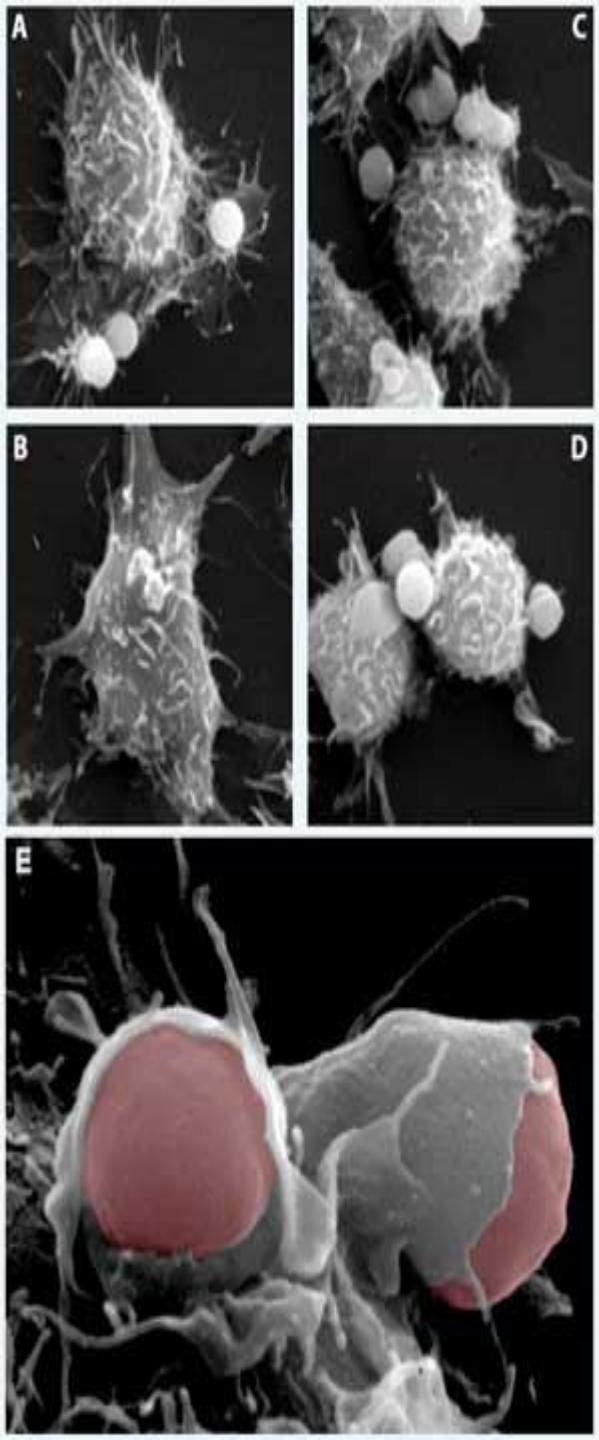
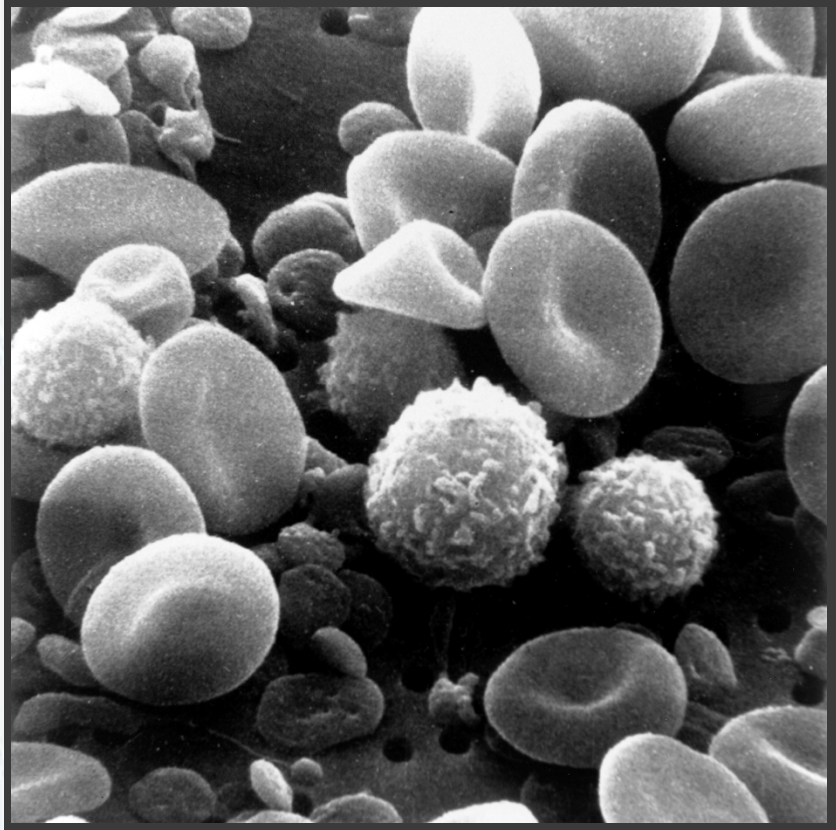
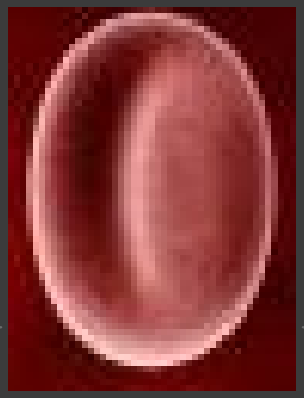




DISEASE OF THE BLOOD



Danil Hammoudi.MD

Direct Coombs test

The direct Coombs test (also known as the **direct antiglobulin test** or DAT) is used to detect **if antibodies or complement system factors have bound to RBC surface antigens *in vivo*.**

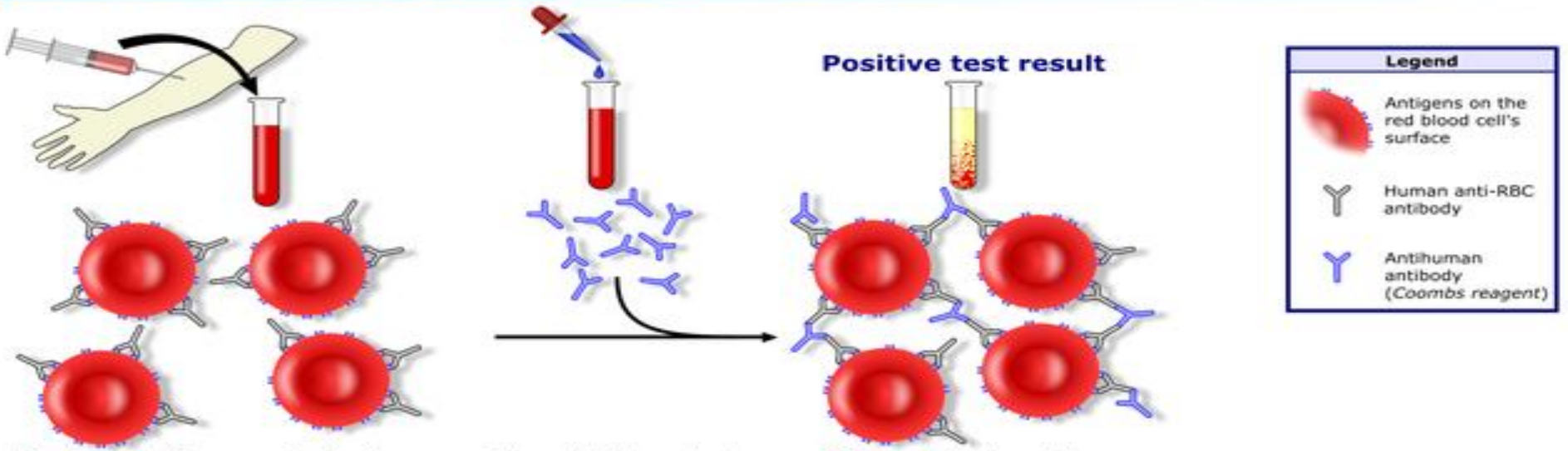
Indirect Coombs test

The indirect Coombs test (also known as the **indirect antiglobulin test** or IAT)
is a used to detect in-vitro antibody-antigen reactions.

Coombs reagent: Coombs reagent is antihuman globulin.

Coombs reagent (also known as **Coombs antiglobulin** or **antihuman globulin**)

Direct Coombs test / Direct antiglobulin test

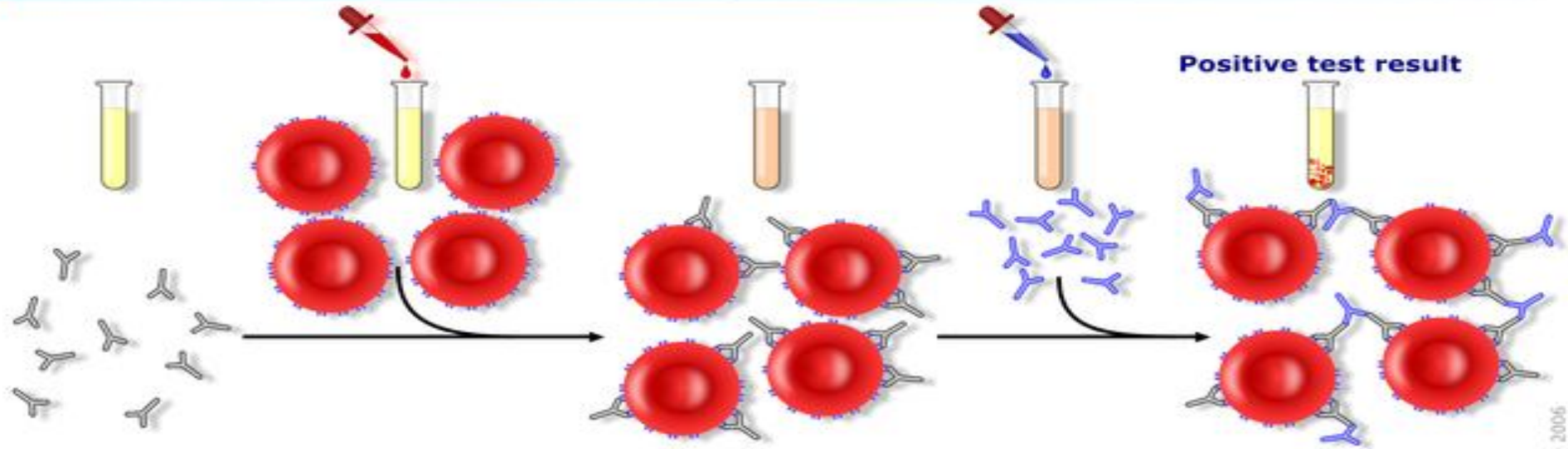


Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.

The patient's washed RBCs are incubated with antihuman antibodies (*Coombs reagent*).

RBCs agglutinate: antihuman antibodies form links between RBCs by binding to the human antibodies on the RBCs.

Indirect Coombs test / Indirect antiglobulin test



Recipient's serum is obtained, containing antibodies (Ig's).

Donor's blood sample is added to the tube with serum.

Recipient's Ig's that target the donor's red blood cells form antibody-antigen complexes.

Anti-human Ig's (*Coombs antibodies*) are added to the solution.

Agglutination of red blood cells occurs, because human Ig's are attached to red blood cells.

Erythrocyte Disorders

By number

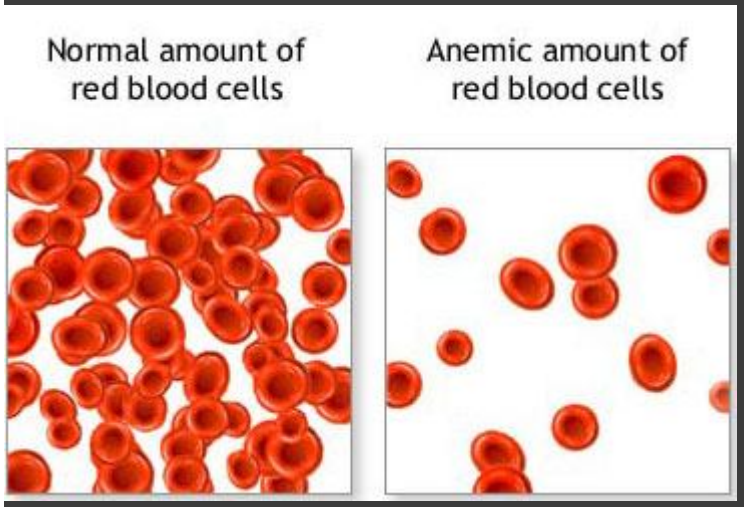
By SHAPE

By hemoglobin

By size

Anisocytosis – various sizes
Poikilocytosis – various shapes

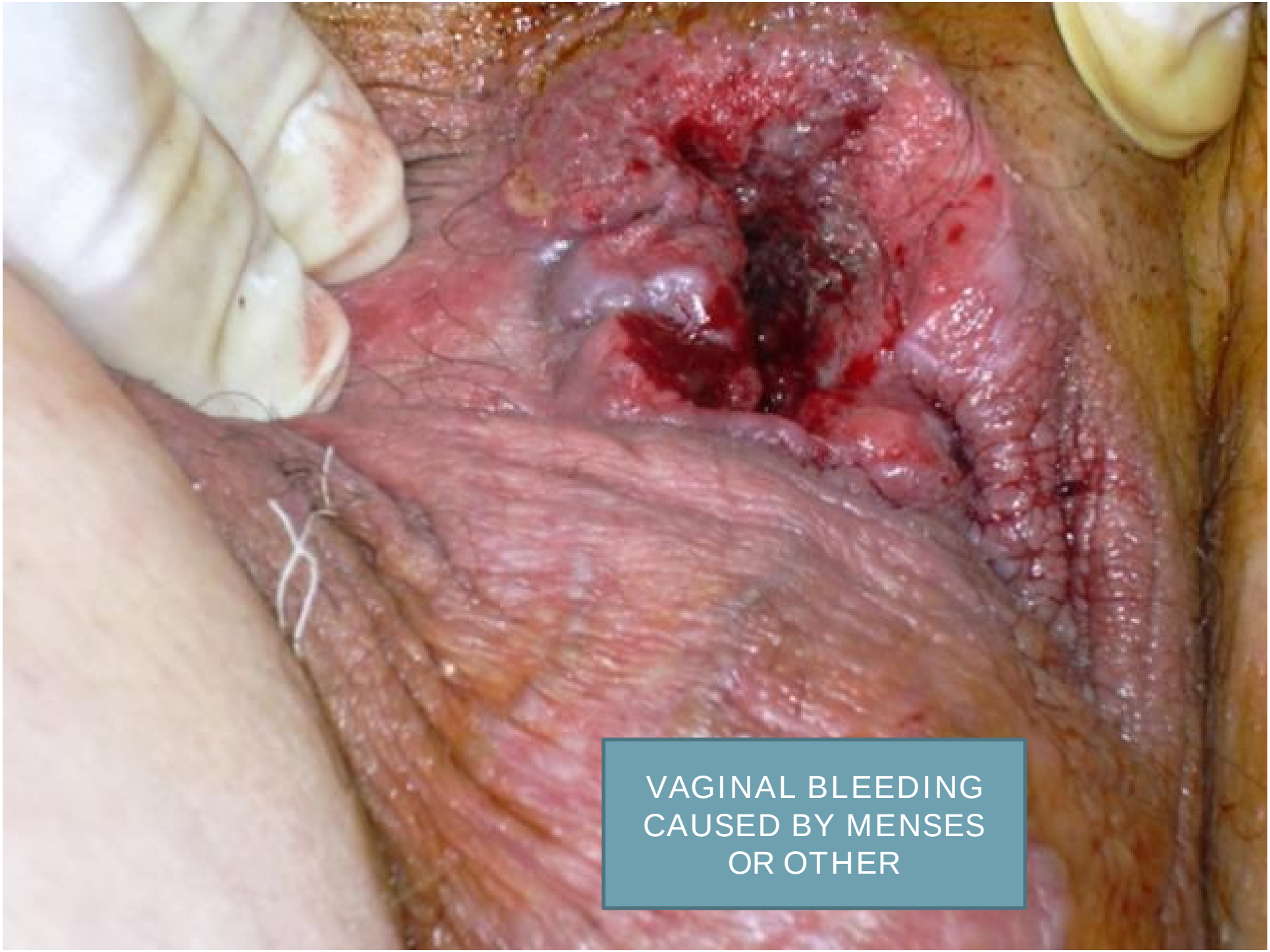
ERYTHROCYTE DISORDERS



- **Anemia** –
- blood has abnormally low oxygen-carrying capacity
  - It is a symptom rather than a disease itself
  - Blood oxygen levels cannot support normal metabolism
  - Signs/symptoms include fatigue, paleness, shortness of breath, and chills

ANEMIA

Low Retic count & Normal Bili/LDH **Hypoproliferative Anemia**	*High Retic count & High Bili/LDH* **Hemolytic Anemia**
Low Retic count & High Bili/LDH **Ineffective Erythropoiesis**	*High Retic count & normal Bili/LDH* **Blood Loss**


VAGINAL BLEEDING
CAUSED BY MENSES
OR OTHER

LAB EVALUATION OF HYPOPROLIFERATIVE ANEMIAS

	Fe	TIBC	Ferritin
Fe Deficiency	low	High(>300)	low
Anemia of Chronic Dx	low	low	Normal to high
Aplastic anemia	High	Extremely high	Normal to high

EVALUATION OF THE PATIENT

- HISTORY
  - Is the patient bleeding?
    - Actively? In past?
  - Is there evidence for increased RBC destruction?
  - Is the bone marrow suppressed?
  - Is the patient nutritionally deficient? Pica?
  - PMH including medication review, toxin exposure

EVALUATION OF THE PATIENT (2)

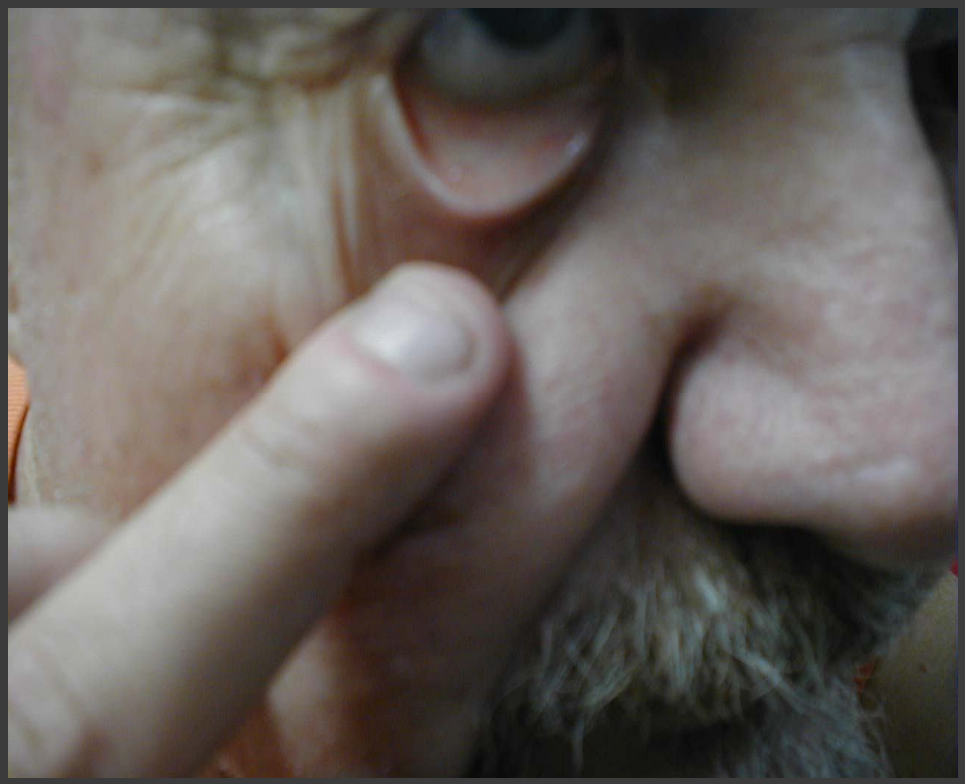
REVIW OF SYMPTOMS

- Decreased oxygen delivery to tissues
  - Exertional dyspnea
  - Dyspnea at rest
  - Fatigue
  - Signs and symptoms of hyperdynamic state
    - Bounding pulses
    - Palpitations
  - Life threatening: heart failure, angina, myocardial infarction
- Hypovolemia
  - Fatiguablitiy, postural dizziness, lethargy, hypotension, shock and death

EVALUATION OF THE PATIENT (3)

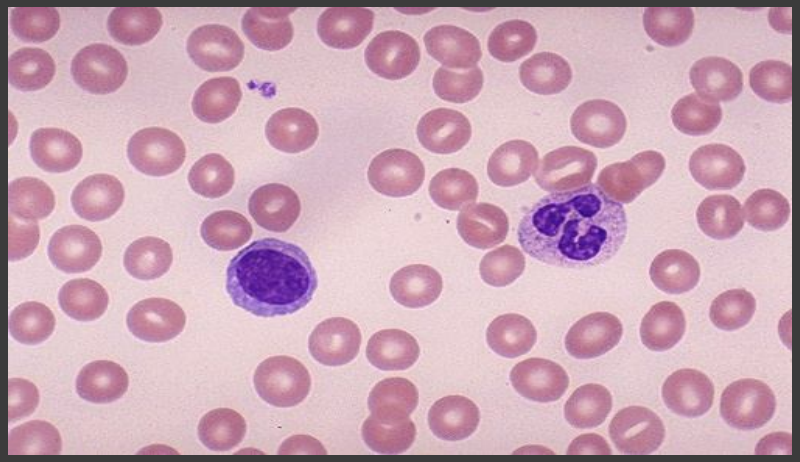
PHYSICAL EXAM

- Stable or Unstable?
  - -ABCs
  - -Vitals
- Pallor
- Jaundice
  - -hemolysis
- Lymphadenopathy
- Hepatosplenomegally
- Bony Pain
- Petechiae
- Rectal-? Occult blood



LABORATORY EVALUATION

- Initial Testing
  - CBC w/ differential (includes RBC indices)
  - Reticulocyte count
  - Peripheral blood smear



LABORATORY EVALUATION (2)

- Bleeding
  - Serial HCT or HGB
- Iron Deficiency
  - Iron Studies
- Hemolysis
  - Serum LDH, indirect bilirubin, haptoglobin, coombs, coagulation studies
- Bone Marrow Examination
- Others-directed by clinical indication
  - hemoglobin electrophoresis
  - B12/folate levels

DIFFERENTIAL DIAGNOSIS

- Classification by Pathophysiology
  - Blood Loss
  - Decreased Production
  - Increased Destruction
- Classification by Morphology
  - Normocytic
  - Microcytic
  - Macrocytic

- **Normochromic, normocytic anemia (normal MCHC, normal MCV).** These include:
  - **anemias of chronic disease**
  - **hemolytic anemias (those characterized by accelerated destruction of rbc's)**
  - **anemia of acute hemorrhage**
  - **aplastic anemias (those characterized by disappearance of rbc precursors from the marrow)**

- **Hypochromic, microcytic anemia (low MCHC, low MCV).** These include:
  - **iron deficiency anemia**
  - **thalassemias**
  - **anemia of chronic disease (rare cases)**

- **Normochromic, macrocytic anemia (normal MCHC, high MCV).** These include:
  - **vitamin B_{12} deficiency**
  - **folate deficiency**

Mean corpuscular volume [MCV]

Is a measure of the **average red blood cell volume** (i.e. **size**) that is reported as part of a standard complete blood count.

In patients with anemia, it is the MCV measurement that allows classification as either a microcytic anemia (MCV below normal range) or macrocytic anemia (MCV above normal range).

Mean corpuscular hemoglobin concentration

is a measure of the concentration of hemoglobin in a given volume of packed red blood cell.

It is calculated by dividing the hemoglobin by the hematocrit. A normal value is 32 to 36 g/dl. Hb/ht

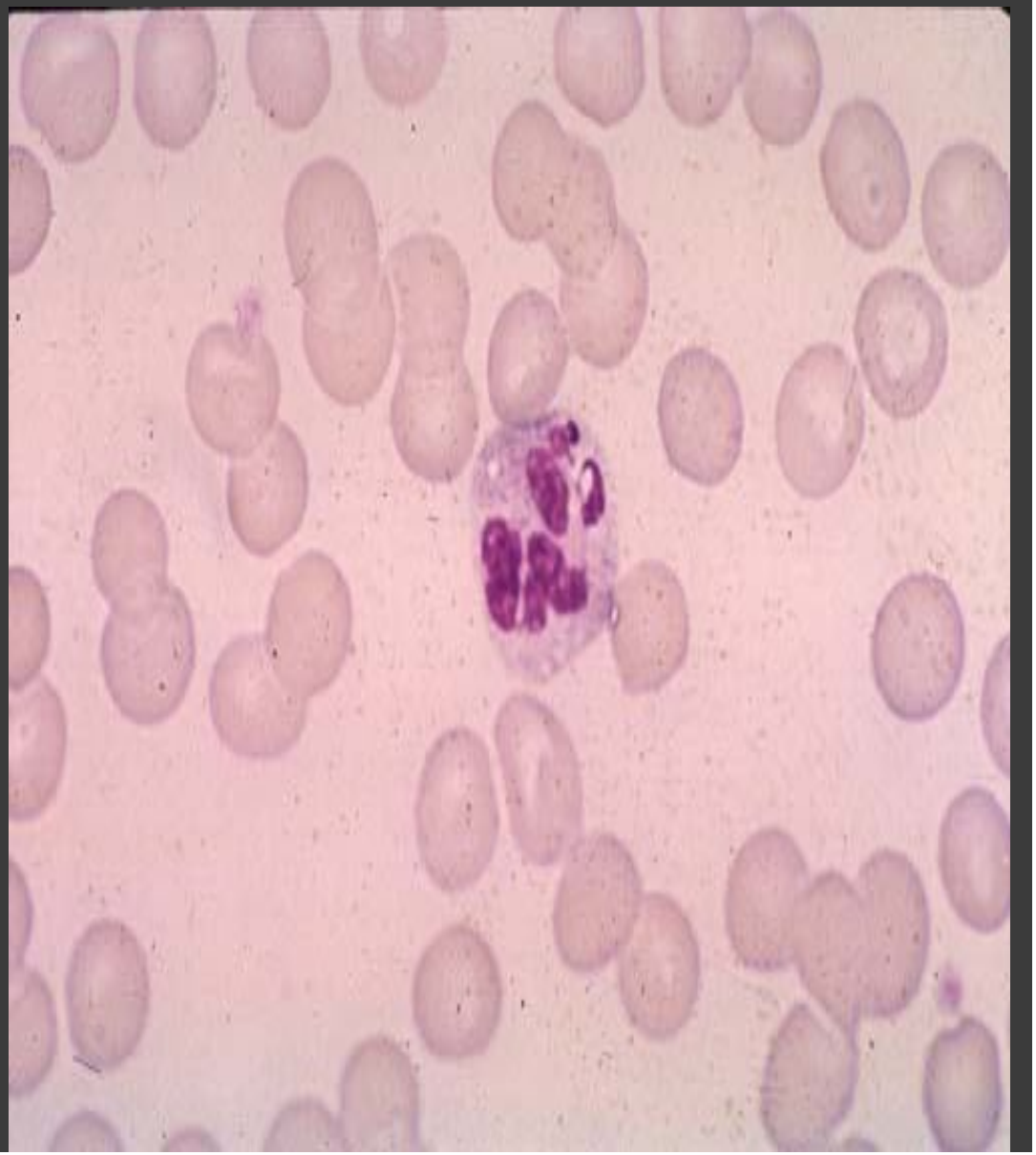
It is diminished ("hypochromic") in microcytic anemias, and normal ("normochromic") in macrocytic anemias (due to larger cell size, though the hemoglobin **amount** or MCH is high, the concentration remains normal). MCHC is elevated in hereditary spherocytosis.

Anemia

Type	Etiology	Comments
Microcytic, hypochromic (MCV < 80)	Iron deficiency—↓ serum iron, ↑ TIBC, ↓ ferritin (intracellular iron stores) (see Color Image 20).	Vitamin B_{12} and folate deficiencies are associated with hypersegmented PMNs. Unlike folate deficiency, vitamin B_{12} deficiency (e.g., pernicious anemia) is associated with neurologic problems.
	Thalassemias—target cells (see Color Image 18).	
	Lead poisoning, sideroblastic anemias.	
Macrocytic (MCV > 100)	Megaloblastic—vitamin B_{12}/folate deficiency.	
	Drugs that block DNA synthesis (e.g., sulfa drugs, phenytoin, AZT).	
	Marked reticulocytosis (bigger than mature RBCs).	↓ serum haptoglobin and ↑ serum LDH indicate RBC hemolysis. Direct Coombs' test is used to distinguish between immune- vs. non-immune-mediated RBC hemolysis.
Normocytic, normochromic	Acute hemorrhage.	
	Enzyme defects—G6PD deficiency (X-linked), PK deficiency (AR).	
	RBC membrane defects (e.g., hereditary spherocytosis).	
	Bone marrow disorders (e.g., aplastic anemia, leukemia).	
	Hemoglobinopathies (e.g., sickle cell disease).	
	Autoimmune hemolytic anemia.	
	Anemia of chronic disease (ACD)—↓ TIBC, ↑ ferritin, ↑ storage iron in marrow macrophages.	

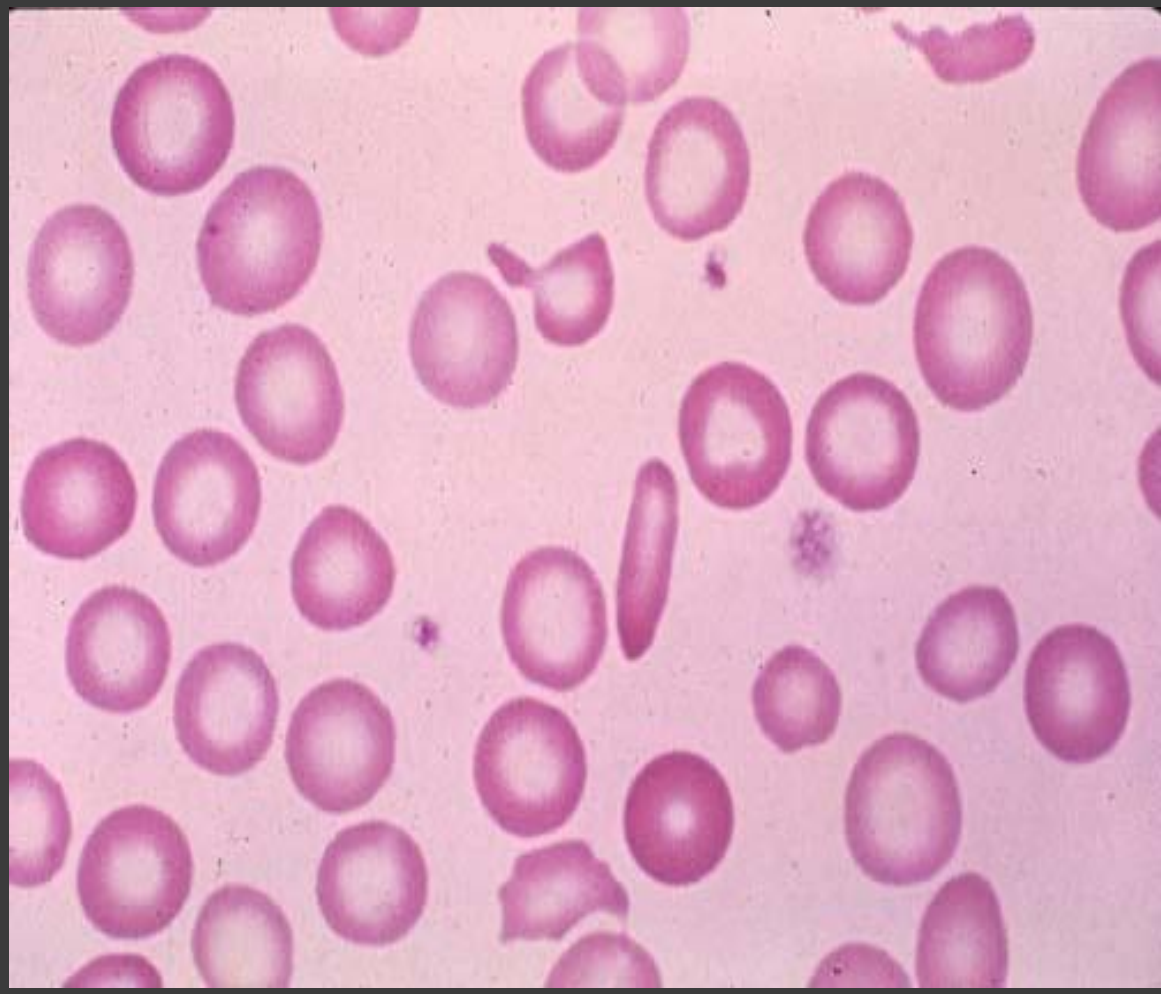
MACROCYTIC ANEMIA

- MCV > 100
- Megaloblastic:Abnormalities in nucleic acid metabolism
  - B12, Folate
- Non-megaloblastic:Abnormal RBC maturation
  - Myelodysplasia
- ETOH, liver dz, hypothryroidism, chemotherapy/drugs



MICROCYTIC ANEMIA

- MCV <80
- Reduced iron availability
- Reduced heme synthesis
- Reduced globin production



Stages of iron deficiency

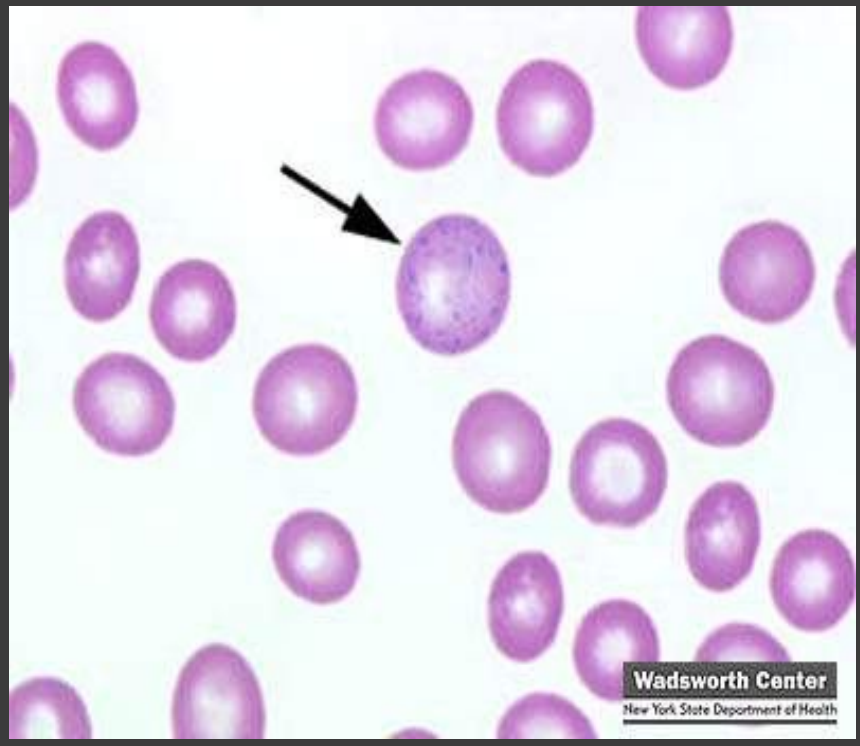
	Normal	Iron deficiency without anemia	Iron deficiency with mild anemia	Iron deficiency with severe anemia
Serum iron	Normal	Normal	Low	Very low
TIBC	Normal	Normal	Normal / High	High
Iron saturation	Normal	Normal	Low	Low
Marrow iron	Present	Absent	Absent	Absent
Hemoglobin	Normal (12-15g/dL)	Normal	Mildly reduced (9-12 g/dL)	Severely reduced (<9 g/dL)
Ferritin	Normal	Low	Very low	Very low
Peripheral changes	None	None	None	Present

MICROCYTIC ANEMIA
REDUCED IRON AVAILABILTY

- Iron Deficiency
  - Deficient Diet/Absorption
  - Increased Requirements
  - Blood Loss
  - Iron Sequestration
- Anemia of Chronic Disease
  - Low serum iron, low TIBC, normal serum ferritin
  - MANY!!
    - Chronic infection, inflammation, cancer, liver disease

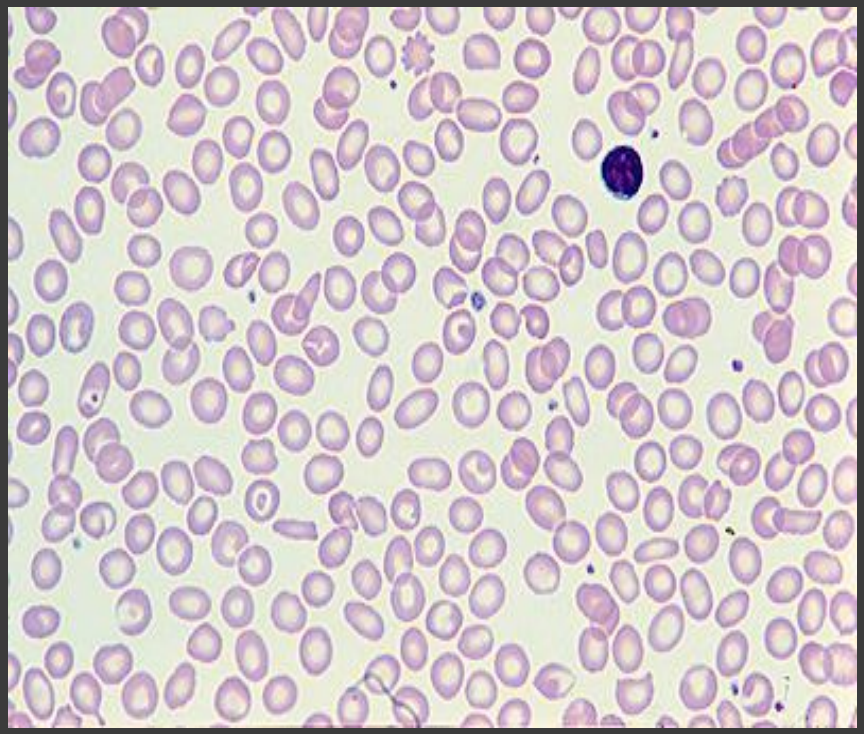
MICROCYTIC ANEMIA
REDUCED HEME SYNTHESIS

- Lead poisoning
- Acquired or congenital sideroblastic anemia
- Characteristic smear finding: Basophylic stippling



MICROCYTIC ANEMIA
REDUCED GLOBIN PRODUCTION

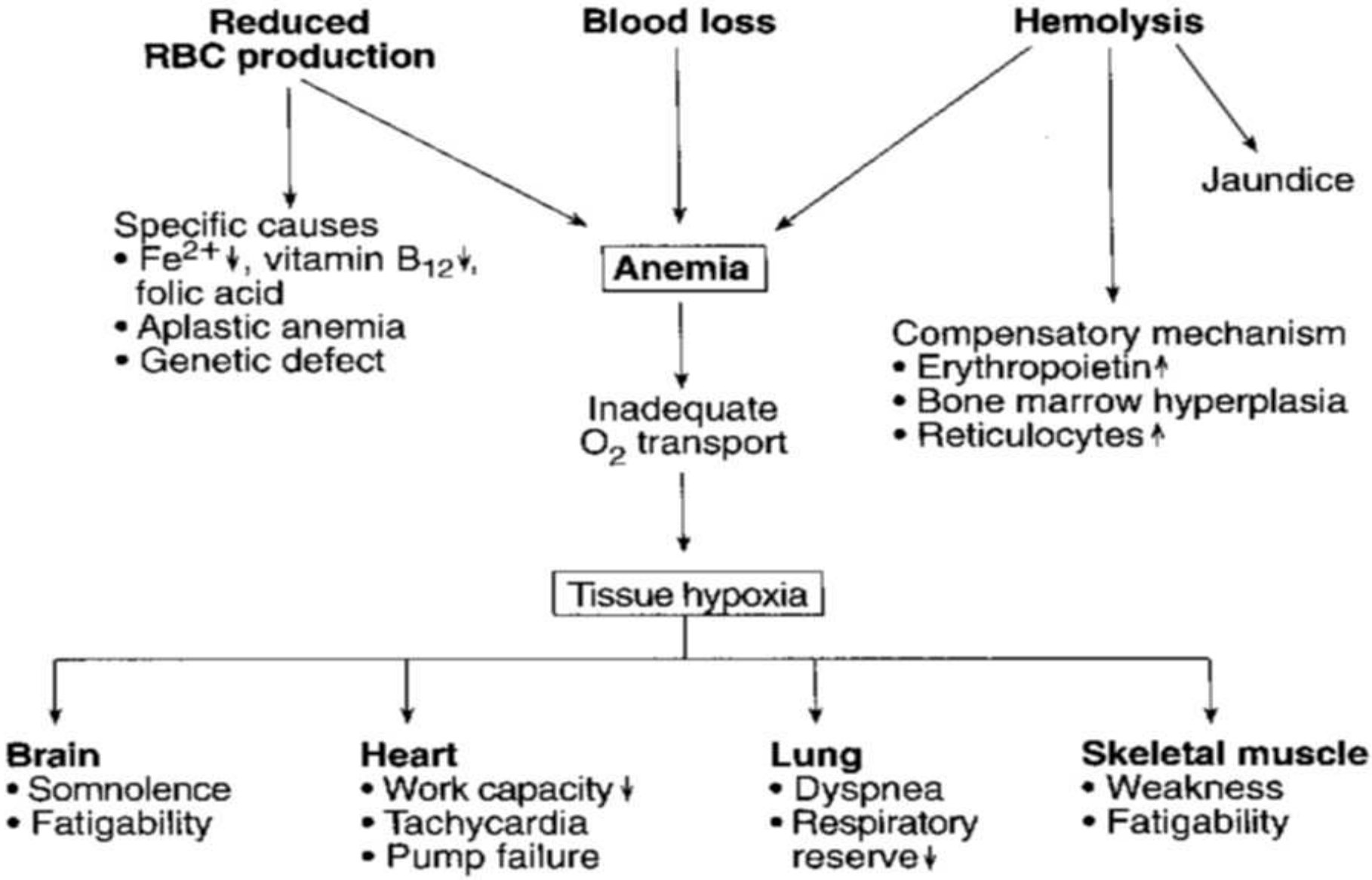
- Thalassemias
- Smear Characteristics
  - Hypochromia
  - Microcytosis
  - Target Cells
  - Tear Drops

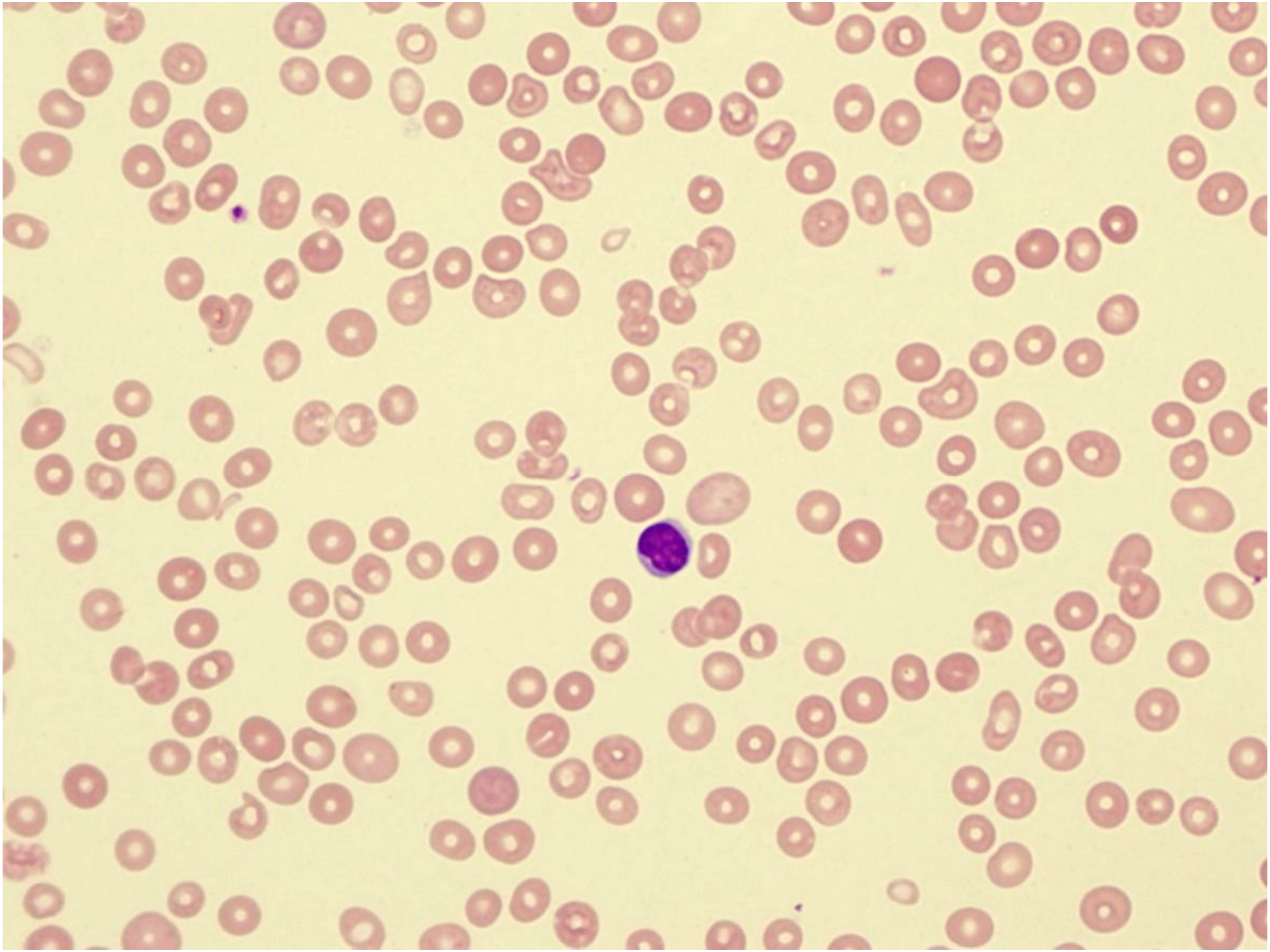


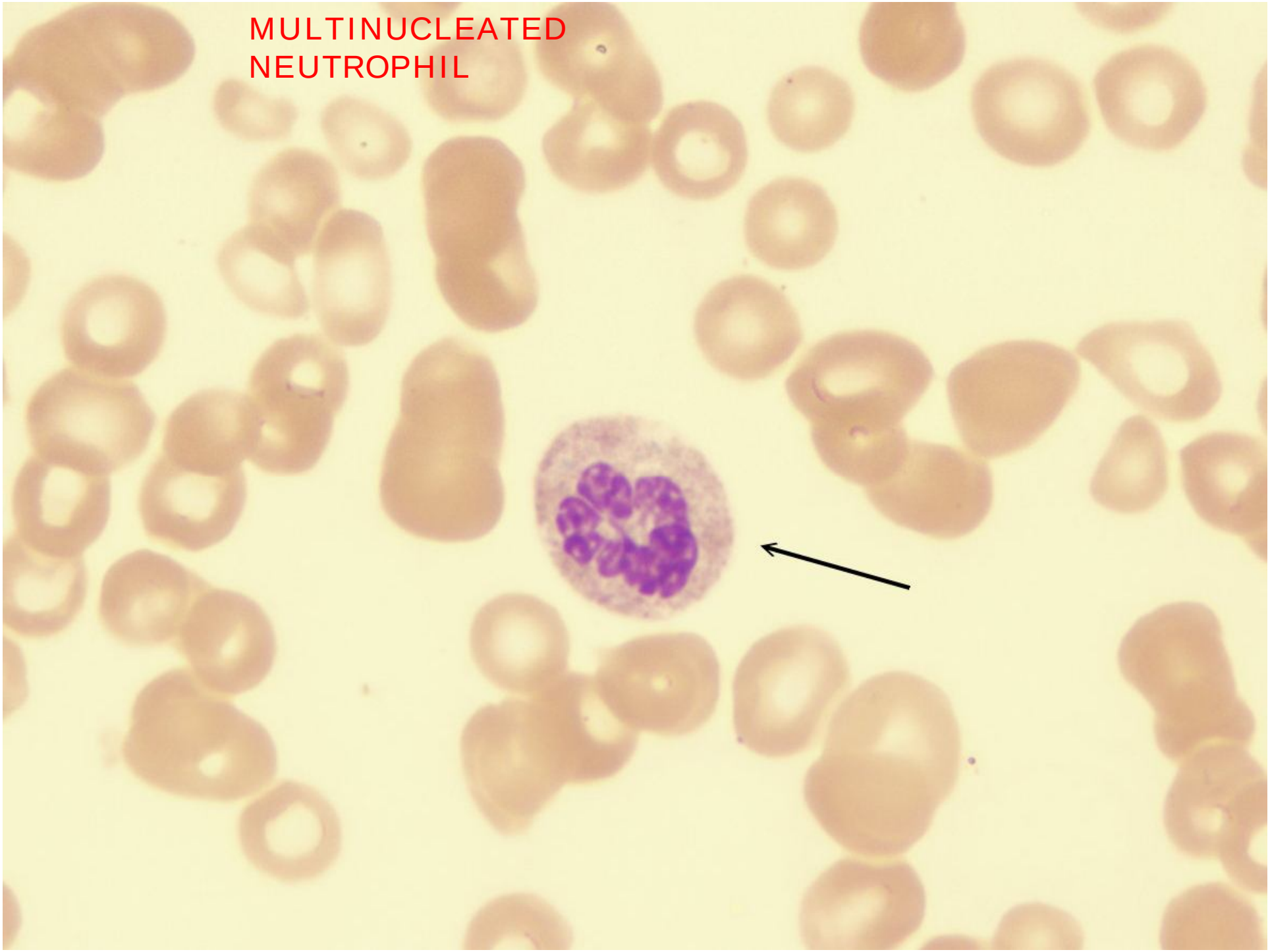
LAB TESTS OF IRON DEFICIENCY OF INCREASED SEVERITY

	NORMAL	Fe deficiency Without anemia	Fe deficiency With mild anemia	Fe deficiency With severe anemia
Serum Iron	60-150	60-150	<60	<40
Iron Binding Capacity	300-360	300-390	350-400	>410
Saturation	20-50	30	<15	<10
Hemoglobin	Normal	Normal	9-12	6-7
Serum Ferritin	40-200	<20	<10	0-10

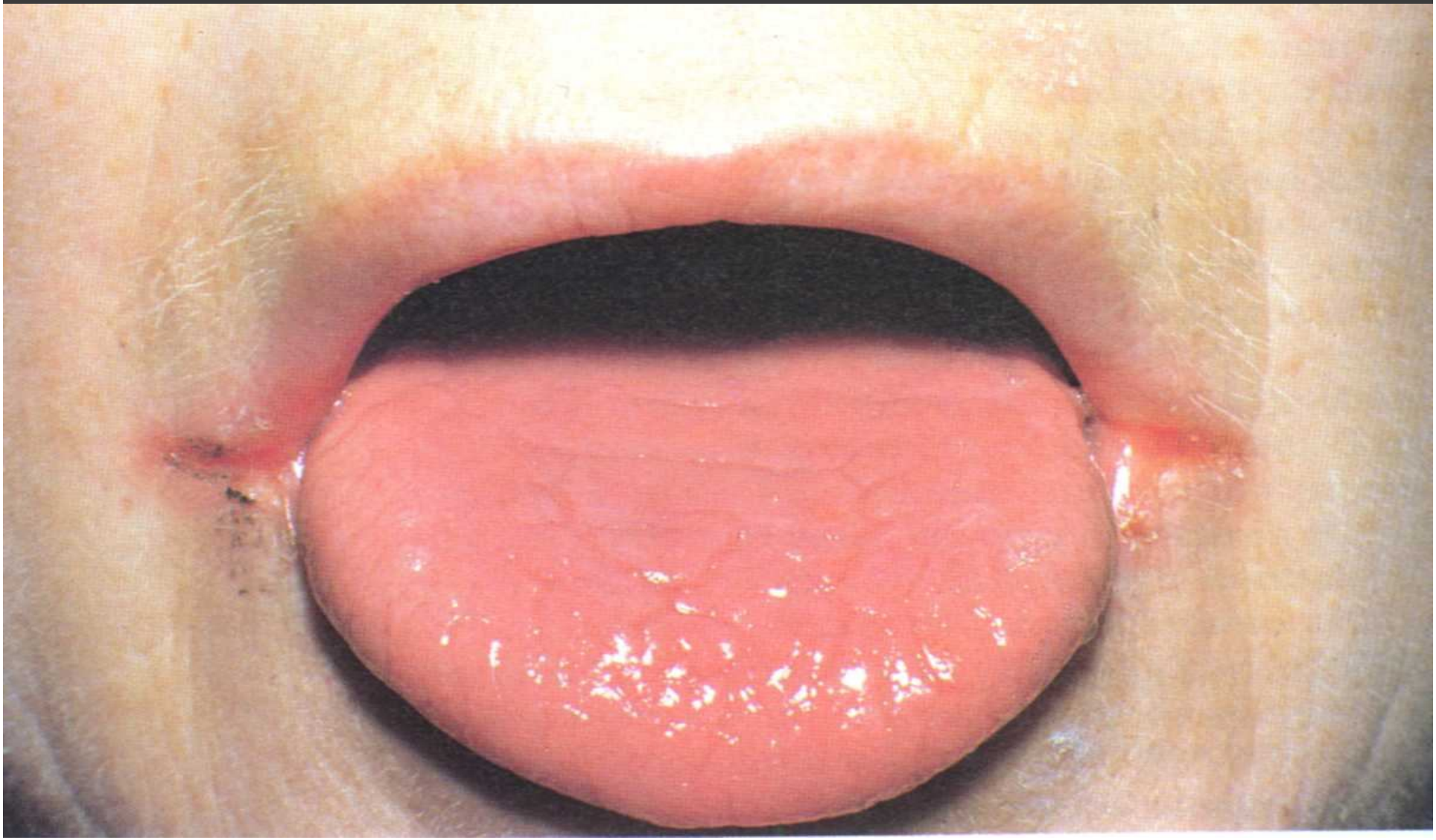
PATHOLOGY, SYMPTOMS, AND SIGNS OF ANEMIA






MULTINUCLEATED
NEUTROPHIL

ANGULAR CHEILITIS AND SMOOTH TONGUE IN IRON DEFICIENCY



Lab values in anemia

	Iron deficiency	Chronic disease	Pregnancy/ OCP use	Hemo-chromatosis
Serum iron	↓(1°)	↓	–	↑(1°)
Transferrin/ TIBC (indirectly proportional to transferrin)	↑	↓*	↑(1°)	↓
Ferritin	↓	↑(1°)	–	↑
% transferrin saturation (serum Fe/TIBC)	↓↓	–	↓	↑↑

*Evolutionary reasoning—pathogens use circulating iron to thrive. The body has adapted a system in which iron is stored within the cells of the body and prevents pathogens from acquiring circulating iron.

- The anemia of chronic disease

  Iron deficiency anemia

  Beta thalassemia minor

  Anemia of chronic renal failure

  Anemia in cancer patients on chemotherapy

  Aplastic anemia

Dysplastic and sideroblastic anemias

Sickle cell anemia

Glucose 6 phosphate dehydrogenase deficiency and hemolysis

Hereditary spherocytosis

Macrocytic anemia – folate versus vitamin B12 deficiency

Thalassemia

Anemia in the elderly

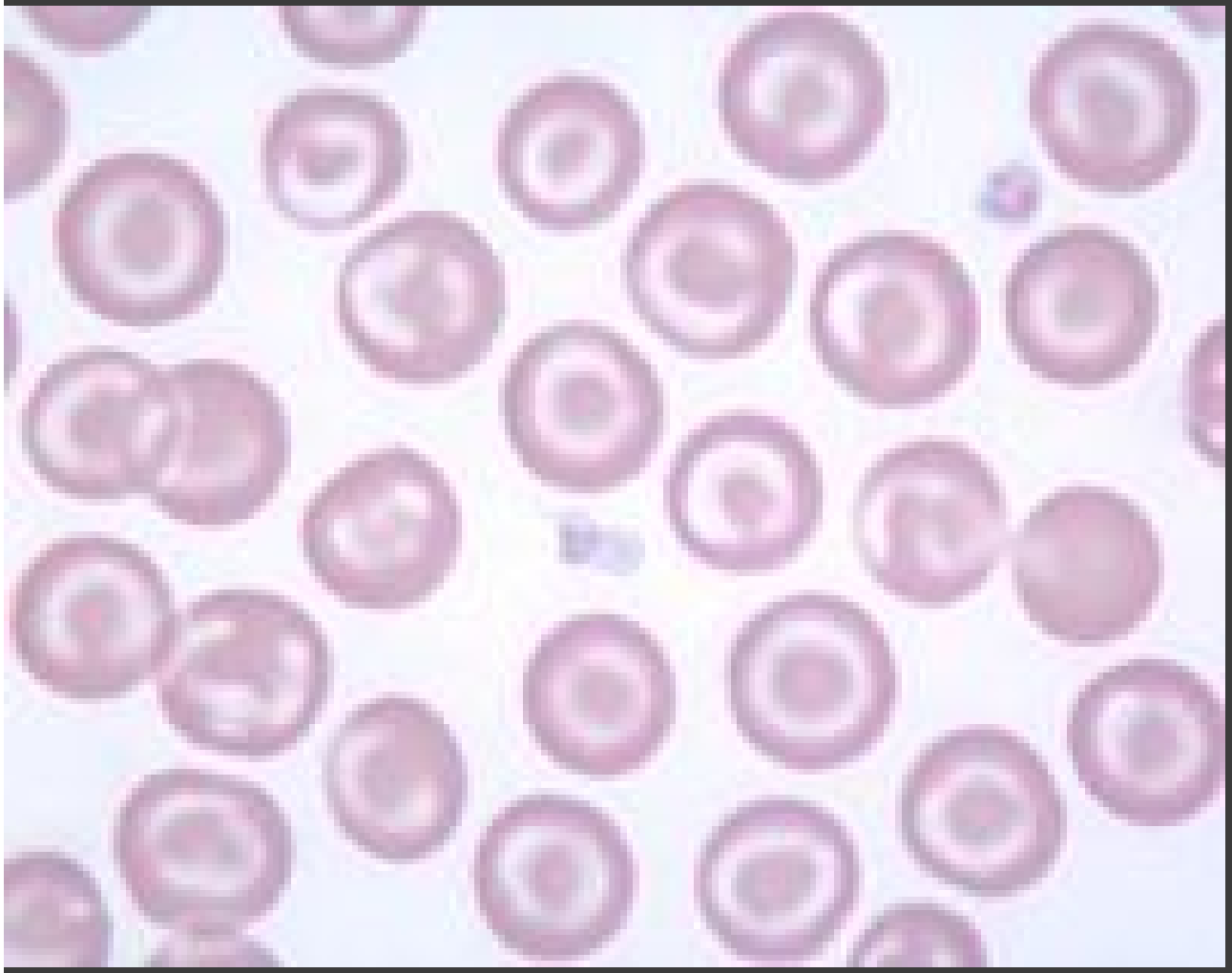
Iron loading and hemachromatosis

Differential diagnosis of iron loading

ANEMIA: INSUFFICIENT ERYTHROCYTES

- **Hemorrhagic anemia** – result of acute or chronic loss of blood
- **Hemolytic anemia** – prematurely ruptured RBCs
- **Aplastic anemia** – destruction or inhibition of red bone marrow

TARGET CELLS



Target cells (from red blood cells) are associated with

- Hemoglobin C (HbC) disease,
- Asplenia,
- Liver Disease, Thalassemia
- severe Iron deficiency anemia

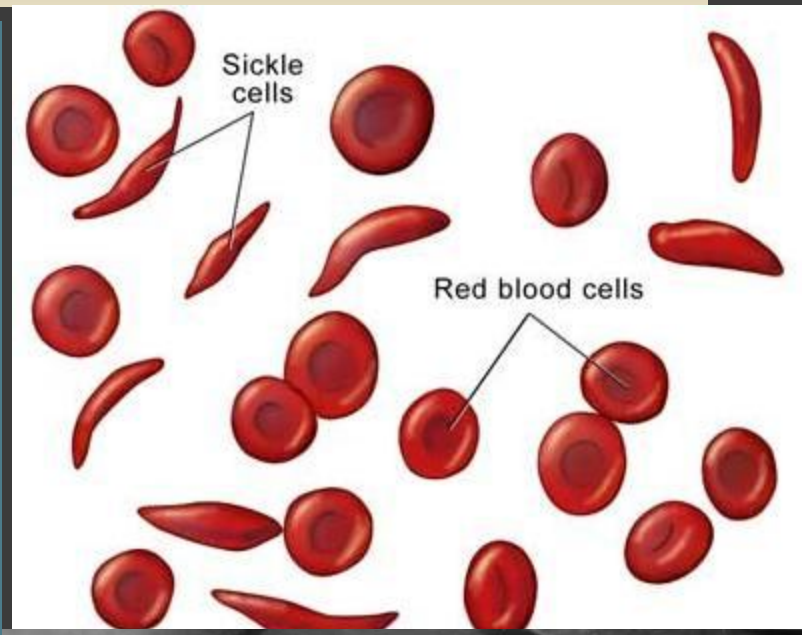
Graphic accessed http://diaglab.vet.cornell.edu/clinpath/modules/hemogram/images/target.jpg, 2009.

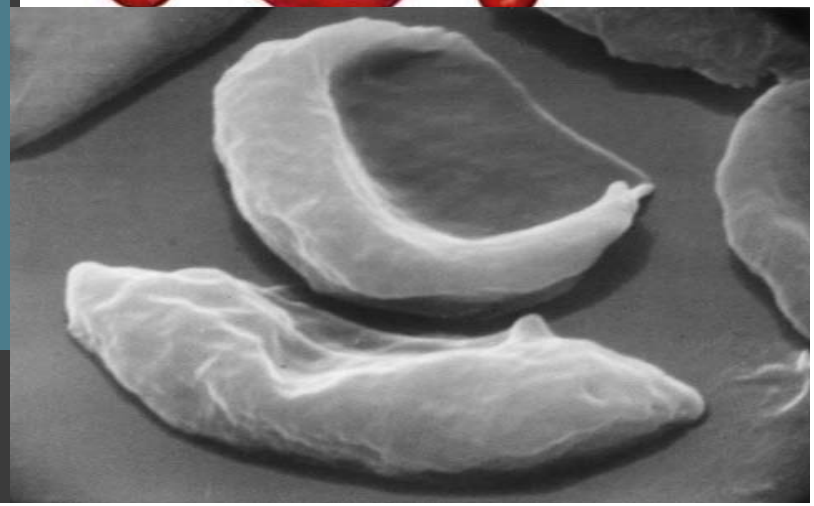
ANEMIA: DECREASED HEMOGLOBIN CONTENT

- Iron-deficiency anemia results from:
  - A secondary result of hemorrhagic anemia
  - Inadequate intake of iron-containing foods
  - Impaired iron absorption
- Pernicious anemia results from:
  - Deficiency of vitamin B_{12}
  - Lack of intrinsic factor needed for absorption of B_{12}
- Treatment is intramuscular injection of B_{12}; application of Nascobal

ANEMIA: ABNORMAL HEMOGLOBIN

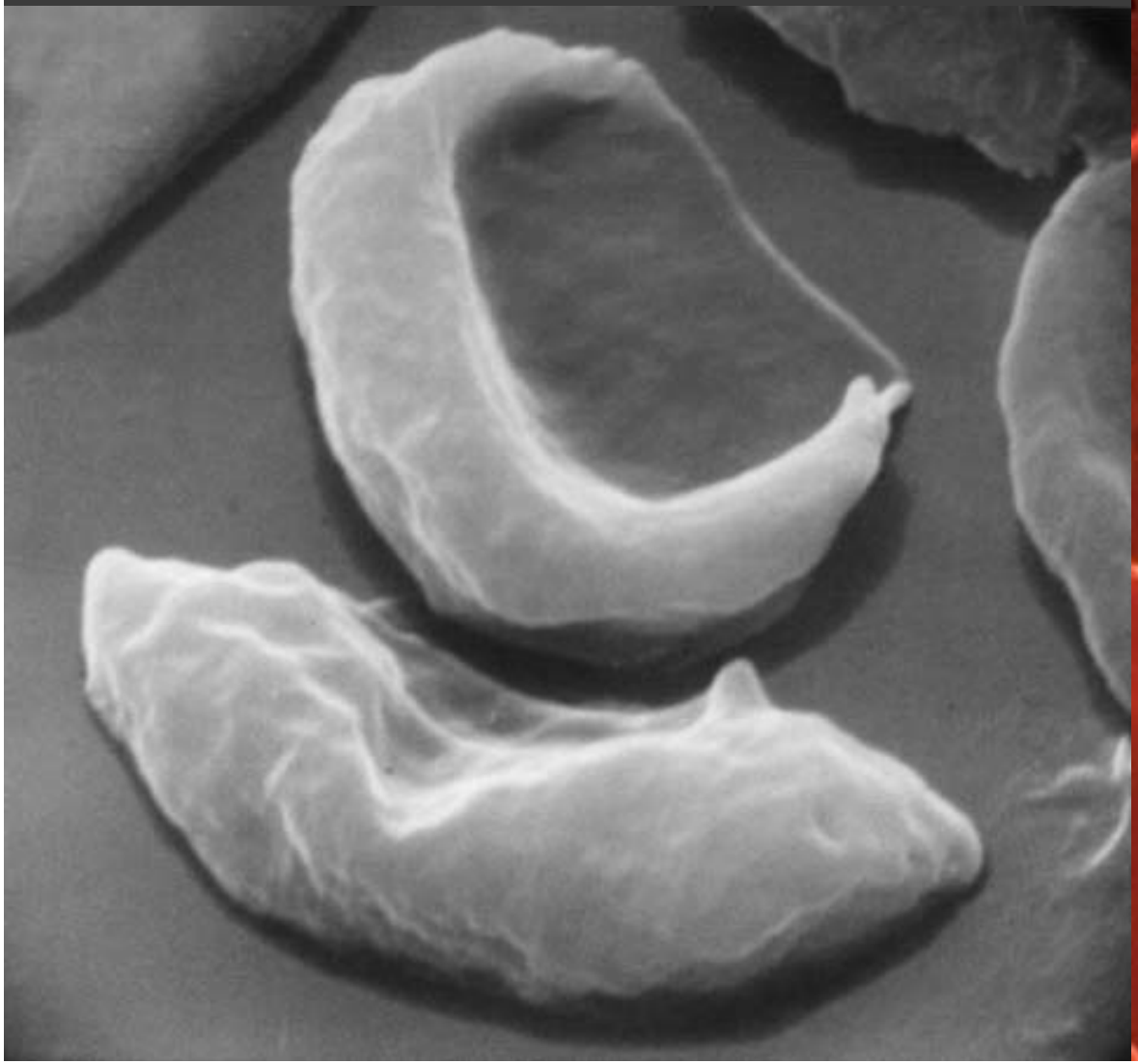
- **Thalassemias** – absent or faulty globin chain in Hb
  - RBCs are thin, delicate, and deficient in Hb
- **Sickle-cell anemia** – results from a defective gene coding for an abnormal Hb called **hemoglobin S** (HbS)
  - HbS has a single amino acid substitution in the beta chain
  - This defect causes RBCs to become sickle-shaped in low oxygen situations

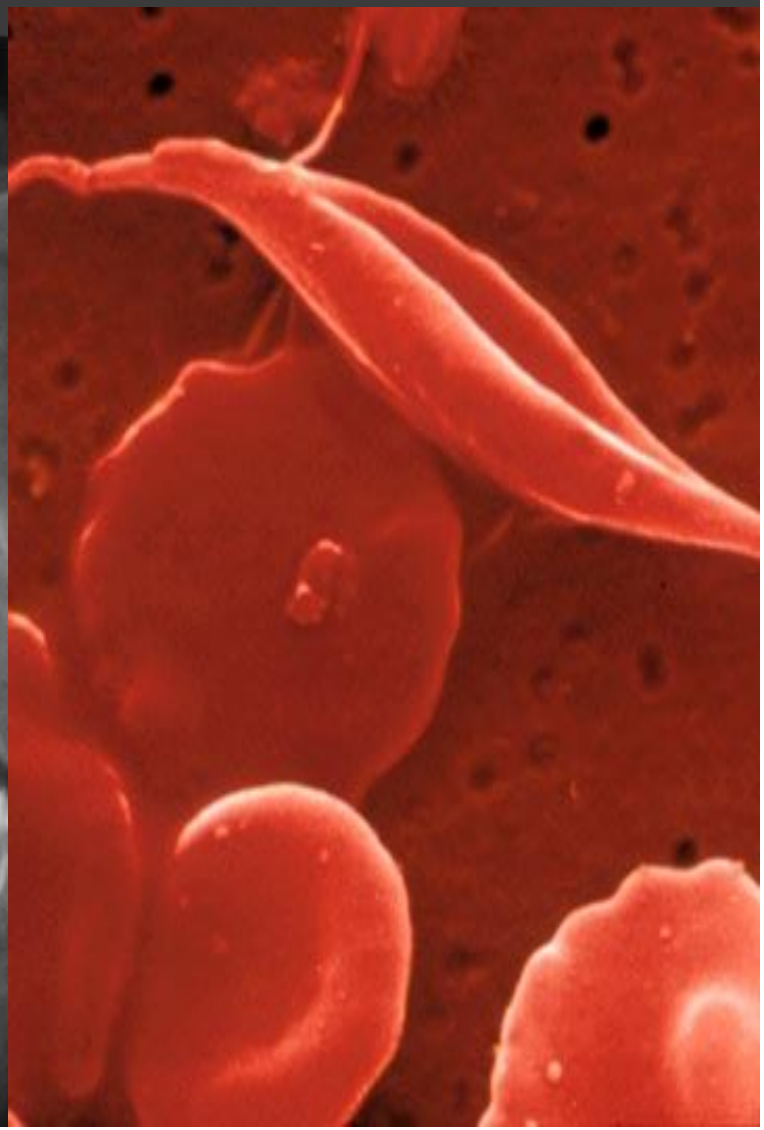




α-thalassemia	There are 4 α-globin genes. In α-thalassemia, the α-globin chain is underproduced (as a function of number of bad genes, 1–4). There is no compensatory ↑ of any other chains. HbH (β_4-tetramers, lacks 3 α-globin genes). Hb Barts (γ_4-tetramers, lacks all 4 α-globin genes) results in hydrops fetalis and intrauterine fetal death.	α-thalassemia is prevalent in Asia and Africa. β-thalassemia is prevalent in Mediterranean populations.
β-thalassemia	In β-thalassemia minor (heterozygote), the β chain is underproduced; in β-thalassemia major (homozygote), the β chain is absent. In both cases, fetal hemoglobin production is compensatorily ↑ but is inadequate. HbS/β-thalassemia heterozygote has mild to moderate disease (see Color Image 19).	β-thalassemia major results in severe anemia requiring blood transfusions. Cardiac failure due to 2° hemochromatosis. Marrow expansion ("crew cut" on skull x-ray) → skeletal deformities.

SICKLE CELL ANEMIA



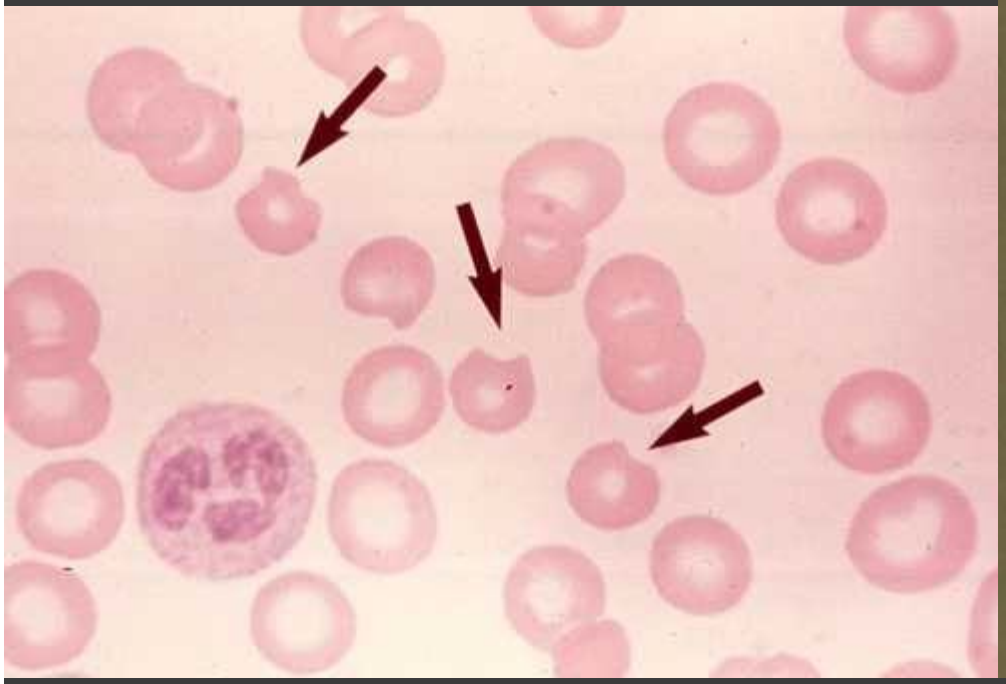


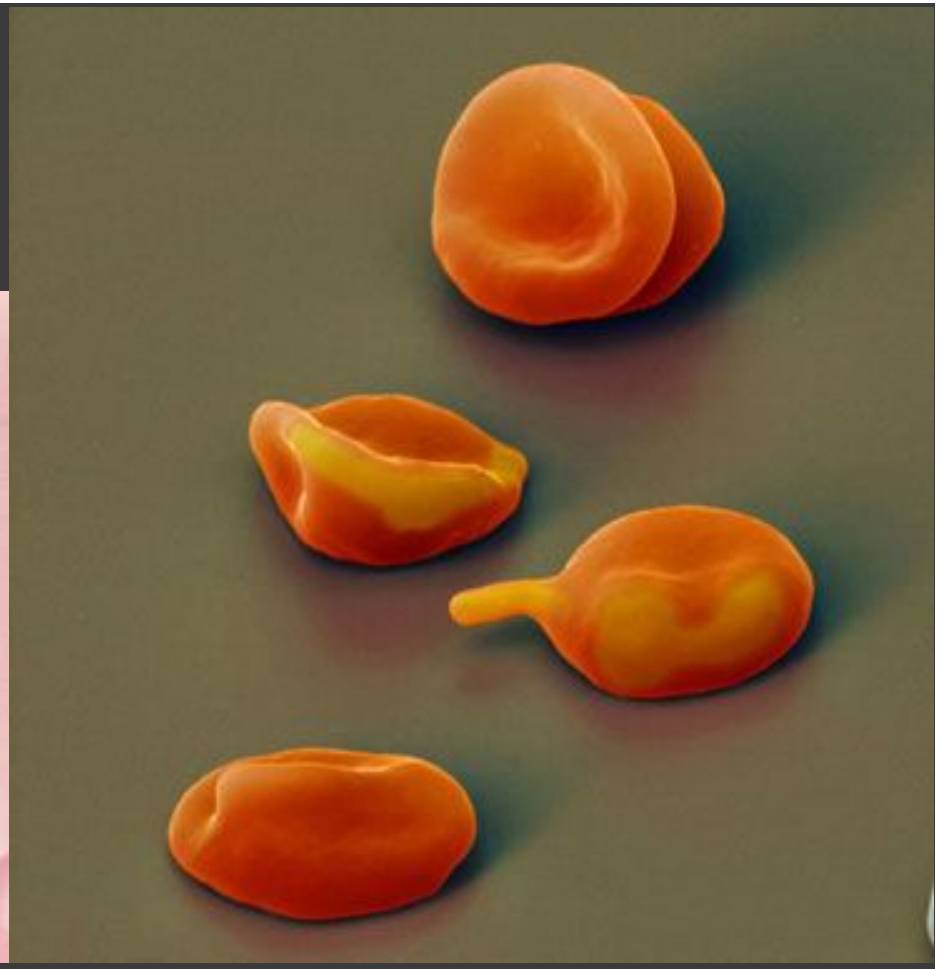
RBC forms

Biconcave	Normal.
Spherocytes	Hereditary spherocytosis, autoimmune hemolysis.
Elliptocyte	Hereditary elliptocytosis.
Macro-ovalocyte	Megaloblastic anemia (also hypersegmented PMNs), marrow failure.
Helmet cell, schistocyte	DIC, traumatic hemolysis.
Sickle cell	Sickle cell anemia.
Bite cell	G6PD deficiency.
Teardrop cell	Myeloid metaplasia with myelofibrosis.
Acanthocyte	Spiny appearance in abetalipoproteinemia.
Target cell	**H**bC disease, **A**splenia, **L**iver disease, **T**halassemia.
Poikilocytes	Nonuniform shapes in TTP/HUS, microvascular damage, DIC.
Burr cell	TTP/HUS.
Basophilic stippling	**T**halassemias, **A**nemia of chronic disease, **I**ron deficiency, **L**ead poisoning.

Hemolytic anemias	↑ serum bilirubin (jaundice, pigment gallstones), ↑ reticulocytes (marrow compensating for anemia).	
Autoimmune anemia	Mostly extravascular hemolysis (accelerated RBC destruction in liver Kupffer cells and spleen). **Warm** agglutinin (Ig**G**)—chronic anemia seen in SLE, in CLL, or with certain drugs (e.g., α-methyldopa). **Cold** agglutinin (Ig**M**)—acute anemia triggered by cold; seen with *Mycoplasma pneumoniae* infections or infectious mononucleosis. Erythroblastosis fetalis—seen in newborn due to Rh or other blood antigen incompatibility → mother's antibodies attack fetal RBCs.	Autoimmune hemolytic anemias are Coombs positive. Direct Coombs' test: anti-Ig Ab added to patient's RBCs agglutinate if RBCs are coated with Ig. Indirect Coombs' test: normal RBCs added to patient's serum agglutinate if serum has anti-RBC surface Ig. **Warm** weather is **GG**Great. **Cold** ice cream . . . **MMM**.
Hereditary spherocytosis	Intrinsic, extravascular hemolysis due to spectrin or ankyrin defect. RBCs are small and round with no central pallor → less membrane → ↑ MCHC, ↑ RDW. Howell-Jolly bodies present after splenectomy.	Coombs negative. Osmotic fragility test used to confirm.
Paroxysmal nocturnal hemoglobinuria	Intravascular hemolysis due to membrane defect → ↑ sensitivity of RBCs to the lytic activity of complement (impaired synthesis of GP I anchor in RBC membrane).	↑ urine hemosiderin.
Microangiopathic anemia	Intravascular hemolysis seen in DIC, TTP/HUS, SLE, or malignant hypertension.	Schistocytes (helmet cells) seen on blood smear.

G6PD DEFICIENCY





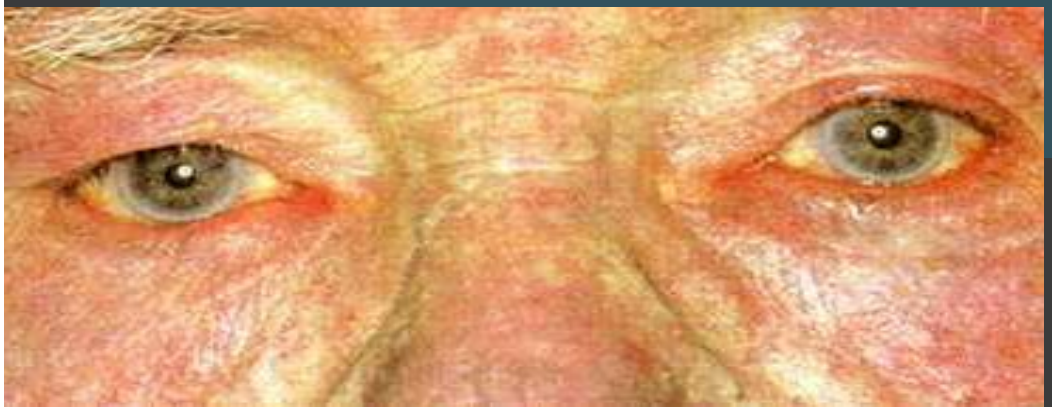
Patients with G6PD deficiency are prone to devloping hemolytic anemia in response to sulfonamides such as dapsone and sulfasalazine.

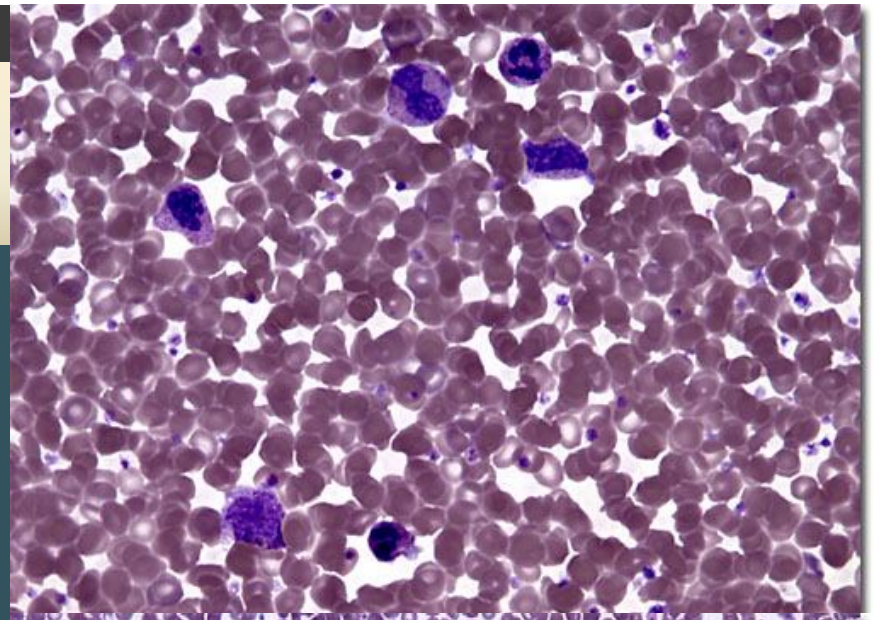
Other precipitating factors are infections, diabetic ketoacidosis, and **favism**.

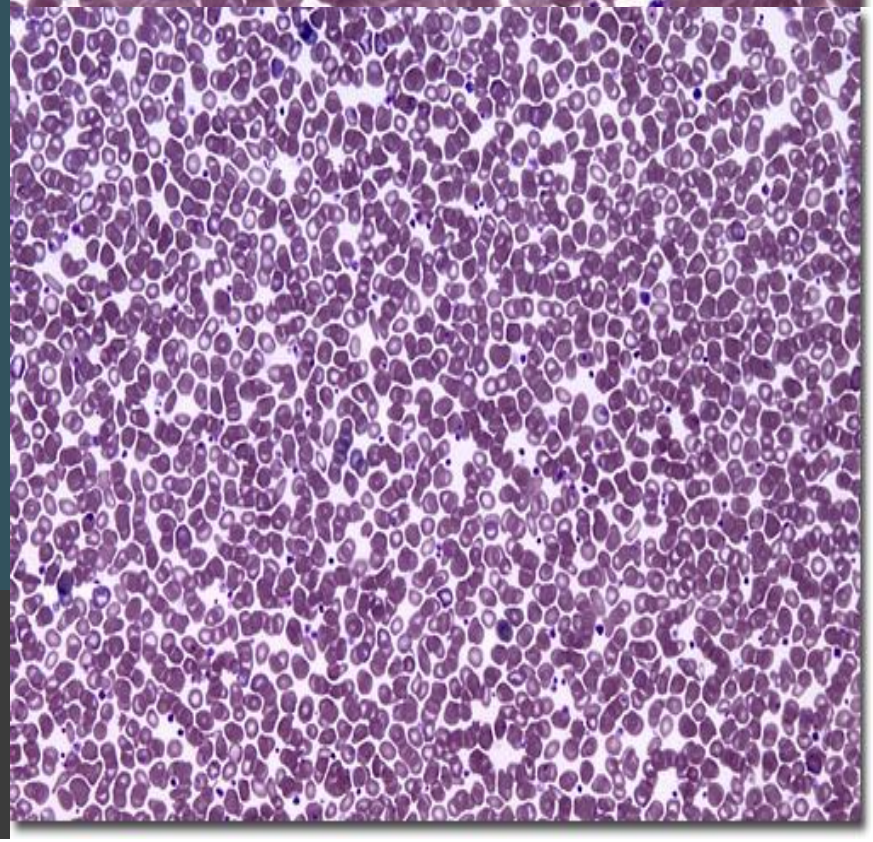
POLYCYTHEMIA

POLYCYTHEMIA

- Polycythemia – excess RBCs that increase blood viscosity
- Three main polycythemias are:
  - **Polycythemia vera**
  - **Secondary polycythemia**
  - **Blood doping**





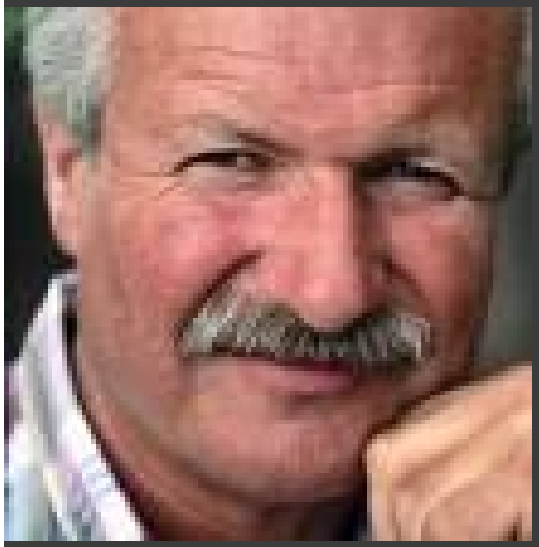


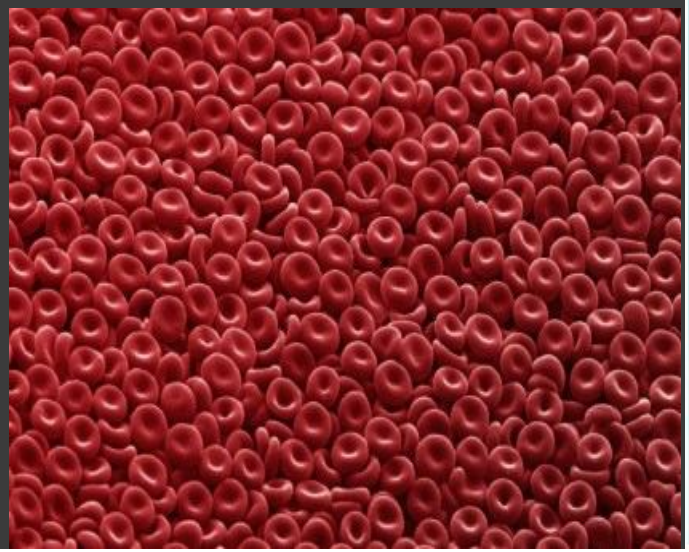
- When polycythemia occurs and it is not associated with any known underlying cause, it is typically referred to as primary polycythemia, polycythemia vera, or erythremia.

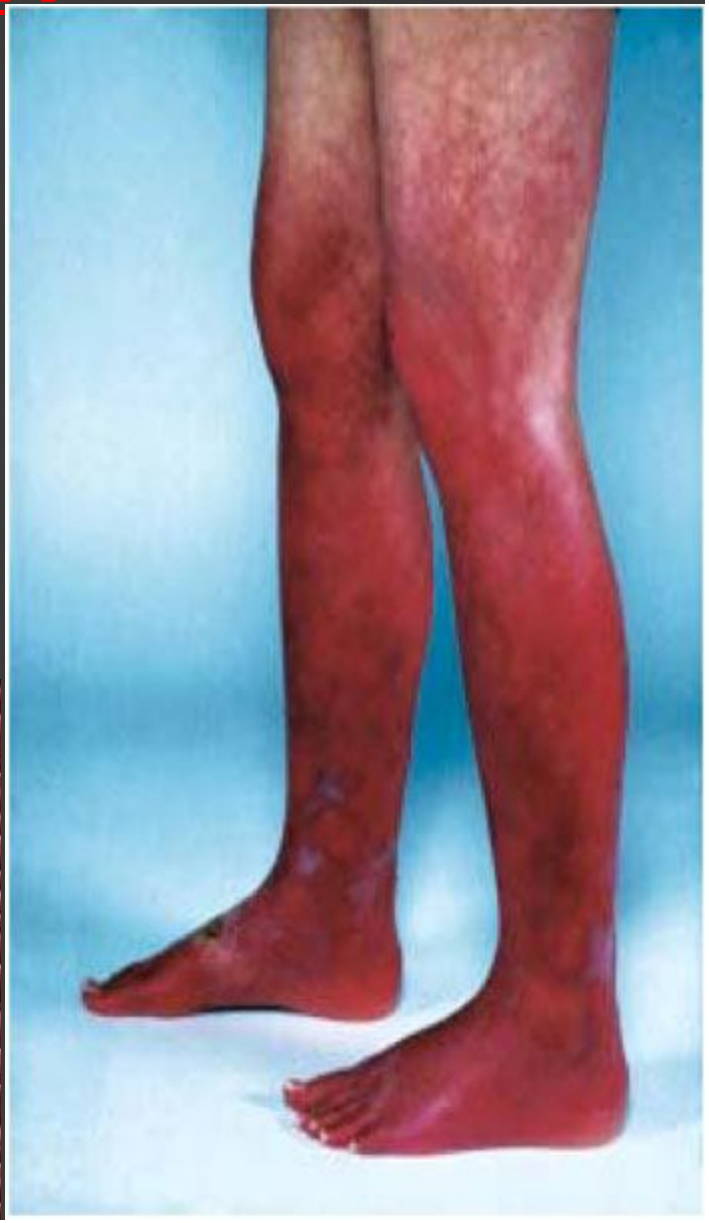
- This form of the disease is most common in middle-aged men and people of Jewish descent.
- Primary polycythemia is typically a chronic condition and tends to be progressive.
- In addition to an increase in red blood cells, individuals with the disease generally experience tumorous overgrowth of bone marrow, enlargement of the spleen, and excessive production of platelets and white blood cells.
- There is no known cure for the myeloproliferative disease, but various treatments can help normalize erythrocyte levels and provide symptomatic relief

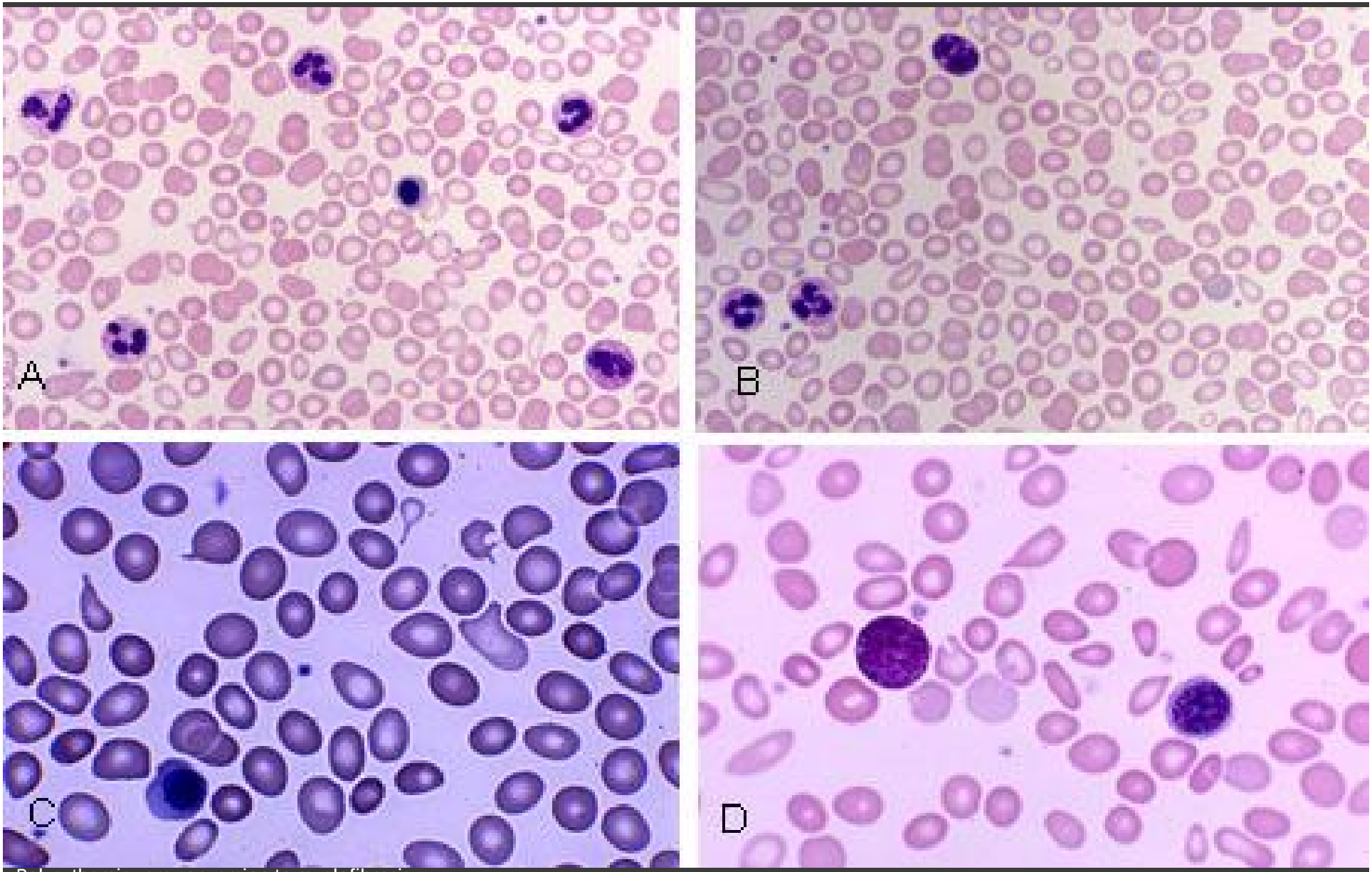
CAUSES **POLYCYTHEMIA**

- prolonged habitation of high altitudes,
- smoking,
- certain types of cancer,
- pulmonary disease,
- heart disorders,



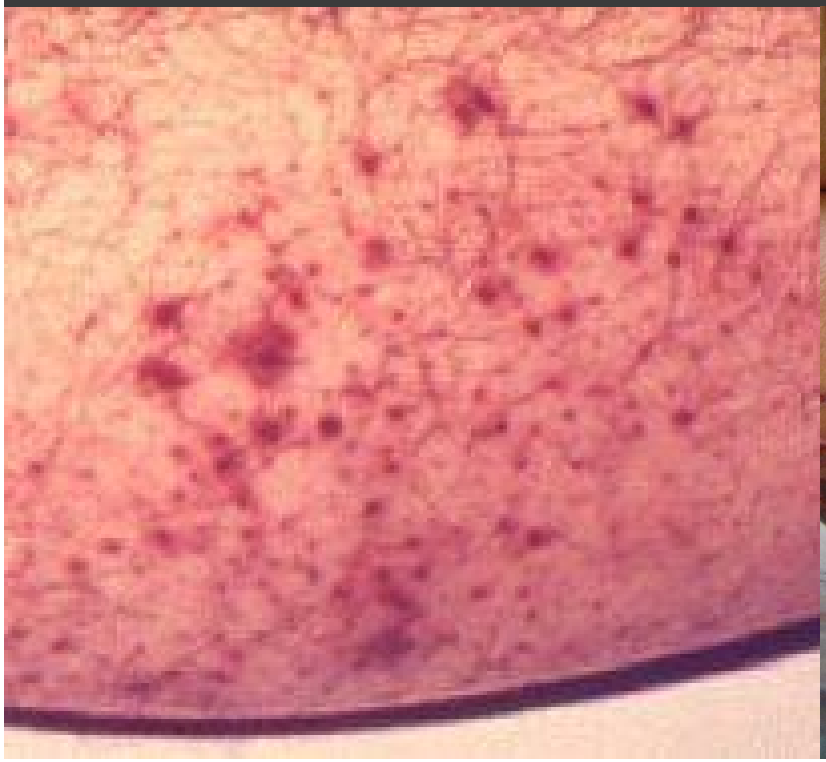


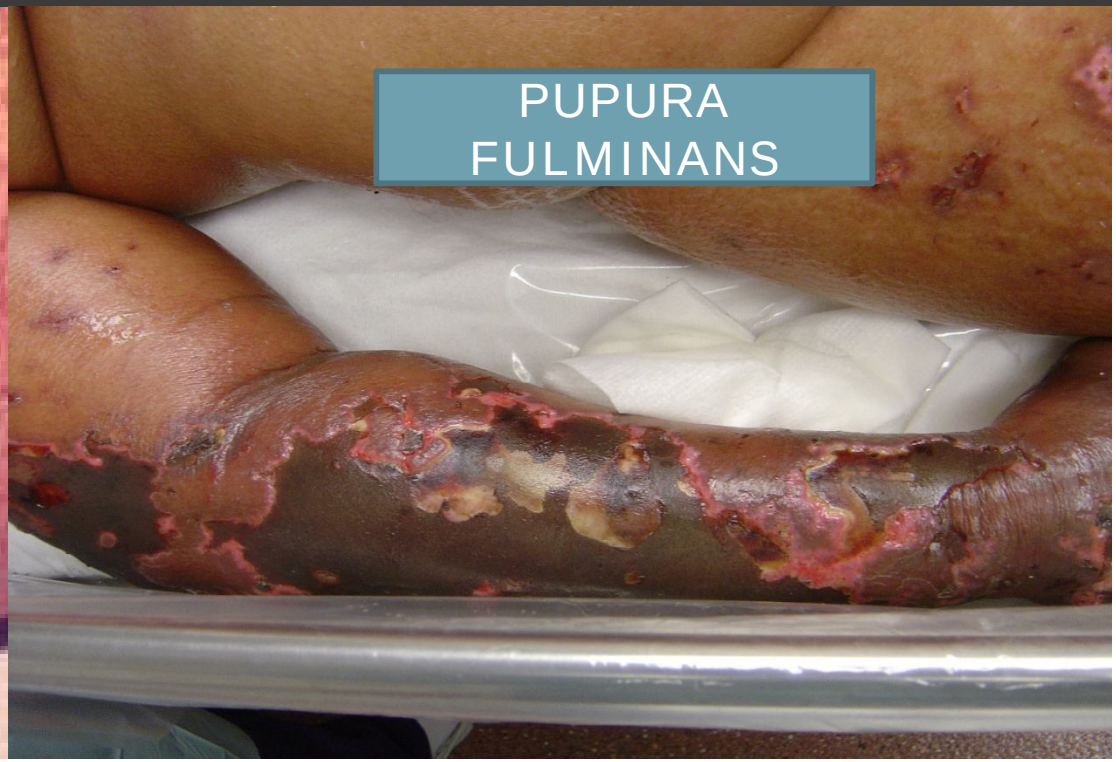


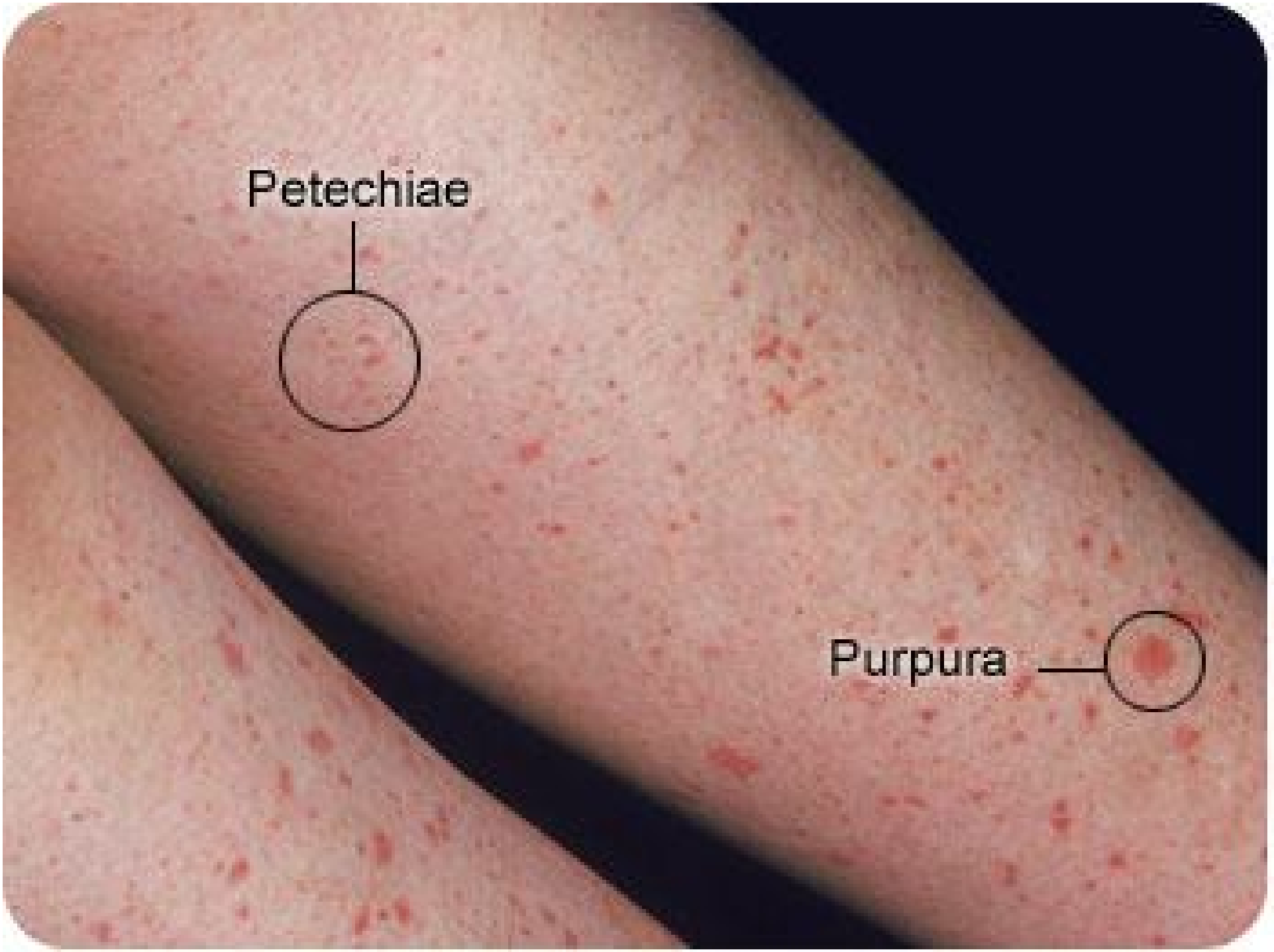


Polycythemia vera conversion to myelofibrosis.
(**A**) Blood film. Red cells anisocytosis and mild poikilocytosis with occasional elliptocytes. Neutrophilia, nucleated red cell.
(**B**) Blood film. Red cells. Anisocytosis, anisochromia, poikilocytosis with elliptocytes, occasional tear drop cells. Neutrophils.
(**C**) Blood film. Anisocytosis with poikilocytes including tear drop cells.
(**D**) Red cells. Anisocytosis, poikilocytosis with elliptocytes and tear drop cells. Nucleated red cells and basophil.

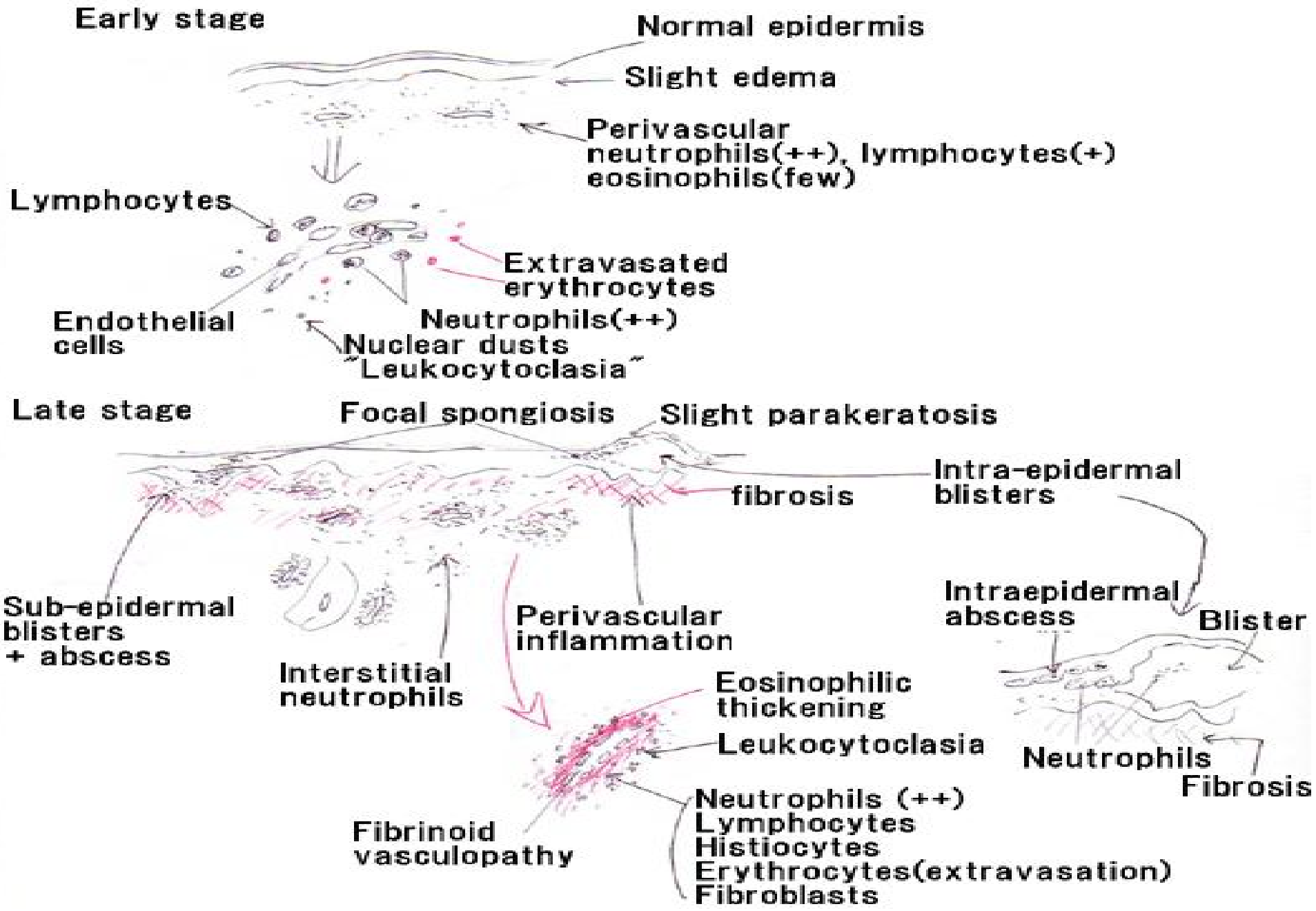
BLEDDING, HEMORRHAGE, HEMATOMAS, PURPURA, PETECHIAE



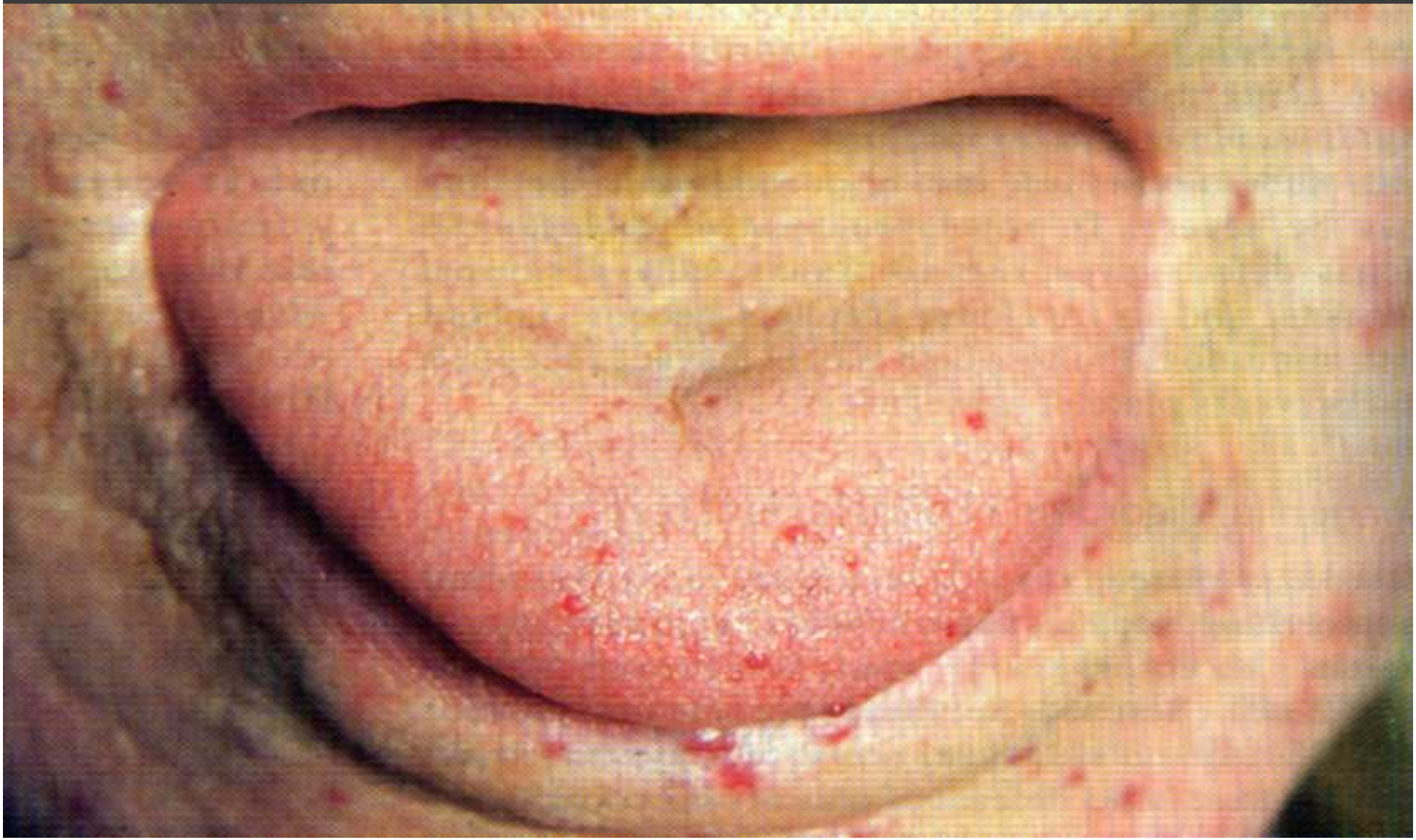



Petechiae
Purpura

Henoch-Sehönlein Purpura



HEREDITARY HEMORRHAGIC TELANGIECTASIA



PATHOGENETIC CLASSIFICATION OF BLEEDING DISORDERS

Pathogenetic Mechanism	Platelet Count	Bleeding Time	Activated Partial Thromboplastin Time	Prothrombin Time	Diseases
Intrinsic pathway defect	N	N	Prolonged	N	Hemophilia, von Willebrand disease, autoantibodies
Extrinsic pathway defect	N	N	N	Prolonged	Liver disease, vitamin K deficiency
Common pathway defect	N	N	Prolonged	Prolonged	Liver disease, vitamin K deficiency, disseminated intravascular coagulation (late)
Platelet defect	Decreased	Prolonged	N	N	Thrombocytopenia
Blood vessel defect	N, decreased	Prolonged	N	N	Vascular purpura

N, normal.

HEMOSTASIS ISSUES

Acquired Disorders of Coagulation

- Hemodilution
- Liver disease
  - ↓ Synthesis of coagulation proteins
  - Thrombocytopenia due to splenomegaly
  - ↑ Fibrinolysis
  - Abnormal fibrinogen (dysfibrinogen)
- Vitamin K deficiency
- Circulating anticoagulants
  - Antibody to coagulation proteins (Factor VIII)
  - Antibody to phospholipid (lupus anticoagulant)
- Disseminated intravascular coagulation (DIC)

Qualitative Platelet Disorders

(Normal Platelet Count, Abnormal Platelet Function)

- Acquired Disorders
  - Exogenous agents impair platelet function
    - Aspirin, non-steroidal drugs
    - Severe liver disease
    - Renal failure (uremic metabolites)
- Inherited Disorders
  - A genetic deficiency or abnormality of specific platelet receptors important in normal platelet function
    - Glanzmann's thrombasthenia
    - Bernard-Soulier syndrome
    - Storage pool disease
  - Platelet aggregation tests are useful to diagnose the inherited disorders

THROMBOCYTOPENIA

• Normal platelet count: 140,000 – 440,000/mm³

Thrombocytopenia results from:
• Decreased marrow production
• Increased peripheral destruction
• Splenic sequestration
• Hemodilution (multiple transfusions)

• Physical examination and bone marrow evaluation distinguish between these possibilities

- Decreased Platelet Production
- • Inadequate number of megakaryocytes
- • Aplastic anemia, marrow injury from
- drugs, radiation, infection, alcohol,
- fibrosis, metastatic tumor
- • Ineffective thrombopoiesis (adequate
- megakaryocytes)
- • B12/folate deficiency, myelodysplastic
- disorders
- • Bone marrow evaluation will establish the
- diagnosis

Increased Platelet Destruction

(Bone marrow evaluation reveals increased number of megakaryocytes)

- Immunologic disorders
- Antiplatelet antibodies or immune complexes mediate platele destruction
- Idiopathic thrombocytopenic purpura (ITP)

    Children: self-limited disorder, usually follows viral Infection

    Adults: chronic disorder, immunosuppression usually necessary
- Drug-induced (quinine, sulfa)
- Sepsis (independent of DIC)
- Connective tissue disorders (SLE), lymphoma
- Non-immunologic disorders
- DIC
- Other microangiopathic conditions (TTP, prosthetic cardiac valve)

Mechanism of Immune Thrombocytopenia

Thrombotic Thrombocytopenic Purpura (TTP)

- TTP is a multisystem disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever and renal disease. Virtually all untreated patients will die.
- Etiology: Platelet thrombi occur in small vessels of involved organs (brain, kidney, etc).
- Therapy: large volume plasmapheresis and steroids

Clinical Aspects of Thrombocytopenia

- With normal functioning platelets, a count of $\geq 100{,}000/mm^3$ should protect against bleeding.

- Platelet counts <10-20,000/mm^3 may be associated with spontaneous bleeding.

- Antiplatelet drugs (aspirin) will increase the bleeding tendency of thrombocytopenic patients.

- Platelet transfusion is most useful in treating thrombocytopenia due to decreased marrow production and hemodilution.

- The efficacy of platelet transfusion should be documented

Hemorrhagic disorders

Disorder	Platelet count	Bleeding time	PT	PTT
Thrombocytopenia	↓	↑	–	–
Hemophilia A or B	–	–	–	↑
von Willebrand's disease	–	↑	–	↑
DIC	↓	↑	↑	↑
Vitamin K deficiency	–	–	↑	↑
Bernard-Soulier disease	↓	↑	–	–
Glanzmann's thrombasthenia	–	↑	–	–

Bernard-Soulier disease = defect of platelet adhesion (↓ GP Ib).

Glanzmann's thrombasthenia = defect of platelet aGgregation (↓ GP IIb-IIIa).

Note: platelet count must reach a very low value (15,000–20,000/mm^3) before generalized bleeding occurs; thrombocytopenia = < 100,000/mm^3.

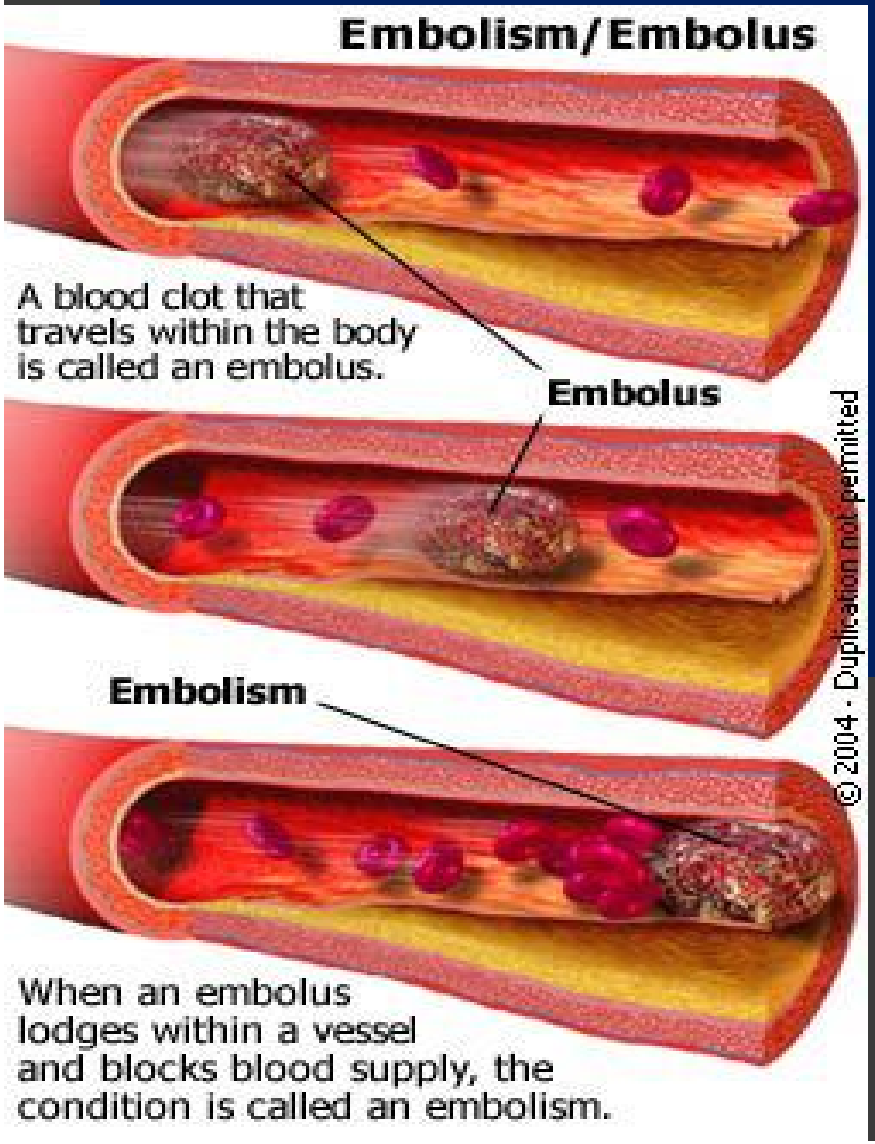
PT (extrinsic)—factors II, V, VII, and X.

PTT (intrinsic)—all factors except VII.

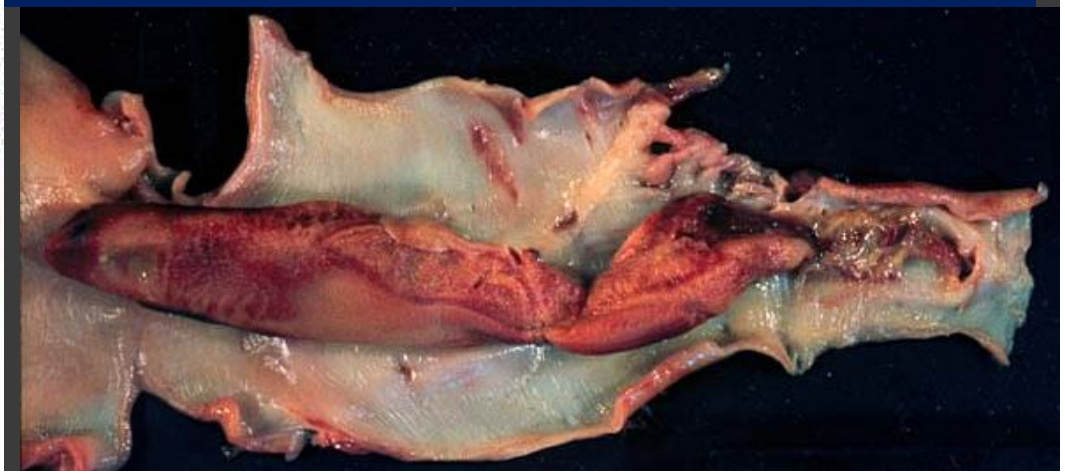
HEMOSTASIS DISORDERS: THROMBOEMBOLYTIC CONDITIONS

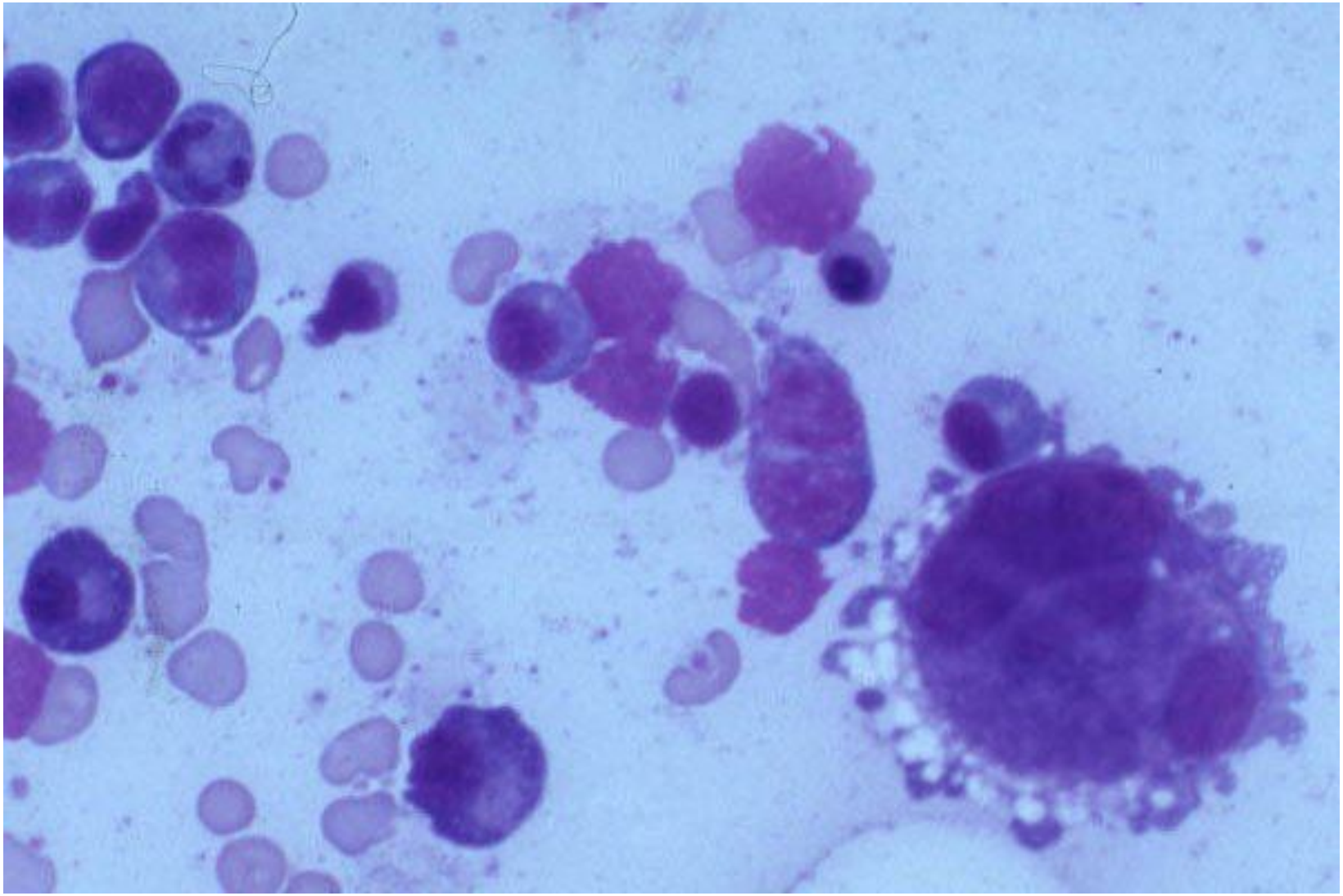
- Thrombus – a clot that develops and persists in an unbroken blood vessel
  - Thrombi can block circulation, resulting in tissue death
  - Coronary thrombosis – thrombus in blood vessel of the heart

HEMOSTASIS DISORDERS: THROMBOEMBOLYTIC CONDITIONS

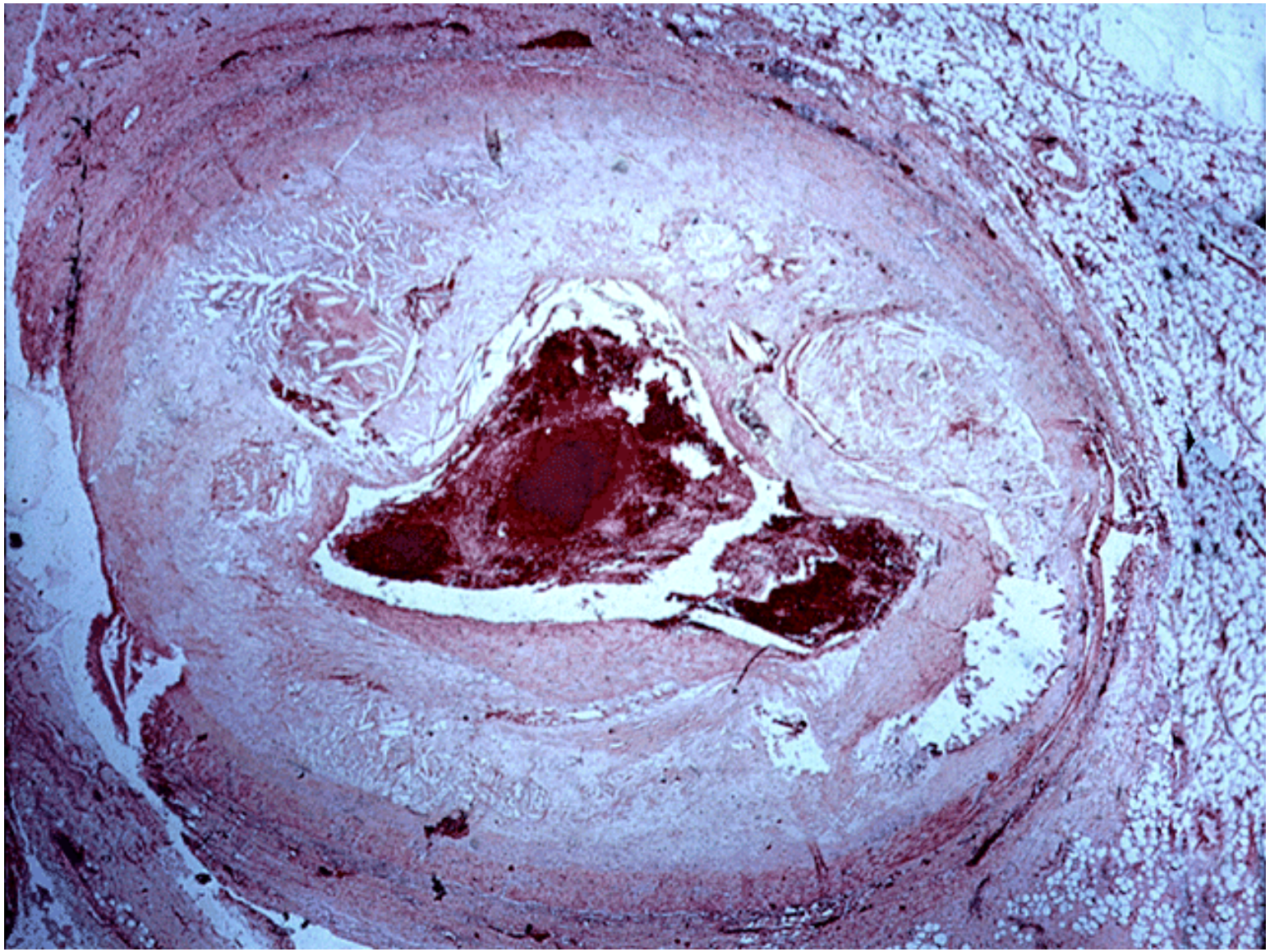


- Embolus – a thrombus freely floating in the blood stream
  - Pulmonary emboli can impair the ability of the body to obtain oxygen
  - Cerebral emboli can cause strokes

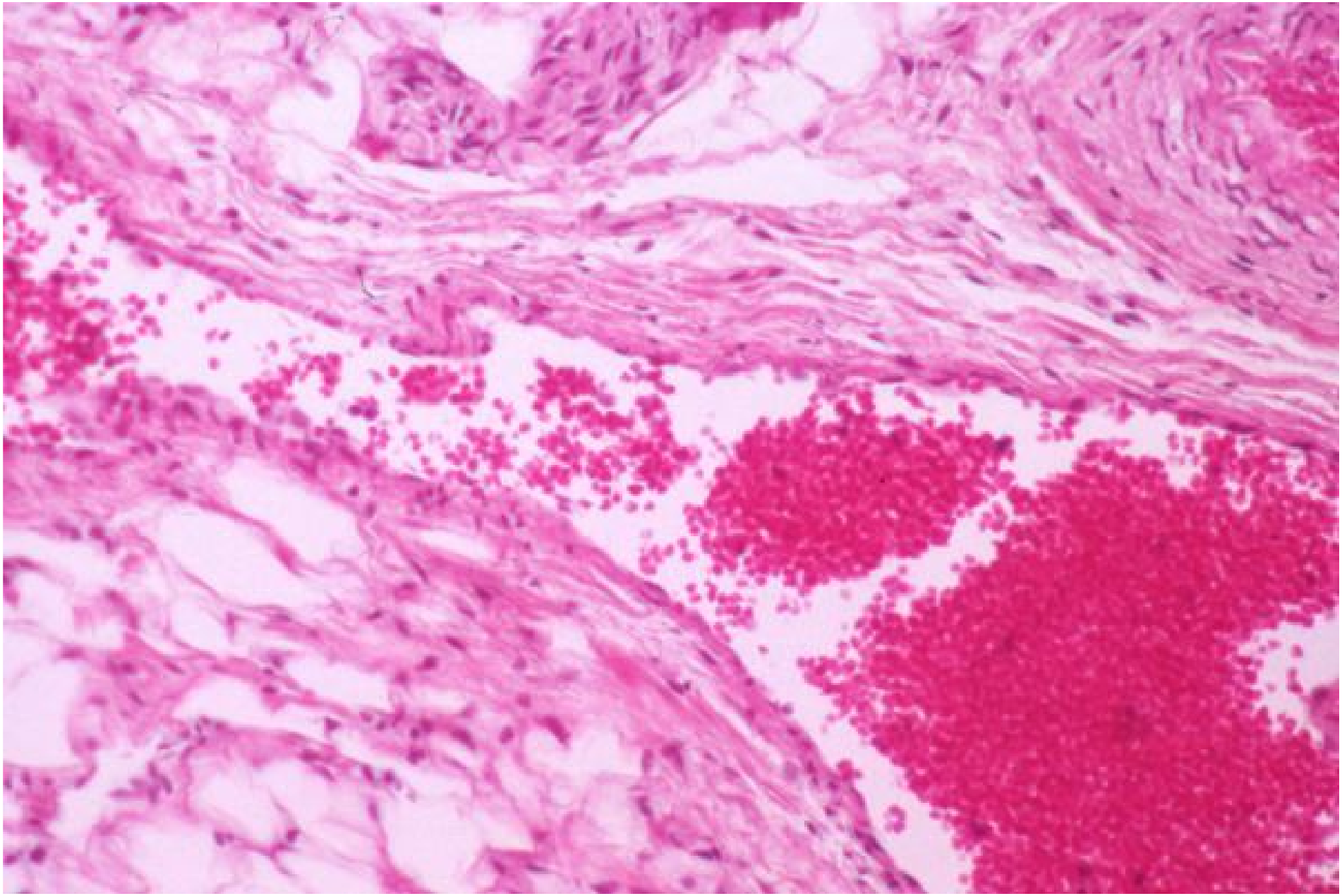




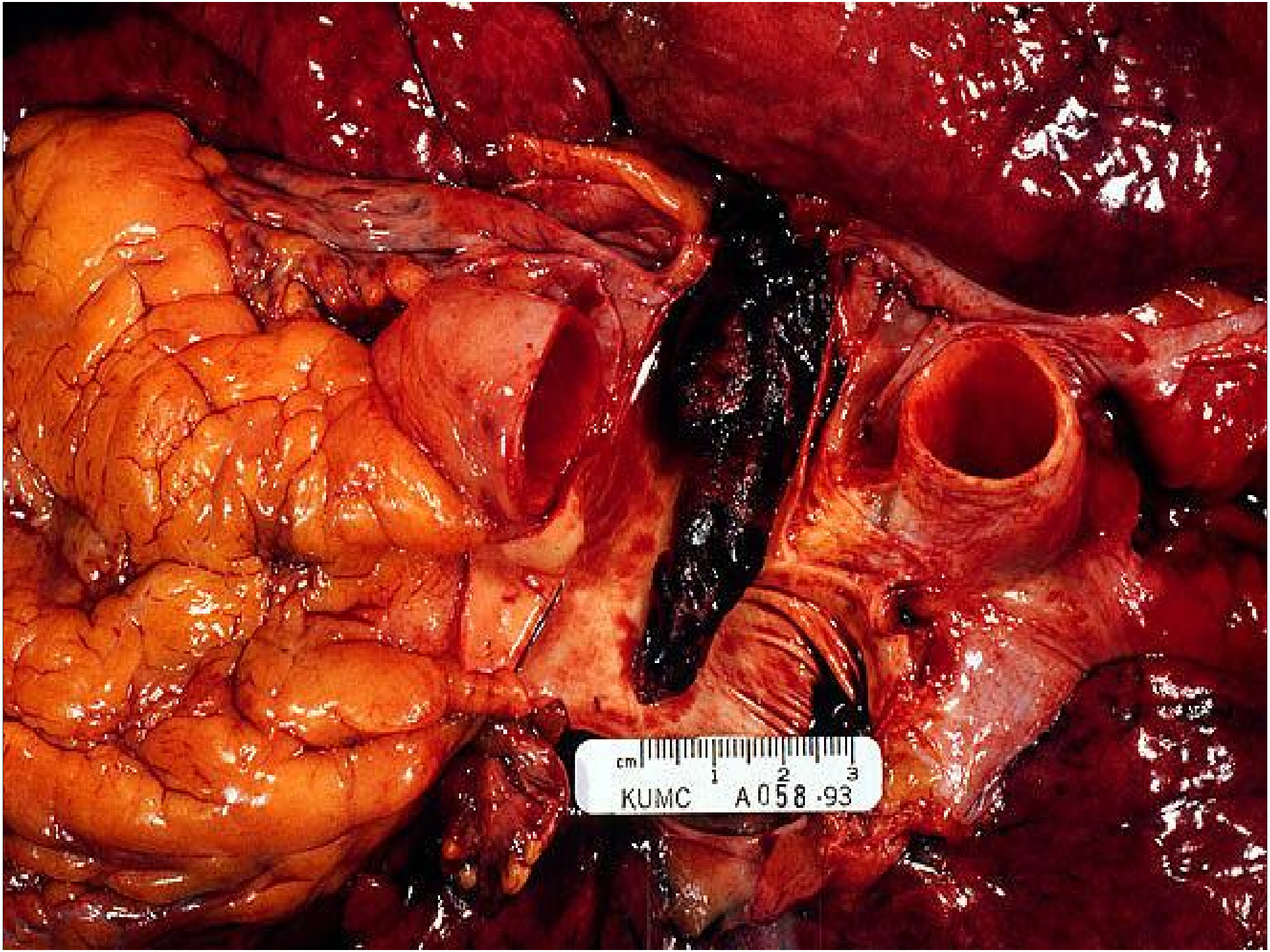
Bone Marrow Megakaryocyte.



CORONARY EMBILSM AND ATHEROSCLEROSIS



Emboli formation.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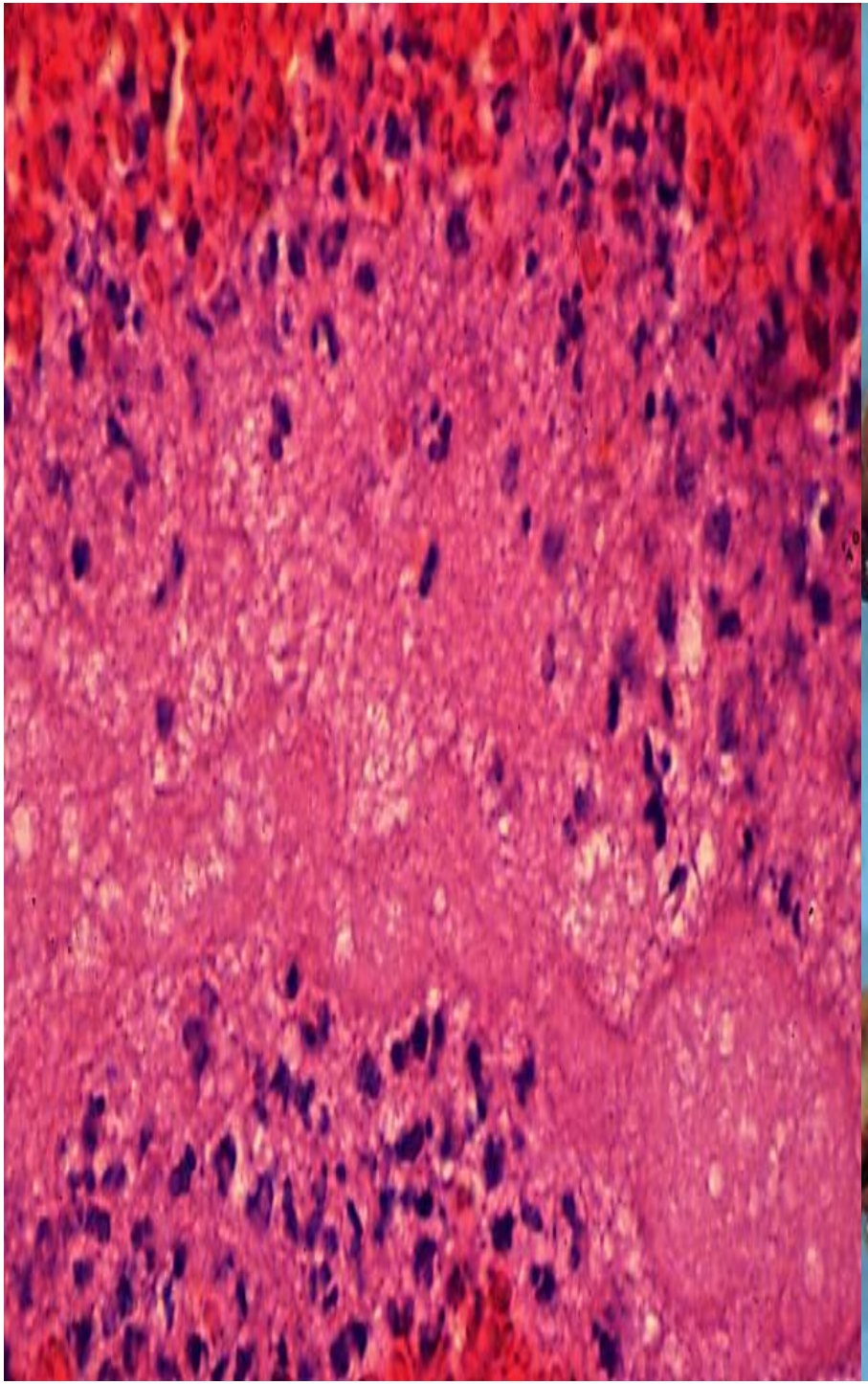
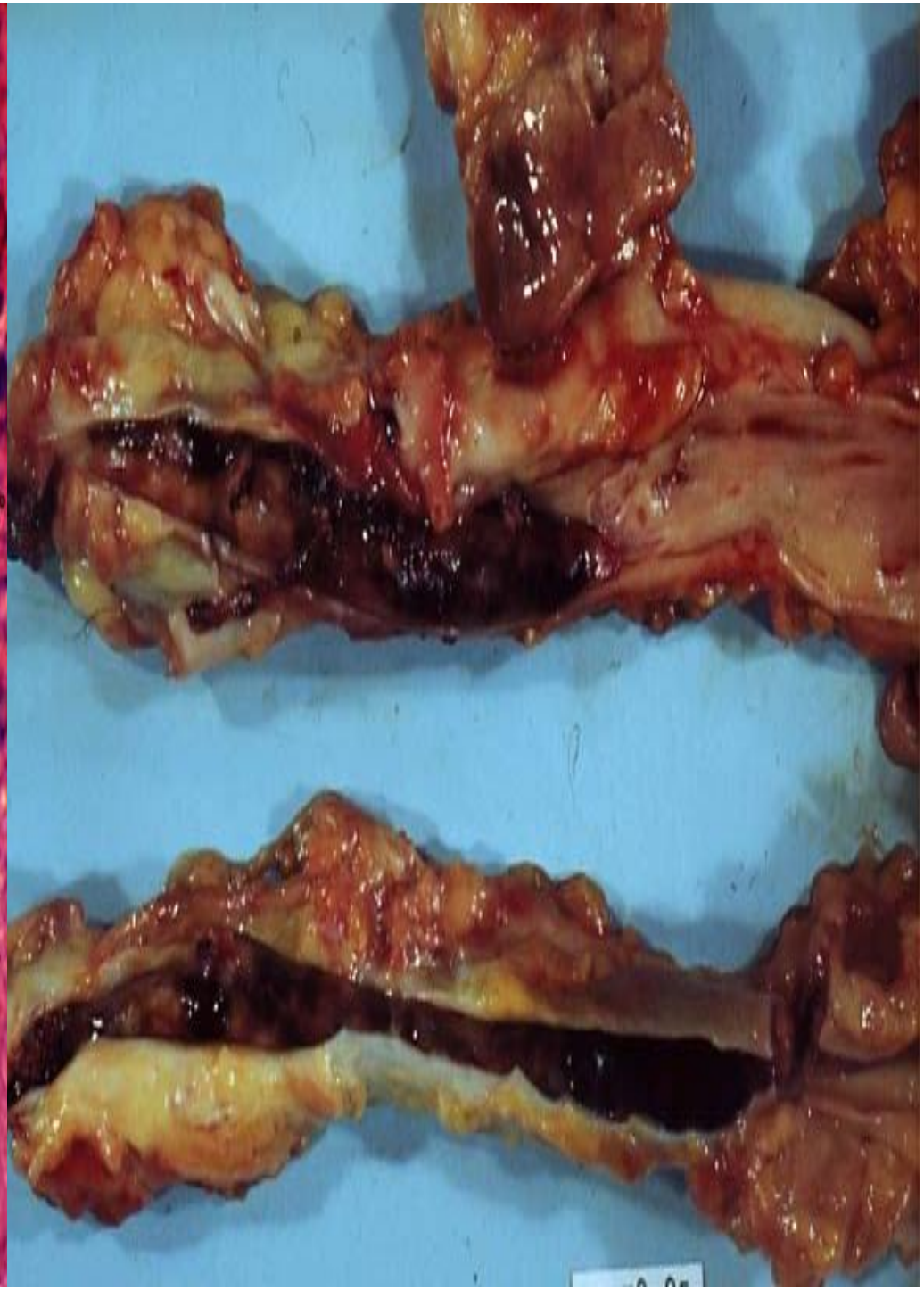
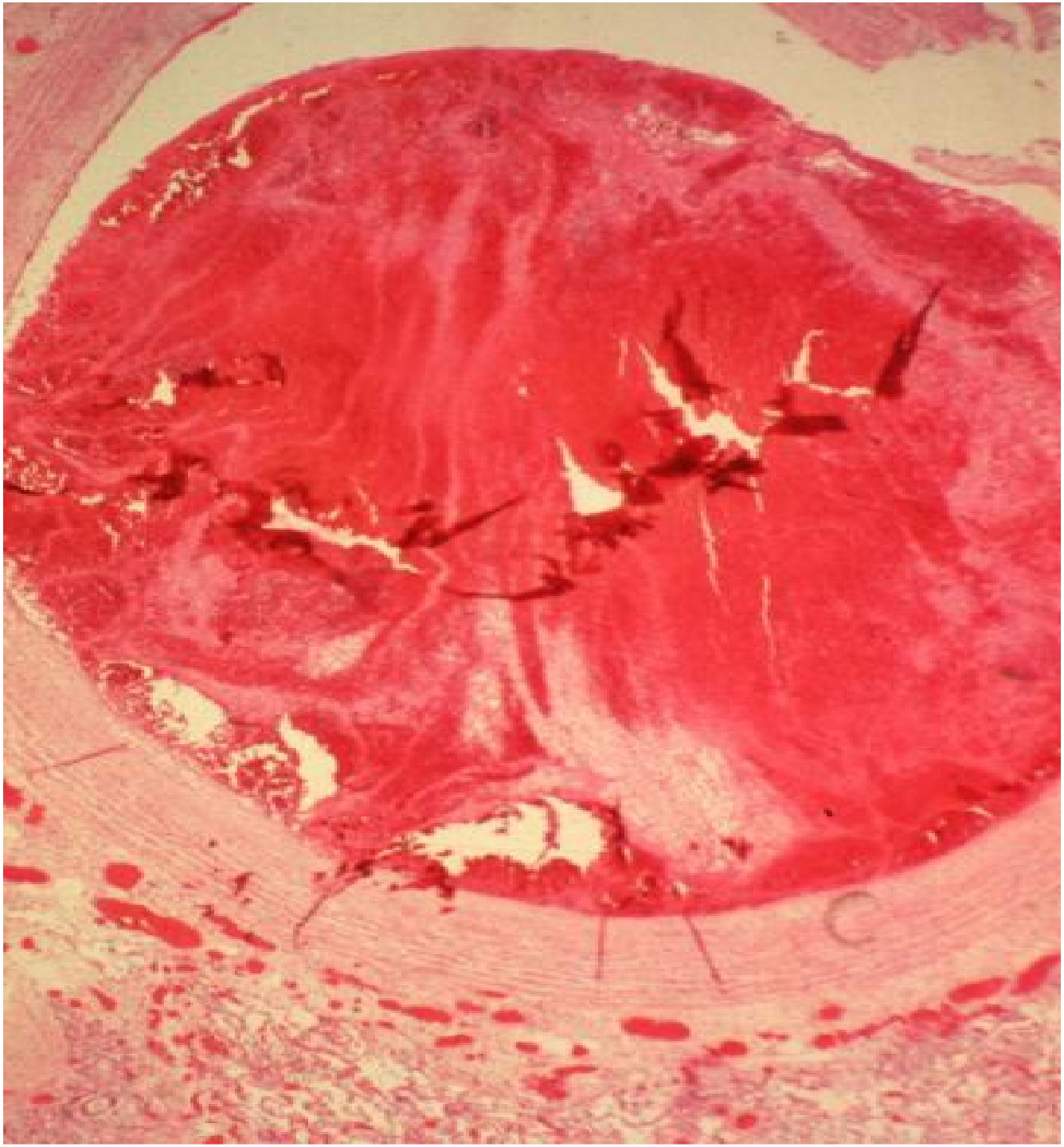
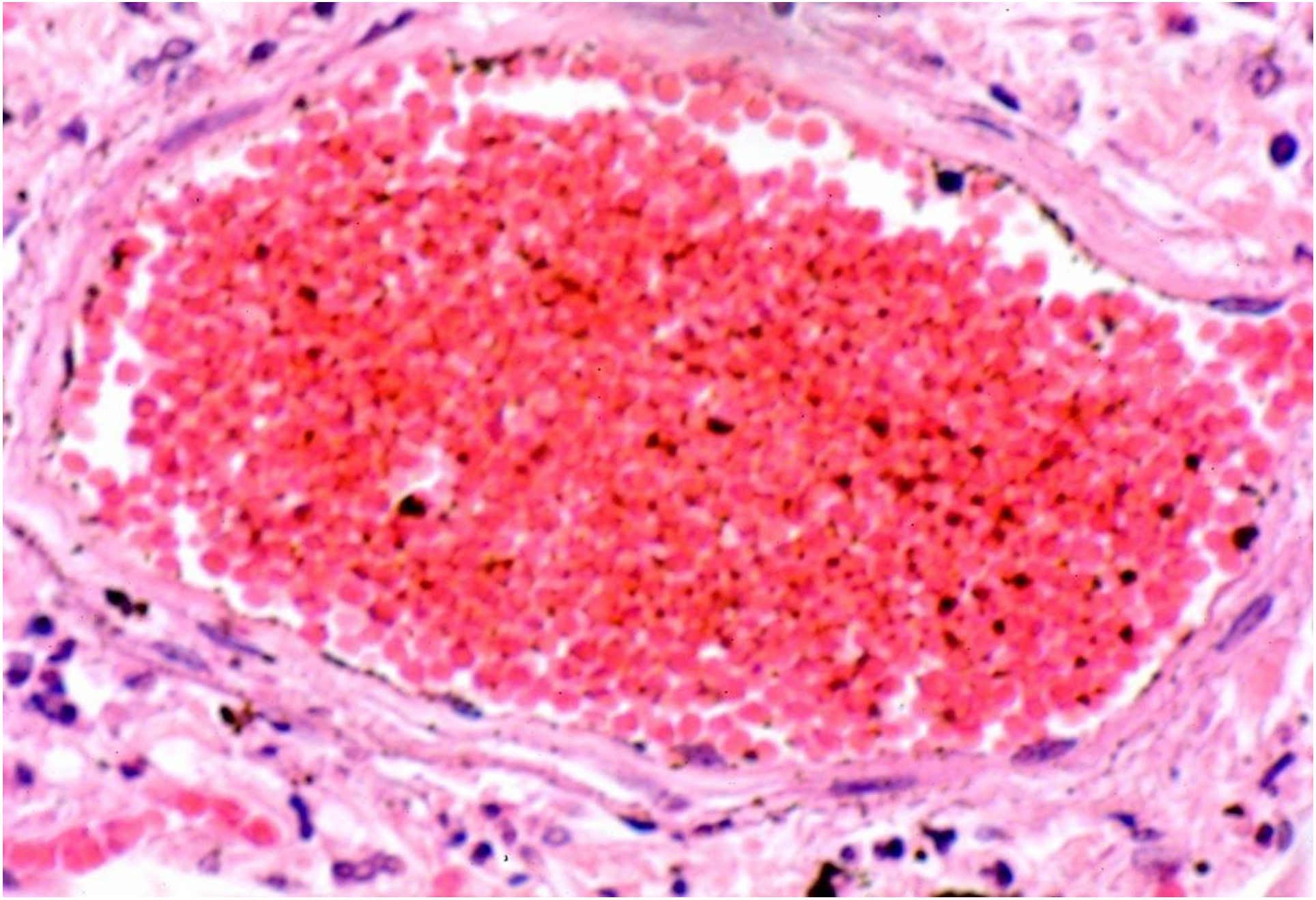


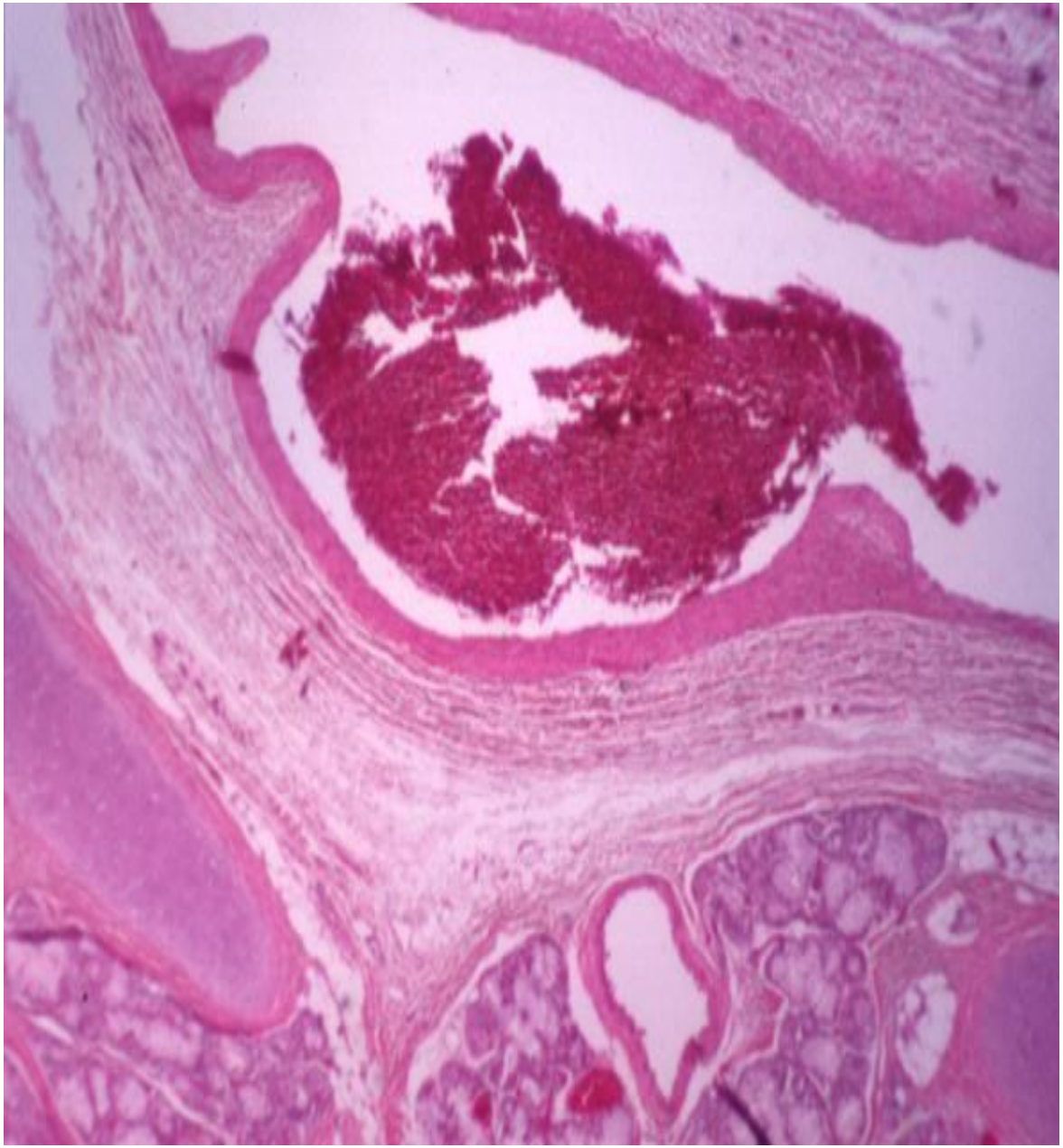




Coronary thromboembolism ligne zahn.



Embolism .



Embolism .

Clinical Aspects of Thrombosis

- **Arterial Thrombosis**
  - Primarily involves platelet deposition
  - Occlusive thrombi result in ischemia or infarction
  - Underlying vascular disease is a major predisposing factor
- **Venous Thrombosis**
  - Primarily involves fibrin deposition
  - Occlusive thrombi result in edema
  - Major predisposing factors are stasis and hypercoagulable states (acquired, inherited)
  - Embolization of venous thrombi is a major cause of morbidity and mortality

PREVENTION OF UNDESIRABLE CLOTS

- Substances used to prevent undesirable clots:
  - **Aspirin** – an antiprostaglandin that inhibits thromboxane A_2
  - **Heparin** – an anticoagulant used clinically for pre- and postoperative cardiac care
  - **Warfarin** – used for those prone to atrial fibrillation

HEMOSTASIS DISORDERS

- Disseminated Intravascular Coagulation (DIC): widespread clotting in intact blood vessels
- Residual blood cannot clot
- Blockage of blood flow and severe bleeding follows
- Most common as:
  - A complication of pregnancy
  - A result of septicemia or incompatible blood transfusions

PLATELET FUNCTION DEFECTS

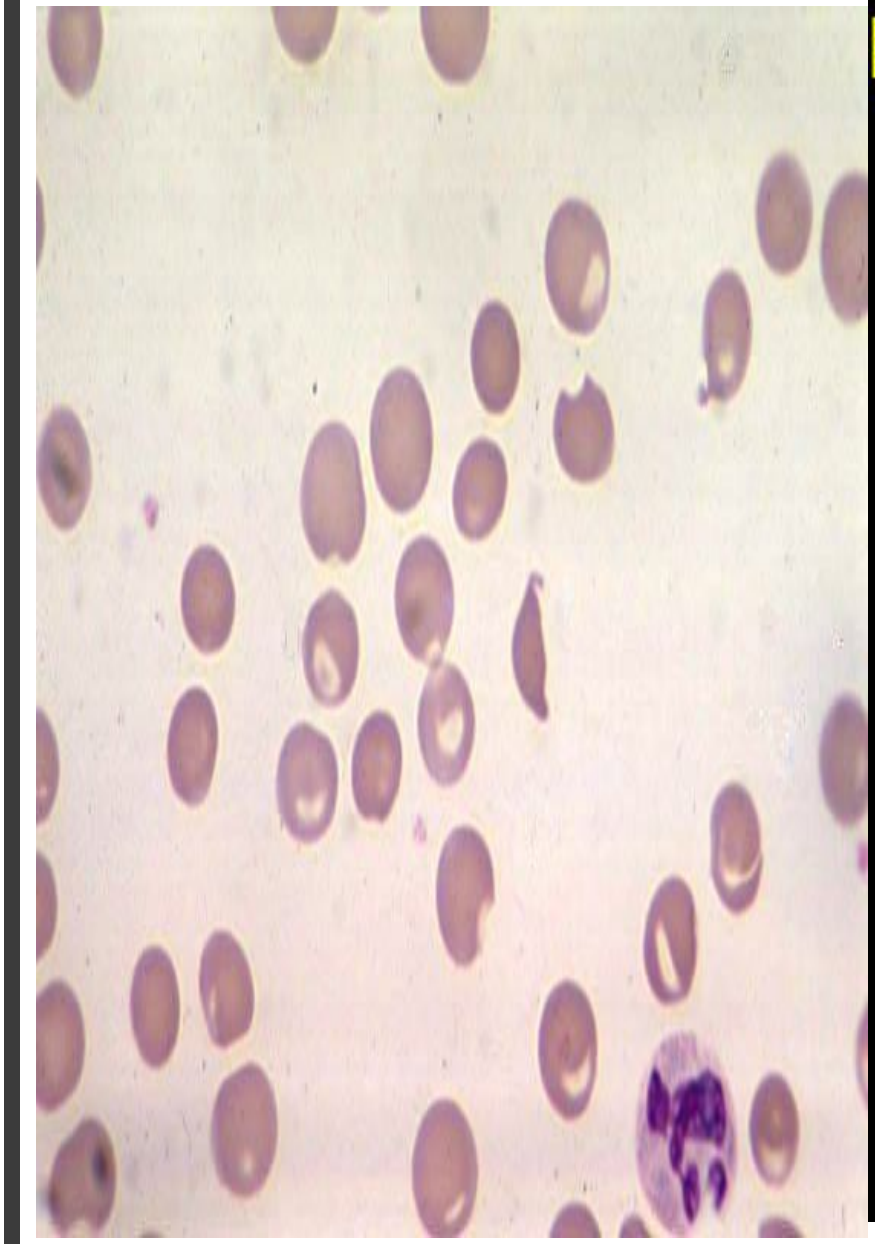
Prolonged Bleeding Time

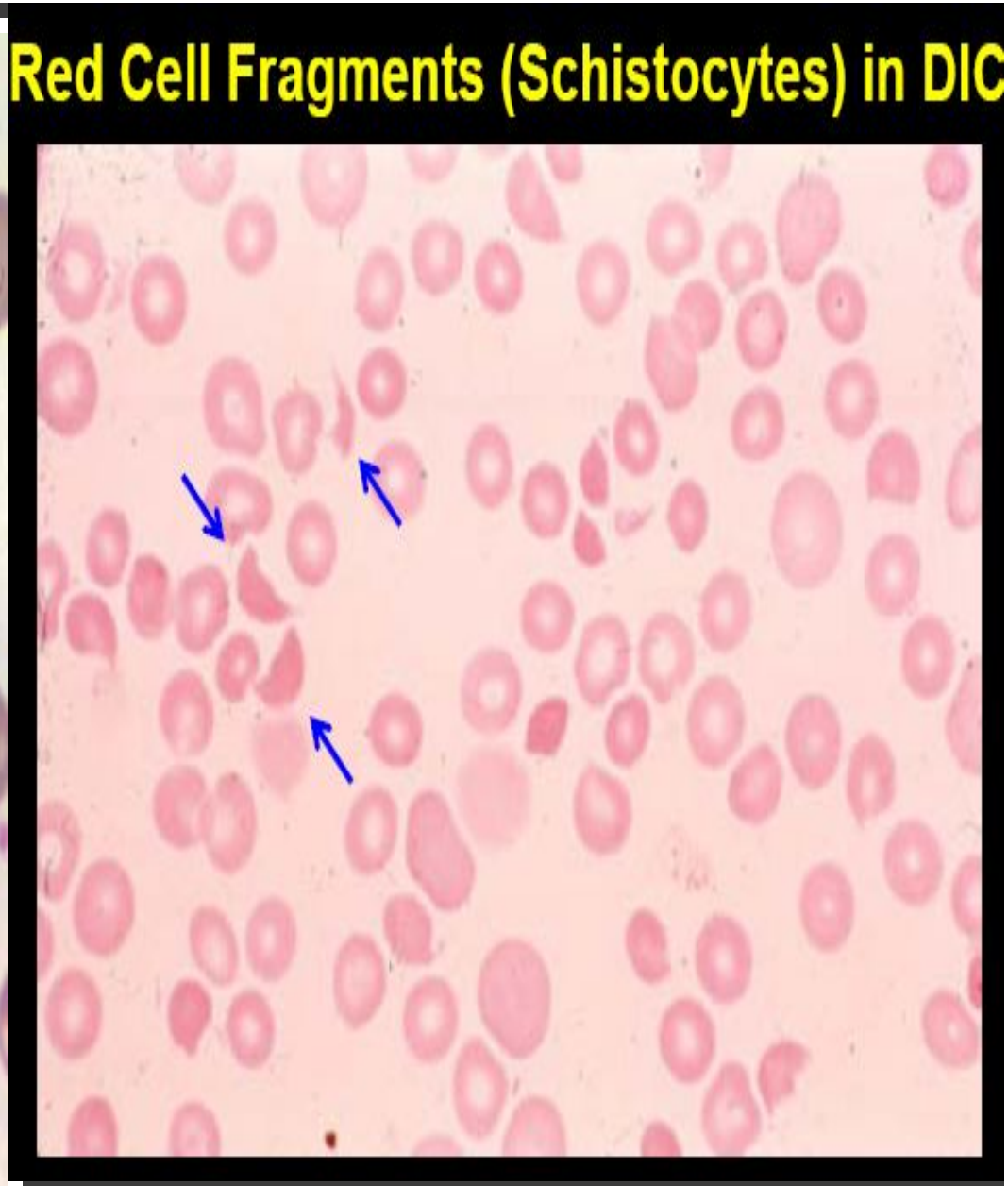
- Congenital
- Drugs
- Alcohol
- Uremia
- Hyperglobulinemias
- Fibrin/fibrinogen split products
- Thrombocythemia
- Cardiac Surgery

PLATELET FUNCTION DEFECTS

Platelet Adhesion

- **Bernard Soulier Disease**
  - Abnormal GPIb-IX Complex
  - Receptor for von Willebrand factor
  - Only adhesion mediator @ high shear stress
  - Tested by ability to aggregate platelets in presence of ristocetin
- **Von Willebrand disease**
  - Reduced or dysfunctional von Willebrand factor

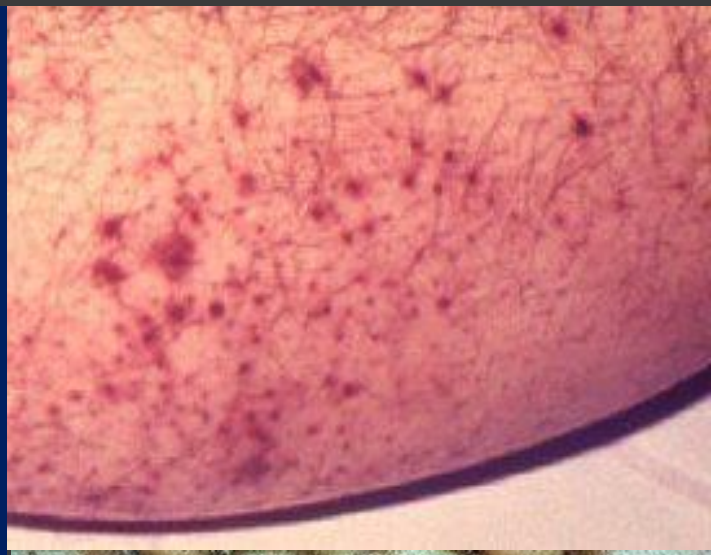


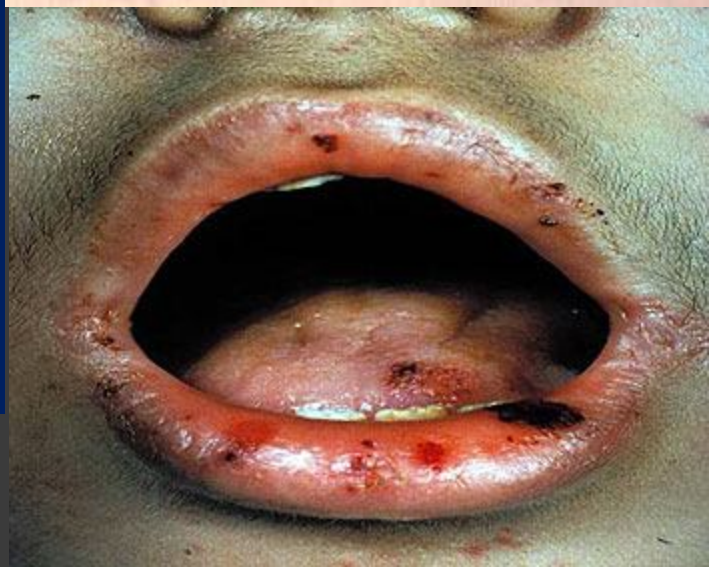


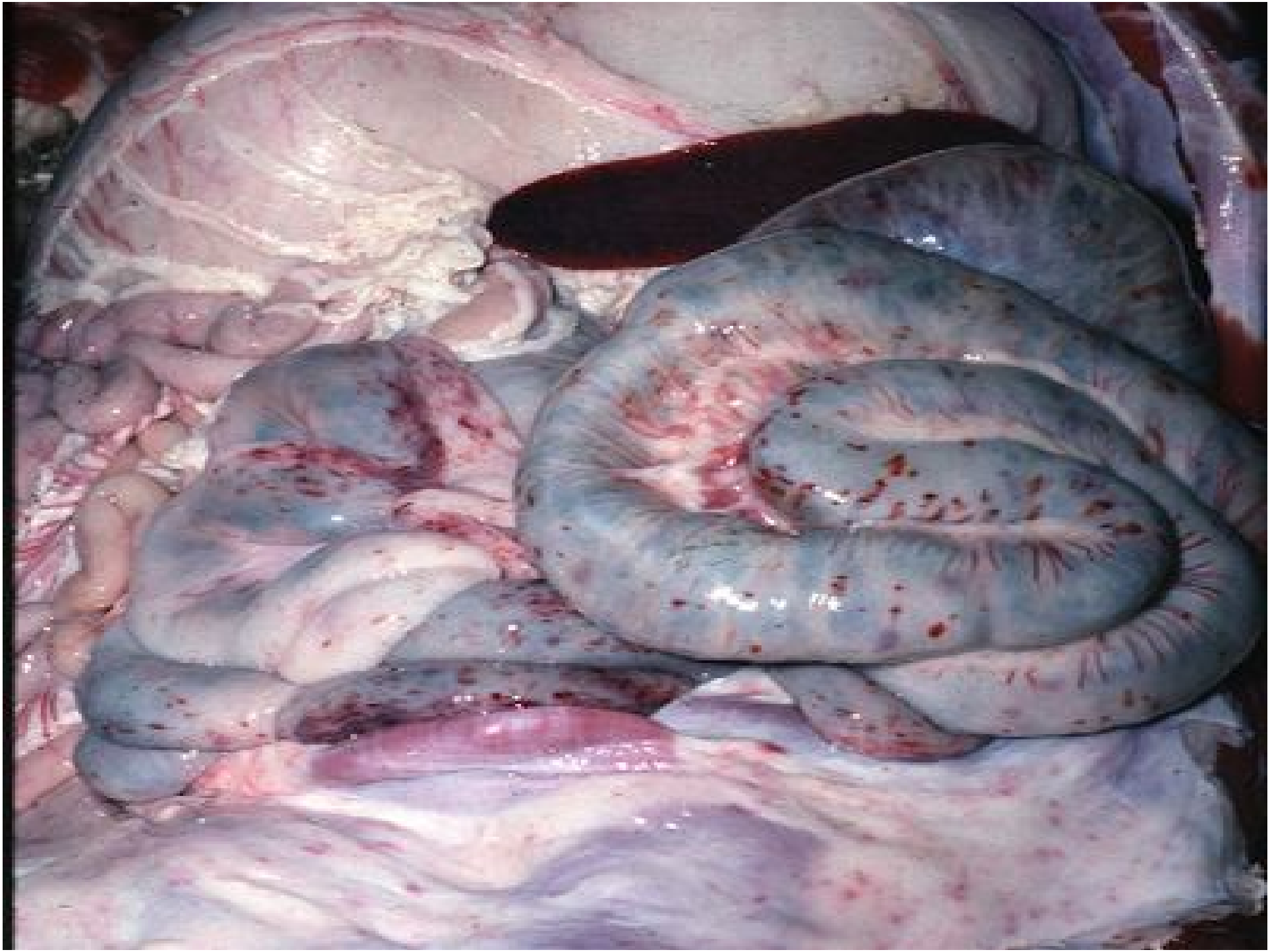
DIC.

HEMOSTASIS DISORDERS: BLEEDING DISORDERS

- **Thrombocytopenia** – condition where the number of circulating platelets is deficient
  - Patients show **petechiae** due to spontaneous, widespread hemorrhage
  - Caused by suppression or **destruction of bone marrow (e.g., malignancy, radiation**)
  - Platelet counts less than 50,000/mm^3 is diagnostic for this condition
  - Treated with whole blood transfusions





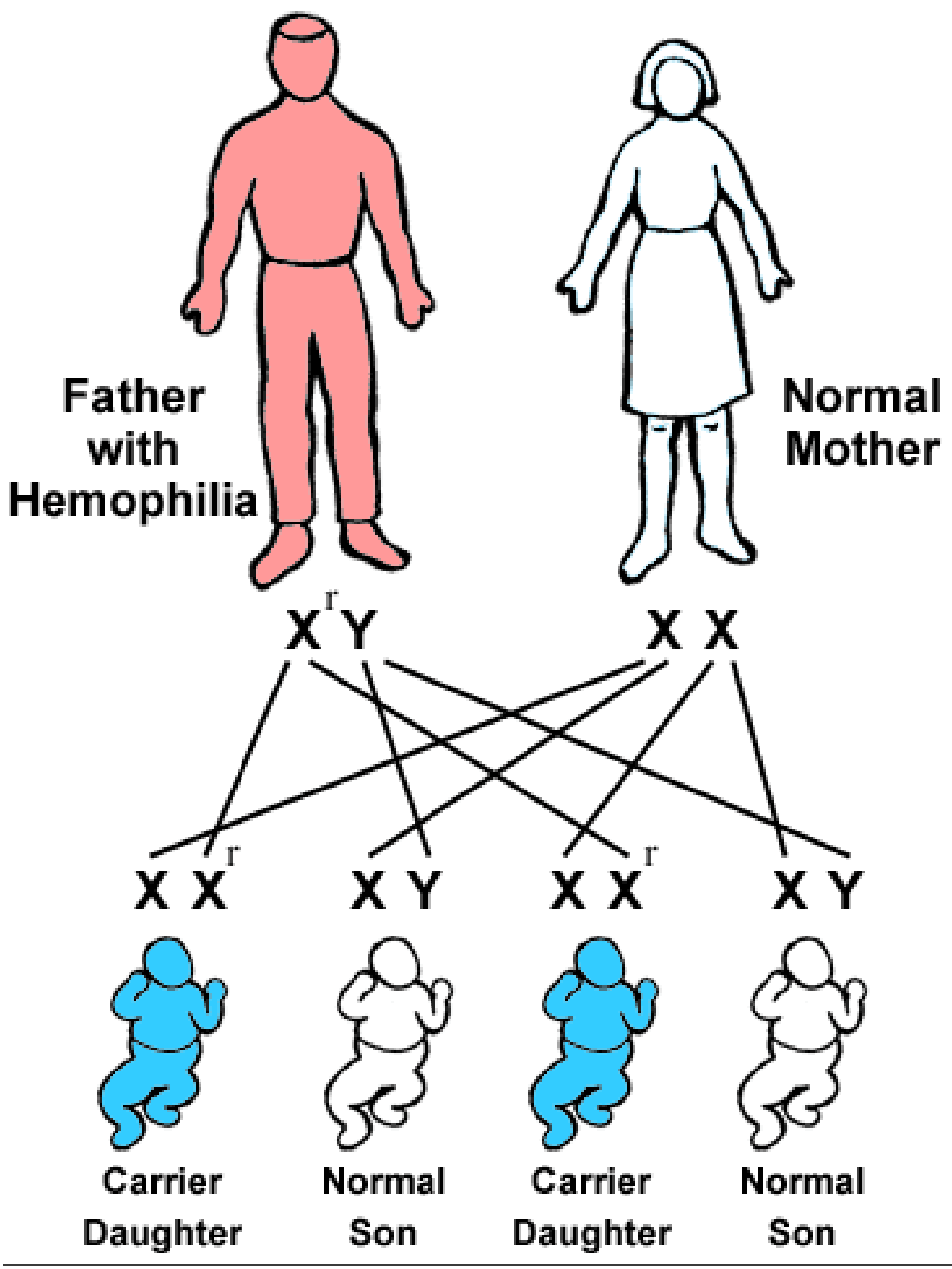


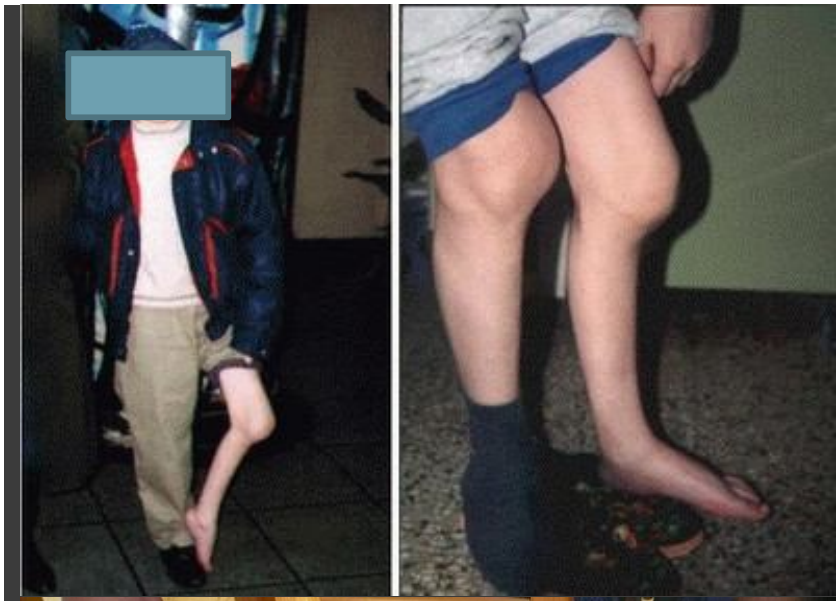
HEMOSTASIS DISORDERS: BLEEDING DISORDERS

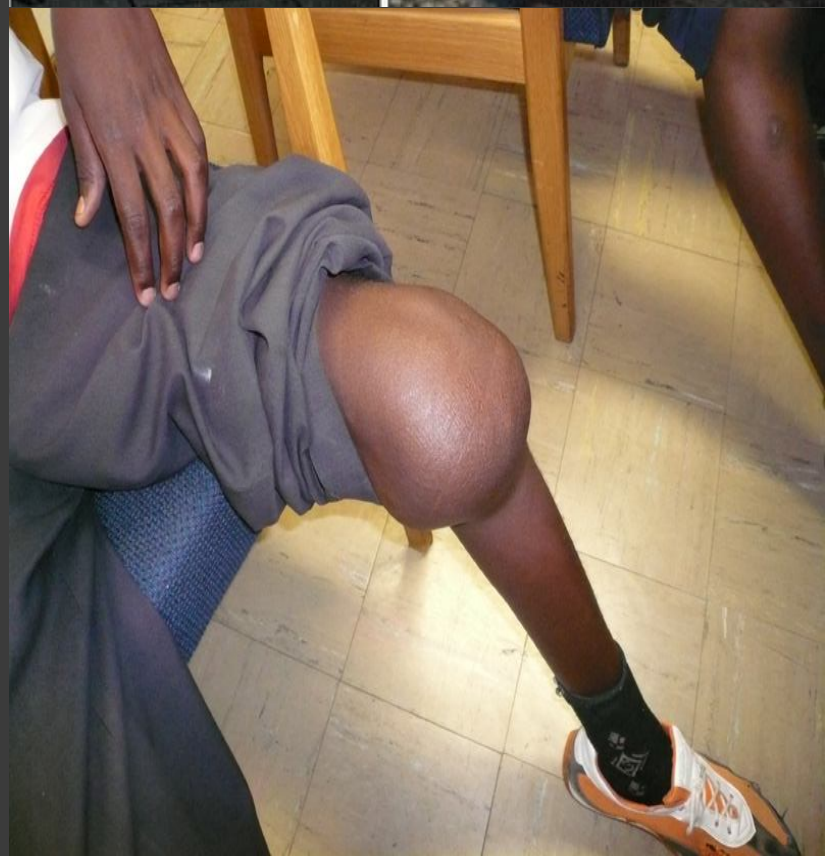
- Inability to synthesize procoagulants by the liver results in severe bleeding disorders
- Causes can range from vitamin K deficiency to hepatitis and cirrhosis
- Inability to absorb fat can lead to vitamin K deficiencies as it is a fat-soluble substance and is absorbed along with fat
- Liver disease can also prevent the liver from producing bile, which is required for fat and vitamin K absorption

HEMOSTASIS DISORDERS: BLEEDING DISORDERS

- **Hemophilias – hereditary bleeding disorders caused by lack of clotting factors**
  - **Hemophilia A – most common type (83% of all cases) due to a deficiency of factor VIII**
  - **Hemophilia B – due to a deficiency of factor IX**
  - **Hemophilia C – mild type, due to a deficiency of factor XI**


Father with Hemophilia
Normal Mother
X r Y
X X
X X r
X X r
X Y
X Y
Carrier Daughter
Normal Son
Carrier Daughter
Normal Son





Czar Nicholas II of Russia and his family, photographed c. 1916, showing his wife Alexandra (who was a carrier of hemophilia), his four daughters, and (in the foreground) his son Alexis, perhaps the most famous European royal with hemophilia. Corbis.

History's most famous carrier of the gene for hemophilia was Victoria (1819-1901), Queen of England and grandmother to most of the royalty in Europe. In 1853, Queen Victoria gave birth to her eighth child, Leopold, Duke of Albany, who had hemophilia and died at the age of 31 from internal bleeding after a fall.

Two of Queen Victoria's four daughters, Alice (b. 1843) and Beatrice (b. 1857), also carried the gene for hemophilia and subsequently transmitted the disease to three of Victoria's grandsons and to six of her great-grandsons.

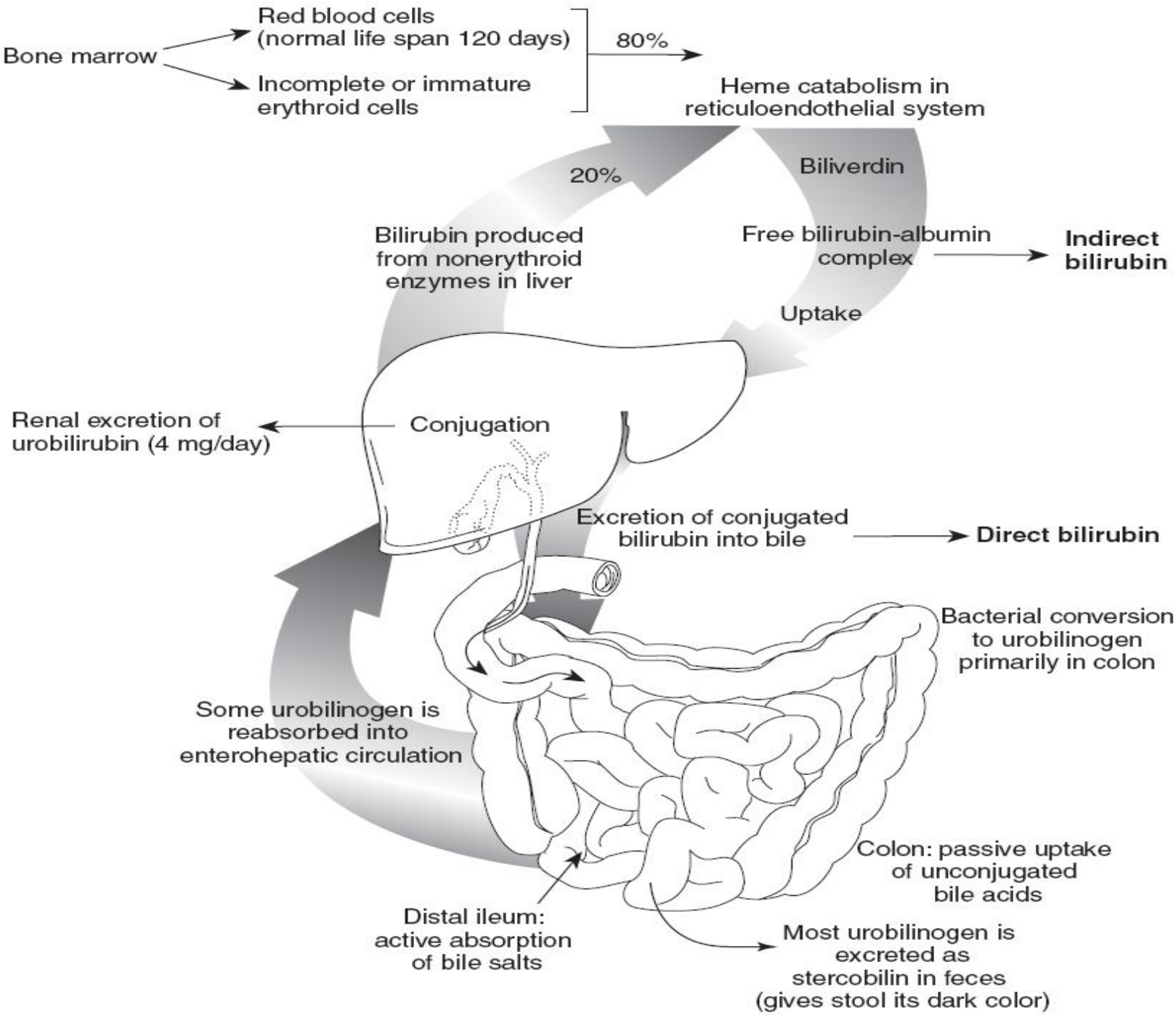
Alice's daughter Alexandra also was a carrier of hemophilia, and she transmitted the disease to her son Alexis (b. 1904), whose father was Czar Nicholas 11 (1868—1918) of Russia. Alexis is perhaps the most famous of the European royals with hemophilia. Alexis was the heir to his father's throne and his medical condition caused much anxiety in the royal household. Historians are still discussing the role Alexis's condition played in the Russian revolution of 1918.

HEMOSTASIS DISORDERS: BLEEDING DISORDERS

- Symptoms include prolonged bleeding and painful and disabled joints
- Treatment is with blood transfusions and the injection of missing factors

- **hemophilia A (factor VIII deficiency),**
- **hemophilia B (factor IX deficiency, Christmas disease)**

BILIRUBIN ISSUES

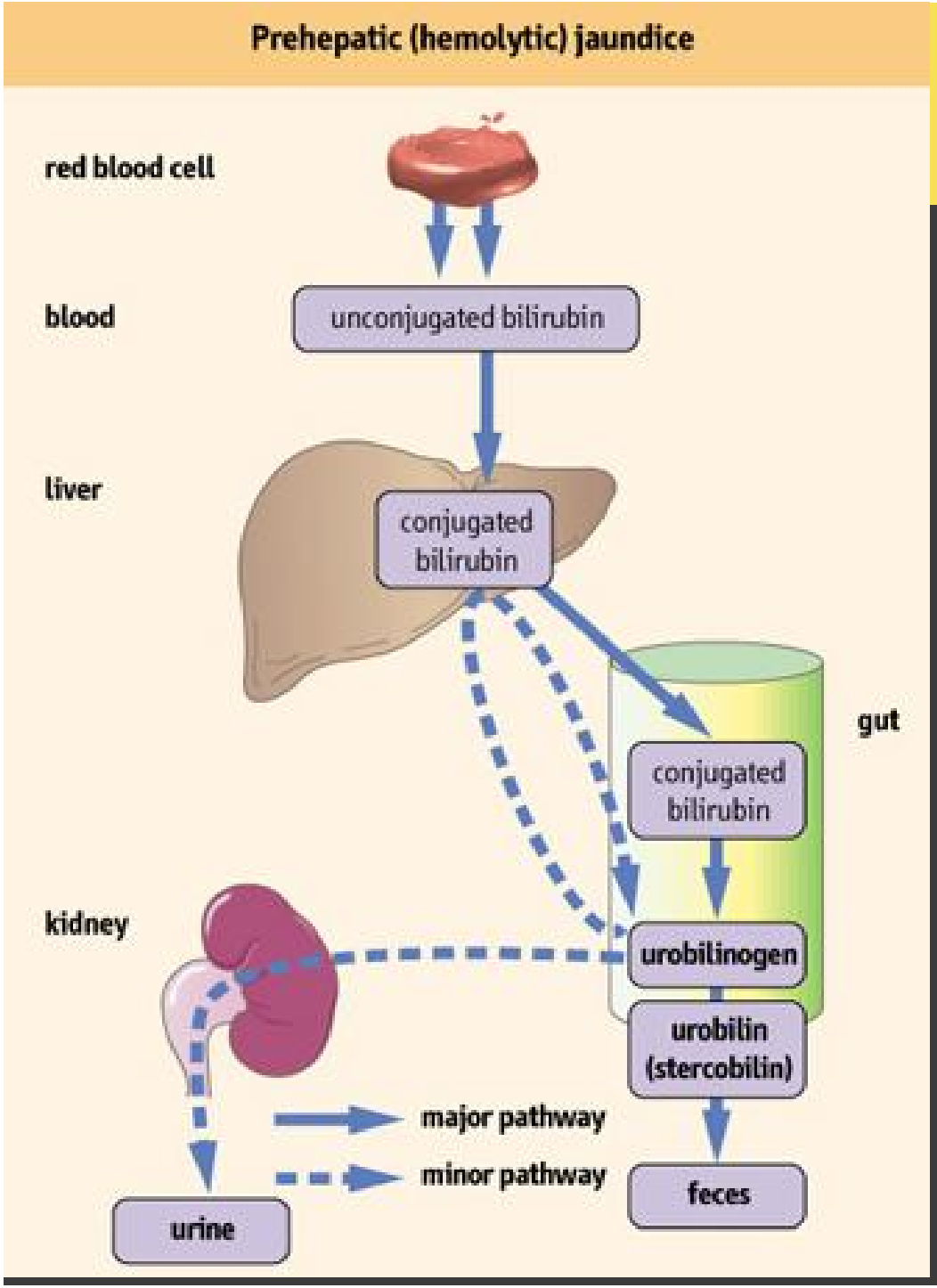

Bone marrow
Red blood cells
(normal life span 120 days)
Incomplete or immature
erythroid cells
80%
Heme catabolism in
reticuloendothelial system
Biliverdin
20%
Bilirubin produced
from nonerythroid
enzymes in liver
Free bilirubin-albumin
complex
Indirect
bilirubin
Uptake
Renal excretion of
urobilirubin (4 mg/day)
Conjugation
Excretion of conjugated
bilirubin into bile
Direct bilirubin
Bacterial conversion
to urobilinogen
primarily in colon
Some urobilinogen is
reabsorbed into
enterohepatic circulation
Colon: passive uptake
of unconjugated
bile acids
Distal ileum:
active absorption
of bile salts
Most urobilinogen is
excreted as
stercobilin in feces
(gives stool its dark color)

HYPERBILIRUBINEMIA

- Increased plasma concentrations of bilirubin (> 3 mg/dL) occurs when there is an imbalance between its production and excretion
- Recognized clinically as jaundice

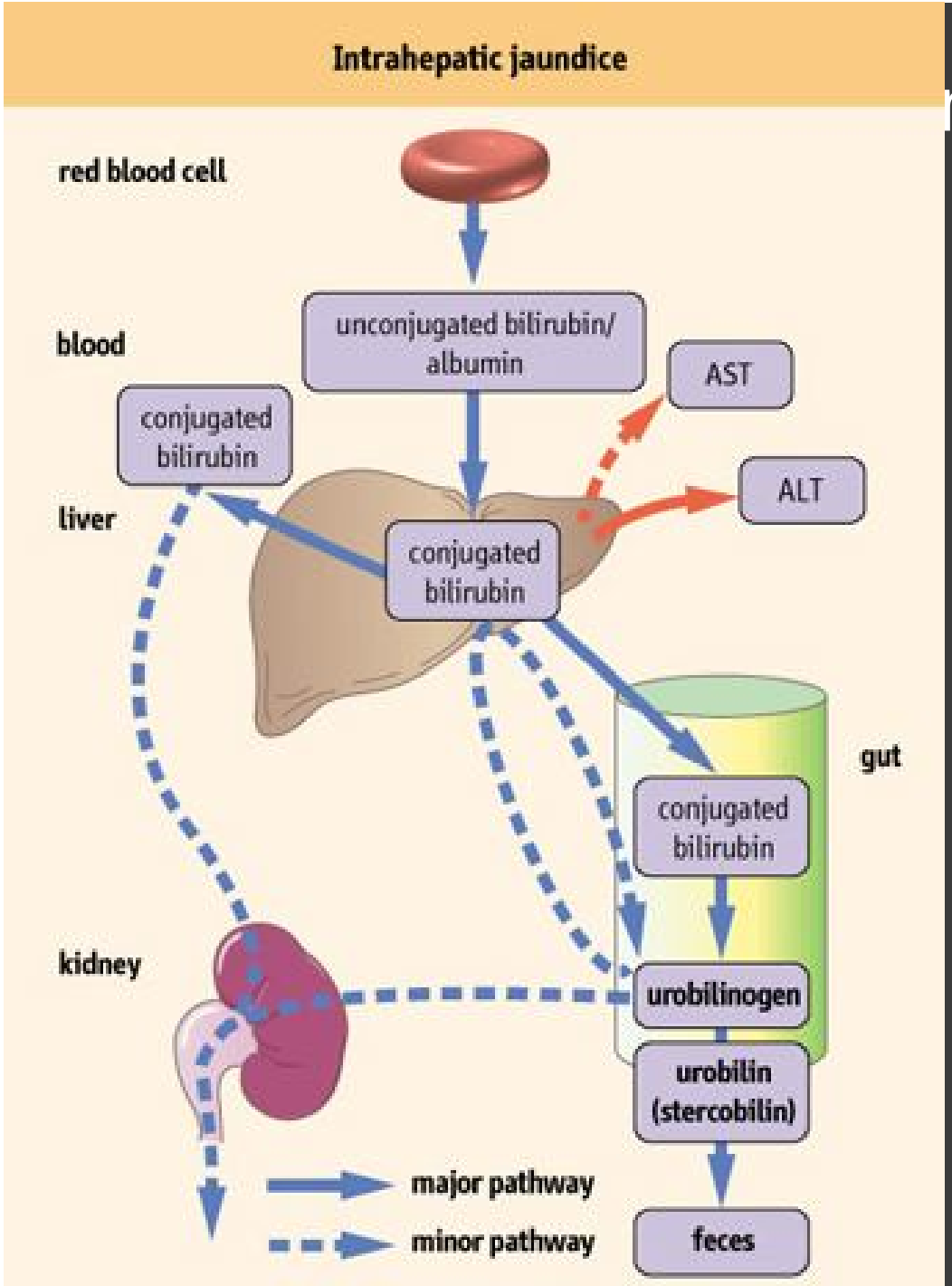
The causes of jaundice

Type	Cause	Clinical example	Frequency
Prehepatic	hemolysis	autoimmune abnormal hemoglobin	uncommon depends on region
intrahepatic	infection	hepatitis A, B, C	common/very common
	chemical/drug	acetaminophen alcohol	common common
	genetic errors: bilirubin metabolism	Gilbert's syndrome Crigler–Najjar syndrome Dubin–Johnson syndrome Rotor's syndrome	1 in 20 very rare very rare very rare
	genetic errors: specific proteins	Wilson's disease α_1 antitrypsin	1 in 200 000 1 in 1000 with genotype
	autoimmune	chronic active hepatitis	uncommon/ rare
	neonatal	physiologic	very common
Posthepatic	intrahepatic bile ducts	drugs primary bilary cirrhosis cholangitis	common uncommon common
	extrahepatic bile ducts	gall stones pancreatic tumor cholangiocarcinoma	very common uncommon rare



Prehepatic (hemolytic) jaundice

- Results from excess production of bilirubin (beyond the livers ability to conjugate it) following hemolysis
- Excess RBC lysis is commonly the result of autoimmune disease; hemolytic disease of the newborn (Rh- or ABO-incompatibility); structurally abnormal RBCs (Sickle cell disease); or breakdown of extravasated blood
- High plasma concentrations of unconjugated bilirubin (normal concentration ~0.5 mg/dL)

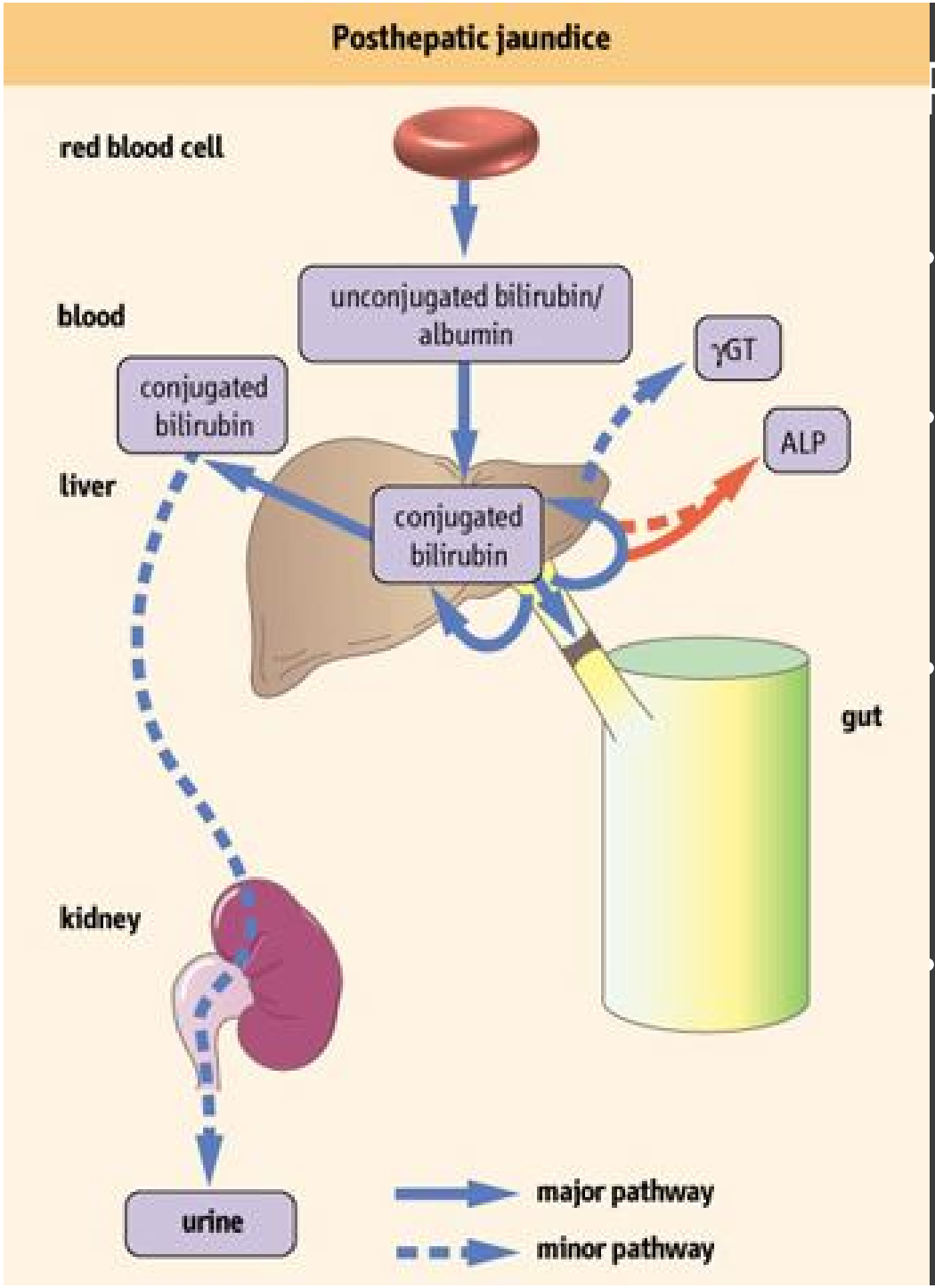


ntrahepatic jaundice

Impaired uptake, conjugation, or secretion of bilirubin

Reflects a generalized liver (hepatocyte) dysfunction

In this case, hyperbilirubinemia is usually accompanied by other abnormalities in biochemical markers of liver function



Posthepatic jaundice

- Caused by an obstruction of the biliary tree
- Plasma bilirubin is conjugated, and other biliary metabolites, such as bile acids accumulate in the plasma
- Characterized by pale colored stools (absence of fecal bilirubin or urobilin), and dark urine (increased conjugated bilirubin)
- In a complete obstruction, urobilin is absent from the urine

DIAGNOSES OF JAUNDICE

Differential diagnosis of jaundice

	Prehepatic	Intrahepatic	Posthepatic
conjugated bilirubin	absent	↑	↑
AST or ALT	normal	↑	normal
ALP	normal	normal	↑
urine bilirubin	absent	present	present
urine urobilinogen	present	present	absent

NEONATAL JAUNDICE

- Common, particularly in premature infants
- Transient (resolves in the first 10 days)
- Due to immaturity of the enzymes involved in bilirubin conjugation
- High levels of unconjugated bilirubin are toxic to the newborn – due to its hydrophobicity it can cross the blood-brain barrier and cause a type of mental retardation known as kernicterus
- If bilirubin levels are judged to be too high, then phototherapy with UV light is used to convert it to a water soluble, non-toxic form
- If necessary, exchange blood transfusion is used to remove excess bilirubin
- Phenobarbital is oftentimes administered to Mom prior to an induced labor of a premature infant – crosses the placenta and induces the synthesis of UDP glucuronyl transferase
- Jaundice within the first 24 hrs of life or which takes longer then 10 days to resolve is usually pathological and needs to be further investigated

CAUSES OF HYPERBILIRUBINEMIA

The causes of jaundice

Type	Cause	Clinical example	Frequency
Prehepatic	hemolysis	autoimmune abnormal hemoglobin	uncommon depends on region
intrahepatic	infection	hepatitis A, B, C	common/very common
	chemical/drug	acetaminophen alcohol	common common
	genetic errors: bilirubin metabolism	Gilbert's syndrome Crigler–Najjar syndrome Dubin–Johnson syndrome Rotor's syndrome	1 in 20 very rare very rare very rare
	genetic errors: specific proteins	Wilson's disease α_1 antitrypsin	1 in 200 000 1 in 1000 with genotype
	autoimmune	chronic active hepatitis	uncommon/ rare
	neonatal	physiologic	very common
Posthepatic	intrahepatic bile ducts	drugs primary bilary cirrhosis cholangitis	common uncommon common
	extrahepatic bile ducts	gall stones pancreatic tumor cholangiocarcinoma	very common uncommon rare

Gilbert's Syndrome

- **Benign liver disorder**

- **½ of the affected individuals inherited it**

- **Characterized by mild, fluctuating increases in unconjugated bilirubin caused by decreased ability of the liver to conjugate bilirubin – often correlated with fasting or illness**

The source of this hyperbilirubinemia is reduced activity of the enzyme **glucuronyltransferase** which. conjugates bilirubin and some other lipophilic molecules.

- **Males more frequently affected then females**

- **Onset of symptoms in teens, early 20's or 30's**

- **Can be treated with small doses of phenobarbital to stimulate UDP glucuronyl transferase activity**

GILBERT'S SYNDROME

Alternative, less common names for this disorder include:

- Familial benign unconjugated hyperbilirubinaemia
- Constitutional liver dysfunction
- Familial non-hemolytic non-obstructive jaundice
- Icterus intermittens juvenilis
- Low-grade chronic hyperbilirubinemia
- Unconjugated benign bilirubinemia
- Morbus

Crigler-Najjar Syndrome

- Autosomal recessive
- Extremely rare < 200 cases worldwide – gene frequency is < 1:1000
- High incidence in the “plain people of Pennsylvania” (Amish and Mennonites)
- Characterized by a complete absence or **marked reduction in bilirubin conjugation**
- Present with a **severe unconjugated hyperbilirubinemia that usually presents at birth**
- Afflicted individuals are at a high risk **for kernicterus**
- Condition is fatal when the enzyme is completely absent
- Treated by phototherapy (10-12 hrs/day) and liver transplant by age 5

Dubin-Johnson and Rotor's Syndromes

- Characterized by impaired biliary secretion of conjugated bilirubin

- Present with a conjugated hyperbilirubinemia that is usually mild

LEUKOCYTES DISORDERS

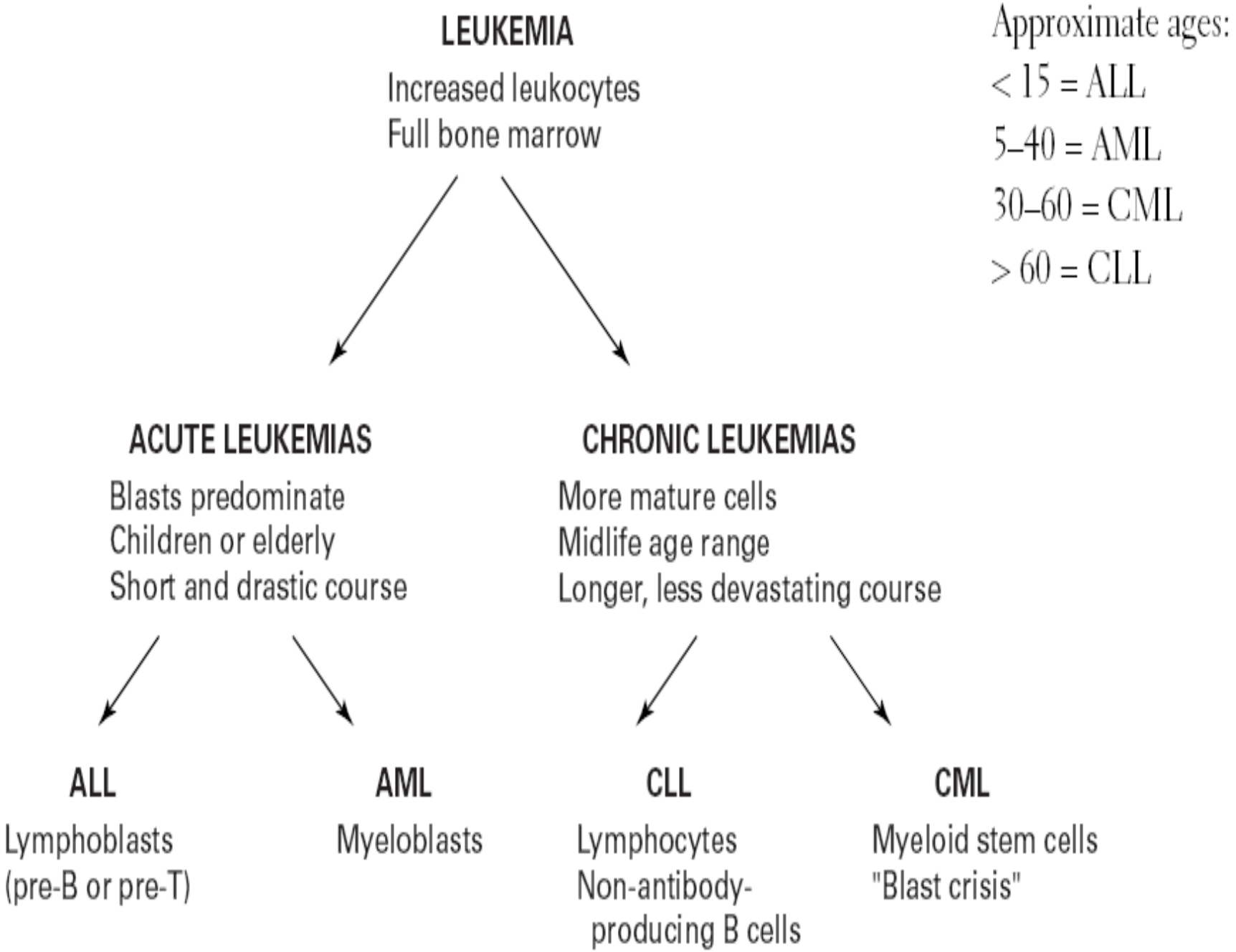
LEUKOCYTES DISORDERS: LEUKEMIAS

- Leukemia refers to cancerous conditions involving WBCs
- Acute in kids , chronic in elderly

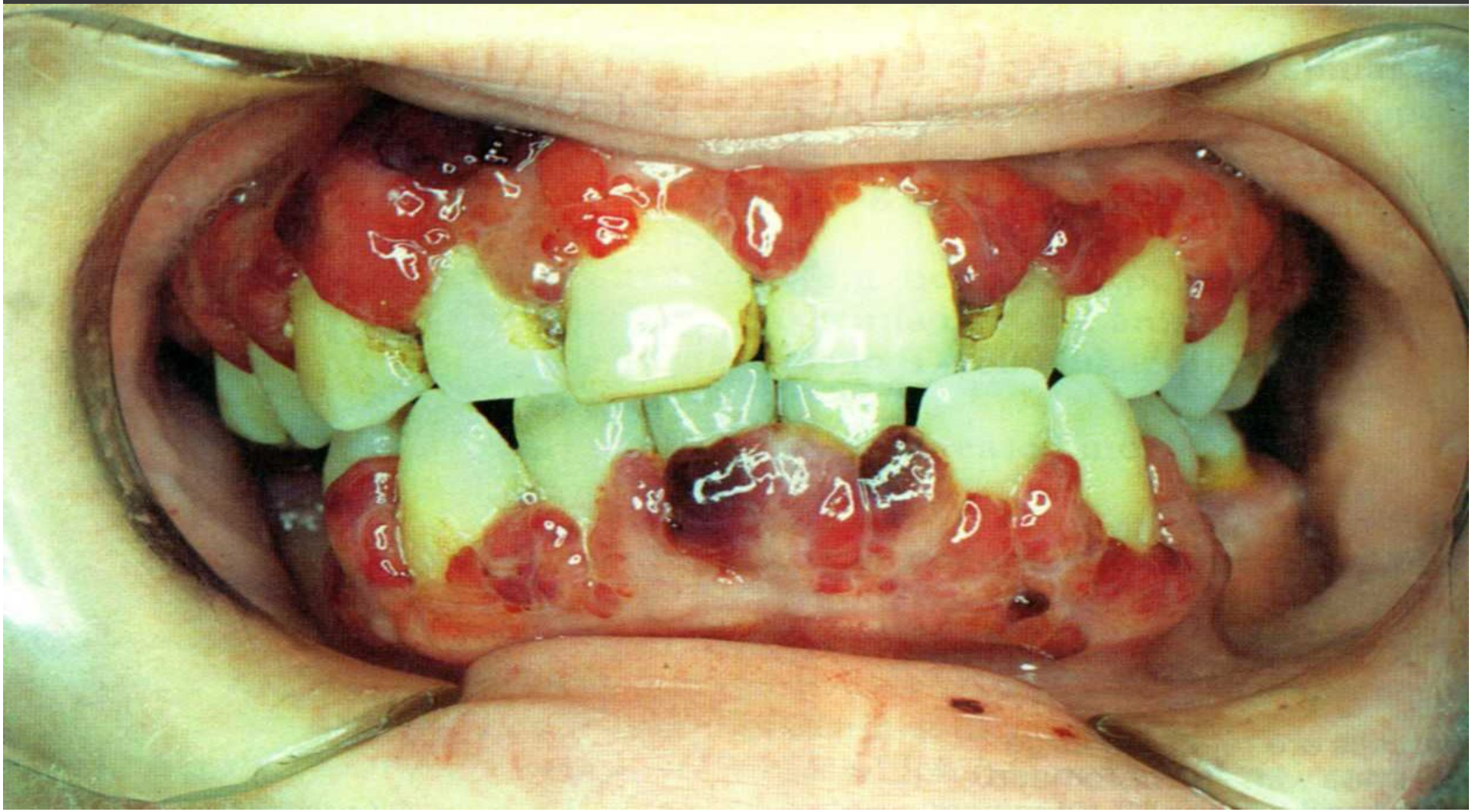
- Leukemias are named according to the abnormal WBCs involved
  - **Myelocytic leukemia** – involves myeloblasts [AML.CML]
  - **Lymphocytic leukemia** – involves lymphocytes [ALL,CLL

- Acute leukemia involves ***blast-type cells*** and primarily affects children

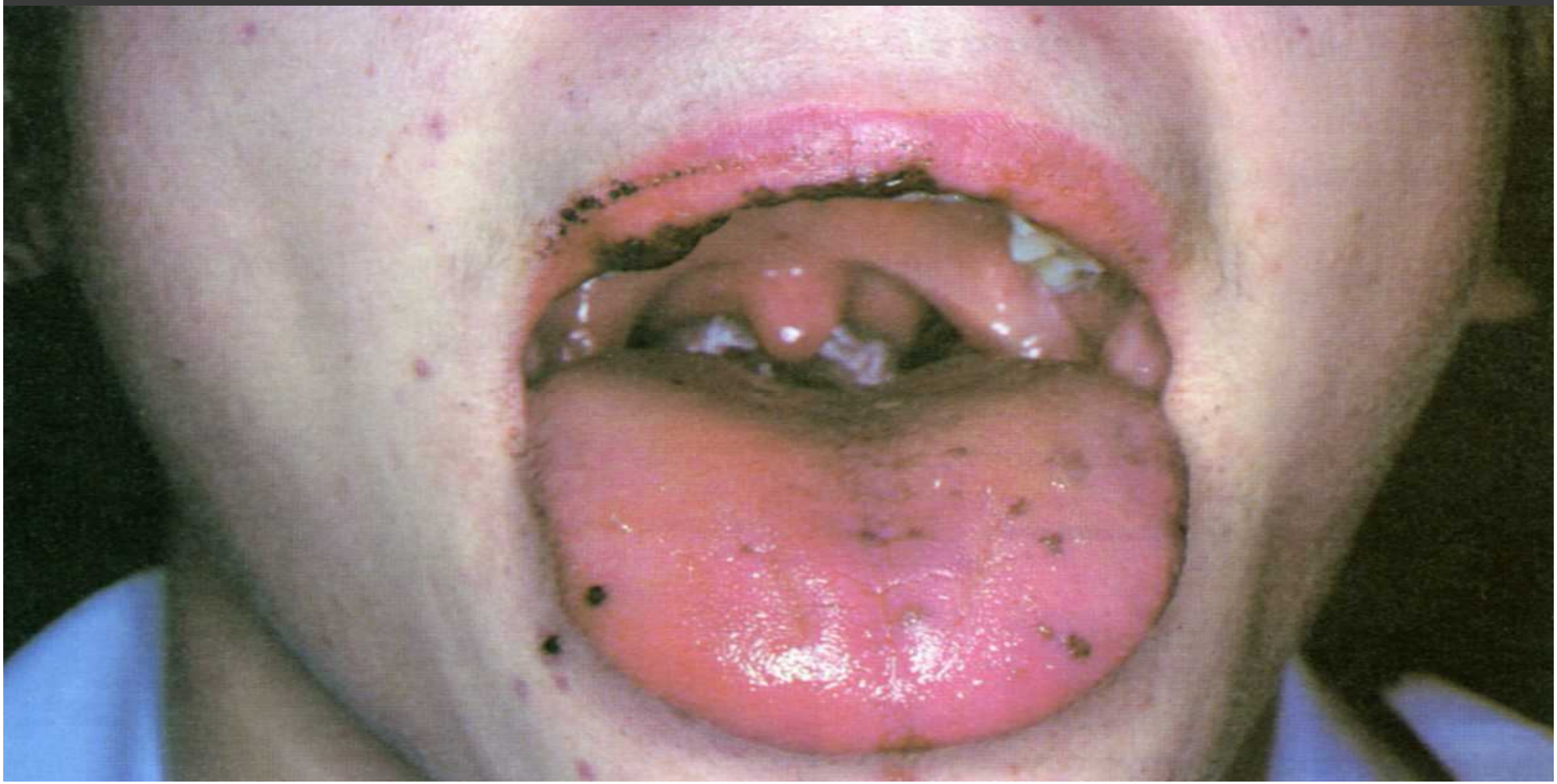
- Chronic leukemia is more prevalent in older people

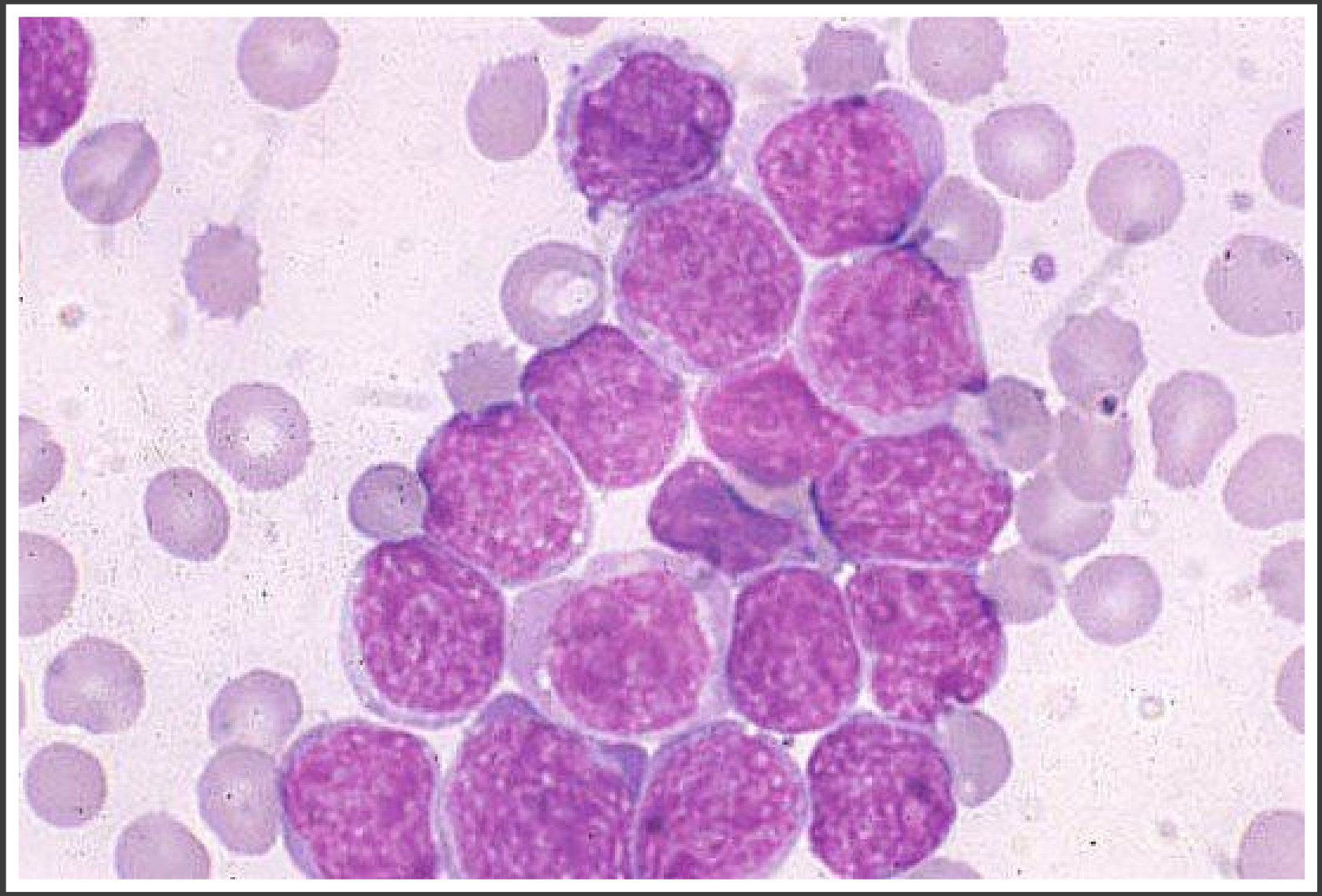

LEUKEMIA
Increased leukocytes
Full bone marrow
Approximate ages:
< 15 = ALL
5–40 = AML
30–60 = CML
> 60 = CLL
ACUTE LEUKEMIAS
Blasts predominate
Children or elderly
Short and drastic course
CHRONIC LEUKEMIAS
More mature cells
Midlife age range
Longer, less devastating course
ALL
Lymphoblasts
(pre-B or pre-T)
AML
Myeloblasts
CLL
Lymphocytes
Non-antibody-producing B cells
CML
Myeloid stem cells
"Blast crisis"

GUM HYPERTROPHY AND HEMORRHAGE IN ACUTE MONOCYTIC LEUKEMIA



MUCOSAL HEMORRHAGE DUE TO SEVERE THROMBOCYTOPENIA IN ACUTE LEUKEMIA

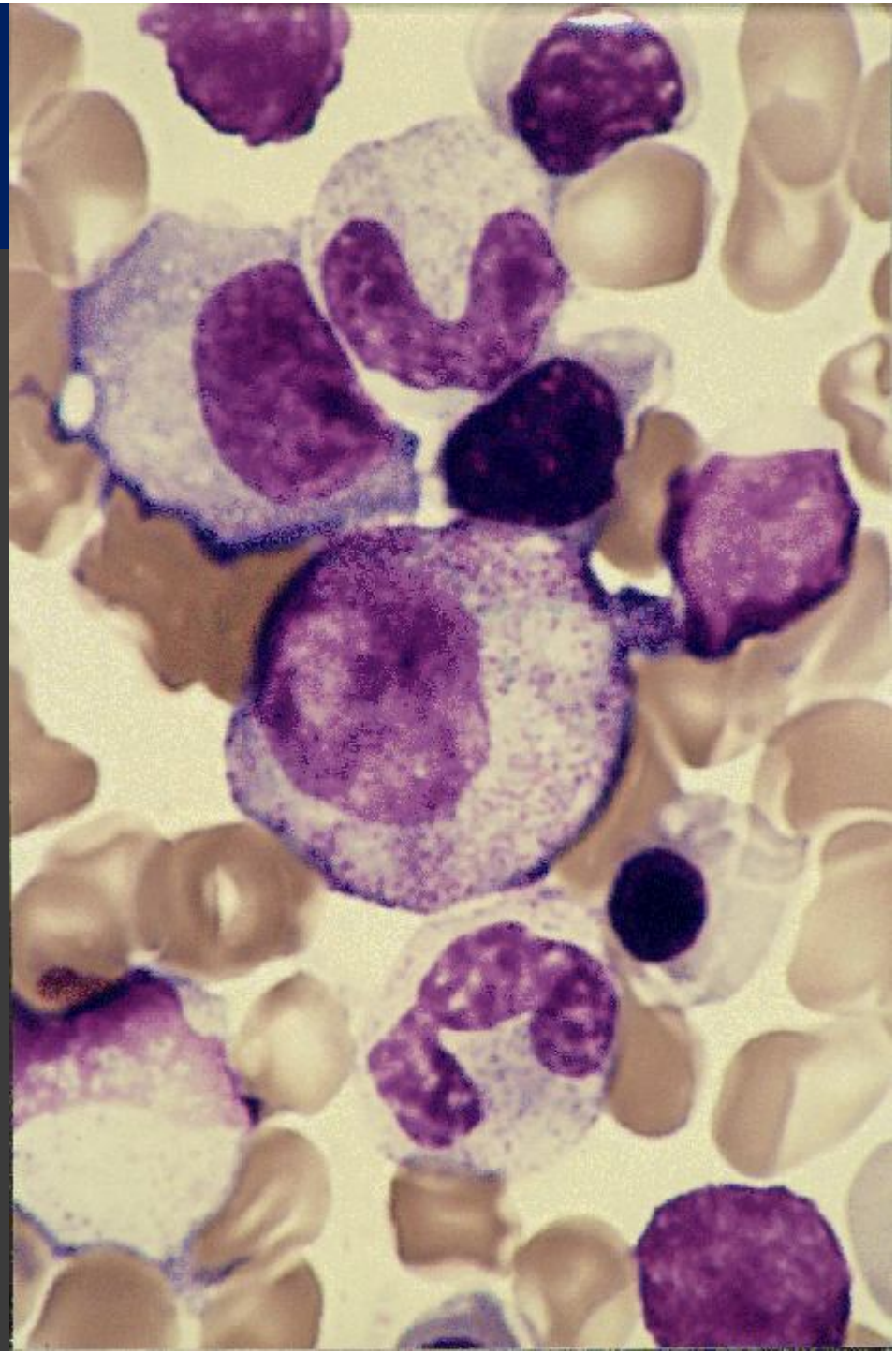




ALL.

LEUKEMIA

- Immature WBCs are found in the bloodstream in all leukemias
- Bone marrow becomes totally occupied with cancerous leukocytes
- The WBCs produced, though numerous, are not functional
- Death is caused by internal hemorrhage and overwhelming infections
- Treatments include irradiation, antileukemic drugs, and bone marrow transplants

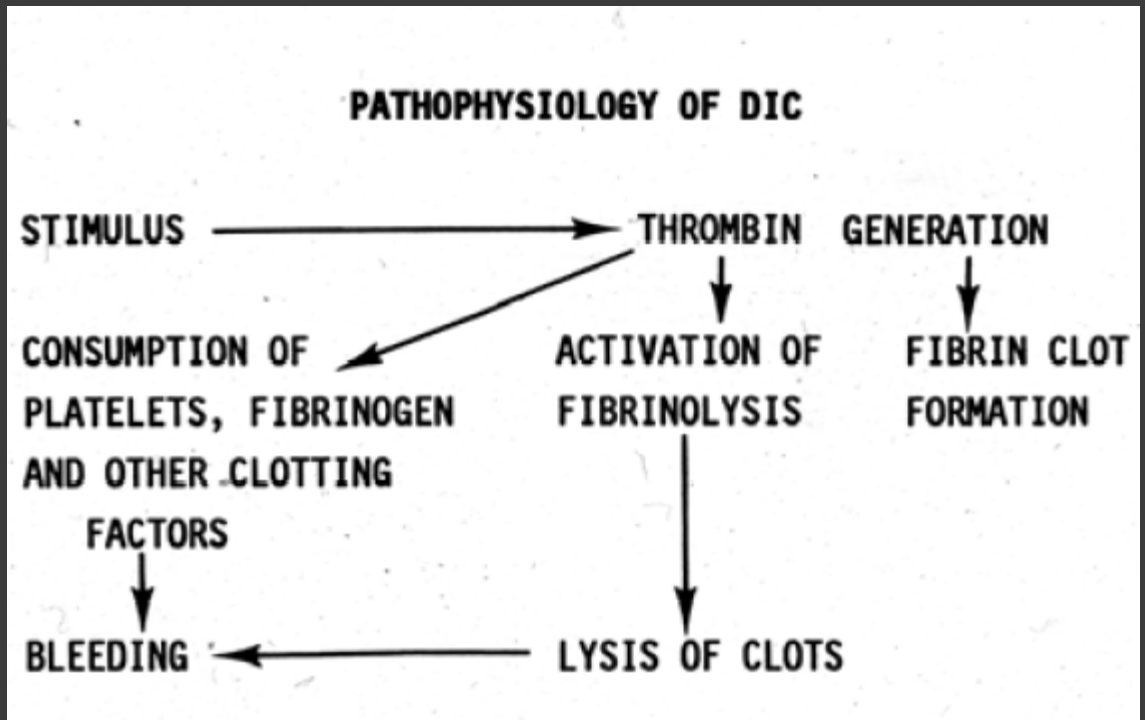


DIC — Activation of coagulation cascade leading to microthrombi and global consumption of platelets, fibrin, and coagulation factors.

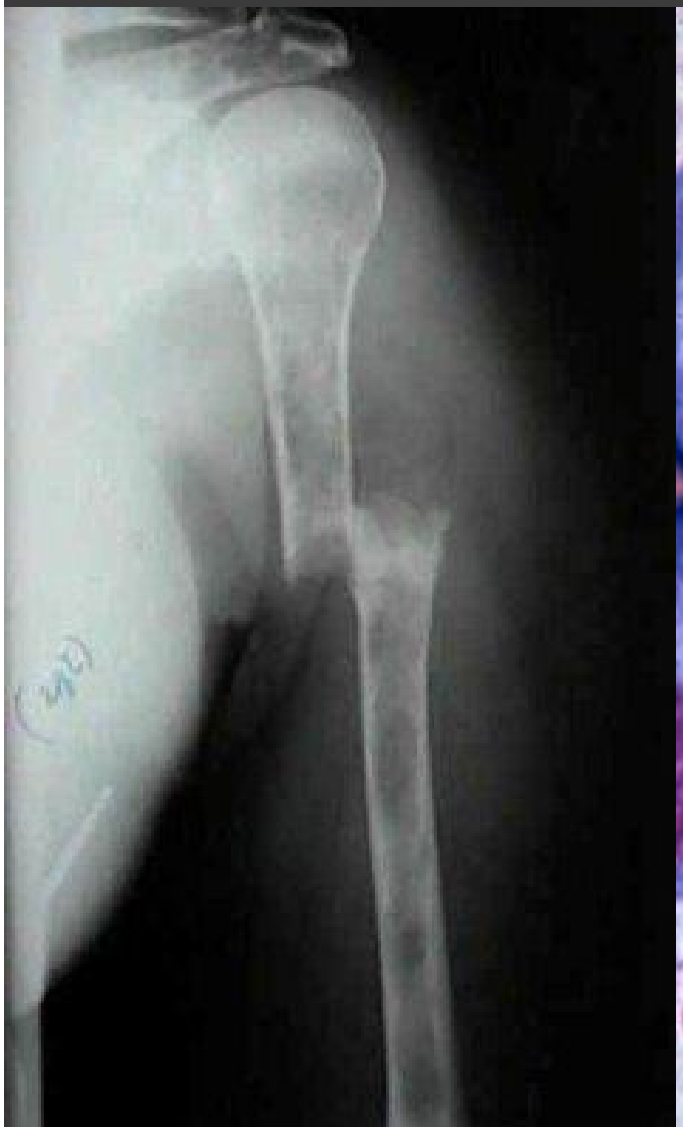
Causes — Sepsis (gram-negative), Trauma, Obstetric complications, acute Pancreatitis, Malignancy, Nephrotic syndrome, Transfusion.

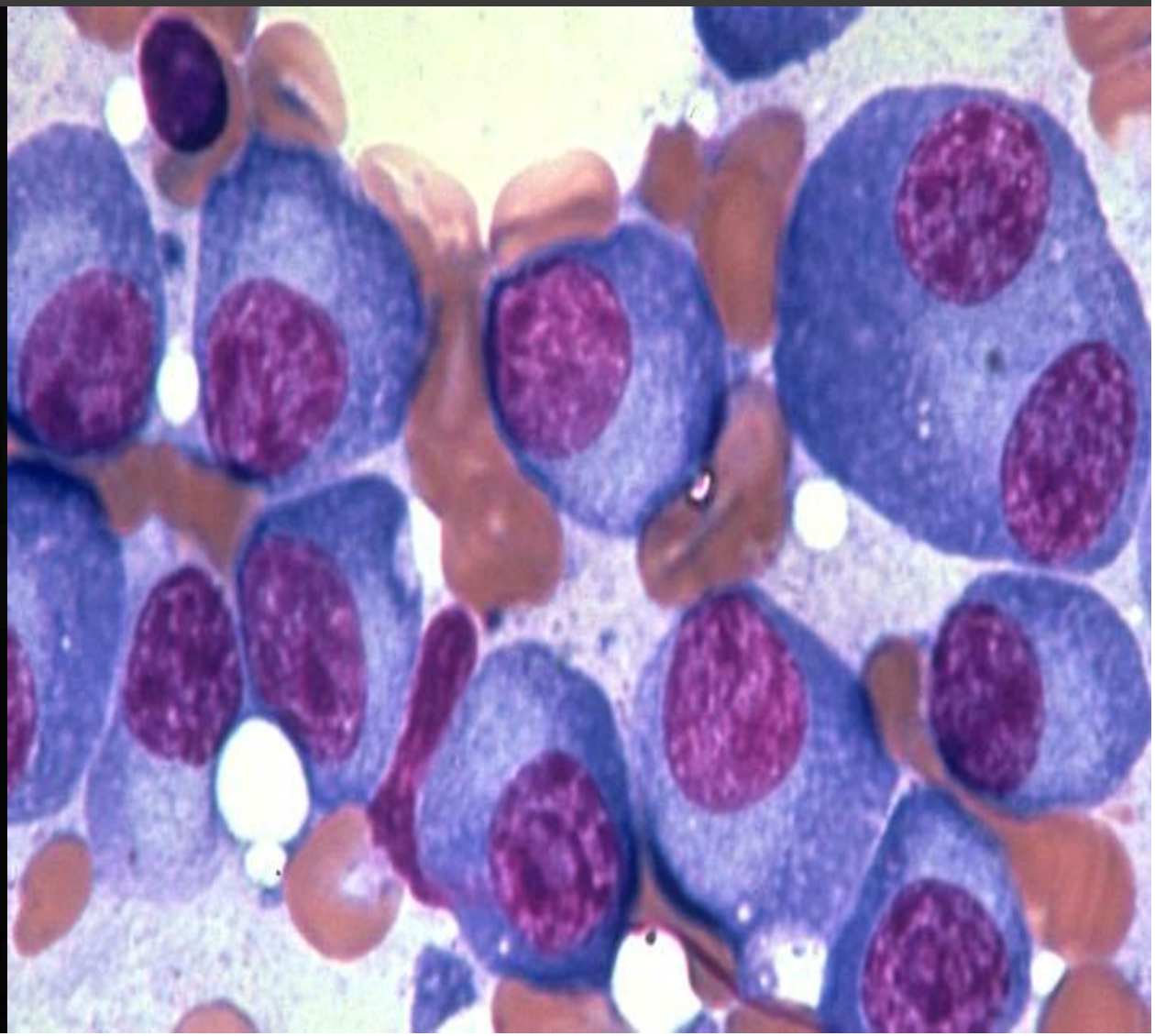
Lab findings — ↑ PT, ↑ PTT, ↑ fibrin split products (D-dimers), ↓ platelet count. Helmet-shaped cells and schistocytes on blood smear.

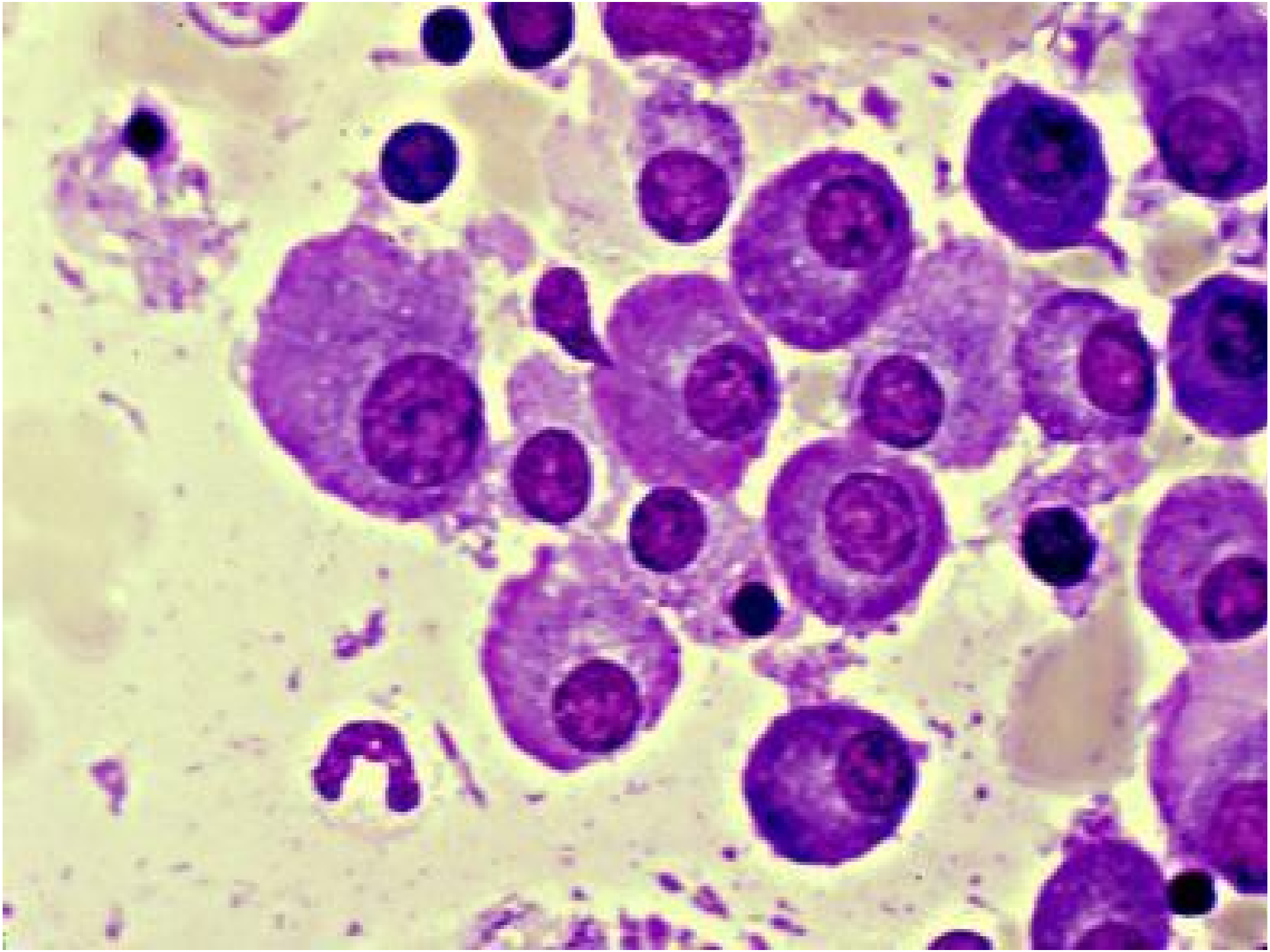
STOP Making New Thrombi!

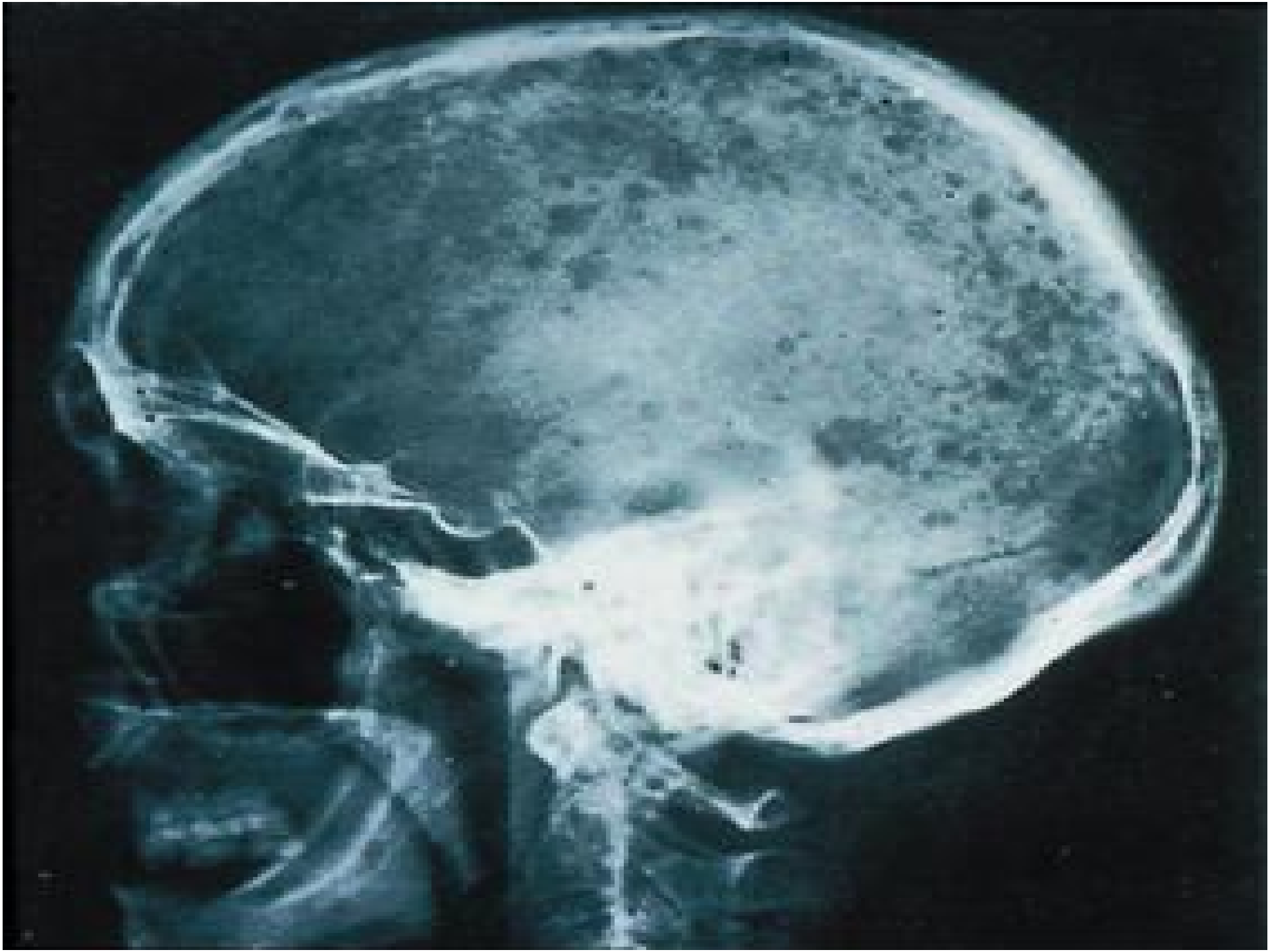


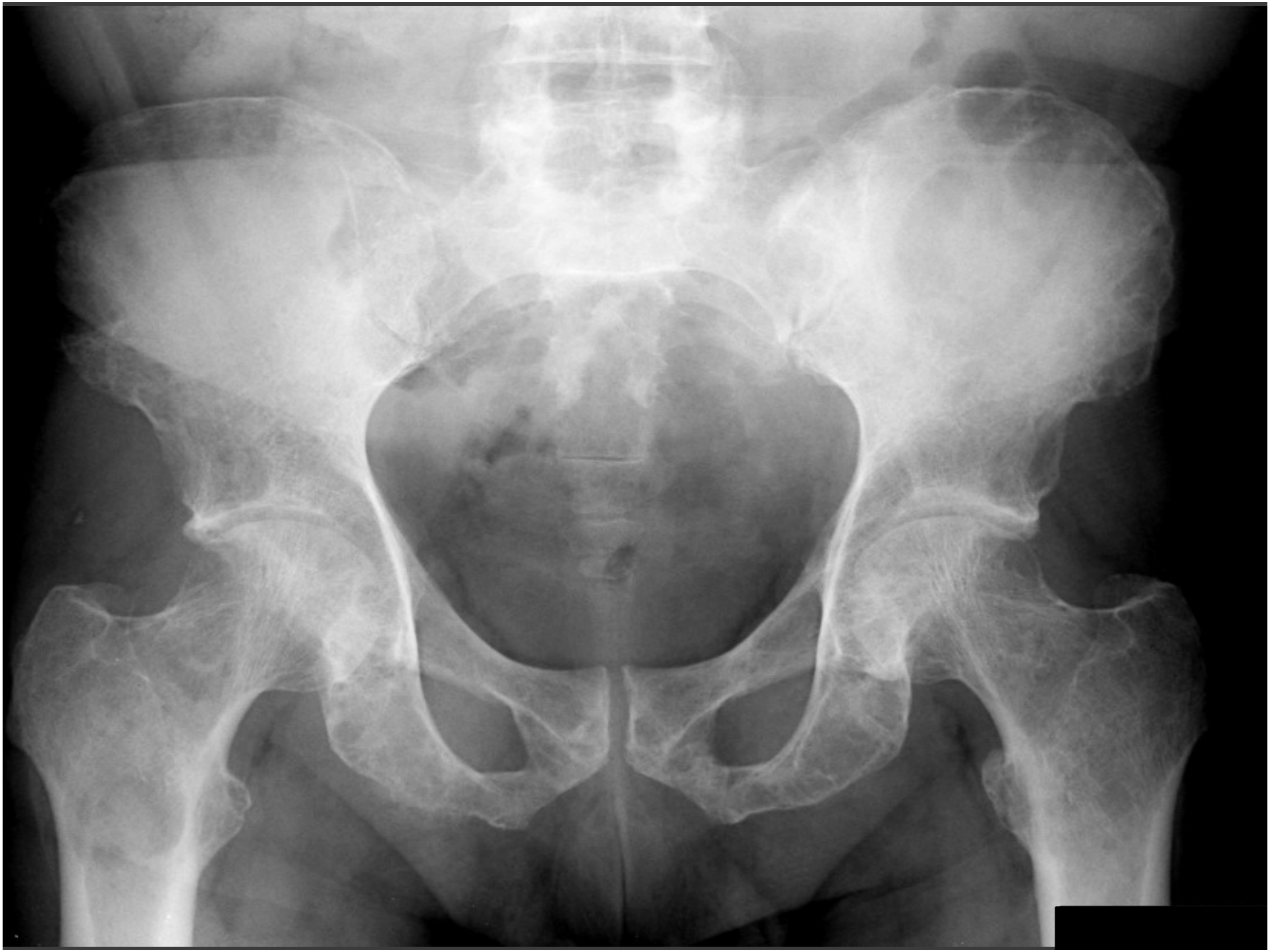
MULTIPLE MYELOMA



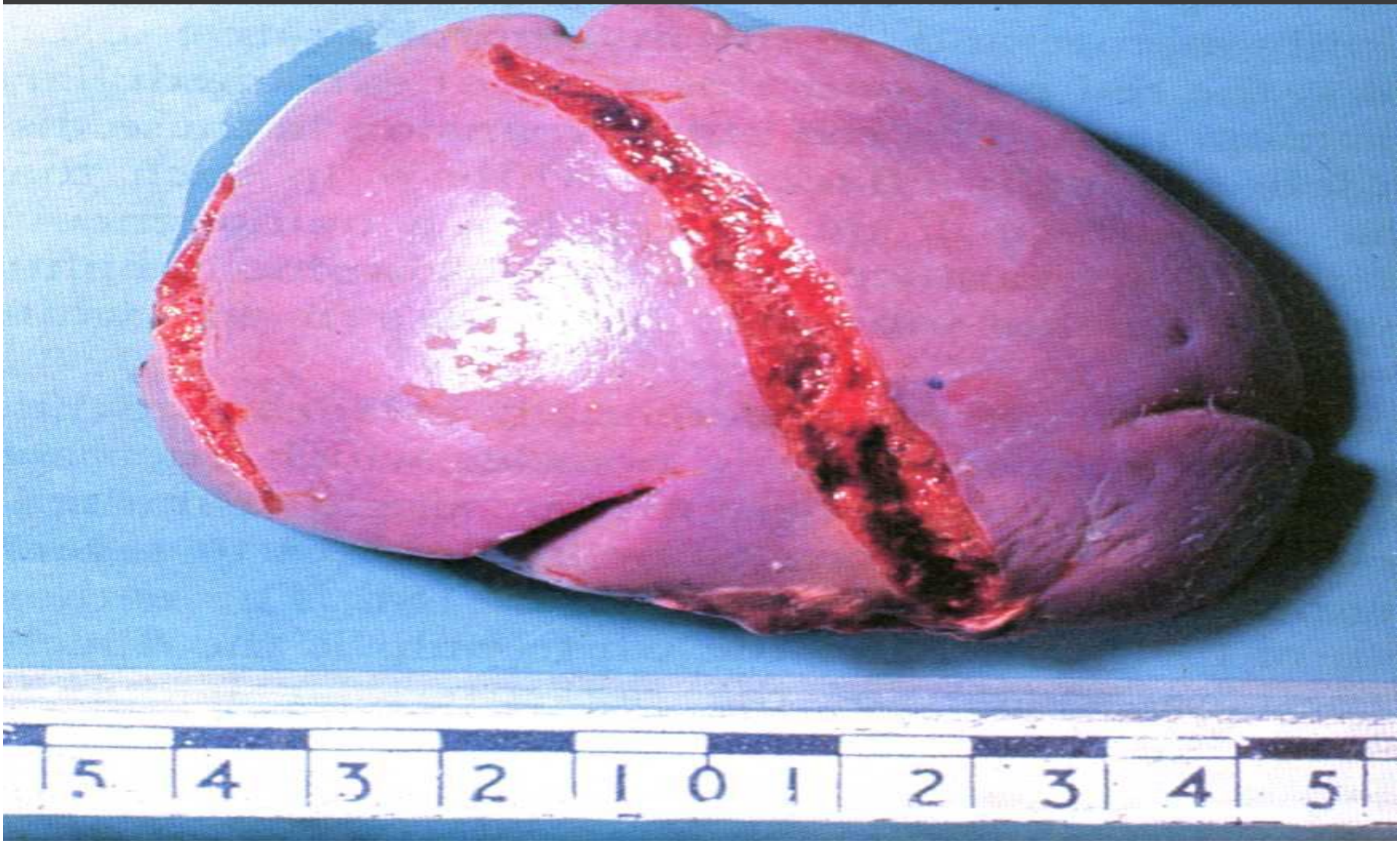




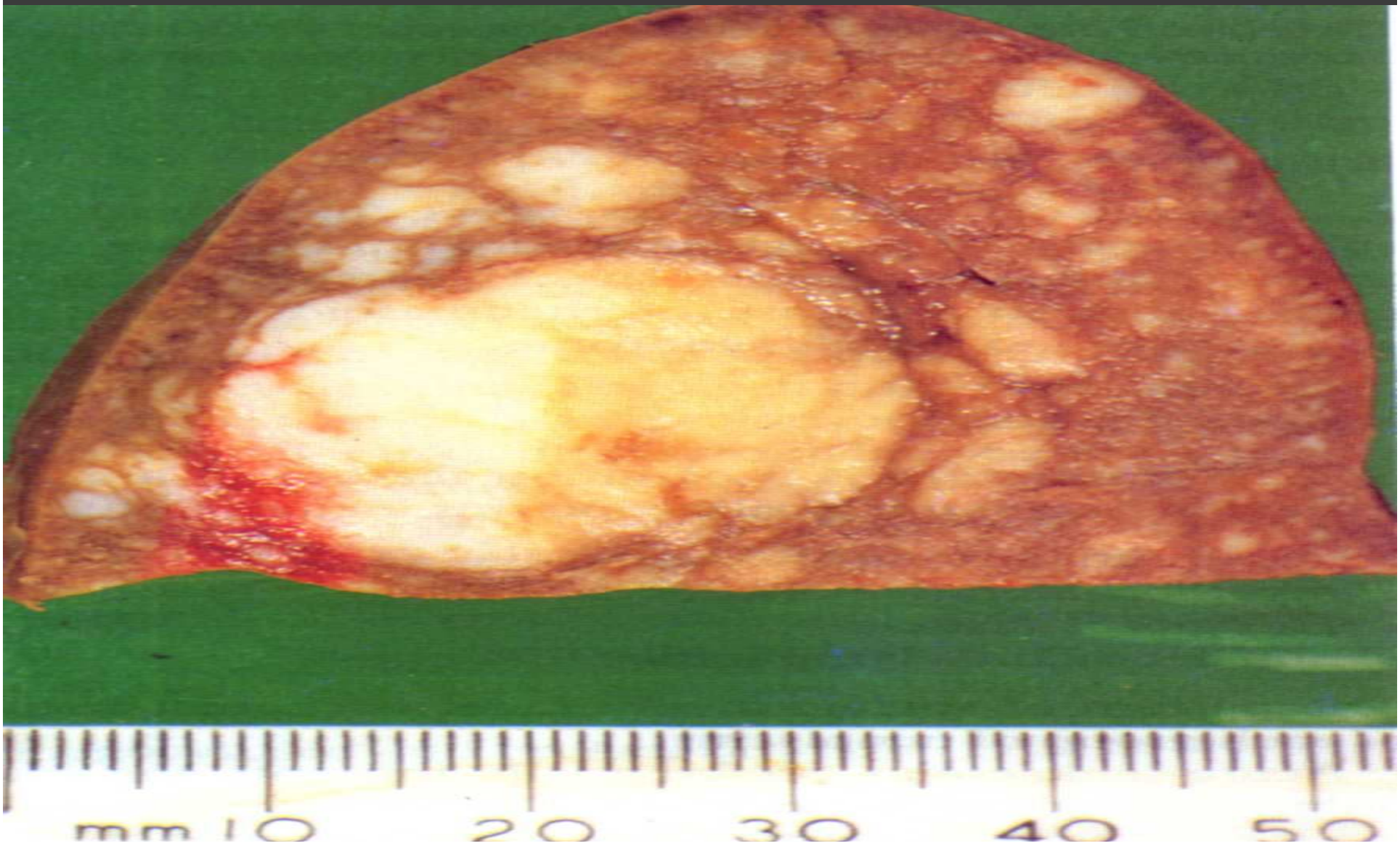




SPLENIC RUPTURE IN INFECTIOUS MONONUCLEOSIS



SPLEEN INFILTRATED BY HODGKIN'S DISEASE



NEUTROPHILS CONDITION

LOW NEUTROPHIL COUNTS ARE TERMED *NEUTROPENIA*. :

-CONGENITAL (GENETIC DISORDER) OR IT CAN DEVELOP LATER, AS IN THE CASE OF APLASTIC ANEMIA OR SOME KINDS OF LEUKEMIA.

-SIDE-EFFECT OF MEDICATION, MOST PROMINENTLY CHEMOTHERAPY. NEUTROPENIA MAKES AN INDIVIDUAL HIGHLY SUSCEPTIBLE TO INFECTIONS. NEUTROPENIA CAN BE THE RESULT OF COLONIZATION BY INTRACELLULAR NEUTROPHILIC PARASITES.

-FUNCTIONAL DISORDERS OF NEUTROPHILS ARE OFTEN HEREDITARY. THEY ARE DISORDERS OF PHAGOCYTOSIS OR DEFICIENCIES IN THE RESPIRATORY BURST (AS IN CHRONIC GRANULOMATOUS DISEASE, A RARE IMMUNE DEFICIENCY, AND MYELOPEROXIDASE DEFICIENCY).

-IN ALPHA 1-ANTITRYPSIN DEFICIENCY, THE IMPORTANT NEUTROPHIL ENZYME ELASTASE IS NOT ADEQUATELY INHIBITED BY ALPHA 1-ANTITRYPSIN, LEADING TO EXCESSIVE TISSUE DAMAGE IN THE PRESENCE OF INFLAMMATION - MOST PROMINENTLY PULMONARY EMPHYSEMA.

-IN FAMILIAL MEDITERRANEAN FEVER (FMF), A MUTATION IN THE *PYRIN* (OR *MARENOSTRIN*) GENE, WHICH IS EXPRESSED MAINLY IN NEUTROPHIL GRANULOCYTES, LEADS TO A CONSTITUTIVELY ACTIVE ACUTE PHASE RESPONSE AND CAUSES ATTACKS OF FEVER, ARTHRALGIA, PERITONITIS, AND - EVENTUALLY - AMYLOIDOSIS.