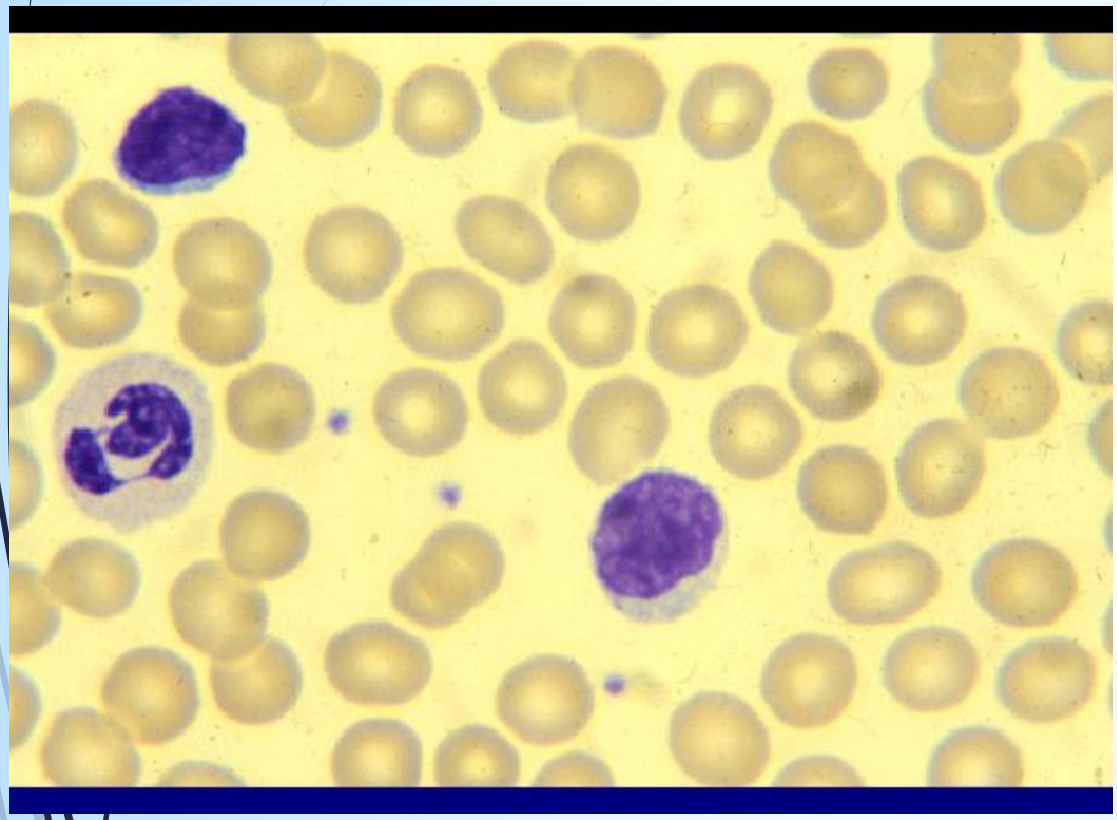
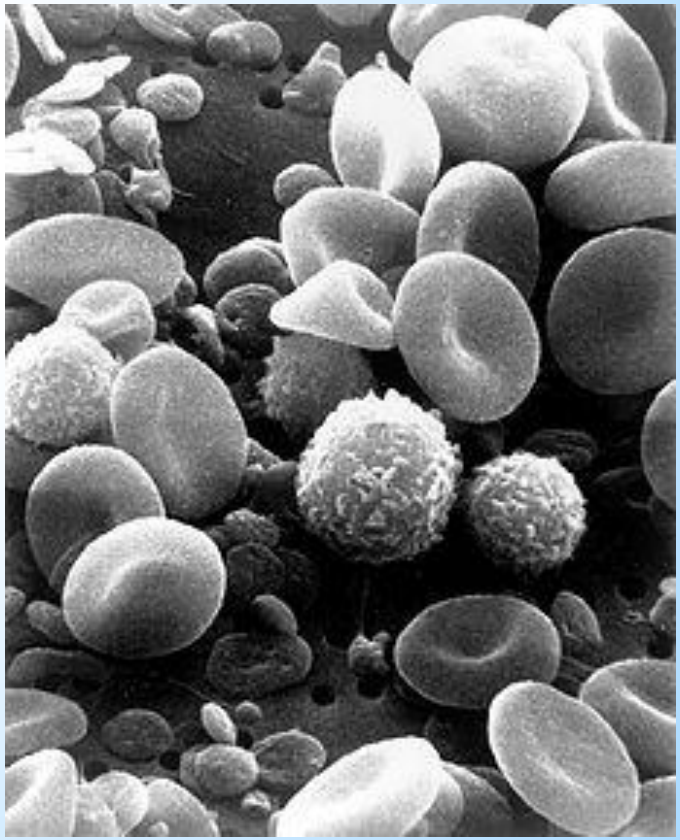
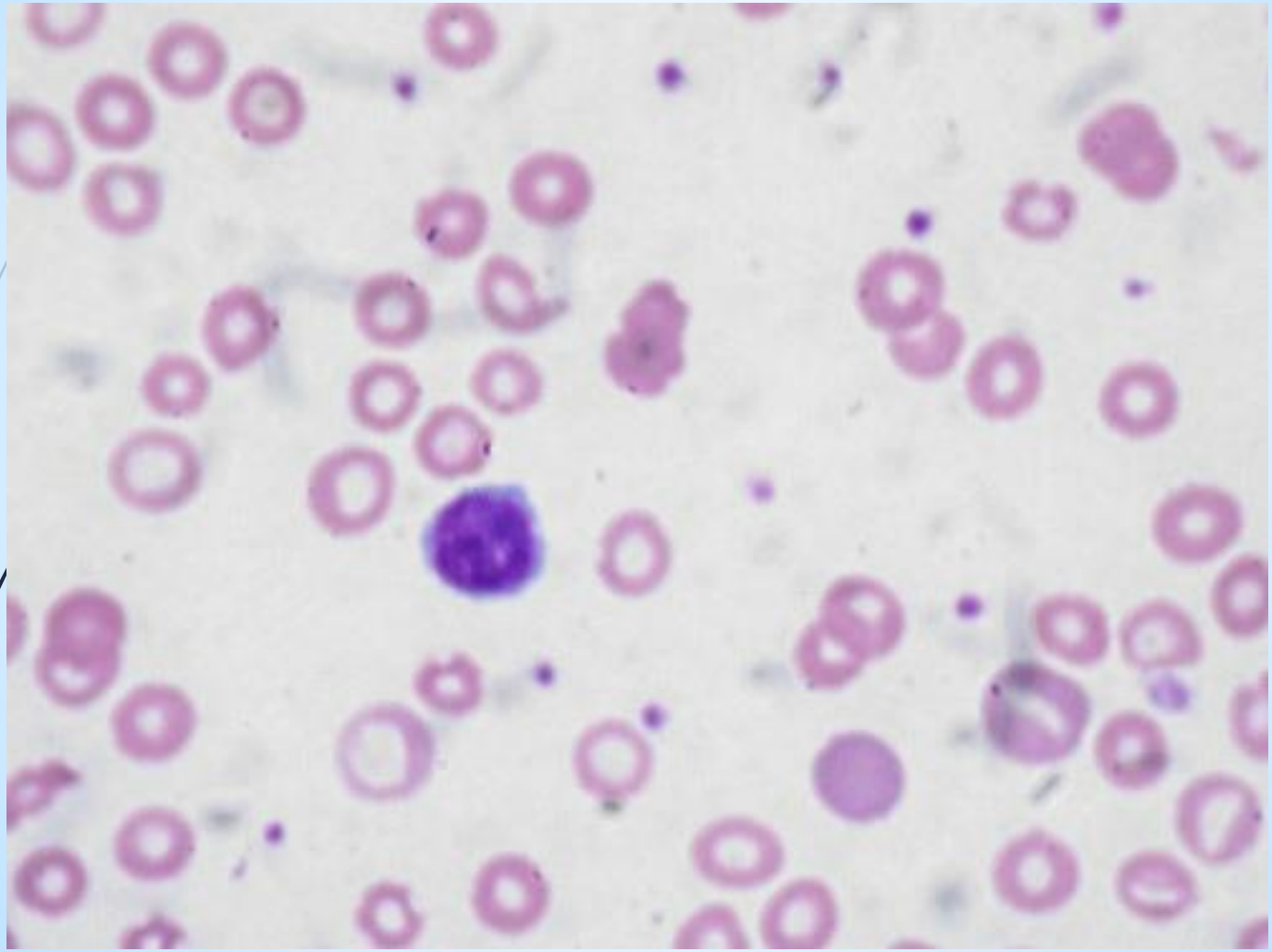
Anemias

„Normal“ blood smear

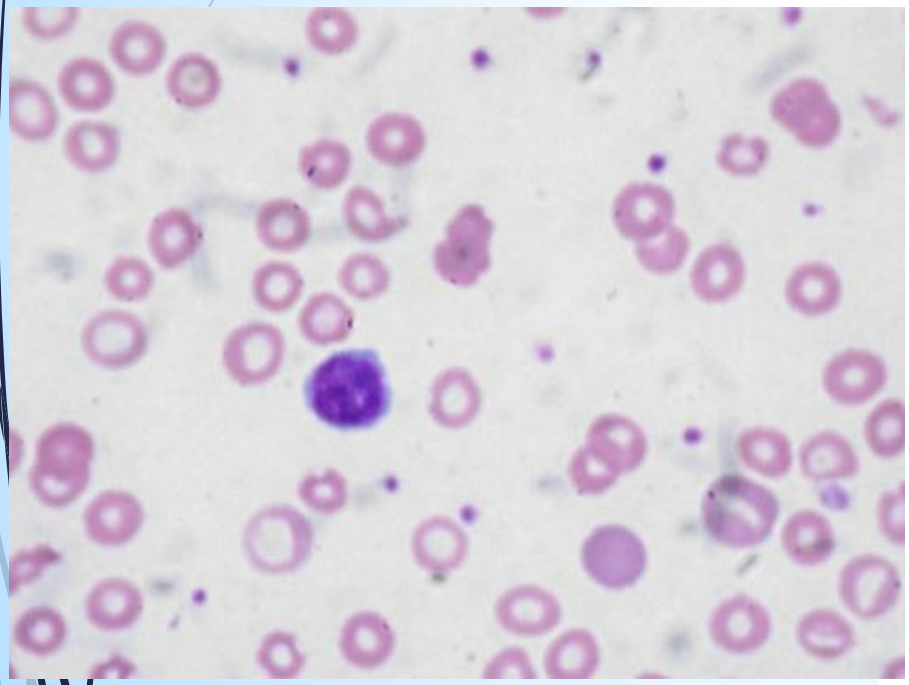




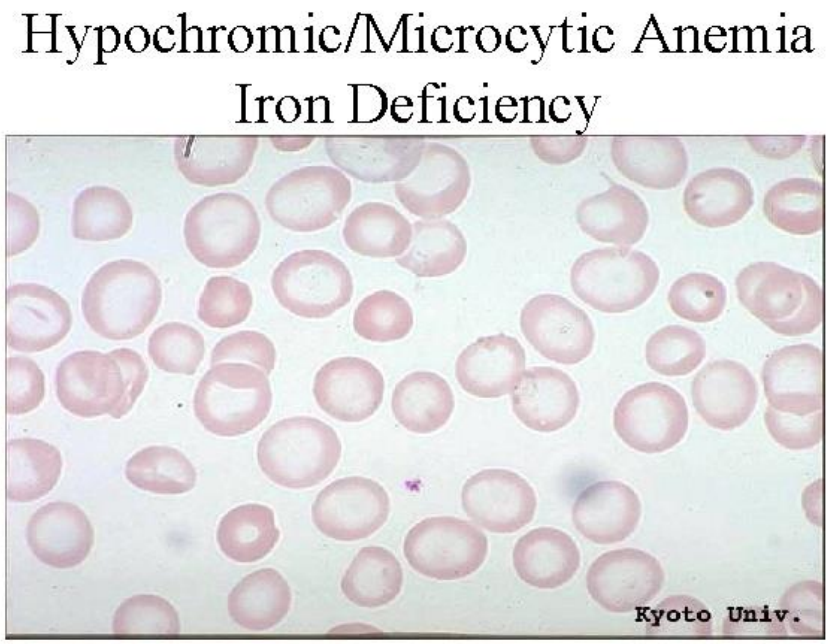


Iron deficiency

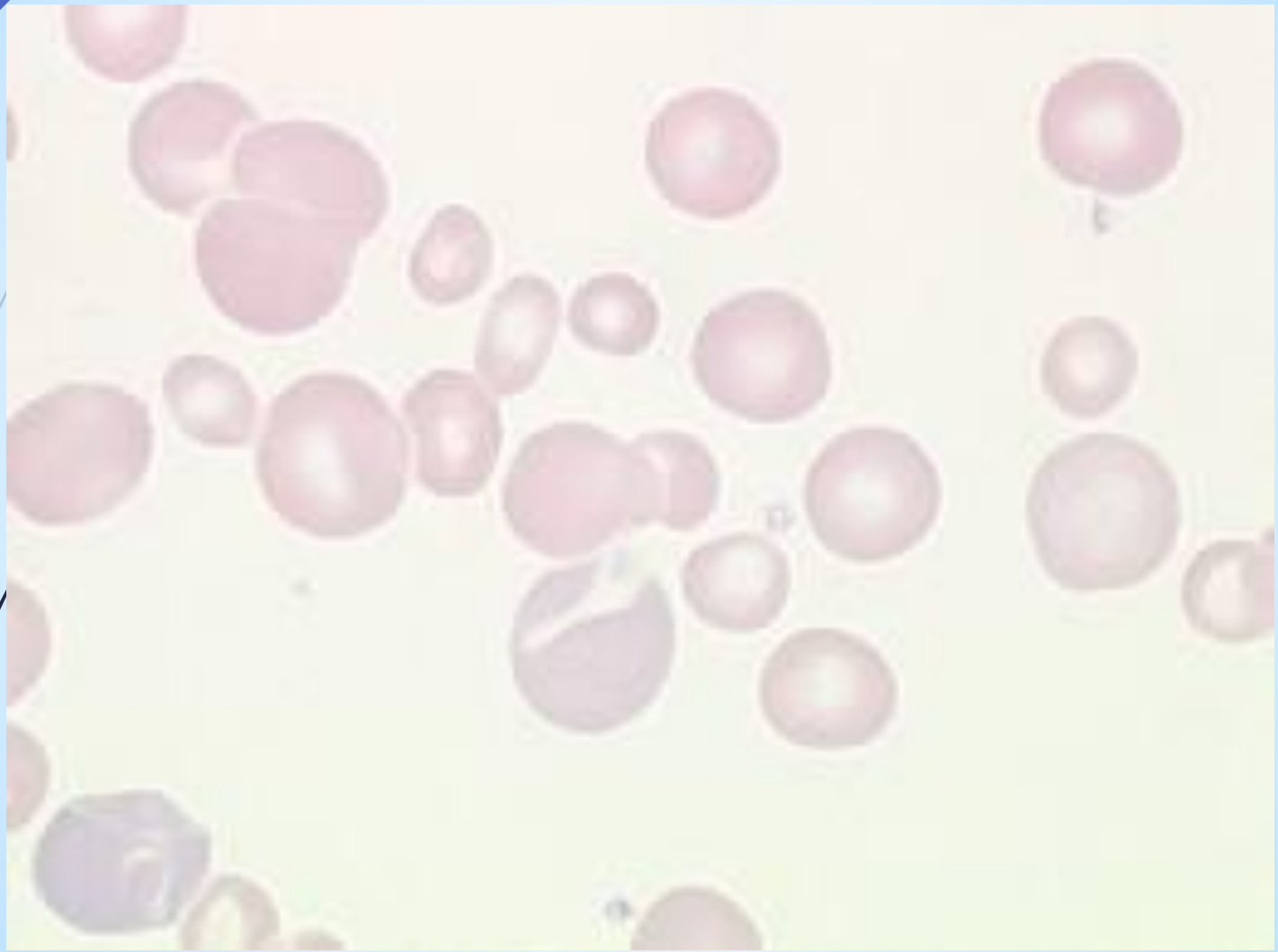
hypochromic
microcytic anemia



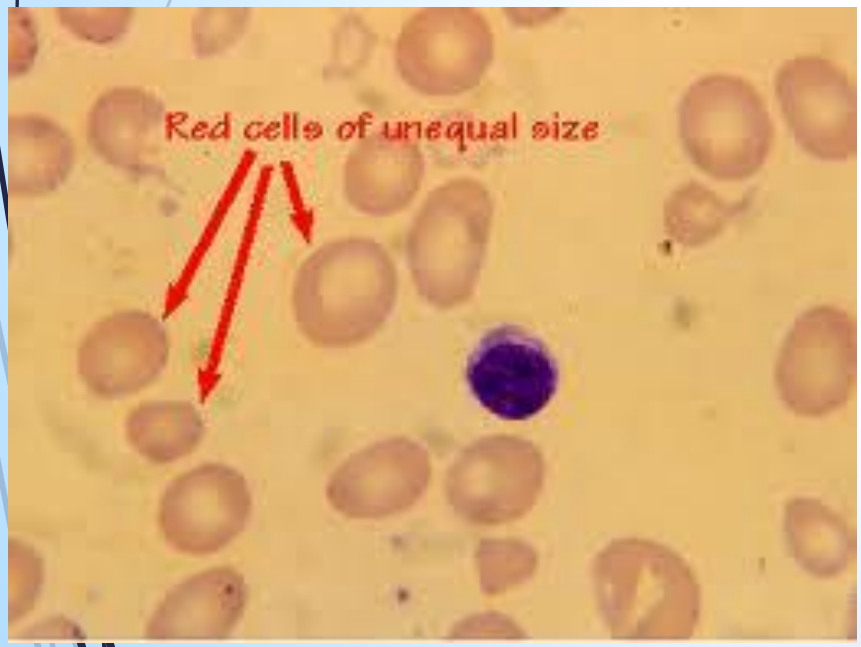
hypochromic
microcytic anemia

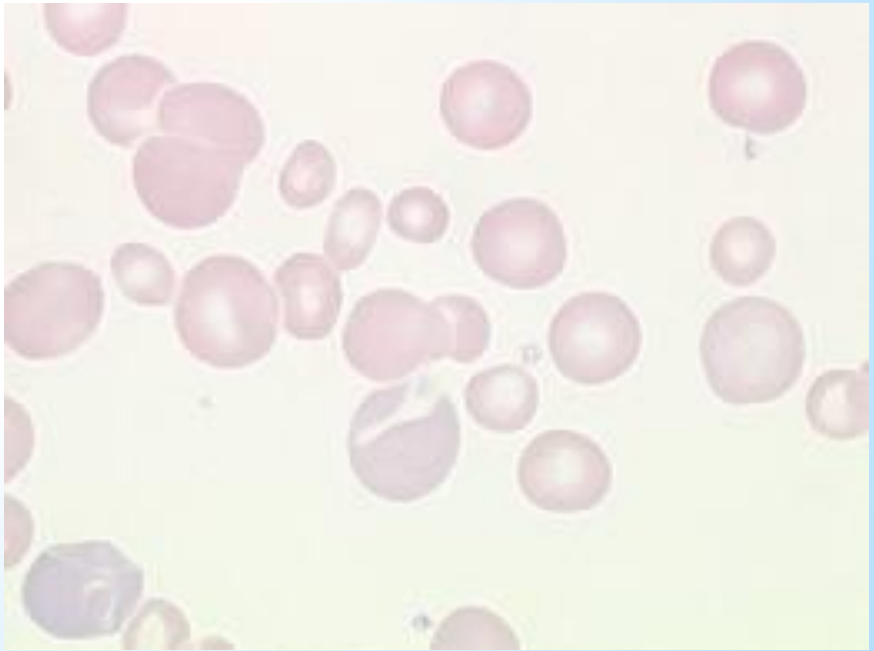


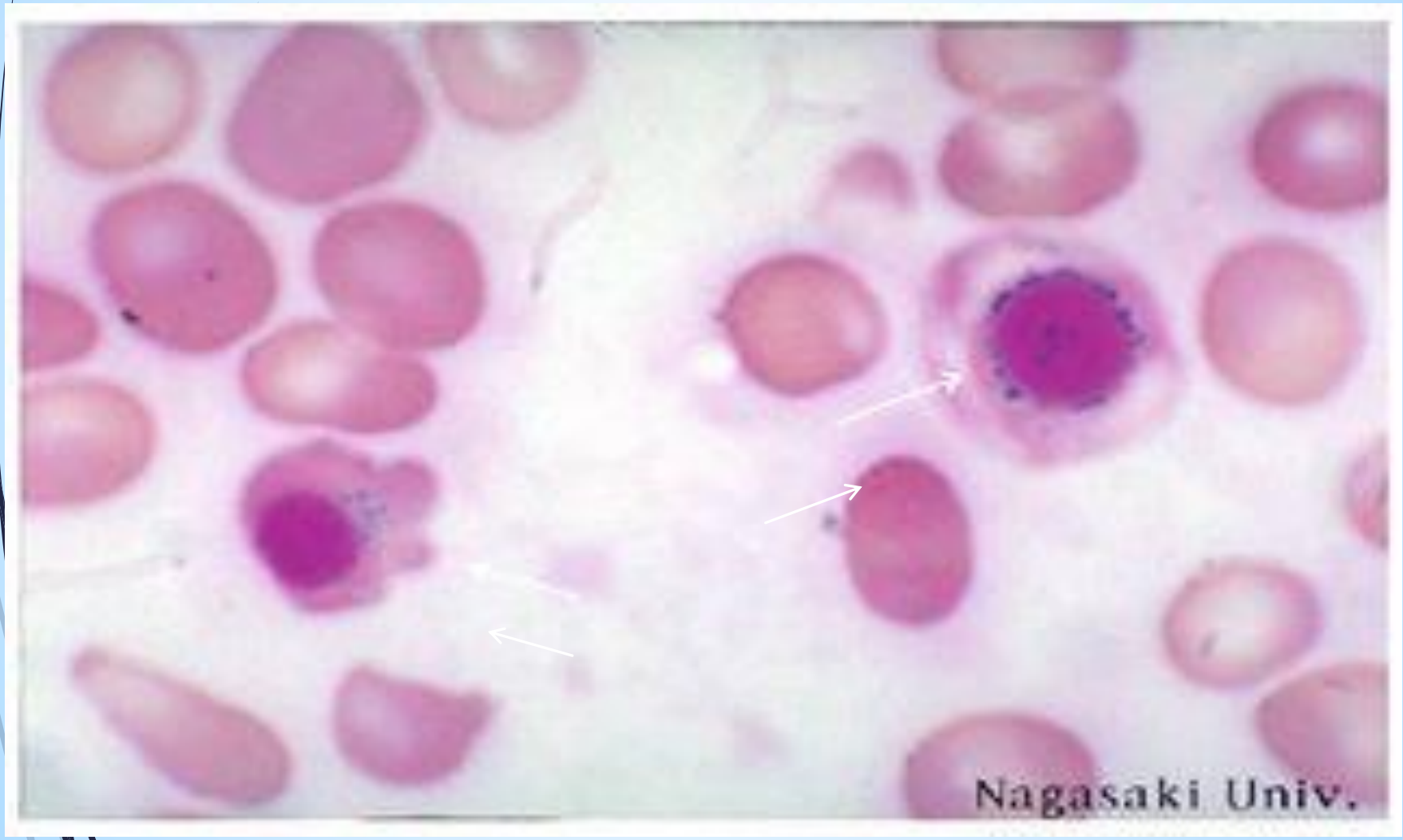
Anizocytes



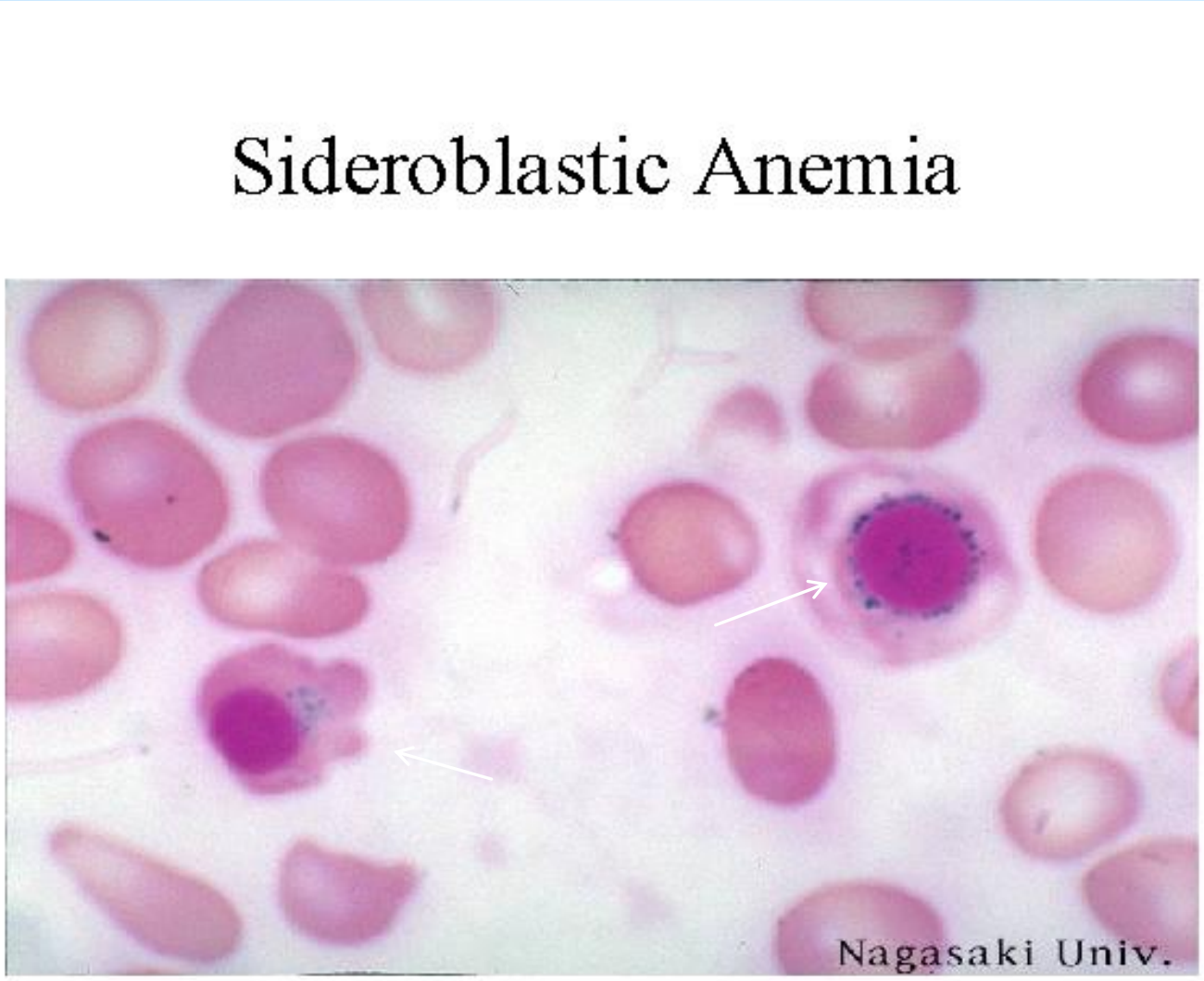
Anizocytes

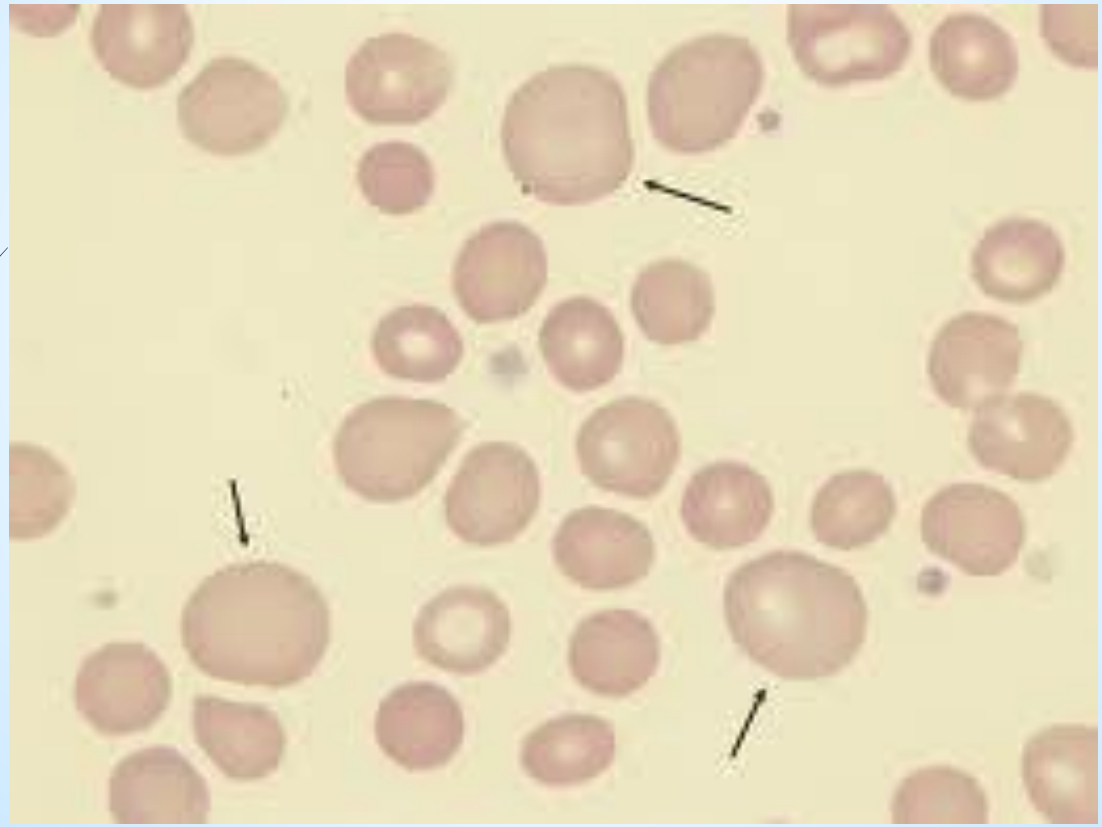




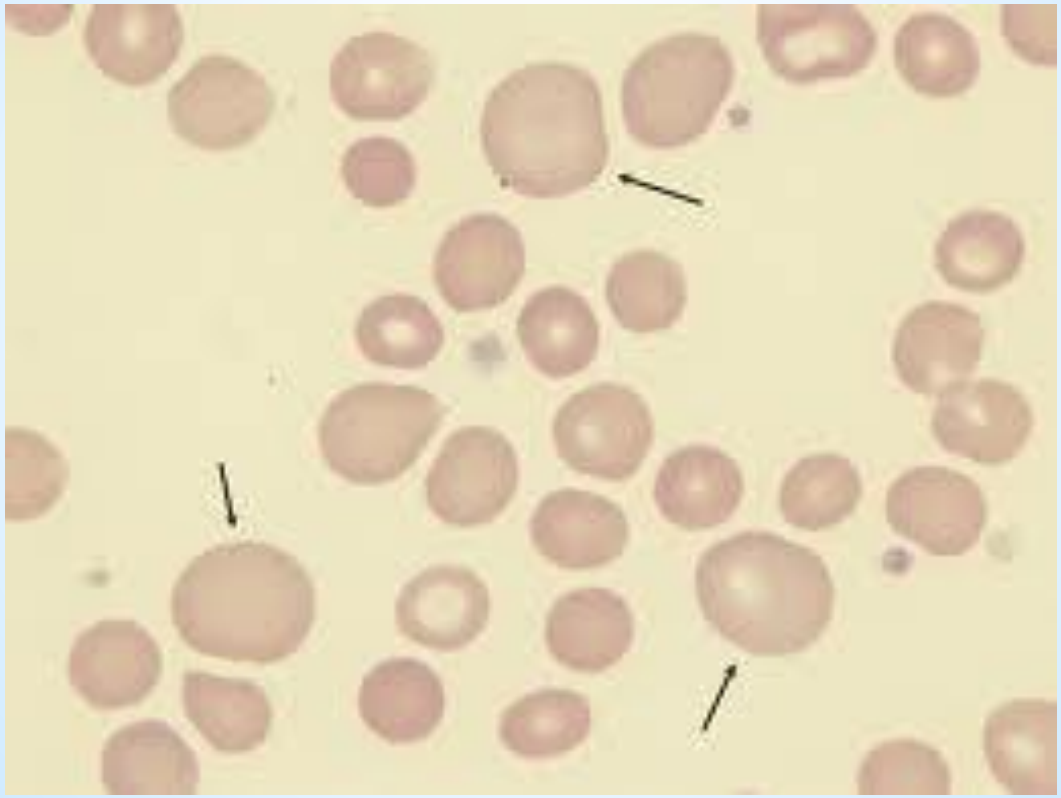

Nagasaki Univ.

Sideroblastic anemia



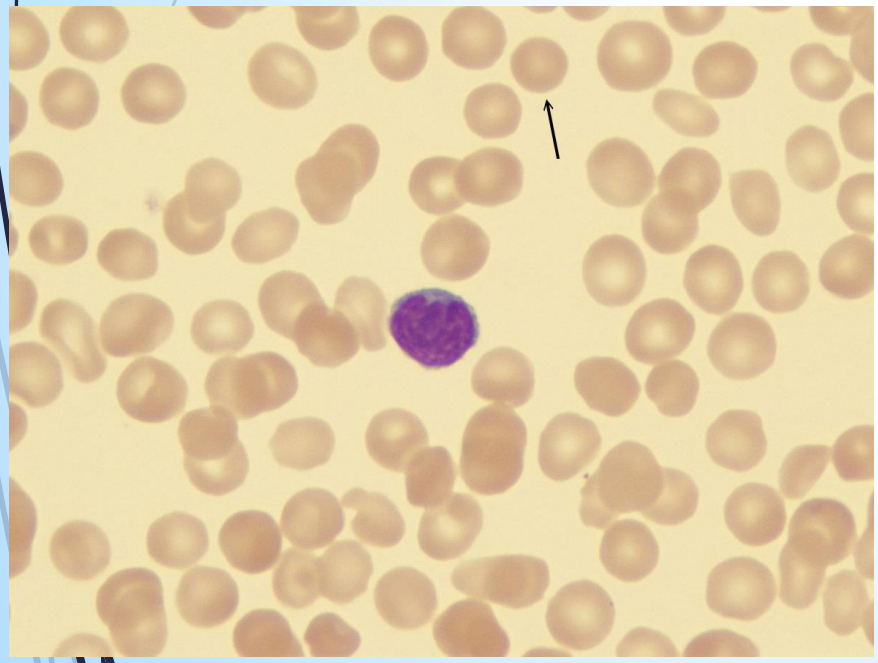


Macrocytosis

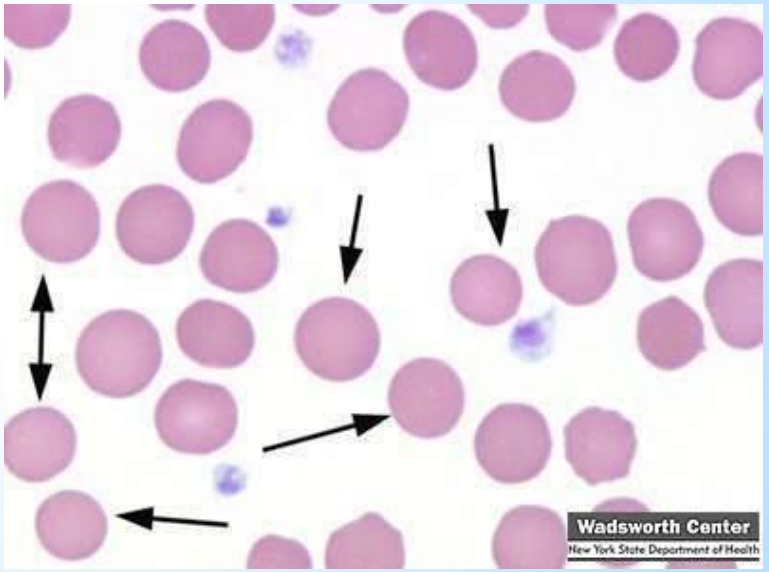


RBC deformations - poikilocytes

Spherocytes

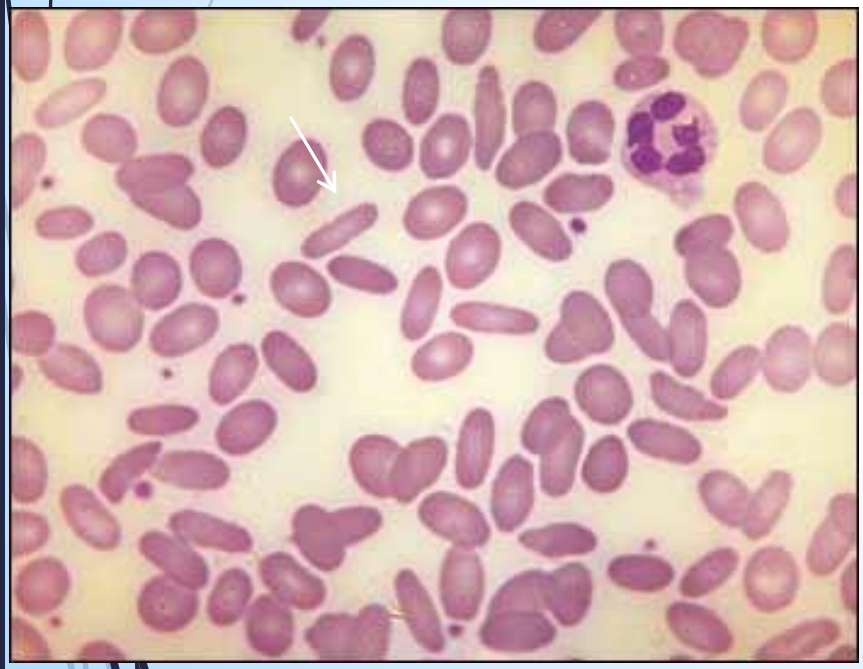


Spherocytes

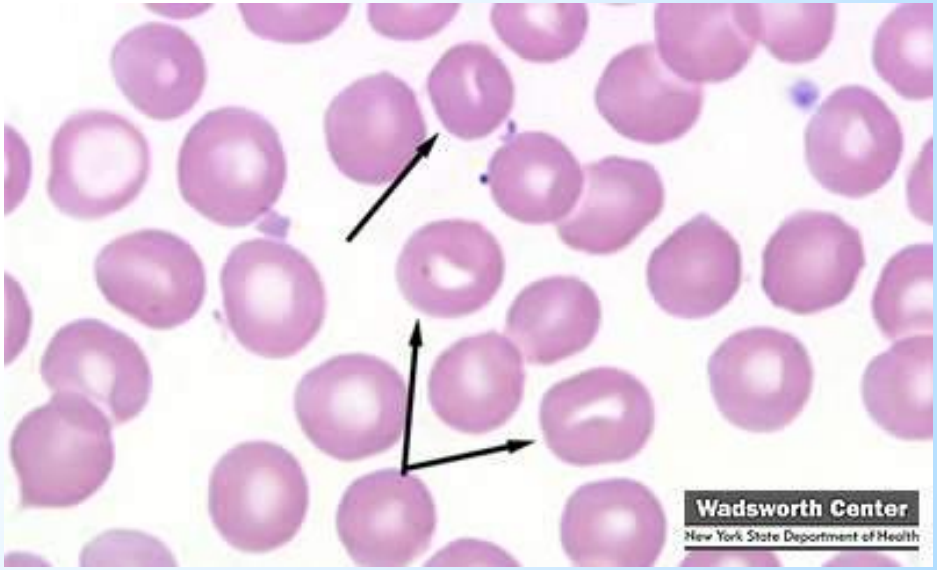


RBC deformations

Eliptocytes



Stomatocytes



RBC deformations

Eliptocytes

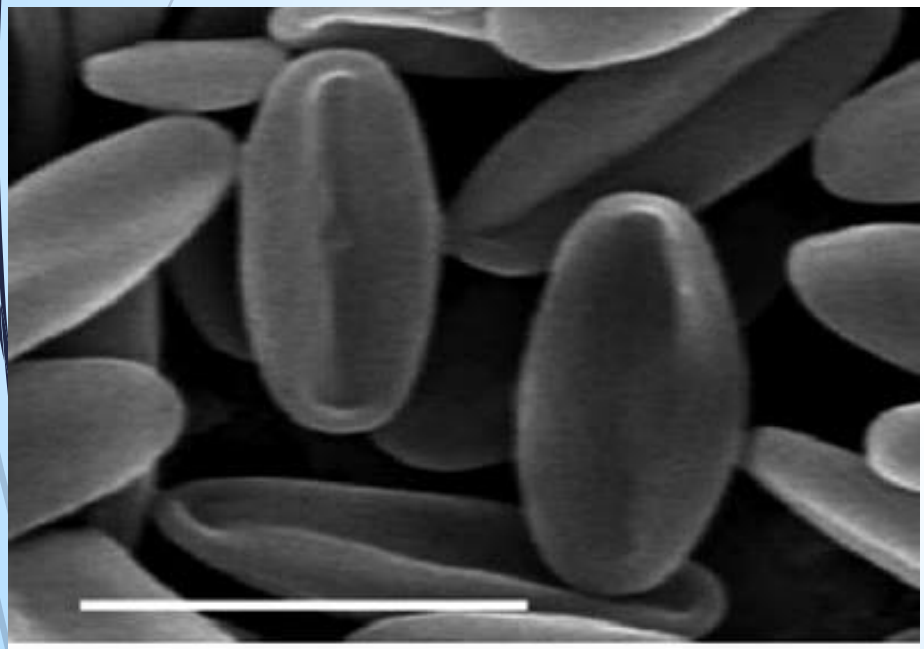
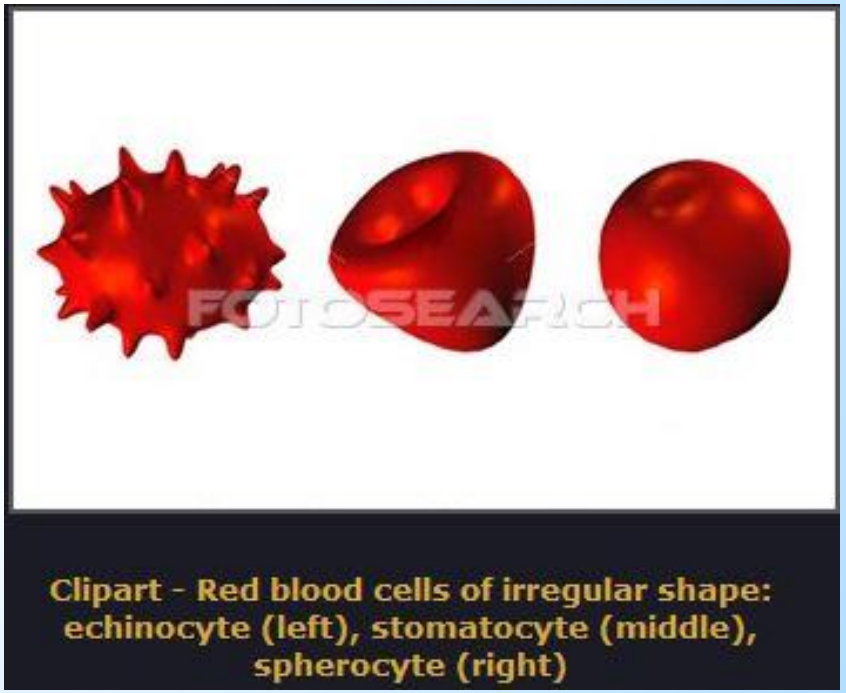


Fig. S6. Particles that mimic the shape of elliptocytes. (Scale bar, 2 μm.)

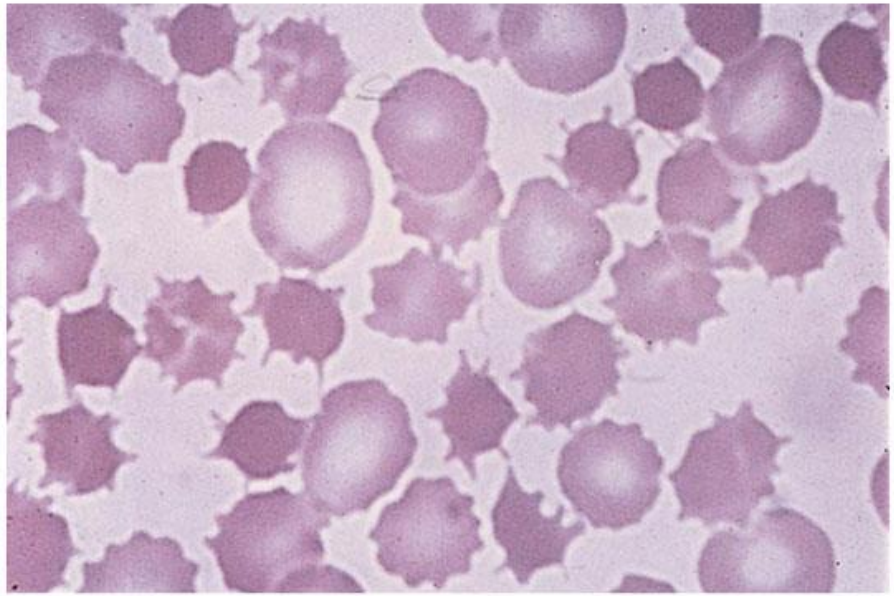
Stomatocytes



Clipart - Red blood cells of irregular shape: echinocyte (left), stomatocyte (middle), spherocyte (right)

RBC deformations

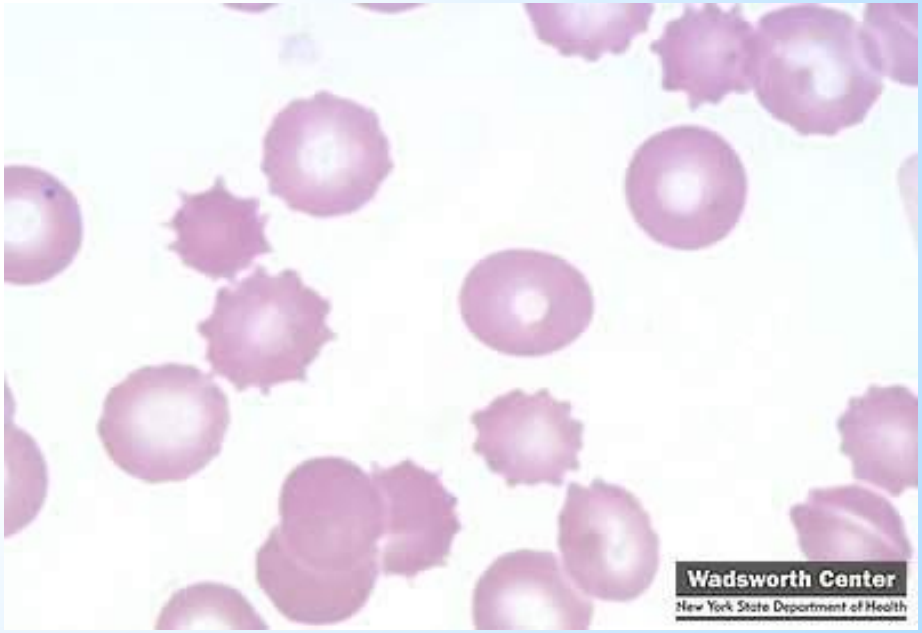
Acanthocytes=spur cells



Liver disease, abetalipoproteinemia, anorexia nervosa, hypothyroidism, alcoholism…

BC deformations

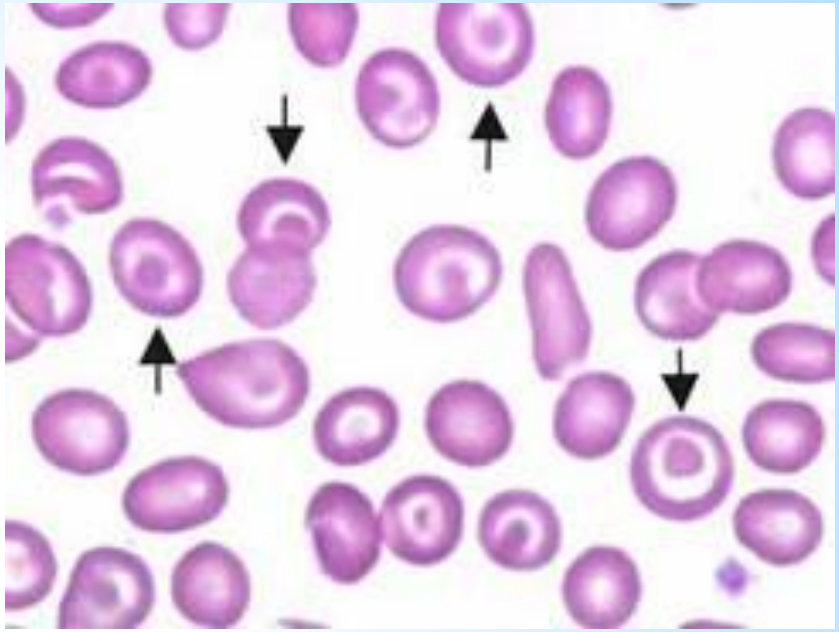
Echinocytes=burr cells



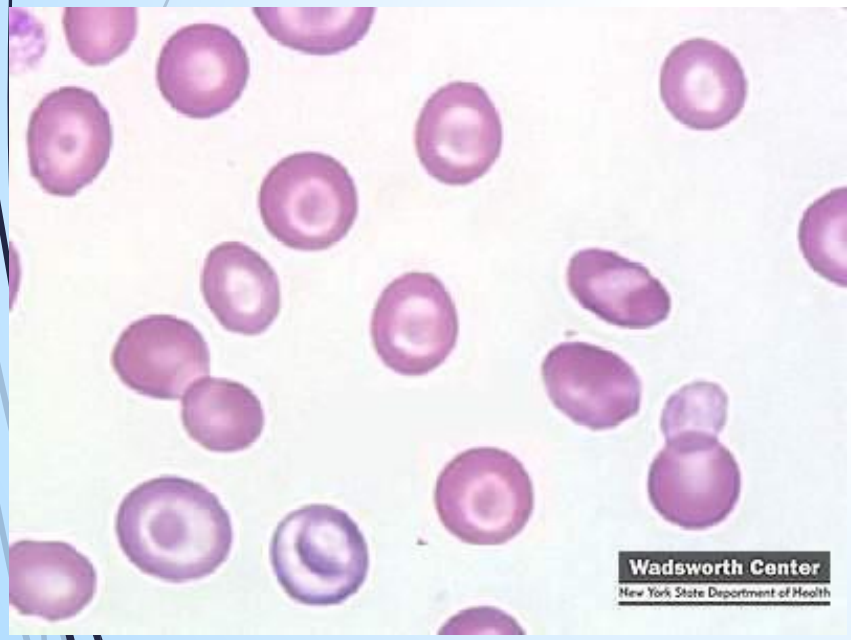
Uremia, pyruvat kinase deficiency, hypomagnesiemia, **artifact produced by EDTA**

Poikilocytes

Kodocyte=target cell=Mexican hat cell

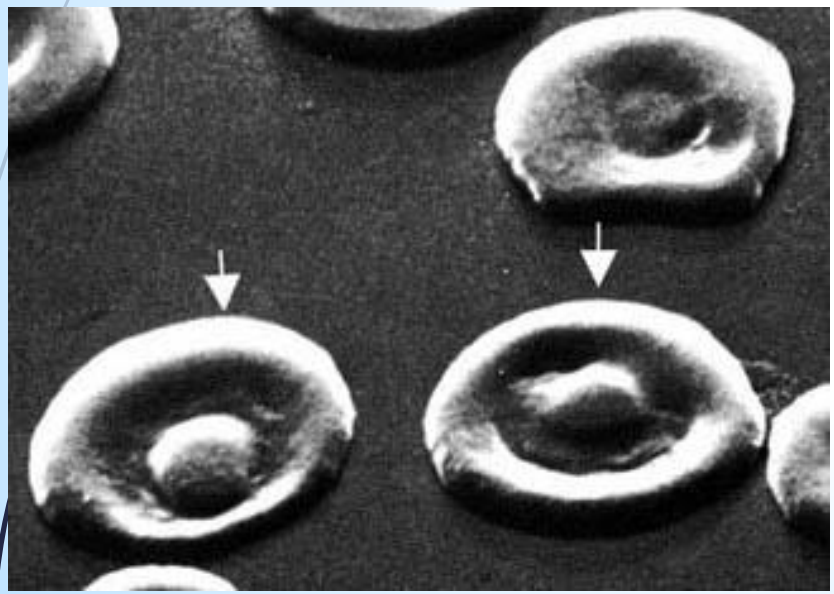


Kodocyte=target cell=Mexican hat cell



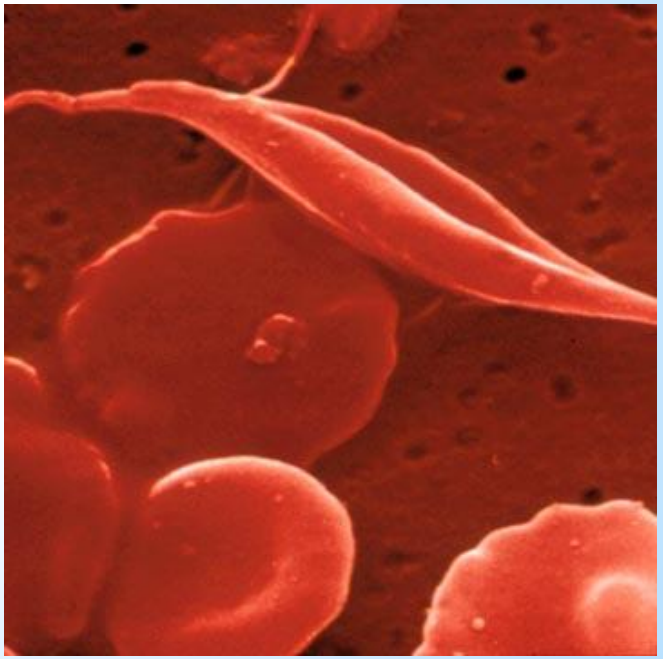
Poikilocytes

Codocyte=target cell=Mexican hat cell=leptocyte=sombrero cell



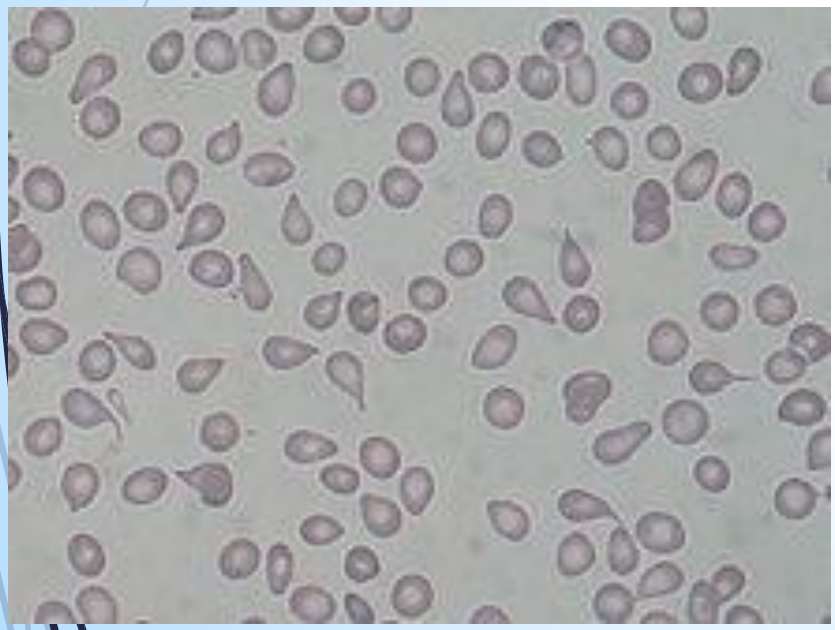
Liver disease, thalassemias, post splenectomy

Drepanocyte=sickle cell



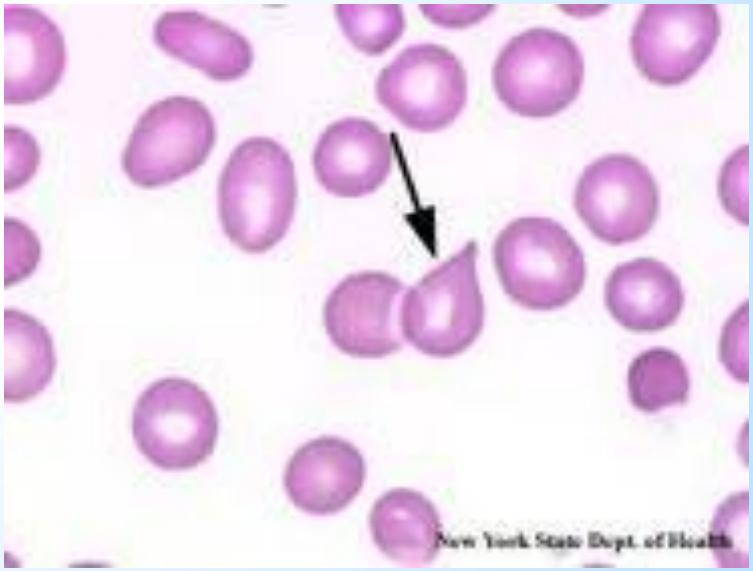
Poikilocytes

Dacrocytes = tear drop cells



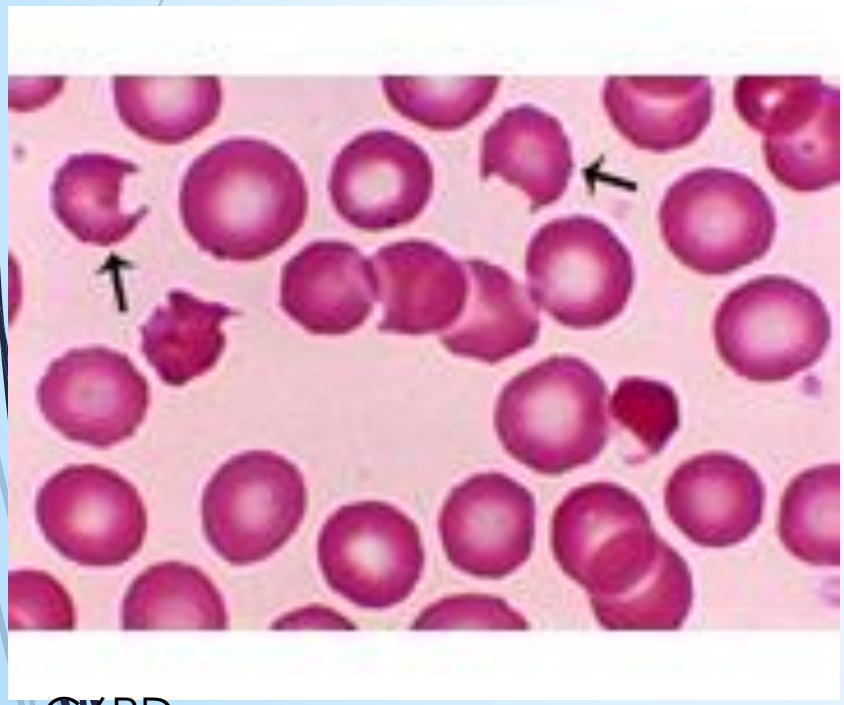
Beta thalassemia, post splenectomy, myelofibrosis

Dakrocyt = tear drop



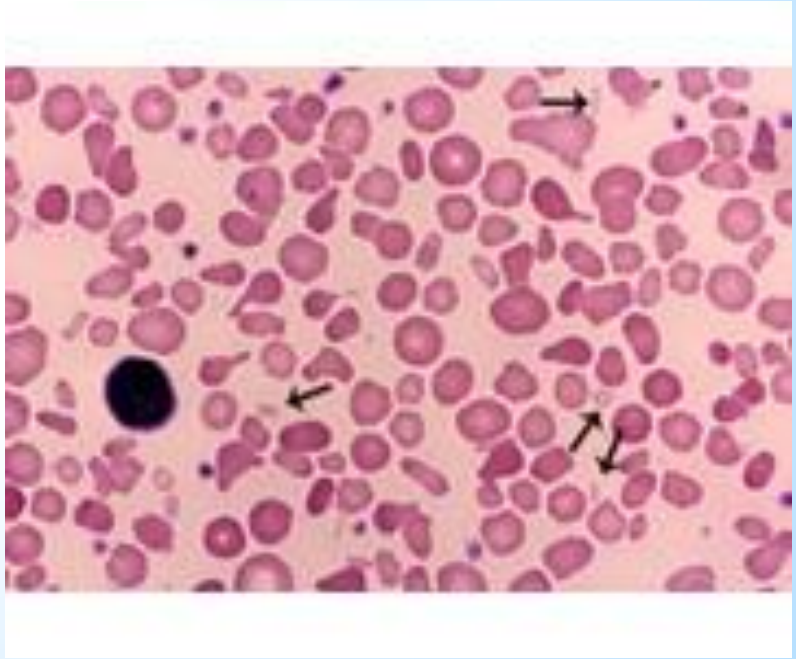
Poikilocytes

Degmacyte=horn cells
= bite cells



G6PD deficiency

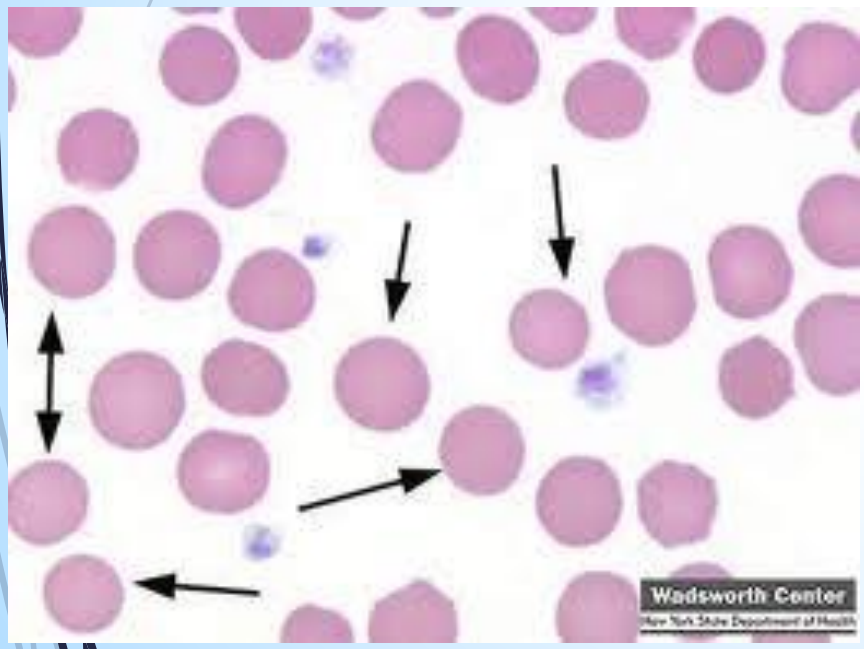
Pyropoikilocyte



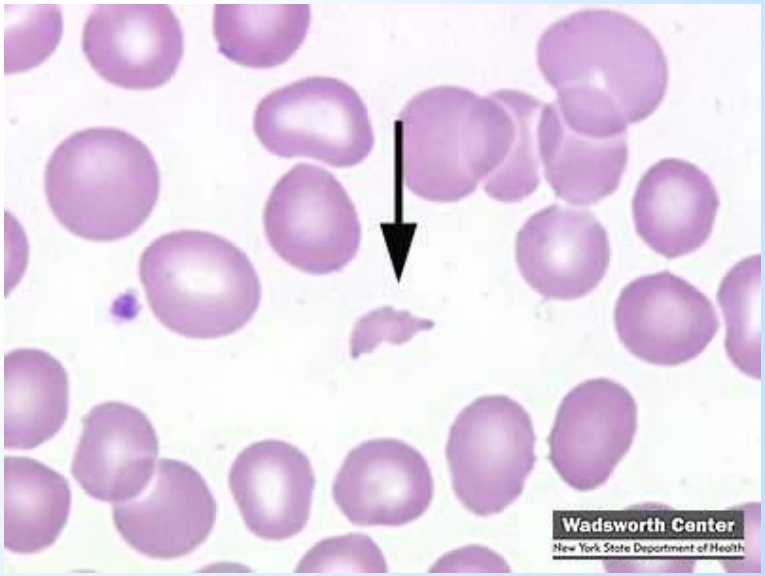
Hereditary hemolytic anemia

Poikilocytes

Microspherocyte



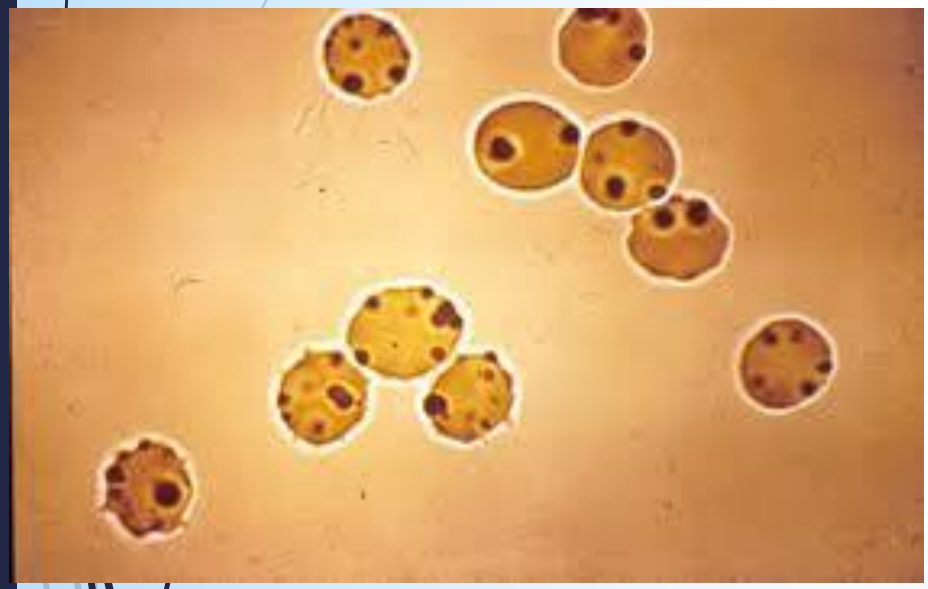
Schistocyte=helmet cell

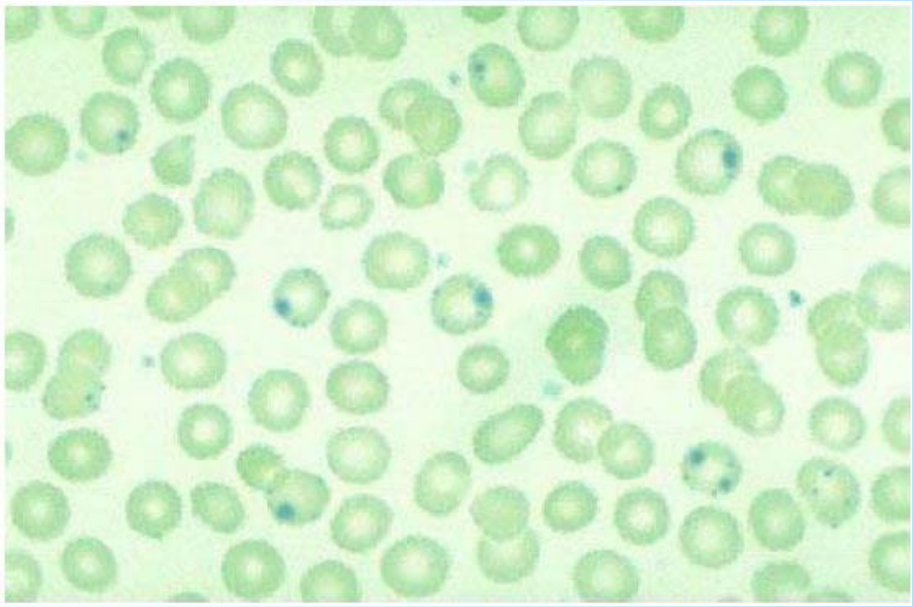


Microangiopathies, DIC, thrombotic angiopathies, hemolytic anemias

Heinz bodies

Precipitated hemoglobin

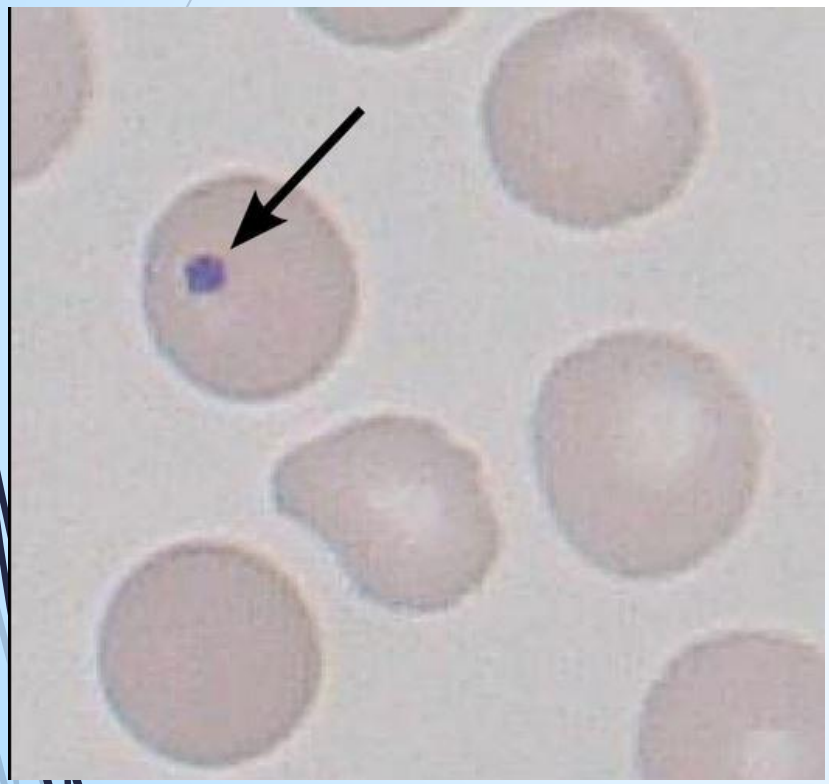


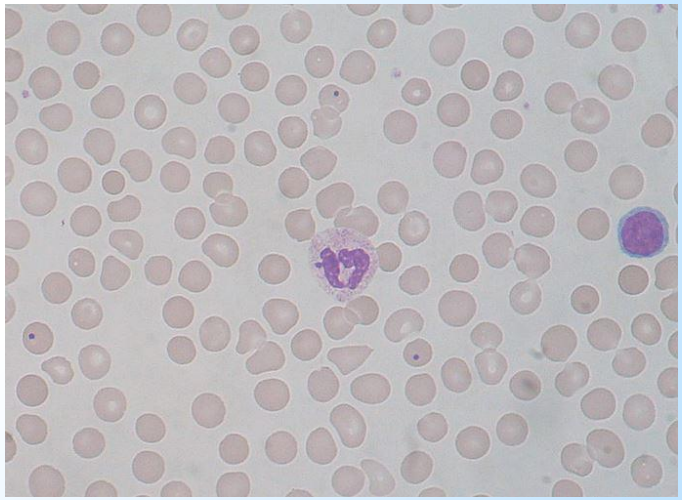


Hemolytic membrane anemias, thalassemias, chronic liver disease, asplenia

Howell-Jolly bodies

Basophilic nuclear remnant

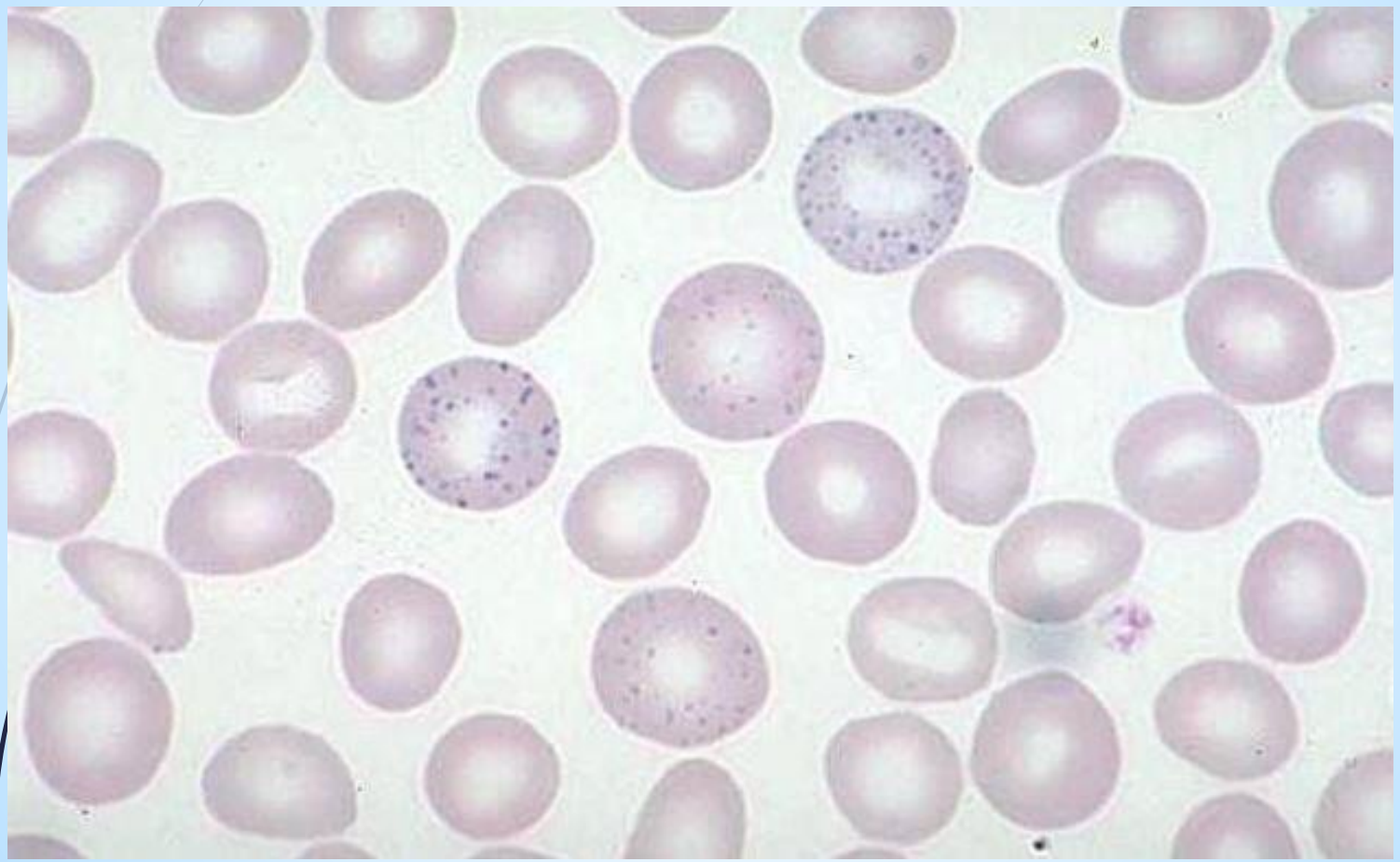




Hereditary spherocytosis, autosplenectomy, amyloidosis, hemolytic anemias, megaloblastic anemia…

Basophilic stippling

Nuclear remnants, mainly RNA

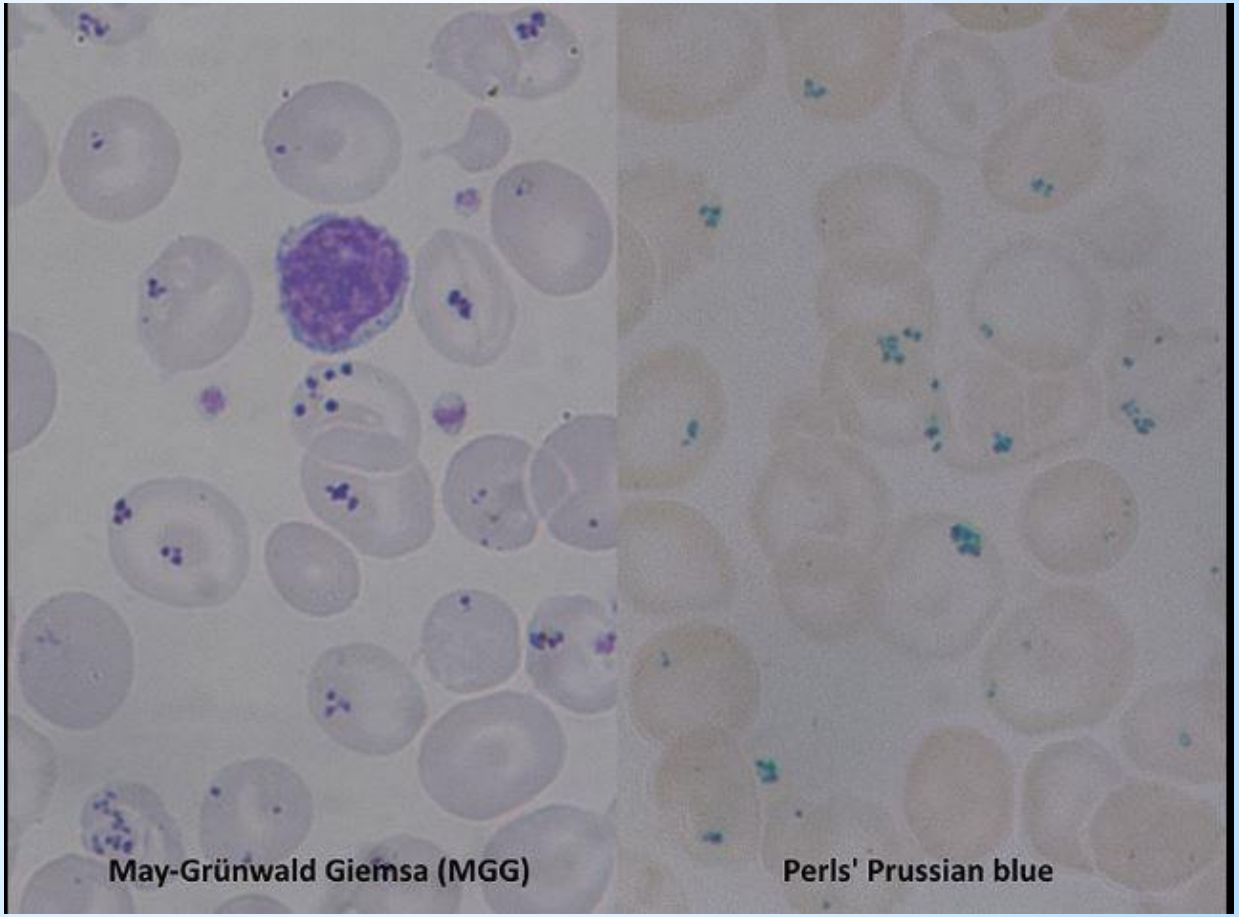


Hemolytic anemia, alcoholism, lead poisoning

Pappenheimer bodies

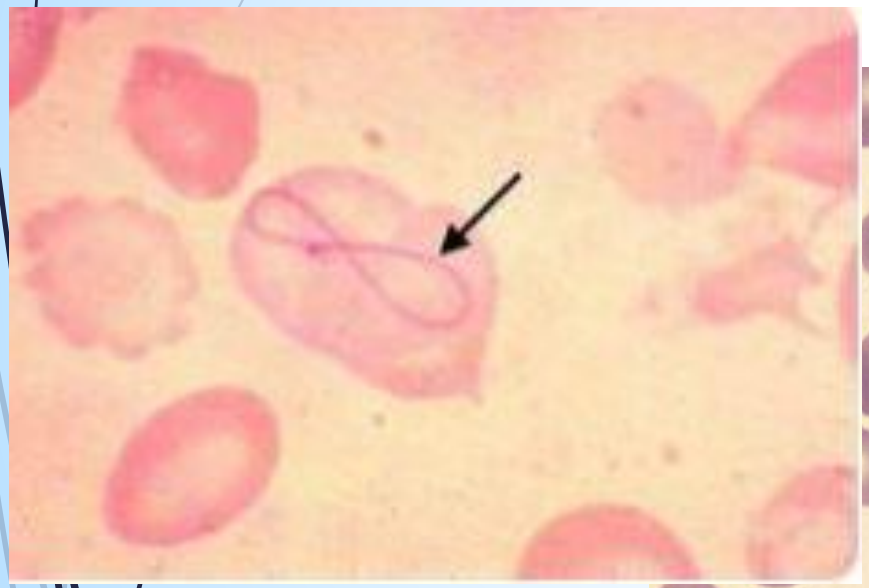
Ferritin aggregates

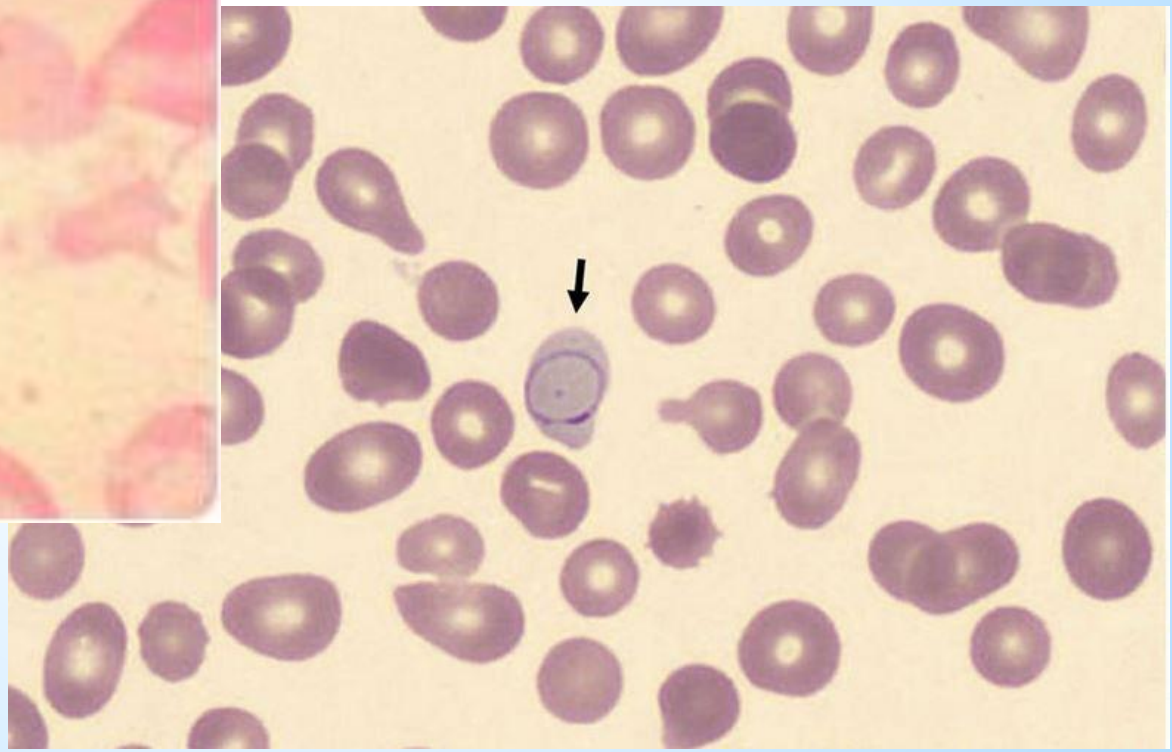
Post splenectomy, lead poisoning, hemolytic anemia, sideroblastic anemia



Cabot rings

Microtubules that are remnants from a mitotic spindle

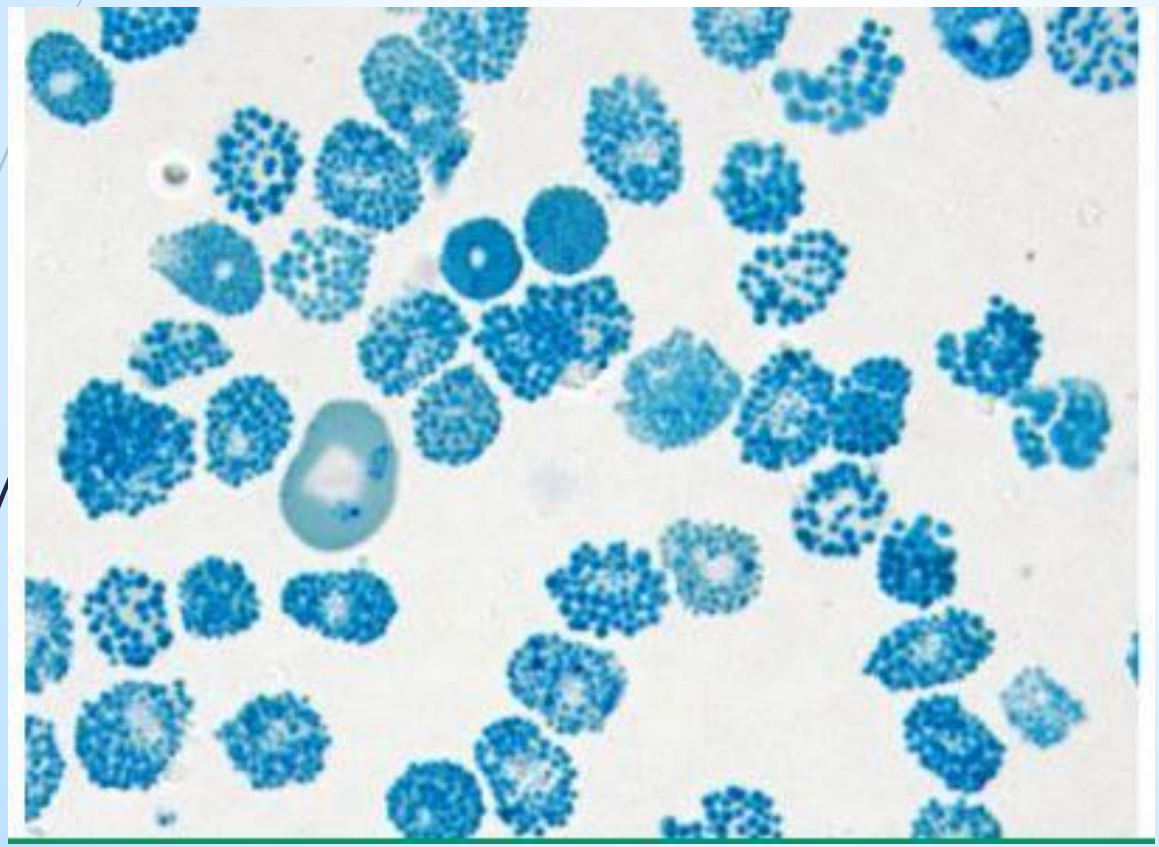




Pernicious anemia, lead poisoning

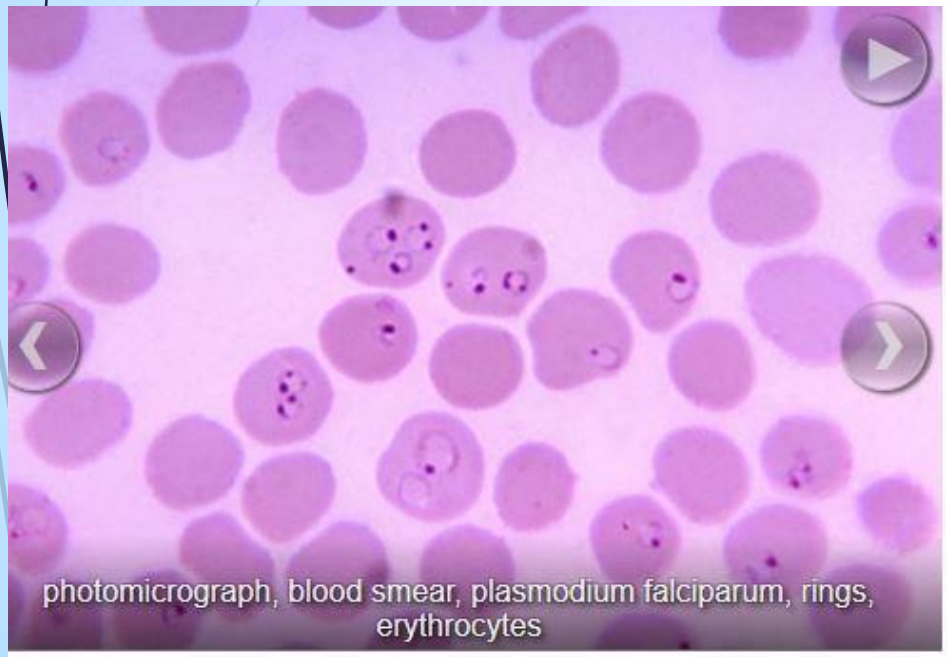
Hemoglobin H inclusio

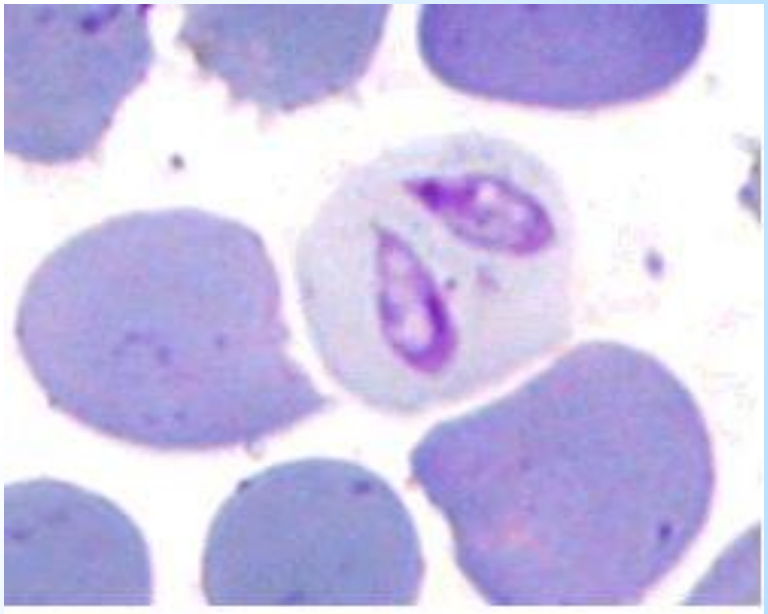
Alfa thallasemia



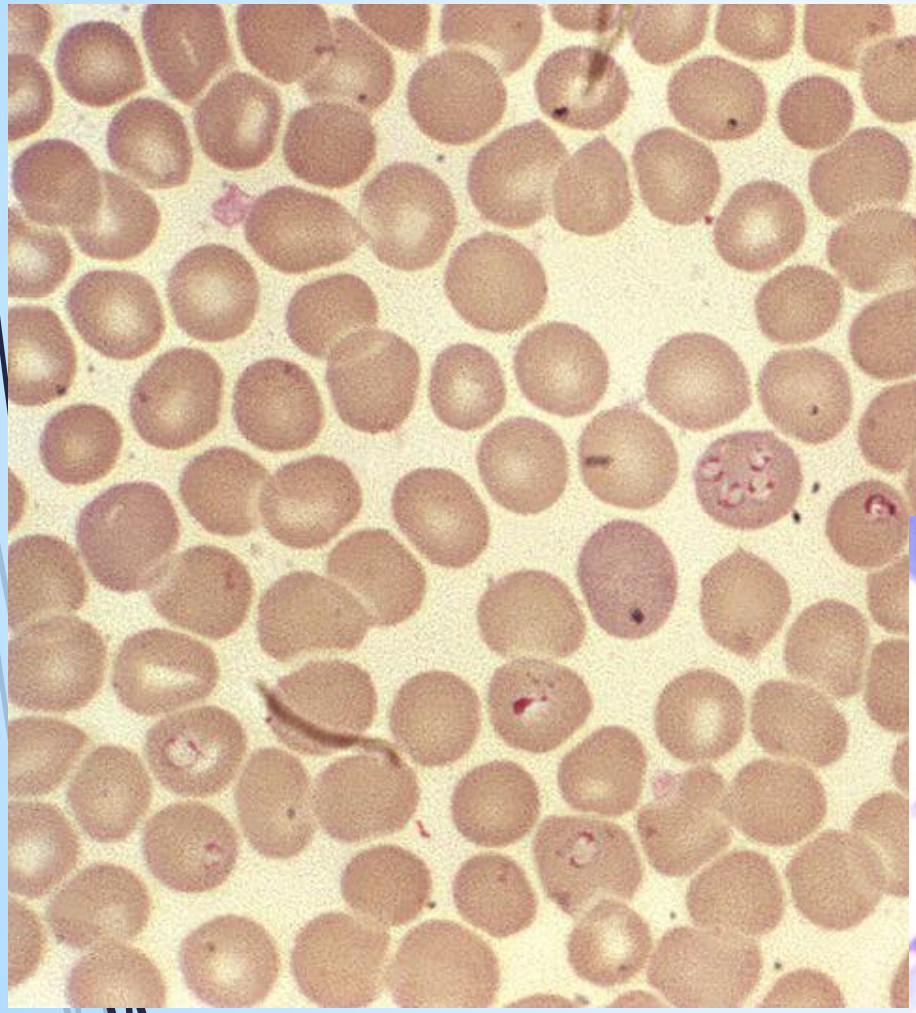
Specific stain greenish-blue inclusion bodies appear in many erythrocytes four drops of blood is incubated with 0.5mL of Brilliant cresyl blue for 20 minutes at 37 °C

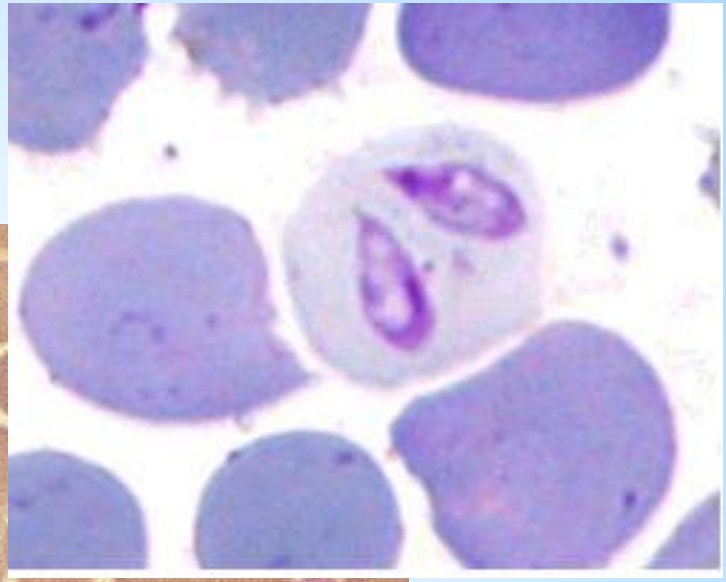
Parasites

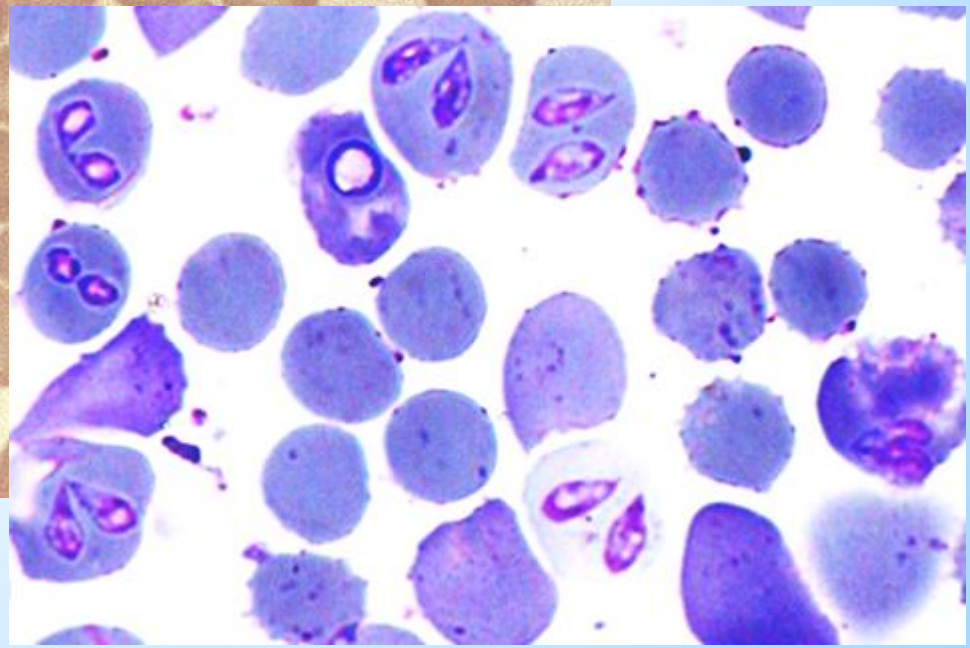

photomicrograph, blood smear, plasmodium falciparum, rings, erythrocytes



Parazity

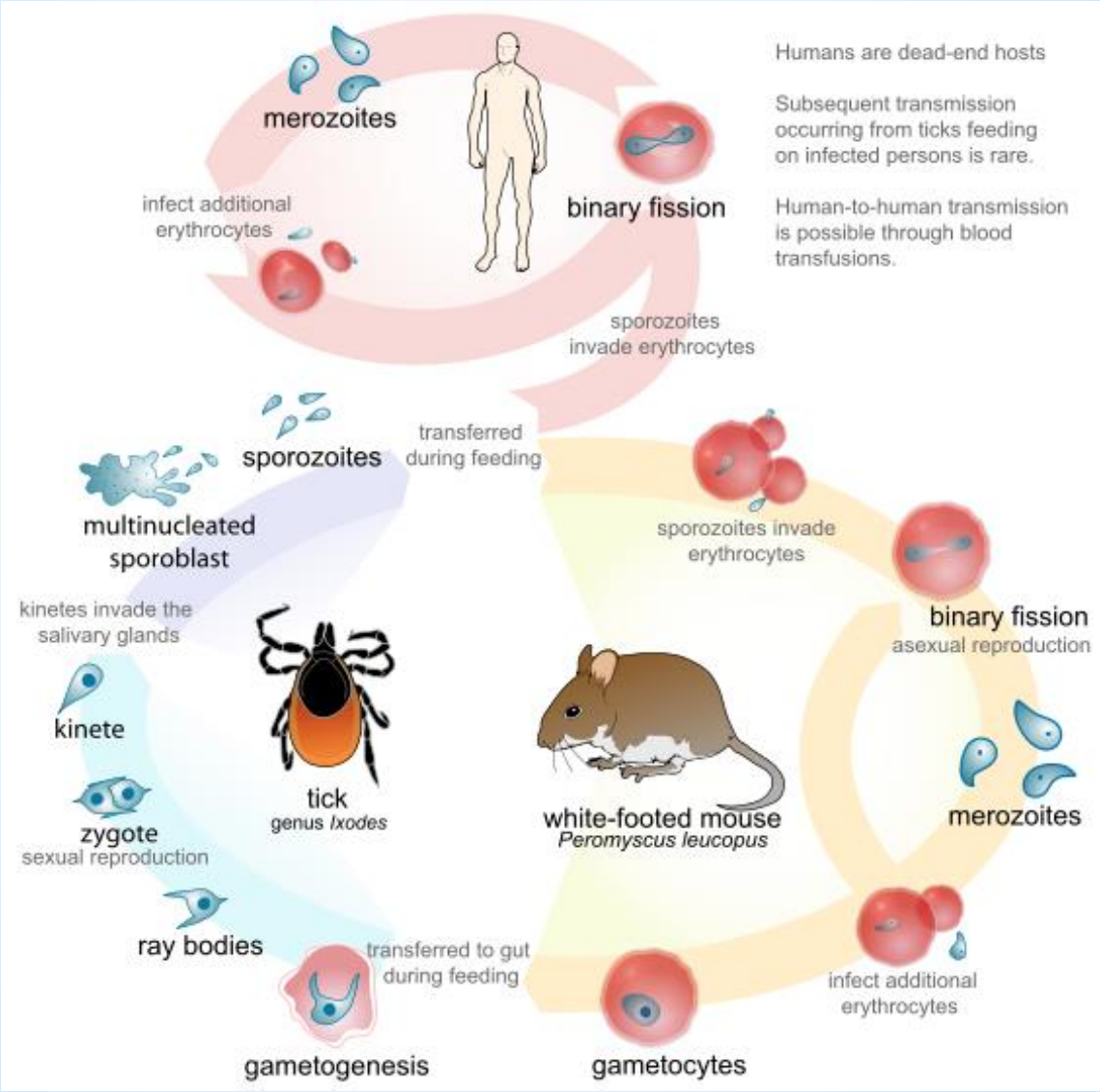


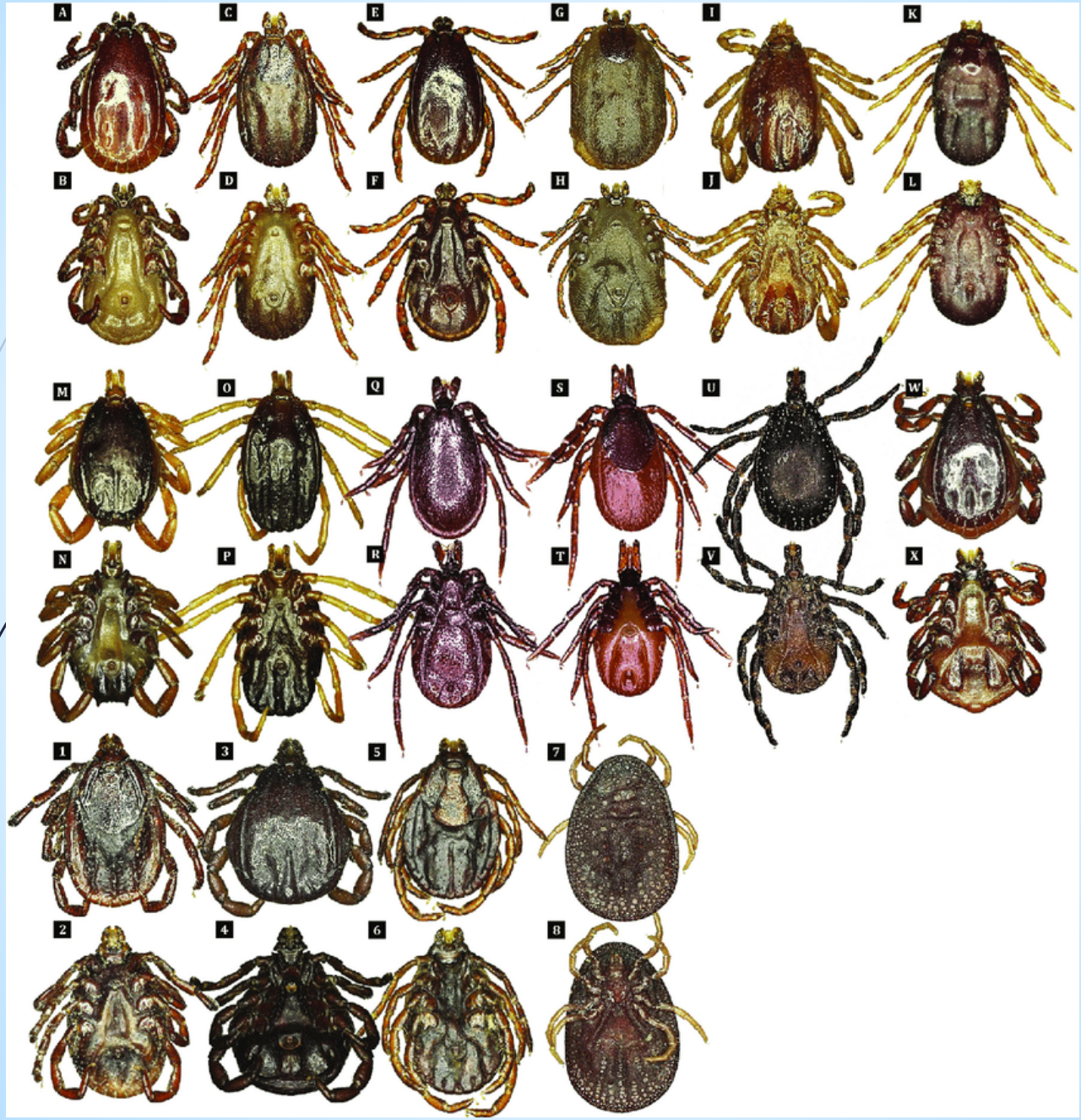




Babesia spp. (napr. microti, divergens, duncani)

Parazity


merozoites
infect additional erythrocytes
binary fission
Humans are dead-end hosts
Subsequent transmission occurring from ticks feeding on infected persons is rare.
Human-to-human transmission is possible through blood transfusions.
sporozoites invade erythrocytes
sporozoites
transferred during feeding
multinucleated sporoblast
sporozoites invade erythrocytes
binary fission
asexual reproduction
kinetes invade the salivary glands
kinete
tick
genus Ixodes
white-footed mouse
Peromyscus leucopus
merozoites
zygote
sexual reproduction
ray bodies
transferred to gut during feeding
infect additional erythrocytes
gametogenesis
gametocytes


A
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8

Differentiation of hematopoietic cells

- formed elements have origin from **pluripotent hematopoietic stem cells**
- it is sitting at the apex of a complex hierarchy of progenitors
- pluripotent stem cell gives rise to two types of multipotent progenitors
  - **common lymphoid stem cell**
  - **common myeloid stem cell**

Differentiation of hematopoietic cells

- **common lymphoid stem cell** gives rise to:
  - **precursors of T cells (pro-T cells)**
  - **precursors of B cells (pro-B cells)**
  - **precursors of natural killer cells**
- from the **common myeloid stem cell** arise at least three types of *committed stem cells* capable of differentiating along the:
  - erythroid/megakaryocytic
  - eosinophilic
  - granulocyte-macrophage pathways

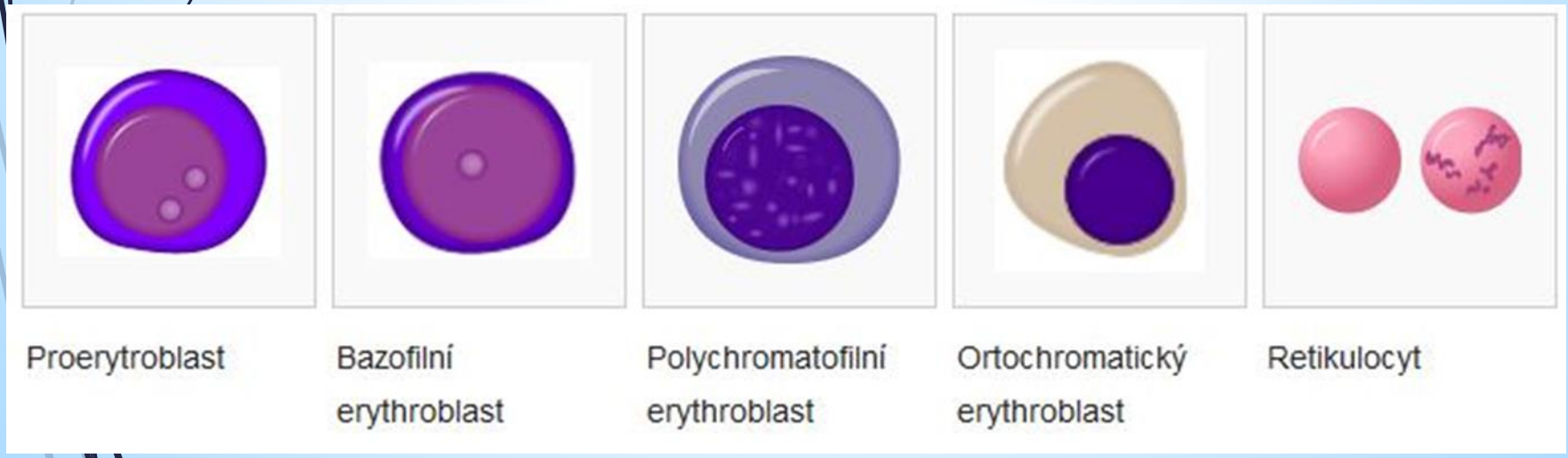
Differentiation of hematopoietic cells

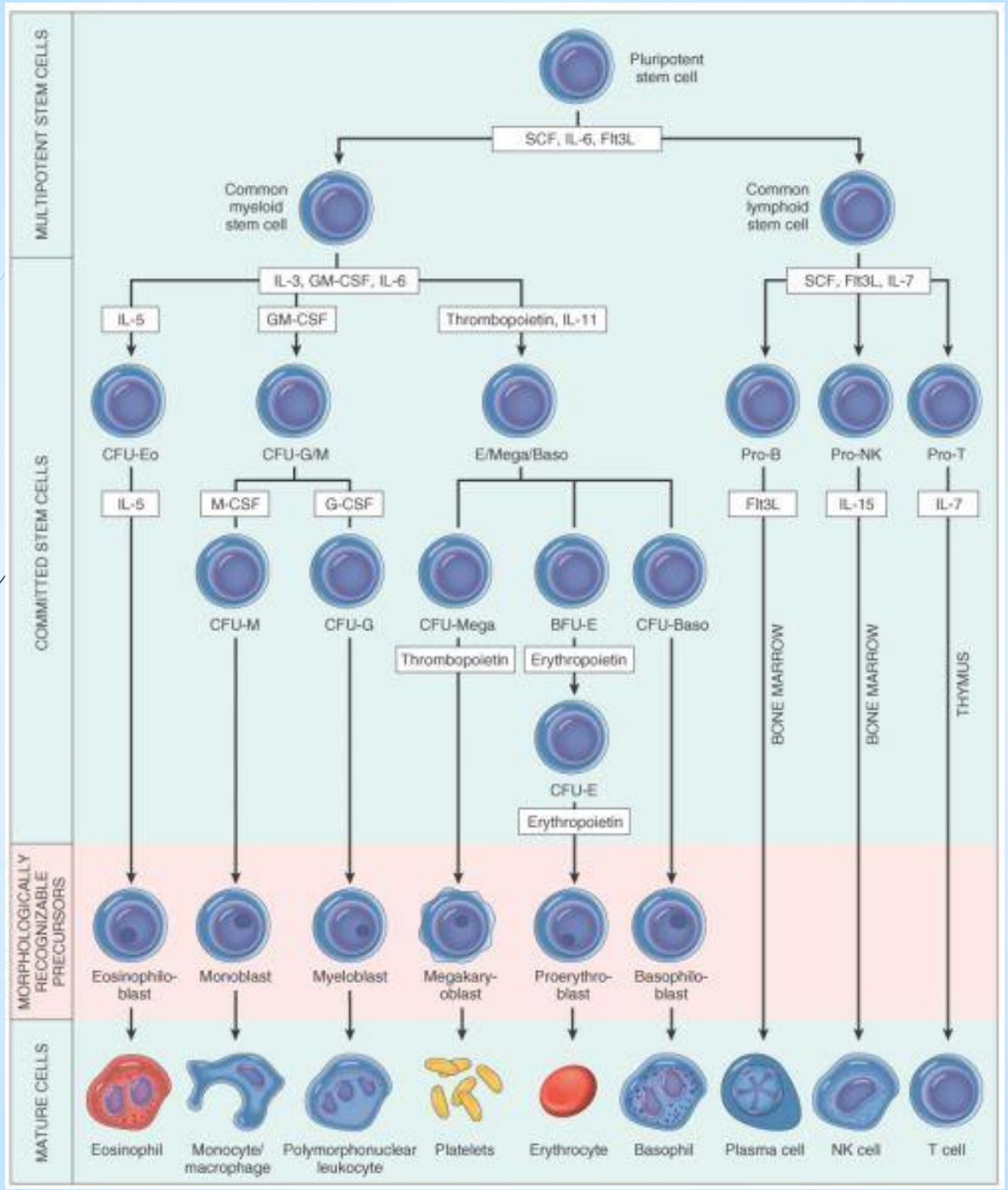
- committed progenitor cells are called colony-forming units (CFU)
  - each can give rise to colonies of differentiated progeny
- from the various committed progenitor cells are derived intermediate stages and ultimately the morphologically recognizable precursors of the differentiated cells
  - proerythroblasts
  - myeloblasts

Differentiation of hematopoietic cells

- megakaryoblasts
- monoblasts
- eosinophiloblasts

- which in turn give rise to mature progeny




MULTIPOTENT STEM CELLS
COMMITTED STEM CELLS
MORPHOLOGICALLY RECOGNIZABLE PRECURSORS
MATURE CELLS
Pluripotent stem cell
SCF, IL-6, Flt3L
Common myeloid stem cell
Common lymphoid stem cell
IL-3, GM-CSF, IL-6
SCF, Flt3L, IL-7
IL-5
GM-CSF
Thrombopoietin, IL-11
CFU-Eo
CFU-G/M
E/Mega/Baso
Pro-B
Pro-NK
Pro-T
IL-5
M-CSF
G-CSF
Flt3L
IL-15
IL-7
CFU-M
CFU-G
CFU-Mega
BFU-E
CFU-Baso
Thrombopoietin
Erythropoietin
BONE MARROW
BONE MARROW
THYMUS
CFU-E
Erythropoietin
Eosinophilo-blast
Monoblast
Myeloblast
Megakary-oblast
Proerythro-blast
Basophilo-blast
Eosinophil
Monocyte/ macrophage
Polymorphonuclear leukocyte
Platelets
Erythrocyte
Basophil
Plasma cell
NK cell
T cell

Anemias

- role of RBC is transport of oxygen to peripheral tissues
- reduced oxygen-carrying capacity of blood usually results from
  - a decreased count of red blood cells or ***anemia***
    - *reduction of the total circulating red cell mass below physiological limits*

Anemias

- For specification of anemias we need:
  - **count of red blood cells**
  - **hematocrit**
  - **hemoglobin concentration**
- false results we can obtain in:
  - **dehydration**
  - **increased volume of plasma (dilution anemia)**

Anemias

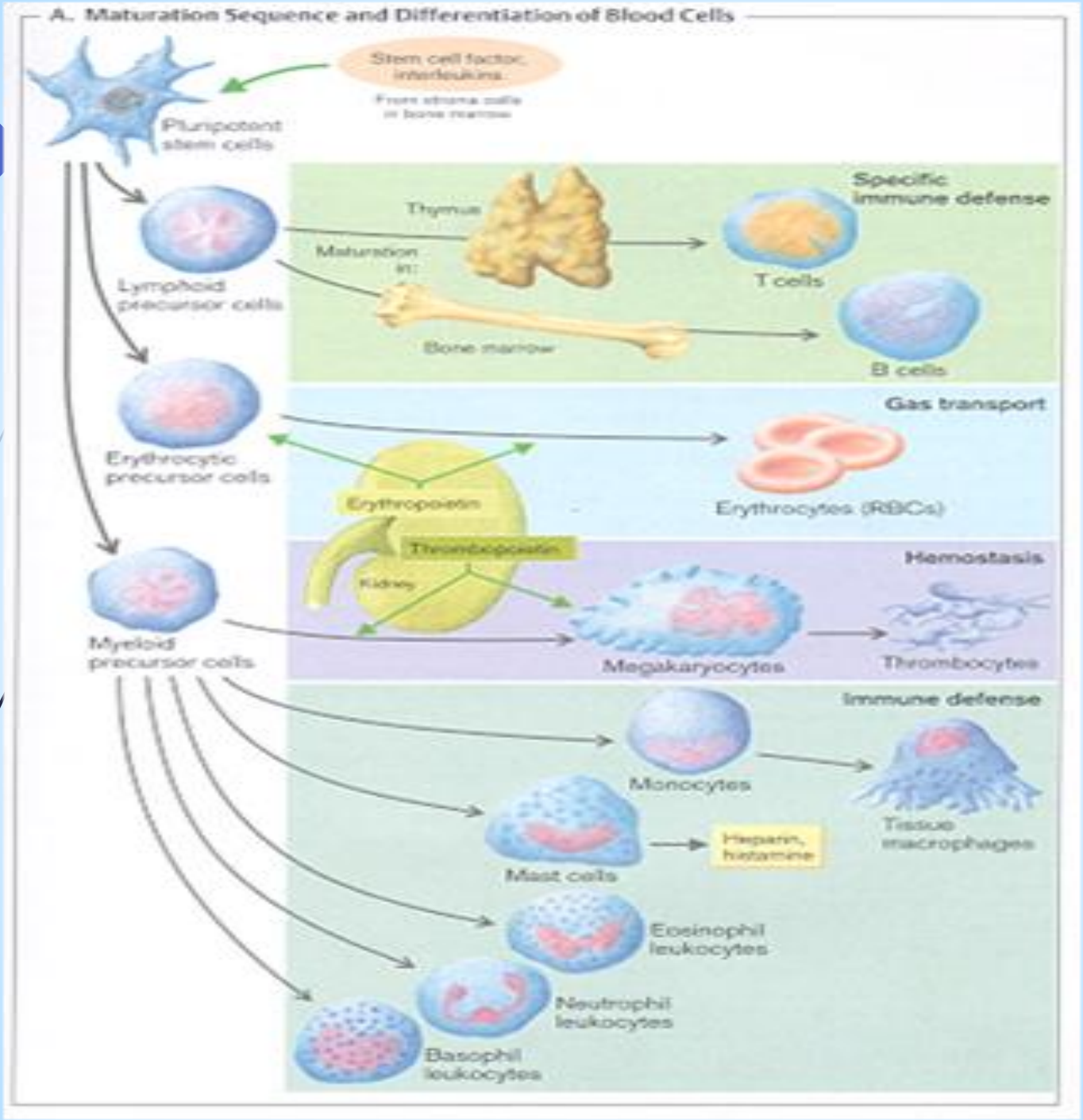
- one of the most common change present in a lot of types of diseases
- nearly 1/3 of internal medicine patients are anemic
- **if concentration of hemoglobin in blood is decreased below physiological parameters** we are talking about **anemia**
  - usually accompanied with decreased count of Er and decreased hematokrit
  - **during dehydration** we can have **false negative result = Hb concentration and count of Er will be in physiological values despite anemia**
  - **false positive result** we will have during **hypervolemia (increased volume of plasma) =** so-called **dilutional (relative) anemia** (patient has no anemia)
- diagnosis is made by laboratory diagnostics plus clinical symptoms = **anemic syndrome**

Anémie

anemic syndrome included:

- pallor of mucosa and skin
- tiredness
- decrease in physical performance (during maximal intensity)
- dyspnoe
- tachycardia

- **physiological values of Hb are 130-160 g/l**
- indicative **anemia division** according Hb concentration:
  - **moderate** (90-110 g/l)
  - **medium** (60-90 g/l)
  - **severe** (under 60 g/l)
- intensity of symptoms depend on how fast anemia developes plus occurance of other diseases


A. Maturation Sequence and Differentiation of Blood Cells
Stem cell factor, interleukins
From stroma cells in bone marrow
Pluripotent stem cells
Lymphoid precursor cells
Thymus
Maturation in:
Bone marrow
T cells
B cells
Specific immune defense
Erythrocytic precursor cells
Erythropoietin
Kidney
Erythrocytes (RBCs)
Gas transport
Thrombopoietin
Megakaryocytes
Thrombocytes
Hemostasis
Myeloid precursor cells
Monocytes
Tissue macrophages
Mast cells
Heparin, histamine
Eosinophil leukocytes
Neutrophil leukocytes
Basophil leukocytes
Immune defense

Physiological ranges

Erytrocytes: men: 4,5 – 6,5 x 10^{12} /l
women: 3,8 – 5,6 x 10^{12} /l

Hemoglobin: men: 135 - 175g/l
women: 115 - 155g/l

Hematokrit: men: 40 - 52 (0,40 – 0,52)
women: 35 – 48 (0,35 – 0,48)

Mean cell volume Er (MCV): 80 – 95 fl
Mean corpuscular hemoglobin (MCH): 27 – 35 pg
Mean corpuscular Hb concentration(MCHC): 30 - 35% (g

Anemias

in anemia pO2 is normal and Hb is normally saturated, but there is decreased count of Ec and this decreased total volume of O2 in arterial blood

- consequence is **tissue hypoxia**

- if **developement of anemia is slow**, compensatory mechanisms have enough time to work:
  - increase of production of 2,3-diphosphoglycerate (2,3-DPG) in Ec → binds to Hb → dissociation curve shift to right side (more O_2 for tissues)
  - compensatory dilation and decrease of peripheralvascular resistance → increase of ejection fraction of heart
  - hypotension

Anemias

hypoxia is cause of more symptoms:

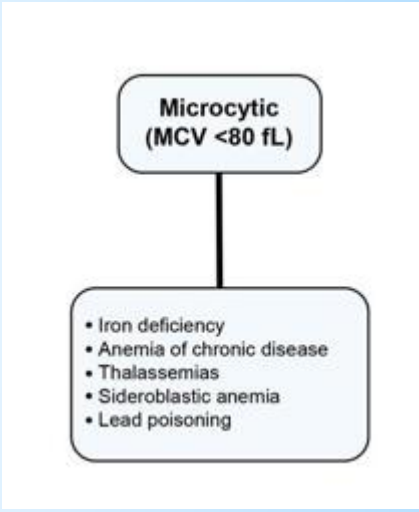
- dyspnoe during exertion, headache, tinnitus, palpitations, synkope, sleep disturbances, fainting, changes of mood
- in older patient can worsen angina pectoris
- can be cause of dementia and claudicatio intermittens
- anorexia, tachycardia, murmurs
- extremities edemas
- trombocytopenia → increase risk of bleeding

- **Examples of symptoms in anemia of different origin:**
  - **blood loss anemia**:
    - hypotension, tachykardia, tachypnoe, decrease of Hb
  - **hemolytic anemias:**
    - pallor, icterus, hepatomegaly, splenomegaly
  - **anemia with trombocytopenia:**
    - pallor, petechie, ecchymosis

Anemias - classificasion

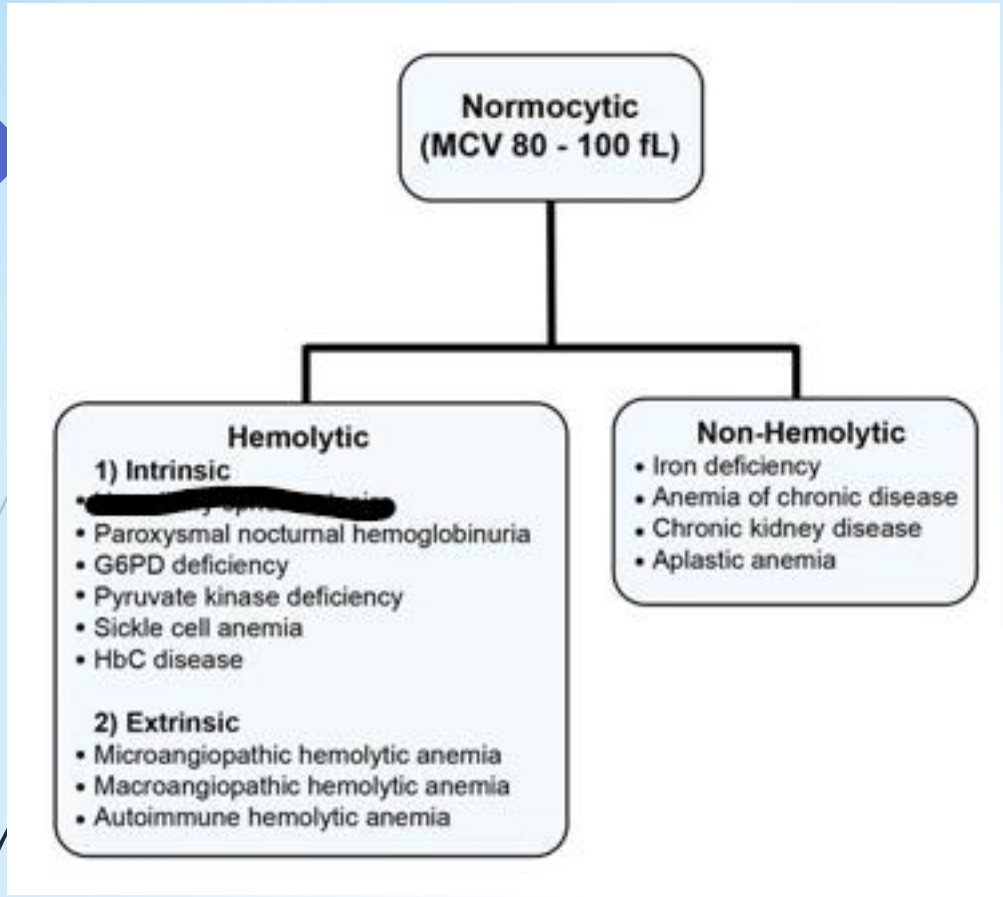
delenie anémií je možné **podľa rôznych kritérií**

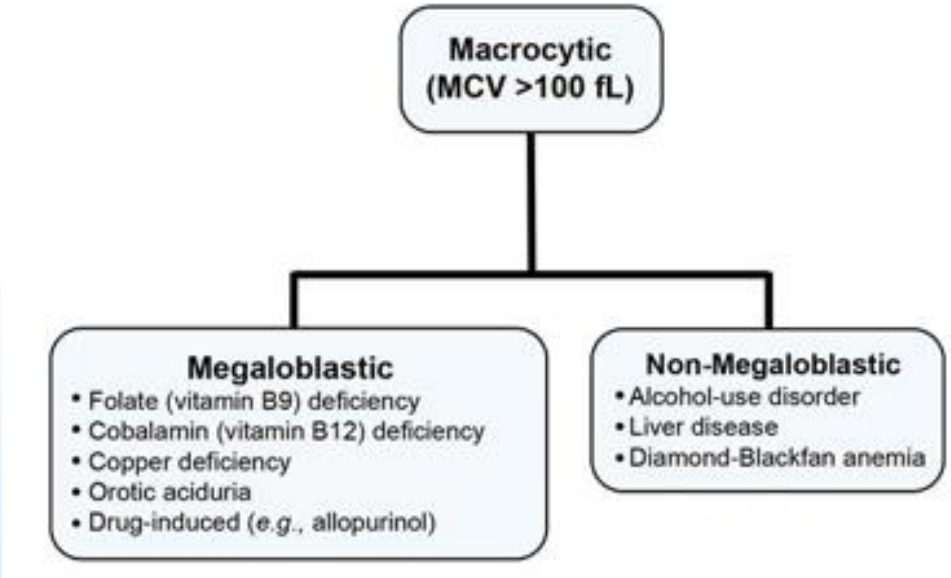
- we can **classify anemias according diferent criterias:**
- **A. according underlying mechanism:**
  - **increased loss of RBC**
    - acute and chronic blood loss
    - hemolytic anemias
  - **decreased production of RBC**
    - erytropoietin deficiency
    - deficiency of essential factors needed for erythopoiesis
    - cellular defects of blood marrow
- **B1. according Ec size:**
  - **mikrocytic anemias (mean cell volume MCV under 80 fl)**
    - Fe deficiency
    - thallasemias and ther hemoglobinopathie
    - chronic infections (inflammatory processes)
    - lead poisoning



Anemias - classificasion

- **makrocytic anemias (MCV over 95 fl)**
  - deficit of vit. B12, deficit of folic acid
  - myelodyspastic syndromes
  - Diamond-Blackfan anemia
- **normocytic anemia (MCV=80-95 fl)**
  - hemolytic anemias
  - aplastic anemias
  - acute infections
  - acute blood loss
  - chronic kidney diseases


Normocytic
(MCV 80 - 100 fL)
Hemolytic
1) Intrinsic
[redacted]
• Paroxysmal nocturnal hemoglobinuria
• G6PD deficiency
• Pyruvate kinase deficiency
• Sickle cell anemia
• HbC disease
2) Extrinsic
• Microangiopathic hemolytic anemia
• Macroangiopathic hemolytic anemia
• Autoimmune hemolytic anemia
Non-Hemolytic
• Iron deficiency
• Anemia of chronic disease
• Chronic kidney disease
• Aplastic anemia


Macrocytic
(MCV >100 fL)
Megaloblastic
• Folate (vitamin B9) deficiency
• Cobalamin (vitamin B12) deficiency
• Copper deficiency
• Orotic aciduria
• Drug-induced (e.g., allopurinol)
Non-Megaloblastic
• Alcohol-use disorder
• Liver disease
• Diamond-Blackfan anemia

Anemias - classificasion

- **B2. according mean cell hemoglobin concentration (MCHC)**
  - **normochromic anemias (MCHC 300-350 g/l erymass)**
    - diferent causes
  - **hypochromic anemias (MCHC under 300 g/l)**
    - Fe deficit
    - β - thalasaemia major
    - pyridoxin responsive anemia
    - lead poisoning anemia
- **B3. shape of Ec**

Repetition of classification

- **Increased cell destruction**
  - Blood loss
  - Hemolytic anemias
- **Impaired production**
  - Lack of erhytropoietin
  - Diseases of blood marrow
  - Lack of substances important for red blood cells production (iron, vitamin B12, folic acid..)

Anemias

- second classification is **morphological** according :
  - **red cell size**
    - normocytic
    - microcytic
    - macrocytic
  - **degree of hemoglobinization**
    - normochromic
    - hypochromic
  - other special features like shape

Anemias

- the most useful red cell indices are:
  - **mean cell volume**
    - the average volume of a red blood cell (fl)
  - ***mean cell hemoglobin***
    - the average content (mass) of hemoglobin per red blood cell (pg)
  - ***mean cell hemoglobin concentration***
    - the average concentration of hemoglobin in a given volume of packed red blood cells (g per dl)
  - ***red blood cell distribution width***
    - the coefficient of variation of red blood cell volume (%)

Physiological ranges

Erytrocytes: men: 4,5 – 6,5 x 10^{12} /l
women: 3,8 – 5,6 x 10^{12} /l

Hemoglobin: men: 135 - 175g/l
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Hematokrit: men: 40 - 52 (0,40 – 0,52)
women: 35 – 48 (0,35 – 0,48)

Mean cell volume Er (MCV): 80 – 95 fl
Mean corpuscular hemoglobin (MCH): 27 – 35 pg
Mean corpuscular Hb concentration(MCHC): 30 - 35% (g

Diagnosis

- haemoglobin men 130 - 175 g/l women 120 - 165 g/l
- haematocrit men 0,40 - 0,54 women 0,35 - 0,45
- RBC count men 4,2 - 5,8 x 10^{12}/l women 3,8 - 5,2 x 10^{12}/l

- Mean corpuscular volume (MCV)

MCV = Htk/RBC count

norm - 80- 95 fl

< 80 fl - microcytosis (i.e. iron def. anaemia)

> 95 fl – macrocytosis (i.e. megaloblastic anaemia)

- Mean corpuscular Hb (MCH)

MCH = Hb/RBC count

norm 27 - 32 pg

< 27 pg - hypochromia

> 32 pg - hyperchromia

- Mean corpuscular Hb concentration (MCHC)

MCHC = Hb/Htk

norm 320 - 370 g/l

< 320 gl - hypochromia

Fyziologické hodnoty

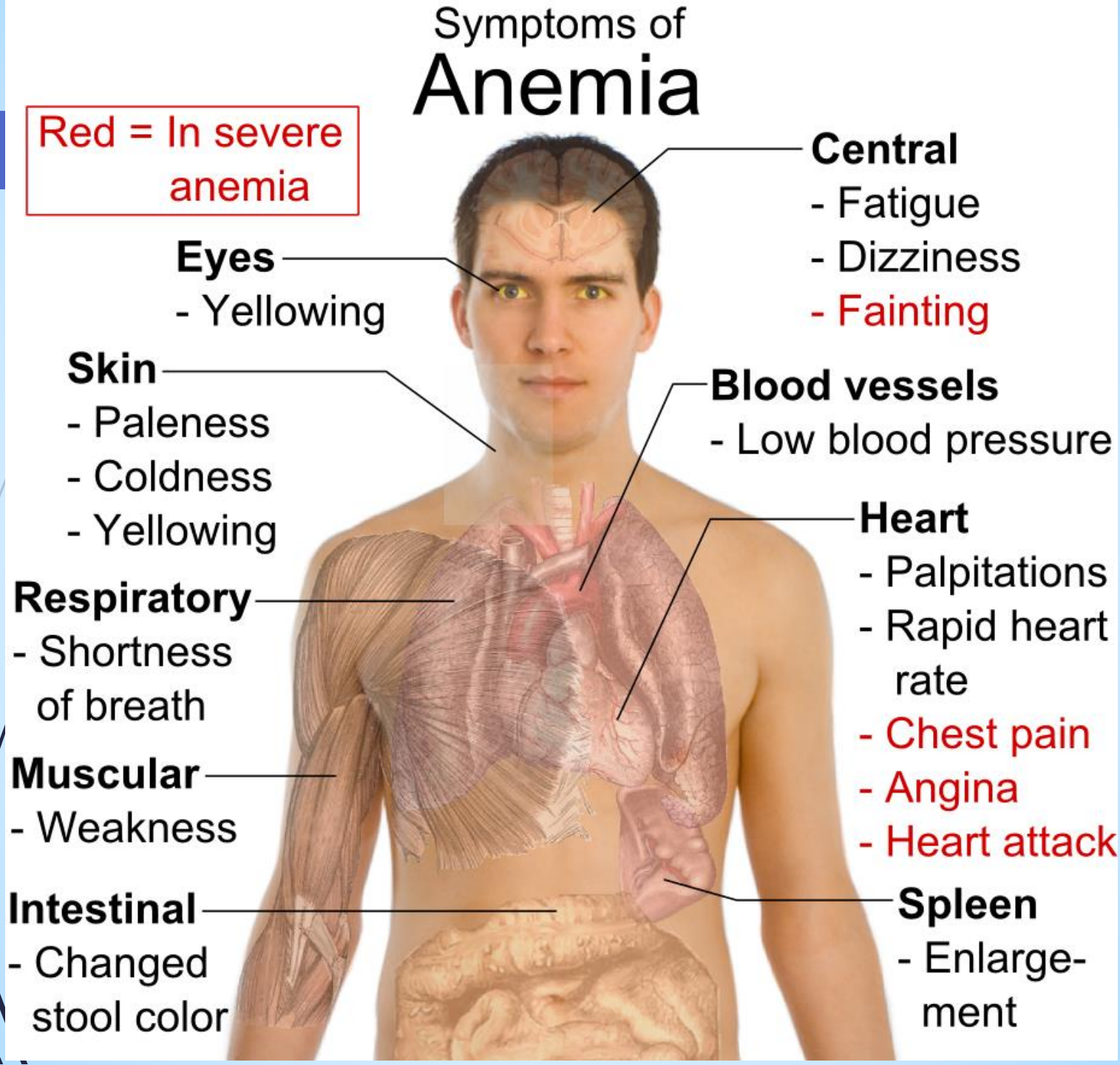
Age (years)	RBC ($\times 10^{-12}$/l)	Hb (g/dl)	MCV (fl)
Birth	3.5–6.7	14–24	100–135
1	4.1–5.3	11–14	71–84
2–5	4.2–5.0	11–14	73–86
6–9	4.3–5.1	11–14	75–88
9–12	4.3–5.1	11.5–15.5	76–91

Age (years)	WBC	Neutrophil count	Lymphocyte count	Mono count
Birth	5–23	1.7–19	1–11	0.1–
1	5.6–17.5	1.5–7	2.5–9	0.15–
2–5	5–13	1.5–8.5	1.5–5.5†	0.15–
6–9	4–10	1.5–6	1.5–4	0.15–
9–12	4–10	1.5–6	1.5–4	0.15–

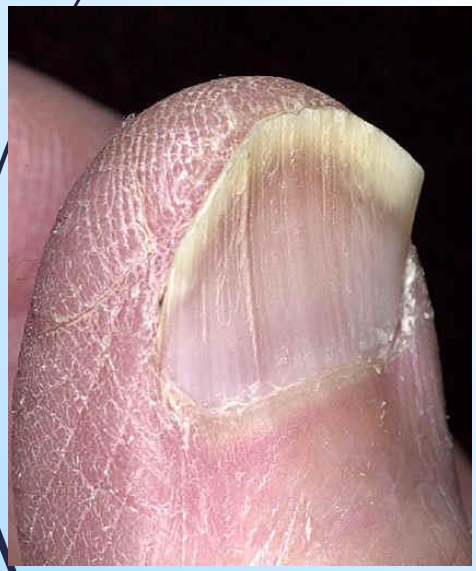
	Males	Females
WBC $\times 10^{-9}$/l	3.7–9.5	3.9–11.1
RBC $\times 10^{-12}$/l	4.32–5.66	3.88–4.99
Hb (g/dl)	13.3–16.7	11.8–14.8
PCV (Hct) (l/l)	0.39–0.5	0.36–0.44
MCV (fl)	82–98	
MCH (pg)	27.3–32.6	
MCHC (g/dl)	31.6–34.9	
RDW	9.5–15.5*	
	11.6–13.9†	
HDW	1.82–2.64†	
Neutrophils $\times 10^{-9}$/l	1.7–6.1	1.7–7.5
Lymphocytes $\times 10^{-9}$/l	1.0–3.2	
Monocytes $\times 10^{-9}$/l	0.2–0.6	
Eosinophils $\times 10^{-9}$/l	0.03–0.06	
Basophils $\times 10^{-9}$/l	0.02–0.29	
Large unstained cells (LUC) $\times 10^{-9}$/l	0.09–0.29	
Platelets $\times 10^{-9}$/l	143–332	169–358

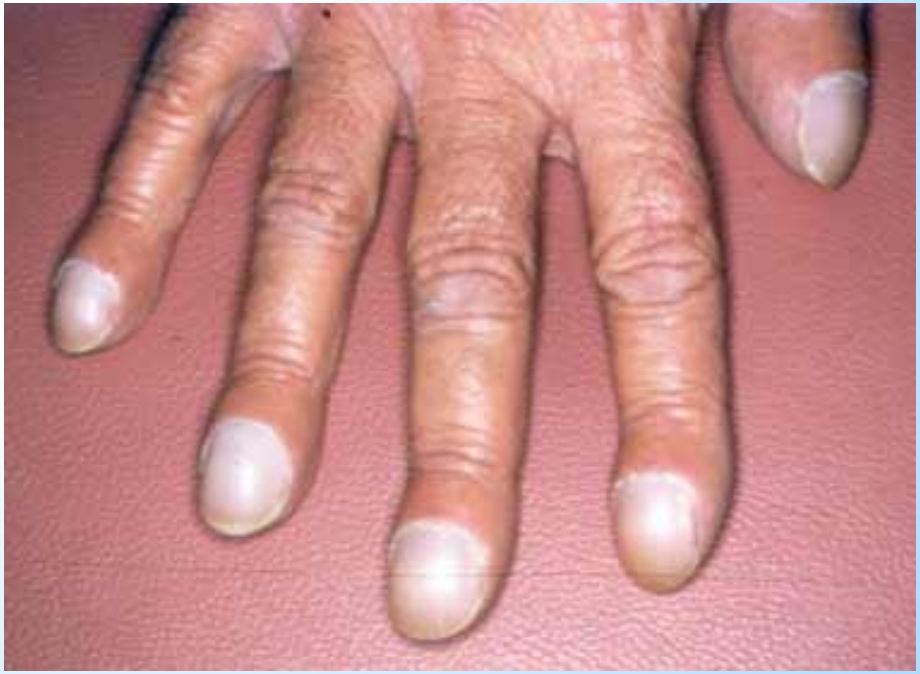
Anemias

- clinical symptoms of anemias
  - paleness
  - weakness
  - nauzea
  - tiredness
  - dyspnoe


Symptoms of
Anemia
Red = In severe anemia
Central
- Fatigue
- Dizziness
- Fainting
Eyes
- Yellowing
Skin
- Paleness
- Coldness
- Yellowing
Blood vessels
- Low blood pressure
Heart
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack
Respiratory
- Shortness of breath
Muscular
- Weakness
Intestinal
- Changed stool color
Spleen
- Enlarge-ment

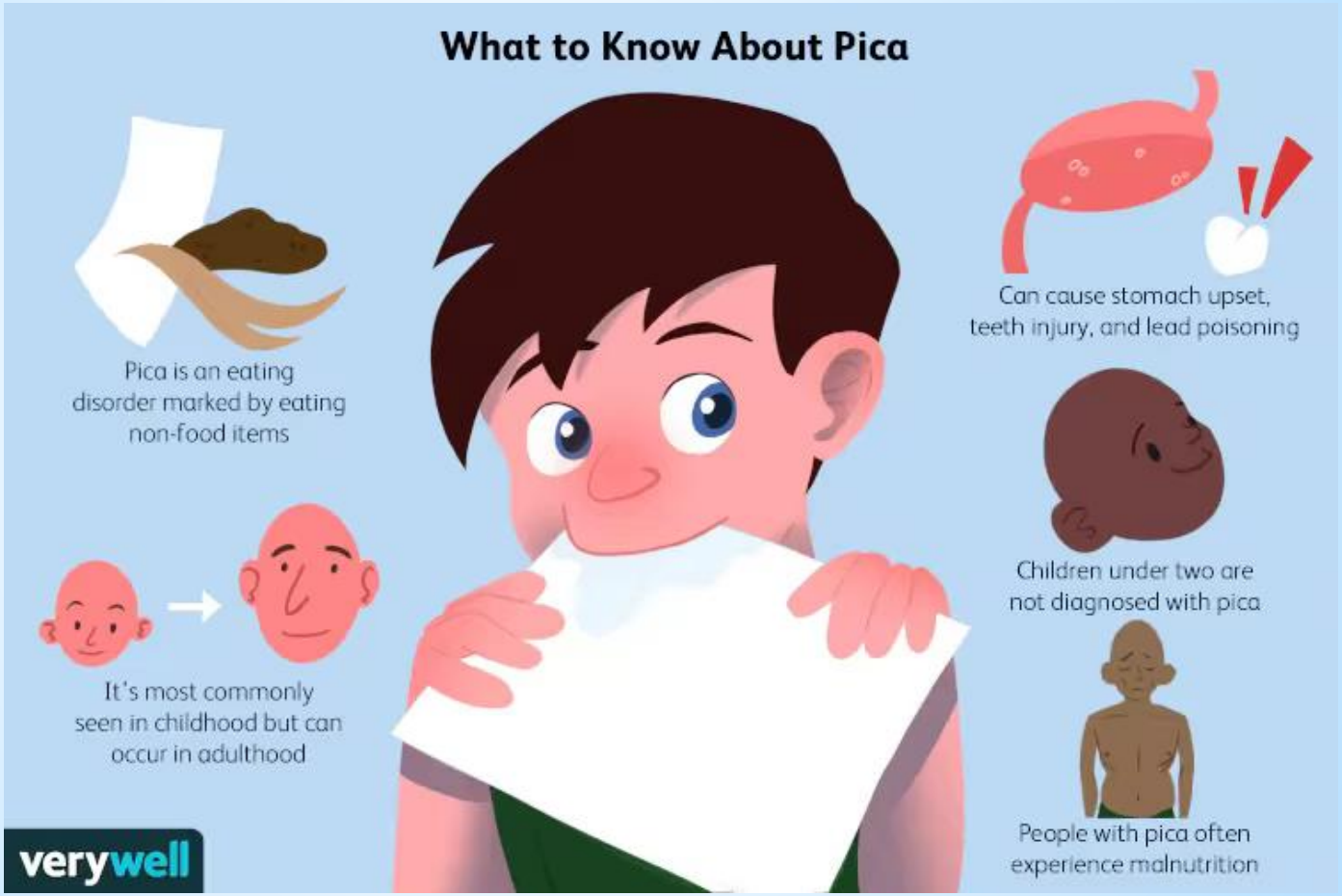
koilonychia





clubbed fingernails

Pica



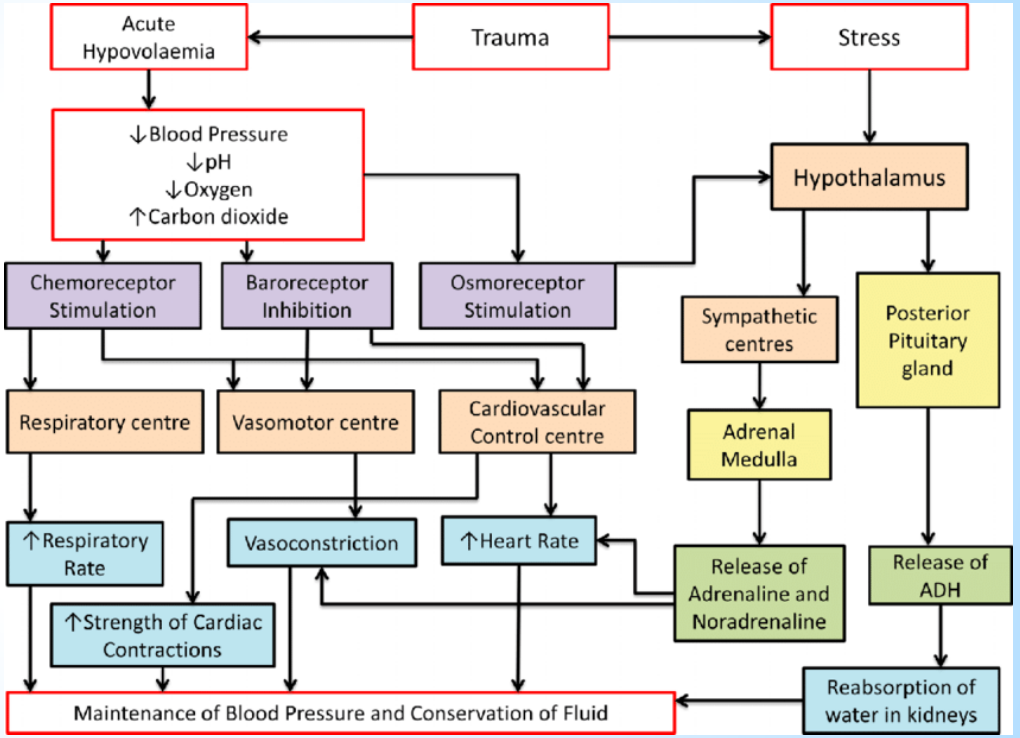
https://www.verywellhealth.com/pica-5083875

Acute blood loss

- body reactions depend on:
  - the rate of hemorrhage
  - character of bleeding
    - external or internal
- the effect depends on intravascular volume decrease
- the most serious consequences are:
  - cardiovascular collapse
  - shock
  - death

Acute blood loss

- the blood volume is rapidly restored by shift of water from the interstitial fluid compartment
  - resulting hemodilution lowers the hematocrit
  - reduction in the oxygenation of renal cells triggers increased production of erythropoietin
    - stimulates the proliferation of committed erythroid stem cells in the marrow
      - it takes about 5 days to release new RBC to the circulation



https://www.researchgate.net/figure/Compensatory-mechanism-ADH-antidiuretic-hormone_fig1_233931452

Acute blood loss

- iron for hemoglobin is recaptured if red cells are lost internally
- external bleeding leads to iron loss and possible iron deficiency
- red cells appear normal in size and colour
  - **normocytic**
  - **normochromic**
  - count of **reticulocytes** increase to 10-15% after 7 days
    - polychromophilic macrocytes
  - leukocytosis
  - thrombocytosis

Chronic blood loss

- the rate of loss exceeds the regenerative capacity of the blood marrow or iron reserves are depleted
  - massive bleeding because of menorrhea
  - peptic ulcer disease

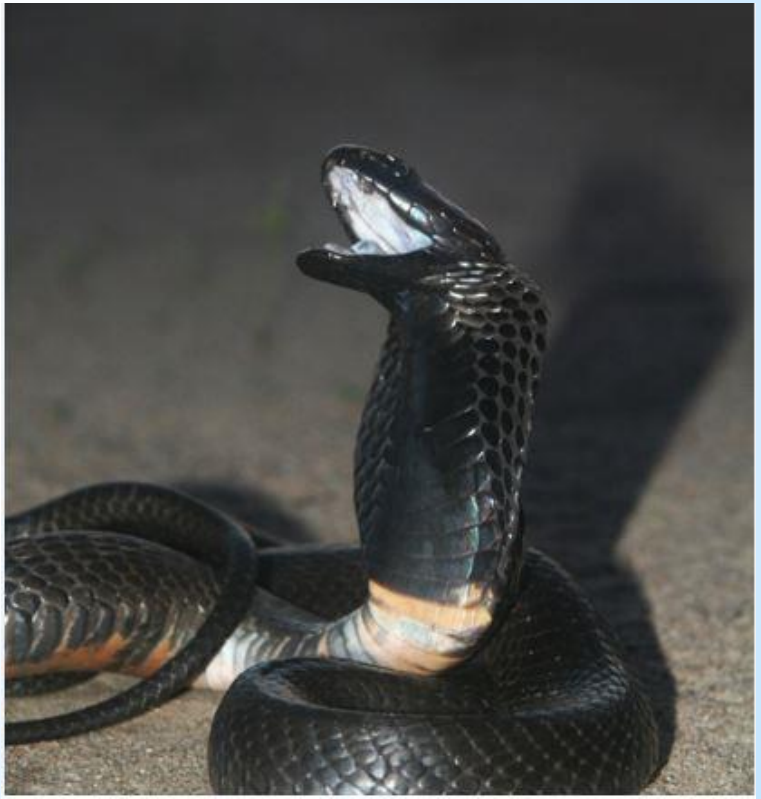
Hemolytic anemias

- share the following features:
  - *shortened red cell life span*
  - *elevated erythropoietin levels and increased erythropoiesis*
  - *accumulation of the products of hemoglobin catabolism*
- ***types:***
  - *extravascular*
  - *intravascular*
    - intracellular
    - extracellular

Hemolytic anemias

- **Intravascular (extracellular) hemolysis**
  - cause of hemolysis is present in blood
  - causes:
    - mechanical injury
      - defective cardiac valves
      - thrombi within the microcirculation
      - repetitive physical trauma (marathon runers)
    - complement fixation
      - transfusion of non compatabile blood
    - toxic injury
      - organic or anorganic substances
      - snakes
      - clostridial sepsis

- Naja nigricollis
- Black-necked spitting cobra



Hemolytic anemias

- intravascular hemolysis is manifested by:
  - ***hemoglobinemia***
  - ***hemoglobinuria***
  - ***jaundice***
  - ***hemosiderinuria***
  - **↓ of serum haptoglobin**
    - it bounds free hemoglobin
  - serum bilirubin is unconjugated
    - level of hyperbilirubinemia depends on the functional capacity of the liver and the rate of hemolysis

Hemolytic anemias

- ***Extravascular hemolysis***
  - red cells are rendered "foreign" or become less deformable
    - successfully to pass the splenic sinusoids need extreme alteration of RBC
    - reduced deformability makes the passage difficult
    - leads to sequestration followed by phagocytosis
    - this is an important pathogenetic mechanism of extravascular hemolysis

Hemolytic anemias

- hemoglobinemia and hemoglobinuria are not observed
- **principal features:**
  - anemia
  - jaundice
  - splenomegalia
- Second pathogenic classification:
  - **extracorpuscular mechanism**
  - **intracorpuscular defects**

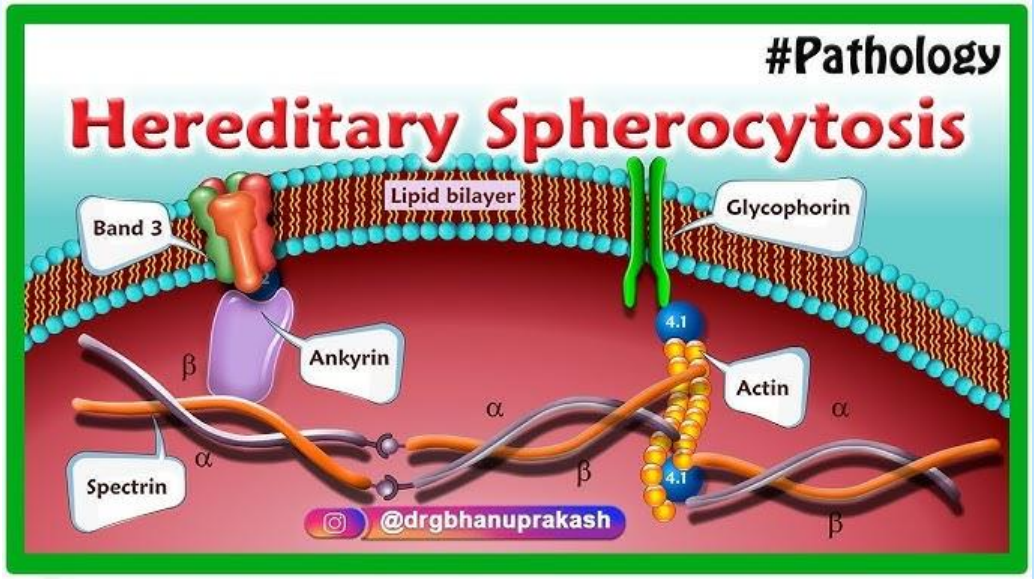
Hemolytic anemias

- some morfologic changes are common in all hemolytic anemias
  - **anemia**
  - lowered tissue oxygen tension **stimulates production of erythropoetin**
    - increased numbers of erythroid precursors (**normoblasts) in the marrow**
- if the anemia is severe, extramedullar hematopoiesis can appear in the liver, spleen, and lymph nodes
- elevated biliary excretion of bilirubin → formation of pigment gallstones (cholelithiasis)
- phagocytosis of red cells leads to hemosiderosis

Hemolytic anemias

Hereditary spherocytosis

- inherited autosomal dominant disorder
- intracellular defect in the red cell membrane
- red cells are:
  - **spheroid**
  - **less deformable**
  - **vulnerable to splenic sequestration**
- prevalence is highest in northern Europe



https://www.youtube.com/watch?v=B0moO86eMUs

Hemolytic anemias

causes are diverse mutations affecting **ankyrin** (most common cause) or spectrin

proteins of RBC membrane skeleton

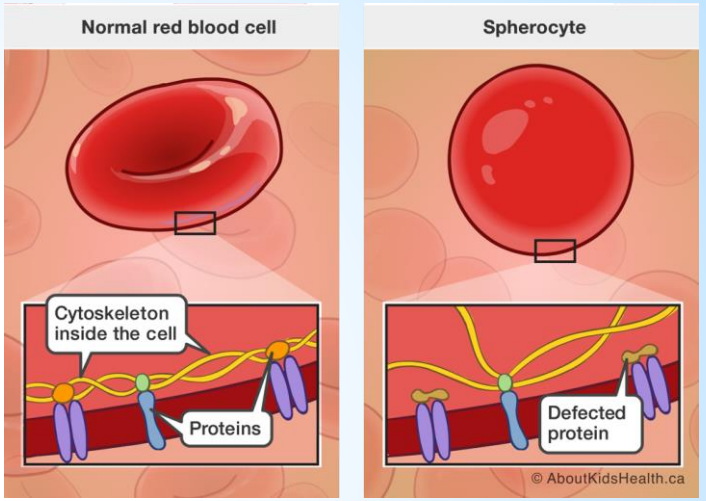
cytoplasm forces cause changing of blood cell shape to sphere

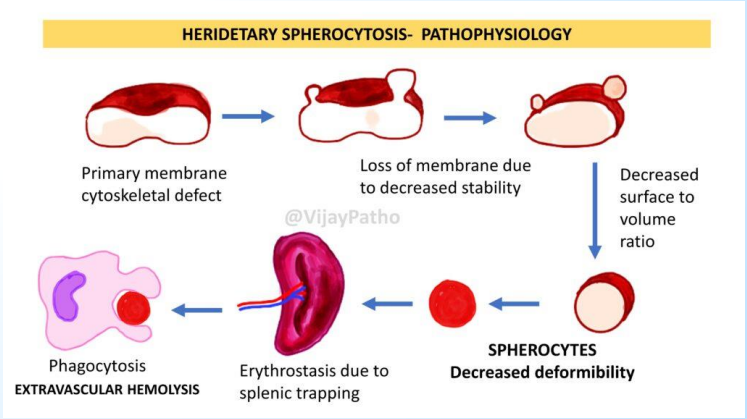
red cells must undergo extreme deformation to pass through spleen sinusoids

spherocytes are trapped in spleen

it causes:

erythrostasis





https://www.aboutkidshealth.ca/hereditary-spherocytosis
https://www.hematology-lessons.com/2020/10/hereditary-spherocytosis-hs.html

Hemolytic anemias

- ↓ of glucose
- ↓ of pH because of higher production of lactic acid
- ↑ macrophage contact

- spleen is cause of premature elimination of the spherocytes
- therapy is **splenectomy**
  - spherocytes persist, but the anemia is corrected
- morphological findings
  - **spherocytes**
    - abnormally small, hyperchromic red cells lacking the normal central zone of pallor

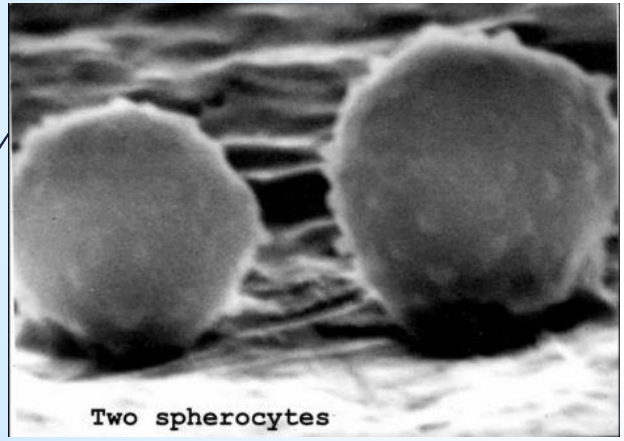
Hemolytic anemias

- reticulocytosis
- marrow hyperplasia
- hemosiderosis
- mild jaundice
- cholelithiasis occurs in 40% to 50%
- splenomegalia

- **Diagnosis**
  - **family histor**y
  - hematologic findings
  - ↑ mean cell hemoglobin concentration

RBC deformations

Spherocytes



RBC deformations

Eliptocytes

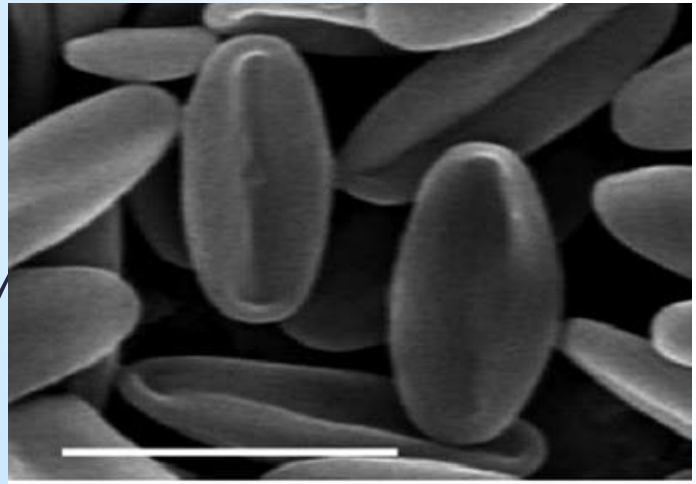
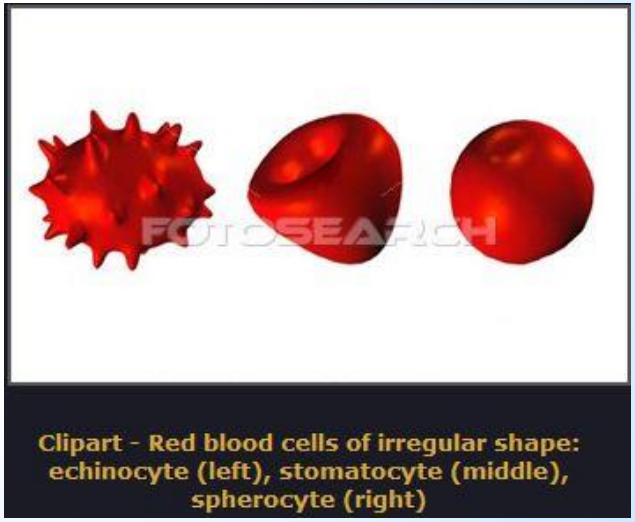


Fig. S6. Particles that mimic the shape of elliptocytes. (Scale bar, 2 μm.)

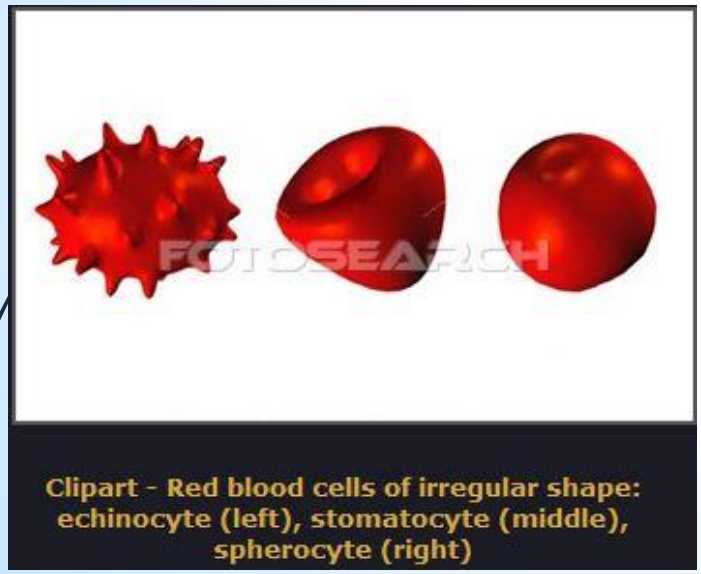
Stomatocytes



Clipart - Red blood cells of irregular shape: echinocyte (left), stomatocyte (middle), spherocyte (right)

RBC deformations

Echinocyte, stomatocyte, spherocyte



Clipart - Red blood cells of irregular shape: echinocyte (left), stomatocyte (middle), spherocyte (right)

Echinocytes

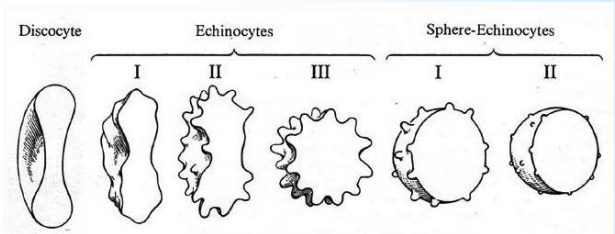


Figure 1. The sequential transformation of discocytes to echinocytes and spheroechinocytes (Bessis M: Blood Smears Reinterpreted, Springer-Verlag, 1977, p. 51).

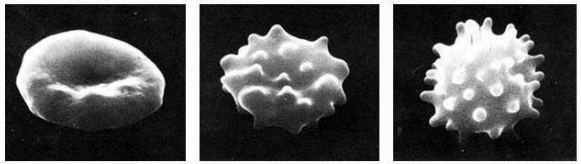
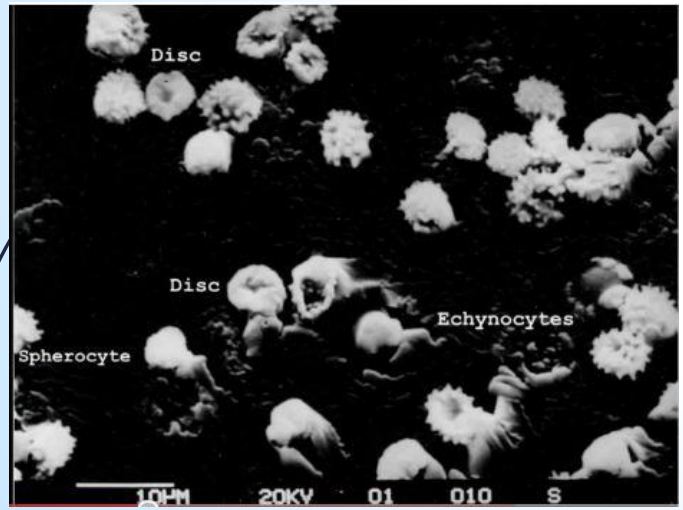


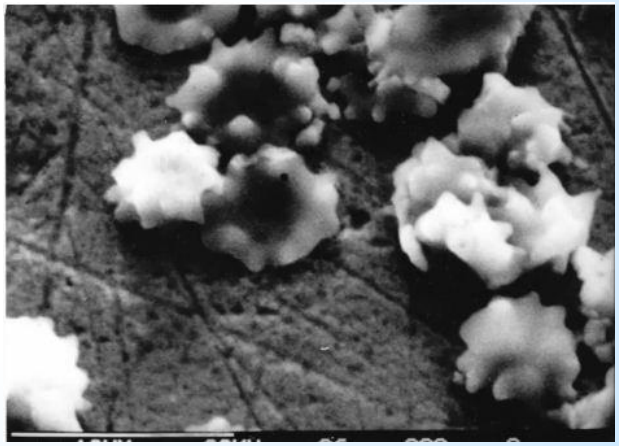
Figure 2. Scanning electron micrographs of discocyte transformation into echinocytes. A. Discocyte, B. Early echinocyte, C. Well developed echinocyte (modified from Bessis M: Blood Smears Reinterpreted, Springer-Verlag, 1977, p. 53).

RBC deformations

Echinocytes

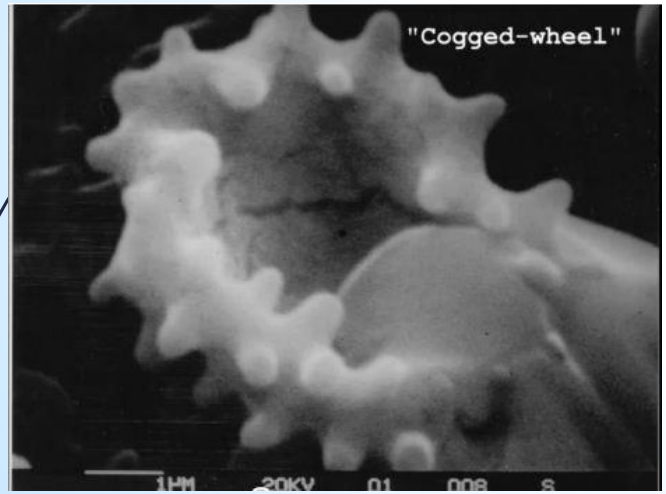


Echinocytes

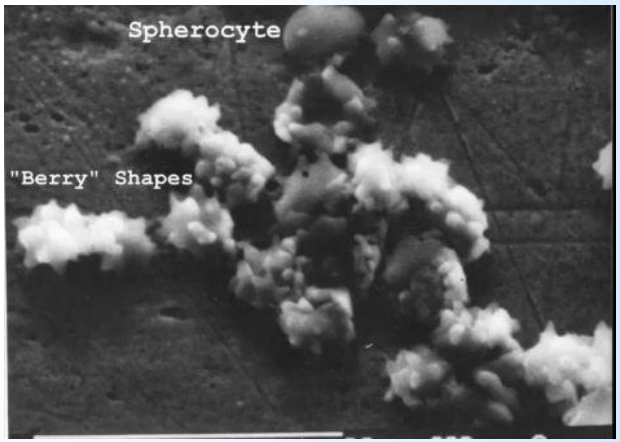


RBC deformations

Echinocytes



Echinocytes

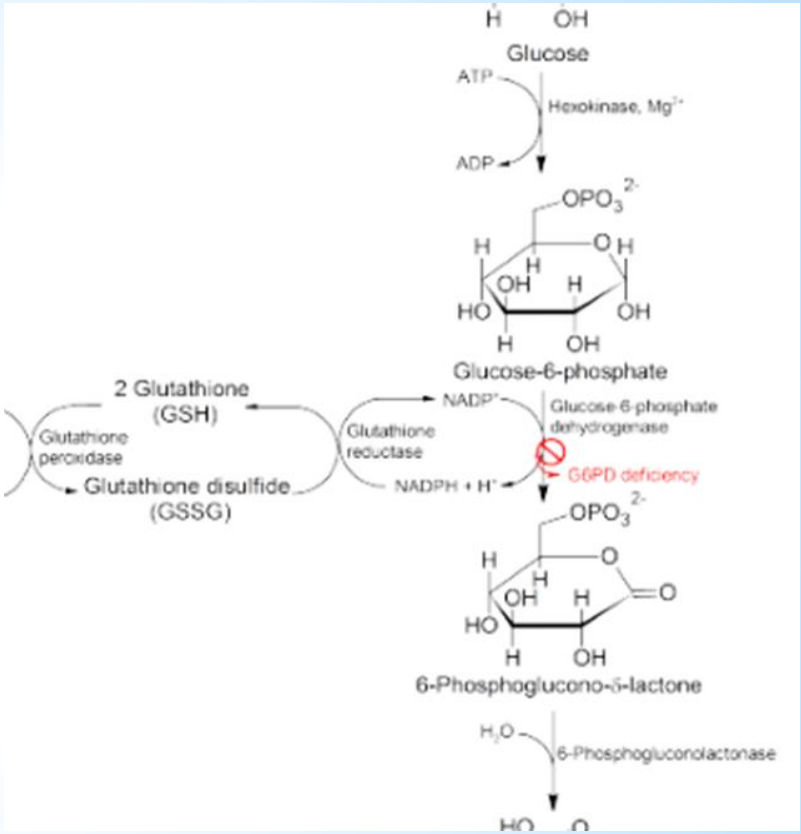


Hemolytic anemias

- **Glucose-6-Phosphate Dehydrogenase Deficiency**
  - the red cell is vulnerable to injury by exogenous and endogenous oxidants
  - abnormalities in the hexose monophosphate shunt or glutathione metabolism resulting from deficient or impaired enzyme function reduce the ability of red cells to protect themselves against oxidative injuries, leading to hemolytic disease

Hemolytic anemias

- G6PD reduces NADP to NADPH while oxidizing glucose-6-phosphate. NADPH then provides reducing equivalents needed for conversion of oxidized glutathione to reduced glutathione
  - it protects against oxidant injury by catalyzing the breakdown of compounds such as H_2O_2
- several hundred G6PD genetic variants are known, but most are harmless



https://en.wikipedia.org/wiki/Glucose-6-phosphate_dehydrogenase_deficiency

G6PD

Descriptive mutations

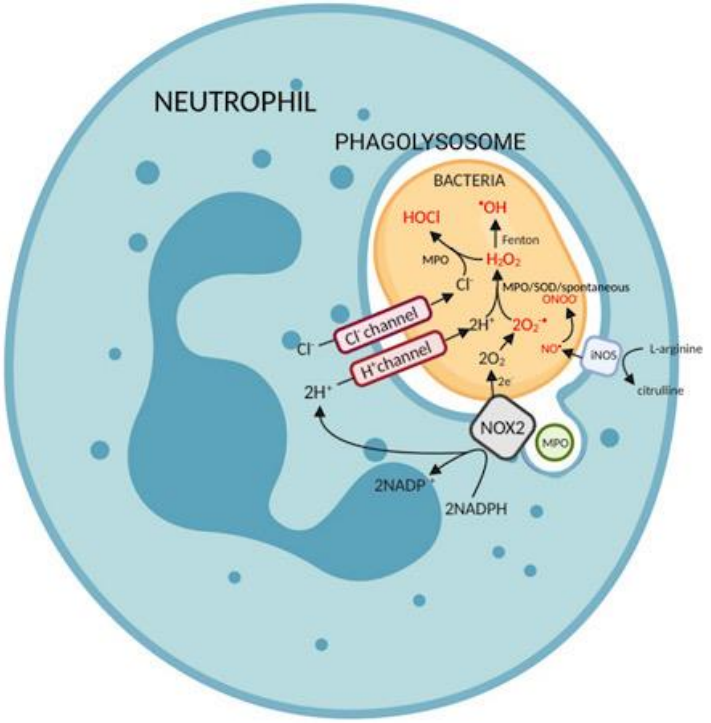
Mutation				Gene			Protein		
Designation	Short name	Isoform G6PD-Protein	OMIM-Code	Type	Subtype	Position	Position	Structure change	Function change
G6PD-A(+)	Gd-A(+)	G6PD A	+305900.0001	Polymorphism nucleotide	A→G	376 (Exon 5)	126	Asparagine→Aspartic acid (ASN126ASP)	No enzyme defect (variant)
G6PD-A(-)	Gd-A(-)	G6PD A	+305900.0002	Substitution nucleotide	G→A	376 (Exon 5) and 202	68 and 126	Valine→Methionine (VAL68MET) Asparagine→Aspartic acid (ASN126ASP)	
G6PD-Mediterranean	Gd-Med	G6PD B	+305900.0006	Substitution nucleotide	C→T	563 (Exon 6)	188	Serine→Phenylalanine (SER188PHE)	Class II
G6PD-Canton	Gd-Canton	G6PD B	+305900.0021	Substitution nucleotide	G→T	1376	459	Arginine→Leucine (ARG459LEU)	Class II
G6PD-Chatham	Gd-Chatham	G6PD	+305900.0003	Substitution nucleotide	G→A	1003	335	Alanine→Threonine (ALA335THR)	Class II
G6PD-Cosenza	Gd-Cosenza	G6PD B	+305900.0059	Substitution nucleotide	G→C	1376	459	Arginine→Proline (ARG459PRO)	G6PD-activity <10%, thus high portion of patients.
G6PD-Mahidol	Gd-Mahidol	G6PD	+305900.0005	Substitution nucleotide	G→A	487 (Exon 6)	163	Glycine→Serine (GLY163SER)	Class III
G6PD-Orissa	Gd-Orissa	G6PD	+305900.0047	Substitution nucleotide	C→G	131	44	Alanine→Glycine (ALA44GLY)	NADP-binding place affected. Higher stability than other variants.
G6PD-Asahi	Gd-Asahi	G6PD A-	+305900.0054	Substitution nucleotide (several)	A→G ± G→A	376 (Exon 5) 202	126 68	Asparagine→Aspartic acid (ASN126ASP) Valine→Methionine (VAL68MET)	Class III.

https://en.wikipedia.org/wiki/Glucose-6-phosphate_dehydrogenase_deficiency

Hemolytic anemias

- deficiency manifests in several distinct clinical patterns
- most common is hemolysis after exposure to oxidant stress
- this can cause:
  - certain drugs
    - antimalarials, sulfonamides, nitrofurantoins
  - certain foods (fava beans)
  - free radicals generated by leukocytes in the course of infection

https://www.feedstrategy.com/blogs/feed-ingredient-insights/blog/15444699/fava-beans-an-alternative-protein-source-in-layer-feeds
https://en.wikipedia.org/wiki/Respiratory_burst

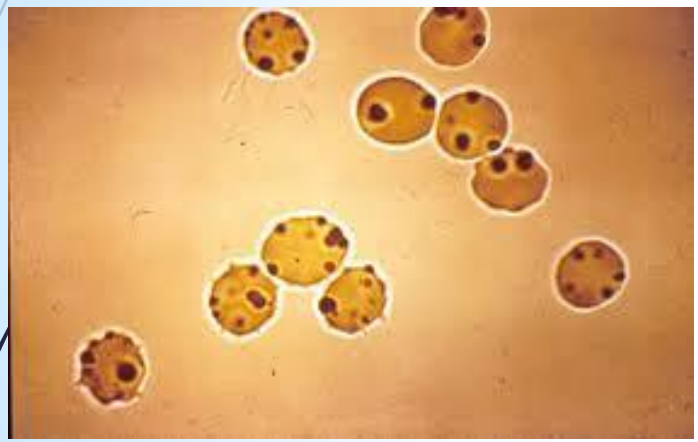


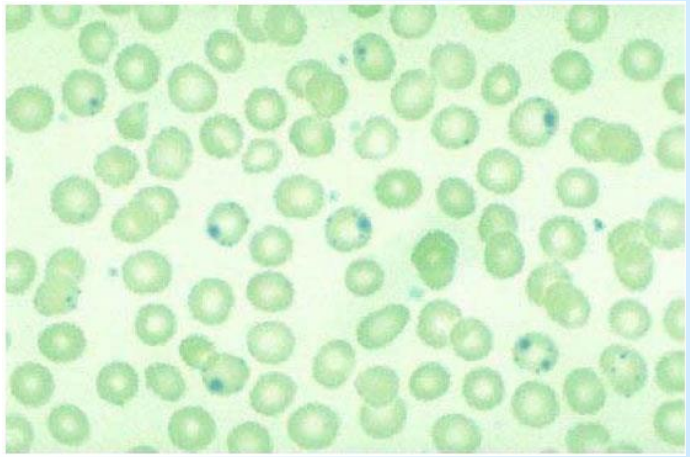
Hemolytic anemias

- G6PD deficiency causes episodic intravascular and extravascular hemolysis
- oxidants cause denaturation of globin chains to Heinz bodies
- they can damage cell membrane and cause hemolysis
- due to membrane damage some of these partially devoured cells retain an abnormal shape
  - bite cells
  - spherocytic cells

Bite cells

Heinz bodies



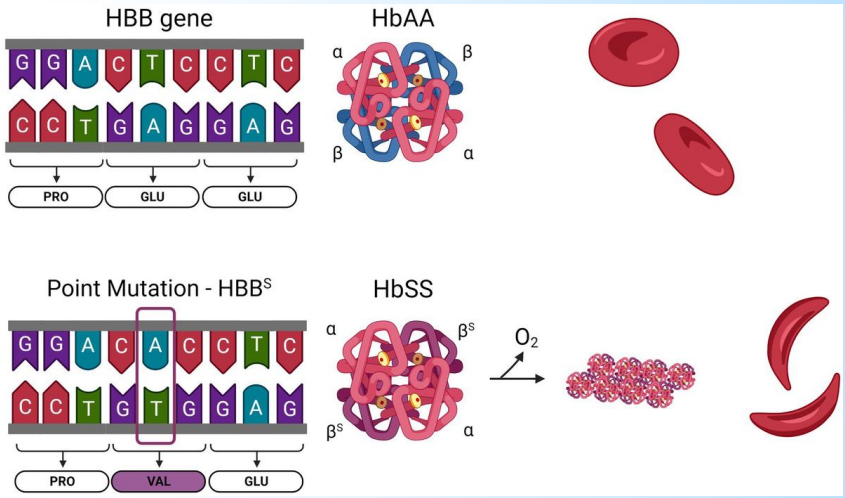


Hemolytic anemias

- symptoms appear 2-3 days following exposure to oxidants:
  - anemia
  - hemoglobinemia
  - hemoglobinuria

Hemolytic anemias

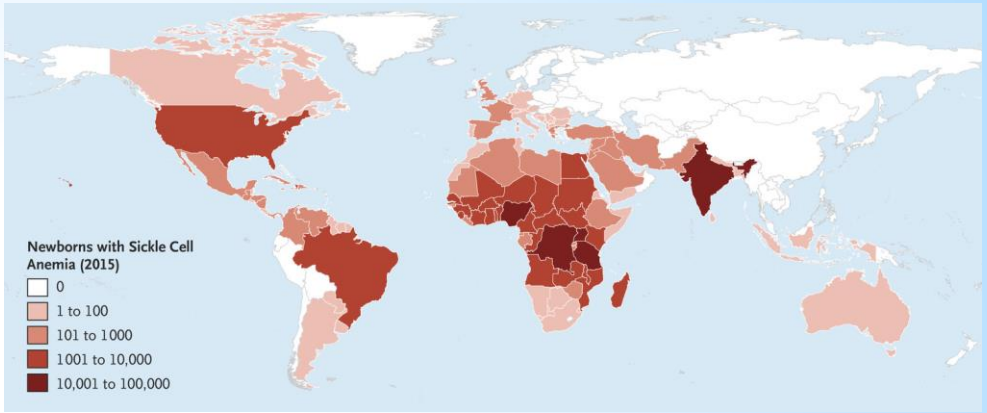
- **Sickle cell disease**
  - an important hereditary hemoglobinopathy
    - type of disease characterized by production of defective hemoglobins
  - normal adult red cells contain mainly HbA ($a_2\beta_2$) along with small amounts of HbA_2 ($a_2\delta_2$) and fetal hemoglobin ($a_2\gamma_2$).
  - sickle cell anemia is caused by a point mutation at the sixth position of the β-globin chain leading to the substitution of a valine residue for a glutamic acid residue
  - the abnormal physiochemical properties of the resulting sickle hemoglobin (HbS) are responsible for sickle cell disease
  - several hundred other abnormal hemoglobins have been identified containing point mutations or deletions in one of the globin chains

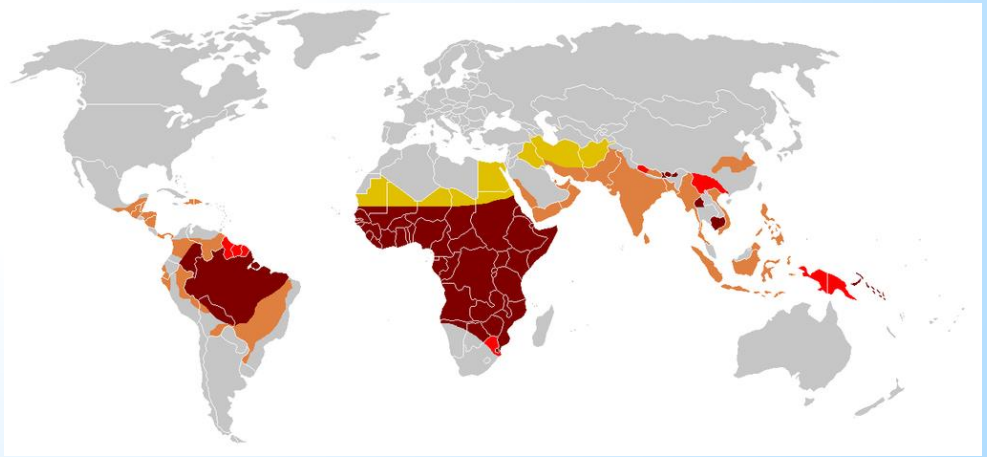


https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2023.1141020/full

Hemolytic anemias

- about 8% of Afroamericans are heterozygous for HbS
- homozygot for the sickle mutation has almost all the hemoglobin in the red cell is HbS ($a_2\beta^s_2$)
- in heterozygotes only about 40% of the hemoglobin is HbS
- where malaria is endemic in Africa, as many as 30% of the native population are heterozygous





https://www.nejm.org/doi/full/10.1056/NEJMra1510865
https://en.wikipedia.org/wiki/Sickle_cell_disease

Hemolytic anemias

- when deoxygenated, HbS molecules undergo aggregation and polymerization
- the red cell cytosol converts from a freely flowing liquid to a viscous gel as HbS aggregates form
- with continued deoxygenation, aggregated HbS molecules assemble into long needle-like fibers within red cells, producing a distorted sickle or holly-leaf shape
  - initially it is reversible phenomenon

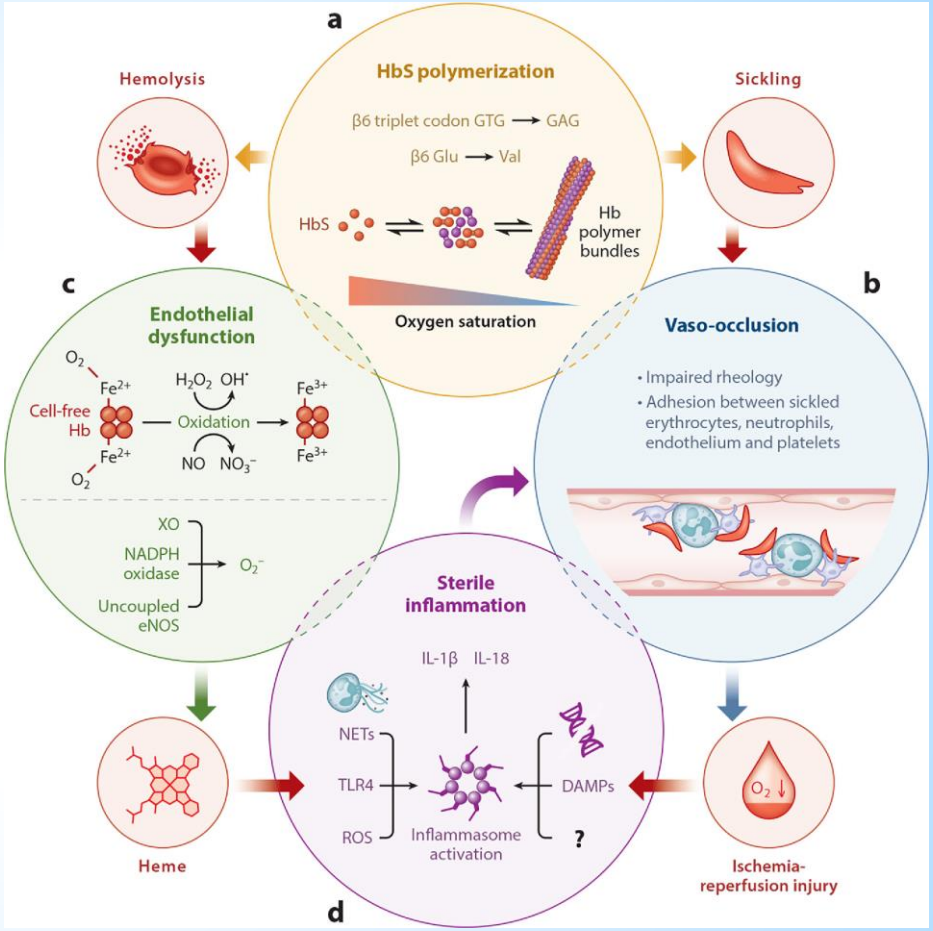
Hemolytic anemias

- with oxygenation, HbS depolymerizes and the cell shape changes to normal
- however, with repeated episodes of sickling membrane damage occurs and cells become irreversibly sickled, retaining their abnormal shape even when fully oxygenated
- the precipitation of HbS fibers also causes oxidant damage
- calcium ions activate a potassium ion channel, leading to the efflux of potassium and water, intracellular dehydration, and an **increase in the mean cell hemoglobin concentration**

Hemolytic anemias

- lessions produced by repeated episodes of deoxygenation render **sickle red cells abnormally sticky**
- membrane changes are important in the pathogenesis of microvascular occlusions

- **symptoms:**
  - chronic hemolysis
  - ischemic tissue damage

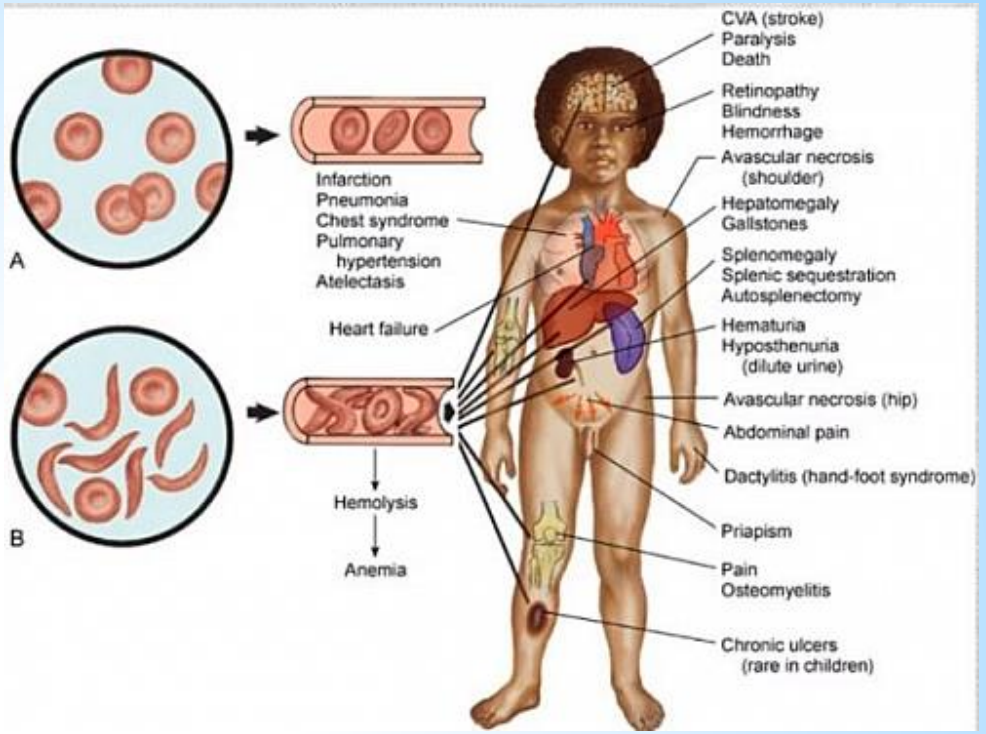


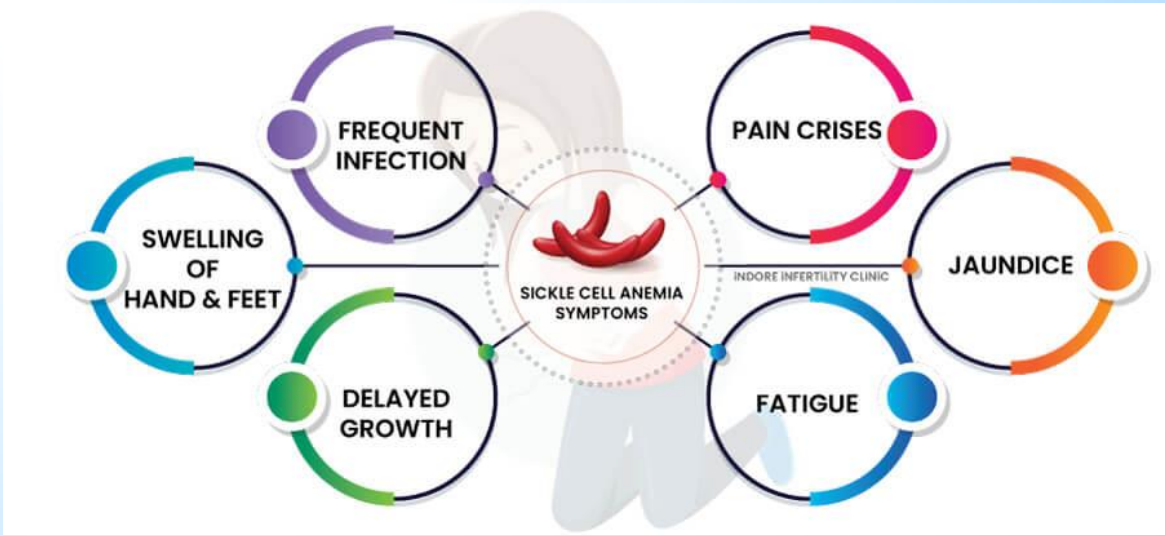
Hemolytic anemias

- irreversibly sickled cells have **rigid and nondeformable** cell membranes
  - it causes sequestretion and rapid phagocytosis in spleen
- increased adhesiveness makes reversibly sickled red cells more likely to arrest during transit through the microvasculature, particularly in areas of slow flow
  - it causes inflammation
- it up-regulates the expression of adhesion molecules on endothelial cells

Hemolytic anemias

- **findings:**
  - chronic hemolysis
  - increase formation of bilirubin
    - gallstones
  - small vessel stasis
    - it causes pain
  - hyperplastic bone marrow
  - hypersplenia





https://littlecellofmine.com/sickle-cell-disease/
https://www.indoreinfertilityclinic.com/sickle-cell-anemia-pregnancy-test-treatment/

Hemolytic anemias

- **Thalassemia syndromes**
  - heterogeneous group of inherited disorders
  - genetic lesions leading to decreased synthesis of either the a- or β-globin chain of HbA ($a_2\beta_2$)
    - β-thalassemia is caused by deficient synthesis of the β chain
    - a-thalassemia is caused by deficient synthesis of the a chain
  - **consequences:**
    - hypochromia
    - excess free a chains aggregate into insoluble inclusions
  - **leading to :**
    - *ineffective erythropoiesis*
    - *hemolysis*

Hemolytic anemias

- **β-thallasemias**
  - the clinical severity of the anemia varies due to heterogeneity in the causative mutations
  - **two categories:**
    - β^0-thalassemia, associated with total absence of β-globin chains in the homozygous state
    - β^+-thalassemia, characterized by reduced (but detectable) β-globin synthesis in the homozygous state

Hemolytic anemias

- it appears approximately 100 different causative mutations
- impaired β-globin synthesis results in anemia by two mechanisms
- deficit in HbA synthesis produces:
  - hypochromic
  - microcytic RBC
- free a chains precipitate within the normoblasts, forming insoluble inclusions
  - it causes cell membrane damage

Hemolytic anemias

- consequence is premature death of RBC in bone marrow
  - it can be up to 85% of RBC
- extramedullary hematopoiesis involves the liver, spleen, and lymph nodes, and in extreme cases produces extraosseous masses in the thorax, abdomen, and pelvis
- the metabolically active erythroid progenitors steal nutrients from other tissues
  - cachexia

Hemolytic anemias

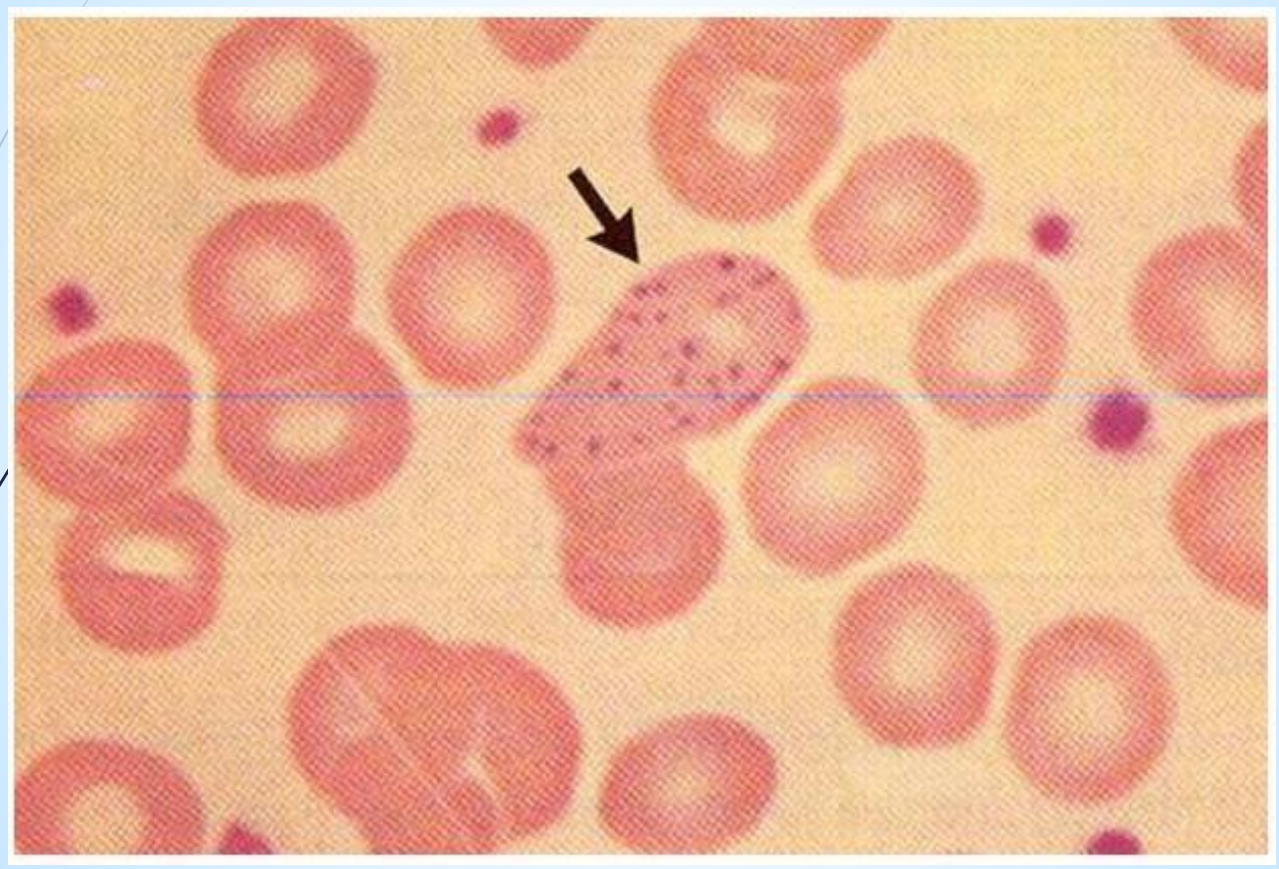
- another disastrous complication is excessive absorption of dietary iron
- it causes secondary hemochromatosis too
- **Thalassemia major**
  - most common in Mediterranean countries and parts of Africa and Southeast Asia
  - the genotype of affected patients can be:
    - β^{+}/β^{+}
    - β^{0}/β^{0}
    - β^{0}/β^{+}

Hemolytic anemias

Clinical Nomenclature	Genotype	Disease	Molecular Genetics
β- *Thalassemias*			
Thalassemia major	Homozygous β^0-thalassemia (β^0/β^0)	Severe; requires blood transfusions	Rare gene deletions in β^0/β^0 Defects in transcription, processing, or translation of β-globin mRNA
	Homozygous β^+-thalassemia (β^+/β^+)		
Thalassemia intermedia	β^0/β	Severe, but does not require regular blood transfusions	
	β^+/β^+		
Thalassemia minor	β^0/β	Asymptomatic with mild or absent anemia; red cell abnormalities seen	
	β^+/β		

Hemolytic anemias

- with all these genotypes, the anemia manifests 6 to 9 months after birth, as hemoglobin synthesis switches from HbF to HbA
- hemoglobin levels range between 3 and 6 g/dL
- **peripheral blood smear shows**:
  - severe red cell morphologic abnormalities
  - including marked anisocytosis and poikilocytosis
  - microcytosis
  - hypochromia
- **common are**:
  - target cells
  - basophilic stippling
  - fragmented red cells



Hemolytic anemias

- reticulocyte count is elevated
- variable numbers of poorly hemoglobinized normoblasts are seen
- **non treated children**
  - growth retardation and death at an early age
- **treated patients with transfusion**
  - improve the anemia
  - suppress secondary features related to excessive erythropoiesis
- cardiac disease resulting from progressive iron overload and secondary hemochromatosis is an important cause of death, particularly in heavily transfused patients
  - administration of iron chelators can forestall or prevent this complication

Hemolytic anemias

- **Thalassemia minor**
  - is much more common than thalassemia major
  - thalassemia trait may offer resistance against falciparum malaria
    - these patients are usually asymptomatic, and anemia is mild if present
  - **peripheral blood smear :**
    - hypochromia
    - microcytosis
    - basophilic stippling
    - target cells

Hemolytic anemias

- mild erythroid hyperplasia of bone marrow

- **alfa-thalassemias**
  - are characterized by reduced or absent synthesis of a-globin chains
  - the severity of alfa-thalassemia varies greatly depending on the number of a-globin genes affected
  - the situation is complicated somewhat by synthesis of different non-a chains at varying times of development

Hemolytic anemias

Clinical Nomenclature	Genotype	Disease	Molecular Genetics
α- *Thalassemias*			
Hydrops fetalis	-/- -/-	Lethal in utero without transfusions	Mainly gene deletions
HbH disease	-/- -/α	Severe; resembles β-thalassemia intermedia	
α-Thalassemia trait	-/- α/α (Asian)	Asymptomatic, like β-thalassemia minor	
	-/α -/α (black African)		
Silent carrier	-/α α/α	Asymptomatic; no red cell abnormality	

Hemolytic anemias

- **Silent carrier state**
  - a single a-globin gene is deleted
  - these individuals are completely asymptomatic
- **alfa-thalassemia trait**
  - this is caused by deletion of two a-globin genes
    - two involved genes can be from **the same chromosome** (a/a -/-) or one a-globin gene can be deleted **from each of the two chromosomes** (a/- a/-)
  - both genotypes produce similar quantitative deficiencies of a-globin chains and are clinically identical

Hemolytic anemias

- **clinical picture**:
  - microcytosis
  - minimal or no anemia
  - no abnormal physical signs
- **Hemoglobin H disease**
  - caused by deletion of three alfa-globin genes
  - the synthesis of a chains is markedly reduced and tetramers of excess beta-globin, called HbH, form
  - HbH has extremely high affinity for oxygen and therefore is not useful for oxygen exchange

Hemolytic anemias

- instability of HbH is a major cause of anemia
  - as precipitates of oxidized HbH form in older red cells
  - removed by splenic macrophages
- **Hydrops fetalis**
  - caused by deletion of all four a-globin genes

Hemolytic anemias

- **Paroxysmal nocturnal hemoglobinuria**
  - it is the only hemolytic anemia caused by an acquired intrinsic defect in the cell membrane
  - it is rare
  - proteins are anchored into the lipid bilayer in two ways
  - the remainder are attached to the cell membrane by covalent linkage to a specialized phospholipid called glycosylphosphatidylinositol (GPI)
  - PNH results from acquired mutations in phosphatidylinositol glycan A (PIGA), which is essential for the synthesis of the GPI anchor

Hemolytic anemias

- PIGA is X-linked
  - only one active copy of the gene for PIGA is present in each cell
- causative somatic mutations occur in pluripotent stem cells
- all its clonal progeny (red cells, white cells, and platelets) are deficient in proteins attached to the cell membrane via GPI
- not all blood cells are affected in PNH patients

Hemolytic anemias

- several of the proteins that anchor to GPI on the cell membrane are used to protect the cell from destruction by the complement system, and, without these anchors, the cells are more easily targeted by the complement proteins
- deficient platelets and granulocytes are also more sensitive to lysis by complement
- the intravascular hemolysis is actually paroxysmal and nocturnal in only 25% of cases

Hemolytic anemias

- chronic hemolysis without dramatic hemoglobinuria is more common
- hemosiderinuria eventually leads to iron deficiency
- **severe clinical manifestation is episodic venous thrombosis**
  - **this thrombosis is fatal in 50% of cases**

Warm Antibody Type
The antibody is of the IgG type, does not usually fix complement, and is active at 37°C.
Primary (idiopathic)
Secondary
Lymphomas and leukemias
Other neoplastic diseases
Autoimmune disorder (particularly systemic lupus erythematosus)
Drugs
Cold Agglutinin Type
The antibodies are IgM and most active in vitro at 0° to 4°C.
Antibodies dissociate at 30°C or above; agglutination of cells by IgM and complement fixation occurs only in peripheral cool parts of the body (e.g., fingers, ears, and toes).
Acute (mycoplasmal infection, infectious mononucleosis)
Chronic
Idiopathic
Associated with lymphoma
Cold Hemolysins (Paroxysmal Cold Hemoglobinuria)
IgG antibodies bind red cells at low temperature, fix complement, and cause hemolysis when the temperature is raised above 30°C.

Hemolytic anemias

- **Imunohemolytic anemia**
  - caused by extracorpuscular mechanisms
  - in some instances the immune reaction is initiated by drug ingestion
  - diagnosis requires detection of antibodies
  - **Warm antibody immunohemolytic anemia**
    - the most common form (48% to 70%) of immune hemolytic anemia
    - about 50% of cases are idiopathic
    - most causative antibodies is the immunoglobulin G
    - sometimes IgA antibodies are responsible
    - RBC destruction is extravascular
    - the loss of cell membrane converts the red cells to spherocytes, which are sequestered and removed in the spleen

Hemolytic anemias

- the cause of autoantibody formation is largely unknown
- the mechanisms of drug-induced hemolysis are better understood
- two predominant immunologic mechanisms
  - **hapten model**
  - **autoantibody model**

- **Cold agglutinin immunohemolytic anemia**
  - is caused by so-called *cold agglutinins,* IgM antibodies that bind and agglutinate red cells mainly at low temperatures

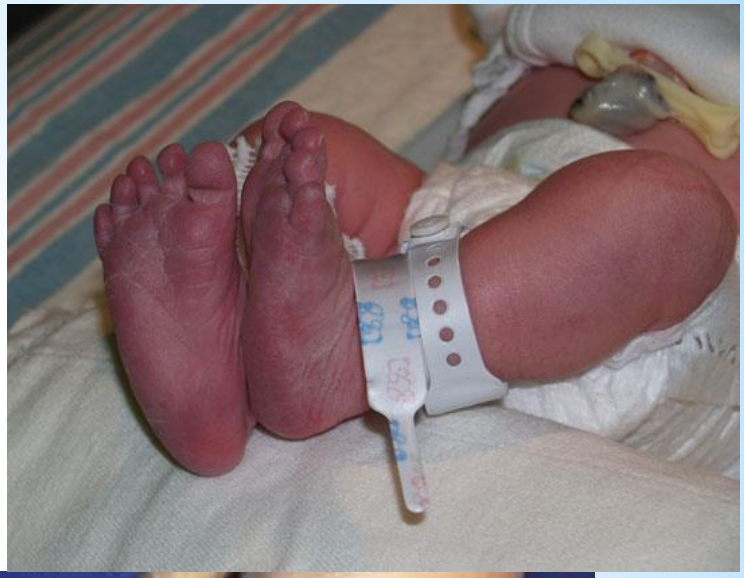
Hemolytic anemias

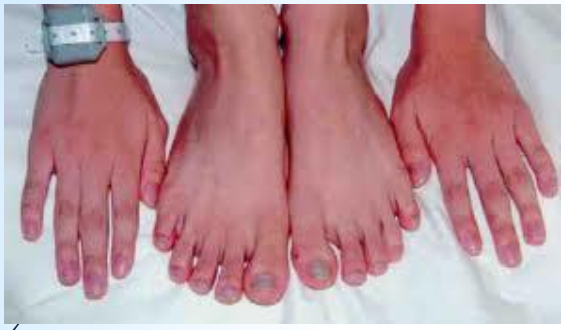
- such antibodies appear *acutely* during the recovery phase of certain infectious the disorder is self-limited and rarely induces clinical manifestations of hemolysis disorders
- chronic cold agglutinin immunohemolytic anemias occur in association with certain lymphoid neoplasms or as an idiopathic condition
- clinical symptoms result from binding of IgM to red cells at sites such as exposed fingers, toes, and ears where the temperature is below 30°C.
- IgM binding agglutinates red cells and rapidly fixes complement on their surface

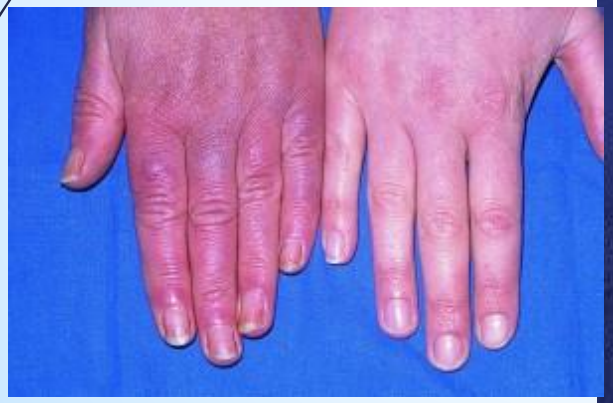
Hemolytic anemias

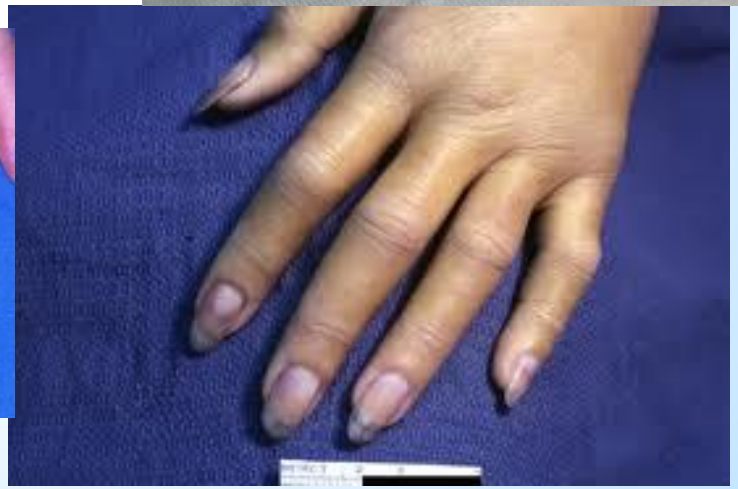
- as the blood recirculates and warms, IgM is rapidly released, usually before complement-mediated hemolysis can occur
- the transient interaction with IgM is sufficient to deposit sublytic quantities of C3b
- leading to rapid removal of affected red cells by mononuclear phagocytes in the liver and spleen
- vascular obstruction caused by red cell agglutination results in pallor, cyanosis of the body parts exposed to cold temperatures, and Raynaud phenomenon

Akrocyanosis









Hemolytic anemias

- **Cold hemolysin hemolytic anemia**
  - cold hemolysins are autoantibodies responsible for an unusual entity known as paroxysmal cold hemoglobinuria
  - characterized by acute intermittent massive intravascular hemolysis, frequently with hemoglobinuria, after exposure to cold temperatures

Hemolytic anemias

- **Hemolytic anemia resulting from trauma to red cell**
  - RBC can be disrupted by physical trauma in a variety of circumstances
  - caused by:
    - valve prostheses
    - narrowing or obstruction of the microvasculature
    - malignant hypertension, systemic lupus erythematosus, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), and disseminated cancer

Hemolytic anemias

- the common feature among all these disorders is a microvascular lesion that causes mechanical injury to circulating red cells
- damage is evident in peripheral blood smears:
  - schistocytes
  - "burr cells"
  - "helmet cells"
  - "triangle cells"

Anemias of diminished erythropoiesis

- **Megaloblastic anemias**
  - **pernicious anemia**
  - **folate deficiency anemia**
  - erythroid precursors and red cells are abnormally large due to defective cell maturation and division
  - **red cells are macrocytic and oval**
  - **neutrophils are also larger than normal and hypersegmented**
    - **that is, they have five to six or more nuclear lobules**

Anemias of diminished erythropoiesis

- megaloblastic change is detected in all stages of red cell development
- the marrow hyperplasia usually seen in megaloblastic anemias is a response to increased levels of growth factors such as erythropoietin
- typical is ineffective erythropoiesis = destruction in bone marrow
- **Vitamin B12 deficiency**
  - specific form of megaloblastic anemia
  - cause:
    - atrophic gastritis and failure of intrinsic factor production

Anemias of diminished erythropoiesis

- **Vitamin B12 metabolism**
  - plants and vegetable contain minimum cobalamin
  - daily requirement is 2 to 3 µg
  - balanced diet contains significantly larger amounts
  - absorption of vitamin B_{12} requires intrinsic factor
    - secreted by the parietal cells of the fundic mucosa
  - vitamin B_{12} is **freed from binding proteins in food through the action of pepsin** in the stomach
    - free vitamin B_{12} binds to salivary proteins called cobalophilins, **or R-binders**

Anemias of diminished erythropoiesis

- in the duodenum, cobalophilin-vitamin B_{12} complexes are broken down by the action of pancreatic proteases, and released vitamin B_{12} then associates with **intrinsic factor**
- it is endocytosed by ileal enterocytes that express **intrinsic factor-specific receptors** on their surfaces
- vitamin B_{12} associates with a major carrier protein, **transcobalamin II**, and is secreted into the plasma

- methylcobalamin is an essential cofactor for methionine synthase
  - it participates on tetrahydrofolic acid synthesis
  - it is required for conversion of deoxyuridine monophosphate to deoxythymidine monophosphate, an immediate precursor of DNA

Anemias of diminished erythropoiesis

- second reaction depended on cobalamin is the isomerization of methylmalonyl coenzyme A to succinyl coenzyme A, which requires adenosylcobalamin as a prosthetic group on the enzyme methylmalonyl-coenzyme A mutase
  - this biochemical abnormality predisposes to myelin breakdown and thereby produces the neurologic complications

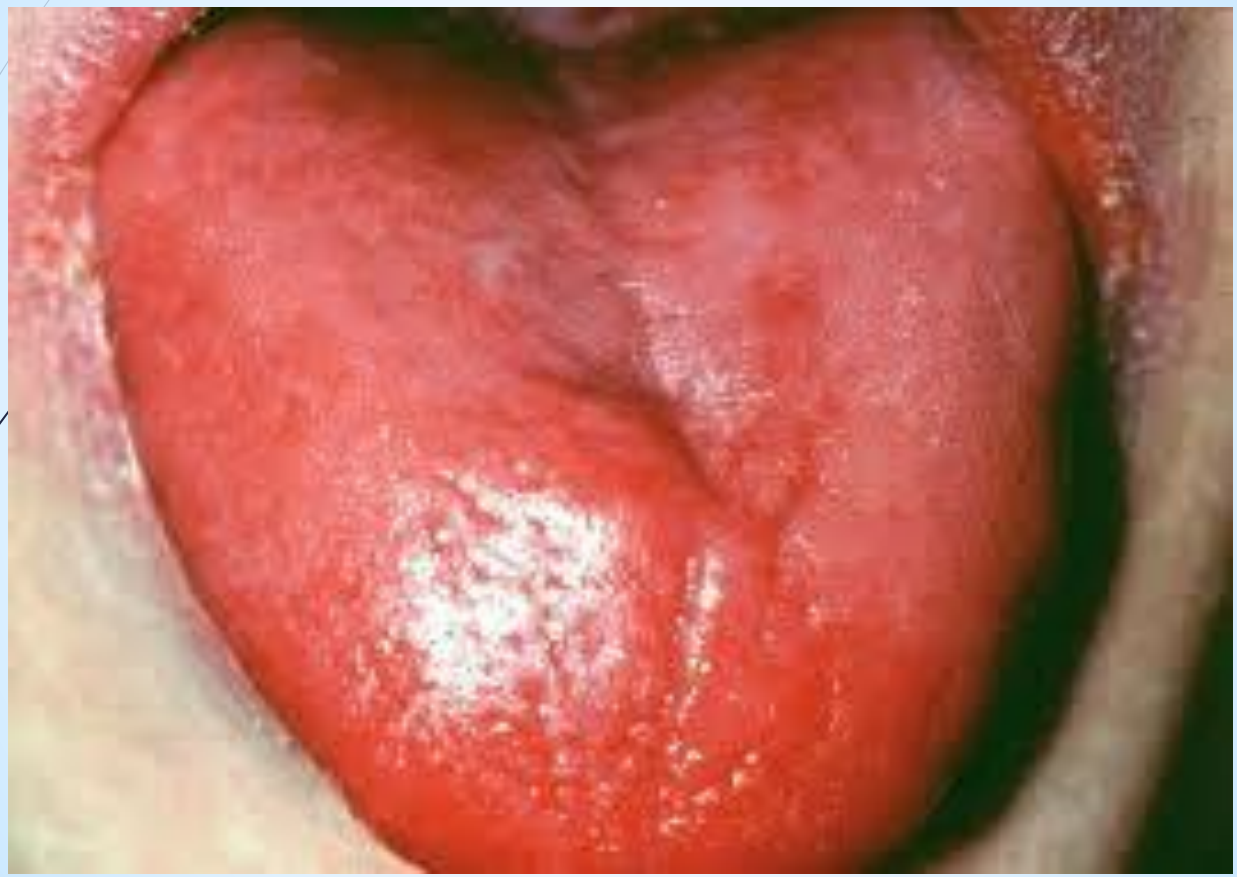
Anemias of diminished erythropoiesis

- it is generally diagnosed in the fifth to eighth decade of life
- immunologically mediated, possibly autoimmune destruction of gastric mucosa
  - *chronic atrophic gastritis*
- major specific changes occur in:
  - **bone marrow**
  - **alimentary tract**
  - **central nervous system**

Vitamin B_{12} Deficiency
Decreased intake
Inadequate diet, vegetarianism
Impaired absorption
Intrinsic factor deficiency
Pernicious anemia
Gastrectomy
Malabsorption states
Diffuse intestinal disease, e.g., lymphoma, systemic sclerosis
Ileal resection, ileitis
Competitive parasitic uptake
Fish tapeworm infestation
Bacterial overgrowth in blind loops and diverticula of bowel
Increased requirement
Pregnancy, hyperthyroidism, disseminated cancer

Anemias of diminished erythropoiesis

- in bone marrow RBC maturation is prolonged
  - it caused increase of cytoplasma and megaloblastosis
- **alimentary system**
  - **atrophic glossitis**
    - tongue is shiny, glazed and „beefy“
    - the most characteristic histologic alteration is the atrophy of the fundic glands
    - the glandular lining epithelium is replaced by mucus-secreting goblet cells that resemble those lining the large intestine
      - a form of metaplasia referred to as **intestinalization**



Anemias of diminished erythropoiesis

- patients with pernicious anemia have a higher incidence of gastric cancer
- the gastric atrophic and metaplastic changes are due to autoimmunity and not vitamin B_{12} deficiency
  - parenteral administration of vitamin B_{12} corrects the bone marrow changes, but gastric atrophy and achlorhydria persist

- **Central nervous system lessions**
  - found in approximately three fourths of all cases
  - **the principal alterations involve the spinal cord, where there is degeneration of myelin in the dorsal and lateral tracts**

Anemias of diminished erythropoiesis

- changes give rise to:
  - **spastic paraparesis**
  - **sensory ataxia**
  - **severe paresthesias in the lower limbs**
- less frequently degenerative changes occur in the ganglia of the posterior roots and in peripheral nerves
- CNS changes are **irreversible**

- **Diagnostic features**
  - a moderate to severe **megaloblastic anemia**
  - **leukopenia with hypersegmented granulocytes**
  - **mild to moderate thrombocytopenia**
  - ***mild jaundice*** *due to ineffective erythropoiesis and peripheral hemolysis of red cells*

Anemias of diminished erythropoiesis

- **neurologic changes** related to involvement of the posterolateral spinal tracts
- achlorhydria even after histamine stimulation
- inability to absorb an oral dose of cobalamin
- **low serum levels of vitamin B_{12}**
- elevated levels of homocysteine and methyl malonic acid in the serum
- a striking reticulocytic response
- *serum antibodies against intrinsic factor are highly specific for pernicious anemia*

Anemias of diminished erythropoiesis

- **Anemia of folate deficiency**
  - megaloblastic anemia having the same characteristics as that caused by vitamin B_{12} deficiency
    - however, the neurologic changes seen in vitamin B_{12} deficiency do not occur
  - FH_4 also serves as an acceptor of one-carbon fragments
  - the most important metabolic processes dependent on such one-carbon transfers are
    - purine synthesis
    - conversion of homocysteine to methionine (requires vitamin B12 too)
    - deoxythmidylate monophosphate synthesis

Anemias of diminished erythropoiesis

- daily requirment is 50 to 200 mikrog daily
  - normal diets contain enough amounts
- the richest source is green vegetable
- there are three major causes of folic acid deficiency
  - **decreased intake**
  - **increased requirements**
  - **impaired use**

Plant sources[115]	Amount as Folate (µg / 100 g)
Peanuts	246
Sunflower seed kernels	238
Lentils	181
Chickpeas	172
Asparagus	149
Spinach	146
Lettuce	136
Peanuts (oil-roasted)	125
Soybeans	111
Broccoli	108
Walnuts	98

Plant sources[115]	Amount as Folate (µg / 100 g)
Peanut butter	92
Hazelnuts	88
Avocados	81
Beets	80
Kale	65
Bread (not fortified)	65
Cabbage	46
Red bell peppers	46
Cauliflower	44
Tofu	29
Potatoes	28

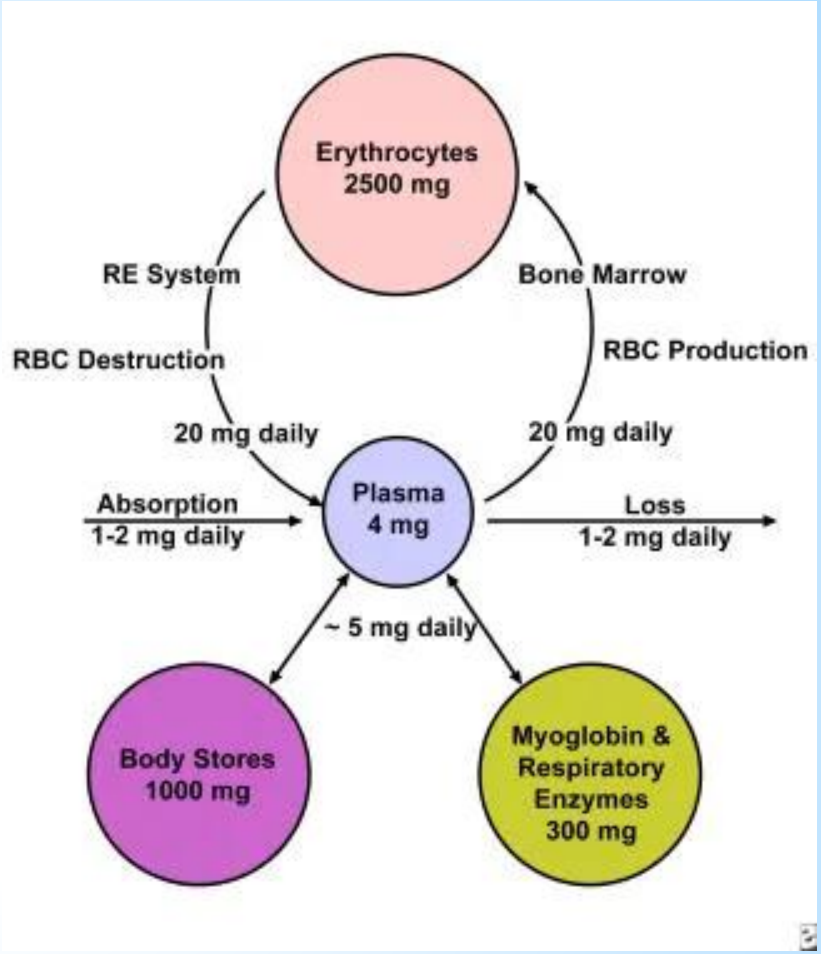
Animal sources[115]	Amount as Folate (µg / 100 g)
Chicken liver	578
Calf liver	331
Cheese	20–60
Chicken eggs	44
Salmon	35
Chicken	12
Beef	12
Pork	8
Yogurt	8–11
Milk, whole	5
Butter, salted	3

Anemias of diminished erythropoiesis

Folic Acid Deficiency
Decreased intake
Inadequate diet—alcoholism, infancy
Impaired absorption
Malabsorption states
Intrinsic intestinal disease
Anticonvulsants, oral contraceptives
Increased loss
Hemodialysis
Increased requirement
Pregnancy, infancy, disseminated cancer, markedly increased hematopoiesis
Impaired use
Folic acid antagonists

Anemias of diminished erythropoiesis

- **Iron deficiency anemia**
  - probably the most common nutritional disorder in the world
  - the prevalence of iron deficiency anemia is higher in developing countries
  - Western diet contains approximately 10 to 20 mg of iron
    - most in the form of heme contained in animal products
  - about 20% of heme iron (in contrast to 1% to 2% of nonheme iron) is absorbable



https://emedicine.medscape.com/article/202333-overview

Anemias of diminished erythropoiesis

- excretion is limited to the 1 to 2 mg per day lost by shedding of mucosal and skin epithelial cells
- there is no regulated pathway for iron excretion
- approximately 80% of the functional iron is found in hemoglobin
- myoglobin and iron-containing enzymes such as catalase and the cytochromes contain the rest
- the storage pool represented by hemosiderin and ferritin contains approximately 15% to 20% of total body iron

Anemias of diminished erythropoiesis

- free iron is highly toxic
- pool of storage iron is tightly bound to either ferritin or hemosiderin
- iron is transported in plasma by an iron-binding glycoprotein called transferrin
  - is synthesized in the liver
  - transferrin is about 33% saturated with iron
- plasma ferritin levels correlate well with body iron stores
- in iron deficiency serum ferritin is always below 12 mikrog/L

Anemias of diminished erythropoiesis

- in iron overload high values approaching 5000 mikrog/L
- most iron is absorbed in the duodenum
- hepcidin inhibits iron uptake in the duodenum and iron release from macrophages
- to maintain a normal iron balance, approximately 1 mg of iron must be absorbed from the diet every day
- only 10% to 15% of ingested iron is absorbed

Anemias of diminished erythropoiesis

- ascorbic acid, citric acid, amino acids, and sugars in the diet enhance absorption of inorganic iron
- tannins (as in tea), carbonates, oxalates, and phosphates inhibit its absorption
- an iron deficiency can result from:
  - **dietary lack**
  - **impaired absorption**
  - **increased requirement**
  - **chronic blood loss**

Anemias of diminished erythropoiesis

- dietary lack is a rare cause of iron deficiency in industrialized countries
- impaired absorption is found in sprue, other causes of intestinal steatorrhea, and chronic diarrhea, gastrectomy
- chronic blood loss is the most common cause of iron deficiency in the Western world
- iron deficiency induces a **hypochromic microcytic anemia**

Anemias of diminished erythropoiesis

- **major findings :**
  - microcytic hypochromic anemia
  - atrophic glossitis
  - esophageal webs
- progressive depletion of these **reserves first lowers serum iron and transferrin saturation** levels **without producing anemia**
- **anemia only appears when iron stores are** completely **depleted**, accompanied by low serum iron, serum ferritin, and transferrin saturation

Anemias of diminished erythropoiesis

- deficit is a problem of losses from organism or decreased intake (easier for diagnostics) and defects of utilisation
- incresed demand during growth and pregnancy
- other cause are parasitic diseases (GIT)
- **decreased absorption is reuslt of:**
  - partial or total gastrectomy
  - achlorhydria
  - chronic diarrhoea
  - malabsorption

Anemias of diminished erythropoiesis

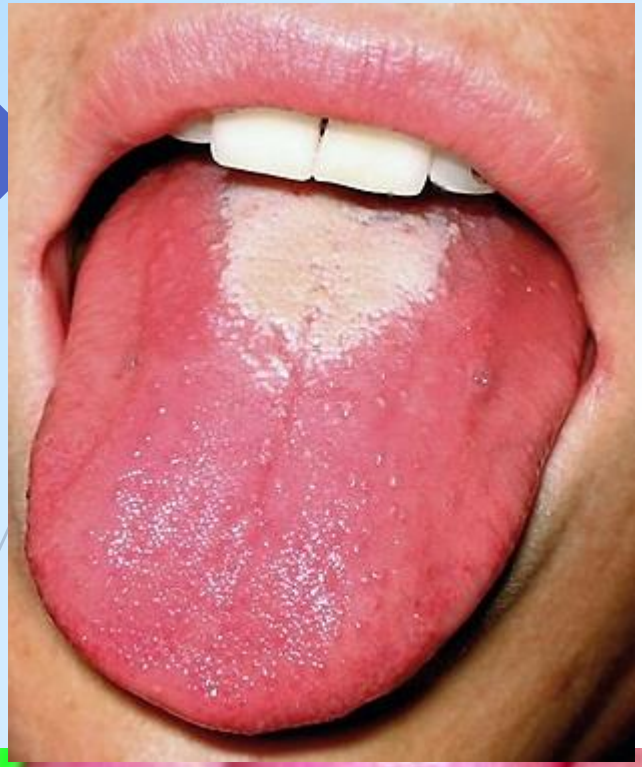
- **increased loss:**
  - physiologically during period and pregnancy
  - GIT diseases – ulcers, gastritis, hemoroids, colorectal carcinoma
  - GIT cancer
  - haemorhagic diateses
  - bloodclotting disorders
  - lung hemorhagies, bronchiectasie
  - losses in genitourinal tract

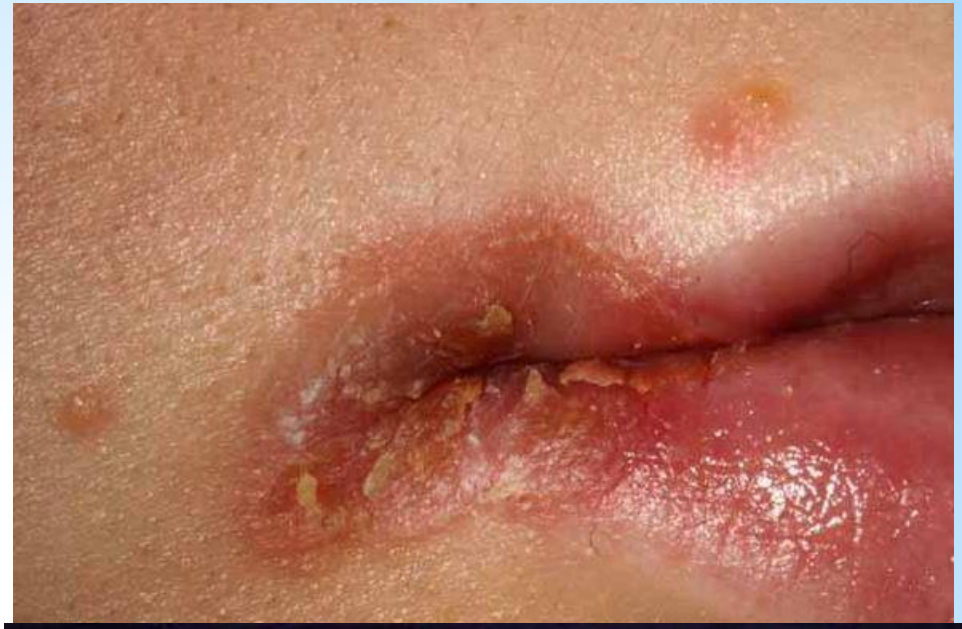
Anemias of diminished erythropoiesis

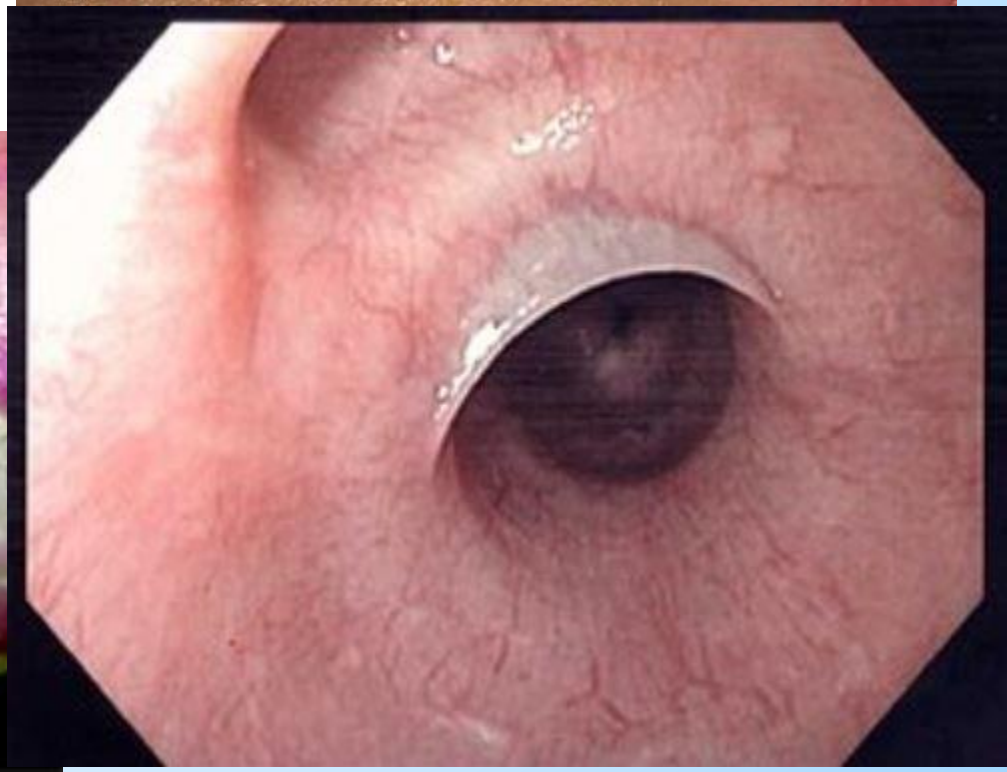
- **results of deficit:**
  - **defect of cell growth and proliferation** → defect of RBC production → **longer time for RBC maturation** → more mitotic divisions → **microcytic anemia** (and hypochromic because of iron deficiency)
  - iron is important for cell division (reductase of ribonucleotides) → changes on mucosa and skin adnexes → changes on nails, ragades of the mouth corner

Anemias of diminished erythropoiesis

- deficiency in food is rare cause in developed countries
- worse absorption is present in chronic diarrhoea, gastrectomy, enhanced passage in GIT
- chronic loss is the most frequent cause in West world
- results to **hypochromic microcytic anemia**
- **4 stages:**
  - negative balance
  - iron depletion (pre-latent sideropenia)
  - defects of erytropoiesis (latent sideropenia)
  - fully developed microcytic hypochromic anemia (manifest sideropenia)

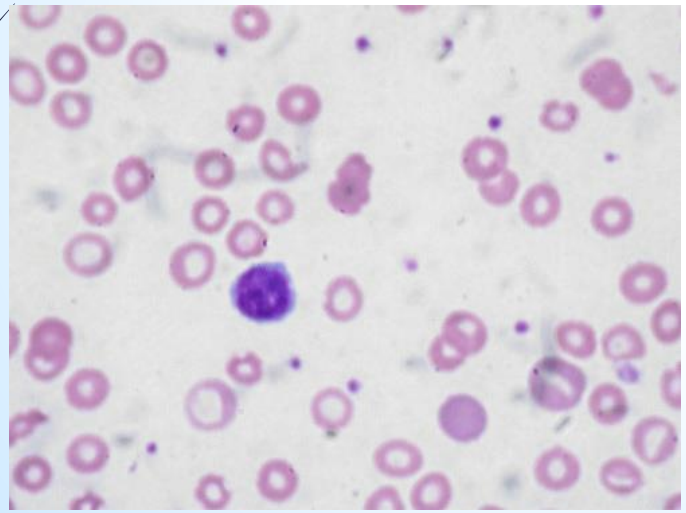




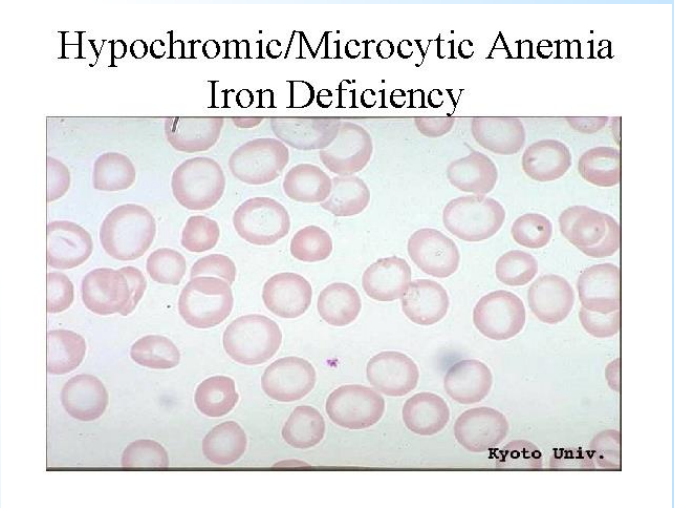


Iron deficiency

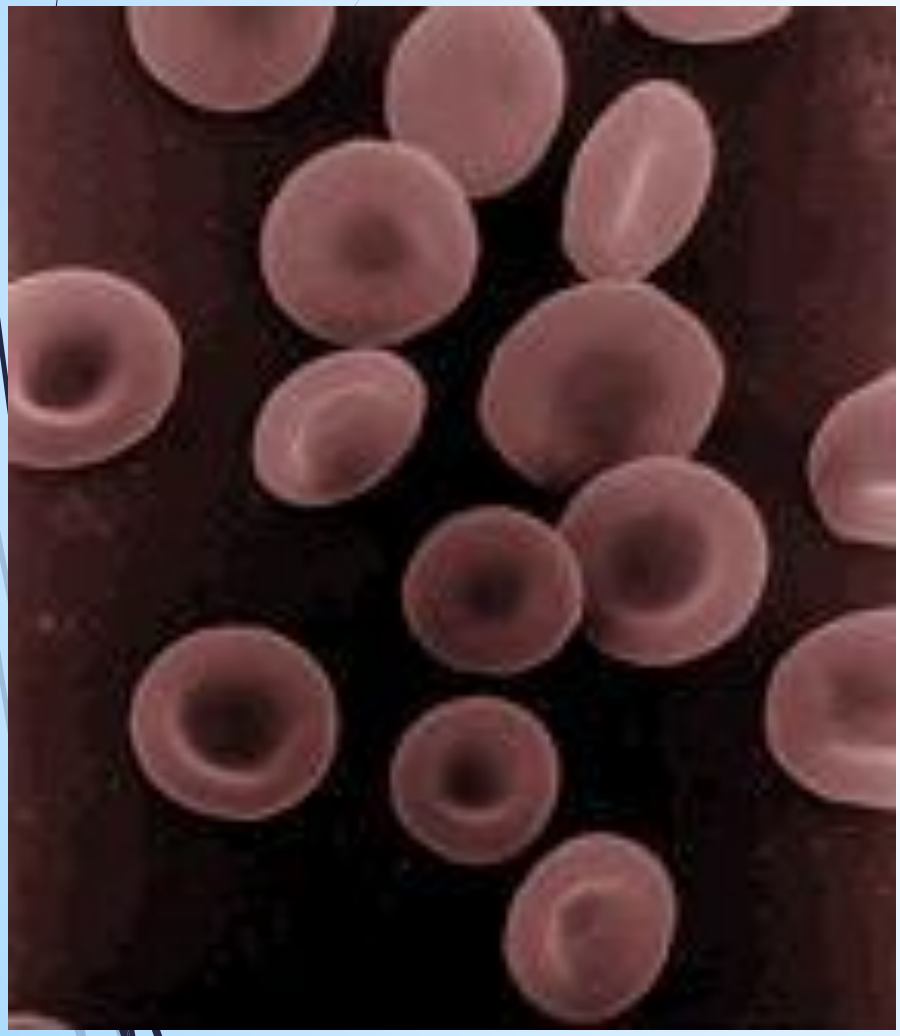
hypochromic microcytic anemia



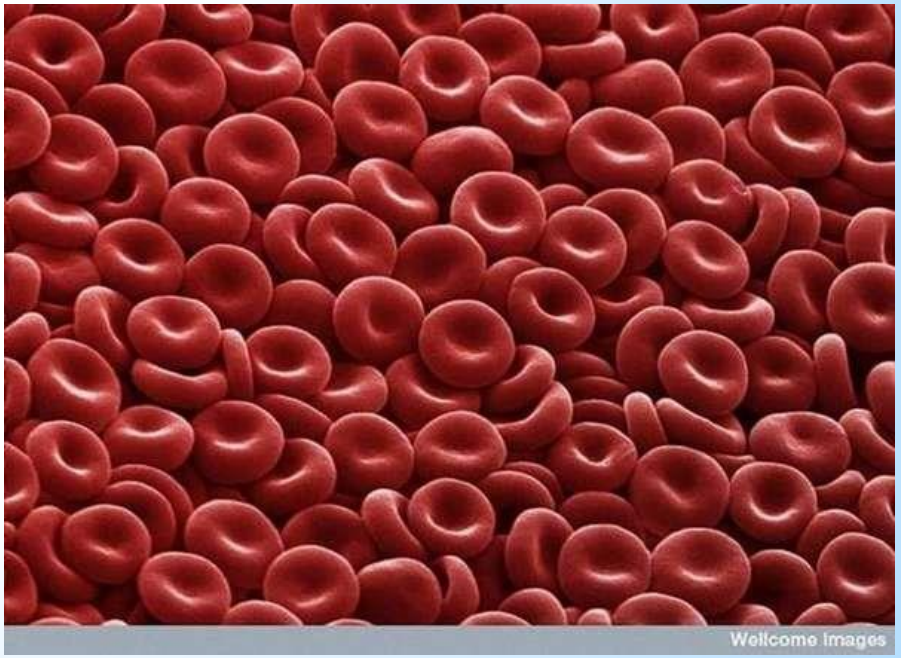
hypochromic microcytic anemia



Iron deficiency

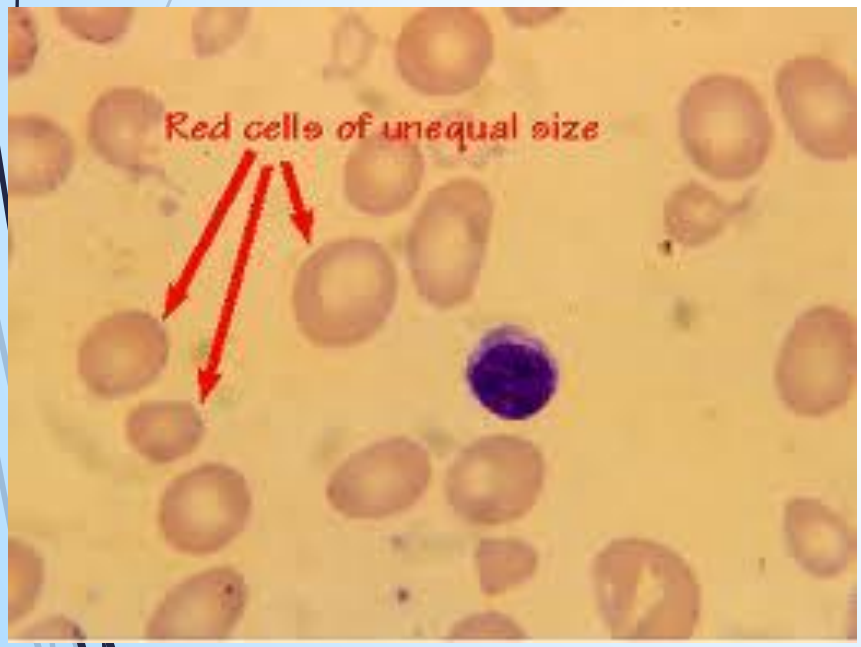


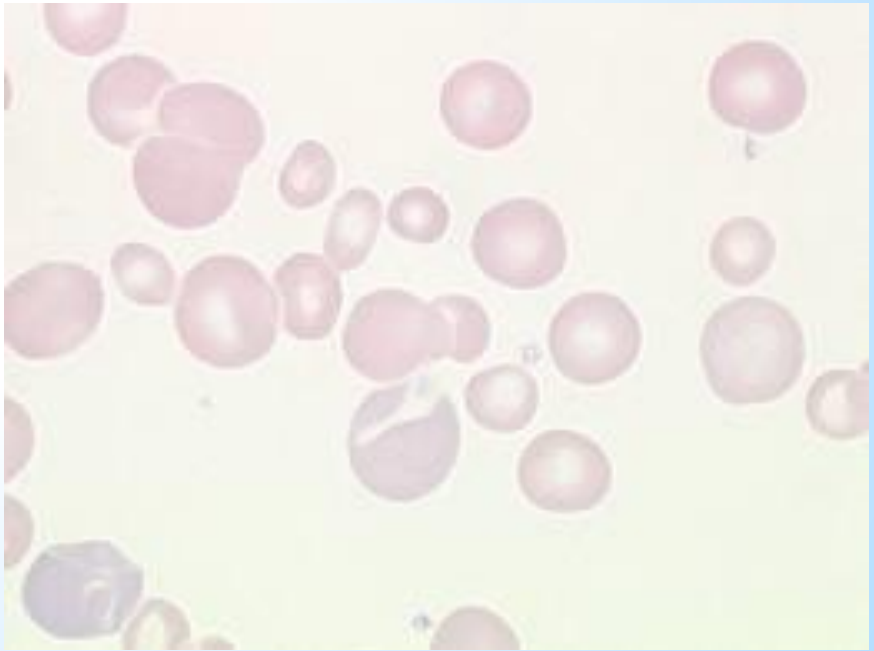
Normal RBC



Different forms of RBC (in size)

Anizocytes





Anemias of diminished erythropoiesis

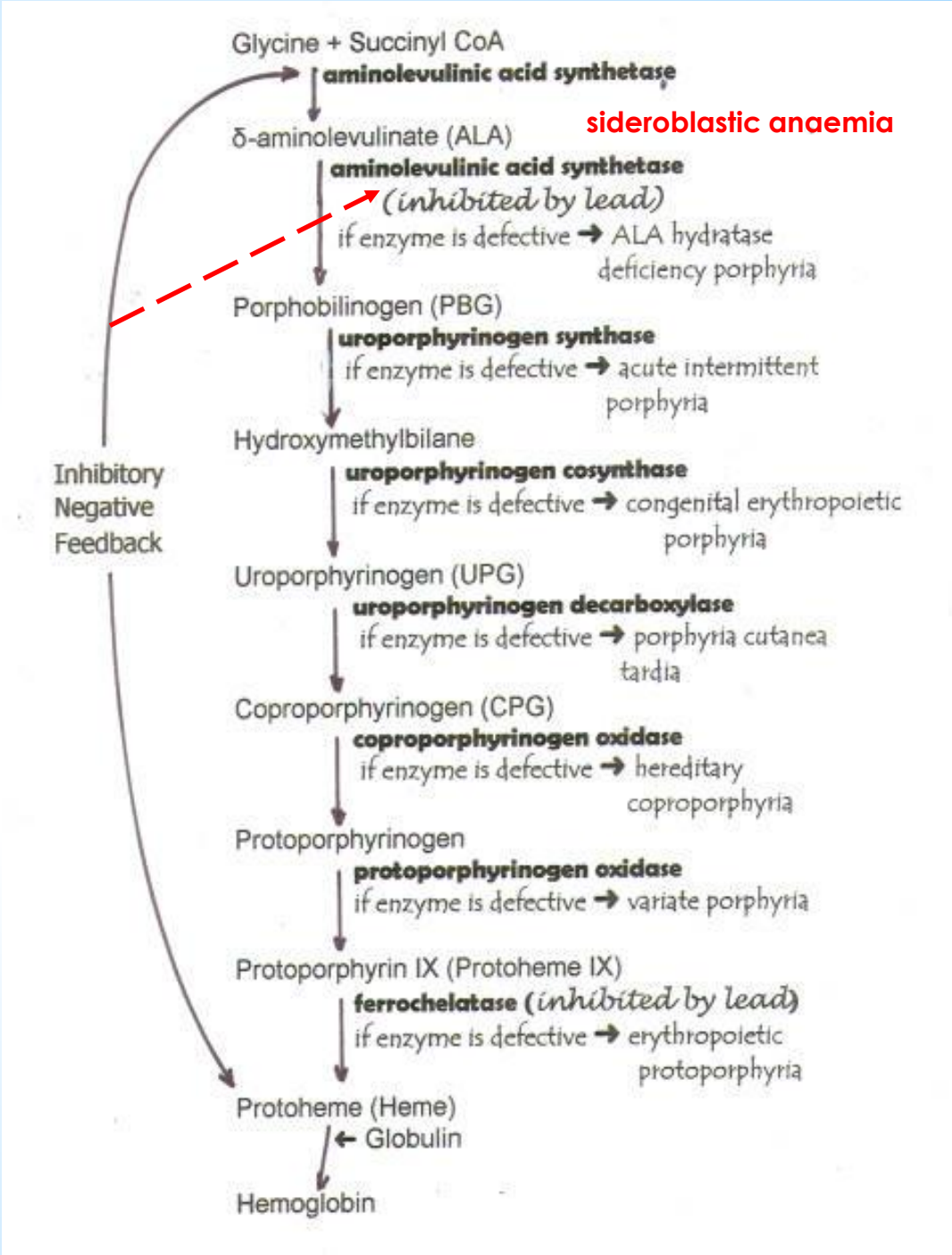
- the clinical manifestations of the anemia are nonspecific
- **diagnosis**
  - ↓ hemoglobin and hematocrit
  - hypochromia, microcytosis and poikilocytosis
  - serum iron and ferritin are low
  - total plasma iron-binding capacity (reflecting transferrin concentration) is high
  - ↓ hepcidin

Anemias of diminished erythropoiesis

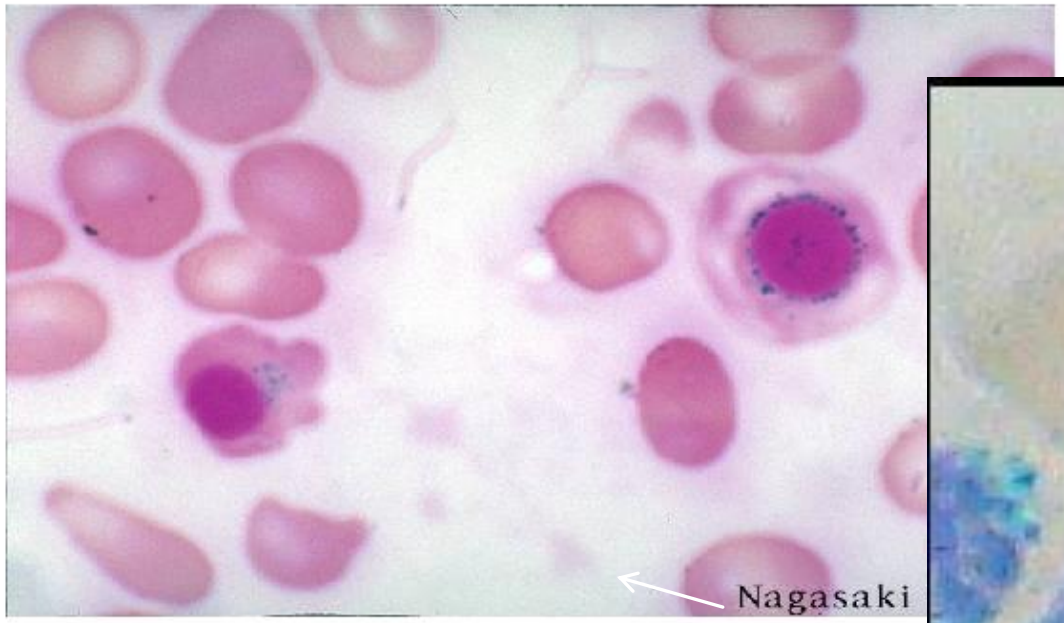
- **sideroblastic anemia**
  - **hypochromic anemia with defective haem synthesis**
  - in periphery **finding of sideroblasts** = normoblast contained nonhemoglobine type of Fe
  - mitochondrias are placed around nucleus = **typical ring**
  - **sideroblasts are smaller like matured RBC**
  - **hereditary form**
    - defective activity of d-aminolevulinic acid
      - pyridoxin dependent enzyme
  - **aquired sideroblastic anemia**
    - diferent substances are responsible
      - azoniazid, lead, high alcohol intake (pyridoxine deficit)

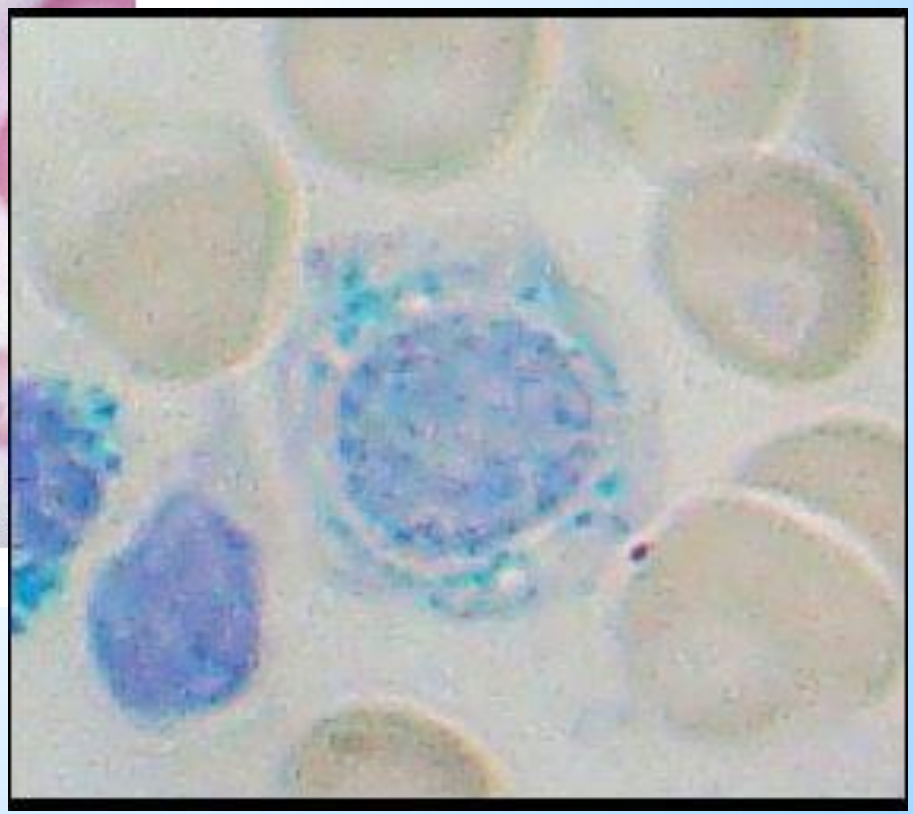
Sideroblastic anaemia

Sideroblast



Sideroblastic anaemia



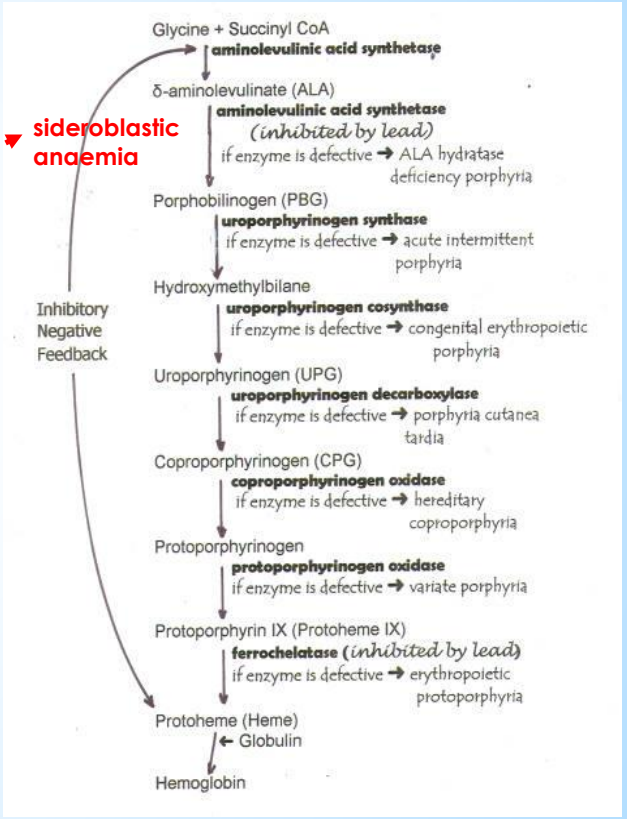


Sideroblastic anaemia

- hypochromic anaemia
- disorder of heme synthesis

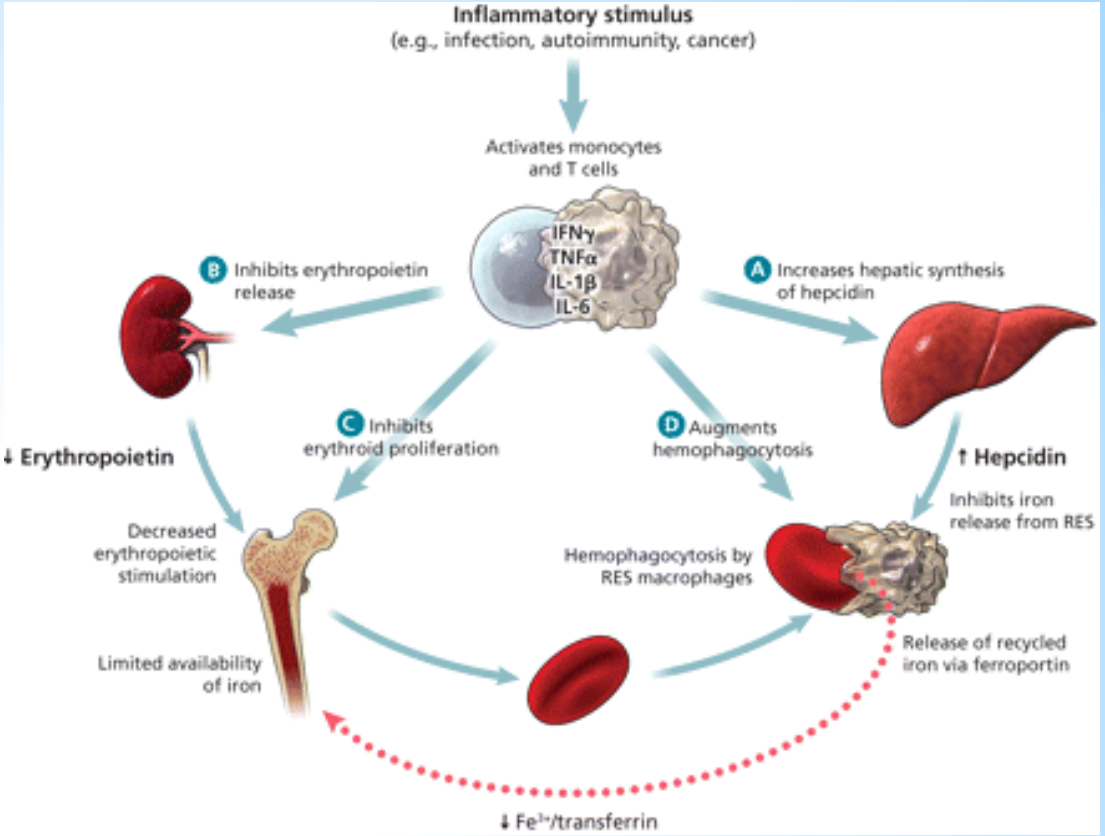
- hereditary
  - δ-amino-levulinic acid synthetase deficiency
- acquired
  - lead intoxication
  - ethanol
  - inflammation
  - chemotherapy


Sideroblast



Anemias of diminished erythropoiesis

- **Anemia of chronic disease**
  - perhaps the most common cause of anemia among hospitalized patients in the United States
  - it is associated with reduced erythroid proliferation and impaired iron utilization
  - can therefore mimic iron deficiency
  - **three categories:**
    - chronic microbial infections
    - chronic immune disorders
    - neoplasms



https://www.cmaj.ca/content/179/4/333

Anemias of diminished erythropoiesis

- **the common features :**
  - low serum iron
  - reduced total iron-binding capacity in association with abundant stored iron in the mononuclear phagocytic cells
  - reduction in renal erythropoietin generation is caused by the action of interleukin-1, tumor necrosis factor (TNF), and interferon-γ
  - cytokines also stimulate hepcidin synthesis in the liver
- anemia is usually mild
- RBC can be normocytic and normochromic or hypochromic and microcytic as in anemia of iron deficiency

Anemias of diminished erythropoiesis

- **Aplastic anemia**
  - syndrome of marrow failure associated with pancytopenia (anemia, neutropenia, and thrombocytopenia)
  - the marrow failure stems from suppression or disappearance of multipotent myeloid stem cells
  - *Fanconi anemia* is a rare autosomal recessive disorder caused by defects in a component of a multiprotein complex required for DNA repair

Major causes of aplastic

Acquired
Idiopathic
Primary stem cell defect
Immune mediated
Chemical agents
Dose related
Alkylating agents
Antimetabolites
Benzene
Chloramphenicol
Inorganic arsenicals
Idiosyncratic
Chloramphenicol
Phenylbutazone
Organic arsenicals
Methylphenylethylhydantoin
Streptomycin
Chlorpromazine
Insecticides (e.g., DDT, parathion)
Physical agents (e.g., whole-body irradiation)
Viral infections
Hepatitis (unknown virus)
Cytomegalovirus infections
Epstein-Barr virus infections
Herpes varicella-zoster
Miscellaneous
Infrequently, many other drugs and chemicals
Inherited
Fanconi anemia

Anemias of diminished erythropoiesis

- most cases of aplastic anemia of "known" etiology follow exposure to chemicals and drugs
- with some agents, marrow damage is predictable, dose related and, in most instances, reversible
- after idiosyncratic reactions, the aplasia can be severe, irreversible, and fatal
- despite all these possible causes 65% of the cases are idiopathic

Anemias of diminished erythropoiesis

- **pathogenesis**
  - not fully understood
  - two major etiologies have been invoked:
    - an immunologically mediated suppression
    - an intrinsic abnormality of stem cells
  - it is postulated that stem cells are first antigenically altered
  - this evokes a cellular immune response, during which activated T cells produce cytokines

Anemias of diminished erythropoiesis

- aplastic anemia results from a fundamental stem cell abnormality is supported by the presence of karyotypic aberrations
  - typically myelodysplasia or acute myelogenous leukemia
- **morphology**
  - hypocellular bone marrow is largely devoid of hematopoietic cells
    - often only fat cells, fibrous stroma, and scattered or clustered foci of lymphocytes and plasma cells remain

Anemias of diminished erythropoiesis

- **Clinical findings**
  - can occur at any age and in either sex
  - initial manifestations vary
  - progressive weakness, pallor, and dyspnea
  - petechiae and ecchymoses
  - frequent and persistent minor infections
  - sudden onset of chills, fever, and prostration
  - RBC are normocytic and normochromic, macrocytosis is occasionally present
  - *reticulocytopenia*

Anemias of diminished erythropoiesis

- diagnosis rests on examination of bone marrow biopsy and peripheral blood
- **Pure red cell aplasia**
  - rare form of marrow failure
  - characterized by a marked hypoplasia of marrow erythroid elements in the setting of normal granulopoiesis and thrombopoiesis
  - it can be primary or secondary
    - associated with neoplasms

Anemias of diminished erythropoiesis

- **Others form of marrow failure**
  - **myelophthisic anemia**
    - immature erythroid and myeloid progenitors appear in the peripheral blood (leukoerythroblastosis)
    - infiltrative diseases of the marrow typically cause reactive fibrosis and distortion of the marrow architecture
      - this disturbs the normal mechanisms
    - the most common cause is metastatic cancer
  - **diffuse liver disease**
    - whether toxic, infectious, or cirrhotic, is associated with an anemia attributed to hypofunction of the marrow
    - concomitant folate deficiency and iron deficiency due to gastrointestinal blood loss (varices, hemorrhoids) can also contribute to the anemia
  - ***chronic renal failure***

Symptoms and lab findings

Acute blood loss

- tachykardia
- decreased blood pressure
- vasoconstriction
- hypovolemic shock
- CVS failure
- death

- normocytic
- normochromic
- ↑ count of retikulocytes
- leukocytosis
- trombocytosis

Chronic blood loss

- mild symptoms in longterm small losses
- tiredness
- dyspnoe
- paleness

- before Fe stores depletion
  - normocytic
  - normochromic
  - can be mild ↑of reticulocytes
- after Fe stores depletion
  - mikrocytic
  - hypochromic
  - anizocytosis
  - changes parameter for Fe deficiency

Iron deficiency

- pale skin and mucosa
- fatique and lack of energy
- dyspnea, chest pain during activity
- tachycardia
- tinnitus
- pica (ice, clay...)
- sore or smooth tongue
- koilonychia
- hair loss

- microcytosis
- hypochromia
- anizocytes
- ↓ hemoglobin and hematocrit
- ↓ MCV and MHC
- ↓ ferritin
- ↓ serum iron
- ↓ iron saturation
- ↑ transferrin and TIBC

Iron deficiency

- blood loss
- inadequate intake
- malabsorption
- inflammation
- parasites
- interfering substances

- States
  - pre-latent
  - latent
  - manifest

Vit. B12 deficiency

- inadequate intake
- impaired absorption
  - intrinsic factor deficiency
    - atrophic gastritis
    - pernicious anemia
- malabsorption
- achlorhydria
- celiac disease
- parasatises
- increased need
  - pregnancy
  - breastfeeding

- megaloblasts
- hypersegmented neutrophils
- normochromic cells
- ↓ serum vit. B12

- fatique
- glossitis
- weakness
- jaundice
- angular cheilitis
- neurological signs

Sideroblastic anemia

- inherited X-linked
  - ALAS2 deficiency
- myelodysplastic syndromes
- pyridoxine deficiency
- lead poisoning
- excess zinc
- some drugs

- sideroblasts
  - type 1 – up to 5 ranules
  - type 2 – 5 or more granules, not perinuclear position
  - type 3 (ring sideroblast) – more than 5 granules surrounded nucleus
    - only in sideroblast anemia
- basophilic stippling
- Pappenheimer bodies
- target cells
- anizocytoses (from micro – to macrocytes)
- RDW increased
- ↑ serum iron and ferritin
- ↓ TIBC

Aplastic anemia

- idiopathic
- drugs (dose related/idiosyncratic raction)
- ionizing radiation
- autoimmune reaction
- viral hepatitis, EBV, cytomegalovirus, HIV

- pancytopenia
- ↓ RBC count
- ↓ paltelets
- ↓ WBC count
- bruising
- bleeding
- repeated infections

Hereditary spherocytosis

- autosomal dominant
- can be recessive
- spectrin, ankyrin
  - band 3 protein, protein 4.2
- extravascular hemolysis

- microcytic
- hyperchromic
- spherocytes
- Howell-Joly bodies
- splenomegalia
- jaundice
- gallstones

- splenectomy

G6PD deficiency

- X-linked recessive
- some drugs
- some food (fava beans)
- infection (inflammation)

- episodic hemolysis

- jaundice
- Heinz bodies
- ↑ LDH
- ↓ haptoglobin
- bite cells