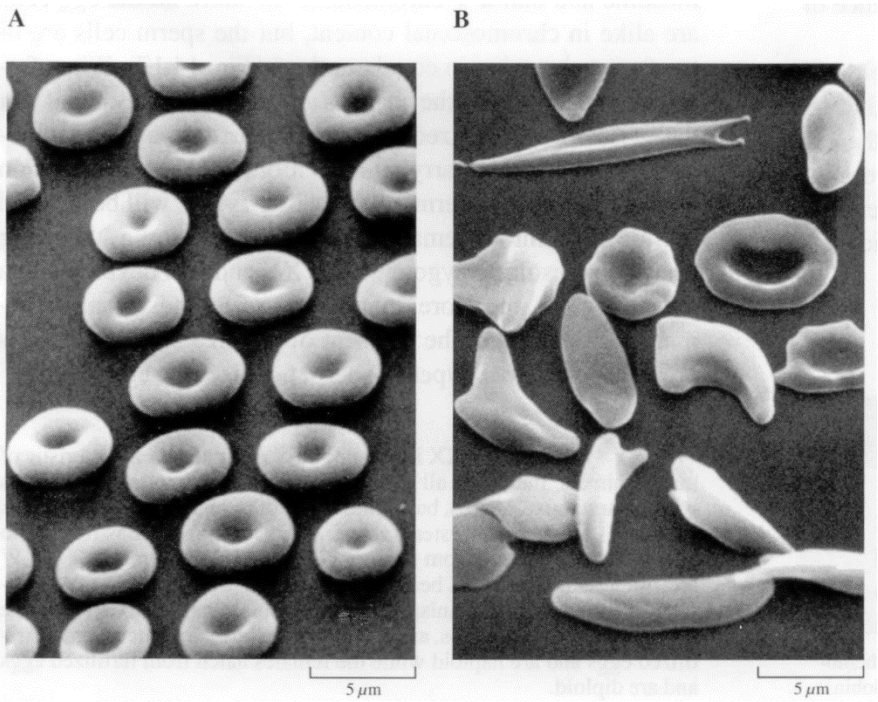




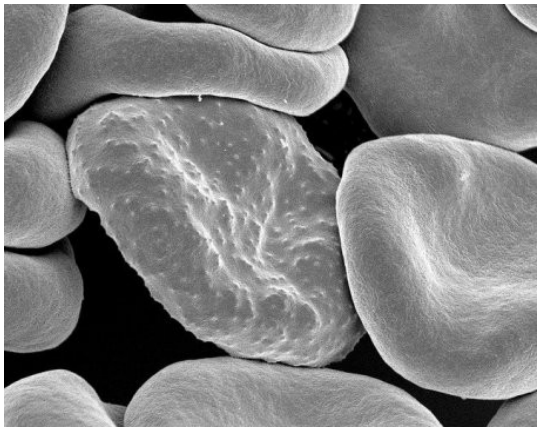
ERYTHROCYTES

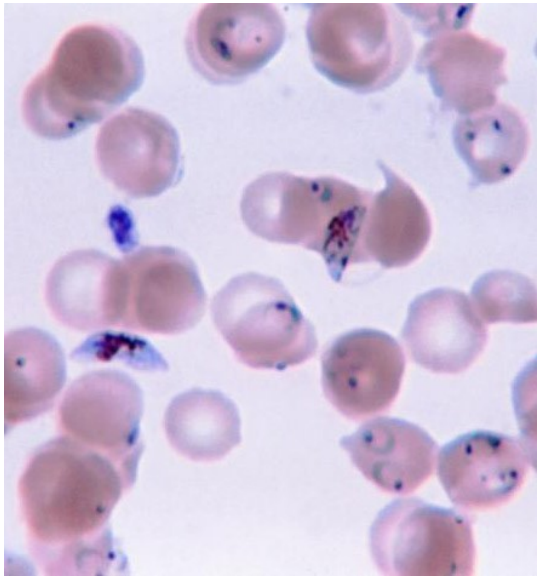
Sickle cell anemia

- pathological genotype (heterozygote HbS/HbA) is beneficial



Malaria

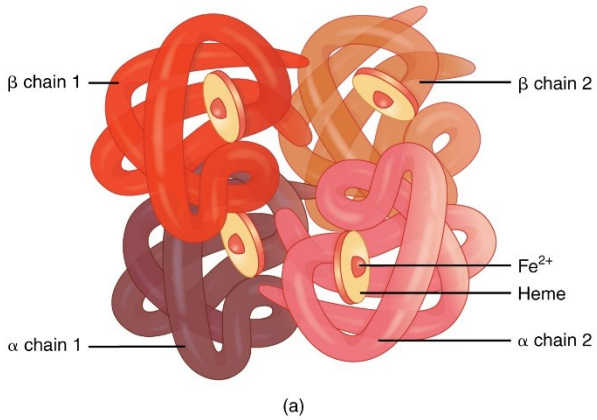


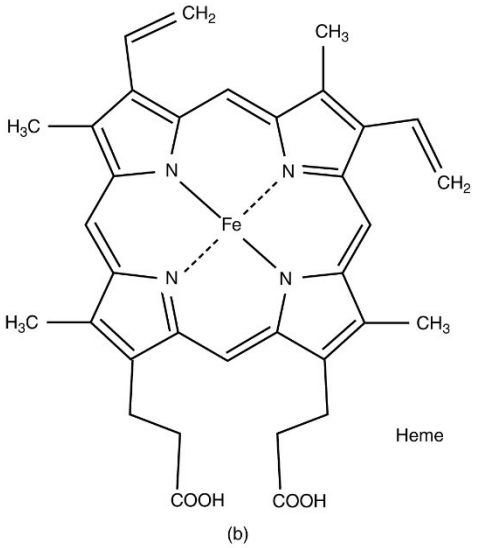


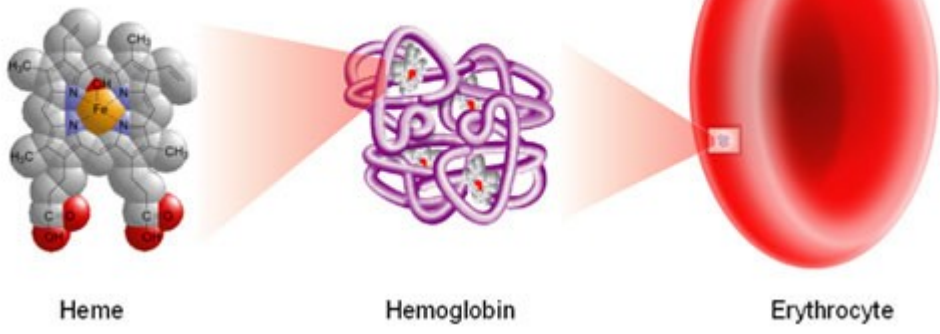
ERYTHROCYTES

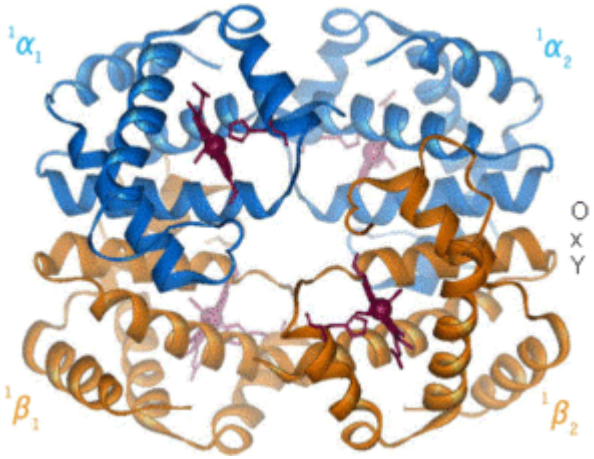
- Erythrocytes lack nucleus and organelles
- Anaerobic glykolysis

- Hemoglobin

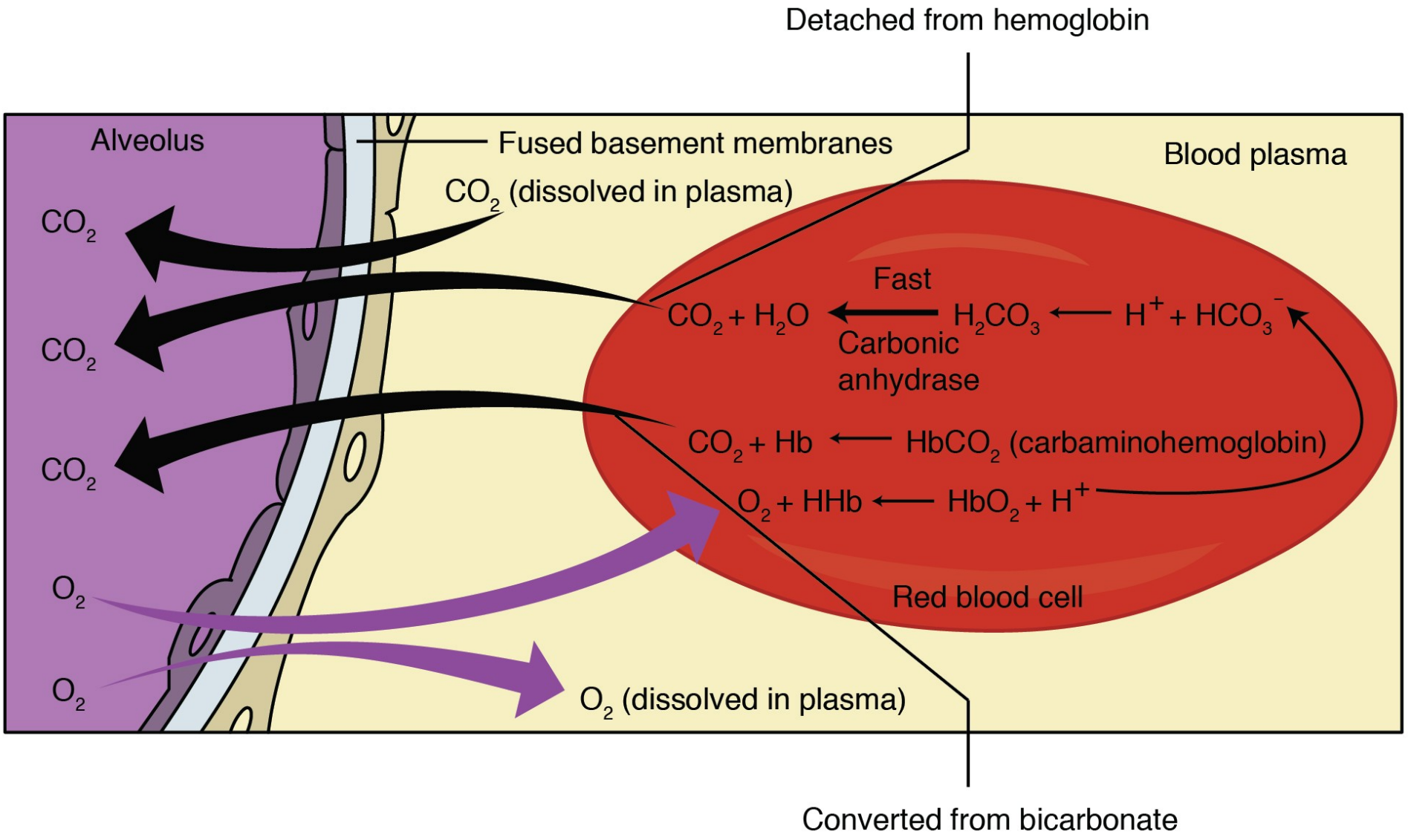






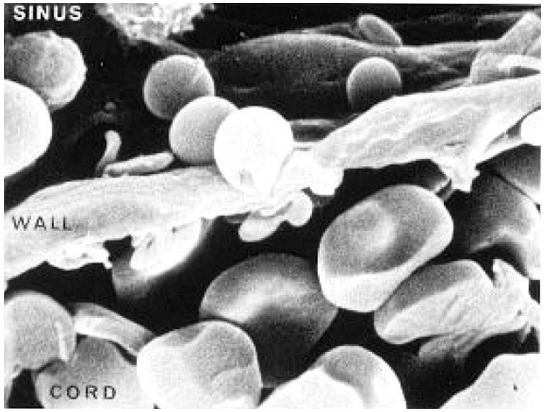


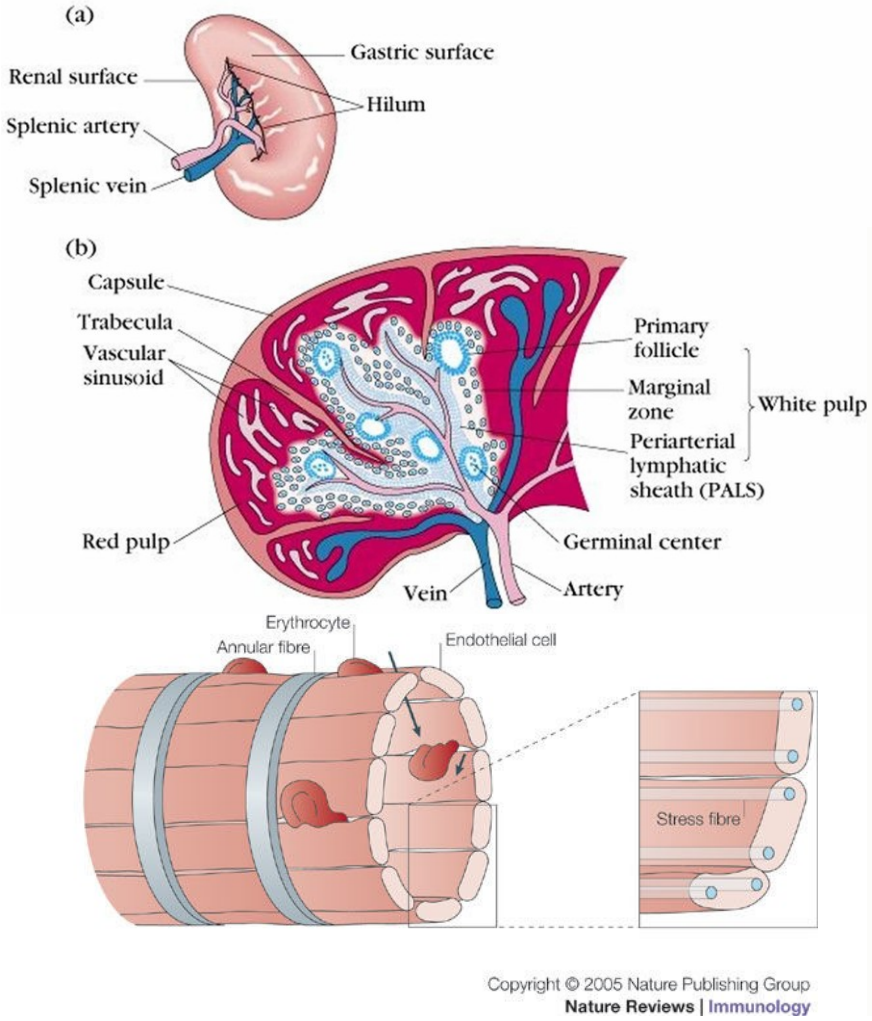
ERYTHROCYTES

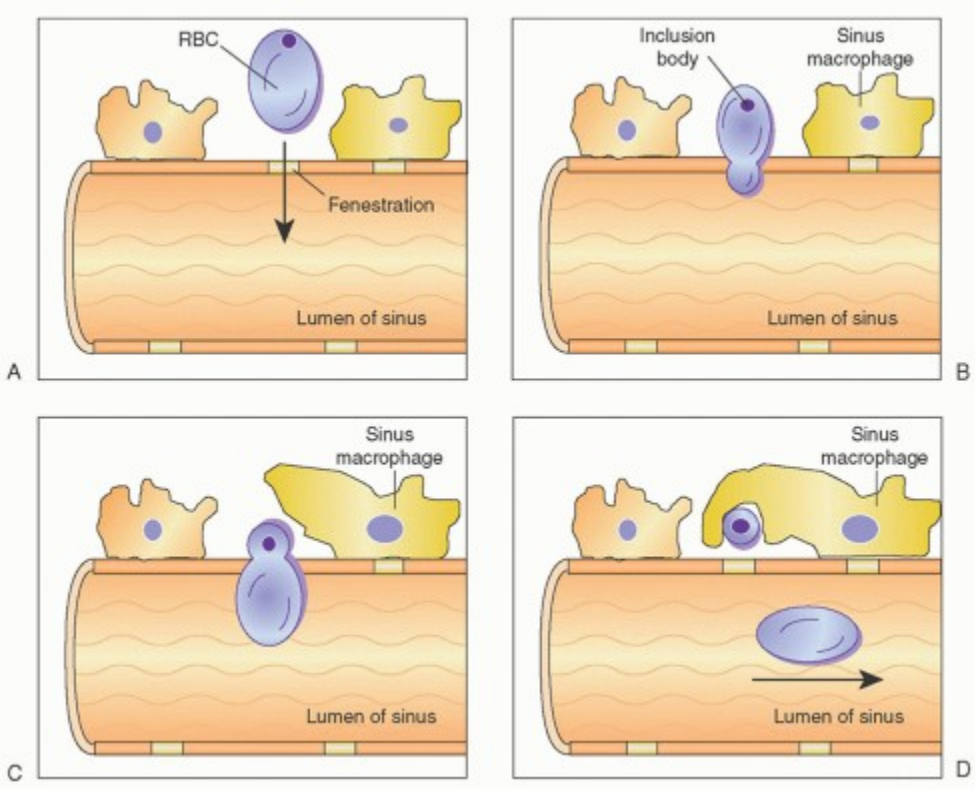


ERYTHROCYTES

- Life span 120 days
- Constant abrasion
- No regeneration
- Removal of aged or damaged erythrocytes in spleen







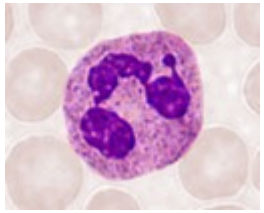
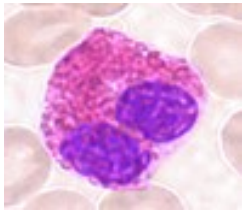
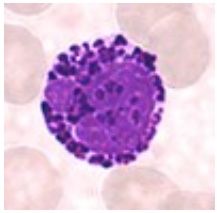
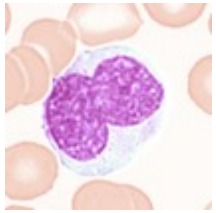
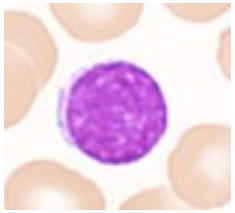
LEUKOCYTES

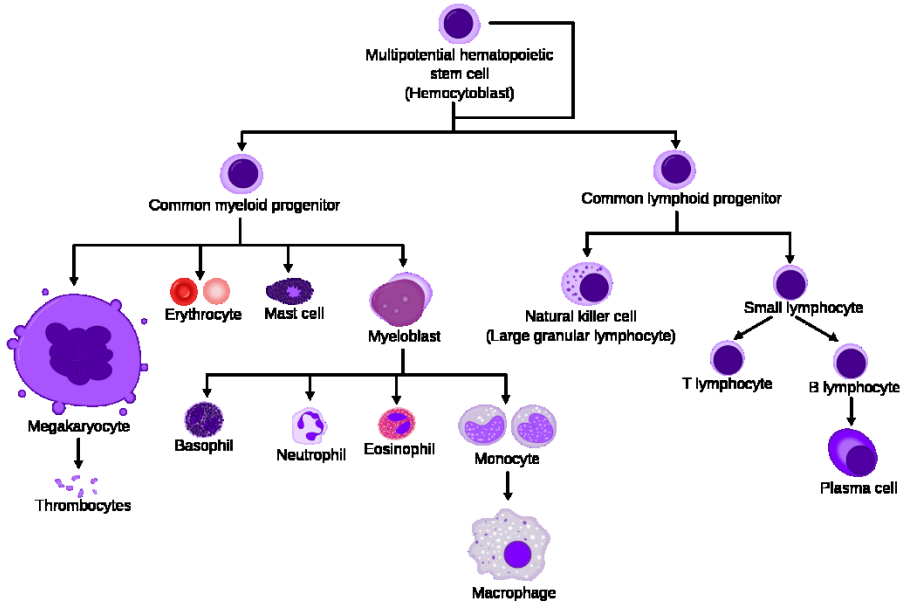
- immune response
- morphological classification – **cytoplasmic granules**

(does not follow hematopoesis)

Granulocytes **Agranulocytes**

Neutrophils Eosinophils Basophils Monocytes Lymphocytes

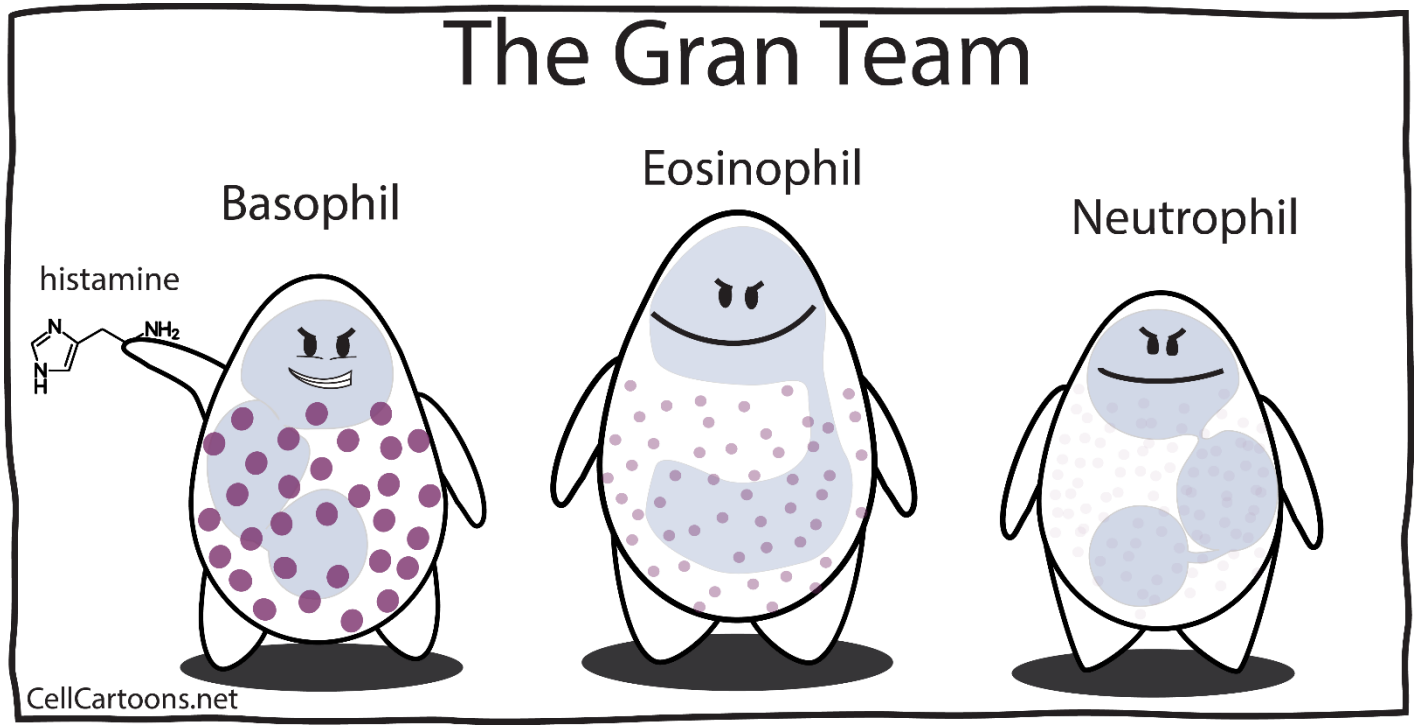








GRANULOCYTES

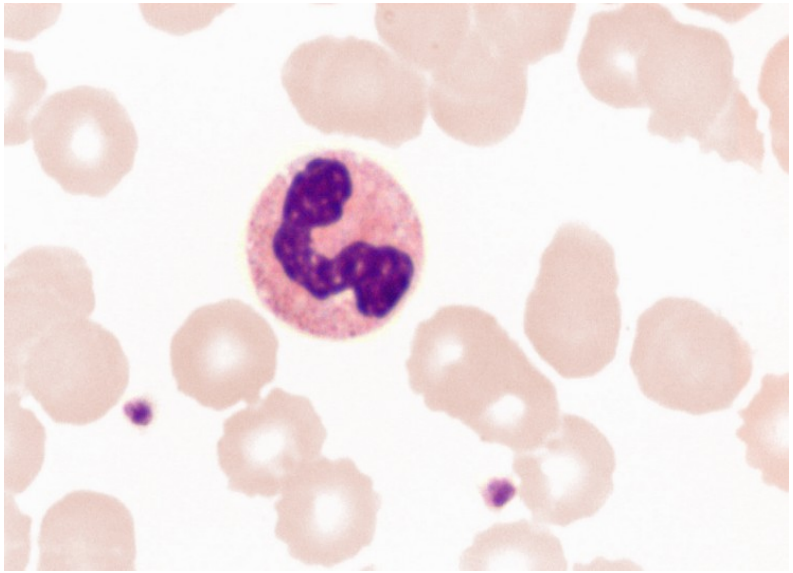
- Lysosomes (primary, azurophilic, nonspecific granules)
- Specific (secondary) granules
- Polymorphic nucleus

- Terminally differentiated
- Short lifespan (hours)
- Reduced ER, GA, mitochondria (anaerobic glycolysis)
- Apoptosis

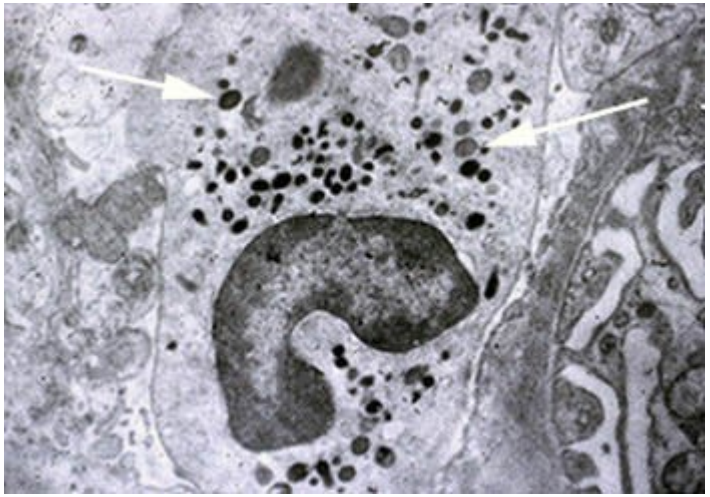


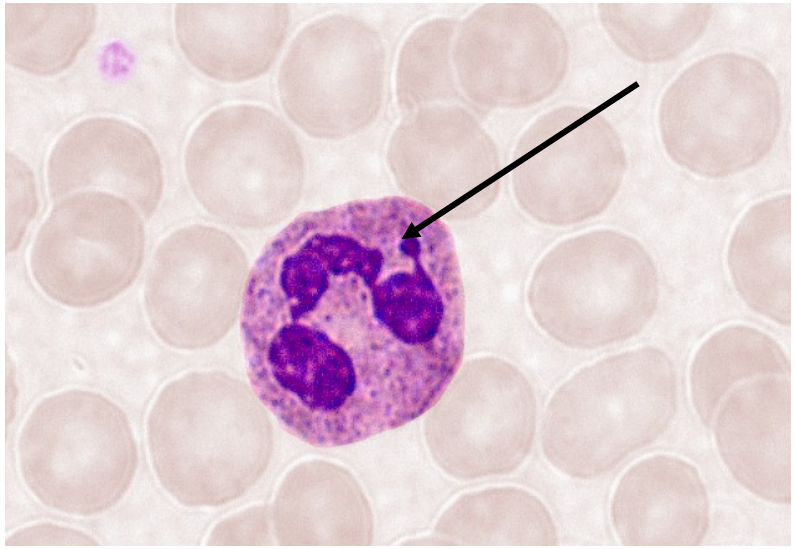
NEUTROPHILIC GRANULOCYTES

- **Neutrophils**
- 50-70% of leukocytes in circulation
- ∅ >12 μm
- Segmented nucleus
- Barr's body in females
- **Azurophilic (primary) granules**
  - myeloperoxidase, lysozyme, proteases, defensins
- **Neutrophilic (secondary) granules**
  - collagenase, bactericidal enzymes
- Chemotaxis of other leukocytes
- Microphages

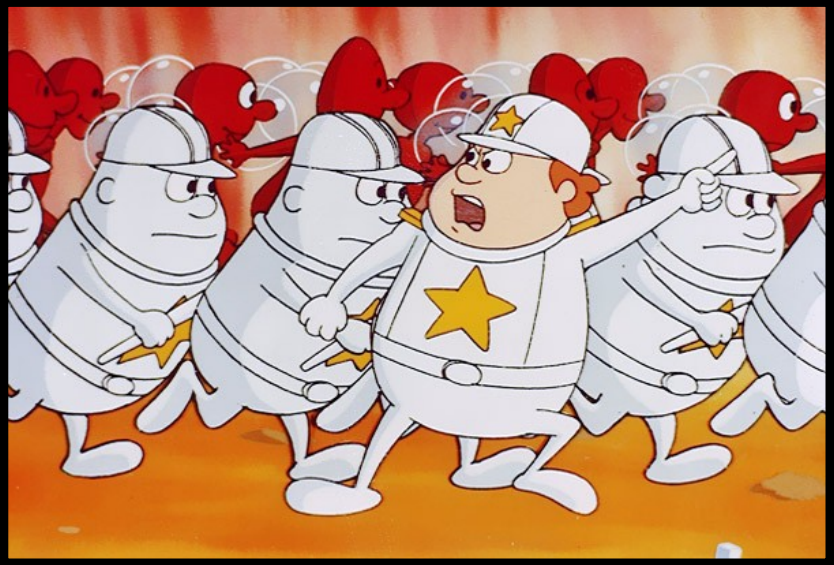


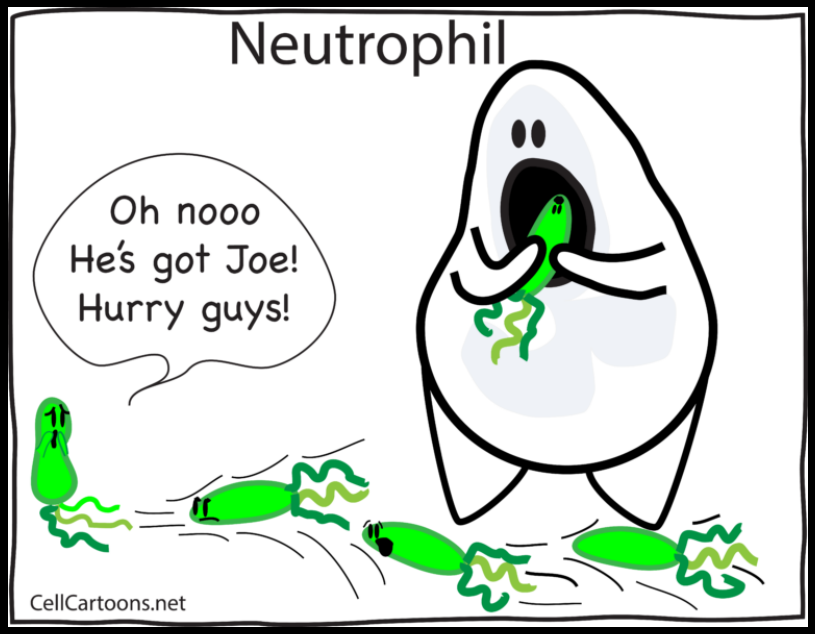
- **Neutrophilic band**
- **Neutrophilic segment**





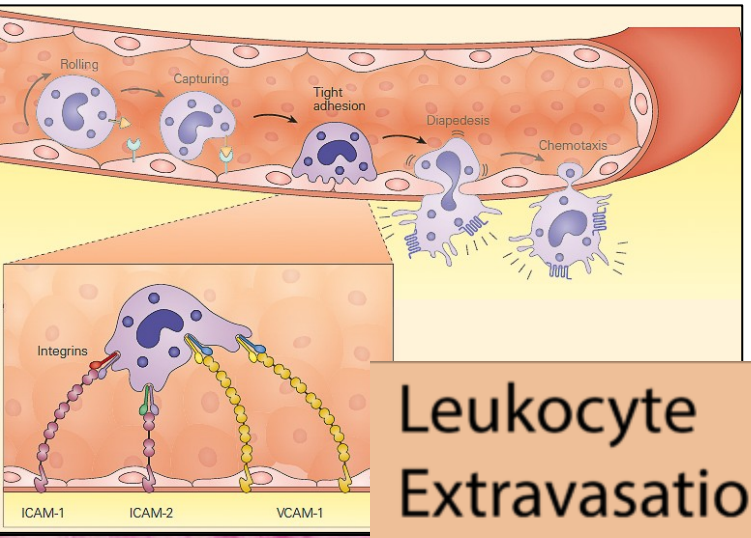
NEUTROPHILIC GRANULOCYTES

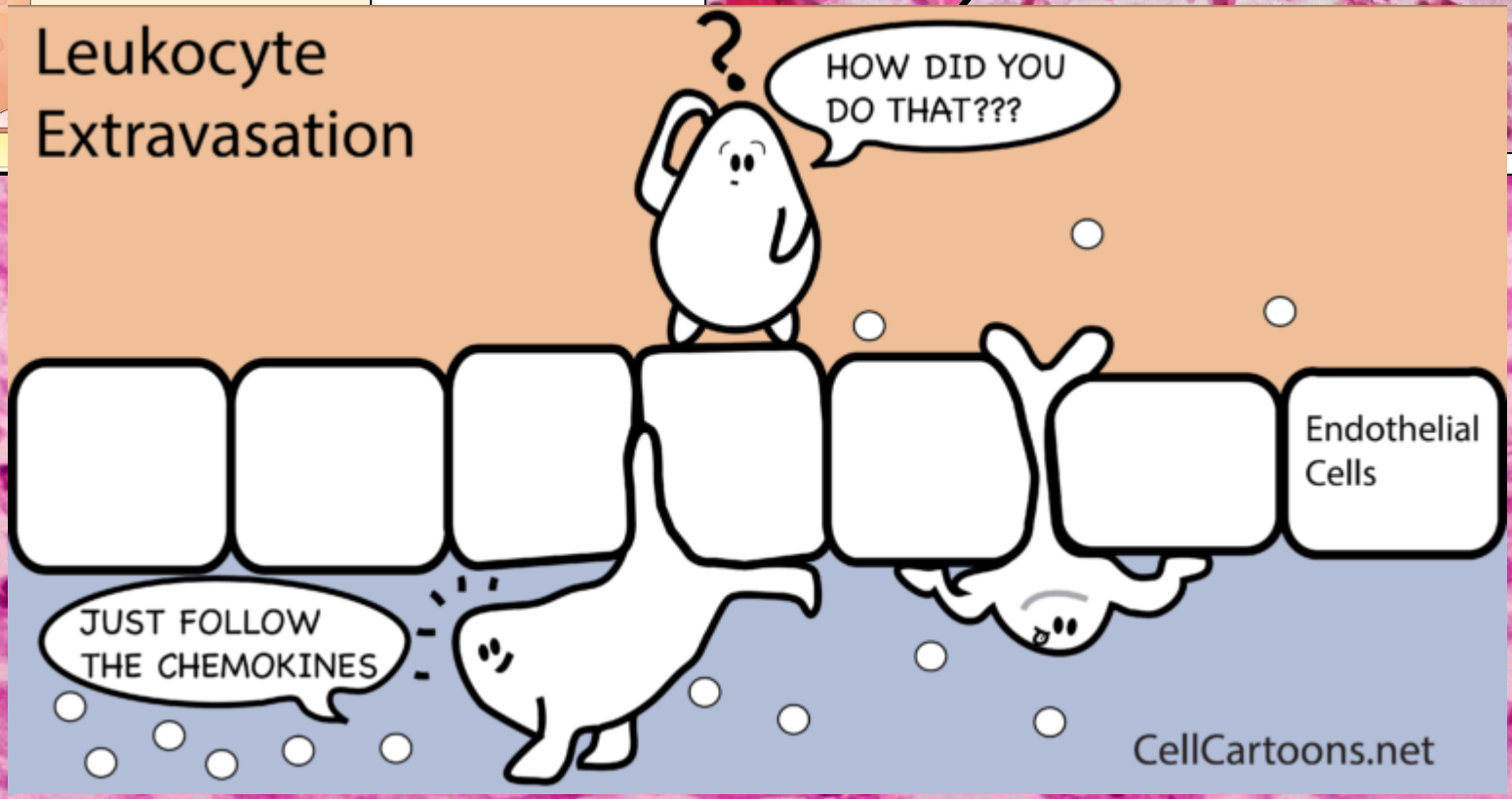




NEUTROPHILIC GRANULOCYTES

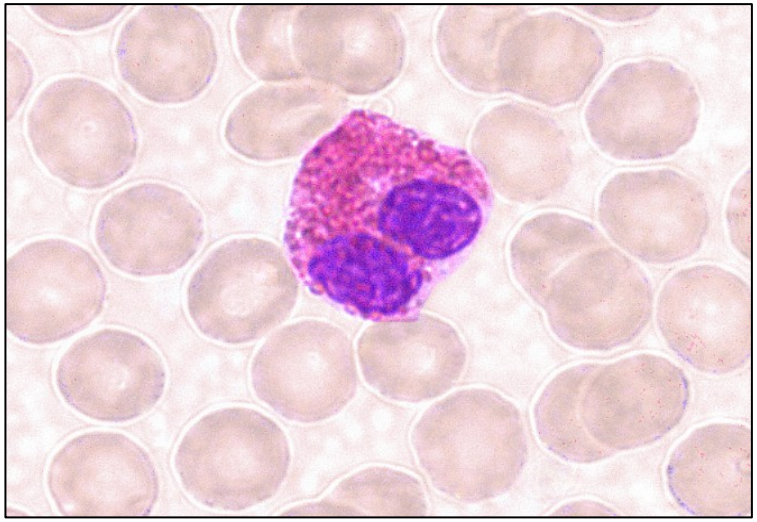
- **Extravasation** (diapedesis)



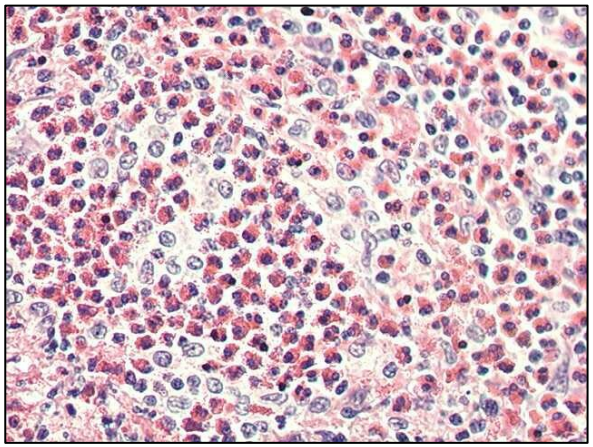


EOSINOPHILIC GRANULOCYTES

- **Eosinophils**
- 1-4% of leukocytes in circulation
- ∅ 12-15 μm
- Irregular, characteristic bi-segmented nucleus
- **Azurophilic (primary) granules**
  - myeloperoxidase, lysozyme, proteases, defensins
- **Eosinophilic (secondary) granules**
  - bright red (eosinophilic)
  - major acidic protein
  - peroxidase
  - cytokines, chemokines



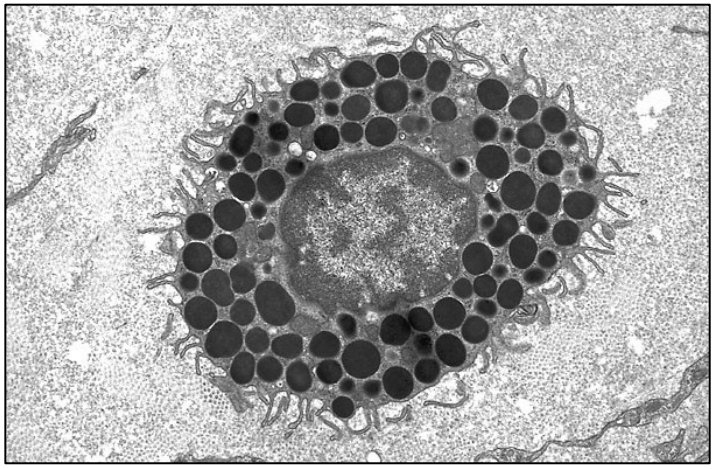
- Chemotaxis of other leukocytes
- Phagocytosis of antibody-antigen complexes
- Parasitic infections, allergic reaction
- Chronic inflammation

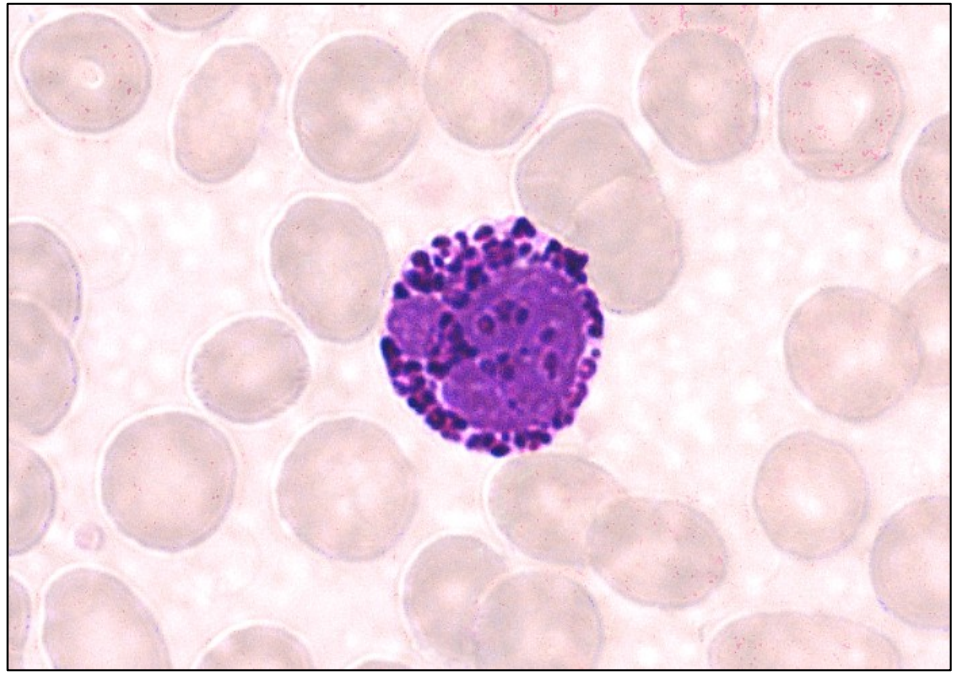


BASOPHILIC GRANULOCYTES

- **Basophils**
- <1% of leukocytes in circulation
- ∅ 12 μm
- Irregular, bisegmented nucleus, masked by granules

- **Azurophilic (primary) granules**
  - myeloperoxidase, lysozyme, proteases, defensins
- **Basophilic (secondary) granules**
  - 0.5 μm
  - large, dark (basophilic)
  - heparin, histamin - vasodilatation
  - phospholipase A
- Analogs of mast cells
- Receptors for IgE
- Allergy, anaphylaxis, inflammation

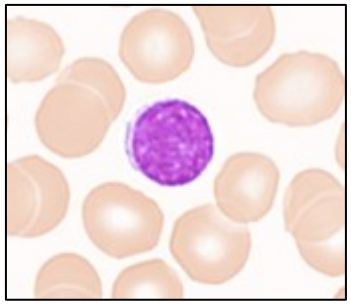




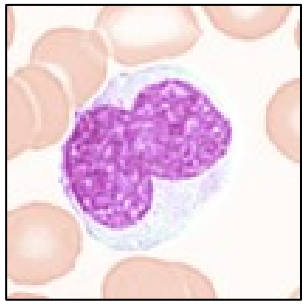
AGRANULOCYTES

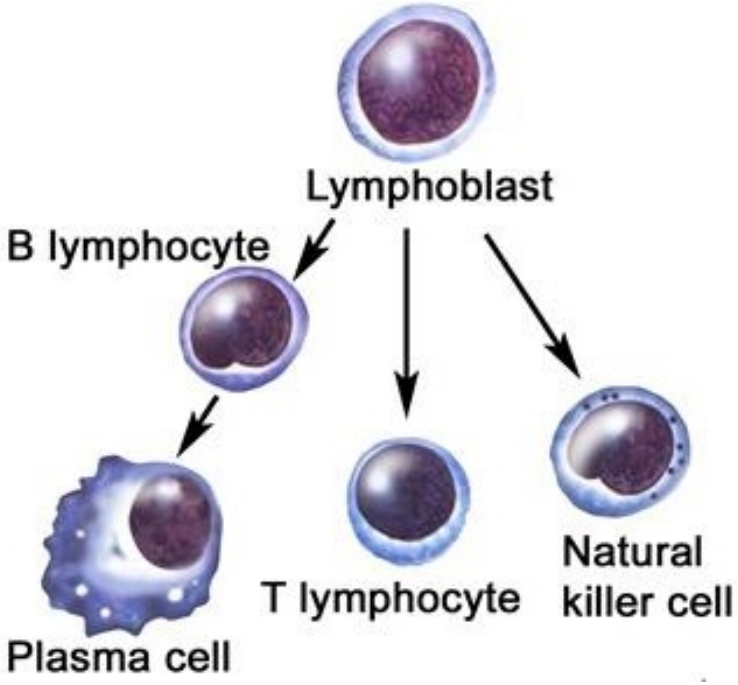
- Lysosomes only (azurophilic, nonspecific granules)
- Specific granules absent
- Non-segmented nucleus

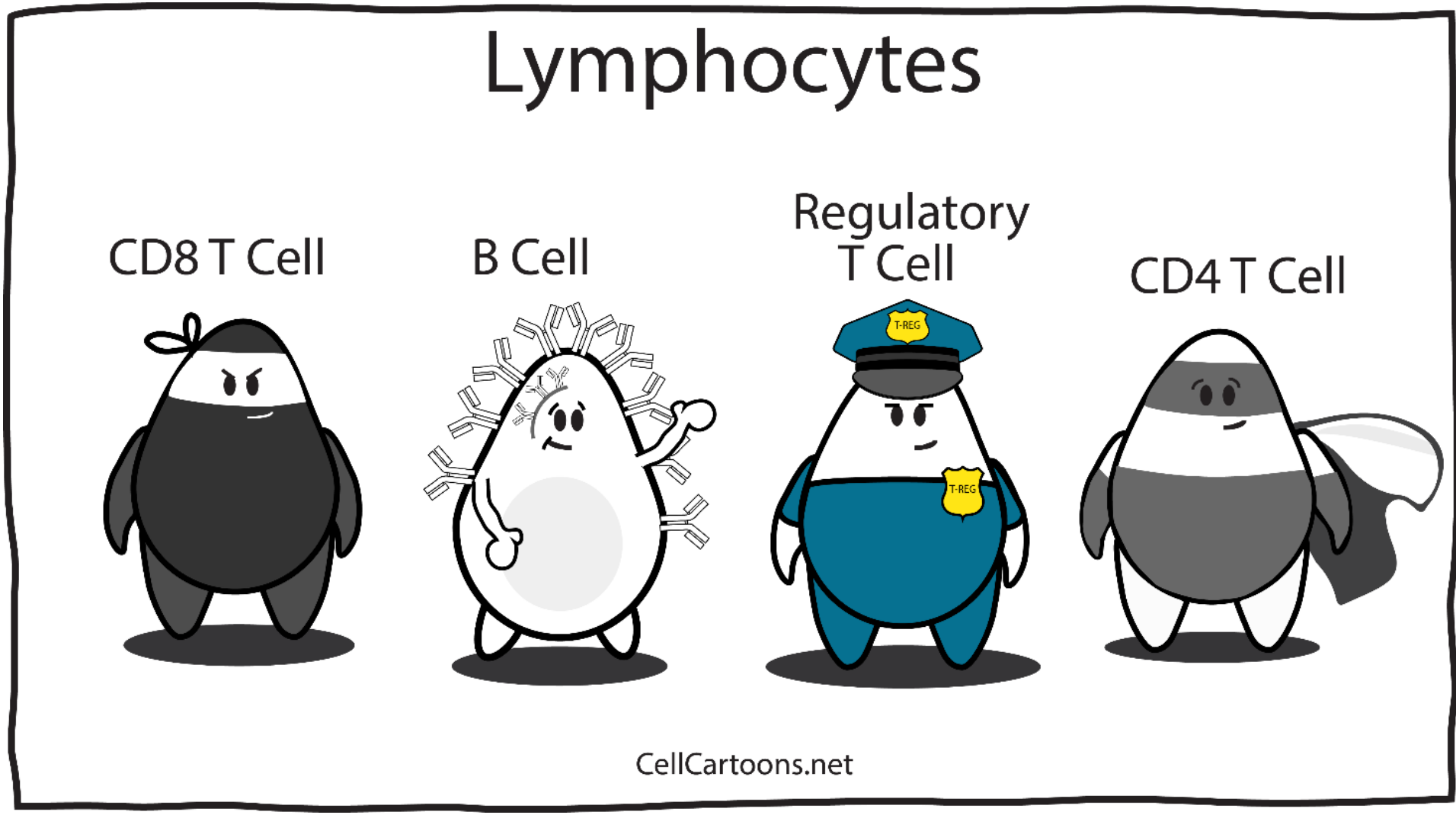
Lymfocytes



Monocytes

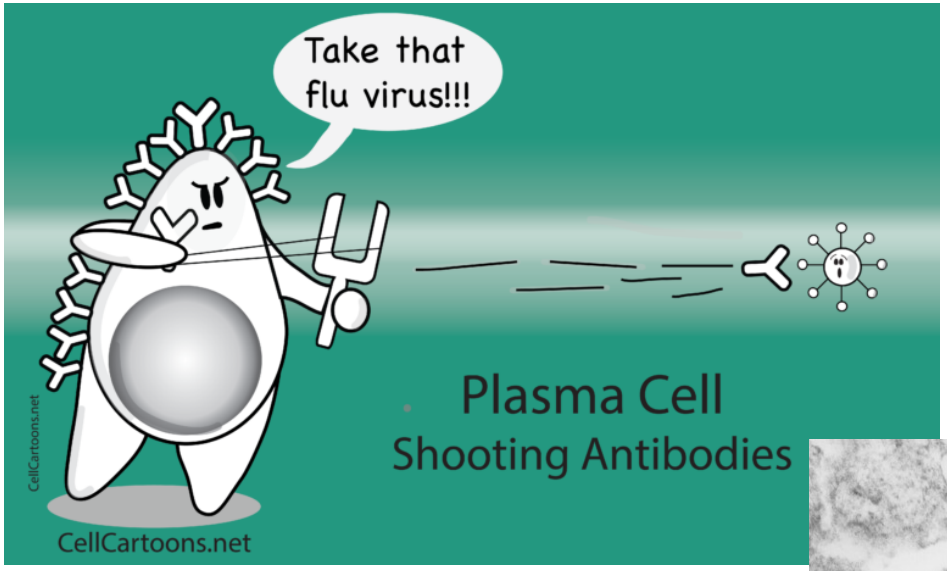


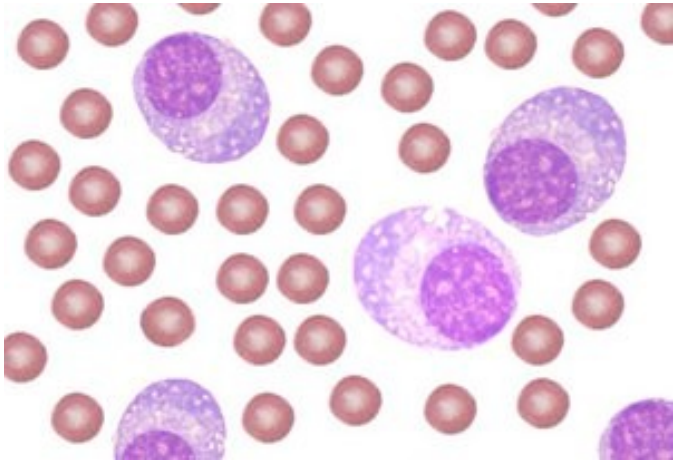


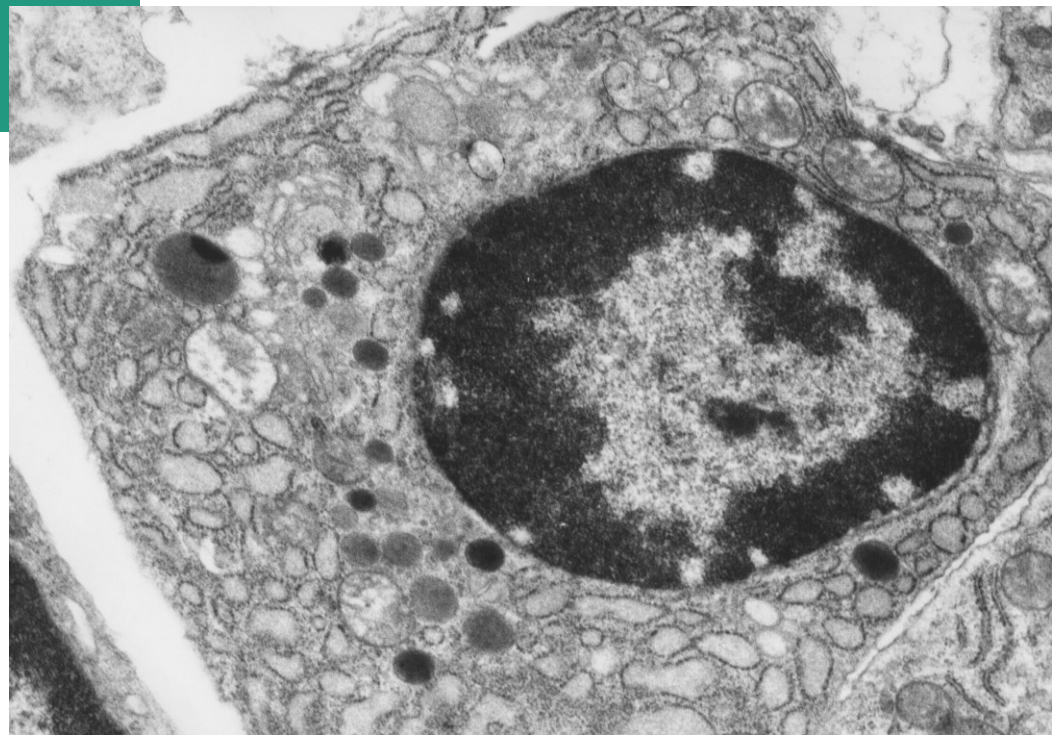

Lymphocytes
CD8 T Cell
B Cell
Regulatory T Cell
CD4 T Cell
T-REG
T-REG
CellCartoons.net

LYMPHOCYTES

- Plasma cells

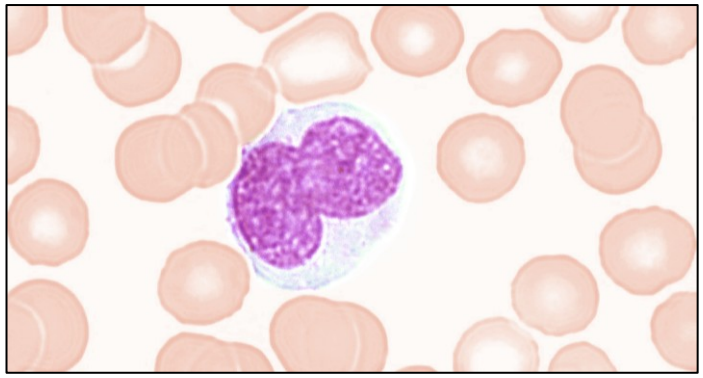


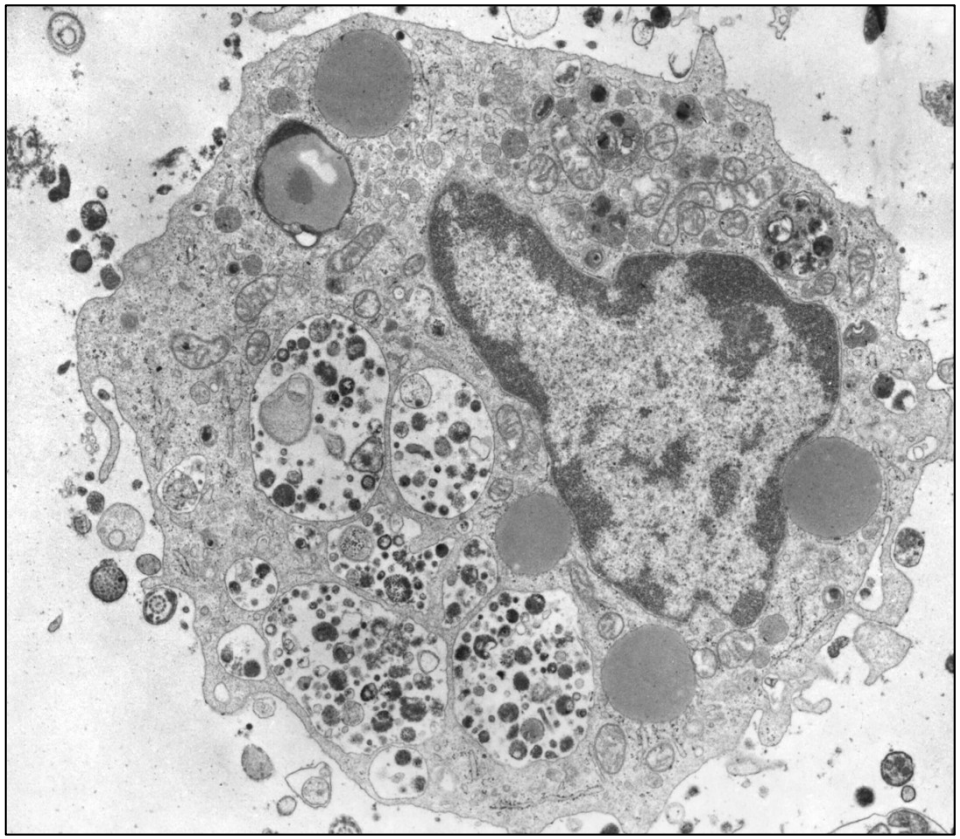


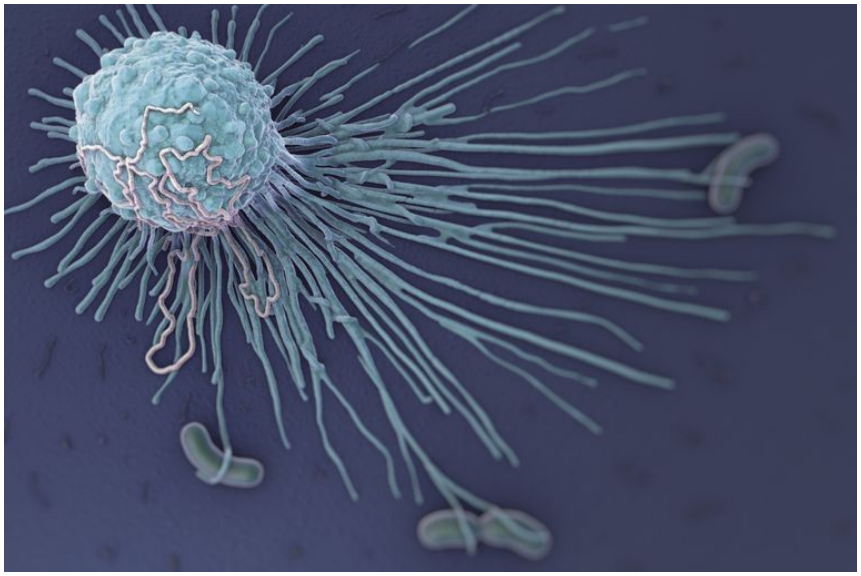


MONOCYTES

- ∅ 12-15 μm
- Circulating precursors of macrophages, osteoclasts, microglia, Kupfer cells and dendritic cells
- Mononuclear phagocytic system
- Large, oval (bean, kidney) nucleus with less condensed chromatin and 2-3 nucleoli
- Basophilic cytoplasm
- Azurophilic granules





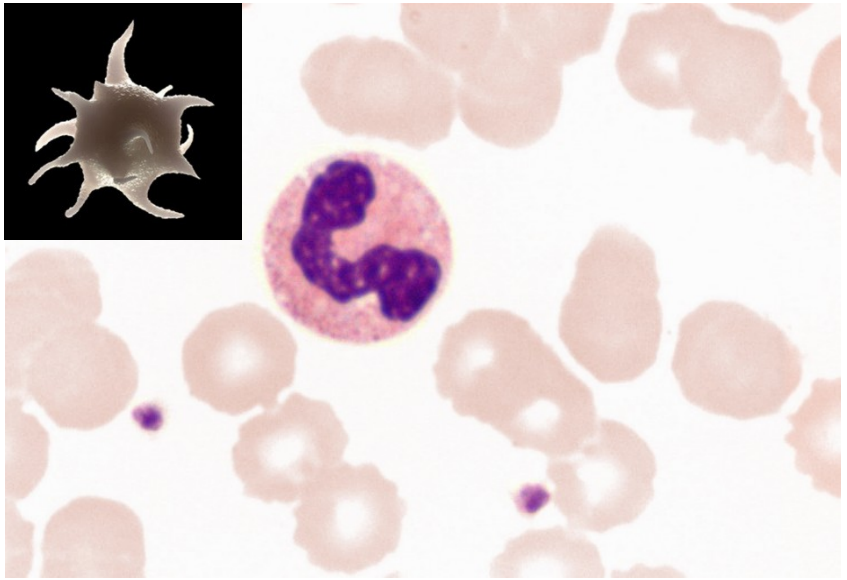


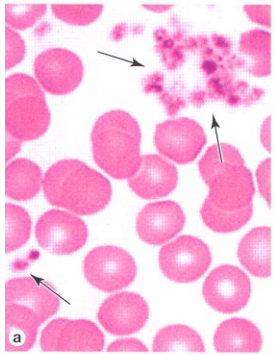
https://www.youtube.com/watch?v=R279Cs1_Itg

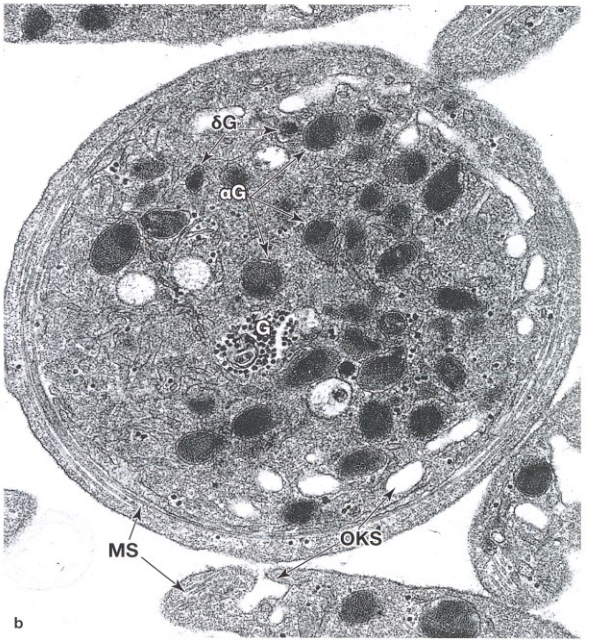
THROMBOCYTES

- Cell fragments without nucleus
- ∅ 2-3 μm, discoid shape
- hyalomere, granulomere
- 150-400 × 10^3/μl
- blood clotting, repair of vessel wall

α-granules 300-500 nm	fibrinogen, PDGF
δ-granules 250-300 nm	serotonin, Ca^{II+} pyrophosphate ADP, ATP
λ-granules 175-200 nm	lyzosomal enzymes

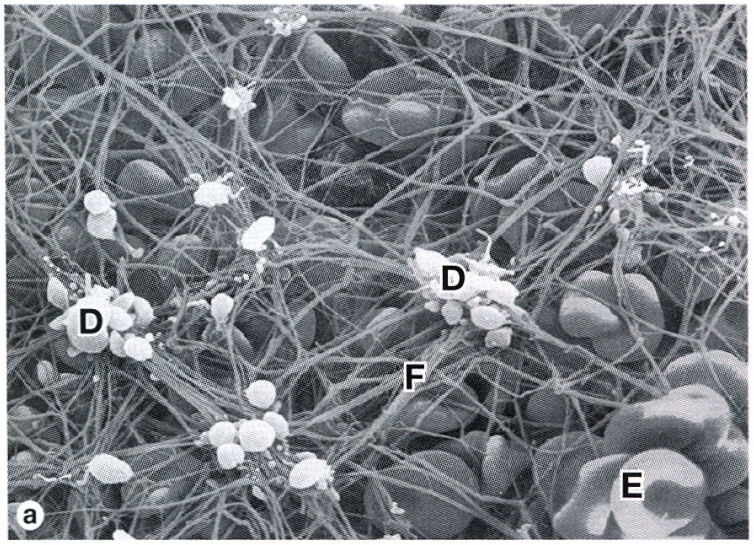


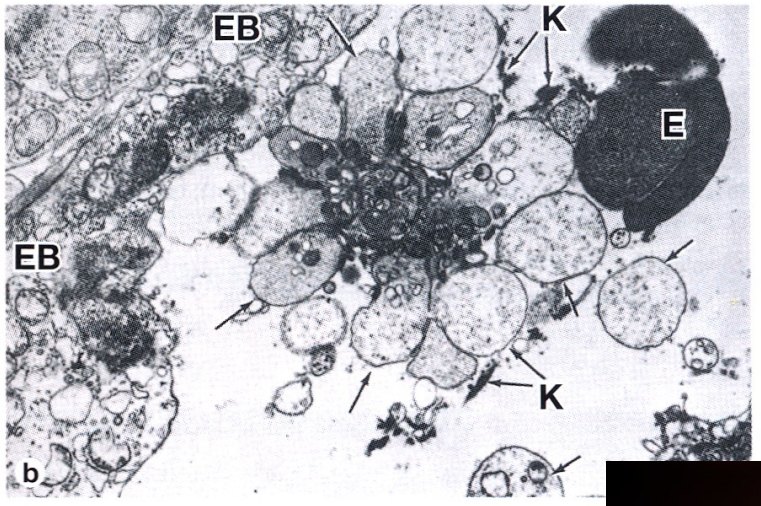




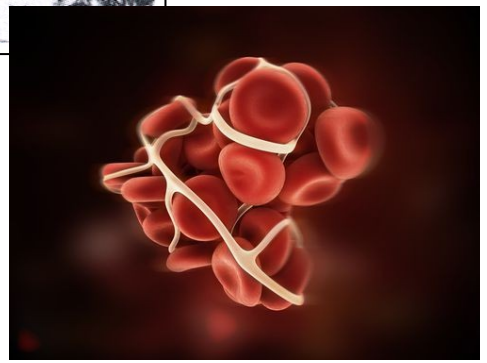
THROMBOCYTES

1. **Primary aggregation of platelets**
   - collagen fibers exposed by endothelial rupture
   - platelet clot
2. **Secondary aggregation of platelets**
   - clotting factors, ADP from thrombocytes attracts other platelets – ***white thrombus***
3. **Coagulation – blood clotting**
   - fibrin mesh capturing erythrocytes – ***red thrombus***

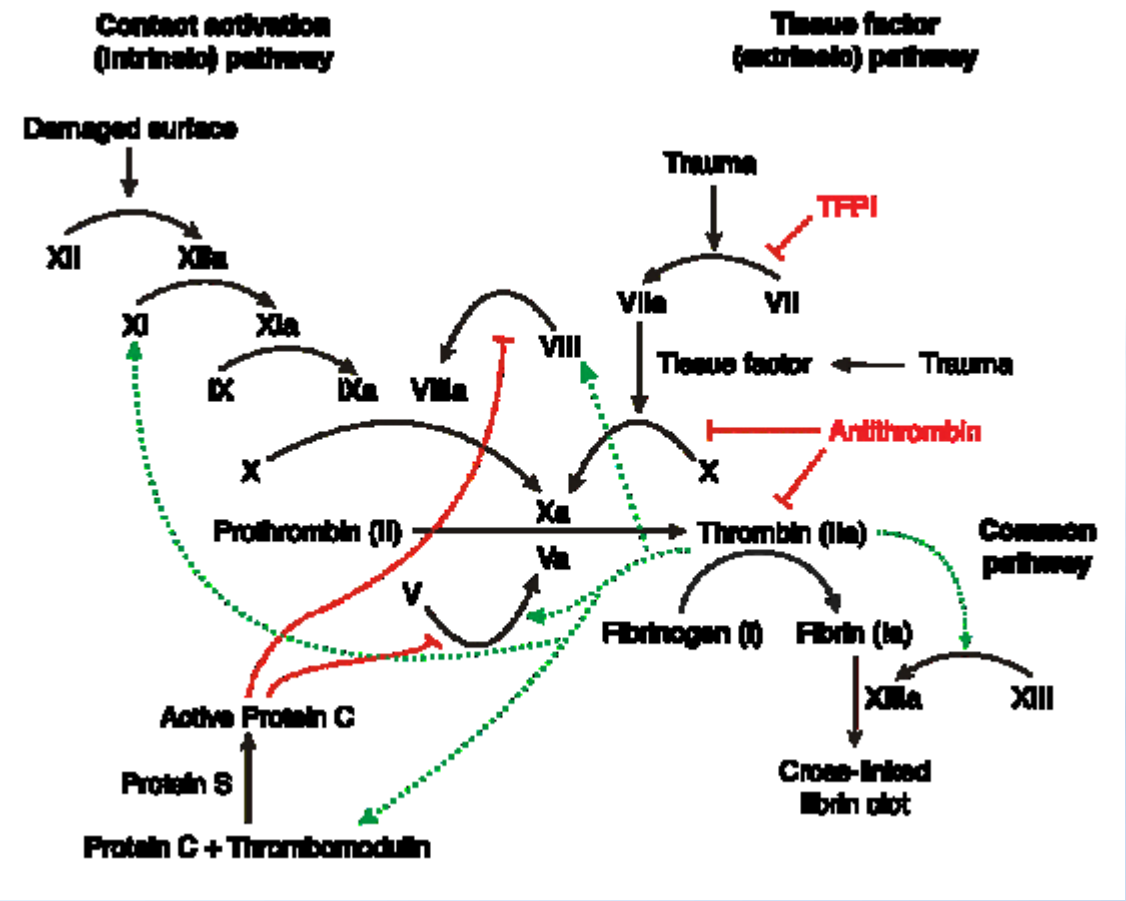




4. **Thrombus retraction**
   - contraction of thrombus (platelet actin and myosin)
5. **Thrombolysis**
   - dissolving of thrombus (plasmin) and tissue regeneration



THROMBOCYTES



DIFFERENTIAL WHITE BLOOD CELL COUNT

Norm

Neutrophil	**band**	**4 %**
	segment	**67 %**
	1:17	
shift to the left		**shift to the right**
more bands		more segments
Eosinophils		**3 %**
Basophils		**1 %**
Lymphocytes		**20 %**
Monocytes		**5 %**

$\sum$ = 100 %

DIFFERENTIAL WHITE BLOOD CELL COUNT

Deviations from norm

	↑ Increased	↓ Decreased
Neutrophils	neutrophil granulocytosis	neutrophil granulocytopenia
Eosinophils	eosinophil granulocytosis	eosinophil granulocytopenia
Basophils	basophil granulocytosis	basophil granulocytopenia
Lymphocytes	lymphocytosis	lymphocytopenia
Monocytes	monocytosis	monocytopenia

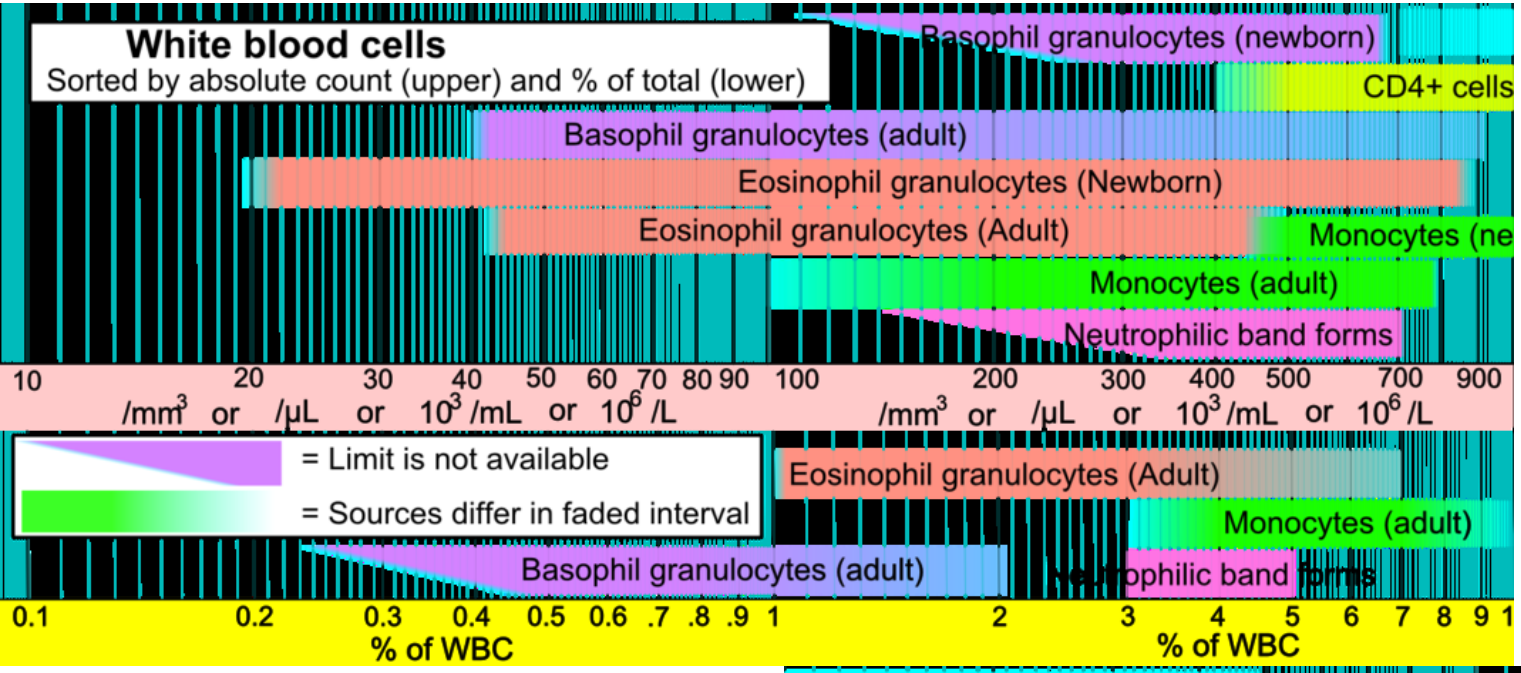
DIFFERENTIAL WHITE BLOOD CELL COUNT

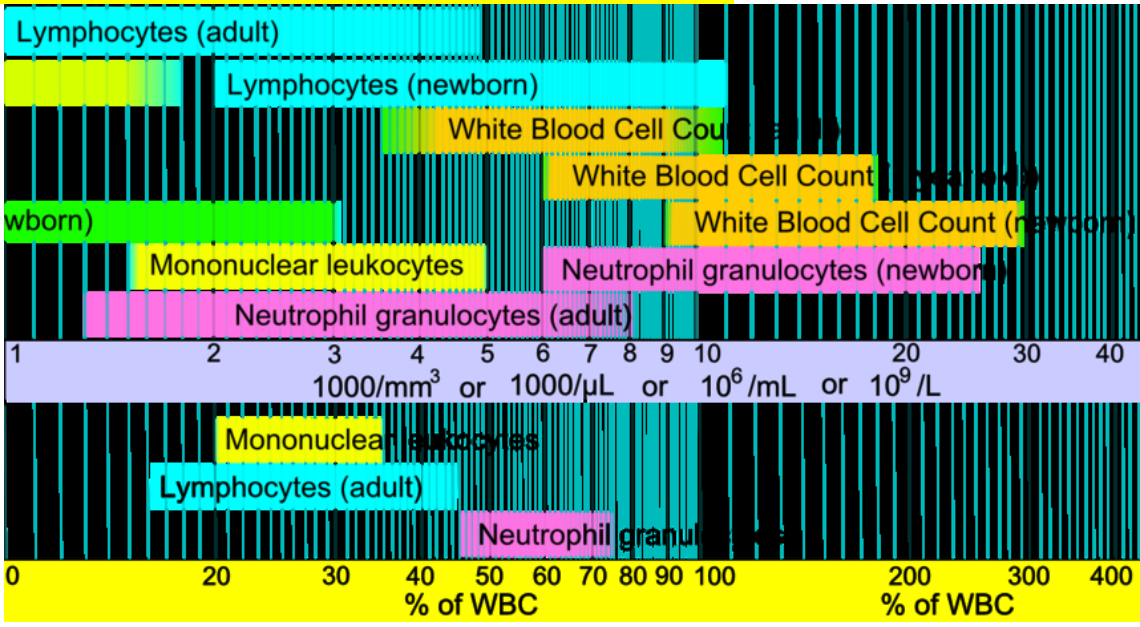
Example of population variability

Neutrophils	**bands**	**0-5 %**
	segments	**35-85 %**
Eosinopils		**0-4 %**
Basophils		**0-1 %**
Lymphocytes		**20-50 %**
Monocytes		**2-6 %**

According to: Haferlach et al. Kapesní atlas hematologie. Grada 2014

DIFFERENTIAL WHITE BLOOD CELL COUNT





Wikipedia

DIFFERENTIAL WHITE BLOOD CELL COUNT

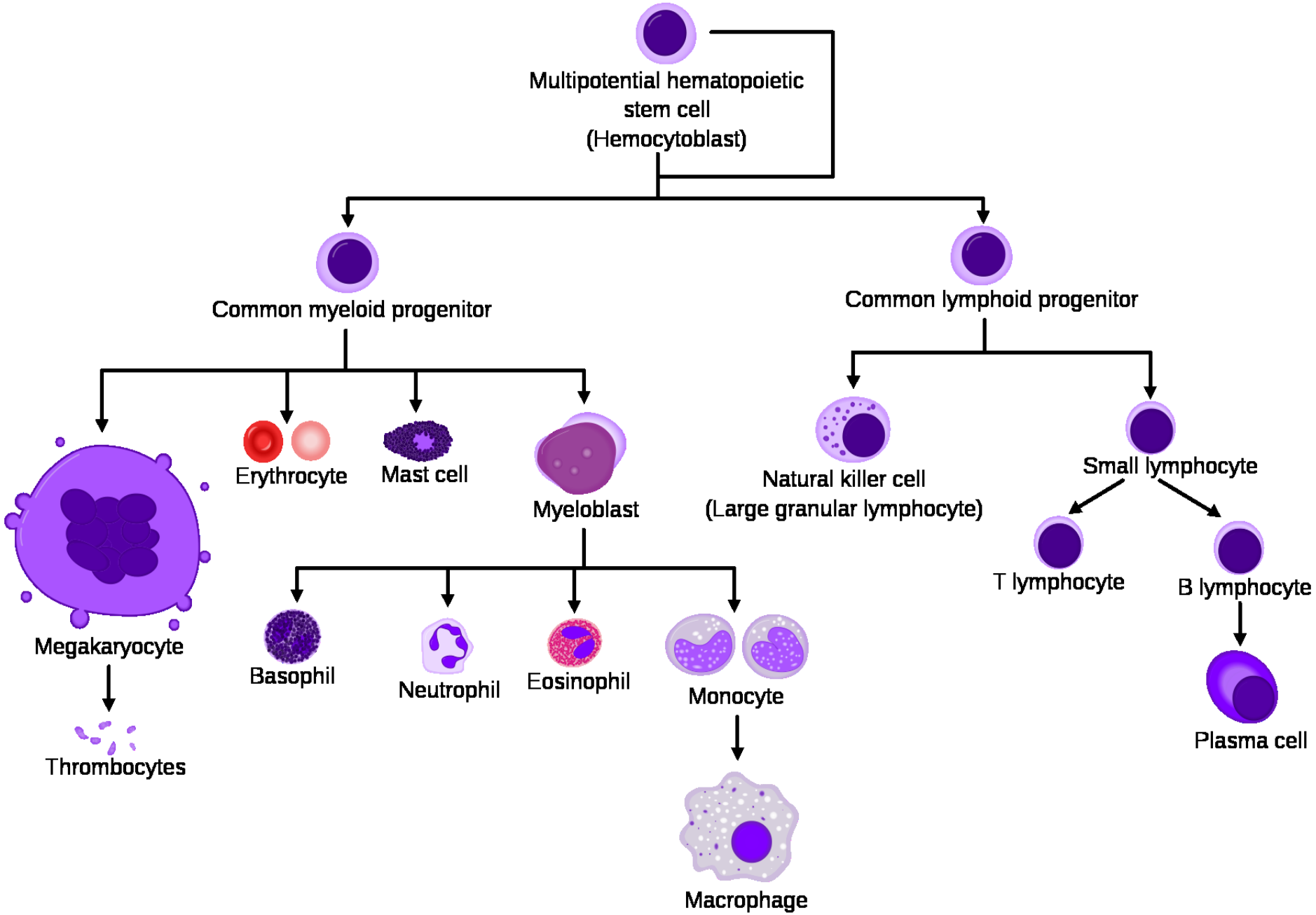
Age dependence

Age	Leukocytes ($\times 10^3$)	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)
Birth	18	61	31	6	2
1 week	12.2	45	41	9	4
1 mo	10.8	35	56	7	3
6 mo	11.9	32	61	5	3
1 yr	11.4	31	61	5	3
4 yr	9.1	42	50	5	3
10 yr	8.1	54	38	4	2
16 yr	7.8	57	35	4	3

WBC, White blood cell.

https://obgynkey.com/elevated-or-depressed-white-blood-cell-count/

HEMATOPOIESIS



ERYTHROPOIESIS

- **2×10^{11} of new erythroyctes daily**

- **proerythroblast** (~14-19 μm)
- mitotically active
- dominant, round nucleus with 1-2 nucleoli
- mildly basophilic cytoplasm

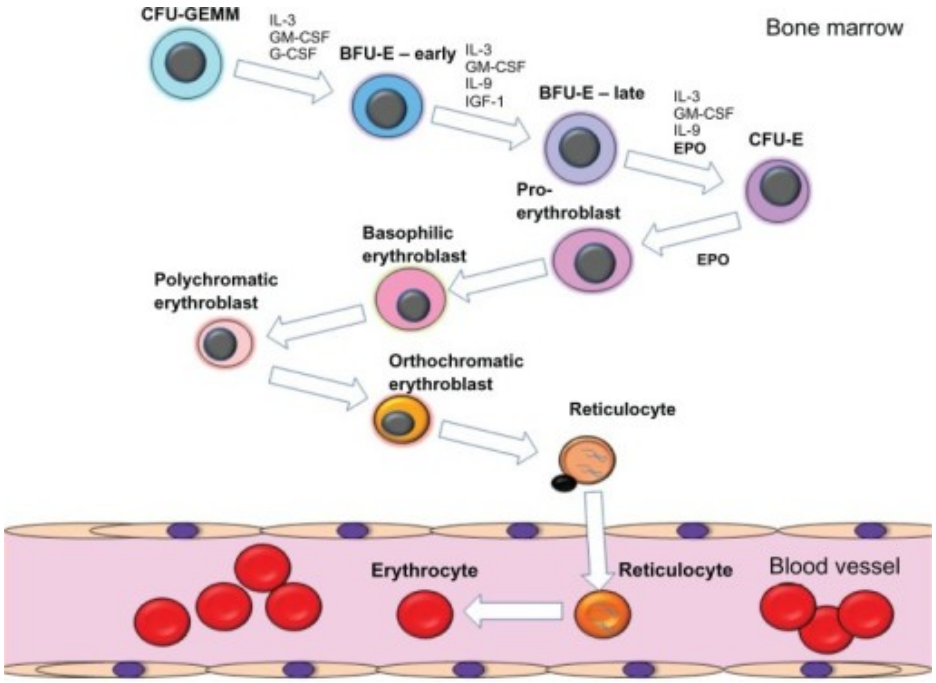
- **basophilic erythroblast** (~13-16 μm)
- mitotically active
- heterochromatic nucleus with inconspicuous nucleoli
- basophilic cytoplasm (sometimes more than in proerythroblast)

- **polychromatophilic erythroblast** (~13-16 μm)
- mitotically active
- **production of hemoglobin**
- blue-gray cytoplasm due to combined basophilic (polyribosomes) and acidophilic aspects (hemoglobin)
- heterochromatic nucleus (checkerboard appearance)

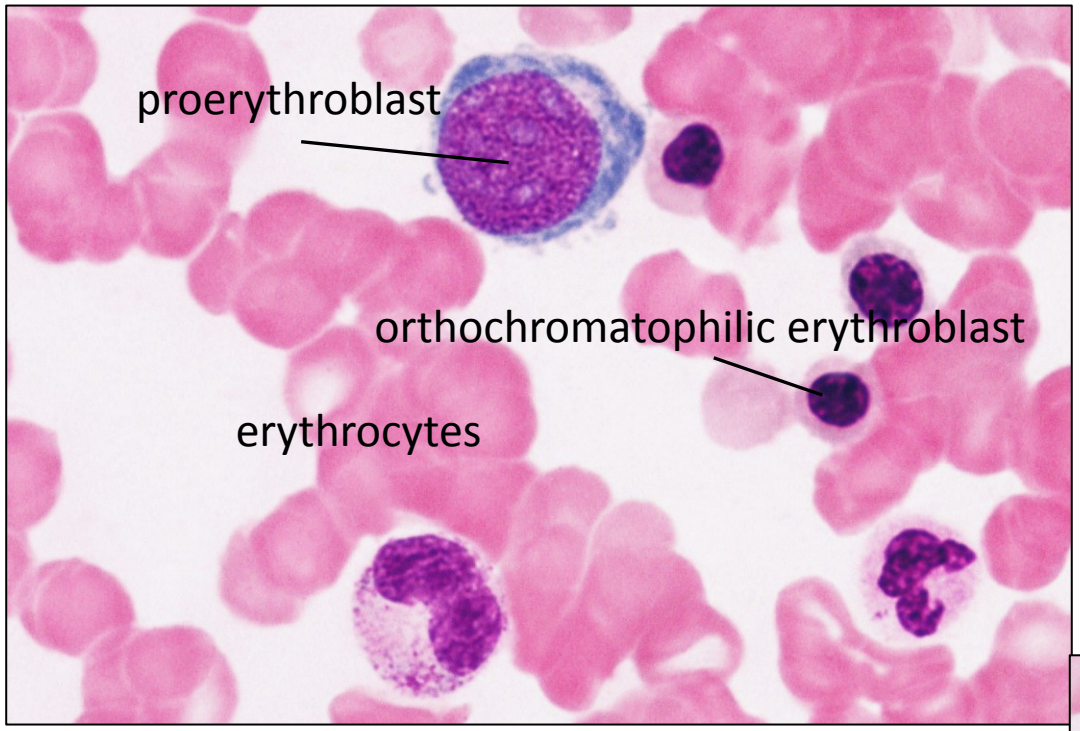
- **orthochromatophilic erythroblast** (~8-10 μm)
- mitotically inactive
- small, compact, eccentric, pycnotic nucleus → **extrusion**
- mildly acidophilic cytoplasm with basophilic residues

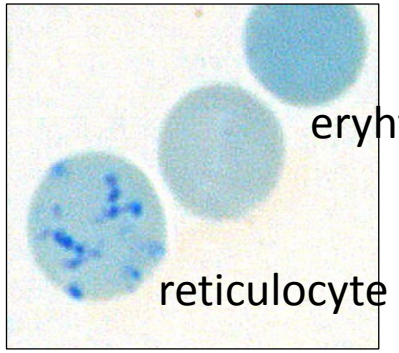
- **reticulocyte** (polychromatophilic erythrocyte, ~ 7-8 μm)
- **lacks nucleus, still spheroid shape**
- acidophilic cytoplasm
- *substantia reticulofilamentosa* visible by supravital staining (brilliant cresyl blue)

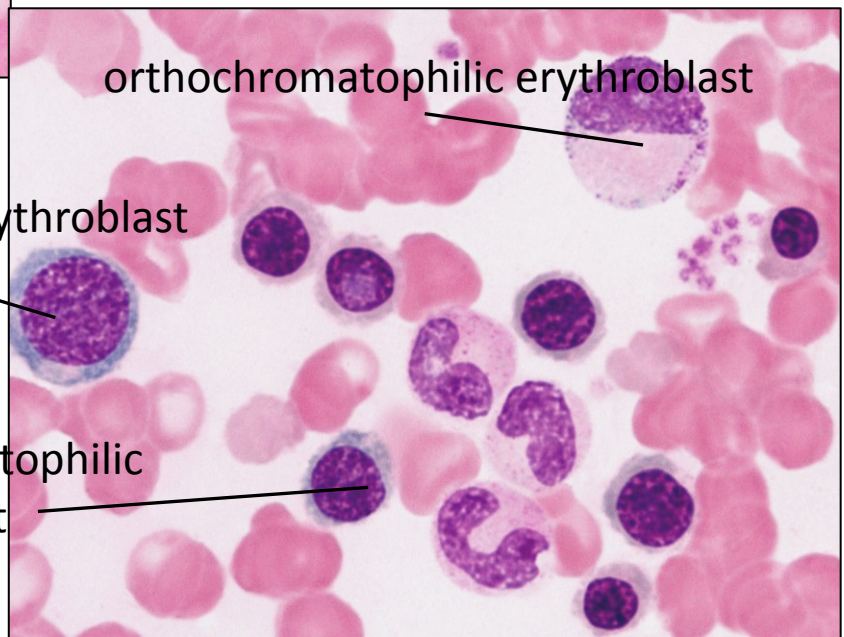
- **erythrocyte** (~7-8 μm)
- anucleate, biconcave disc
- acidophilic cytoplasm



ERYTHROPOIESIS







GRANULOPOIESIS

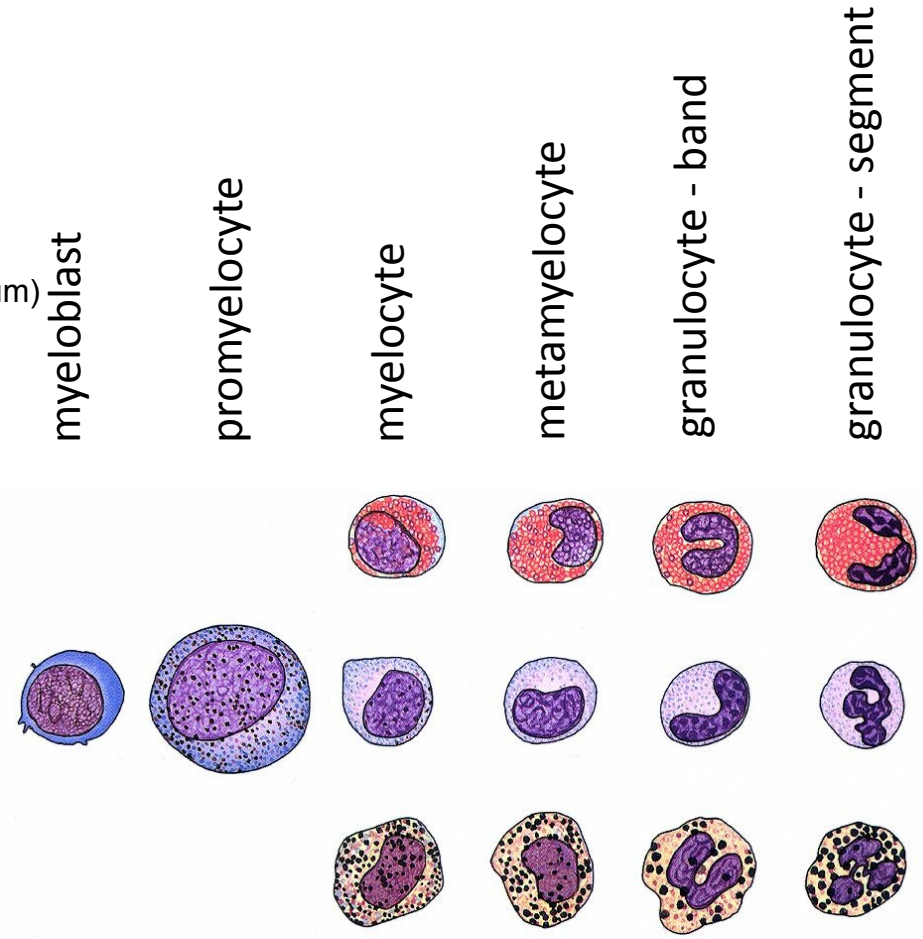
- **myeloblast** (~15 µm)
- mitotically active
- round-oval, euchromatic nucleus
- 2-6 apparent nucleoli
- weakly basophilic cytoplasm without granules

- **promyelocyte** (~15-24 µm)
- mitotically active
- round-oval nucleus with partly condensed chromatin
- basophilic cytoplasm with azurophilic granules

- neutrophilic, eosinophilic or basophilic **myelocyte** (~10-16 µm)
- mitotically active
- oval or bean-shaped nucleus with condensed chromatin
- increasing number of specific granules in cytoplasm

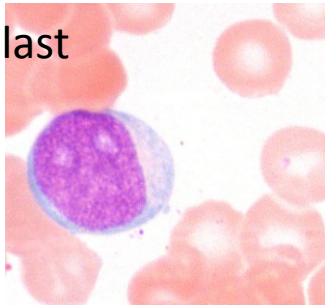
- neutrophilic, eosinophilic or basophilic **metamyleocyte** (~10-12 µm)
- mitotically inactive
- horseshoe-like nucleus with condensed chromatin

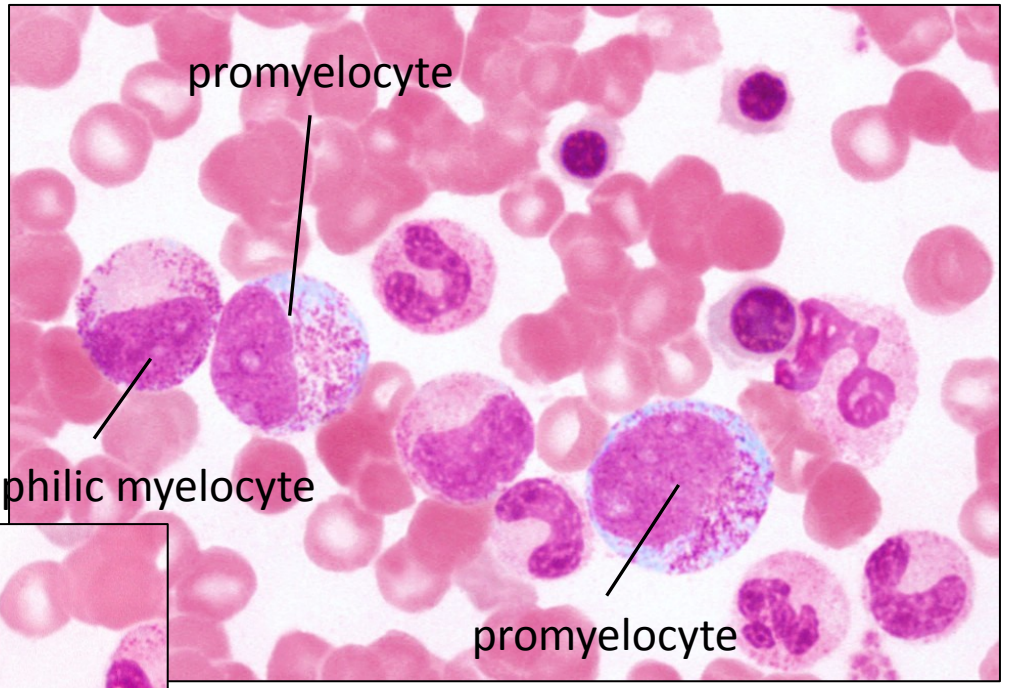
- neutrophilic, eosinophilic or basophilic **granulocyte** (~10-12 µm)
- segmentation of nucleus
- cytoplasm rich in specific and azurophilic granules

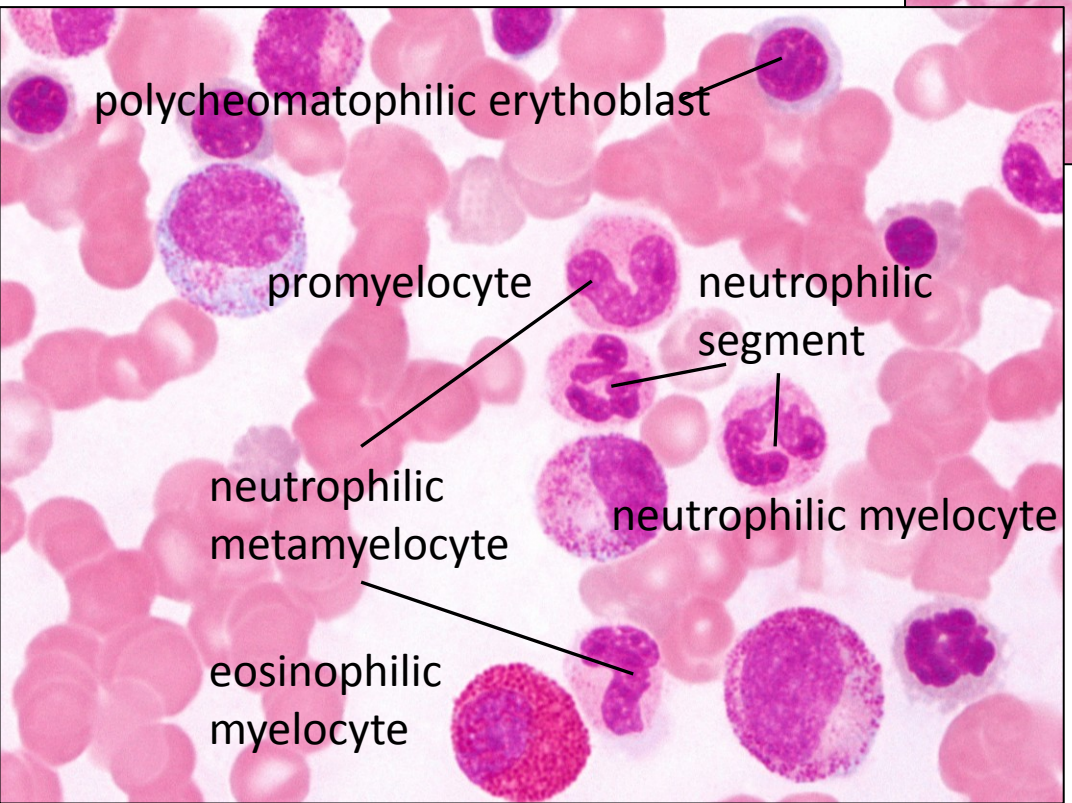


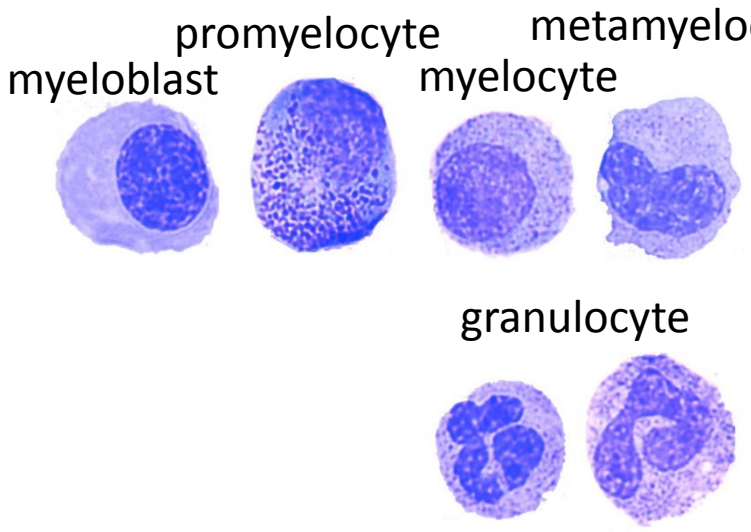
GRANULOPOIESIS

myeloblast



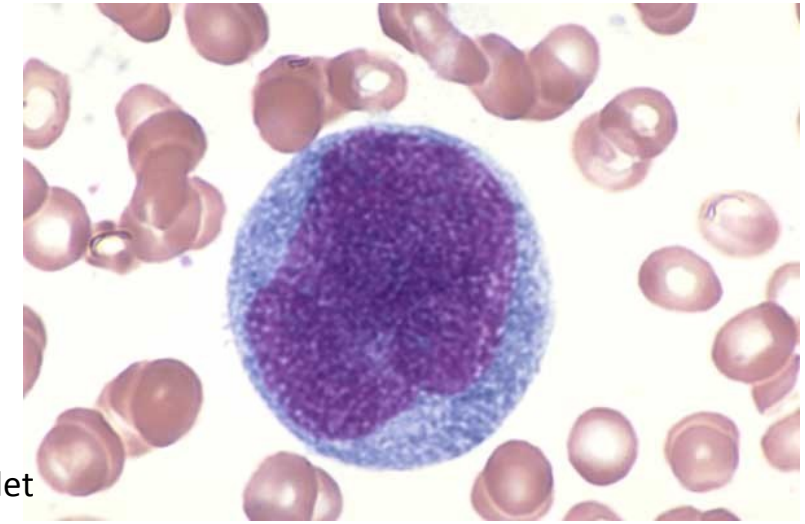


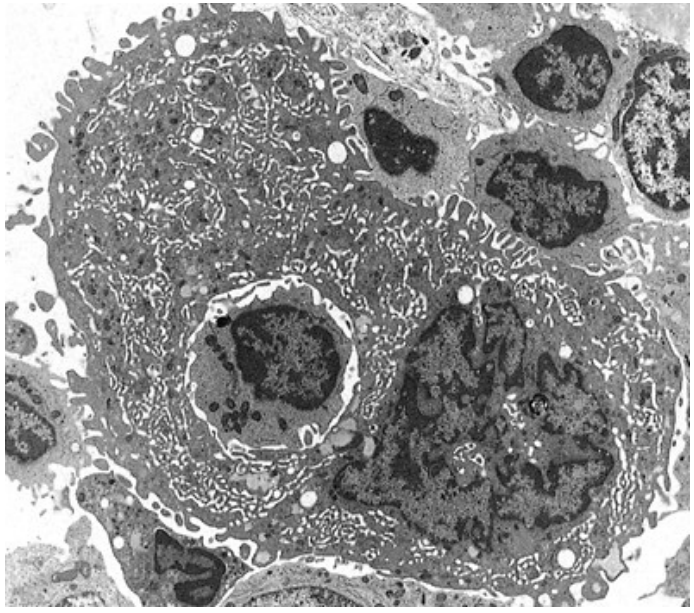


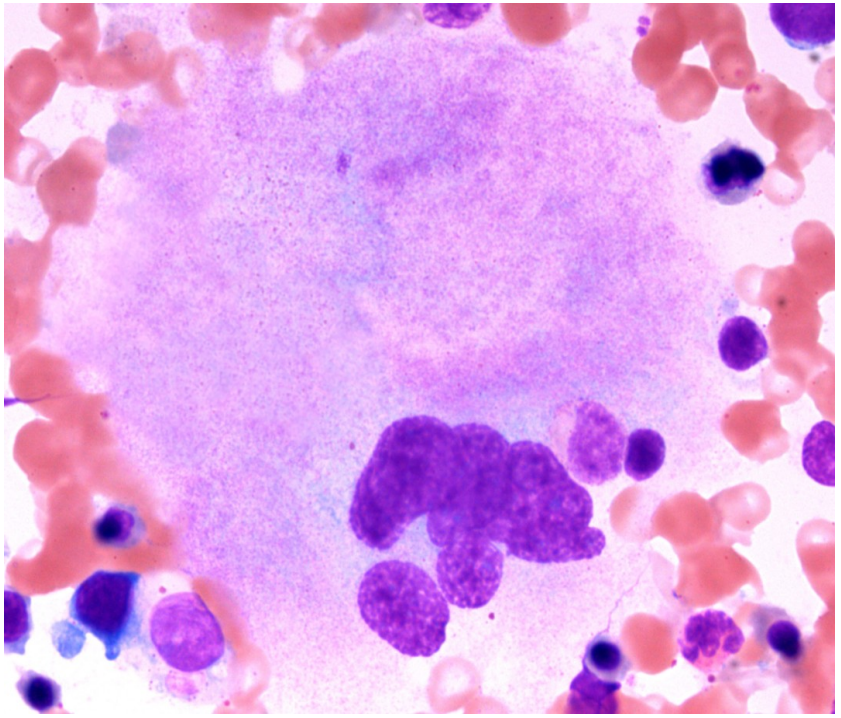


THROMBOPOIESIS

- **megakaryoblast** (up to 30 µm)
- large oval, nonlobed nucleus with prominent nucleoli
- basophilic cytoplasm
- successive endomitoses without karyokinesis and cytokinesis
- **promegakaryocyte** (up to 100 µm)
- large cell with polyploid nucleus (8n-64n)
- **megakaryocyte** (80-150 µm)
- polyploid, multilobed nucleus (8n-64n)
- azurophilic and platelet granules
- multiple centrioles, ER and Golgi apparatus
- numerous peripheral invaginations of plasma membrane – platelet demarcation channels defining individual thrombocytes
- release of **thrombocytes** into bone marrow sinusoids







MONOCYTOPOIESIS AND LYMPHOPOIESIS

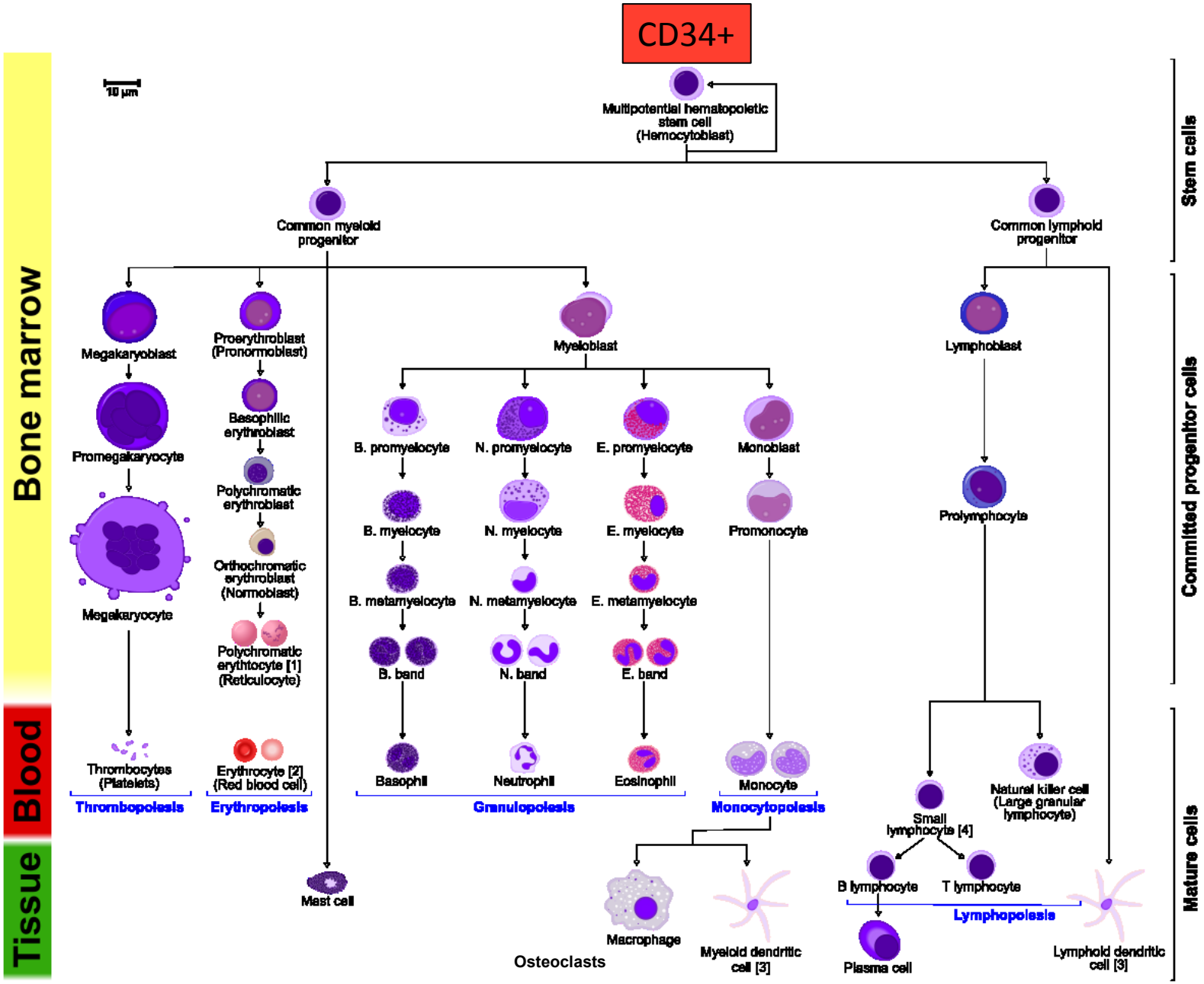
MONOCYTOPOIESIS

- **monoblast** (~16 µm)
  - round, bean shaped nucleus with 2-6 nucleoli
  - mildly basophilic cytoplasm
- **promonocyte** (~16-20 µm)
  - mitotically active (1-2 divisions)
  - large nucleus with mild indentation, unapparent nucleoli
  - basophilic cytoplasm
  - azurophilic granules
- **monocyte**
  - short-time in circulation, then extravasation and differentiation to tissue macrophages

LYMPHOPOIESIS

- **lymphoblast** (~18-20 µm)
  - round-oval nucleus with several nucleoli
  - mildly-basophilic cytoplasm without azurophilic granules
- **prolymphocyte** (~12-15 µm)
  - morphological transition and maturation to lymphocytes
- **lymphocyte**
  - further maturation and differentiation outside bone marrow

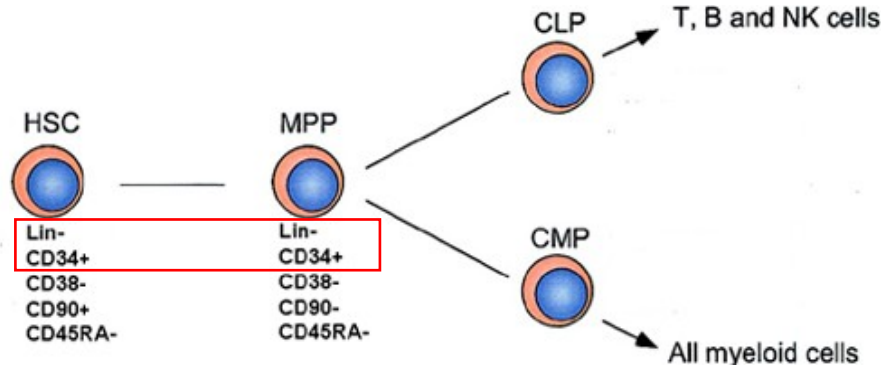
OVERVIEW OF ADULT HEMATOPOIESIS

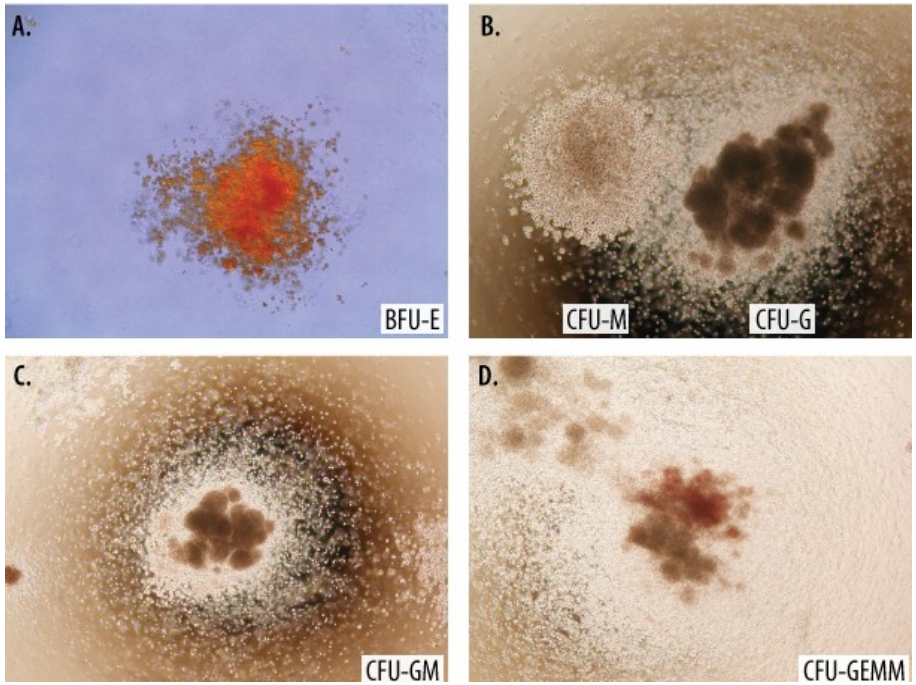


HEMATOPOIETIC STEM CELLS AND PROGENITORS

- **Hematopoietic stem cell**
- Quiescent, slow cell cyle
- Transmembrane phosphoglycoprotein $CD34^+$ - adhesion within niche
- No expression of lineage surface markers (Lineage negative or Lin^-)
- Transplantations

- **Colony/Burst – Forming Unit – CFU/BFU**
- Progenitors of individual lines
- Collonies in vitro





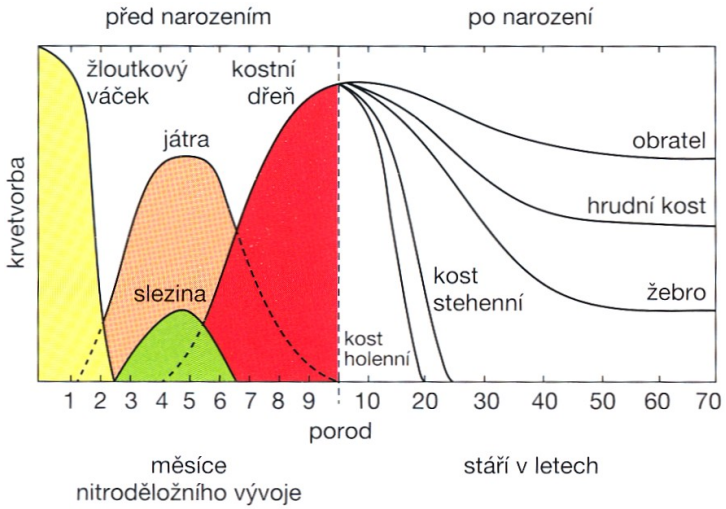
EMBRYONIC HEMATOPOIESIS

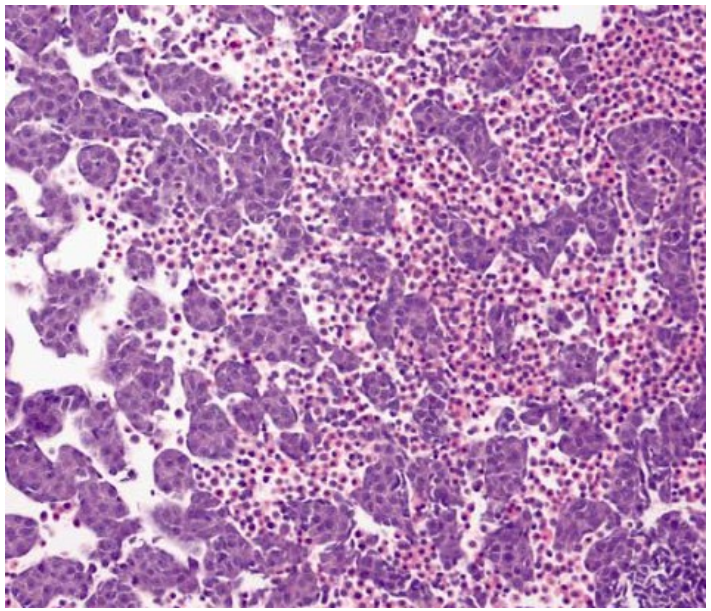
- **Extraembryonic mesoblastic period (day 16-20 – week 8)**
- yolk sac
- classical model – hemangioblasts (bipotent cells)
- large, nucleated erythroid cells

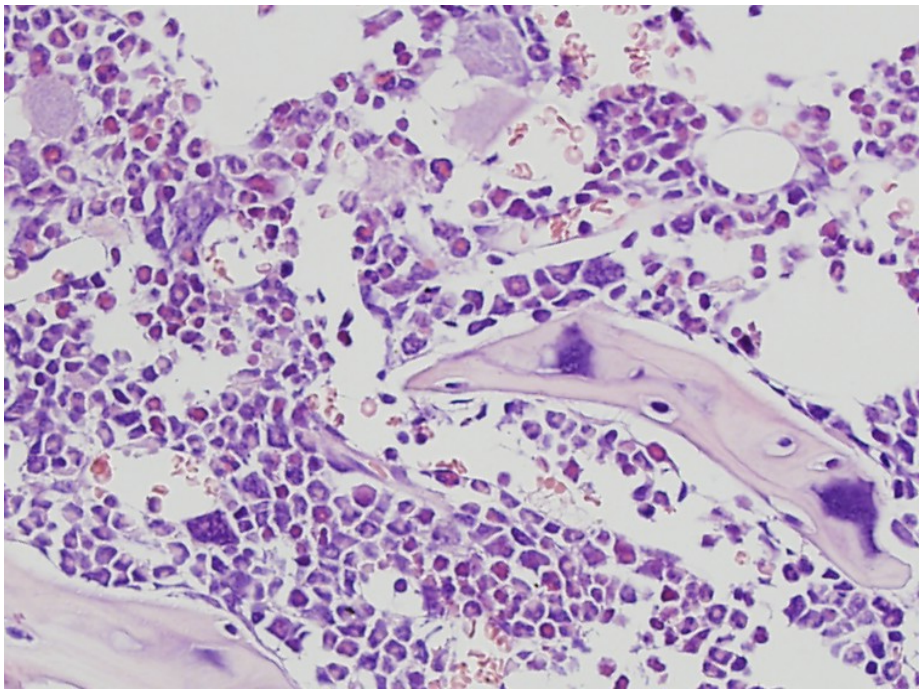
- **aorta-gonad-mesonephros (day 28 – week 4)**

- **hepatolienal period (month 1 – birth)**
- colonization of fetal liver and spleen

- **medullary period (month 4-6. – rest of life)**
- bone marrow

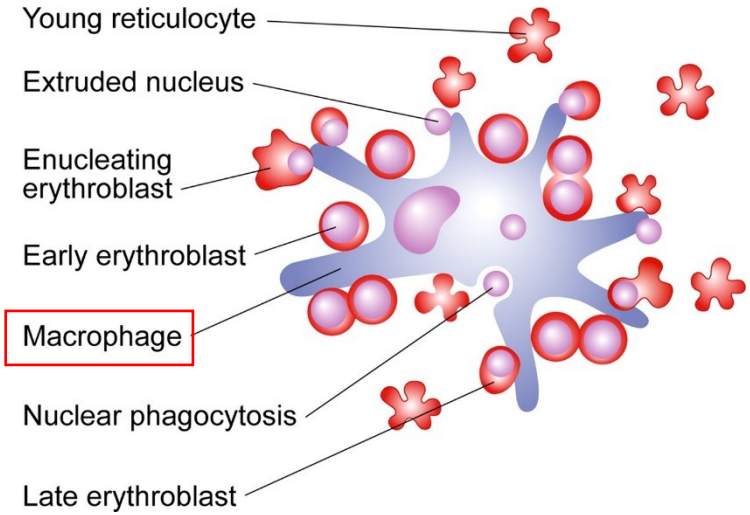


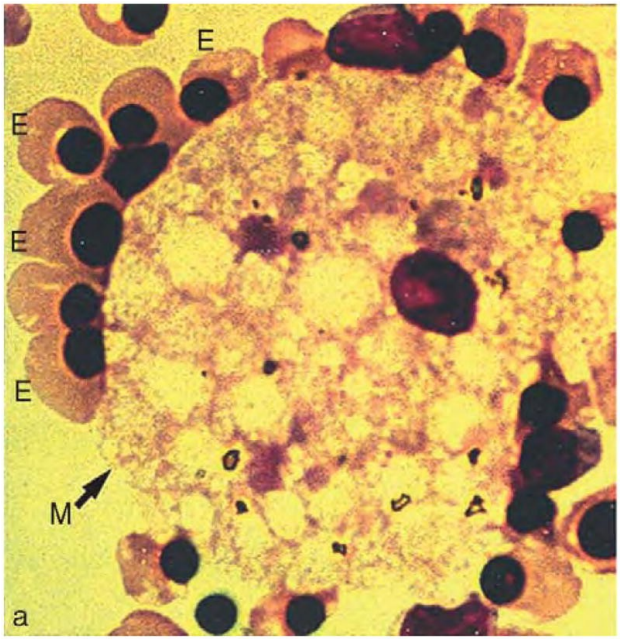




HEMATOPOIETIC ISLANDS

- **hepatolienal and bone marrow hematopoiesis**
- erythroblast islands





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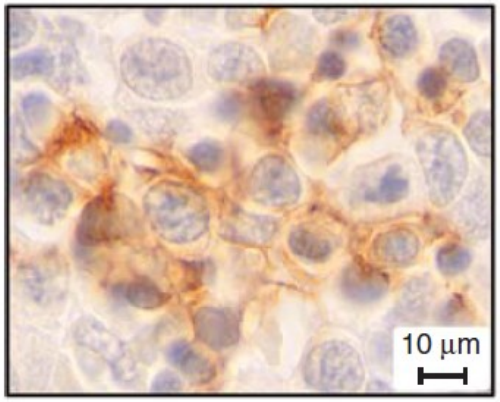

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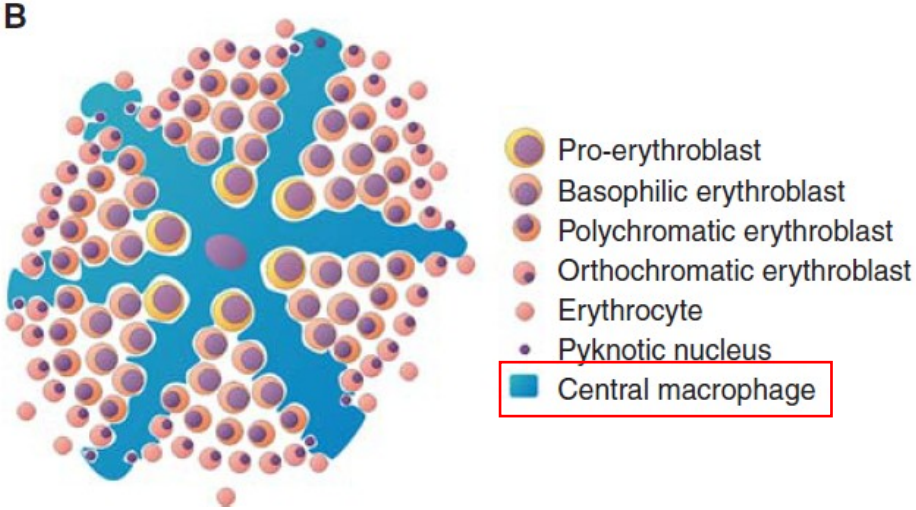
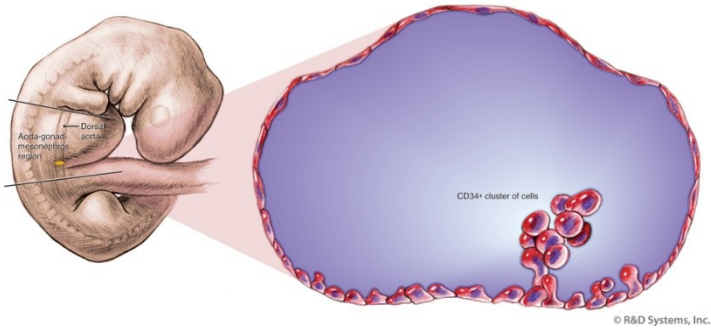
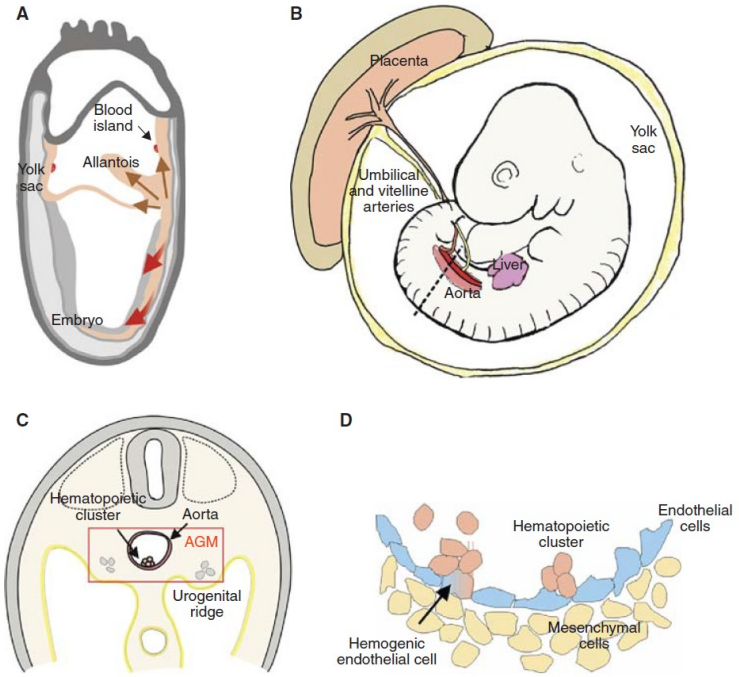


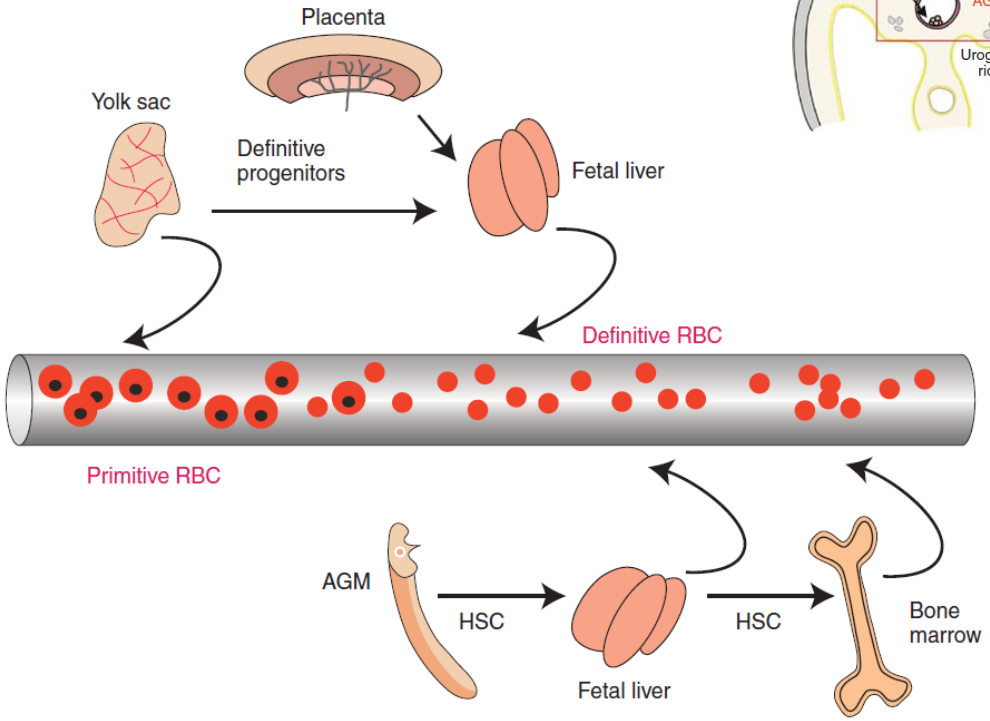
INTRAEMBRYONIC HEMATOPOIESIS

- **Aorta-gonad-mesonephros (day 28 – week 4)**
- para-aortic clusters in mesoderm of splanchnopleura
- source of embryonic HSCs





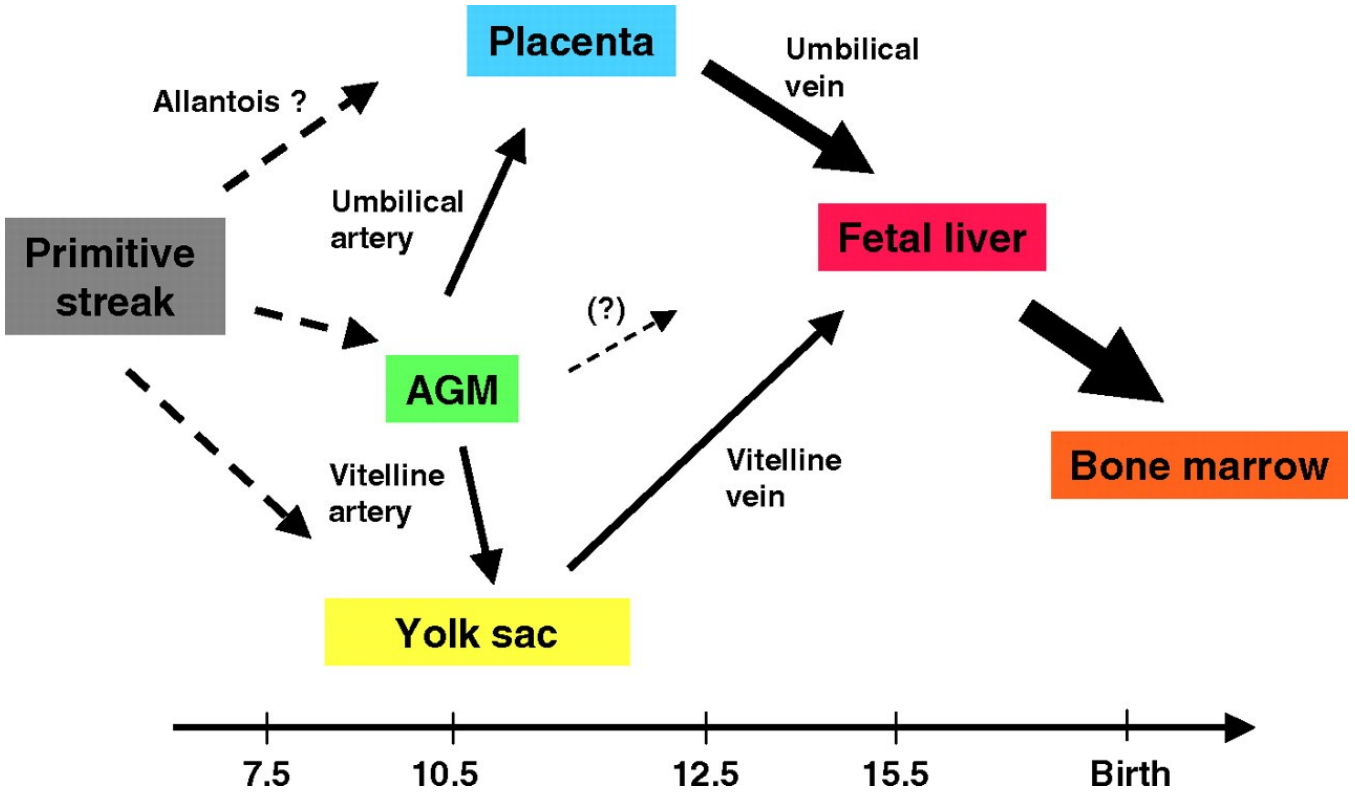
- **Placenta**



SUMMARY OF HEMATOPOIESIS

Embryonic

- yolk sac
- AGM
- liver and spleen
- bone marrow



Adult

- bone marrow (yellow, red)
- extramedullar hematopoiesis rare (pathology)

http://dev.biologists.org/content/133/19/3733

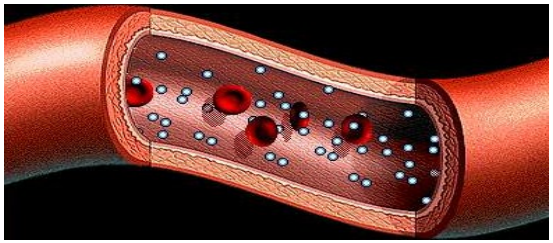
Cardiovascular system

- Overall concept of blood circulation
- Vessels
- Arteries
- Microcirculation
- Lymphatics
- Heart

Cardiovascular system
= part of circulatory system

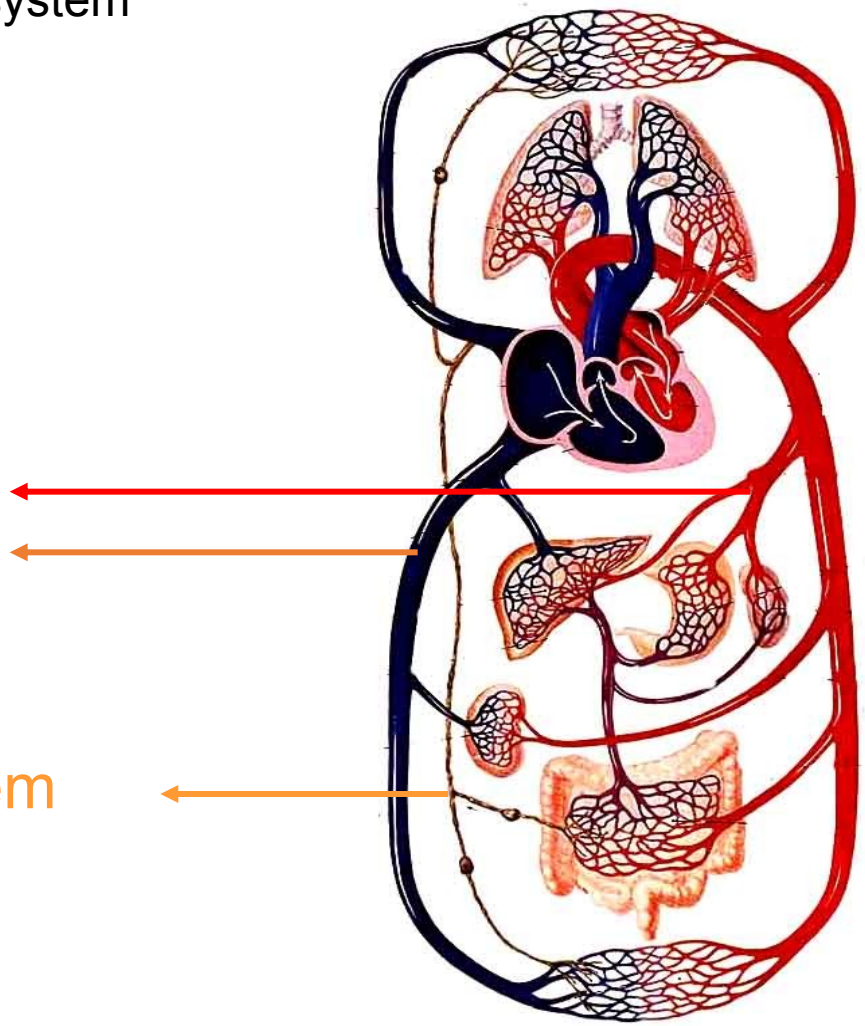
Circulatory s. = Closed tubular system

(carries fluids (blood, lymph) in tubes



Blood cardiovascular

Lymphatic vascular system

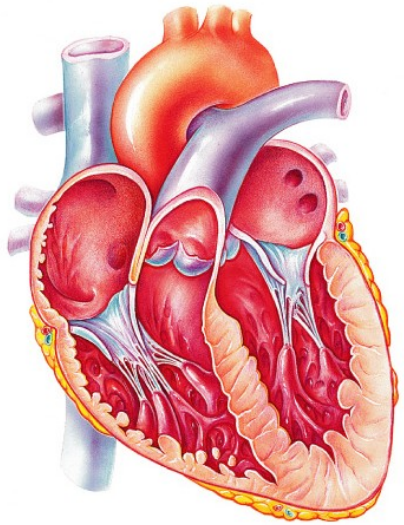


Cardiovascular system – overall composition

Heart

PUMP

- moves bloood with all its elemnents through the body



Blood vessels

TUBES

- distribute the blood to the cells throughout

Three major types

Arteries
- deliver blood from the heart to the capillaries

Capillaries
- intimate with body cells – place of exchange between blood

Blood vessels – several different flavours

Veins

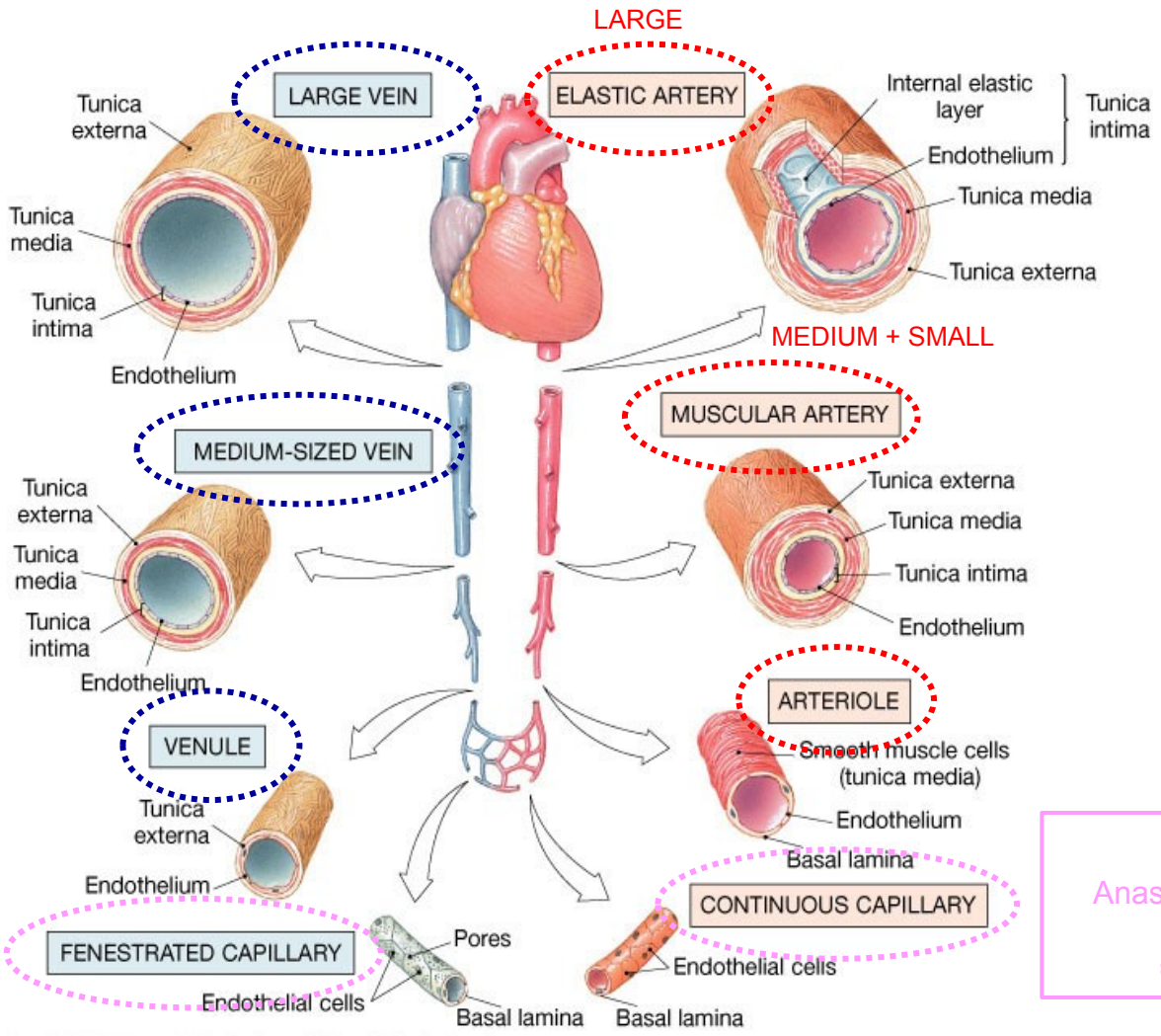
ALWAYS return the blood to the heart
(contain about 2/3 body's blood at any given time)

Arteries

ALWAYS carry blood from the heart to the periphery

Macrovasculature – diameter >0.1 mm

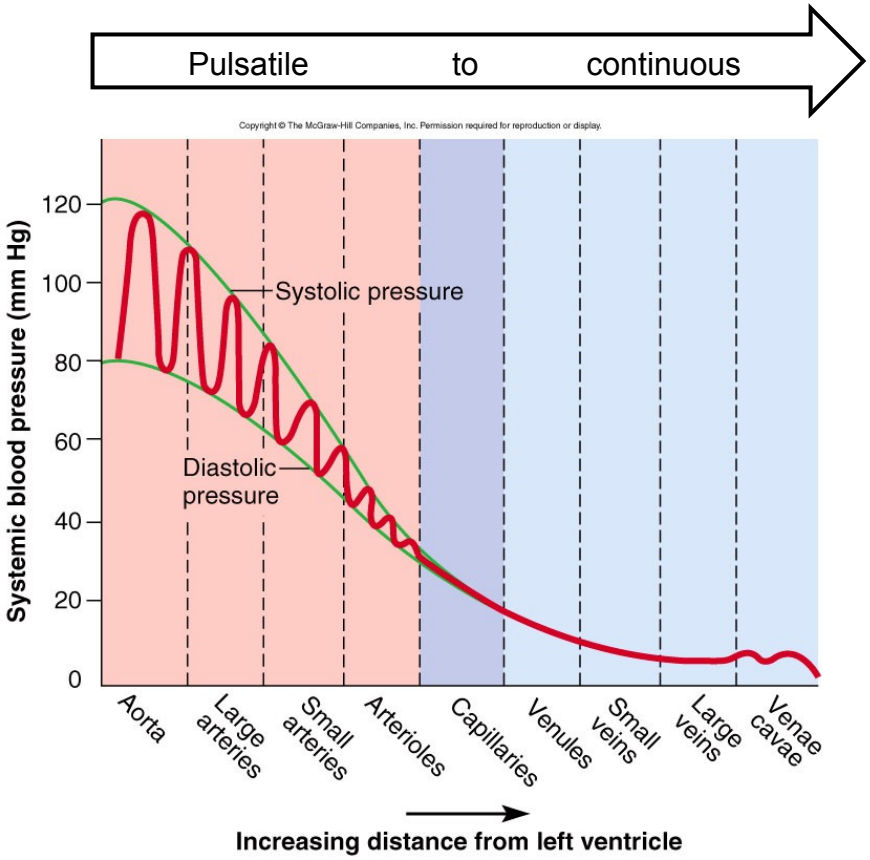
Microvasculature – <0.1 mm



Capillaries

Anastomosing tubules among arteries and veins
= microvascular bed

Blood vessels – flow of blood



Due to specific morphologies of the vessels

Vessel type	Diameter (mm)	Blood velocity (mm/sec)
Aorta	25	1 200 (systolic)
Arterioles	0.02-0.05	15
Capillaries	0.005-0.009	0.4
Venules	0.02	5
Inferior vena cava	30	80

For example

At ventricular diastole:
- the semilunar valves are closed
- no blood enters the arteries
- the blood moves forward due to the action of arteries

…reflected by uneven distribution of blood

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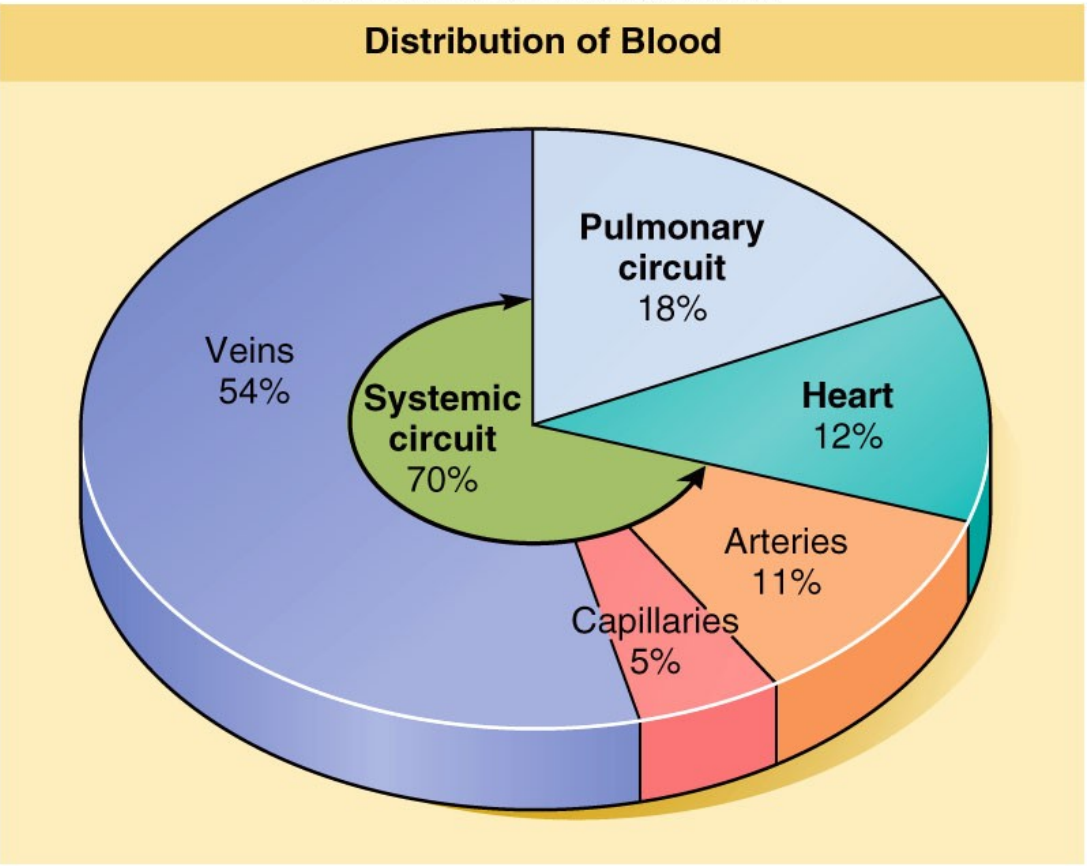


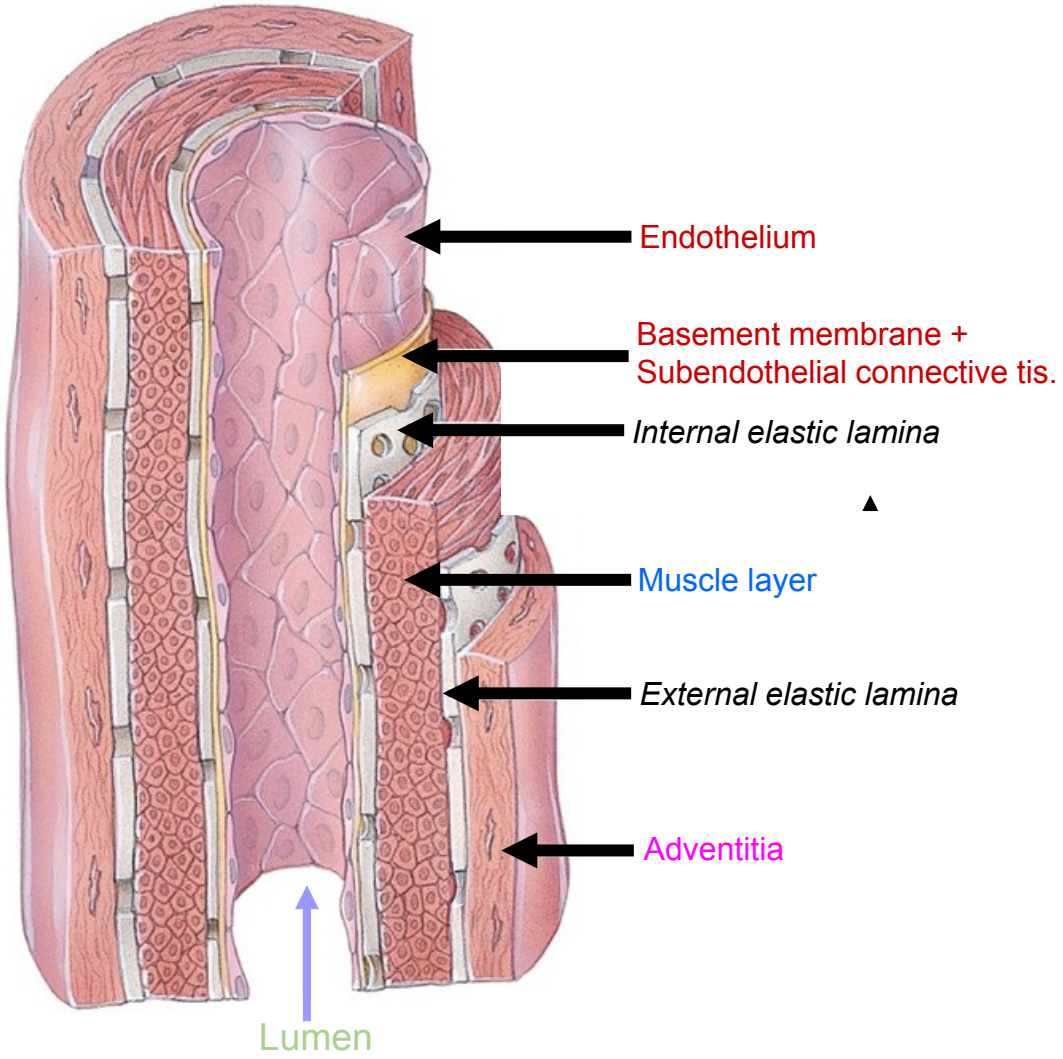
65 – 70% in veins

- Reservoir
- Lumens are larger than in corresponding arterie

Capillaries

~ 100 thousand km (estimate)
&
only 5% of blood volume
&
largest surface area (~ 600 m^2)
&
most of the cells are no farther than 50 μm from a capillary.

Blood vessels – common building plan
(three-layered)



Tunica intima

Endothelial cells:
- polygonal, squamous, elongated
- covered by negatively charged glycocalyx (0.5 μm)
- provide repellent surface for cell elements
- glycocalyx - binding site for various regulators
- regulate permeability
- secrete regulators (e.g. interleukins,

Tunica media

- mainly smooth muscle (circularly arranged in layers)
- collagen and elastic fibers (lamelae), reticular fibers
- proteoglycans
- strenghten the vessels
- provide vasomotion

Tunica externa

- connective tissue (collagen 1 + elastin)
- home for vasa vasorum and nerve fibers
- continuos with stroma of the surrounding tissues

Arteries

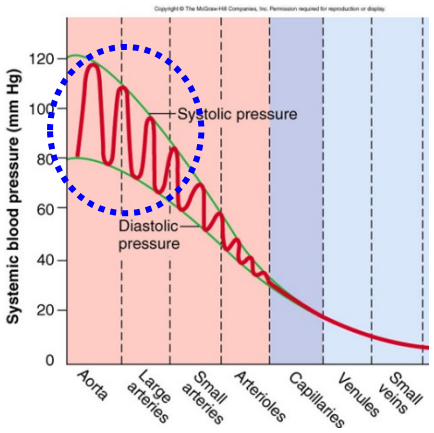
Several categories accoriding to their: size + structure + function

Large = conducting = elastic artery
(*aorta, common carotid, sabclavian a., common iliac a., pulmonary trunk*)

Medium-sized = distributing = muscular artery (D > 1 mm)
(*brachial, ulnar, femoral, renal, …*)

Small artery (D = 0.1 -1 mm)

Arteriole (D < 0.1 mm)



Large = elastic = conducting arteries

Conducting

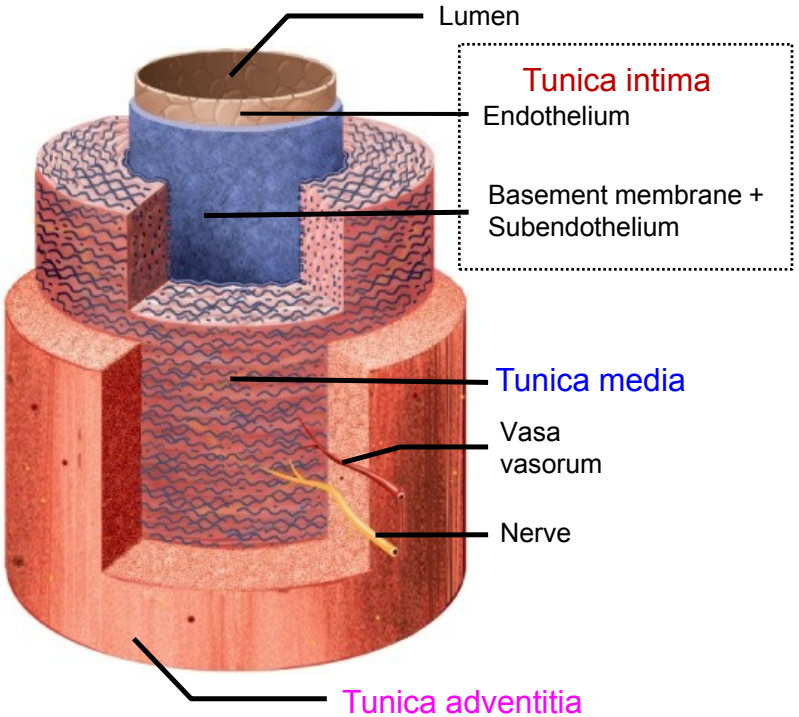
- their major function is to transport blood away from the heart

Elastic

- they absorb and store the contractile energy of the left ventricle and transform the pulsatile flow of blood in smooth out
- during ventricular contraction (systole), the elastic laminae of conducting arteries are stretched and reduce the pressure change
- during ventricular relaxation (diastole) ventricular pressure drops to a low level but the elastic rebound of conducting arteries helps to maintain arterial pressure
- as a consequence, arterial pressure and blood flow decrease and become less variable as the distance from the heart increases

Large = elastic = conducting arteries

Relatively thin wall as compared to their wide lumen (1/10 of the vessel diameter).



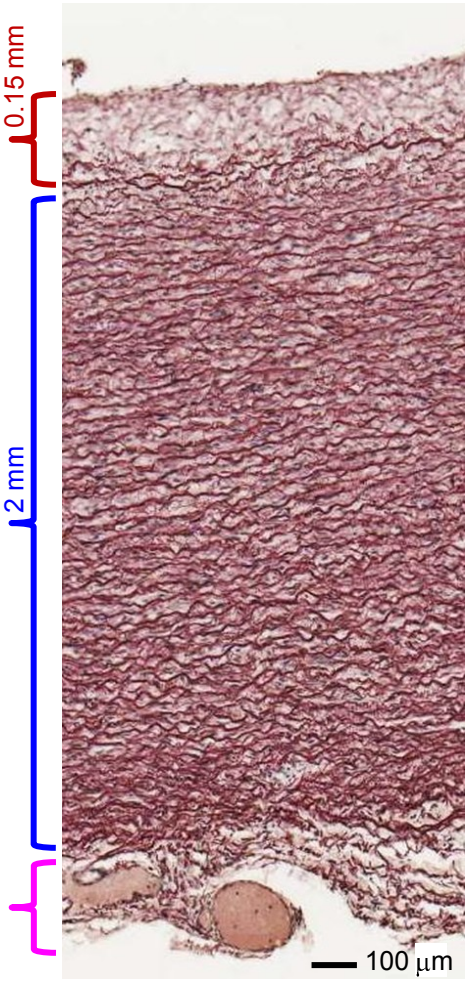
Endothelium
- elongated cells - along the long axis

Subendothelial layer
- loose connective tissue
- contains many fine longitudinal elastic fibres - these gradually merge into the elastic components of t. media
- some smooth muscle cells near the boundary with t. media - longitudinally arranged
- place of atherosclerotic changes

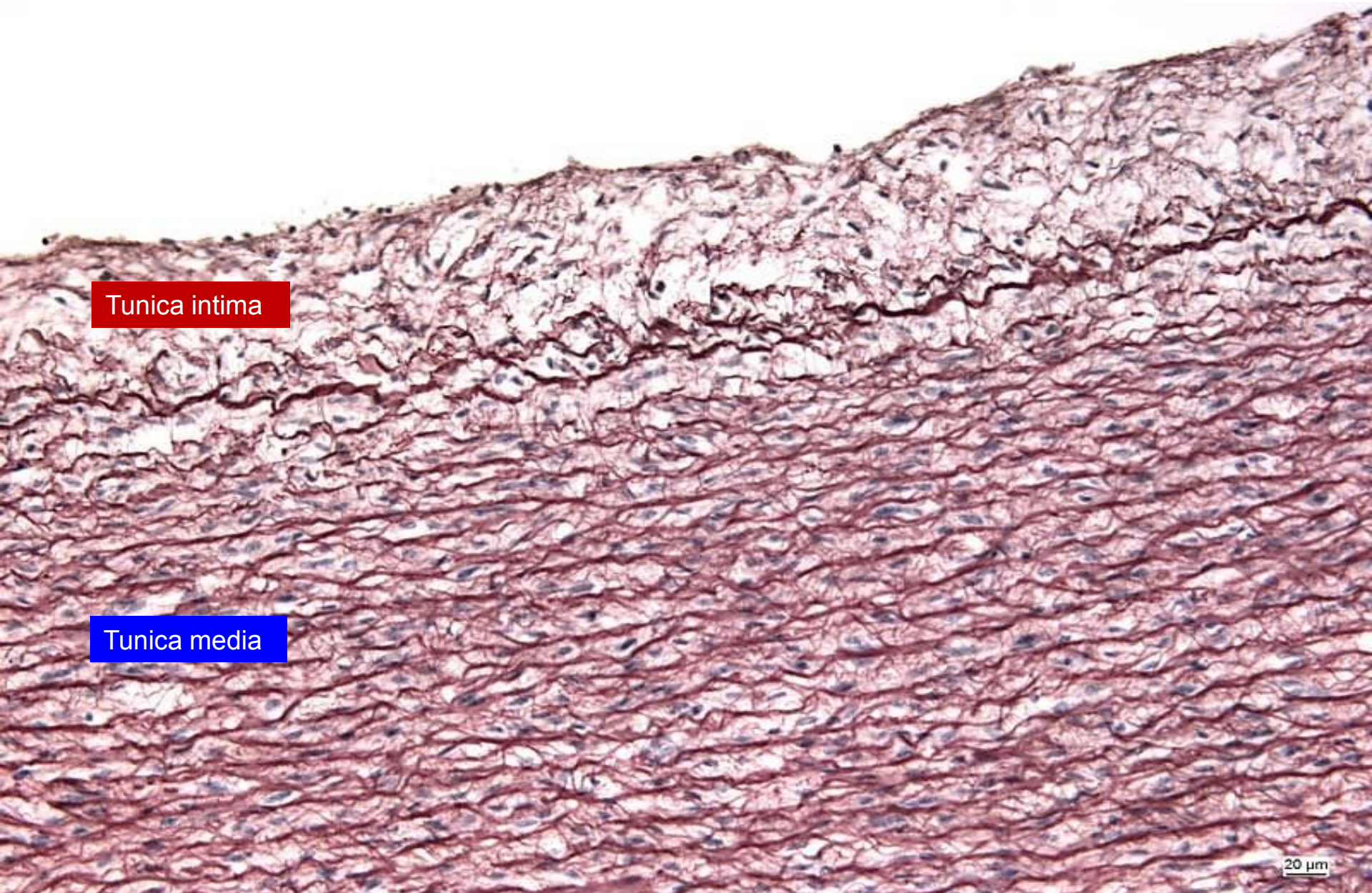
Internal elastic lamina
- not clearly demarcated

- elastic fibers arranged circularly as discontinuous fenestrated membranes about 2.5 μm thick - about 50 lamellae
- smooth muscle cells - circularly oriented, interspersed between elastic membranes

- relatively thin
- loose connective tissue
- some elastic fibers – longitudinally arranged, next to the t. media
- vasa vasorum and lyphatics (some into t. media)
- nerves

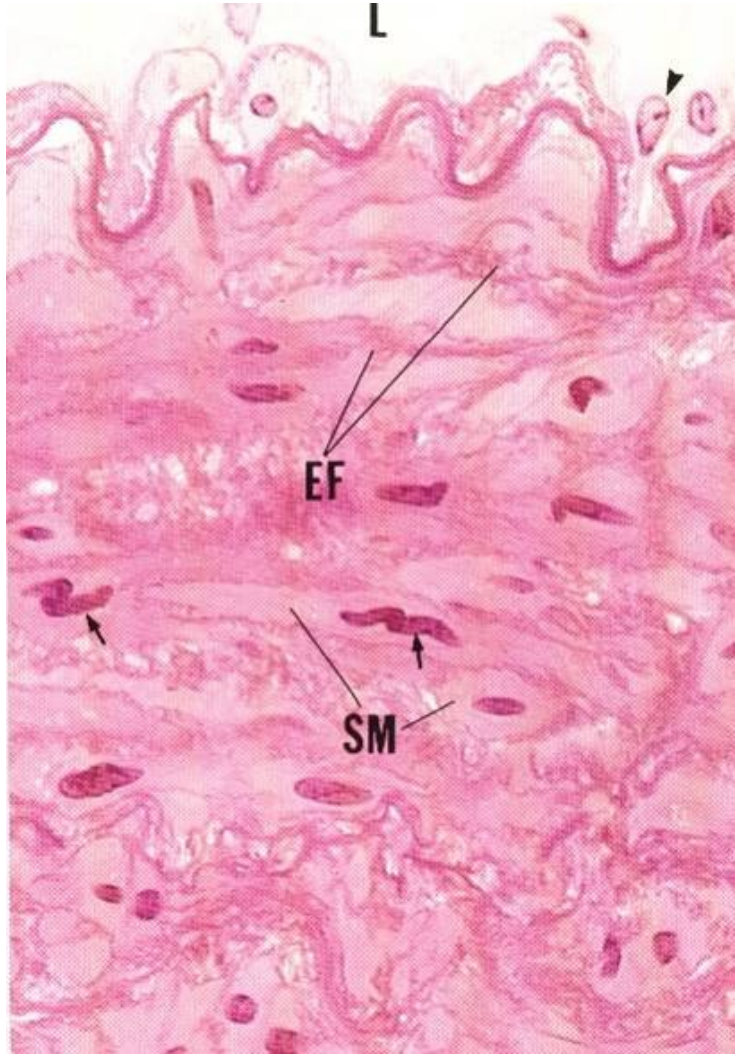


Large = elastic = conducting arteries



Large = elastic = conducting arteries

Monkey
H & E
x540



Tunica intima

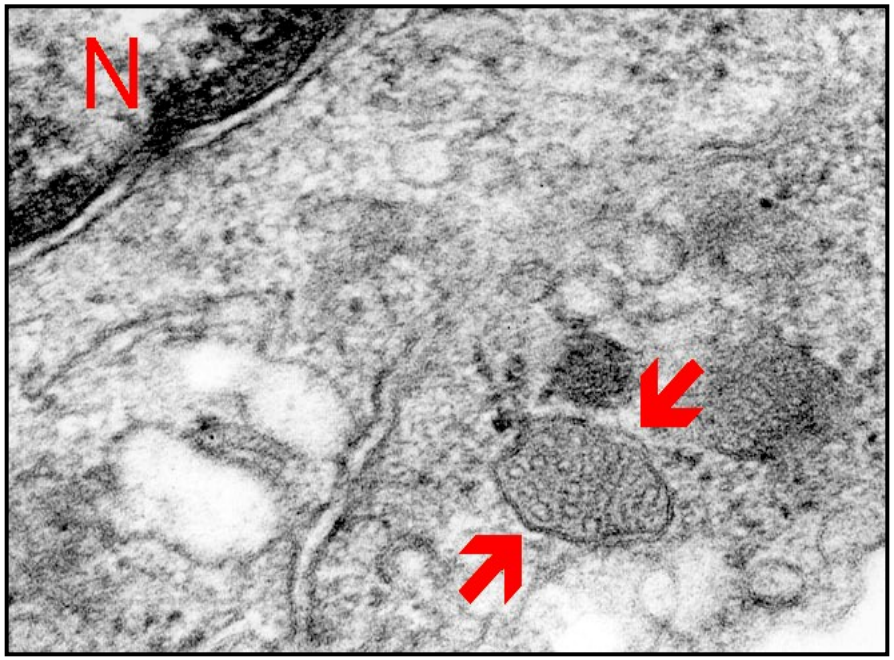
Tunica media

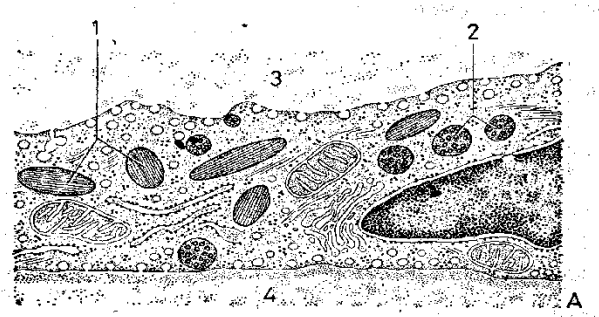
transition

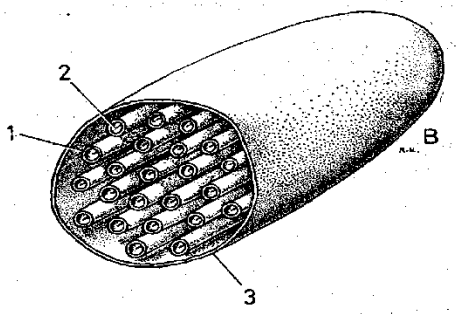
Artery - Endothelium

Weibel-Palade bodies

- organelles that are unique to endothelial cells
- contain von Willebrand factor (activates coagulation factor VIII) + P-selectin







Arteries - Atherosclerotic changes

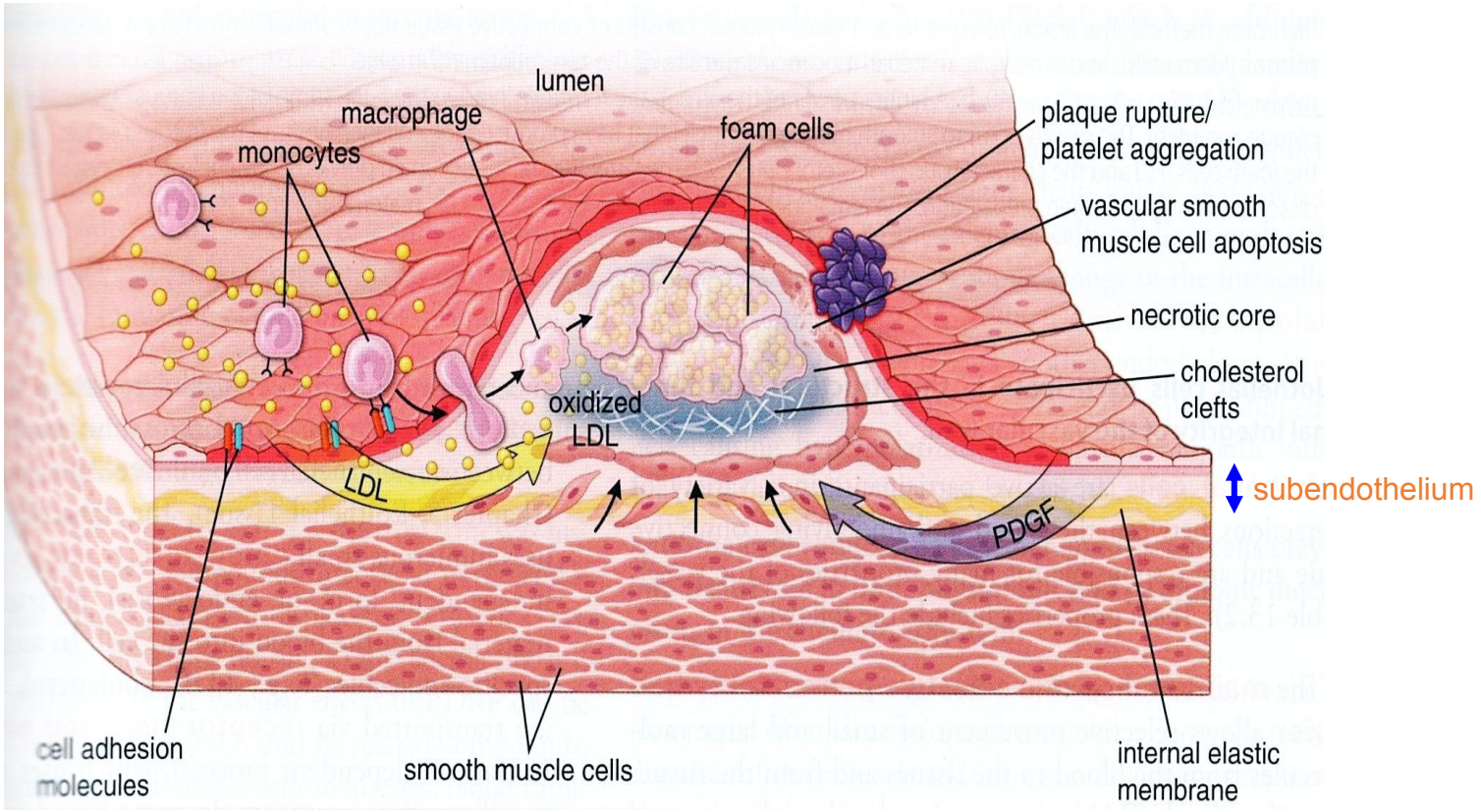
Endothelial injury
(upon predispozing factors)

→ Production of ROS

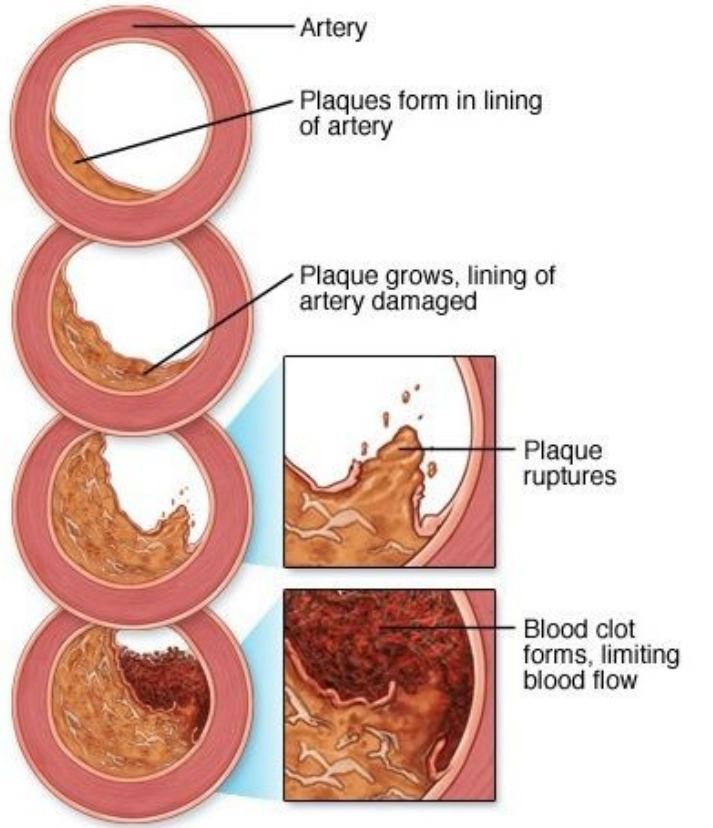
→ Oxidizing of LDL

→ Entry of monocytes
(conversion to foam cells)

→ Plaque formation
(necrosis + lipid accumulation)



Arteries - Atherosclerotic changes



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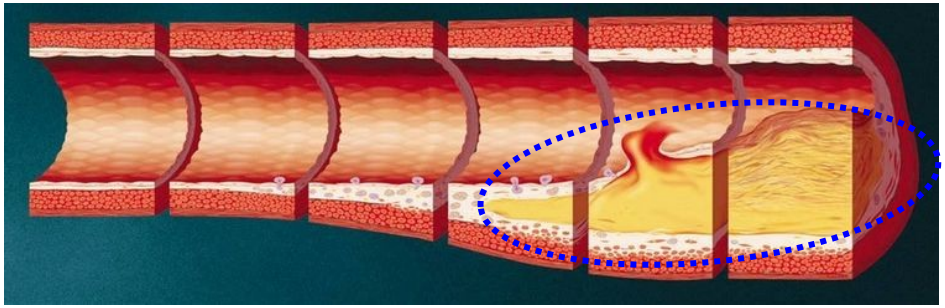
Artery clogging



Atheromatous plaque

Muscular arteries = distributing arteries

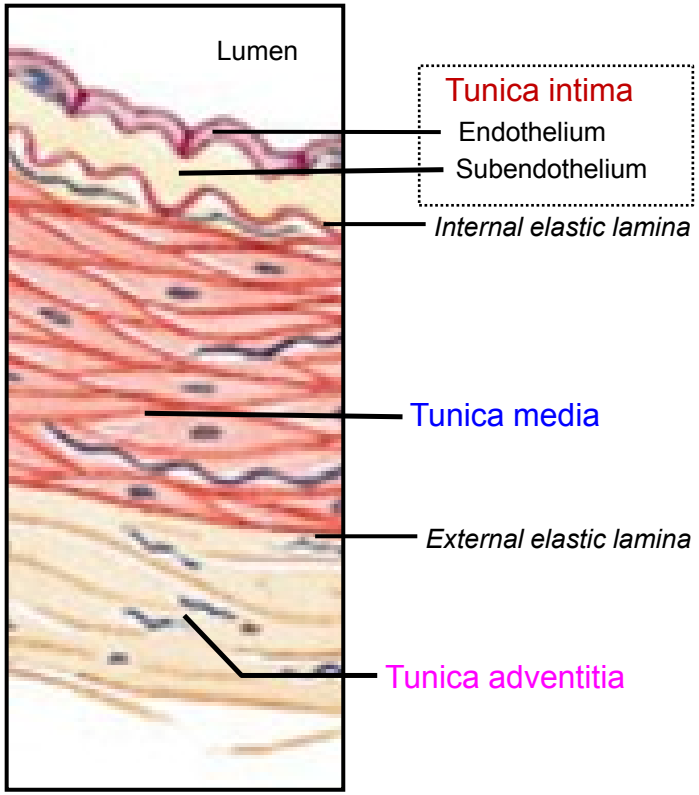
Distributing

- distribute blood to specific destinations/organs
- size varies from centimeter down to just visibility by unaided eye

Muscular

- they regulate the perfusion of different parts of the body under physiological conditions

Muscle arteries = distributing arteries



Muscular artery

Endothelium
- elongated cells along the long axis
- well developed adhesion, tight, and gap junctions
- Glycocalyx

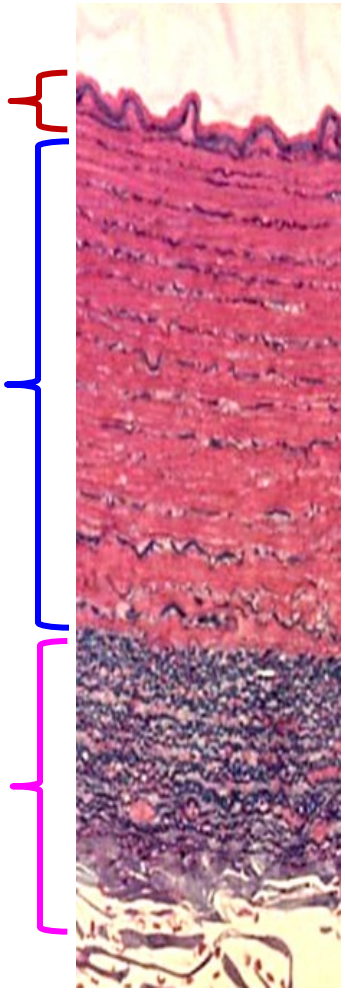
Subendothelial layer
- thickness increases with age
- loose connective tissue
- many fine longitudinal elastic fibres
- some smooth muscle cells

Internal elastic lamina
- well developed

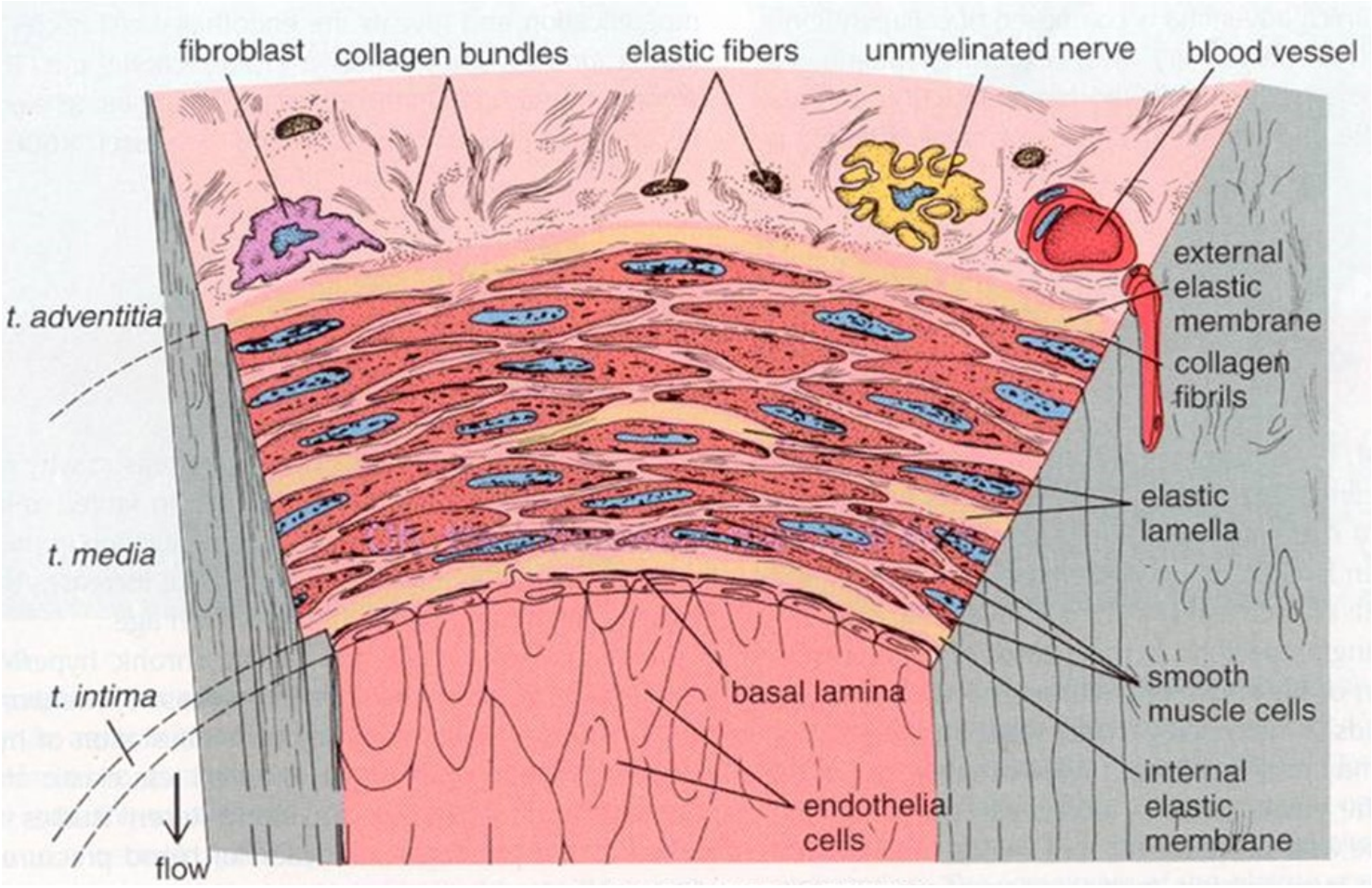
- very thick
- concentrically arranged smooth muscle cells
- up to 50 layers of smc
- ECM with elastic, collagen and reticular fibers
- GAP junctions between smc (coordination)

External elastic lamina
- well demarkated only in large caliber arteries

- relatively thíck (~ ½ of the tunica media)
- collagen and elastic fibers
- some fibroblasts and adipocytes
- vasa vasorum and lyphatics (some into t. media)
- nerves – efferent – maximal in small caliber arteries

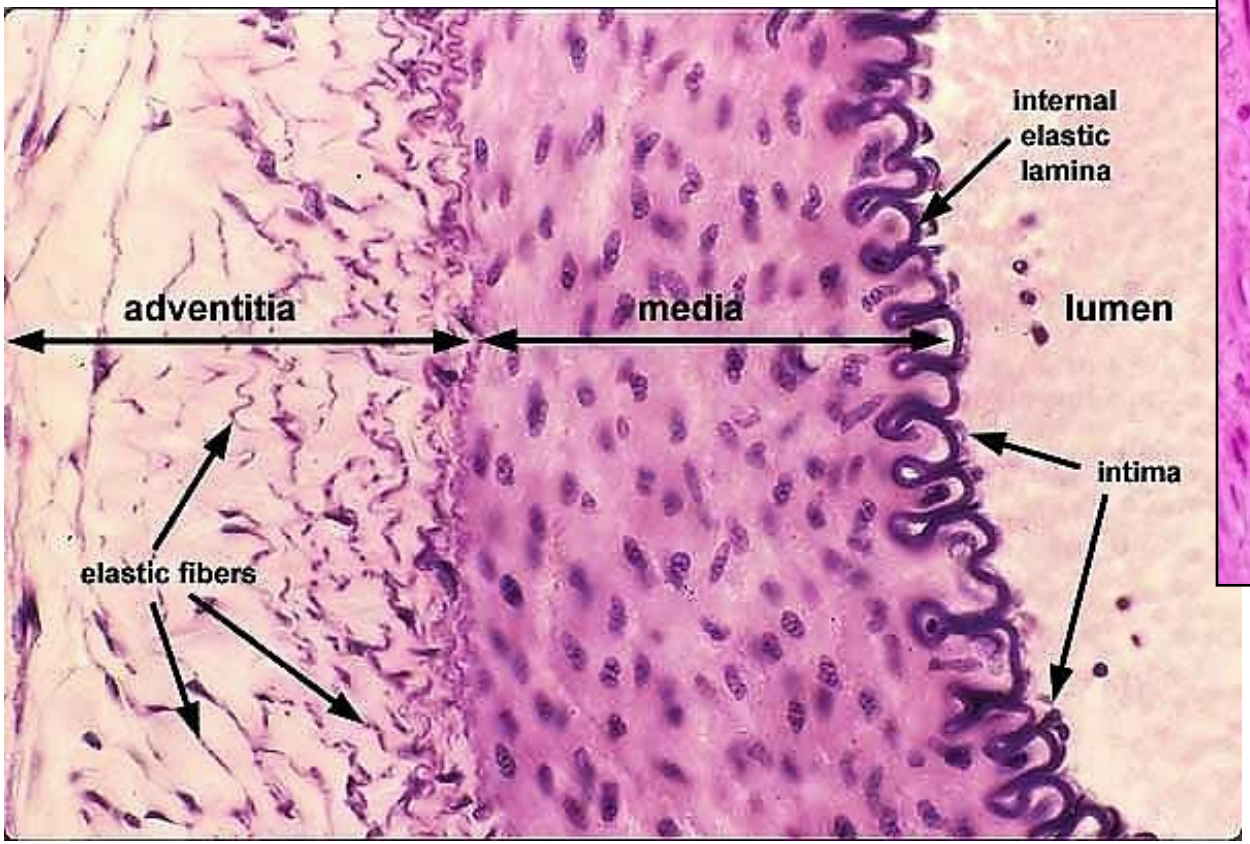


Muscular arteries = distributing arteries

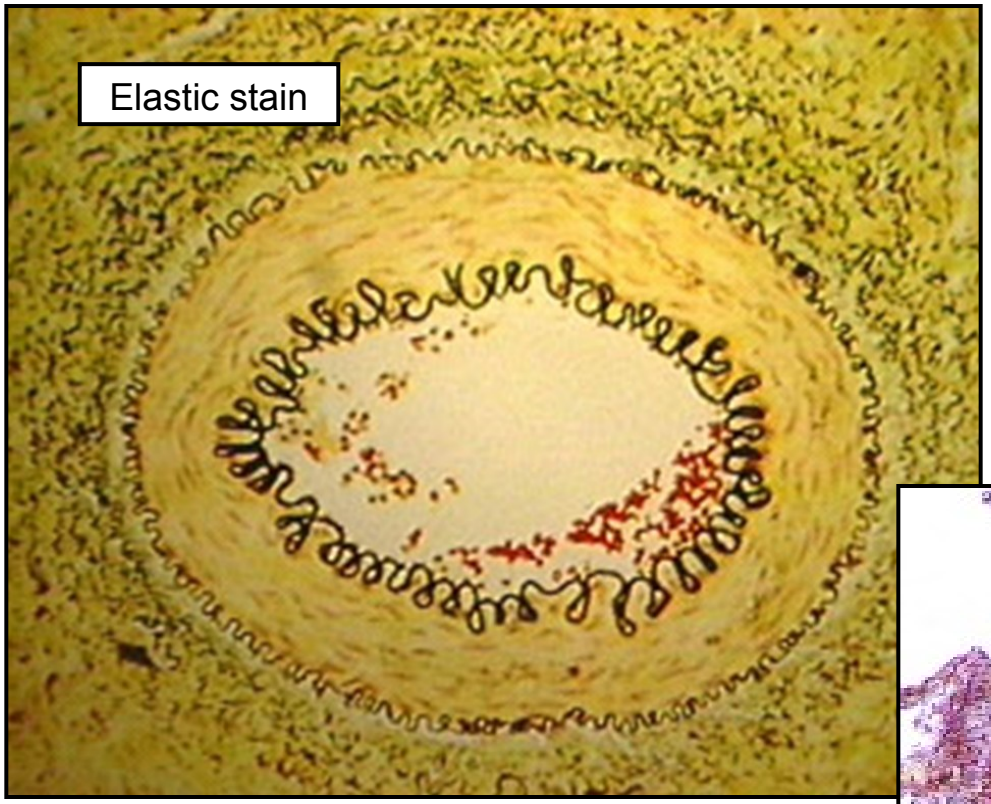


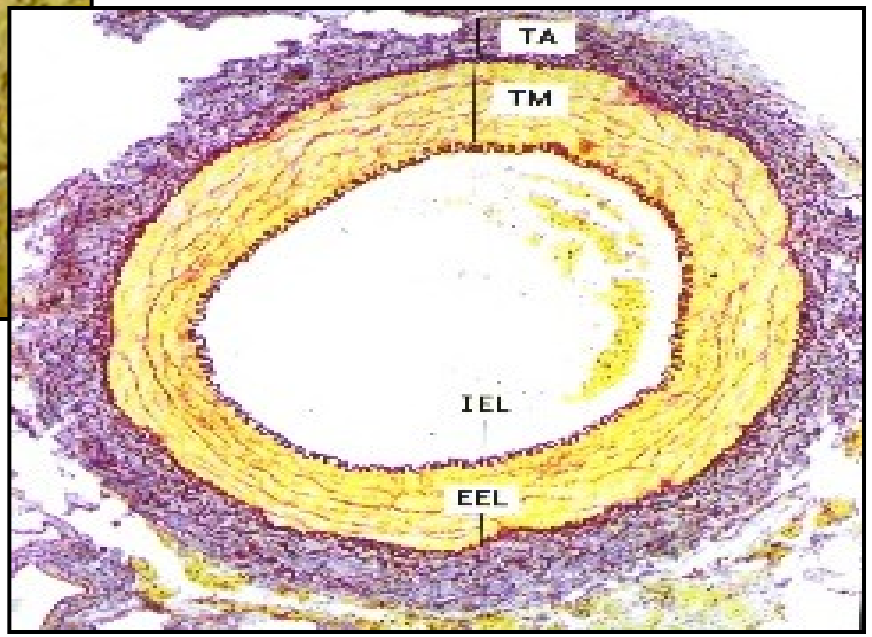
Muscle arteries = distributing arteries

Undulation - Artefact
(due to postmortem contraction of smooth muscle cells)



Muscle arteries = distributing arteries



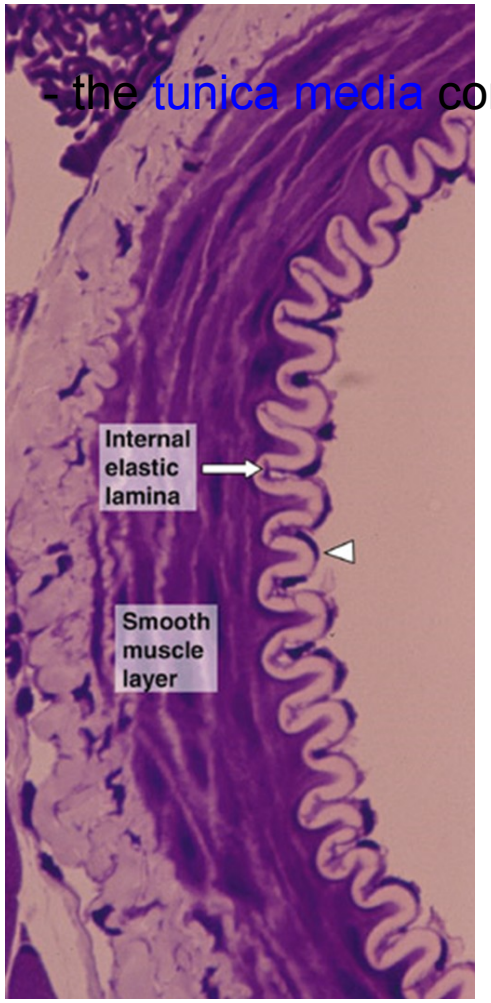


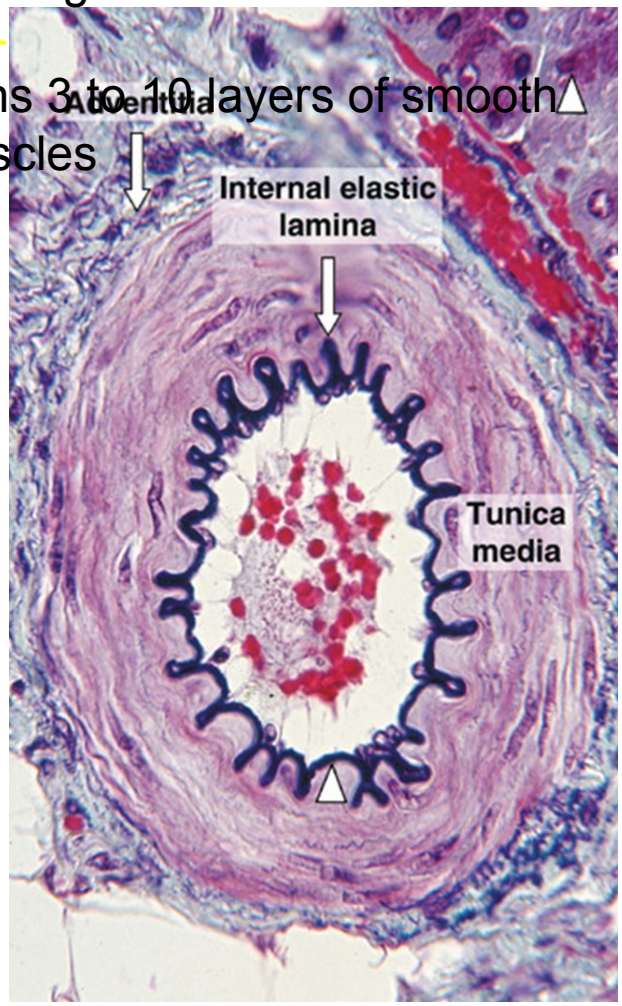
Muscle arteries = distributing arteries – *small sized*

- peripheral resistance vessel (along with arterioles)

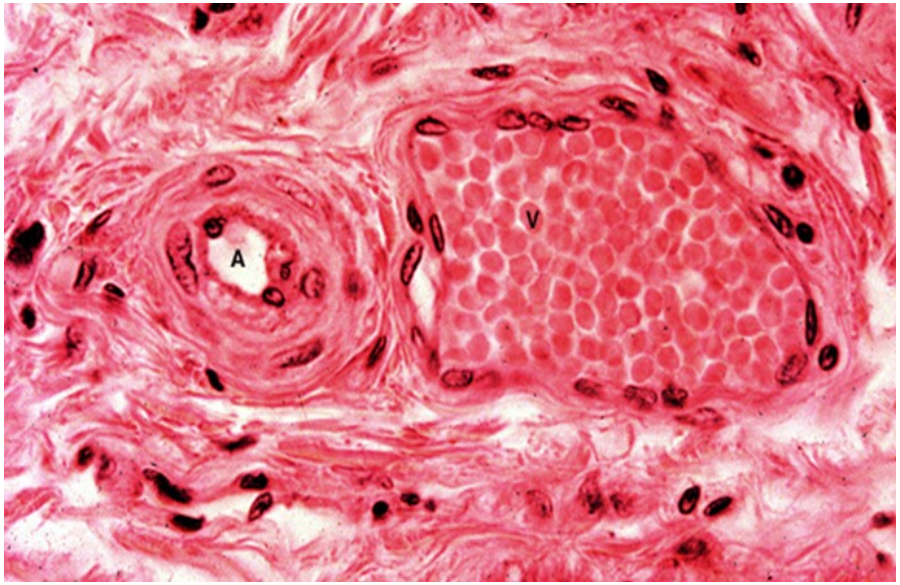
- *internal elastic lamina* is clear x *external elastic lamina* is not distinguished

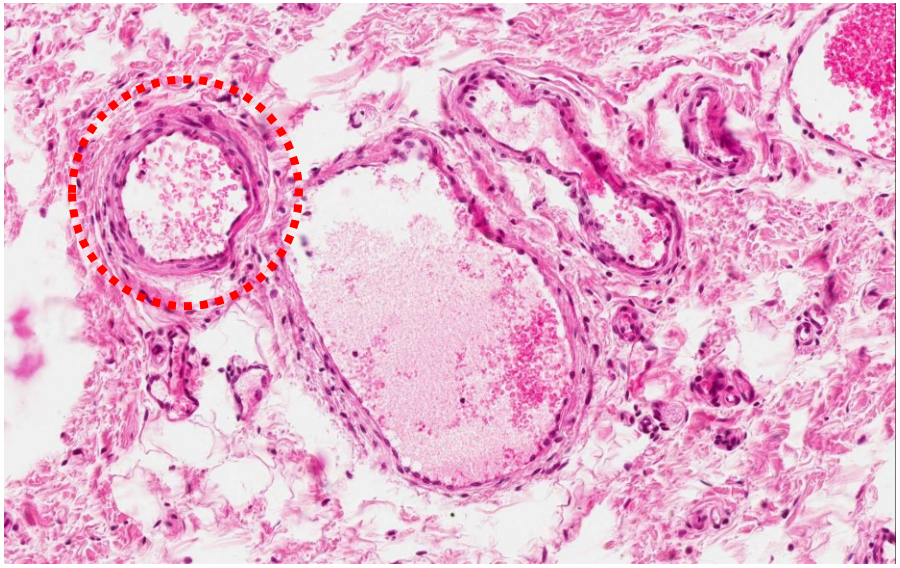
- the tunica media contains 3 to 10 layers of smooth muscles

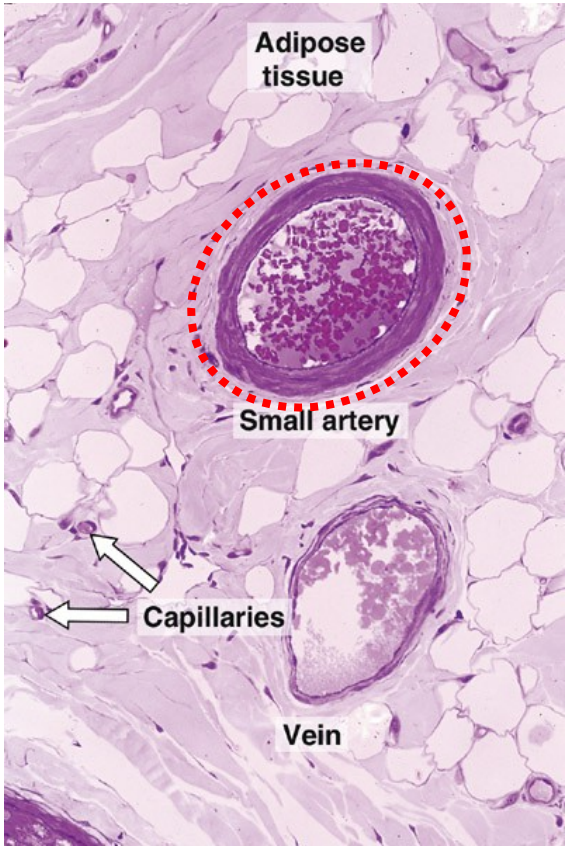




Muscle arteries = distributing arteries – *small sized*



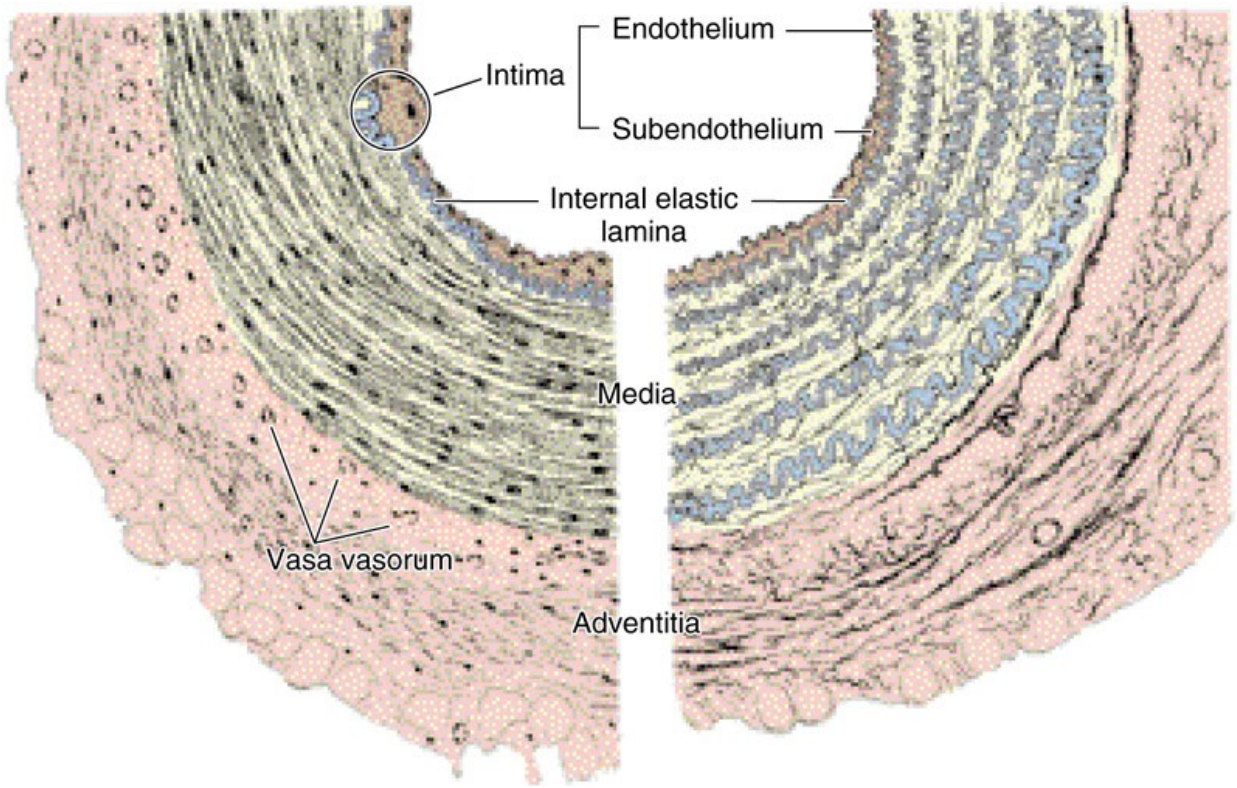




Muscle arteries x Elastic arteries

Smooth muscle cells predominate in their media

Elastic elements predominate in their walls



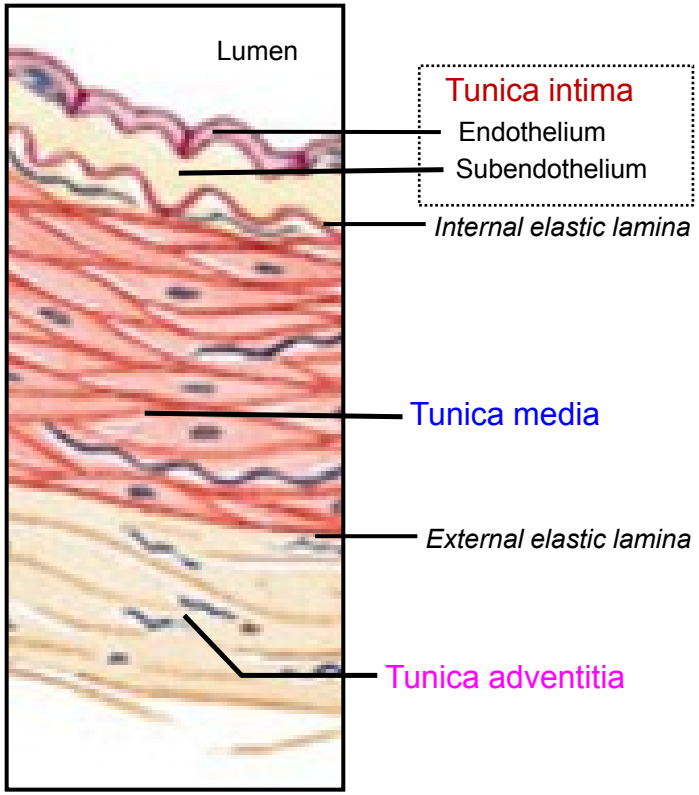
Arterioles

- peripheral resistance vessel (along with small-sized arteries)

- part of the microcirculation (terminal circulation)

- internal diameter < 0.1 mm

- they regulate the flow of blood through capillary bed



Muscular artery

Endothelium
- elongated cells along the long axis

Subendothelial layer
- non-developed

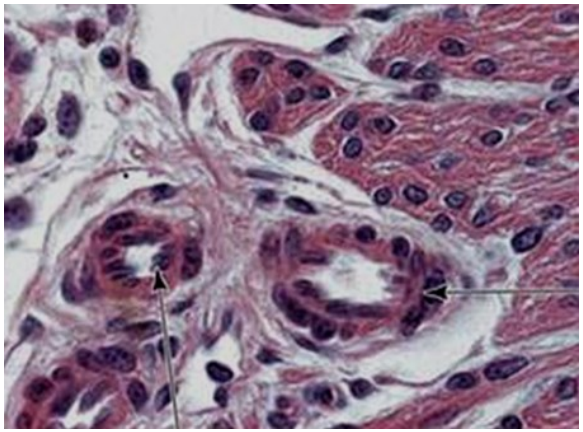
Internal elastic lamina
- non-developed

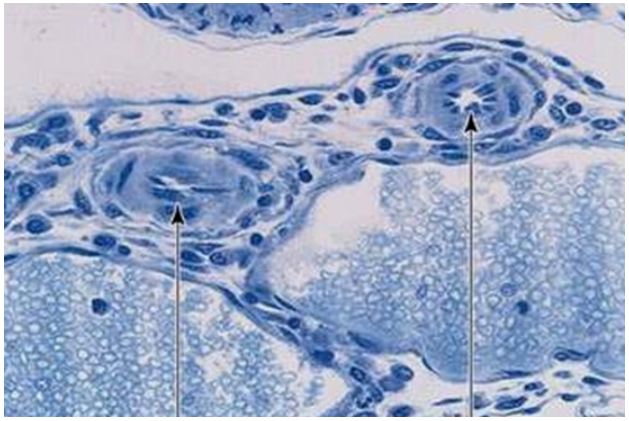
- thin (still the major part of the wall)
- 1 to 2 layers of smooth muscle cells

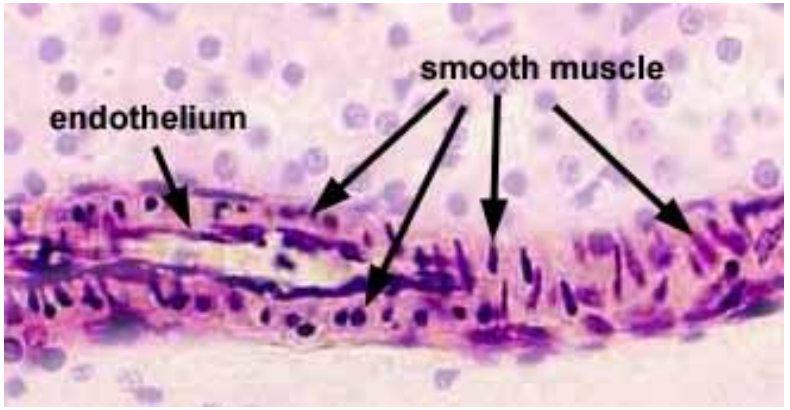
External elastic lamina
- non-developed

- reduced to only sheeth of collagen fibers
- NO vasa vasorum

Arterioles





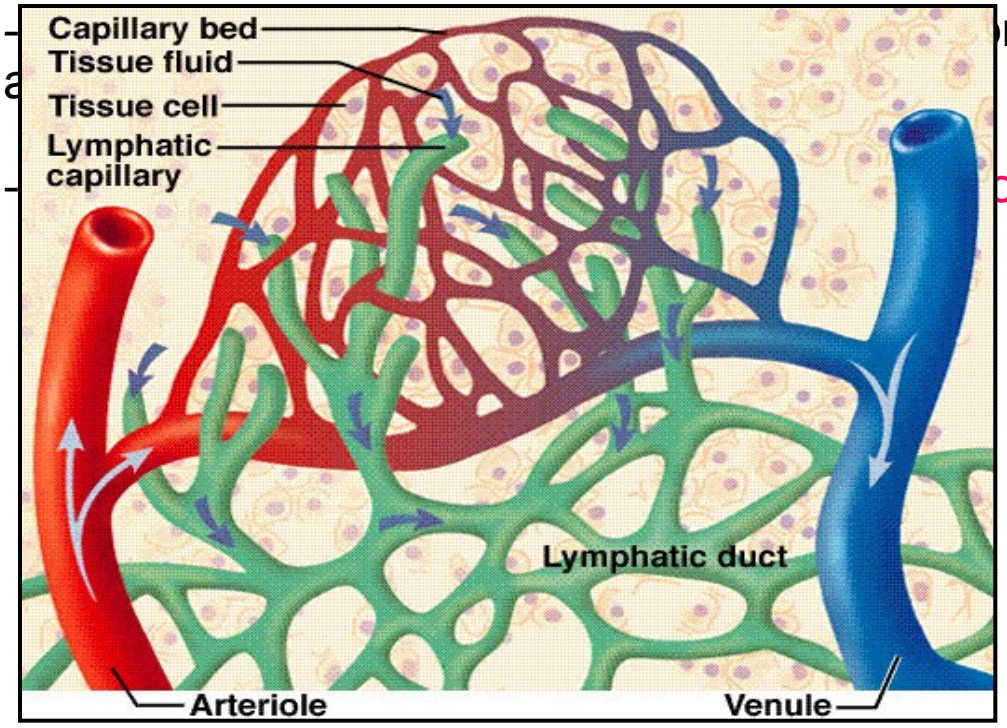


Capillaries

- are the site where materials carried in the blood are unloaded and other materials are loaded into the blood

- are the thinnest, simplest, largest, longest, and most widely distributed functional unit of the blood vascular system

- are inserted between arterial and venous limbs of the circulation



The total length of all the capillaries of the human body =

about 100 000 km

The total cross-sectional area of capillaries =

about 800 x

greater than of the aorta

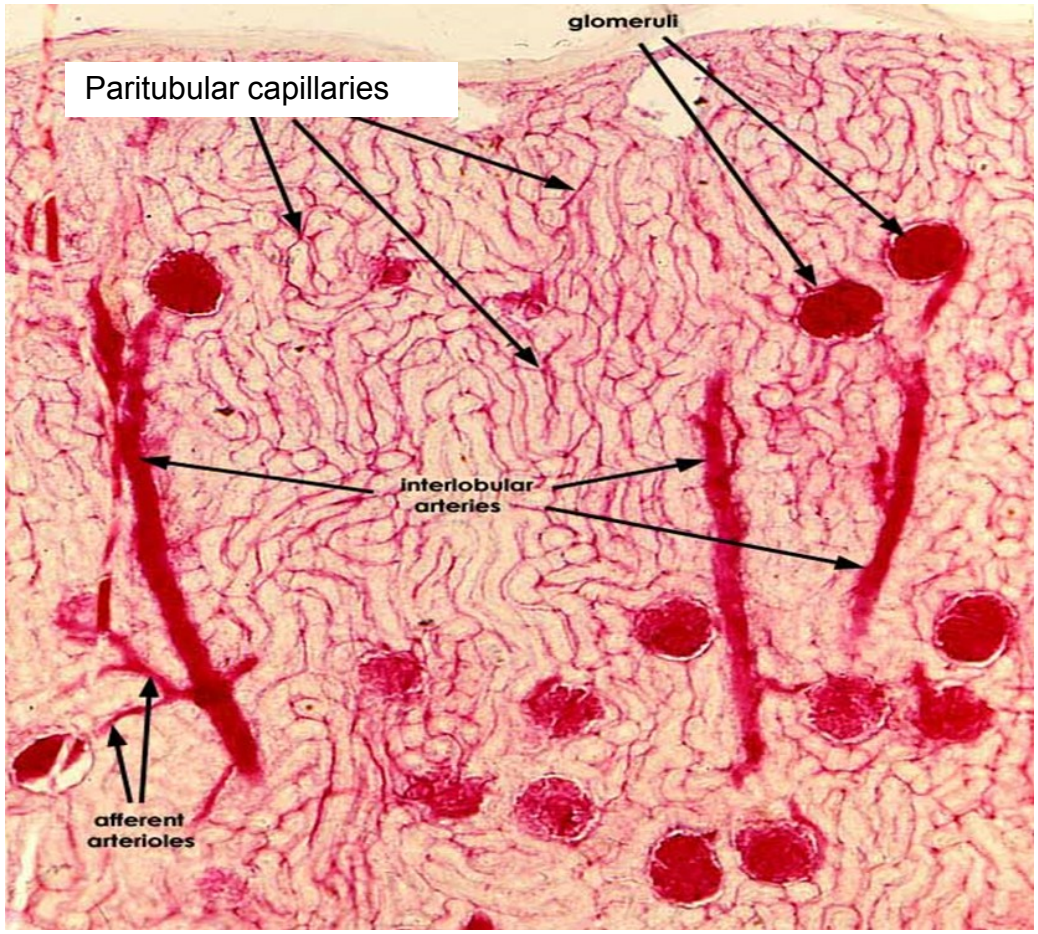
Maximal distance of tissue cell from the capillary =

about 50 μm

The length of the capillaries usually varies between

about 0.25 and 1 mm

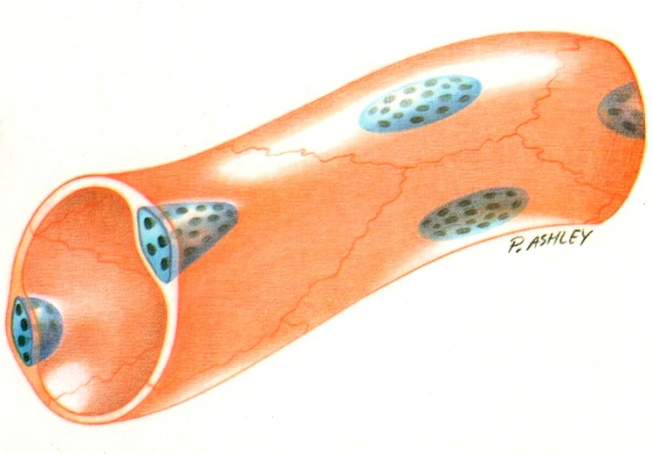
Capillaries



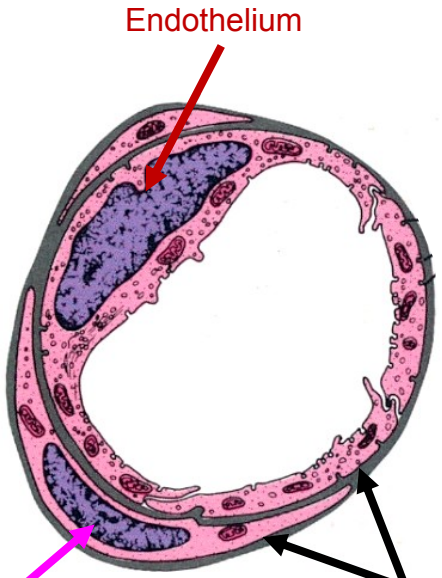
Extensive vasculature of renal cortex (perfused by red dye)

Scarse in: tendons, ligaments
Absent from: cartilage, epidermis, cornea

Capillaries



average diameter about 8 μm



Capillary wall

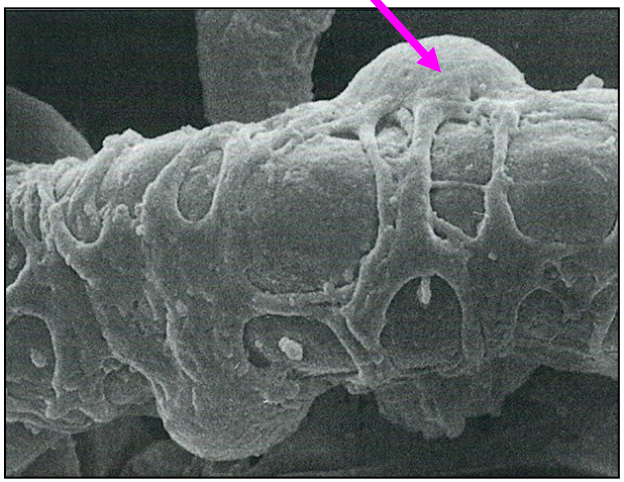
Endothelium

- single layer, squamous
- serrated (wavy) cell borders
- zonulae occludentes + desmosomes + GAP junctions

Basal lamina

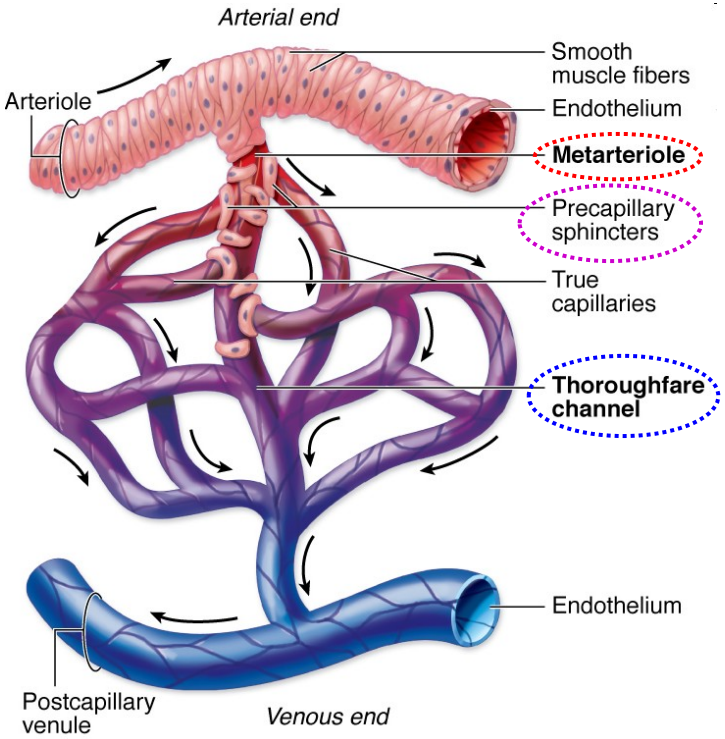
„Envelope“

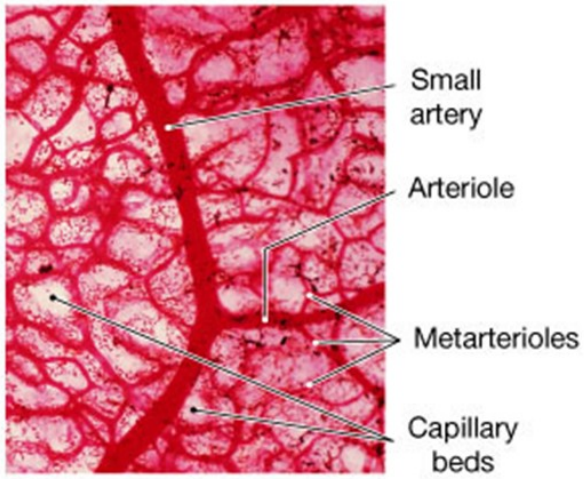
- pericytes (+ reticular fibers and macrophages)

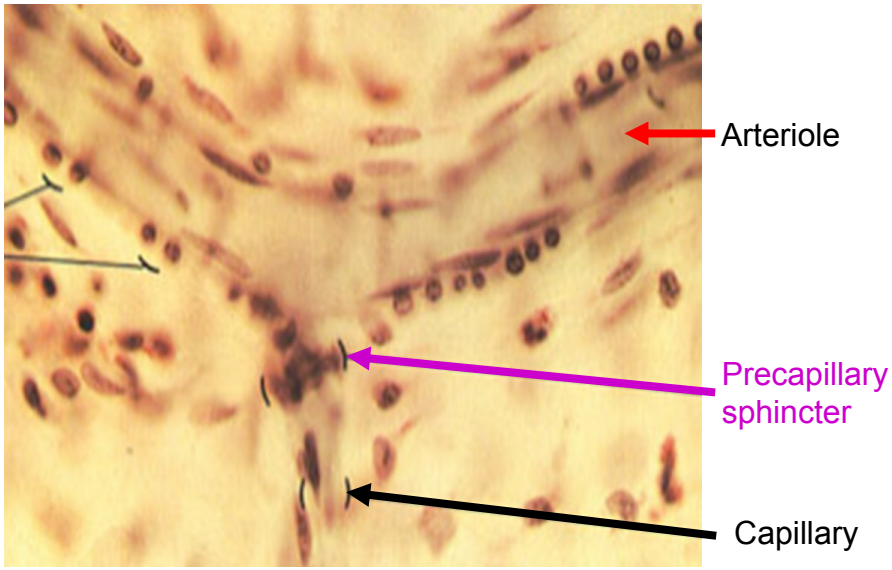


Capillaries

Only about 25 - 50 % of capillary volume is actively moving (containing) blood under normal conditions.







Rabbit mesentery (H+E; 600x)

Capillaries – Regulation of blood flow

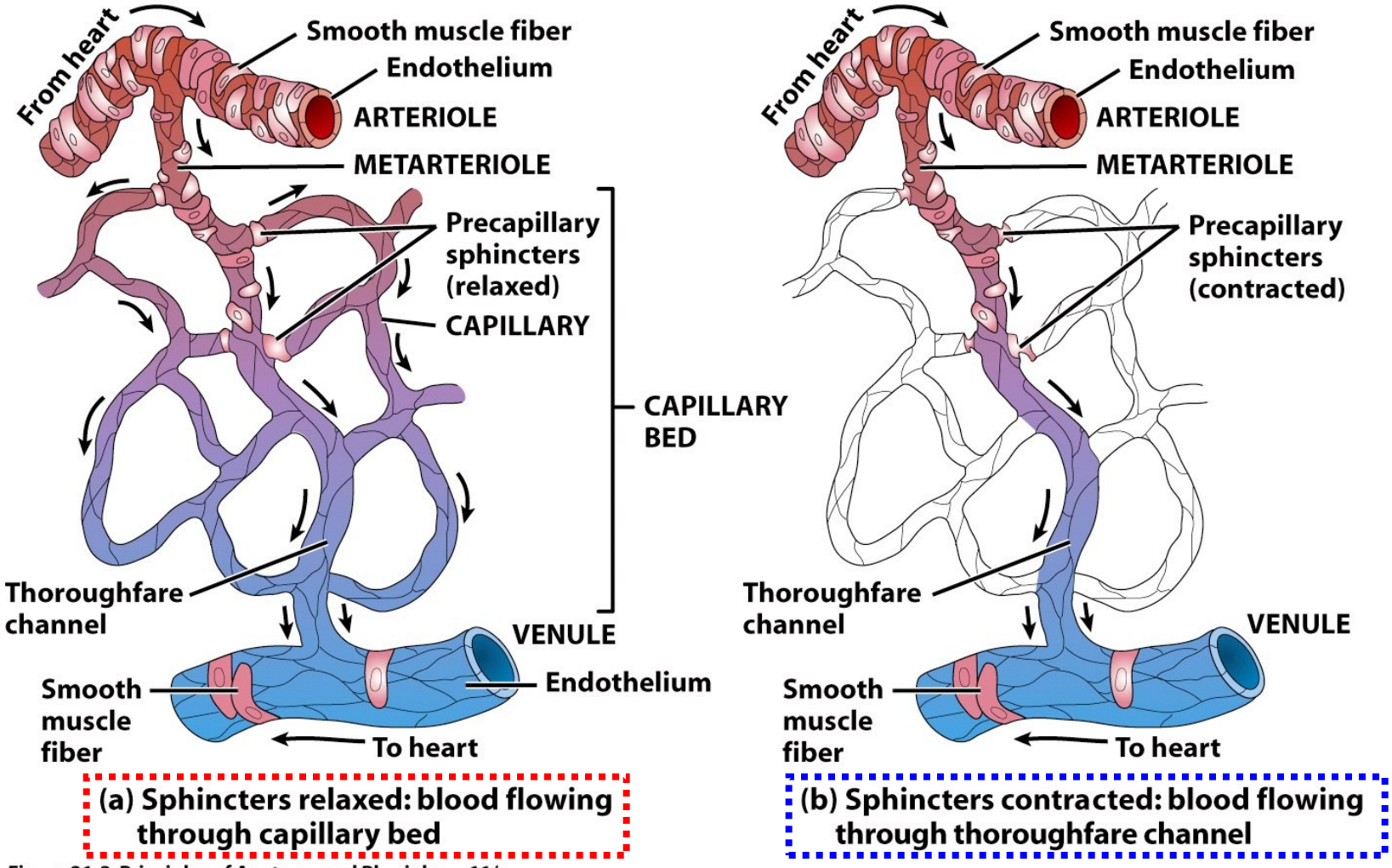


Figure 21-3 Principles of Anatomy and Physiology, 11/e

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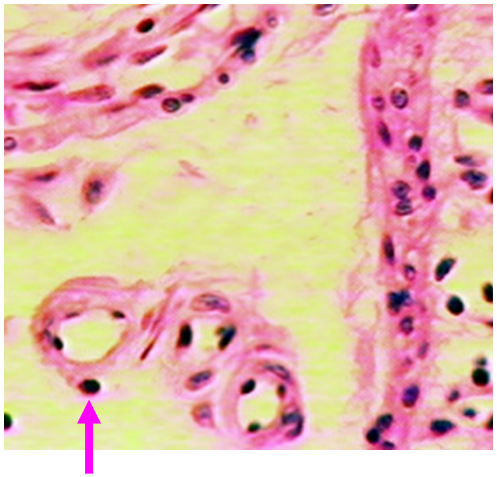
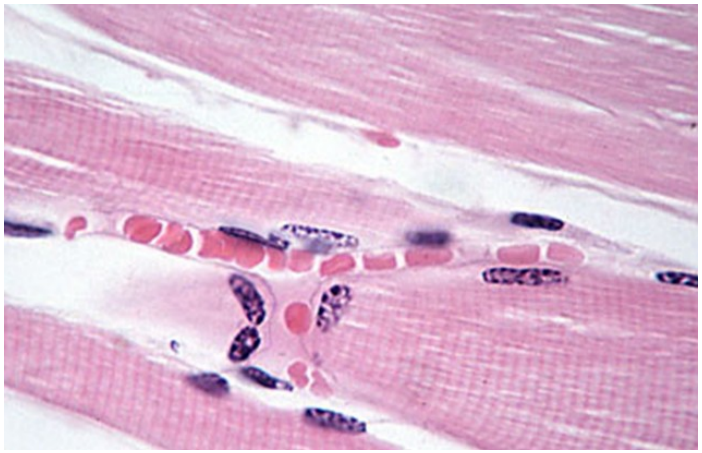
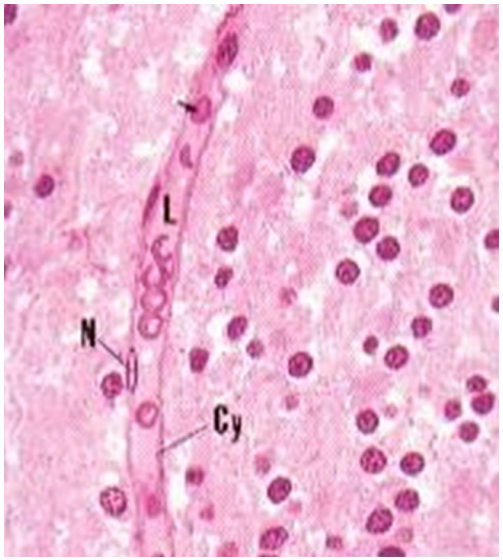
Capillaries



Pericyte



Striated muscle

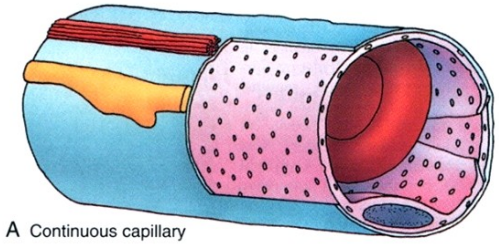


Cerebellum (monkey)

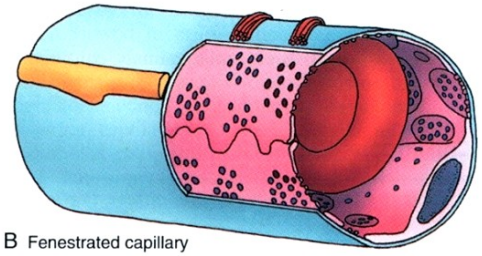
Capillaries

According to the integrity of the endothelium and basement membrane – by TEM:

- Continuous capillary
- Fenestrated capillary
- Sinusoidal



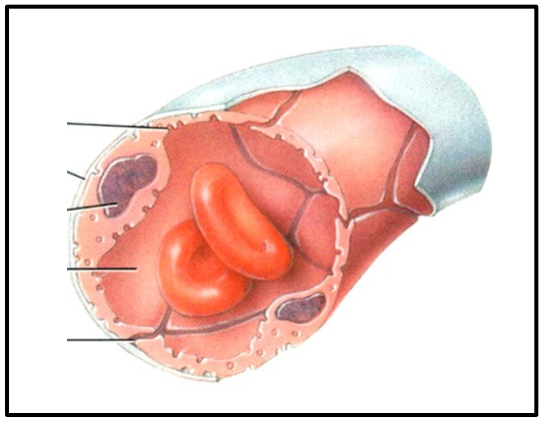
A Continuous capillary

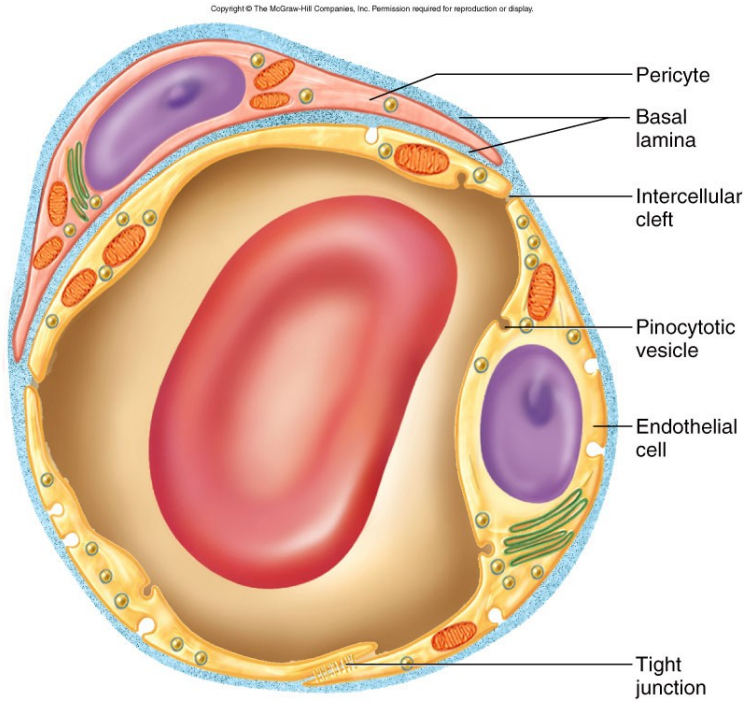


B Fenestrated capillary

C Sinusoidal (discontinuous) capillary

Capillaries - Continuous





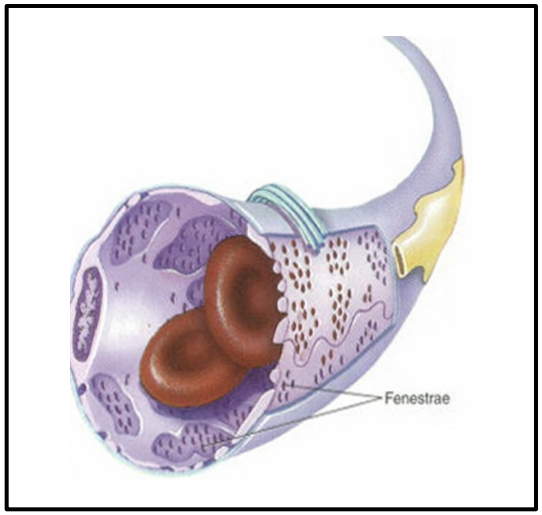
How ?

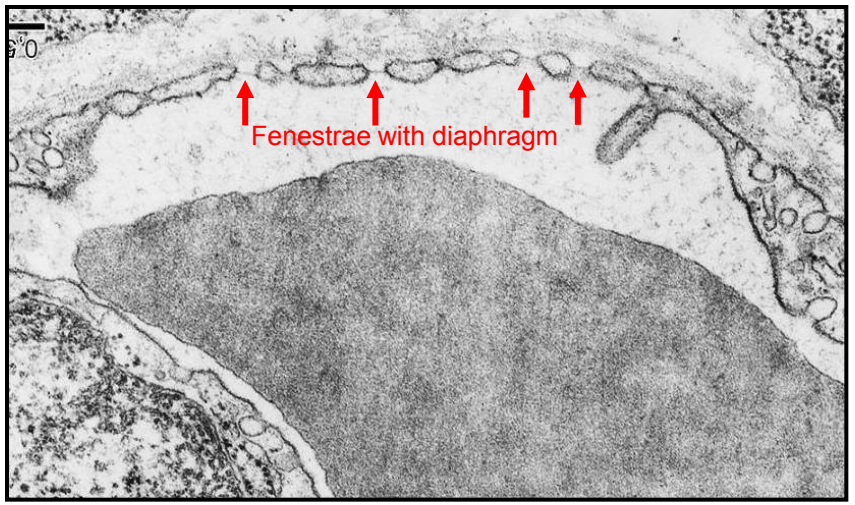
- non-interrupted lining
- no defects in the wall

Where ?

- most common type
- muscle, connective tissue, nerve tissue (blood-brain barrier), exocrine glands

Capillaries - Fenestrated



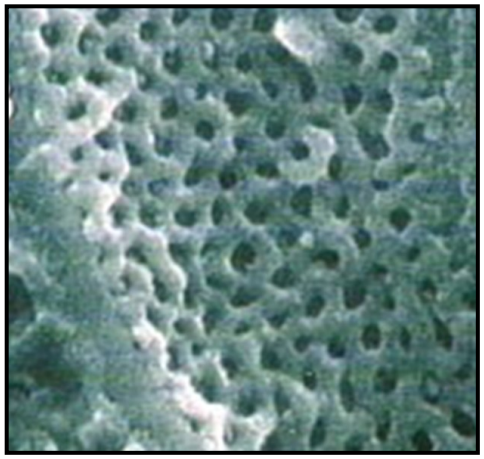


How ?

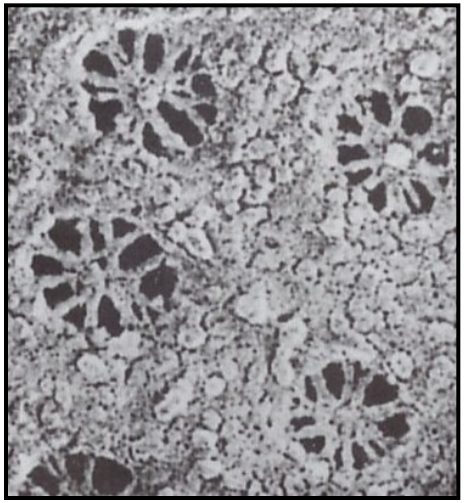
- endothelial cells perforated
  (diameter ~60-80 nm; diphragm 4-6 nm)
- continuous basal lamina

Where ?

- in tissues where rapid interchange of substances occurs between the tissue and the blood
- intestinal mucosa, some endocrine glands, pankreas

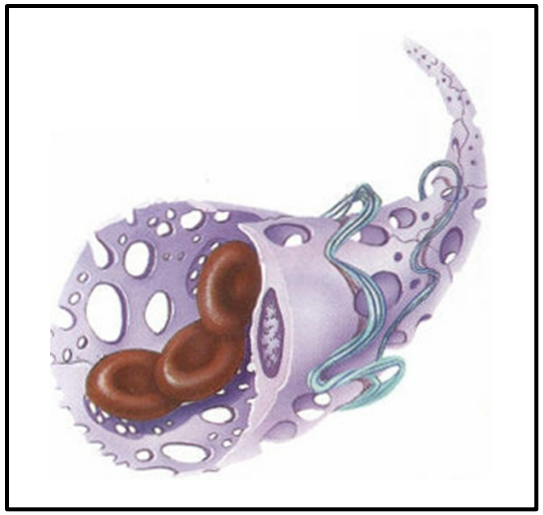


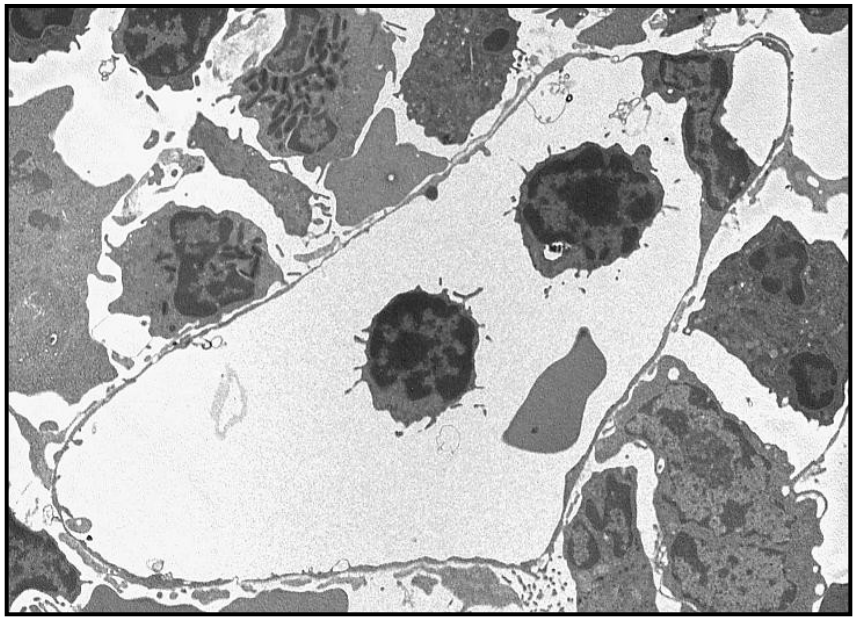
Fenestrated capillary - kidney



Diaphragm

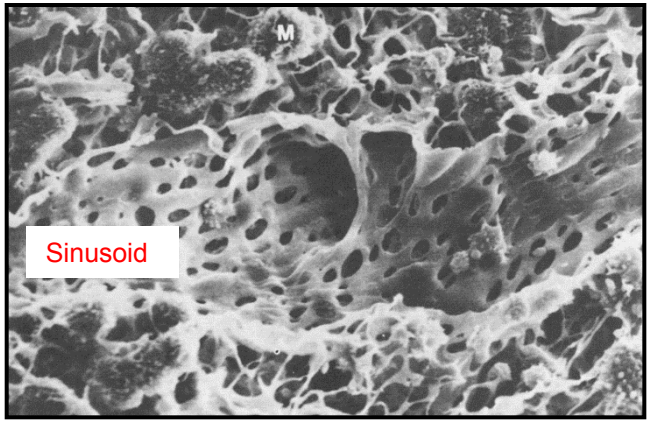
Capillaries – Sinusoidal - Discontinuos





How ?

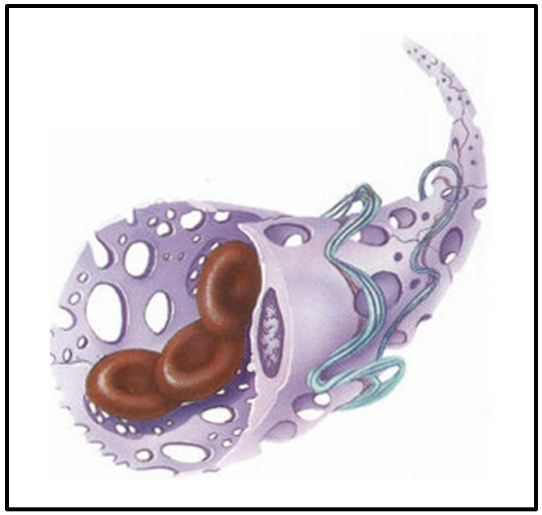
- enlarged diameter (up to 40 μm)
- endothelial cells with large pores without diaphragm
- large clefts between



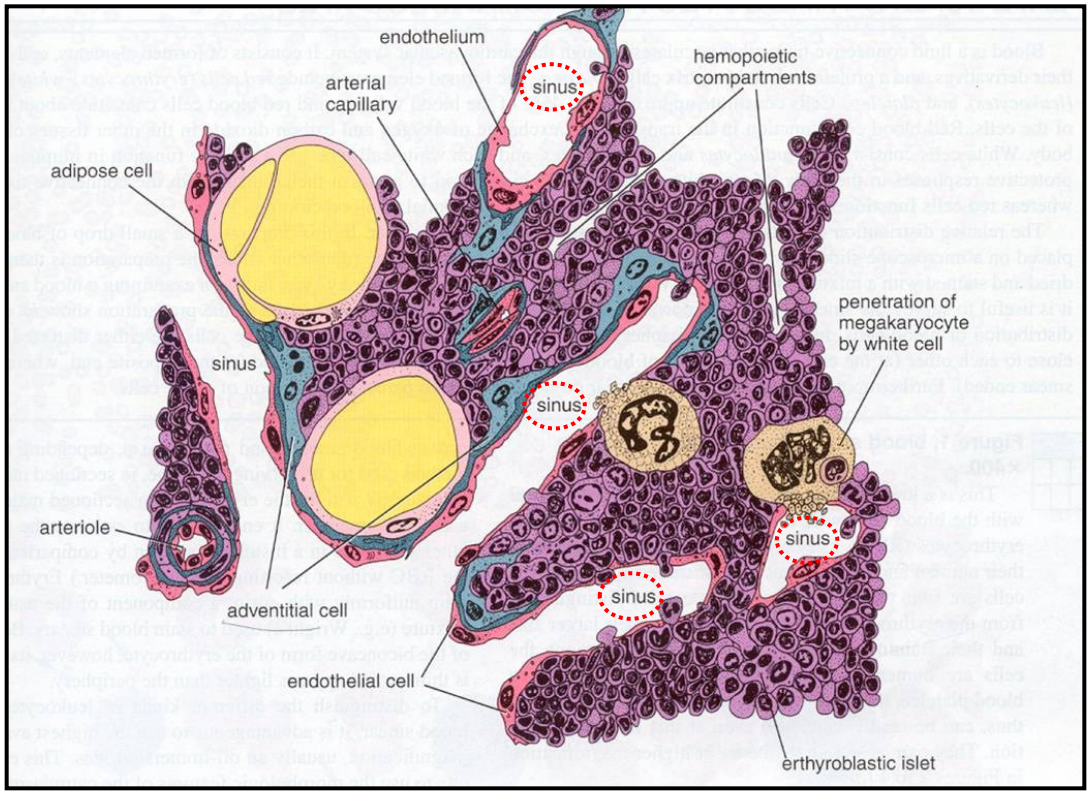
Where ?

- liver (pores 100 nm)
- hematopoietic regions (bone marrow)
(macrophages instead)

Capillaries – Sinusoidal - Discontinuos



Bone marrow



Blood vessels – several different flavours

Veins

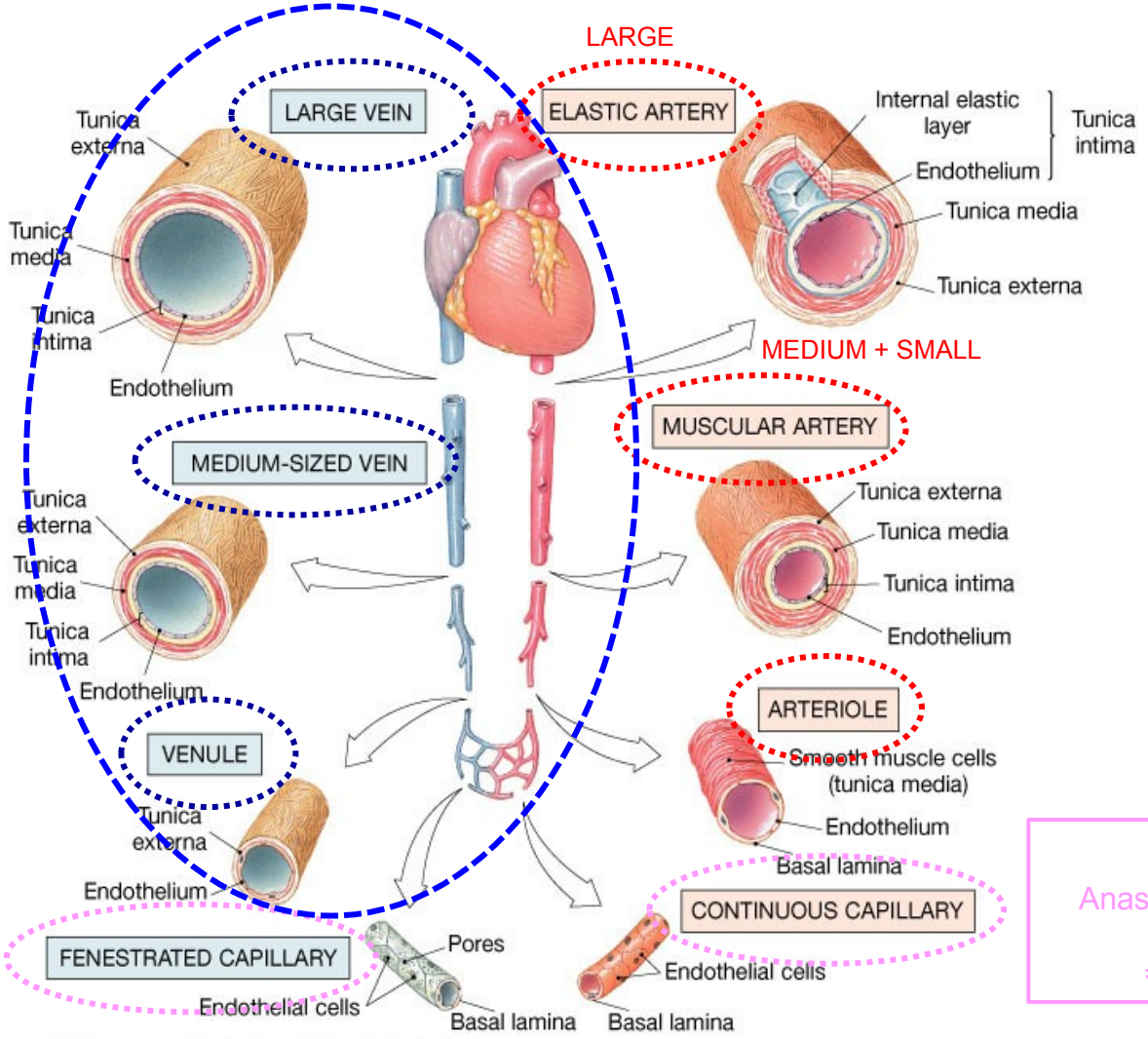
ALWAYS return the blood to the heart
(contain about 2/3 body's blood at any given time)

Arteries

ALWAYS carry blood from the heart to the periphery

Macrovasculature – diameter >0.1 mm

Microvasculature – <0.1 mm



Capillaries

Anastomosing tubules among arteries and veins
= microvascular bed

Veins – capacitance vessels

- they function as blood reservoir - greater capacity for blood containment than arteries due to thinner wall

- lower blood pressure (10 mm Hg with little fluctuation)

- valves aid skeletal muscles in upward blood flow (typically in lower limbs – veins with diameter > 2 mm)

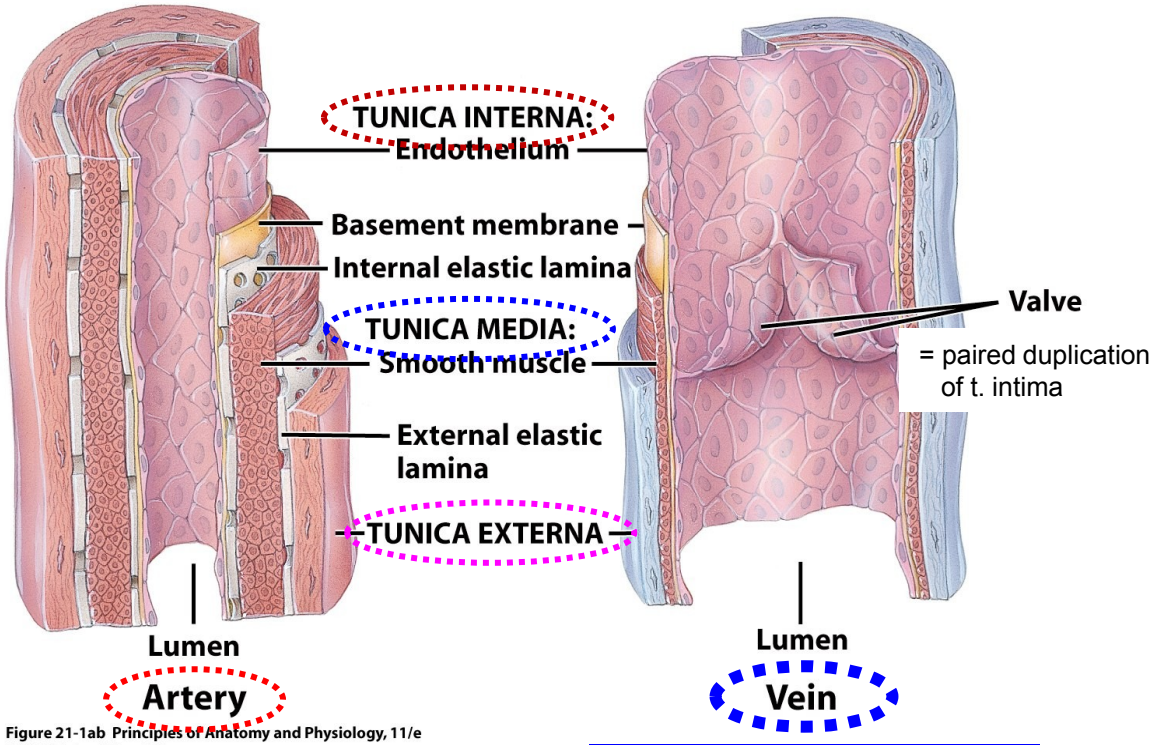


Figure 21-1ab Principles of Anatomy and Physiology, 11/e
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Three layered bulding plan

General features

Endothelium
- very thin

Subendothelial layer
- very thin

Internal elastic lamina
- missing or only very thin

- relatively thin (except for lower limbs)
- Little bundles of smooth muscle cells
- collagen fibers – considerable amount

External elastic lamina
- non-developed

- well developed – thickest layer
- often with longitudinally arranged bundles of smooth muscle cells
- robust vasa vasorum (often penetrate deep to t. media)

Veins – Categories according to their diameter

Postcapillary venules

- endothelial cells + some pericytes
- receive blood from capillaries
- more porous than capillaries
- larger diameter than capillaries (15-20 μm)

Collecting & Muscular venules

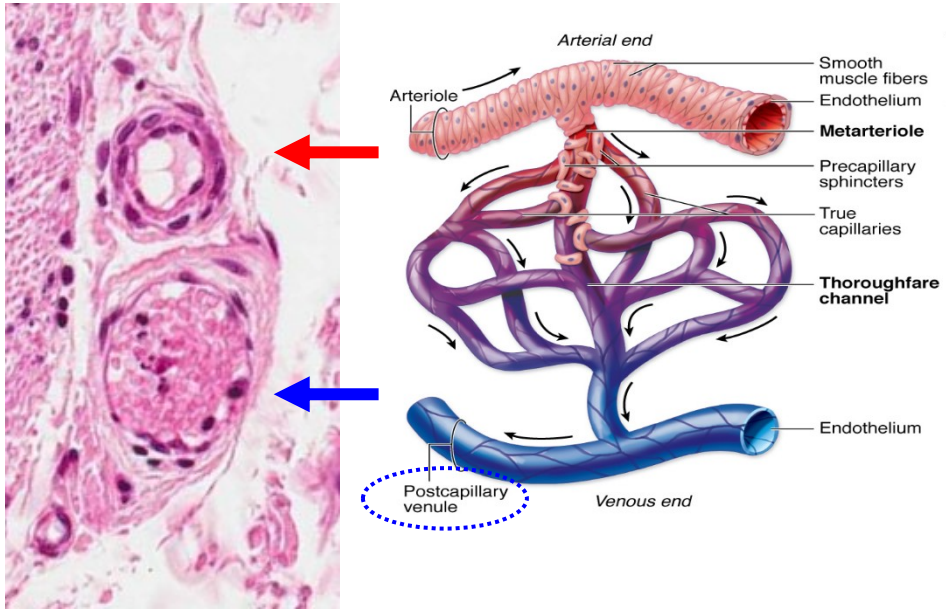
- increasing number of contractile cells
- tunica media is defined in muscular venules

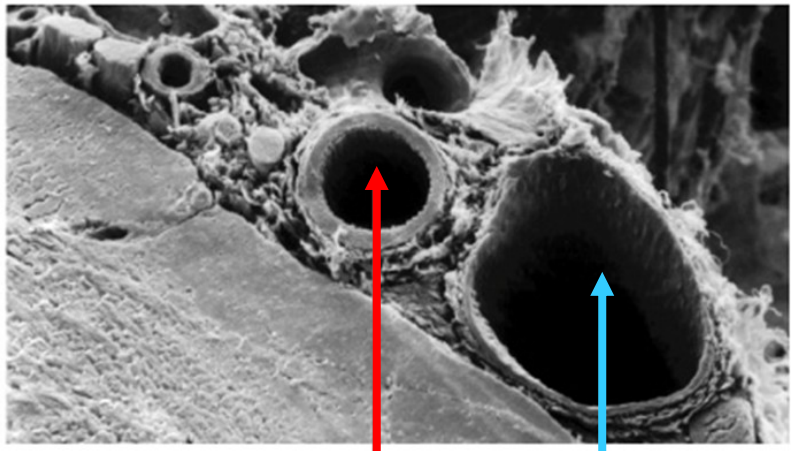
Small- & Medium-sized veins

- most have individual names
- run parallel with corresponding arteries
- many have valves

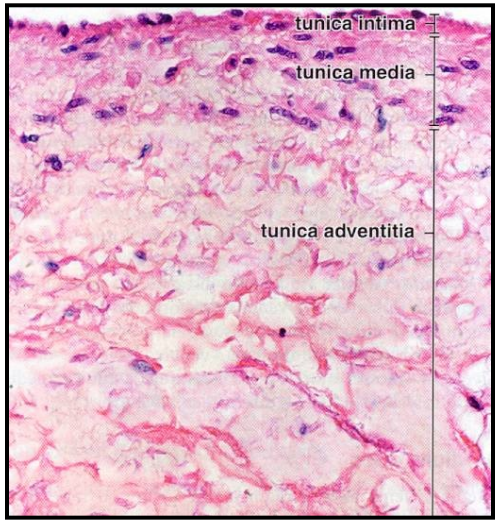
Large veins

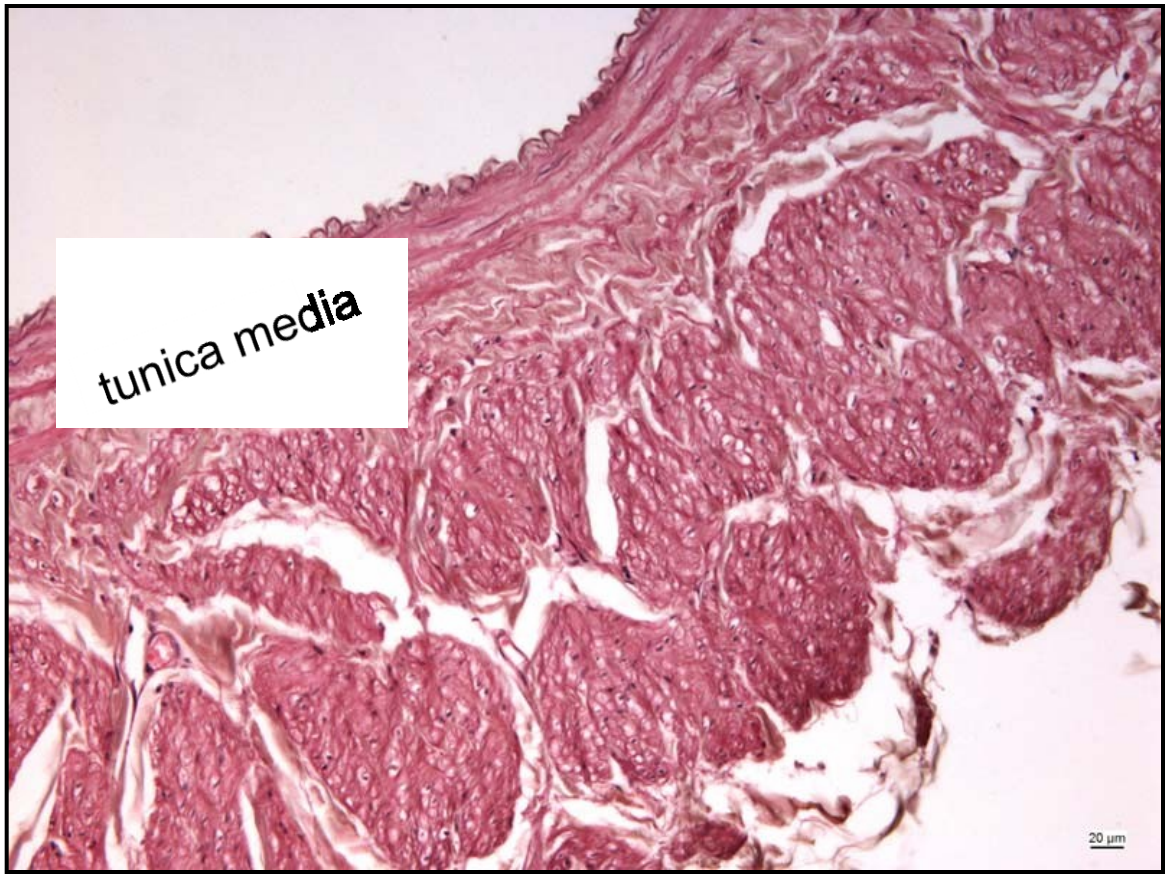
- close to the heart
- *(v.cavae, pulmonary veins, internal jugular veins)*
- paired with elastic arteries
- diameter > 10 mm
- with valves
- t. media is thin (muscle cells+connective tissue)
- thick t. externa (with longitudinal bundles of smc; myocardial sleeves)



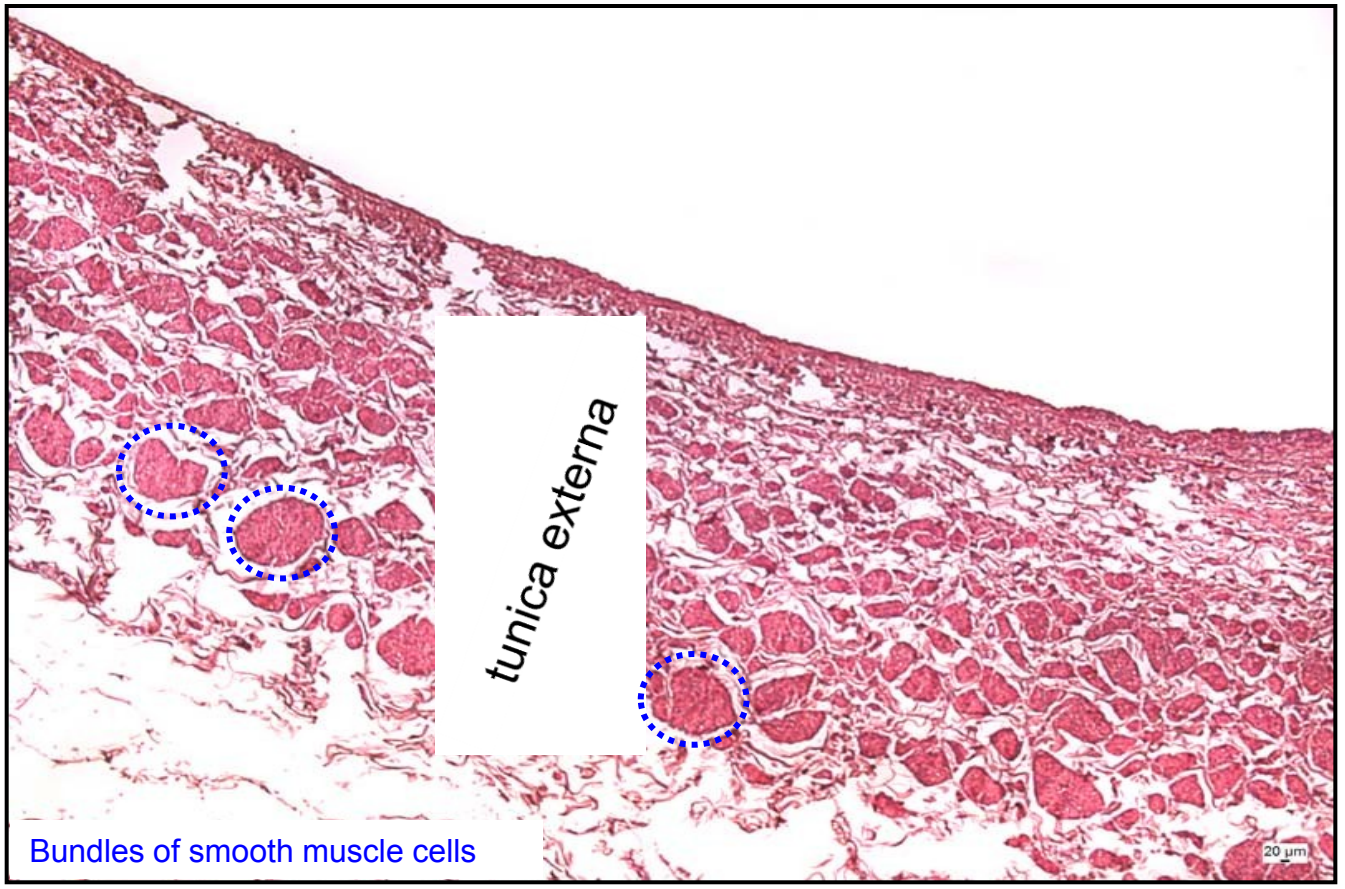


Veins – Middle-sized

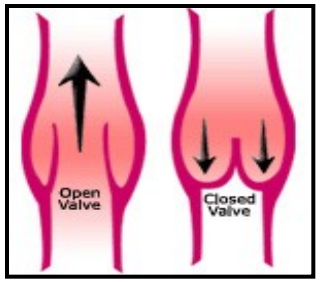




Veins - Large



Vena cava

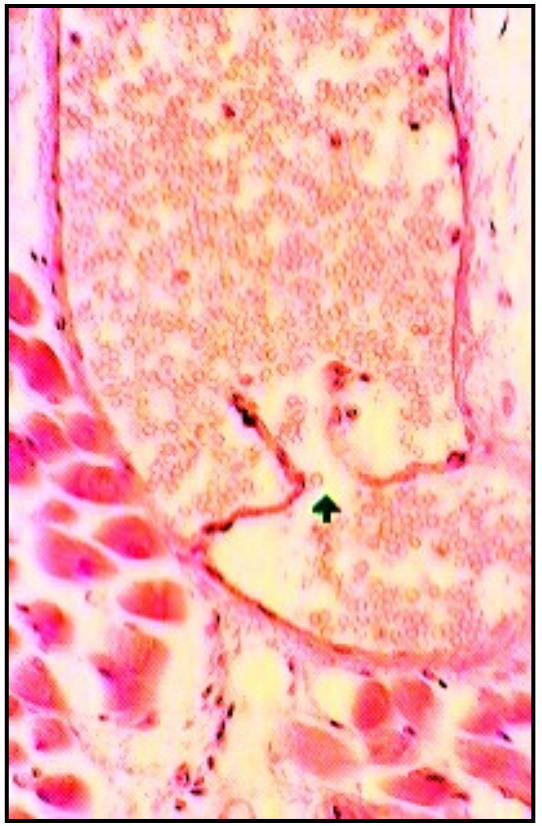


Veins – Valves

- bag-like protrusion of tunica intima, which prevent the blood flow from running to opposite direction

- only in the veins that has low position or far away from heart

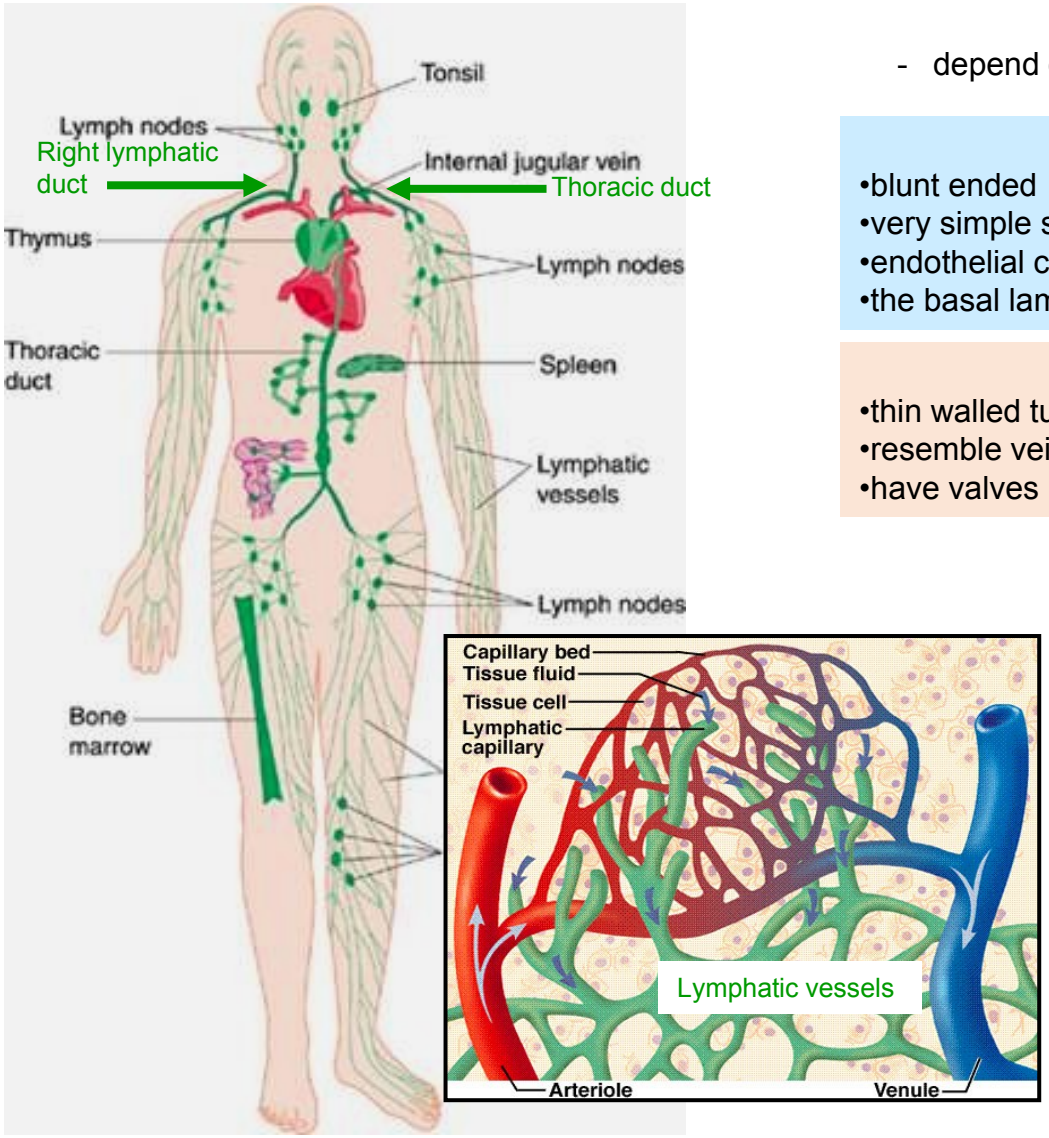
Appearence of internal surface



Histological view

Lymphatic vessels

- return fluid from tissues to the circulatiory system
- depend on skeletal muscles to move fluid

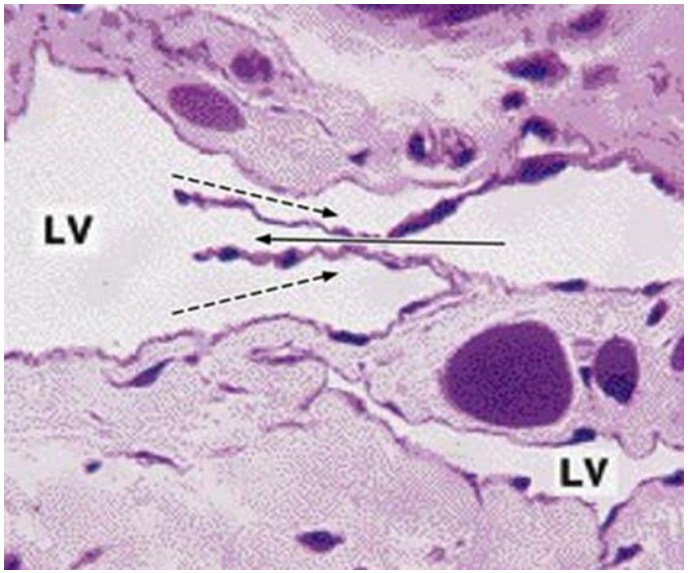


Lymphatic capillaries

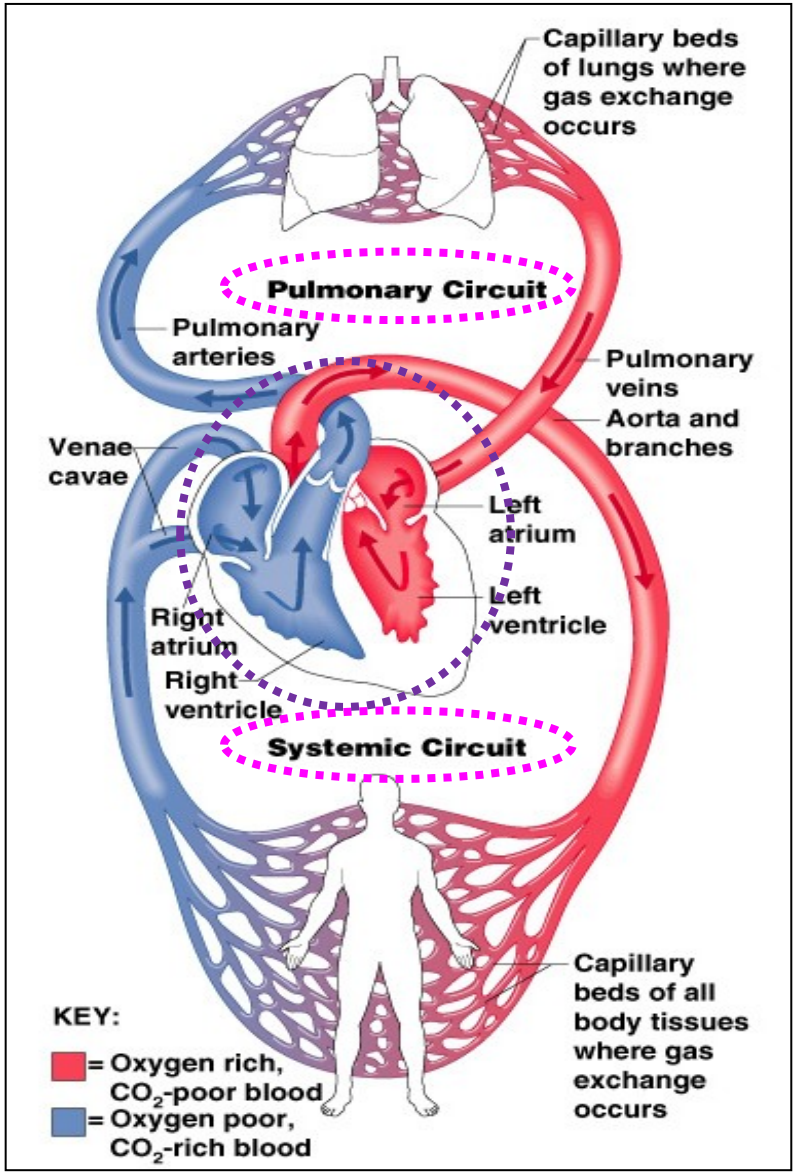
- blunt ended
- very simple structure
- endothelial cells + fine reticular fibres of circular orientation
- the basal lamina is not developed

Lymphatic vessels and ducts

- thin walled tubes
- resemble veins in their structure (intima+media+adventitia)
- have valves



Heart - Anatomy



- a hollow organ that contracts rhytmically

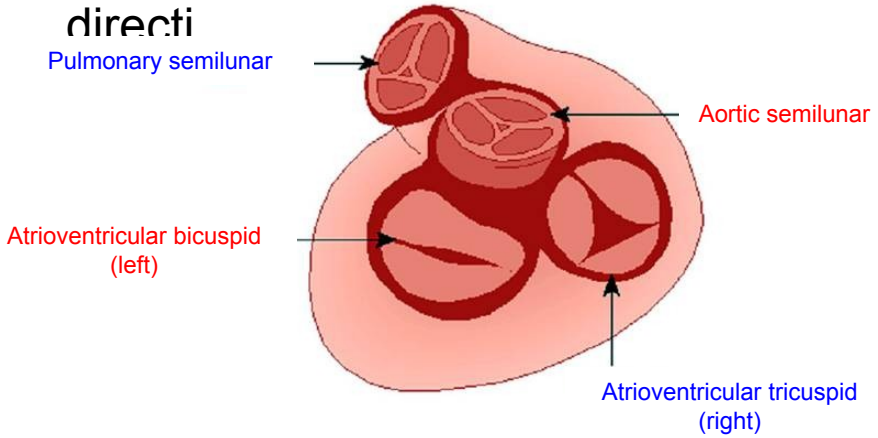
- it functions as a pump

- it is composed of two sets of chambers:

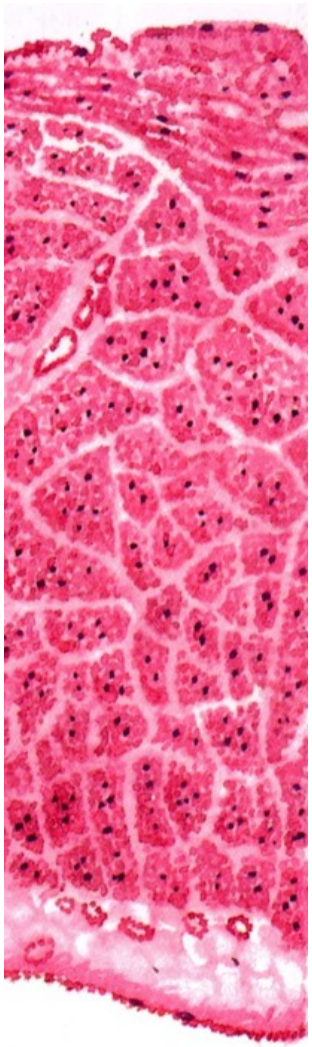
Receiving atria
Right Left

Discharging ventricles
Right Left

- it is equipped by four valves (blood can travel in only one directi



Heart - Wall



Endocardium

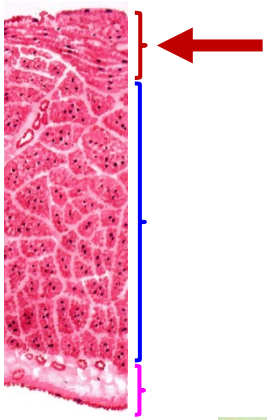
- endothelium
- subendothelial layer
- subendocardial layer

Myocardium

Epicardium

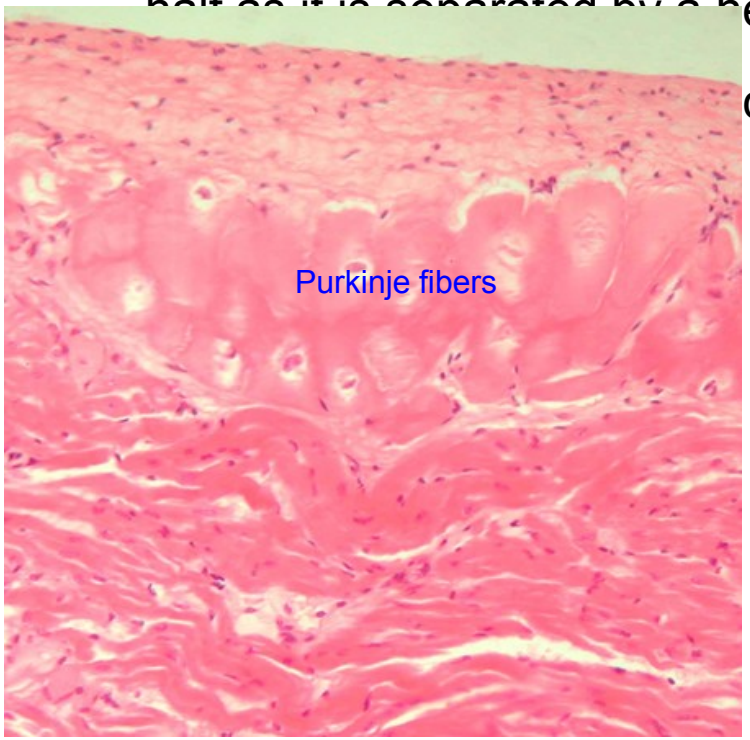
- mesothelium
- submesothelial layer

Heart - Endocardium



- is continuous with the tunica intima of the large vessels entering and leaving the heart

- the endocardium of the left half of the heart is not continuous with the one on the right
half as it is separated by a heart septum

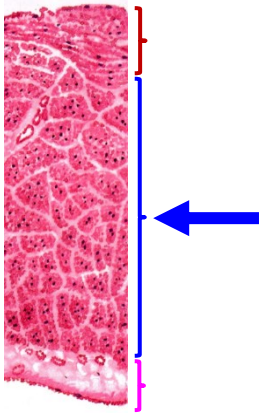


Endothelium
- with continuous basal membrane

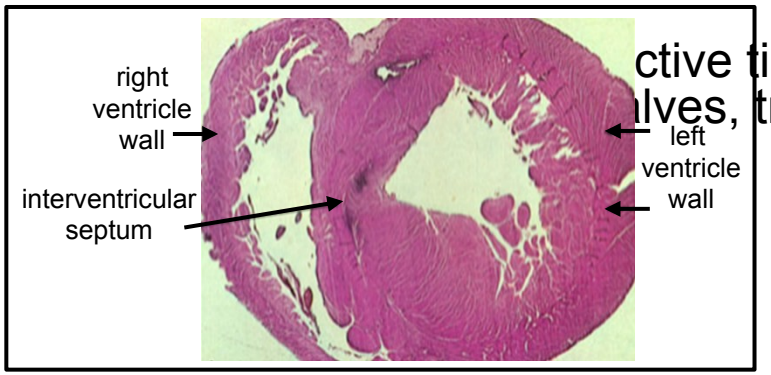
Subendothelial layer
- connective tissue
- collagen, elastics, solitary smc, small blood vessels, nerves

Subendocardial layer
- loose connective tissue
- continuous with endomysium of the myocardium
- nerve fibers, vessels, impuls-conducting system

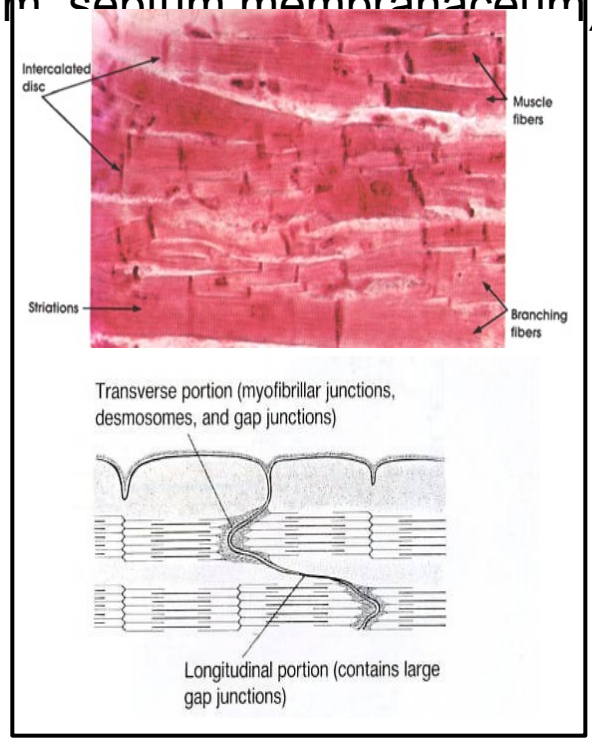
Heart - Myocardium



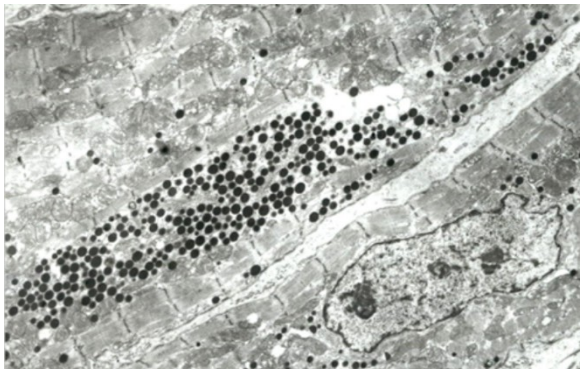
- its thickness varies in different parts (thickest – left ventrikle; thin in
- has rich blood supply (many capillaries)
- has no regenerative capacity
- muscle fibers are arranged circularly around chambers

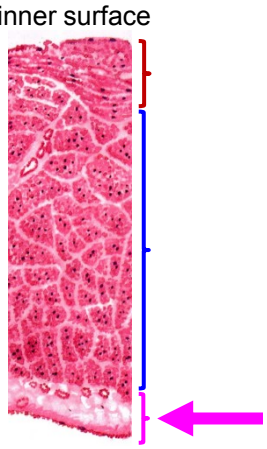


ctive tissue in between the muscles – cardiac ske
lves, trigonum, septum membranaceum)



Atrial natriuretic peptide
(endocrine function of contractile cells; acts on kidney)





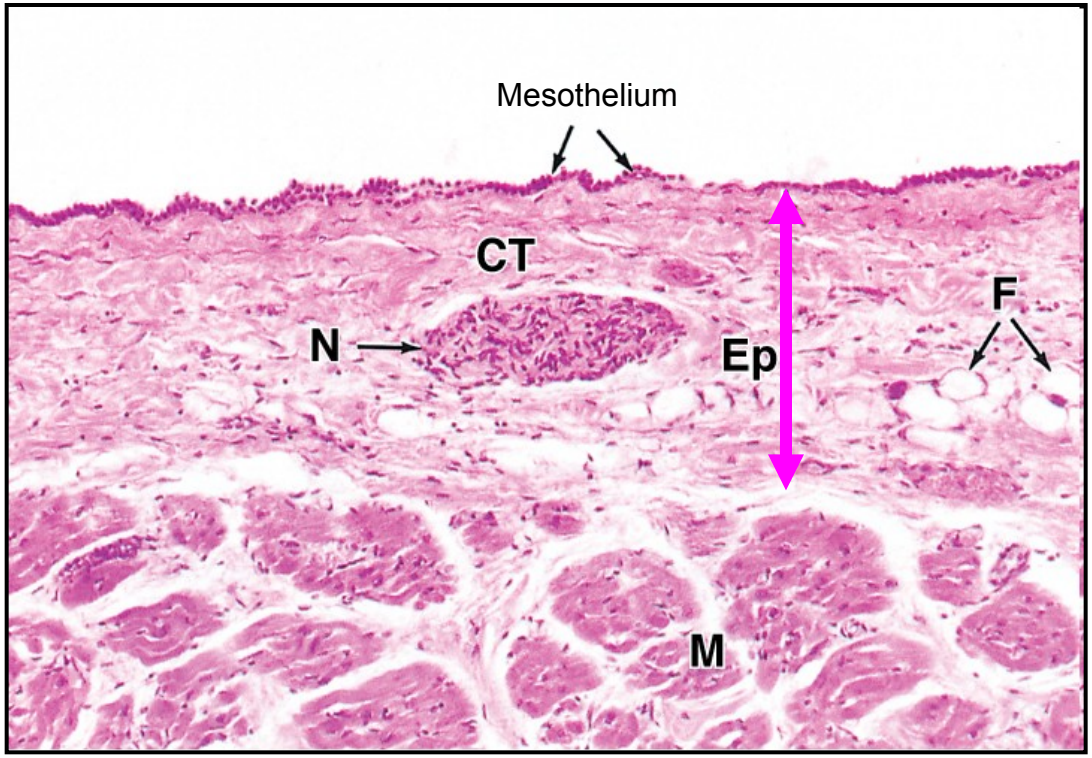
Heart - Epicardium

- represents visceral layer of the pericardium

Pericardium

Fibroserous sac enveloping heart

- mesothelium with basal lamina (faces epicardium)
- fibrous layer (dense connective t. with vessels and nerves)



Mesothelium
- simple squamous epithelium
- basal lamina
- secretes pericardial fluid

Submesothelial layer
- loose connective tissue
- elastic fibers
- nerves
- blood and lymphatic vessels
- home of coronary vessels
- adipocytes (high in obese individuals)

Heart - Valves

- composed of connective tissue layers covered by endothelium on each side

Atrial side

Ventricular side

Spongiosa
- loose collagen

Fibrosa
- dense core of connective tissue

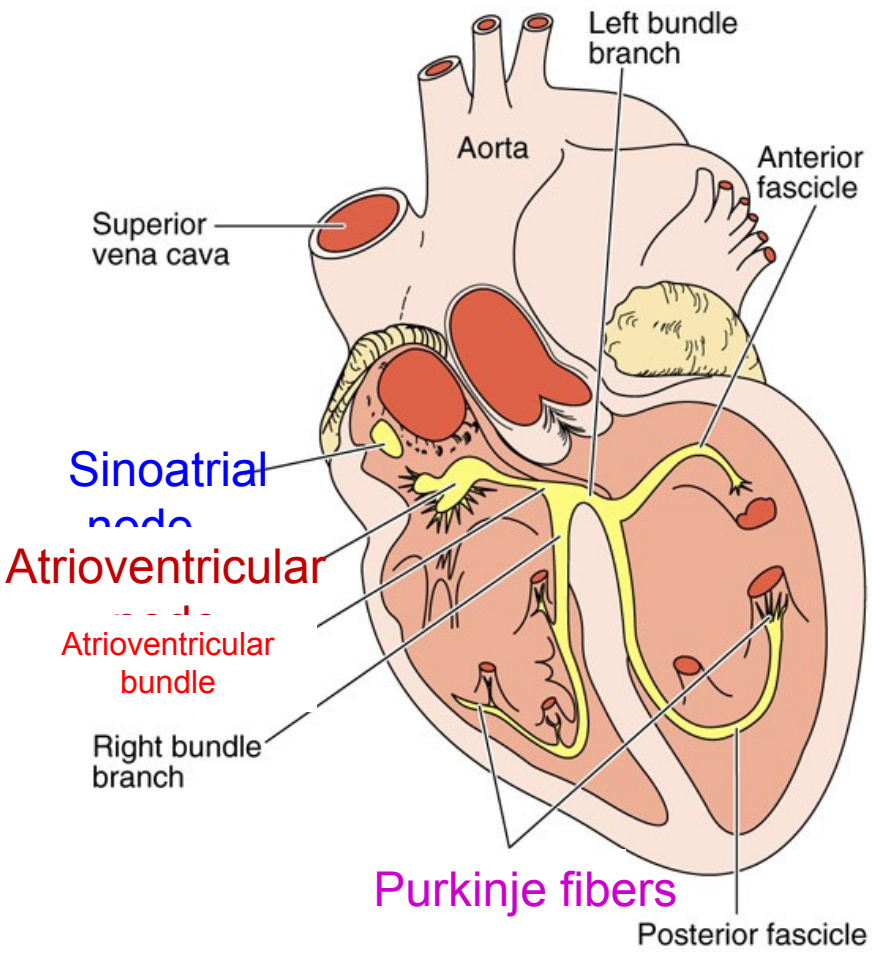
Ventricularis
- dense connective tissue with many elastic and collagen fibers

Heart – Conducting system

- specially modified cardiac muscle cells (non-contracting, less myofibrils, abundant GA junctions)

- generate and conduct impulses of heart contraction to various parts of myocardium

- assure proper succession of beat of atria and ventricles



Sinoatrial node (node of Keith-Flack)

- it lies on the medial wall of the right atrium near the entrance of the superior vena cava
- PRIMARY PACEMAKER

Atrioventricular node (node of Ascoff and Tawara)

- it runs on the right side of the interatrial septum
- SECONDARY PACEMAKER

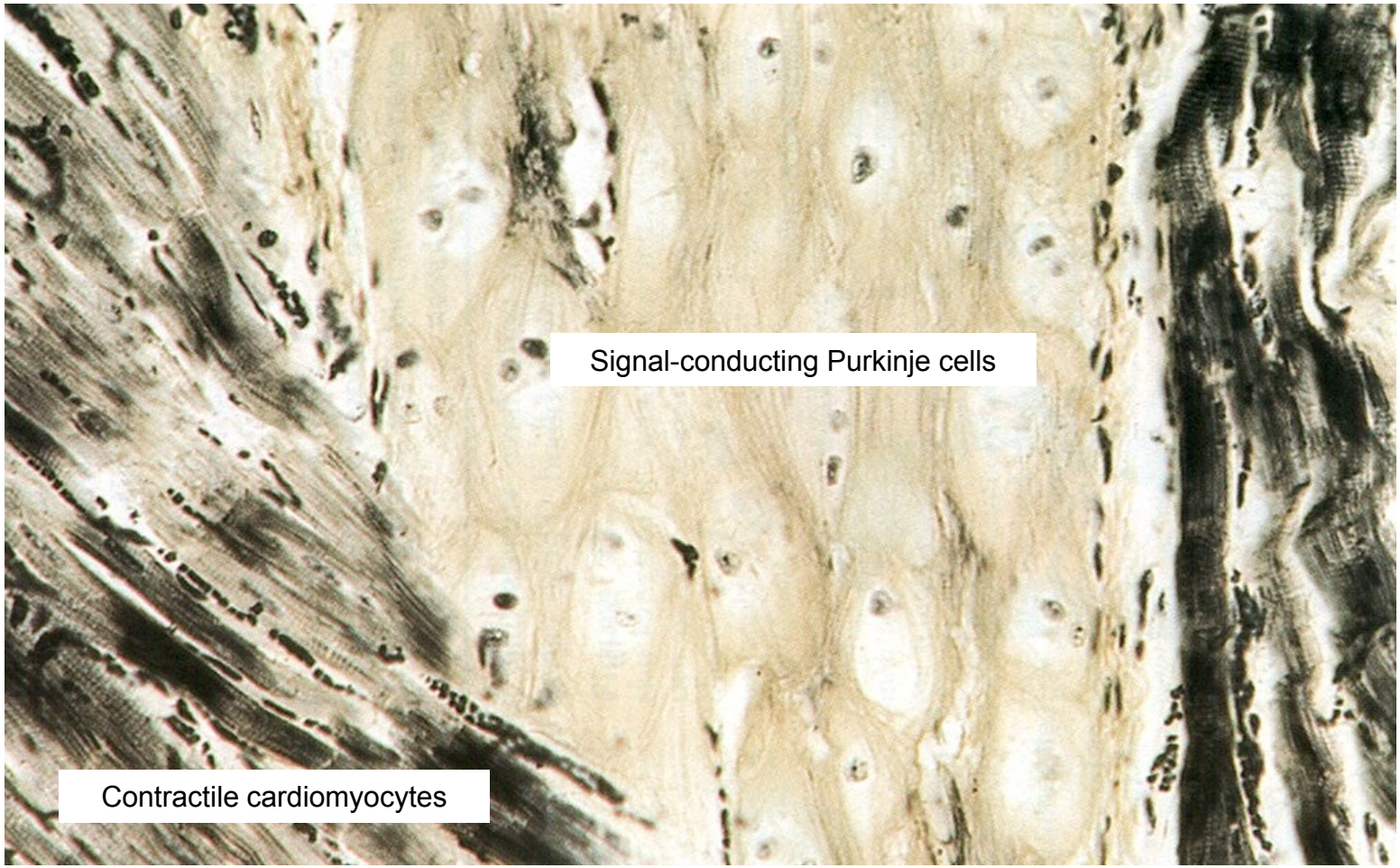
Atrioventricular bundle (bundle of Hiss)

- it divides into 2 branches (for the left and right ventricles)

Purkinje fibres

- terminal ramifications of the AV bundle

Heart – Conducting system



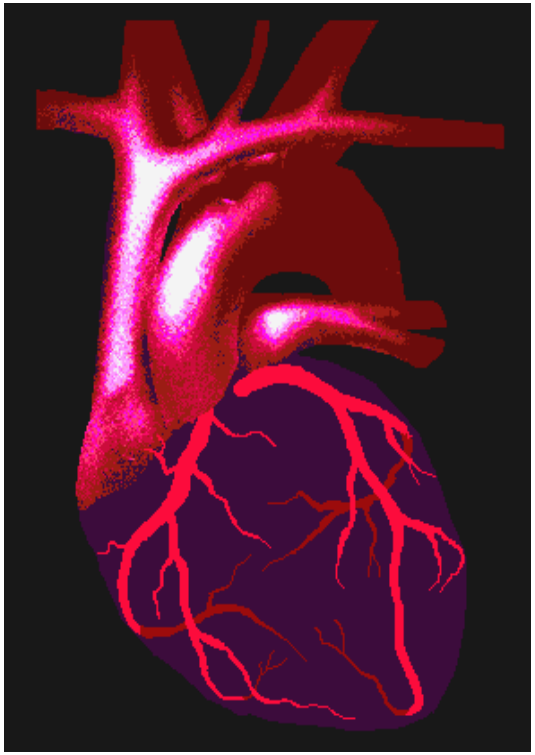
Heart – Coronary circulation

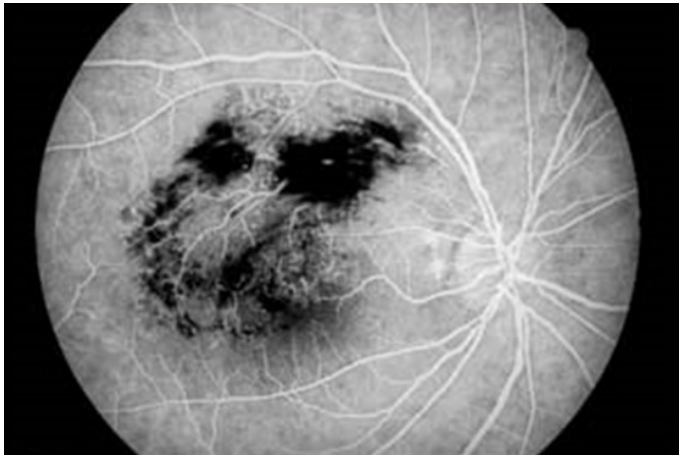
- blood in the heart chambers does not nourish the myocardium

- the heart has its own nourishing circulatory system: Coronary arteries & veins

- 5-7% of blood flows through the coronary arteries

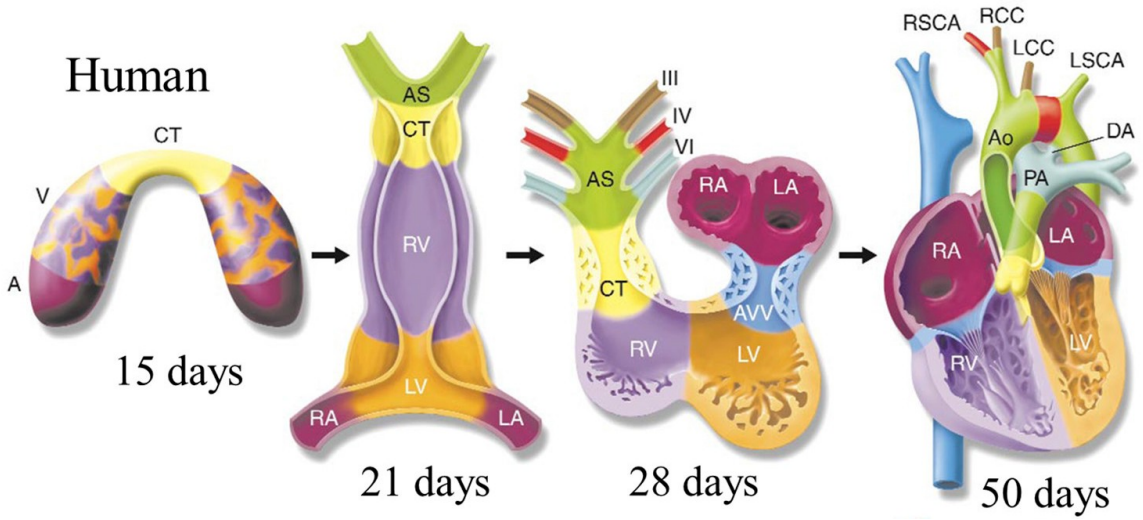
- blood empties into the right atrium via the coronary sinus





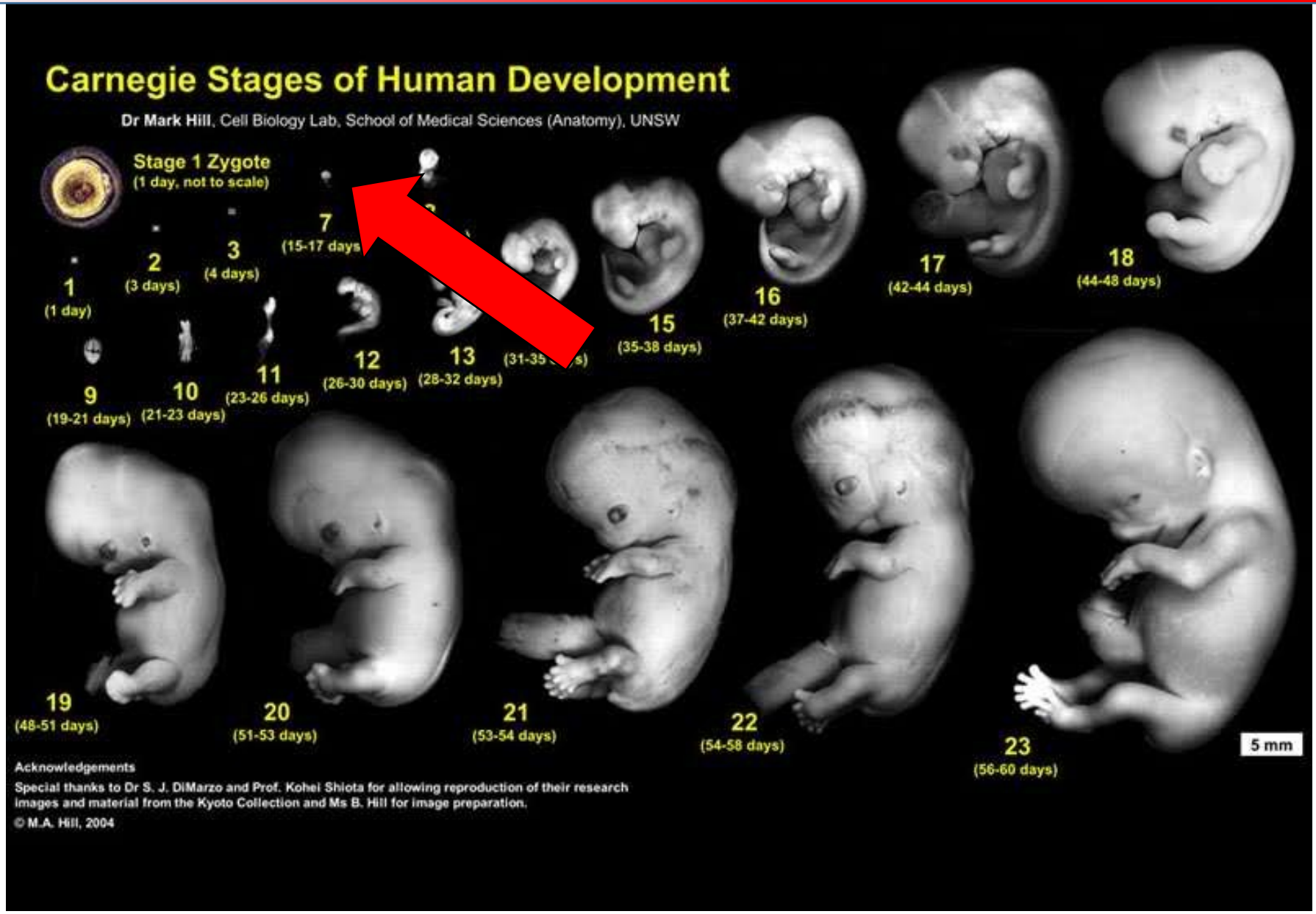
Dye injected into heart
X-ray to examine blockages

DEVELOPMENT OF CARDIOVASCULAR SYSTEM

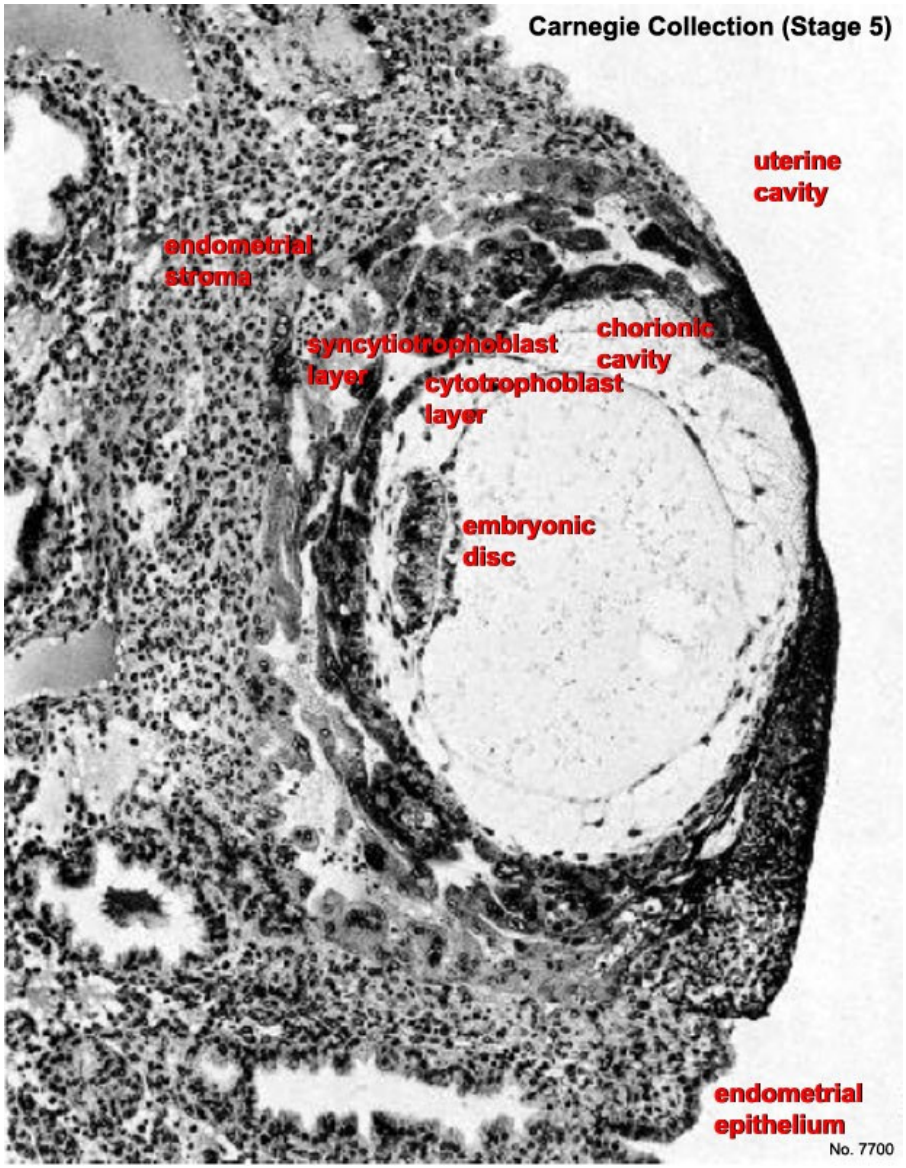


Petr Vaňhara, PhD
Dept. of Histology and Embryology
Faculty of Medicine, Masaryk University

DEVELOPMENT OF CARDIOVASCULAR SYSTEM

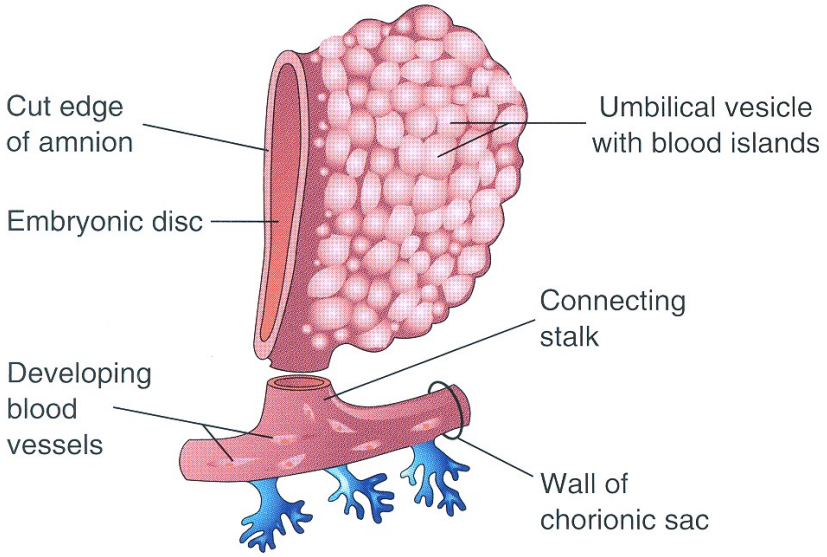


DEVELOPMENT OF CARDIOVASCULAR SYSTEM



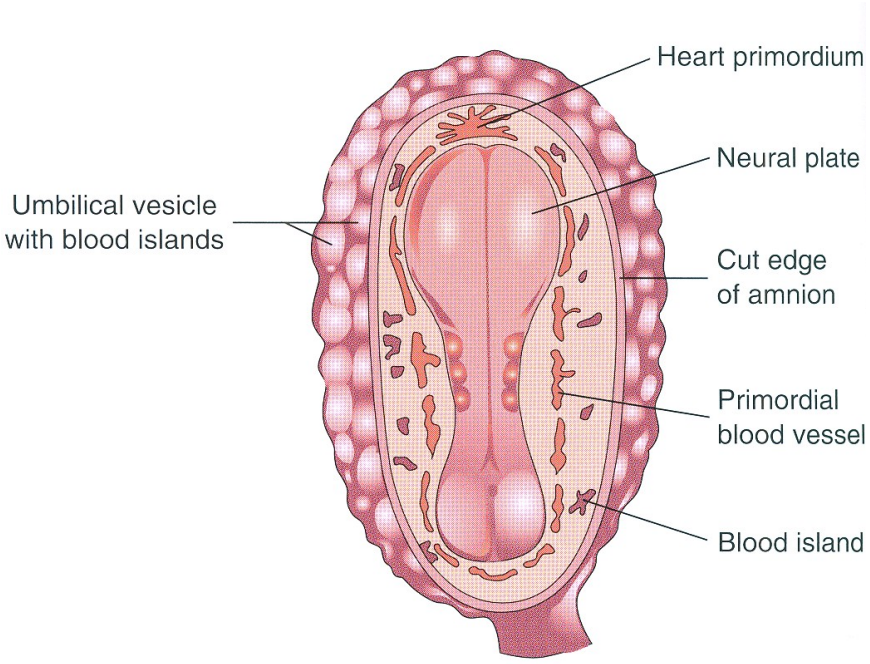
Week 2-3

- rapid growth of embryo
- insuffcient supply by diffusion
- first vascularisation develops **outside** embryo – yolk sac, chorion and connecting stalk
- bipotential (hem)angioblasts in blood islands
- vasculogenesis and angiogenesis
- blood cells formation



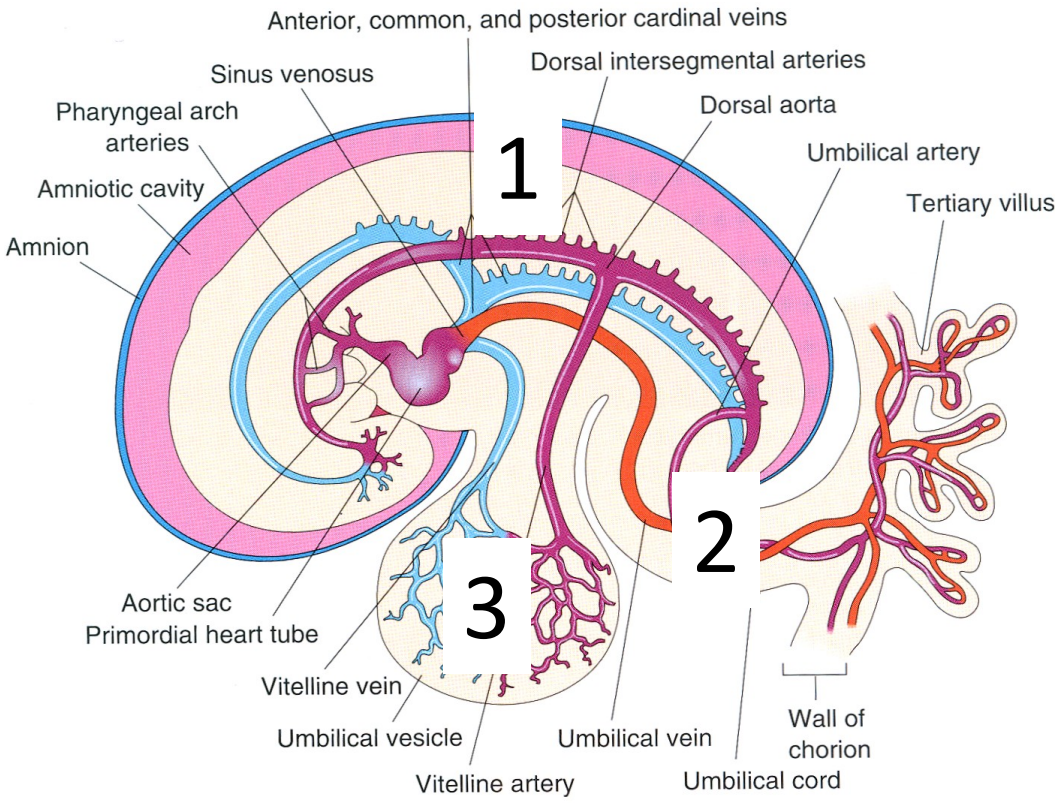
End of week 3

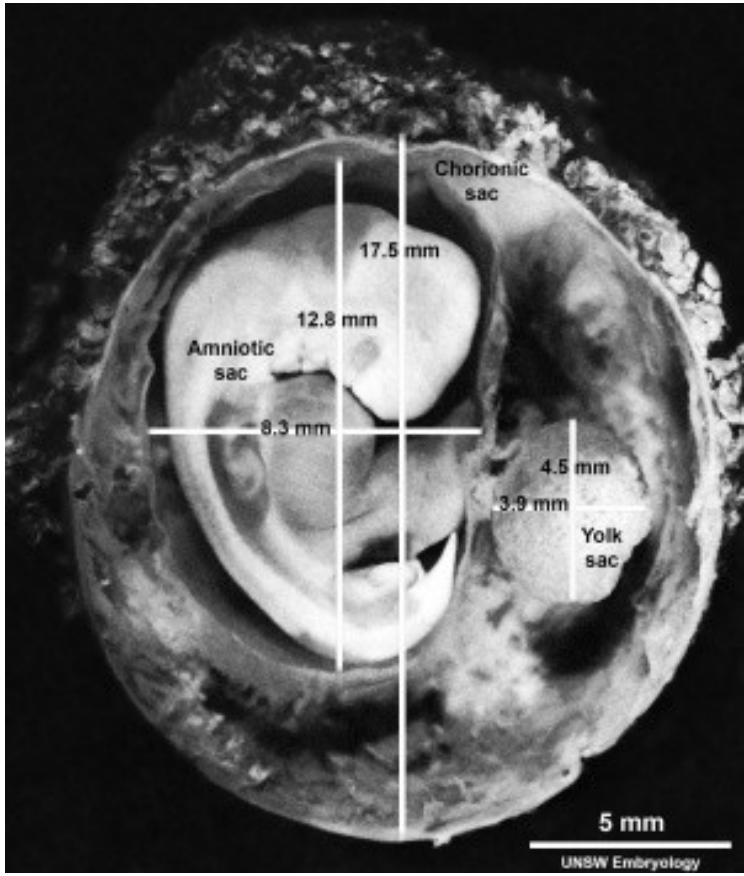
- **embryonic vasculogenesis** approx. 2 days later after establishment of extra-embryonic vessels
- primordial blood vessels
- heart primordium in cardiogenic area
- embryonic hematopoiesis from para-aortic clusters in AGM



DEVELOPMENT OF CARDIOVASCULAR SYSTEM

Week 4

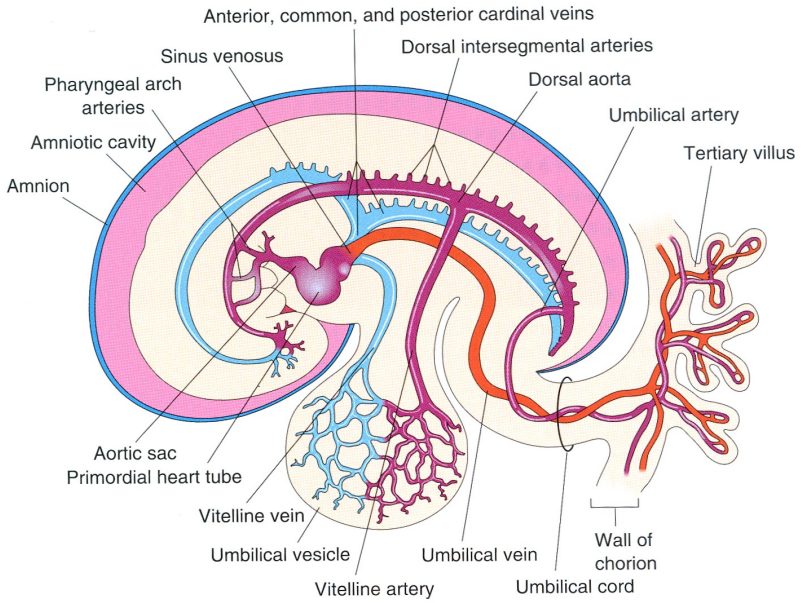




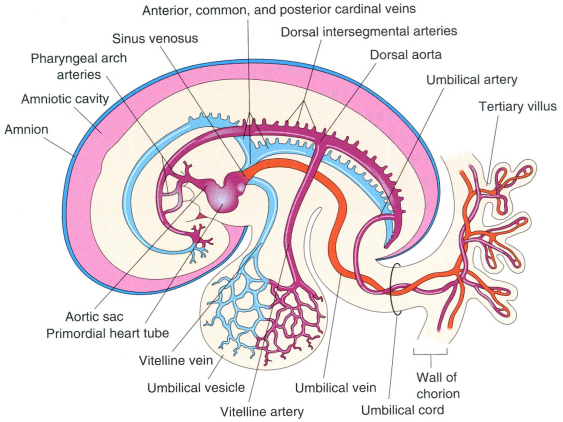
DEVELOPMENT OF CARDIOVASCULAR SYSTEM

Week 4

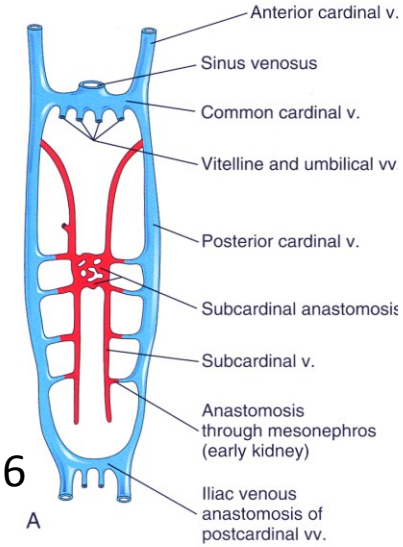
- **embryonic circulation**: heart tube → *truncus arteriosus* → aortal arches → paired dorsal aorta → caudally fuse into single aorta dorsalis → capillary beds → paired cardinal veins (drain pre- and postcardinal veins) → *ductus Cuvieri* → *sinus venosus*
- **vitelinne circulation**: dorsal aorta → *aa. omphalomesentericae* → fuse into single *a. omphalomesenterica* → *vv. omphalomesentericae + vv. umbilicales* → paired *truncus vitelloumbilicalis* → *sinus venosus*
- **umbilical circulation**: dorsal aorta → *aa. umbilicales* → chorion → *vv. umbilicales + vv. omphalomesentericae* → paired *truncus vitelloumbilicalis* → *sinus venosus*



DEVELOPMENT OF CARDIOVASCULAR SYSTEM



Week 4



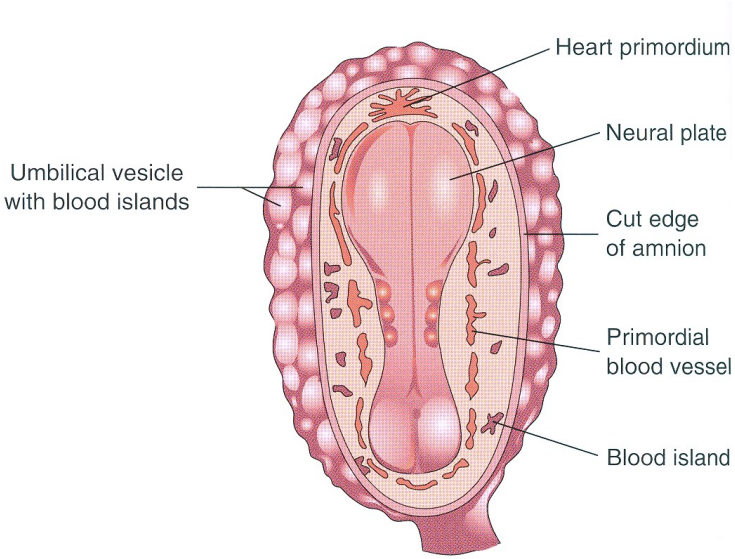
Week 6

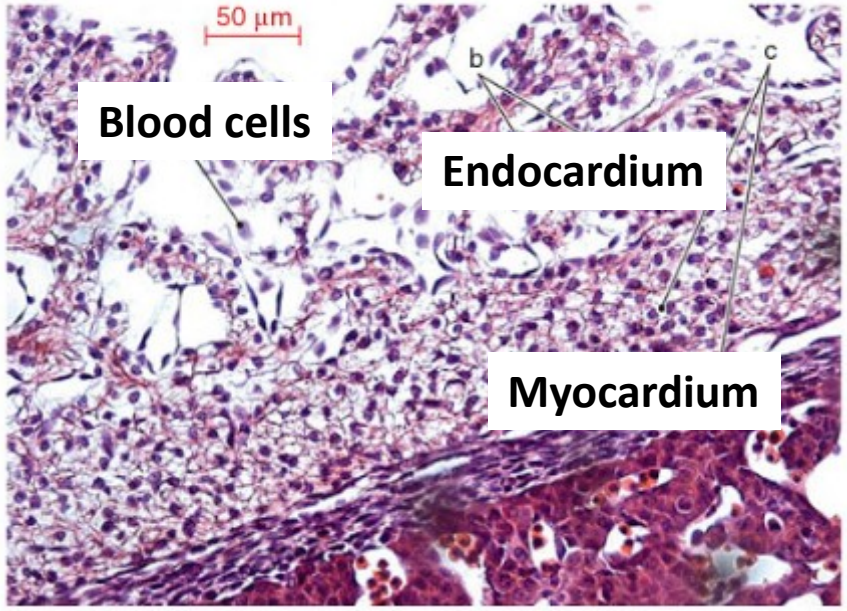
Cardinal, umbilical, and vitelline veins | Subcardinal veins | Supracardinal veins | Hepatic segment | Renal veins

Primitive heart development

Week 3

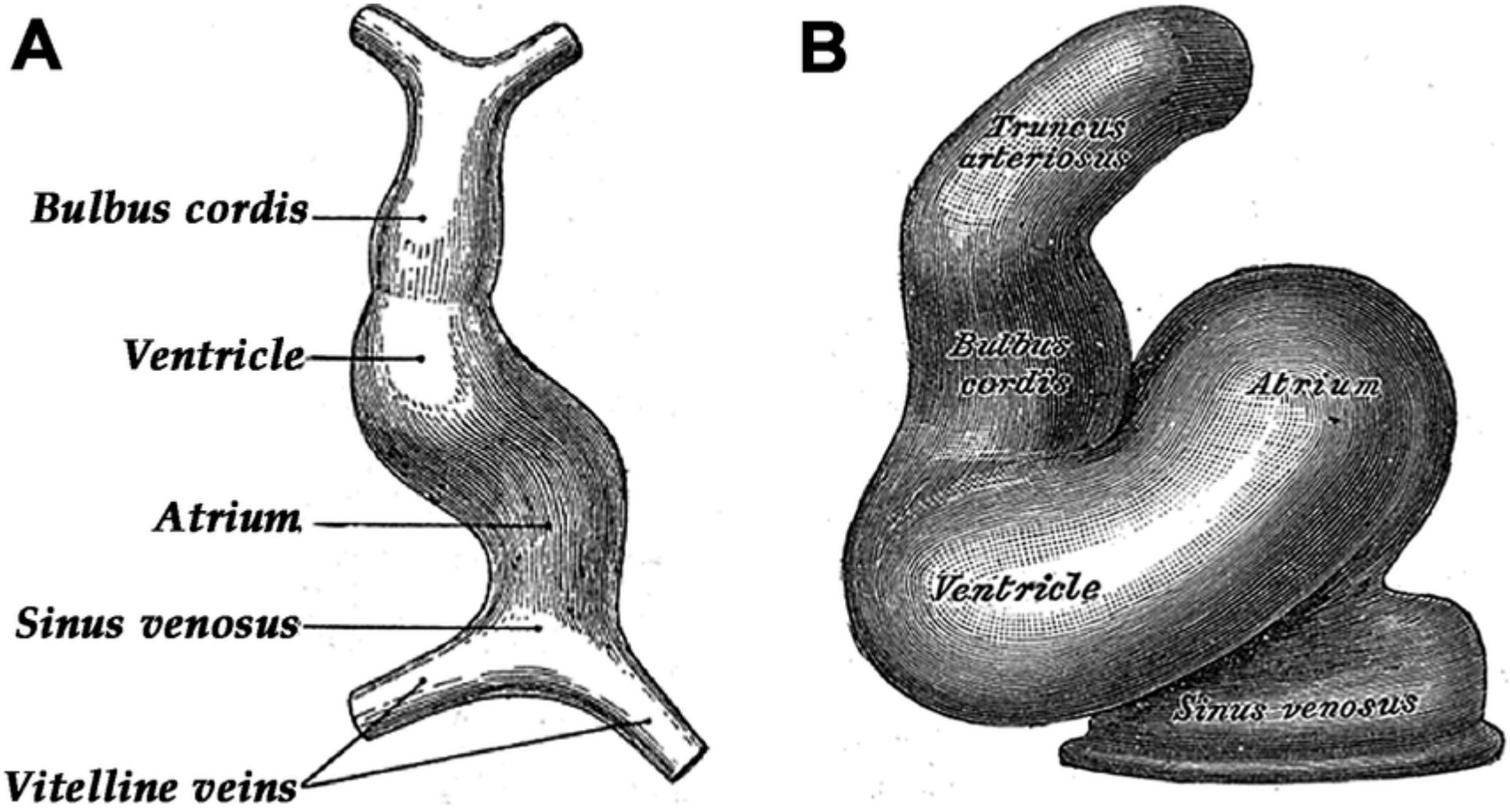
- paired endothelial **heart tubes** (cor tubulare duplex) derived from embryonic splanchnopleura in cardiogenic area
- flexion of the embryo → medial fusion of paired tubes into **simple-tubular heart** (cor tubulare simplex)
- visceral mesoderm constitutes **myoepicardial layer: myocardium** and **epicardium**
- **cardiac jelly** → subendocardial connective tissue
- heart starts beating day 21-22
- blood starts flow ~week 4th





Week 4

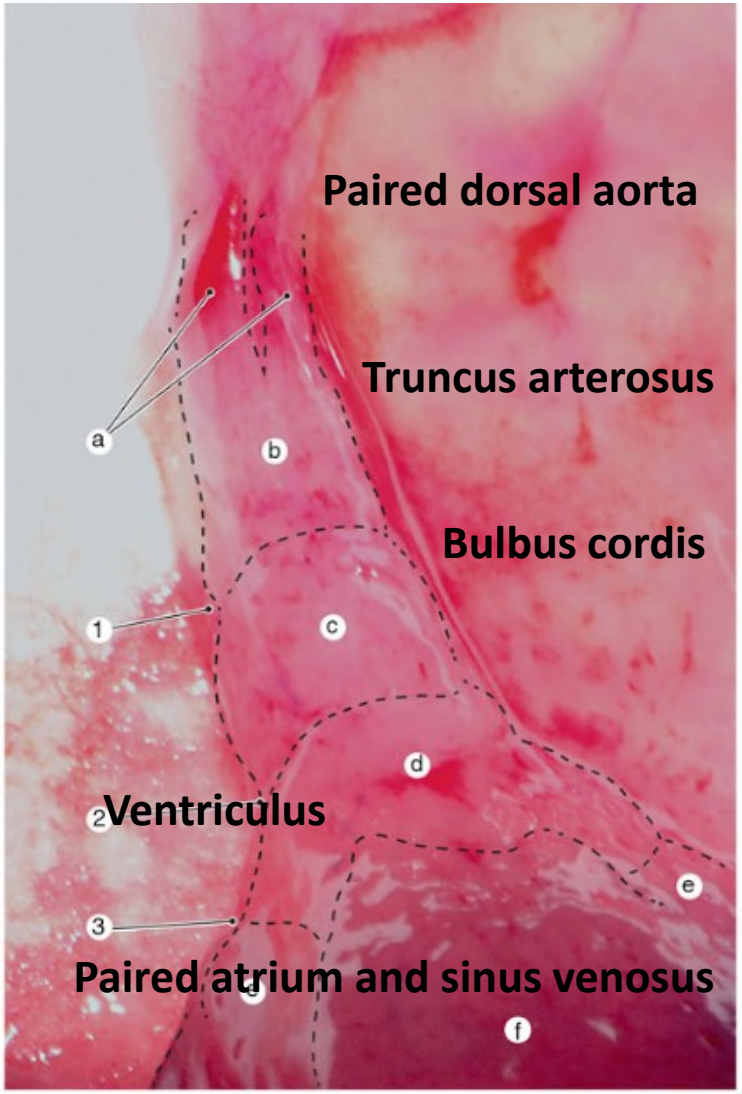
- **simple-tubular heart** (cor tubulare simplex and cor tubulare sigmoideum)
- **sinus venosus → atrium → ventriculus → bulbus cordis→ truncus arteriosus**



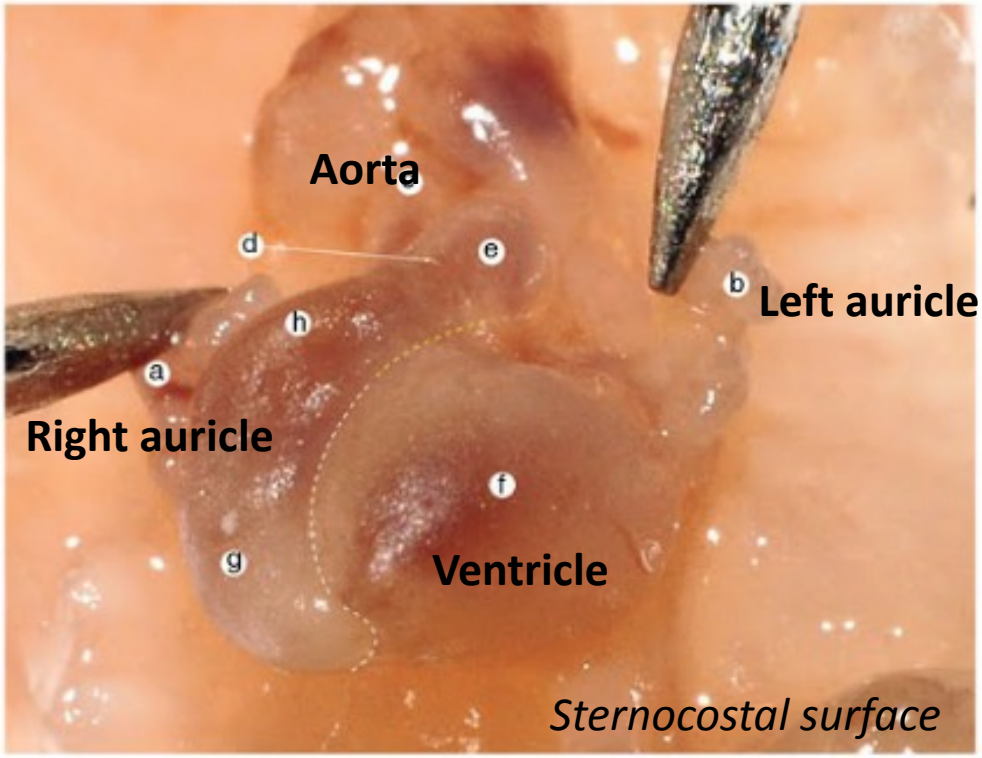
DEVELOPMENT OF CARDIOVASCULAR SYSTEM

Week 4

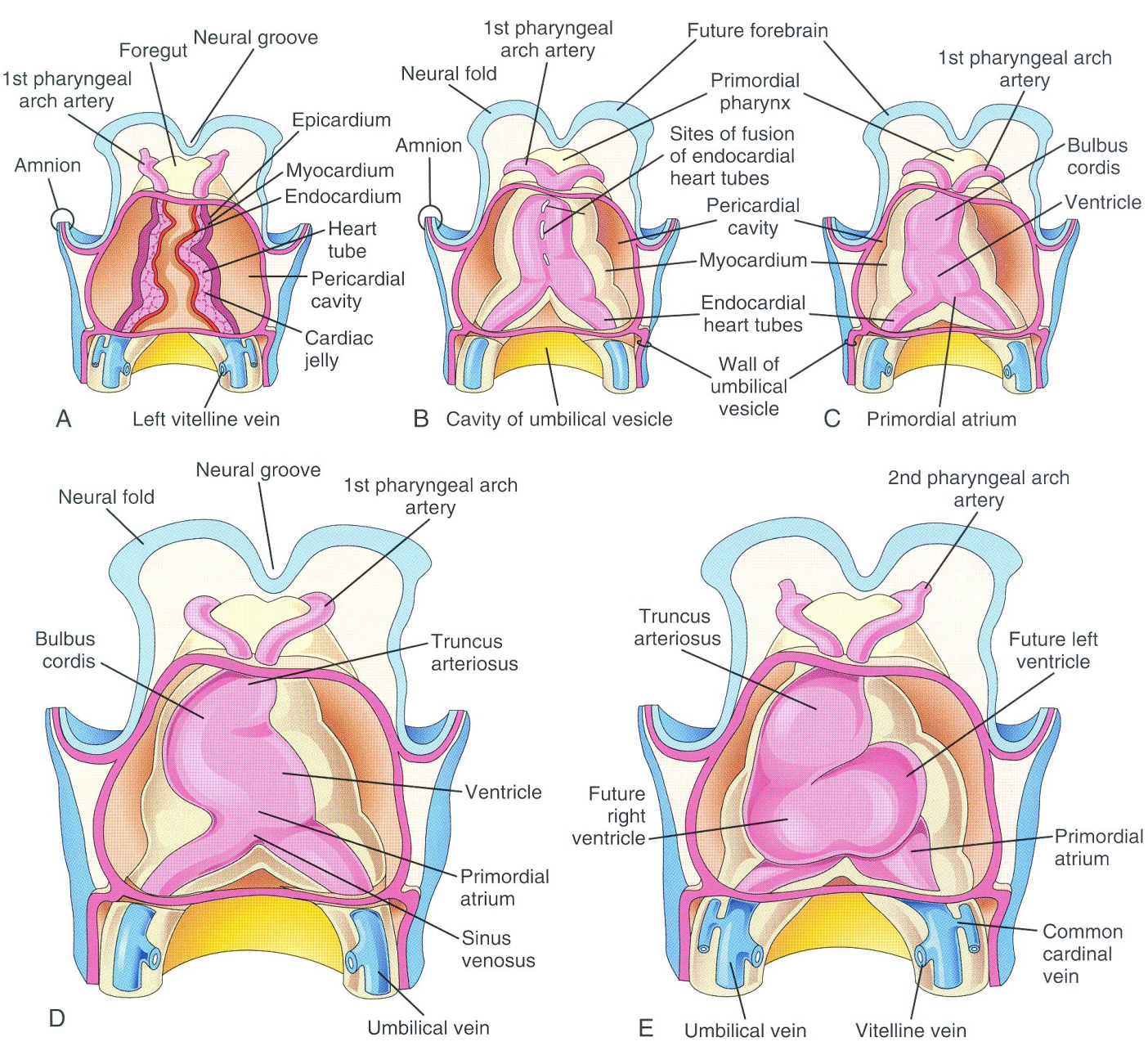
Cor tubulare simplex



Cor tubulare sigmoideum



DEVELOPMENT OF CARDIOVASCULAR SYSTEM

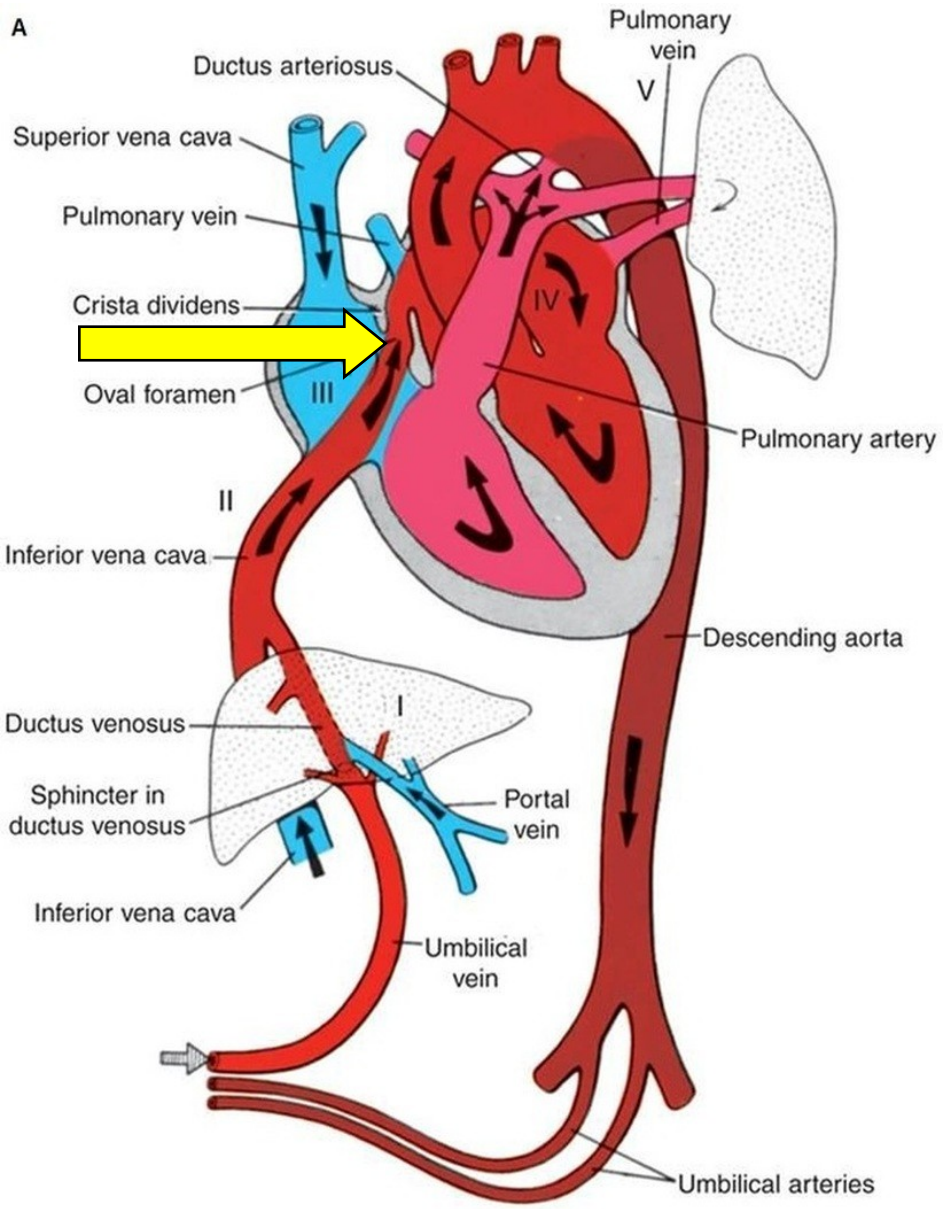


Partitioning of atrium commune

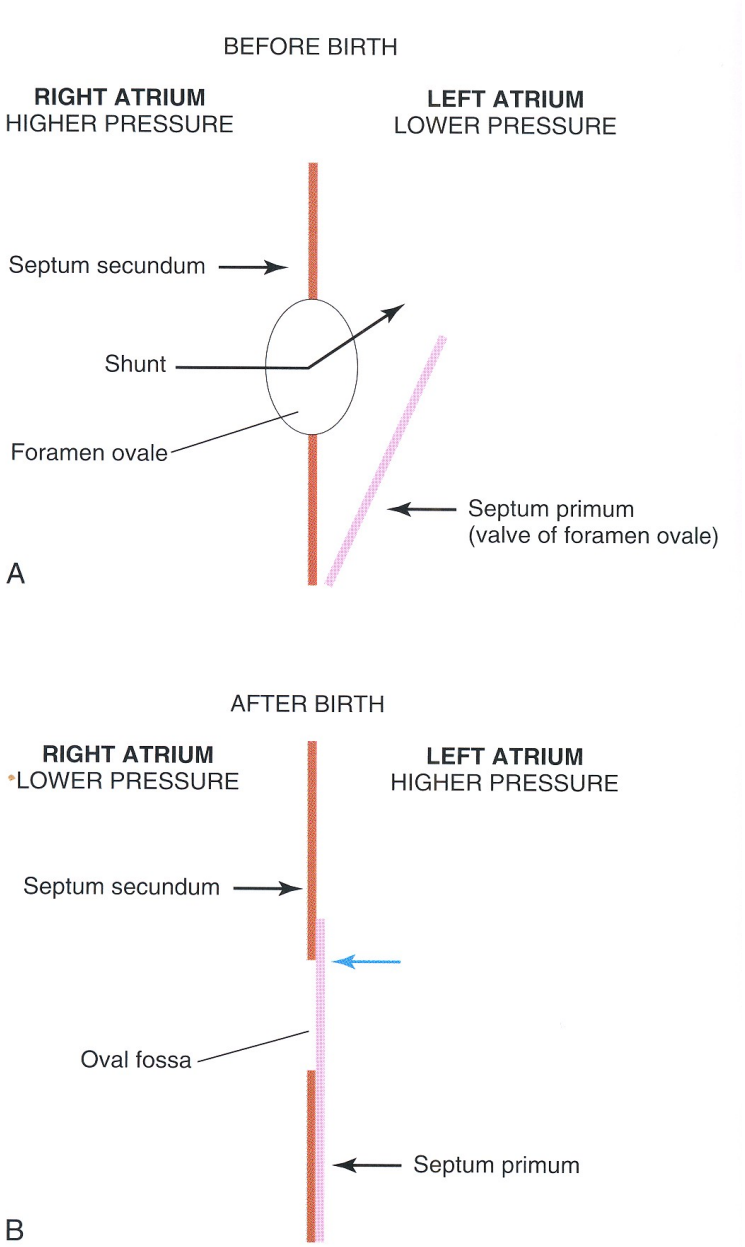
- septum primum grows from dorso-cranial wall towards endocardial cushions
- incoplete closure → **foramen** (ostium) **primum**
- by apoptosis → **foramen secundum**
- **septum secundum** → surrounds **foramen ovale**
- valvula foraminis ovalis from septum primum

- foramen ovale: crucial embryonic shunt
- foramen ovale patens

- after atrial septation:
- opening of sinus venosus shifts to the right
- rest of sinus venosus → sinus coronarius

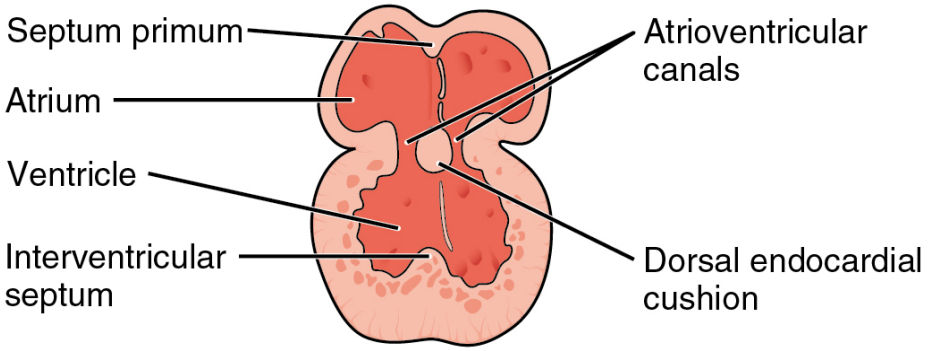


DEVELOPMENT OF CARDIOVASCULAR SYSTEM

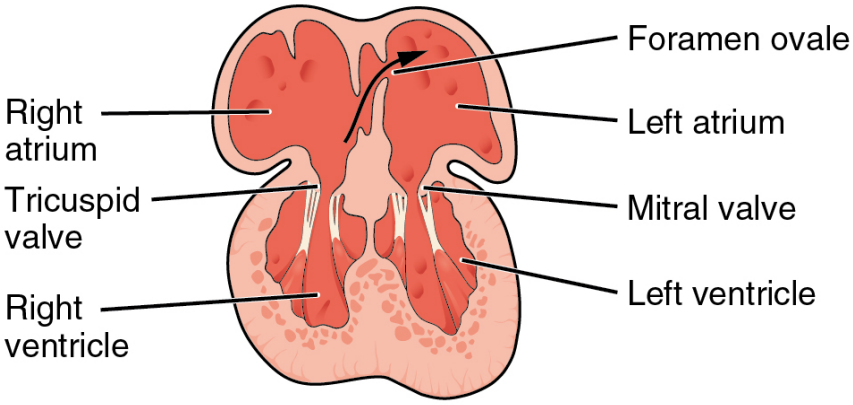


Partitioning of ventriculus communis

- septum interventriculorum primitivum – temporary
- septum interventriculare at the end of week 4 – grows cranially
- foramen interventricualre – closure linked to development of aortico-pulmonary septum



28 days

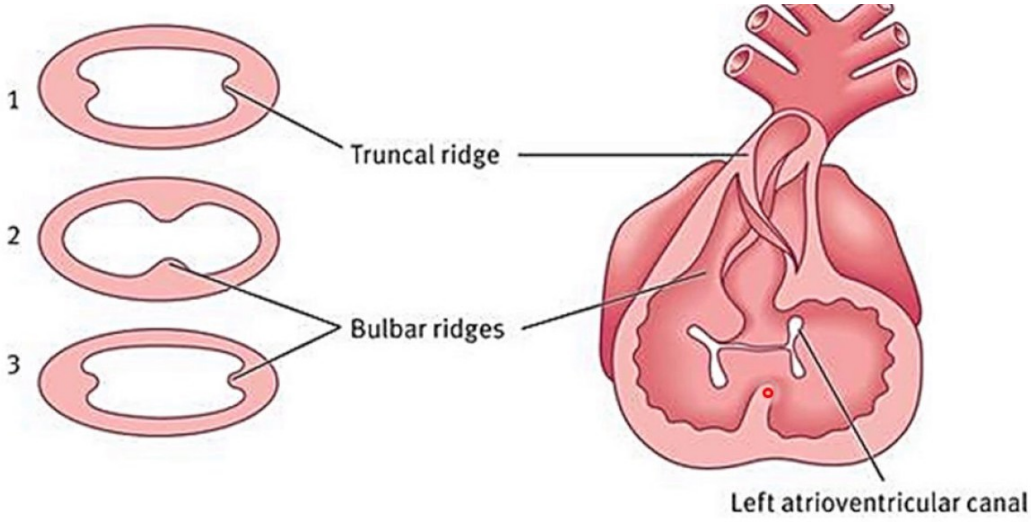


8 weeks

DEVELOPMENT OF CARDIOVASCULAR SYSTEM

- Partitioning of **bulbus cordis and truncus arteriosus**
- 5th week – ridges in bulbus and truncus from neural-crest mesenchyme
- 180° spiraling – spiral aortico-pulmonary septum
- pulmonary trunk twists around aorta

- bulbus cordis is embedded into the definitive ventricles:
- right ventricle: conus arterious (infundibulum) → pulmonary trunk
- left ventricle: aortic vestibule

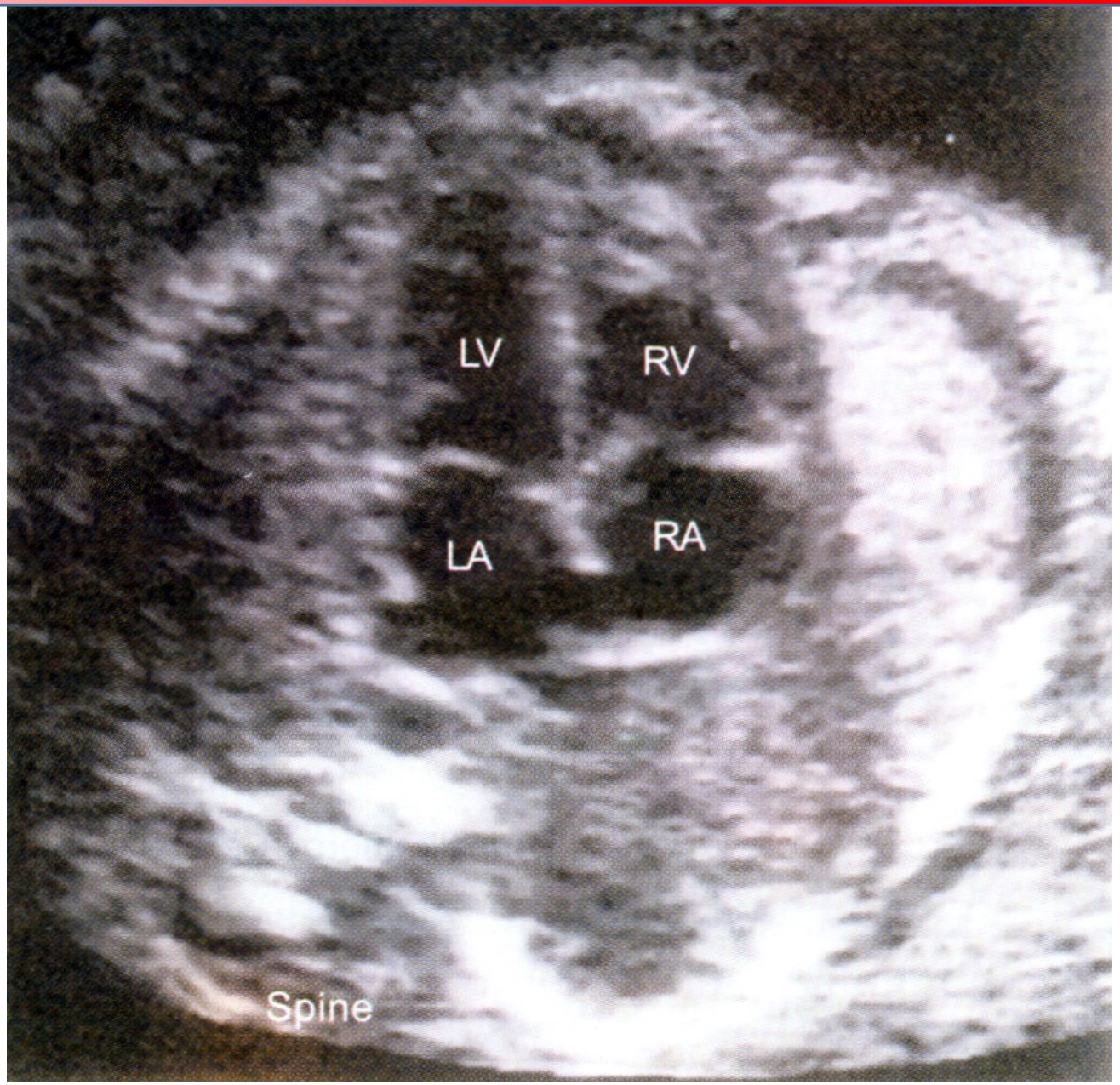


gestation

Intrauterin

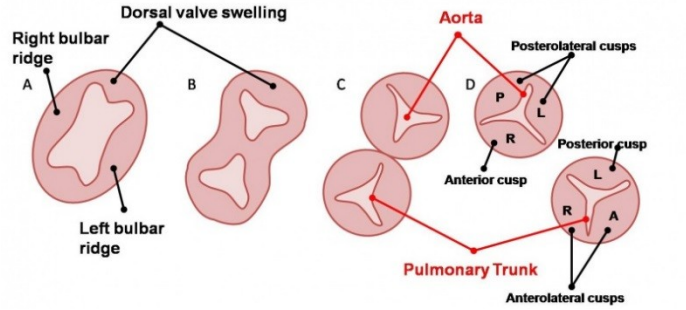
DEVELOPMENT OF CARDIOVASCULAR SYSTEM

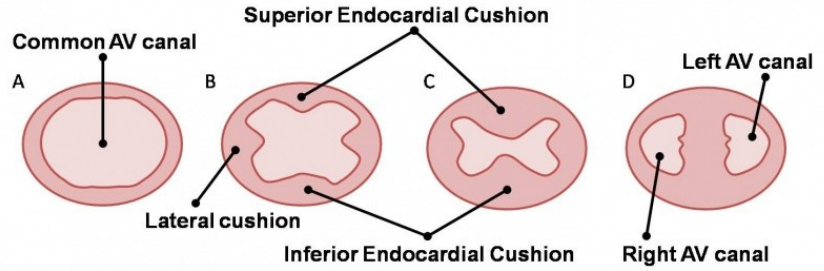
Week 20

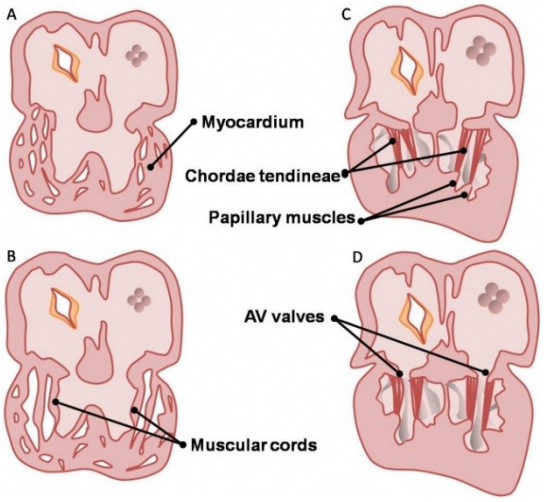


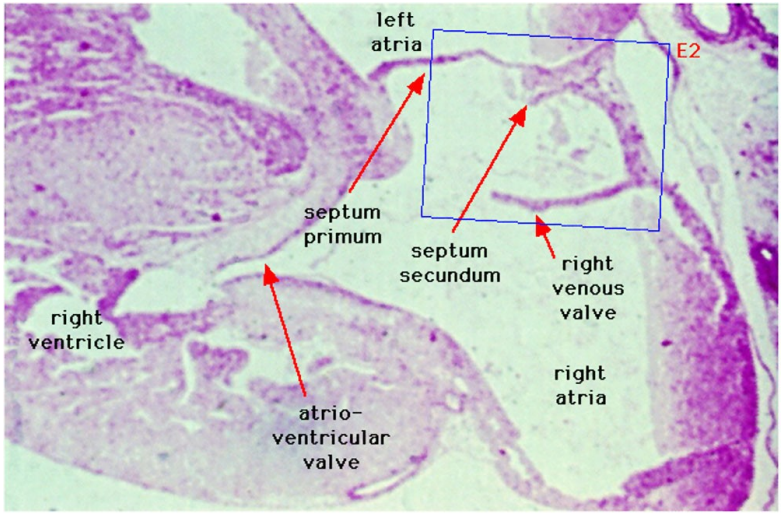
DEVELOPMENT OF CARDIOVASCULAR SYSTEM

- Development of **cardiac valves**
- **semilunar valves** develop by the partitioning of truncus arteriosus from three swellings of endocardial tissue
- neural crest origin
- **AV valves** (tricuspid and mitral) develop similarly at AV canals

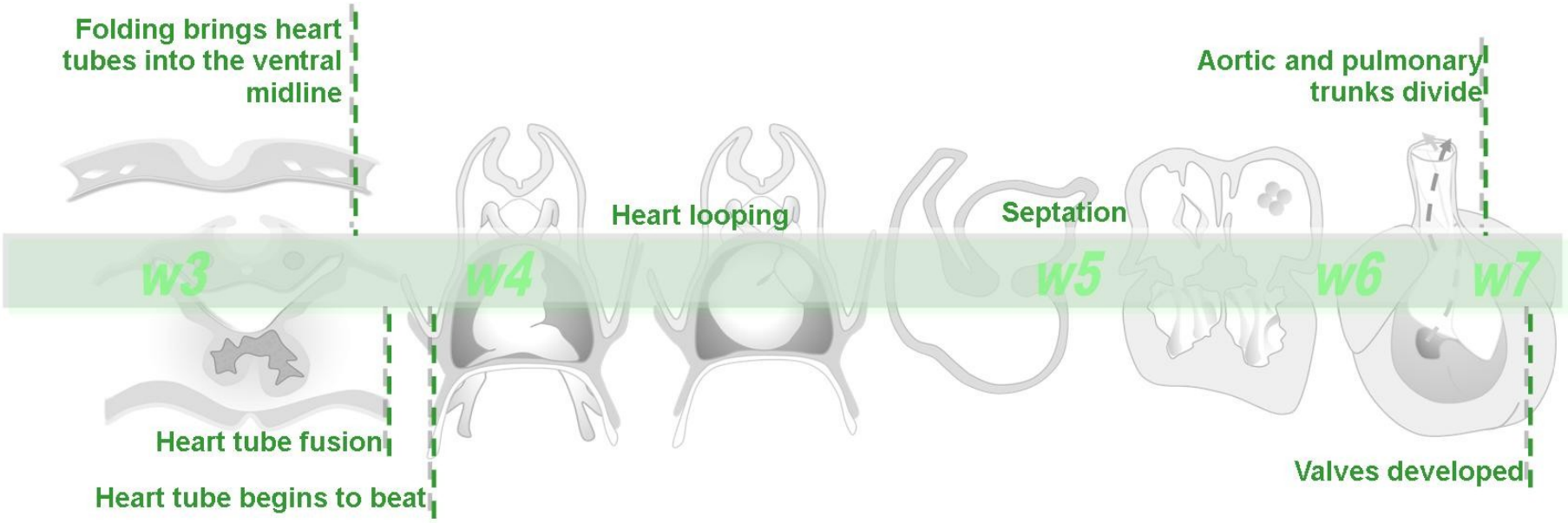


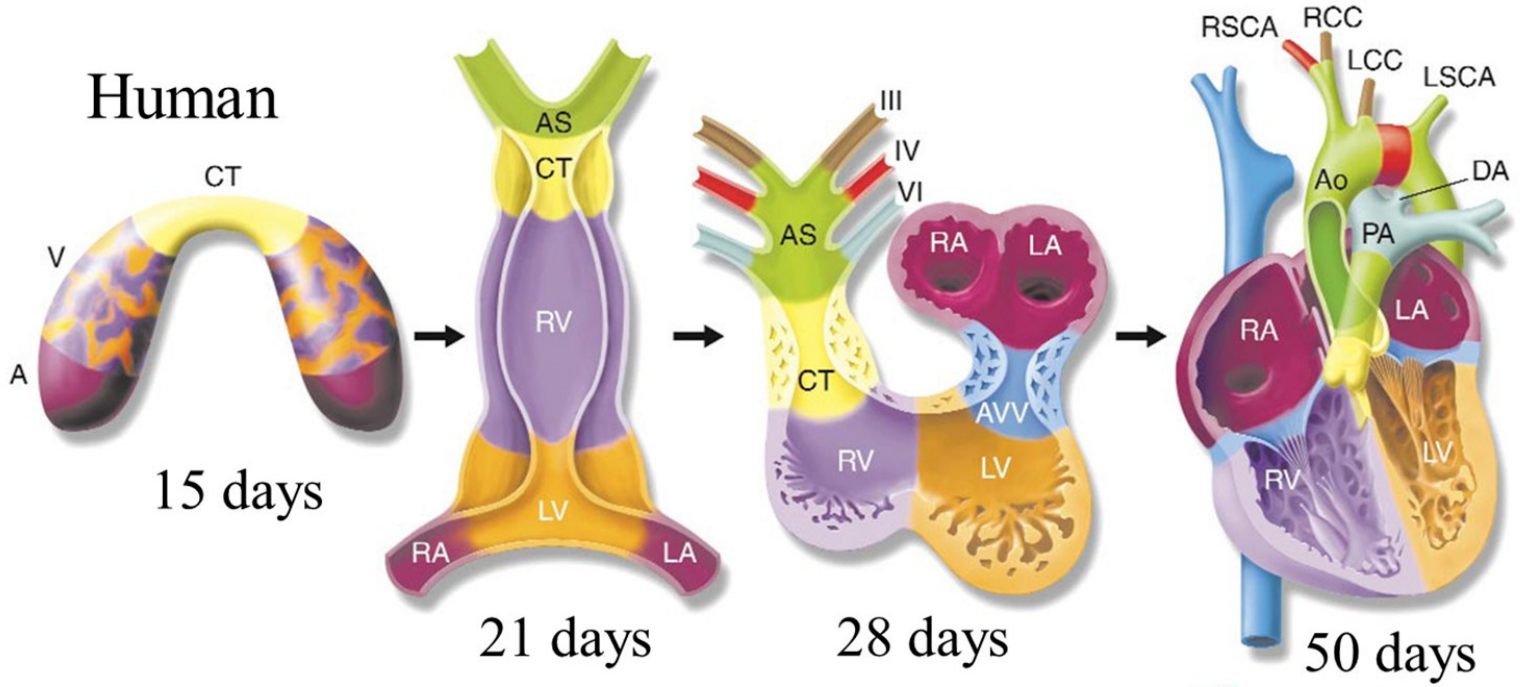




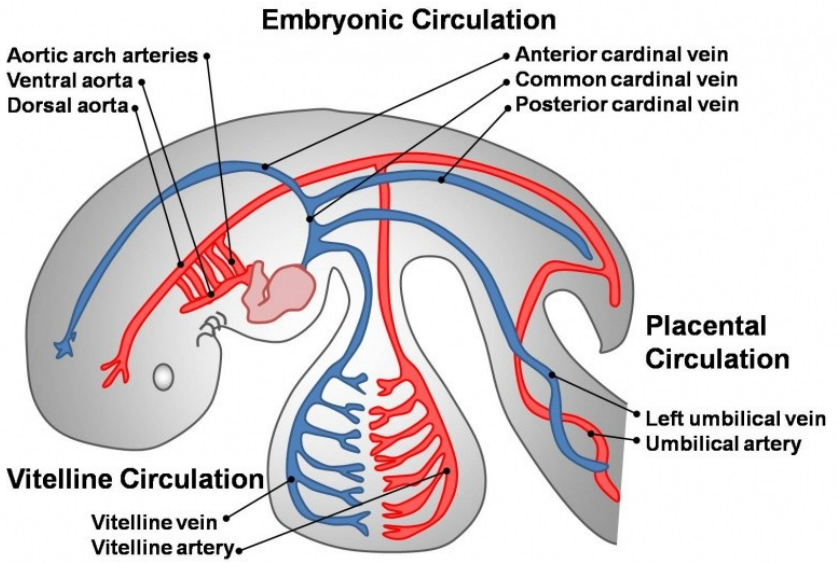


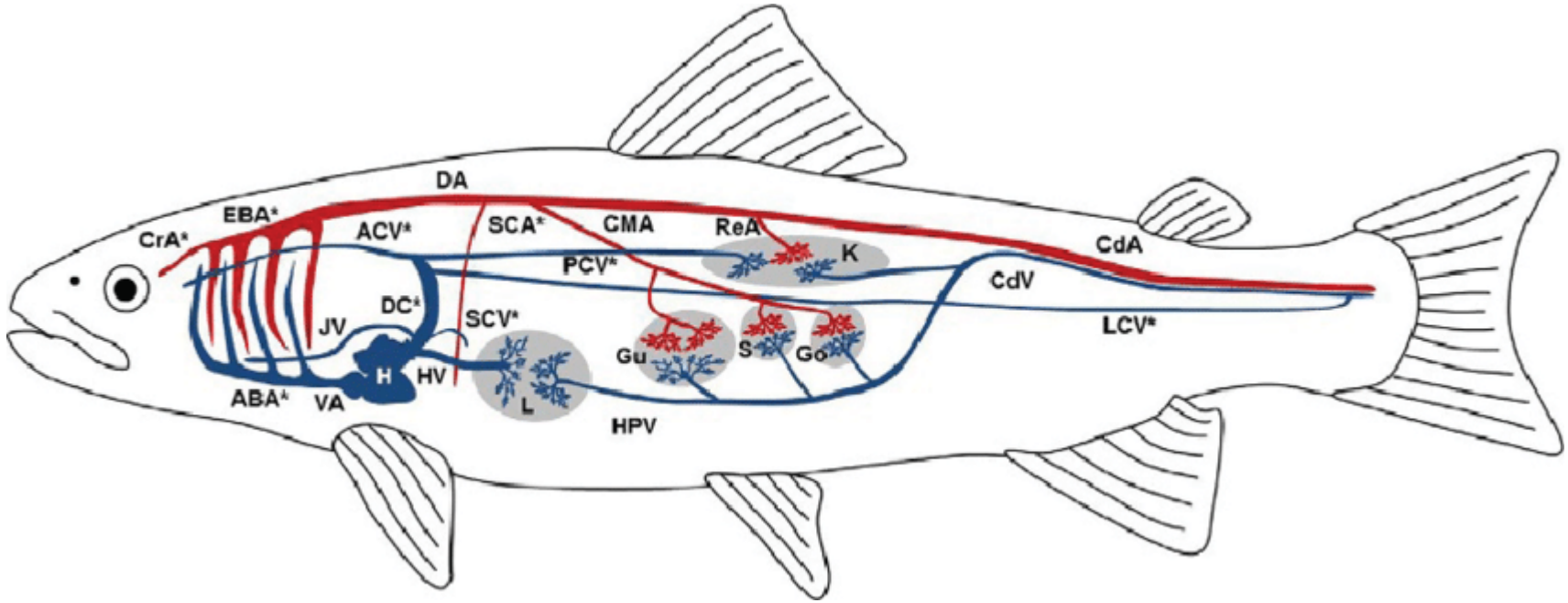
DEVELOPMENT OF CARDIOVASCULAR SYSTEM



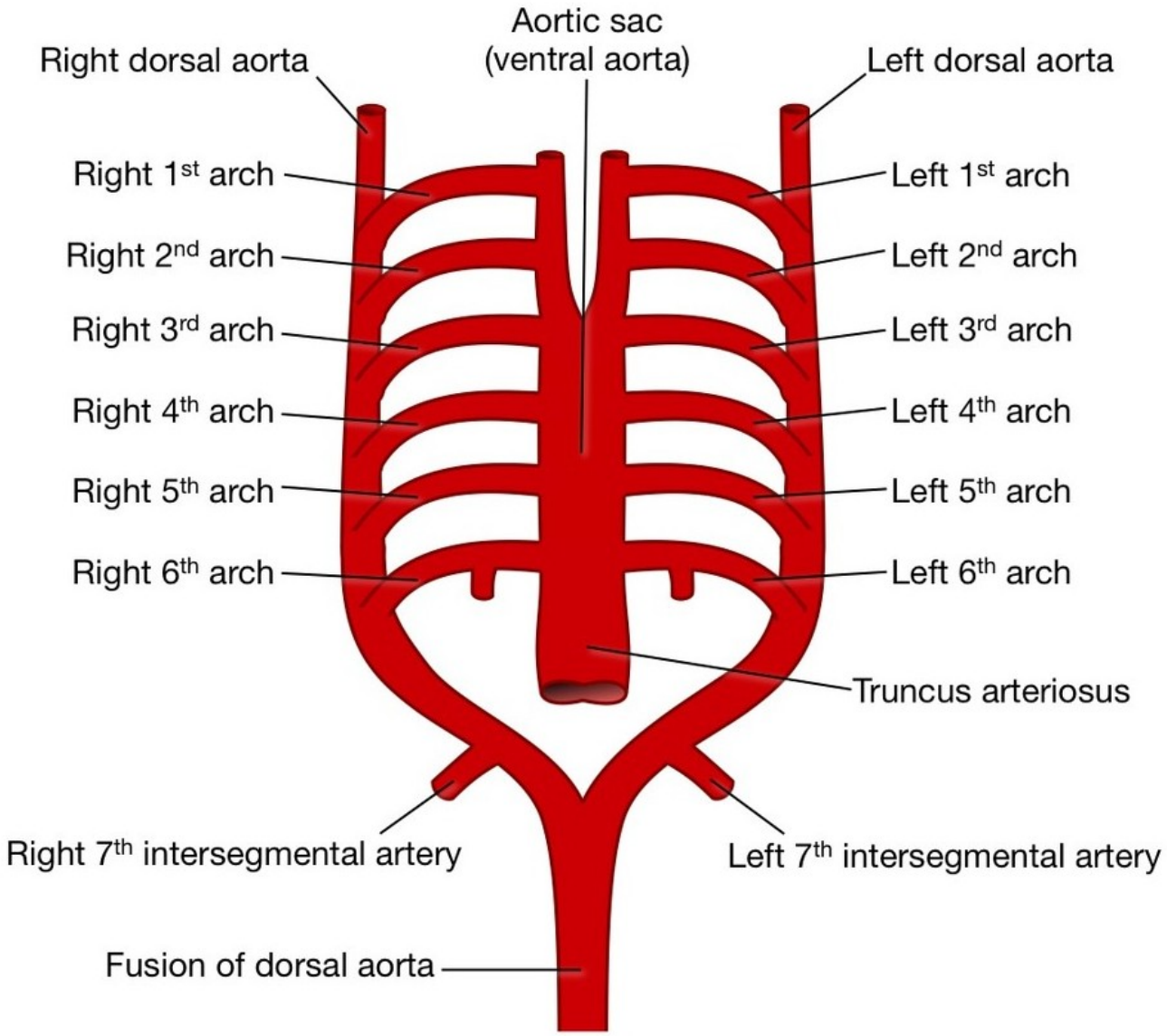


DEVELOPMENT OF CARDIOVASCULAR SYSTEM

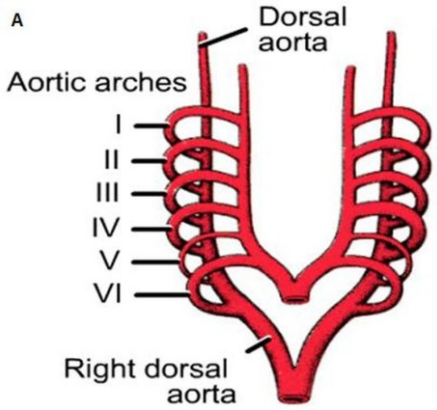




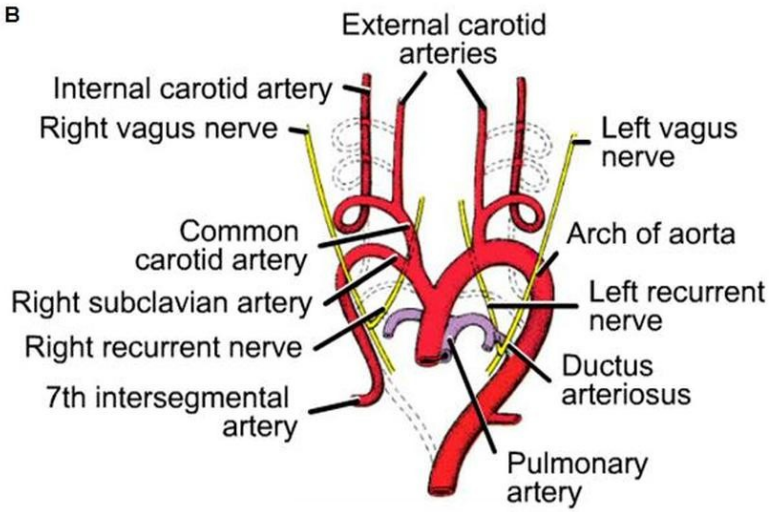
Development of **large arteries – aortic arches**



Aortic arches

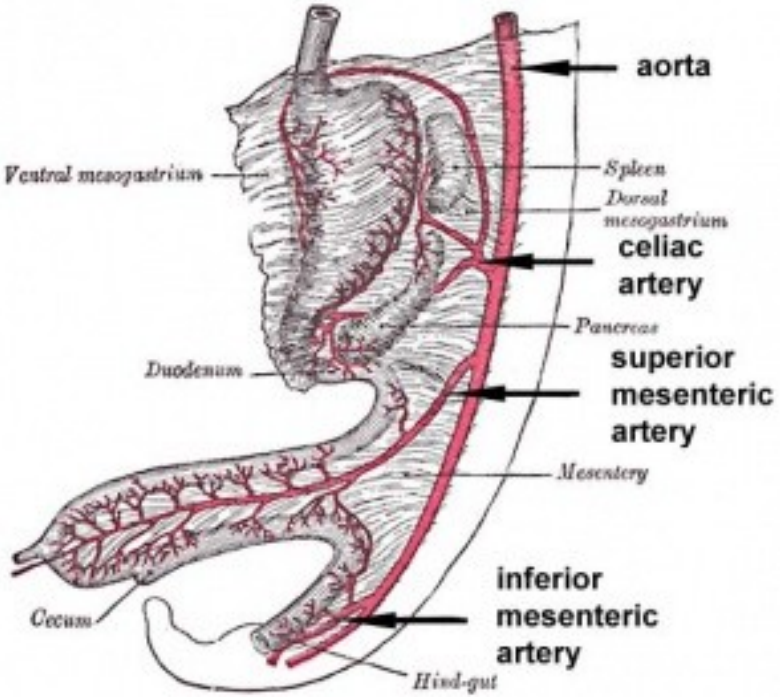


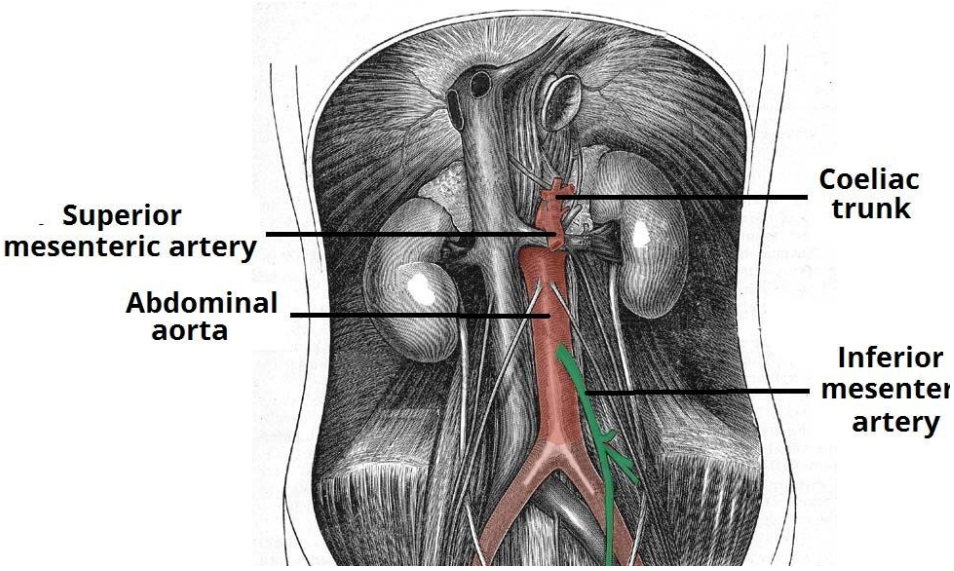
1	mostly disappears, **a. maxillaris**
2	mostly disappears, **a. stapedia** and **a. hyoidea**
3	**a. carotis communis**, **a. carotis interna**
4	right: proximal part of **a. subclavia dextra** (distal part from dorsal aorta and 7th intersegmental artery); left: **arcus aortae**
5	does not develop
6	right: from proximal part: **a. pulmonalis dextra**, distal part disappears left: from proximal part: **a. pulmonalis sinistra**, from distal part: **ductus arteriosus**.



Vitelline arteries

- aa. vitellinae (aa. omphalomesentericae) reduced to three principal vessels:
  1. **truncus coeliacus**
  2. **a. mesenterica superior**
  3. **a. mesentrica inferior**

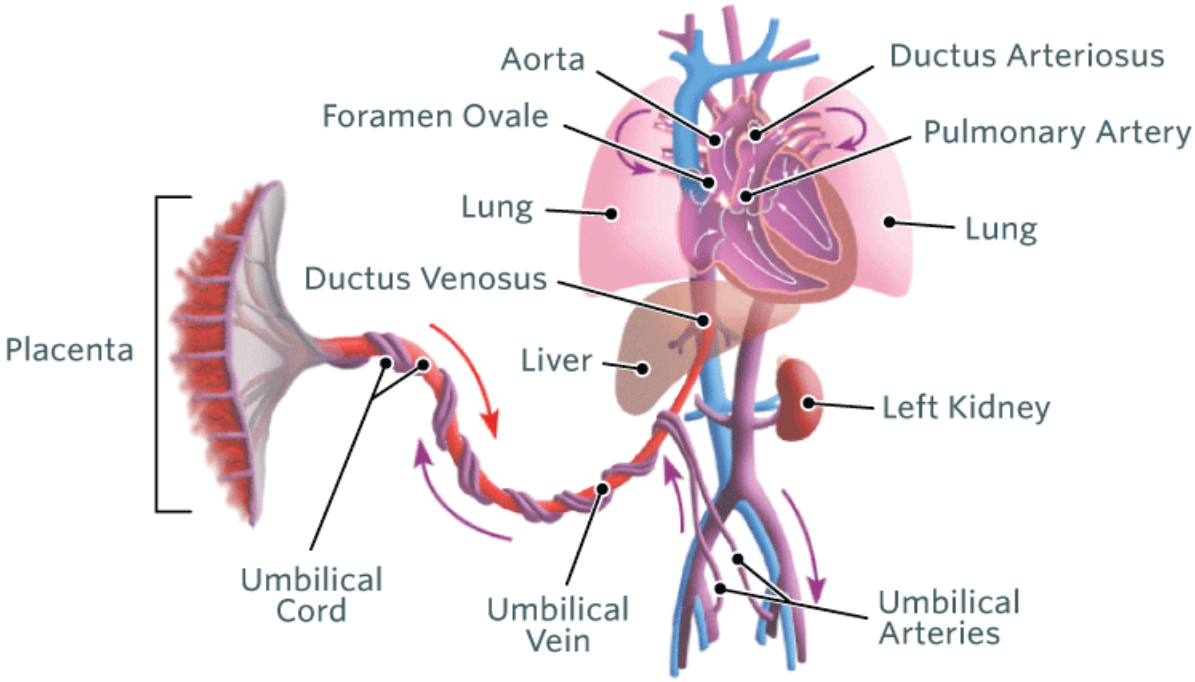




Umbilical arteries

- First, aa. umbilicales are ventral branches of dorsal aorta
- Later, aa. umbilicales are continuations to aa. iliacae communes and aa. communes internae.

- After birth: proximal parts of aa. umbilicales form aa. iliacae internae and aa. vesicales superiores. Distal parts obliterate.



Inferior vena cava

- four primary segments

1 hepatic segment (proximal part of the right vitelline vein = hepatic vein)
2 prerenal segment (right subcardinal vein)
3 renal segment (subcardinal – supracardinal anastomosis)
4 postrenal segment (right supracardinal vein)

- **Anomalies of venae cavae**

- **Double SVC**: persistence of left anterior cardinal vein; Abnormal CVC opens to right atrium through sinus coronarius
- **Left SVC**: right anterior cardinal vein and v. cardinalis communis degenerate
- **Absence of hepatic segment** of IVC: blood drained through v. azygos and hemiazygos into right atrium. Vv. hepaticae opens to right atrium individually.
- **Double IVC**: absence of anastomoses between primitive caudal veins.

Vv. omphalomesentericae

- bring blood from yolk sac
- septum transversum
- sinus venosus (together with umbilical veins as trunci vitelloumbilicales)
- growth of liver – separation of omphalomesenteric veins to proximal (yolk sac-liver) and distal parts (liver-heart)
- distal parts form anastomoses and develop into v. portae
- proximal parts dorm posthepatic part of IVC

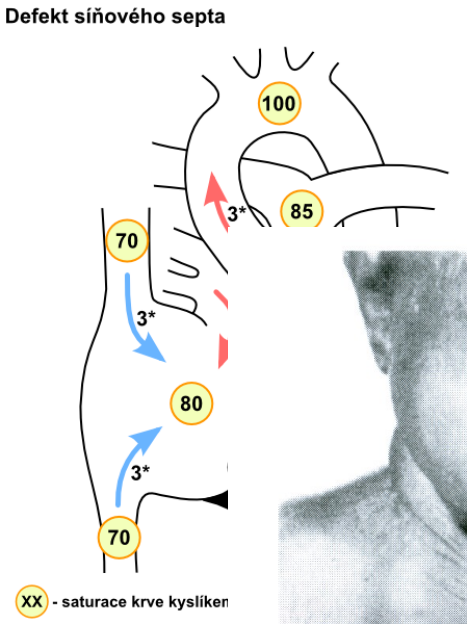
Vv. umbilicales

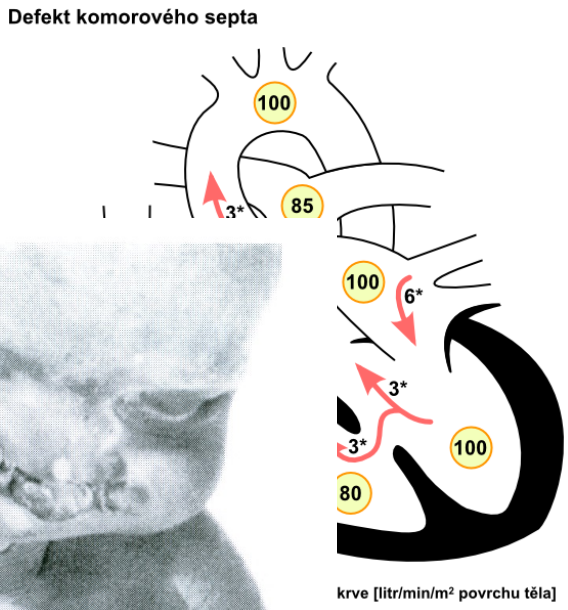
- begin in chorionic villi
- due to liver growth lose connection with sinus venosus
- proximal parts of both veins disappear
- distal part of right v. umbilicalis disappears
- distal part of left v. umbilicalis forms ductus venosus

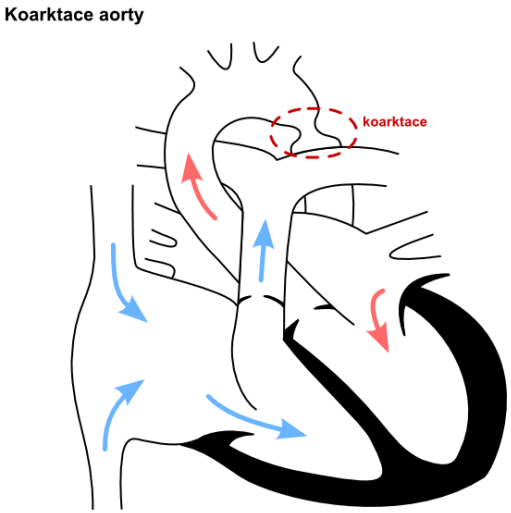
DEVELOPMENT OF CARDIOVASCULAR SYSTEM

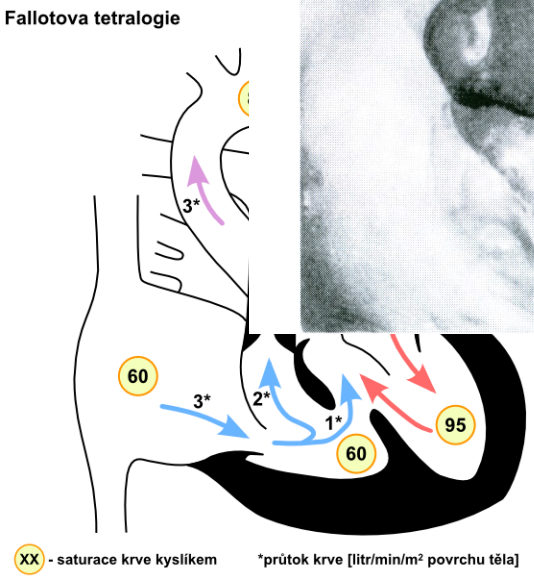
Teratology

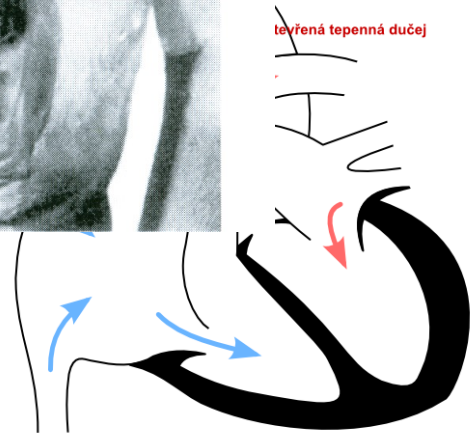
- Acardia
- Ectopia cordis
- Dextrocardia
- Atrial septal defects
- Ventricular septal defects
- Stenosis of truncus pulmonalis
- Atresia pulmonaris
- Tetra (penta)llogy of Fallot
- Coartaction of aorta
- Ductus arteriosus apertus

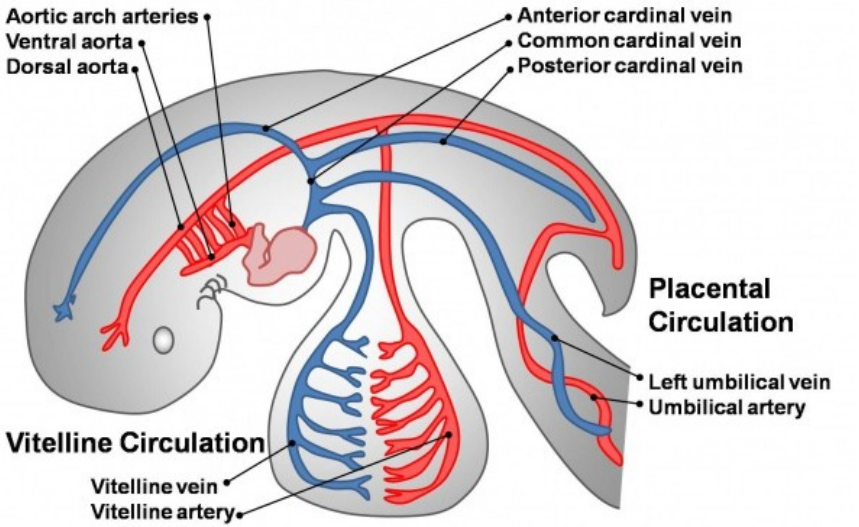






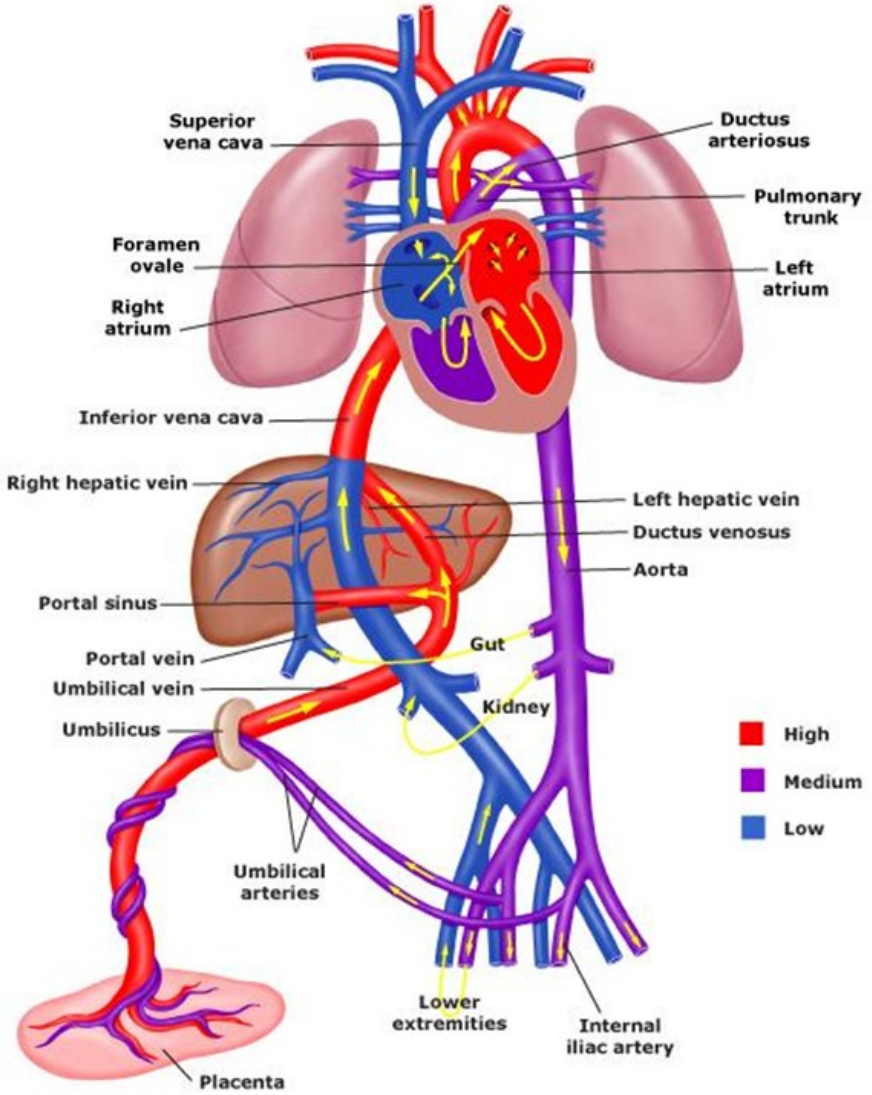




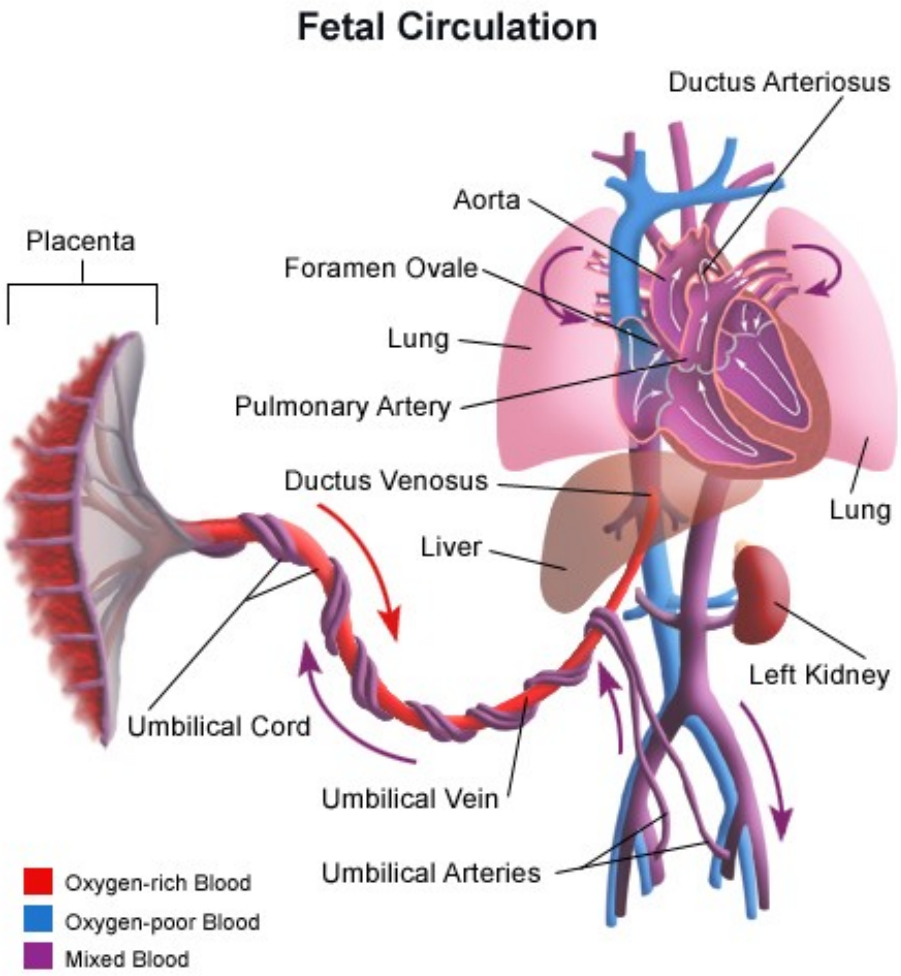


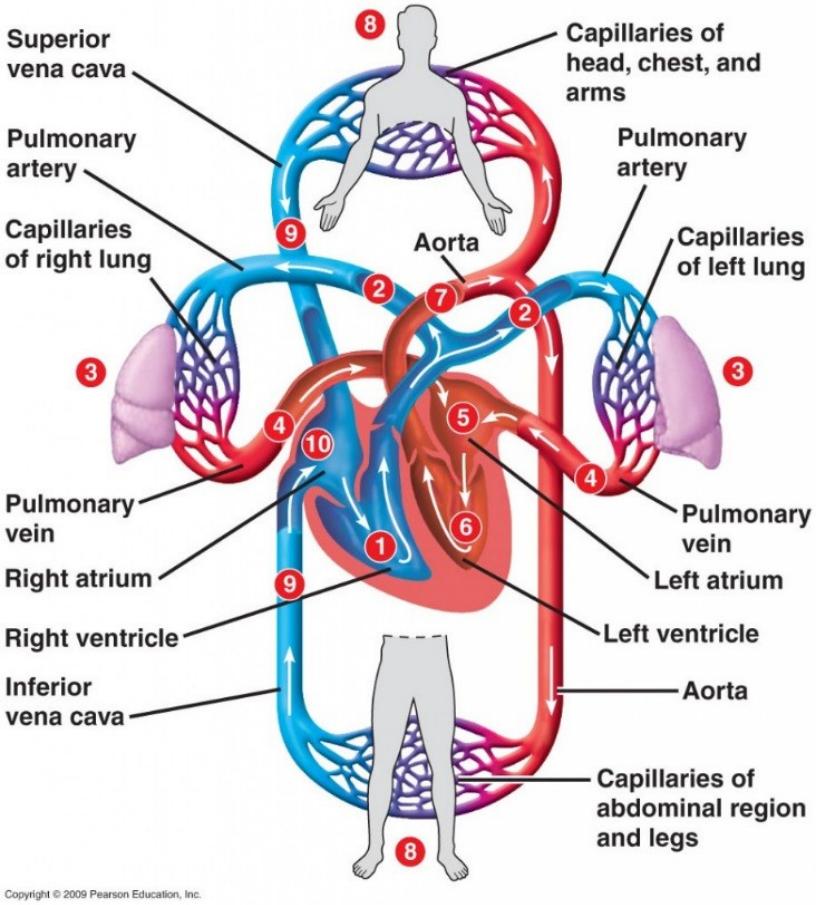
Embryonic circulation

Fetal circulation



DEVELOPMENT OF CARDIOVASCULAR SYSTEM





Thank you for attention

Questions? Comments?

pvanhara@med.muni.cz