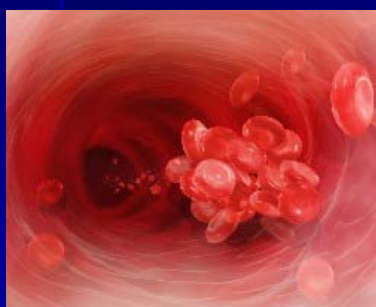


Pathophysiology of the diseases of the blood:

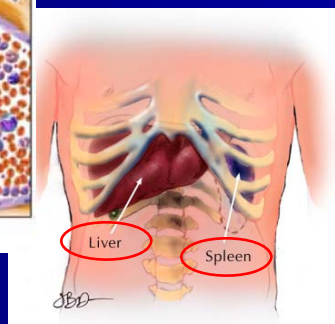
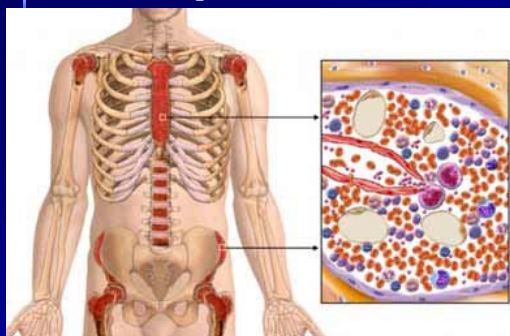
Anemias and haemorrhagic diatheses



Blagoi Marinov, MD, PhD
Pathophysiology Department
Medical University of Plovdiv

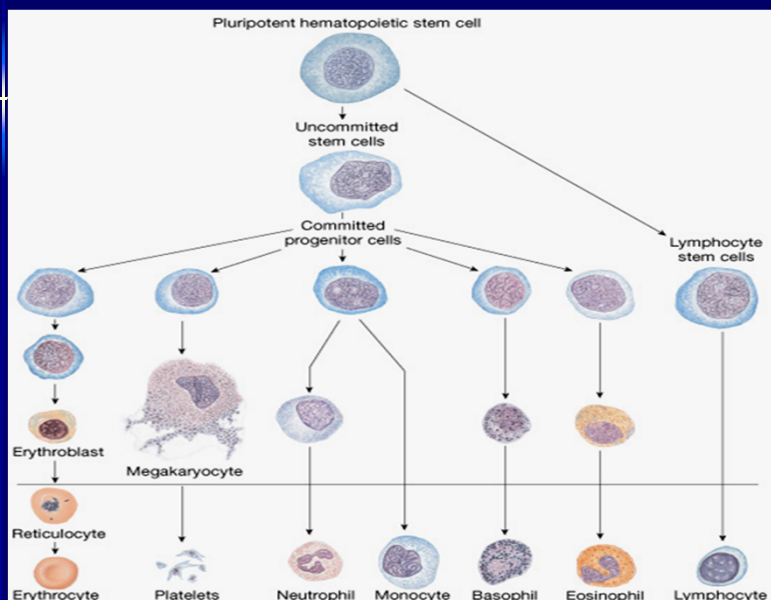
Haemopoietic system

Blood production

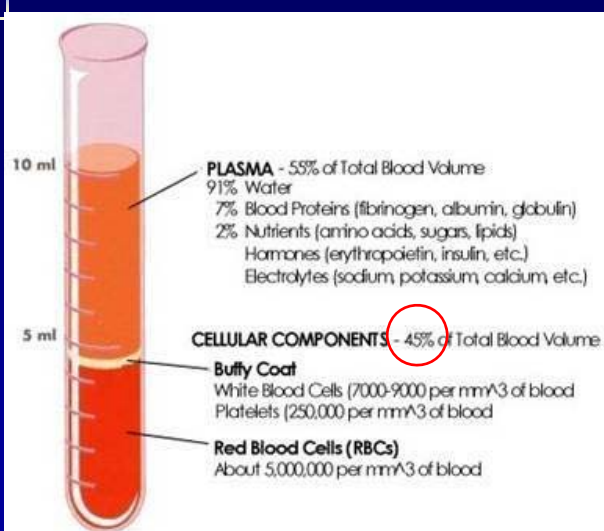


Blood wasting

Haemopoiesis



Blood - structure

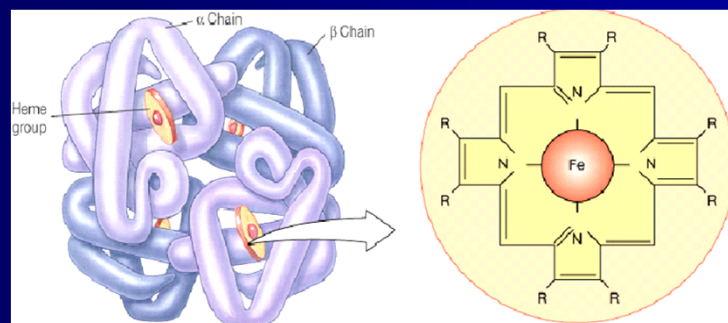


≈ 4-5 L

Characteristics of normal **Er**

- ❑ Highly elastic bi concave discs ($\sim 5 \cdot 10^{12}$).
- ❑ Without nucleus and mitochondria (anaerobic metabolism).
- ❑ Contain large quantities of enzyme carbonic anhydrase
- ❑ Lifecycle ~ 120 days.

Structure and function of **Hb**



90% of the protein content of Ers is haemoglobin.

- transports O_2 and part of the CO_2 .
- represents mighty buffer system

Definition

Anemias are diseases of the blood having less than the normal number of red blood cells or less than the normal quantity of hemoglobin in the blood. The oxygen-carrying capacity of the blood is, therefore, substantially decreased.

Classifications

■ Clinical

- ❖ Acute
- ❖ Subacute
- ❖ Chronic

■ Erythrocytes morphology

- ❖ Microcytic
- ❖ Macrocytic (megaloblastic)
- ❖ Spherocytic

■ Haemoglobin content

- ❖ Hypochromic
- ❖ Hyperchromic

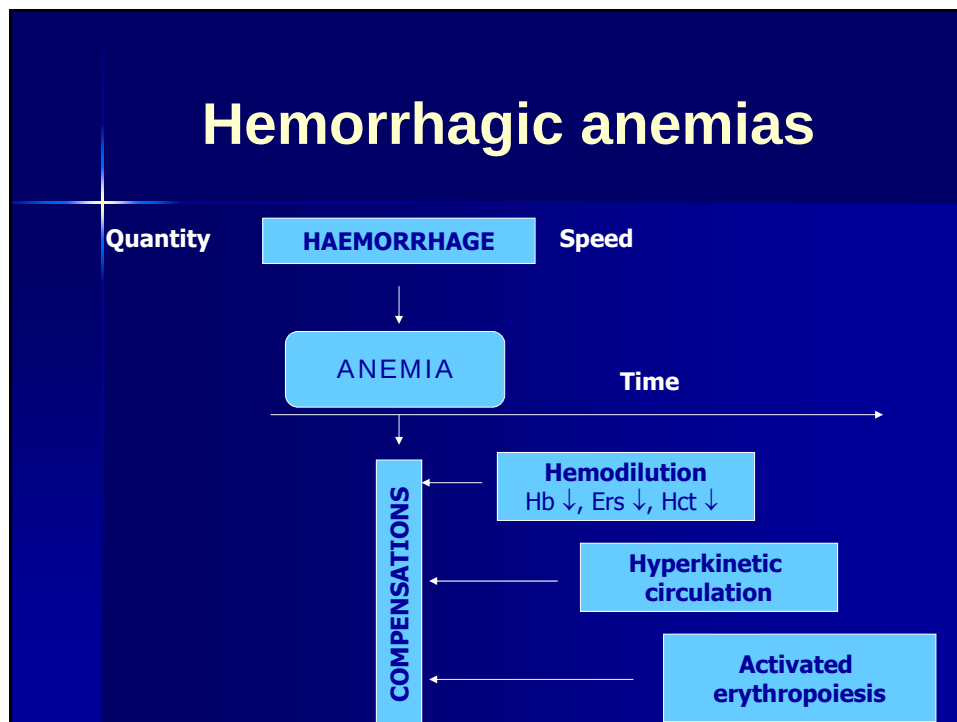
Pathogenetic classification of anemias

- **Haemorrhagic anemias**
- **Impaired erythroproduction**
(*depressed erythropoiesis*)
- **Increased erythrodestruction**
(*pathologic haemolysis*)

Lab tests to consider in anemic states

- | | |
|---|--|
| <p>I. Complete blood count (CBC)</p> <ul style="list-style-type: none"> A. Red blood cell count <ul style="list-style-type: none"> 1. Hemoglobin 2. Hematocrit 3. Reticulocyte count B. Red blood cell indices <ul style="list-style-type: none"> 1. Mean cell volume (MCV) 2. Mean cell hemoglobin (MCH) 3. Mean cell hemoglobin concentration (MCHC) 4. Red cell distribution width (RDW) C. White blood cell count <ul style="list-style-type: none"> 1. Cell differential 2. Nuclear segmentation of neutrophils D. Platelet count E. Cell morphology <ul style="list-style-type: none"> 1. Cell size 2. Hemoglobin content 3. Anisocytosis 4. Poikilocytosis 5. Polychromasia | <p>II. Iron supply studies</p> <ul style="list-style-type: none"> A. Serum iron B. Total iron-binding capacity C. Serum ferritin, marrow iron stain <p>III. Marrow examination</p> <ul style="list-style-type: none"> A. Aspirate <ul style="list-style-type: none"> 1. M/E ratio^a 2. Cell morphology 3. Iron stain B. Biopsy <ul style="list-style-type: none"> 1. Cellularity 2. Morphology |
|---|--|

Hemorrhagic anemias

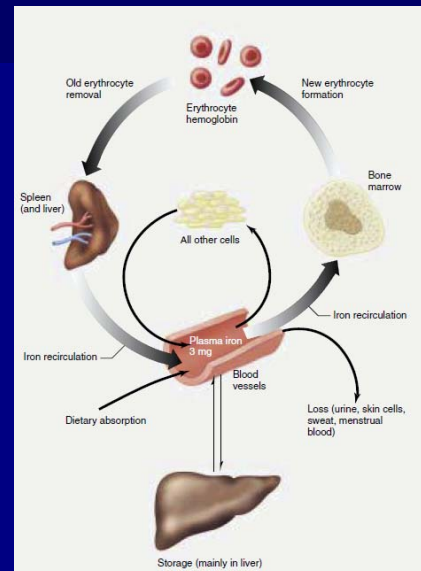
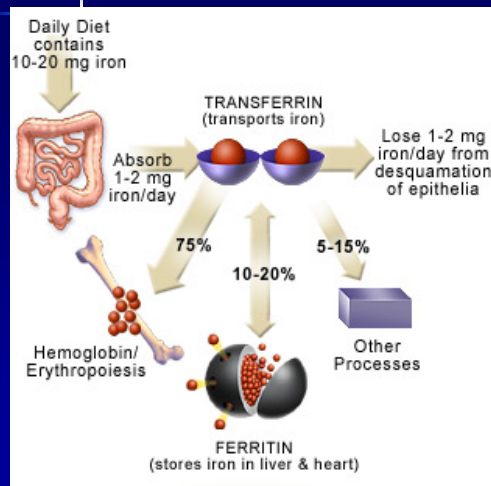


Anemias due to impaired erythroproduction

- Impaired synthesis of haemoglobin
 - ❖ Fe deficit
- Altered DNA synthesis
 - ❖ B₁₂ defect
 - ❖ Folate deficit
- Hypo- and aplastic anemias
 - ❖ Idiopathic (EPO* insensitive)
 - ❖ Erythropoietin deficit

*EPO - Erythropoietin

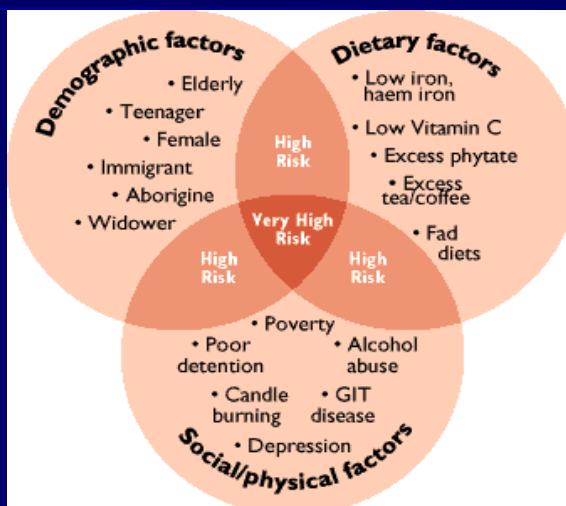
Iron metabolism



Fe-deficient anemias - etiology

- Chronic haemorrhages
- Increased physiologic requirements
- Decreased Fe-uptake
- Altered Fe-transformation
- Decreased Fe-absorption
- Improper Fe-transport to hemopoietic organs

Fe-deficient anemias - etiology



Stages of Fe deficiency

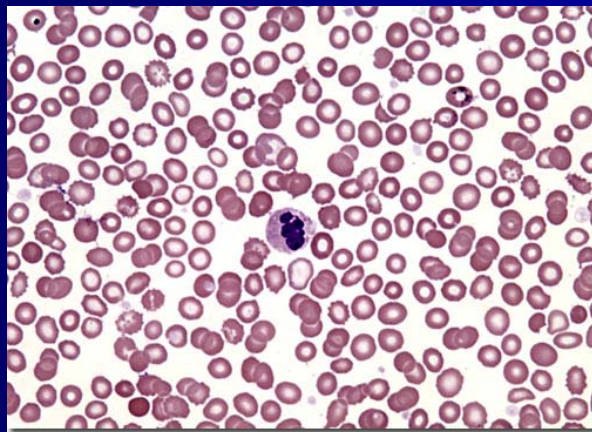
	Normal	Negative iron balance	Iron-deficient erythropoiesis	Iron-deficiency anemia
Iron stores				
Erythron iron				
Marrow iron stores	1-3+	0-1+	0	0
Serum ferritin (µg/L)	50-200	<20	<15	<15
TIBC (µg/dL)	300-360	>360	>380	>400
SI (µg/dL)	50-150	NL	<50	<30
Saturation (%)	30-50	NL	<20	<10
Marrow sideroblasts (%)	40-60	NL	<10	<10
RBC protoporphyrin (µg/dL)	30-50	NL	>100	>200
RBC morphology	NL	NL	NL	Microcytic/hypochromic

Fe-deficient anemias - pathogenesis

Decrease of the Fe stores in the organism

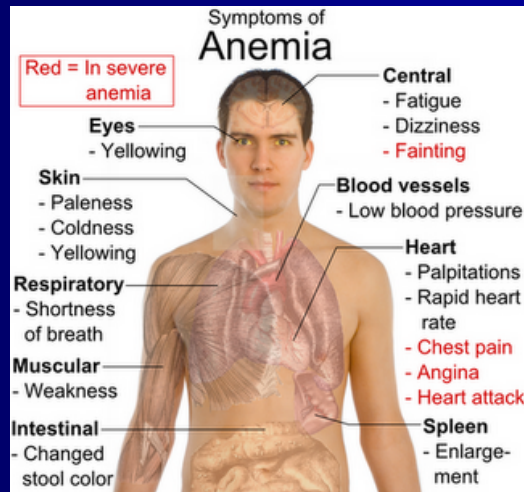
- Prelatent Fe-deficit
 - Feritin ↑
 - Intestinal absorption ↑
- Latent Fe-deficit
 - Serum Fe ↓
 - Feritin ↓
 - total iron binding capability (TIBC) ↑
- Manifest Fe-deficient anemia
 - Ers ↓; Hb ↓; MCV ↓;

Fe-deficient anemia : Ers morphology



Fe-deficient anemia is microcytic and hypochromic !!!

Fe-deficient anemias - signs and symptoms

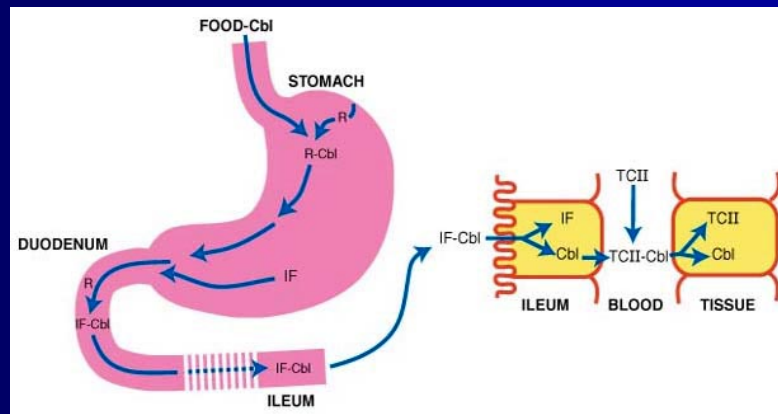


Megaloblastic anemia - etiology

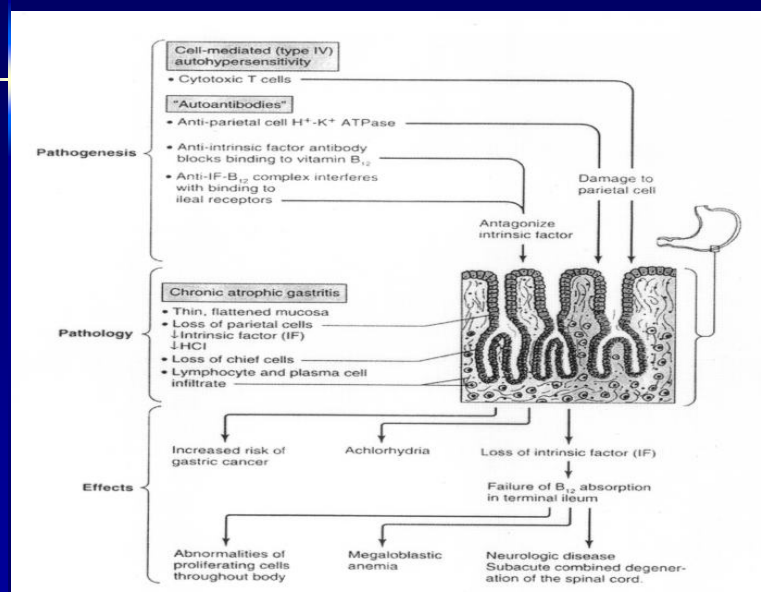
Autosomal-recessive inheritance
(Addison-Biermer anemia)

- Genetic predisposition – HLA-A3, HLA-B7
- Auto AB against:
 - Parietal cells in the gastric mucosa
 - Gastromucoprotein

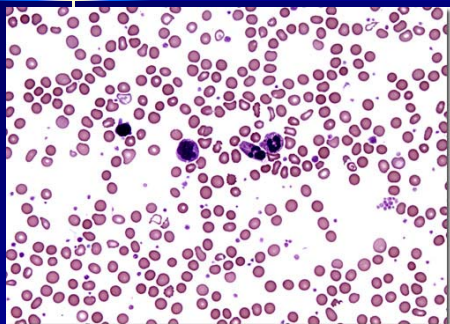
Vit B₁₂ metabolism



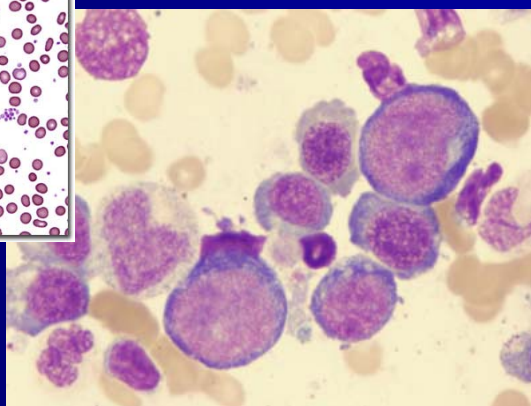
Megaloblastic anemia - pathogenesis



Erythrocyte profile in megaloblastic anemia



- Anisocytosis
- poikilocytosis
- Macrocytes
- Ovalocytes
- Howell-Jolly bodies



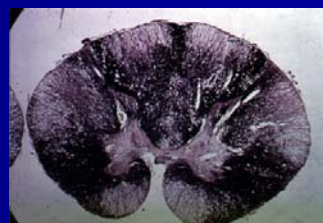
Megaloblastic anemia – signs and symptoms



GI symptoms – Hunter glossitis

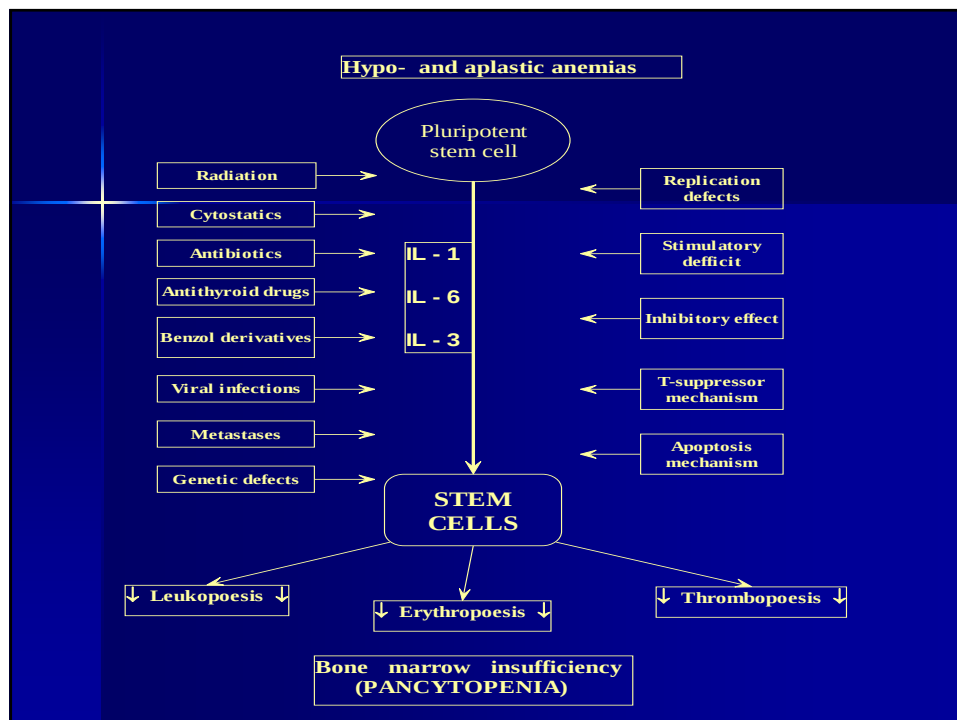


Subacute combined degeneration of spinal cord, due to demyelination secondary to deficiency of vitamin B12.



Secondary megaloblastic anemias

- Primary liver disease
- Surgical interventions on the stomach and intestines
- Neoplastic processes
- Parasitic diseases
- Medications (cytostatics, immunosuppressors, antiepileptics)



Anemias due to increased erythrodestruction

■ Inborn (inherited)

- ❖ Disorders in the structure of Er membrane
- ❖ Disorders in Er's enzymatic content
- ❖ Disorders in the synthesis of the globin molecule
 - Haemoglobinoses
 - Thalassemias

■ Acquired

- ❖ Immunologic mechanisms
 - Isoimmune
 - Drug induced (haptens)
 - Autoimmune
- ❖ Symptomatic (secondary)

Anemias due to disorders in the structure of Er membrane

Microspherocytosis (M. Minkowski-Chauffard)

- Quantitative and qualitative changes of membrane protein *spectrin* (autosomal dominant trait)
- Disturbance in ATP metabolism
- Decreased activity of the enzyme *proteinkinase*

Spectrin deficit

Increased permeability

Shortened life cycle

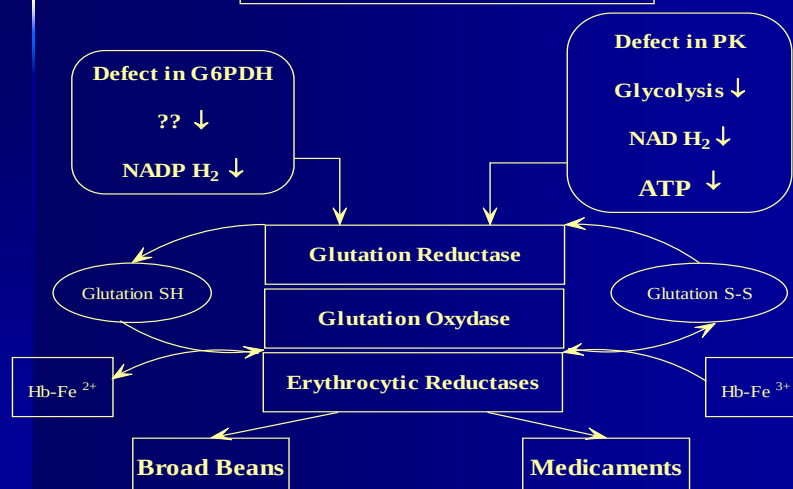
Haemolytic anemia

Anemias due to disorders in Erythrocytic enzymatic content

- Glucose-6-phosphate dehydrogenase deficient anemia
 - ❖ Sex-linked recessive inheritance.
 - ❖ The most common enzymopathy
- Pyruvate kinase deficient anemia
 - ❖ Autosomal-recessive inheritance

Anomalies in Erythrocytic enzymes

Anomalies of erythrocytic enzymes



G6PD

- Genetic defects
- Deficit of G6PD
- Impaired glutathione synthesis
- Oxygen stress
- Denaturation of hemoglobin
- Hemolysis of RBCs with enzyme defects

Thalassemias

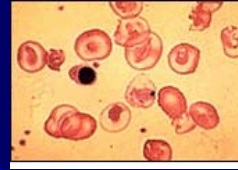
■ Beta thalassemias

- Homozygotic form (β -thalassemia major, Morbus Cooley)
- Heterozygotic forms (β -thalassemia minor)

■ Alpha thalassemias

- Homozygotic form
- Heterozygotic forms

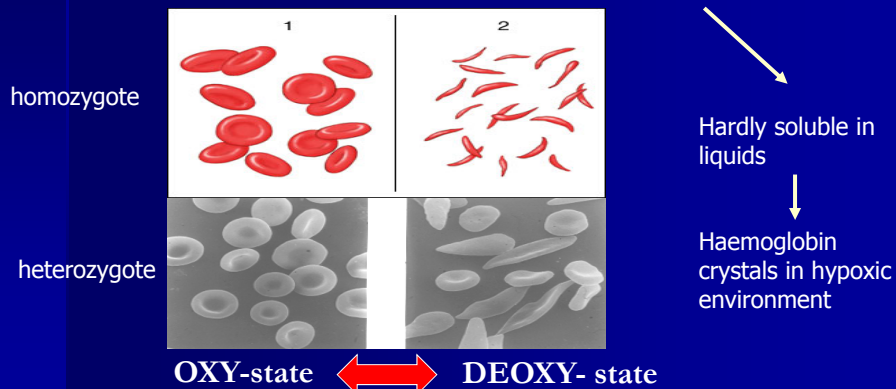
Thalassemia mayor (M. Cooley)



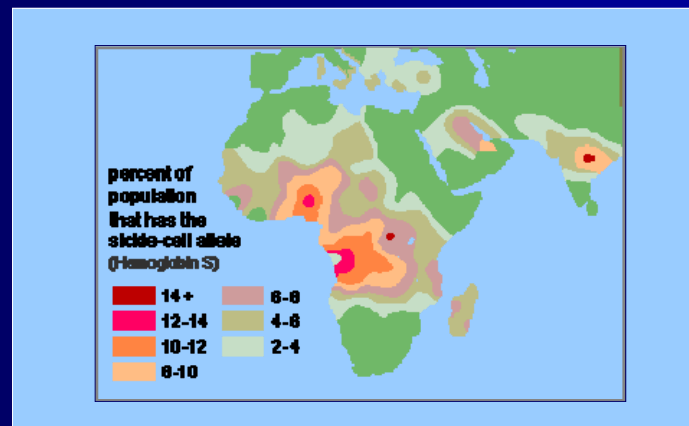
- Abnormally high quantity of Hb F and Hb A₂ is synthesised
- Due to deficit or inappropriate synthesis of β -chains in Ers there is an excess of uncoupled α -chains
- The uncoupled α -chains precipitate
- The permeability of Ers is increased
- Hemolysis

Sickle cell anemia

Impaired β -chain synthesis, with formation of **pathologic haemoglobin S**

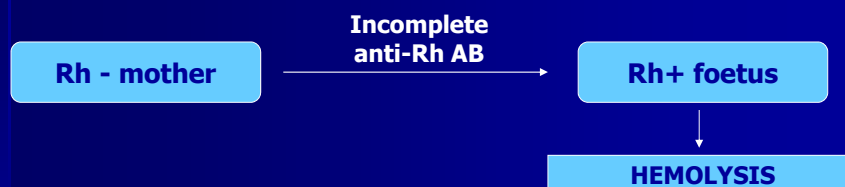


Sickle cell anemia - distribution



Hemolytic disease of the newborn

Isoimmune conflict between the mother and the foetus due to antigen incompatibility in Rh or ABO systems



FORMS

- Hemolytic disease of the newborn
- Icterus gravis
- Foetoplacental anasarca
- Nuclear icterus (Kernicterus)

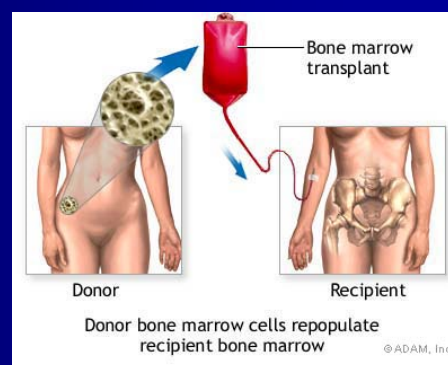
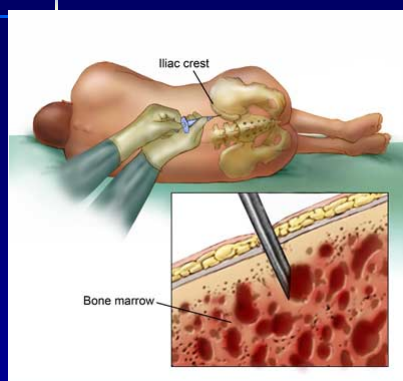
Acquired autoimmune anemias

Autoimmune conflict between specific AB and body's own unchanged erythrocyte antigens

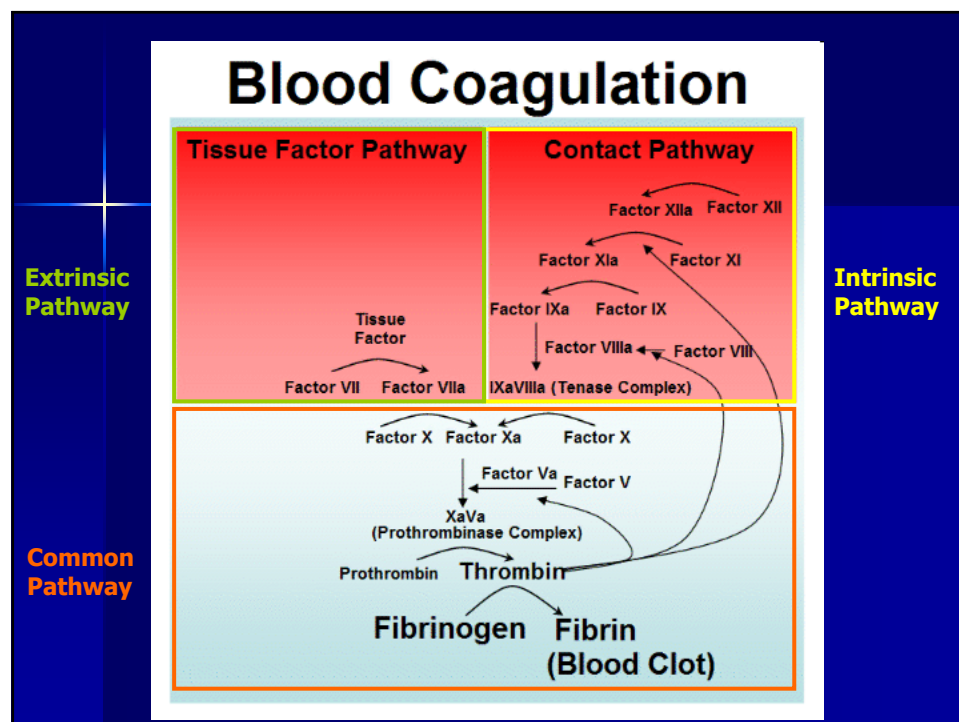
Types of antibodies

- Incomplete heat agglutinins
- Heat hemolysins
- Complete cold agglutinins
- Bi-phase hemolysins

Bone marrow transplantation



Hemorrhagic diatheses



Hemorrhagic diatheses

- **Coagulation abnormalities**
- **Quantitative and qualitative platelet abnormalities** (thrombocitopenias & thrombocitopathias)
- **Damage to the vascular wall** (vasopathies)

Hemophilia

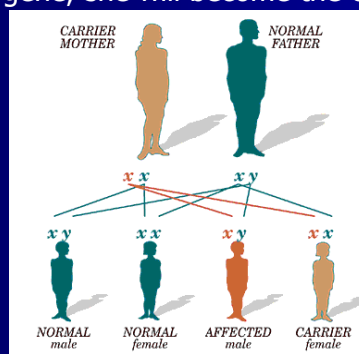
- Disorder of hemostasis, a coagulopathy
- Hemophilia A - Factor VIII deficiency
- Hemophilia B – Factor IX deficiency
- Hemophilia C – Factor XI, XII
- Prevalence: 13.4 cases per 100,000 males
- Incidence: 1 in 5032 live male births

Queen Victoria



How do you get it?

- Hemophilia is a genetic disease and is passed on by the X chromosome (the chromosome that carries the clotting factor).
- If a boy gets the X chromosome that carries the hemophilia gene he will become a hemophiliac.
- If a girl gets the gene, she will become the carrier of the gene,



Severity of Factor Deficiencies

- Severe: <1%
 - Hemarthrosis with minimal trauma or ADLs
- Moderate: 1 to 5%
 - Intermediate symptoms with fewer hemarthroses
- Mild: >5%
 - Joint bleeds rarely develop except with significant trauma

Hemophilic Arthropathy

- As blood is catabolized, it is absorbed by synovium
- Iron is toxic to cells – synovial cells disintegrate releasing lysosomes which destroy cartilage and inflame synovium
- Chondrocytes also affected
- FIBROSIS



Thrombocytopenia

- 1/3 of all Hospital Hematology Consults are for thrombocytopenia
- 5 to 10% of all hospitalized patients are thrombocytopenic in the ICU the number increases to 35%
- Thrombocytopenic patients in the hospital suffer a twofold greater mortality rate than those who are not

Echymoses



Thrombocytopenia

Platelet count	Symptoms
50-100,000	Prolonged bleeding following trauma
< 50,000	Easy bruising Purpura following minor trauma
< 20,000	Spontaneous bleeding Petechiae May suffer spontaneous internal and intracranial bleeding

Mechanisms of Thrombocytopenia

- Decreased platelet production
- Increased platelet destruction
- Dilutional Thrombocytopenia
- Splenomegaly or splenic sequestration
- Pseudothrombocytopenia

The primary reason for evaluating thrombocytopenia is to assess the risk of bleeding and assess the presence of underlying disorders

Decreased Platelet Production

- Factors causing bone marrow suppression or damage
- Viral illness
- HIV (direct damage to Megakaryocytes)
- Chemo- or radiation therapy
- Congenital or acquired bone marrow aplasia or hypoplasia
- *Vit. B12 or Folate deficiency*

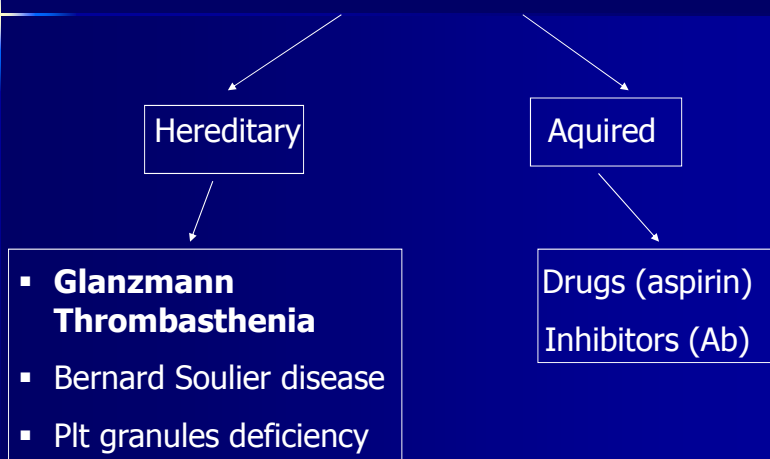
Increased Platelet Destruction

- Idiopathic (Immune) Thrombocytopenic Purpura
- Alloimmune destruction—Posttransfusion, Post-transplantation
- Disseminated Intravascular Coagulation
- Thrombotic Thrombocytopenic Purpura
- Antiphospholipid Antibody Syndrome
- Certain drugs—Heparin, quinidine, valproate

Splenic Sequestration

- Normally, $\sim 1/3$ of platelets are sequestered in the spleen in any given time
- In extreme splenomegaly, up to 90% of platelets can be trapped in the spleen
- Cirrhosis, Portal HTN, splenomegaly can all present with apparent thrombocytopenia, although these pts are not usually at risk for clinical bleeding

Qualitative platelet disorders - thrombocytopathy



Vasopathias

- **Schönlein-Henoch Purpura**
- **Symptomatic hemorrhagic vasculites**
 - Crimean hemorrhagic fever
 - Measels
- **Hereditary vasopathias**
 - Rendu-Osler-Weber

Schönlein-Henoch Purpura anaphylactoid purpura

- Schönlein-Henoch Purpura is a common vasculitis with *cutaneous and systemic complications*.
- The usual location of the **acute small vessel damage** is primarily in the skin, GI tract, and kidneys
- It is the most common cause of nonthrombocytopenic purpura in children.

History



- First described in 1801 by William Heberden, a physician in London, who wrote about a case of a 5 year old boy with hematuria, abdominal pain, joint pains and a skin rash.



- In 1837, Johann Schönlein and later in 1874, Edouard Henoch described multiple case reports of similar cases. They also showed an association of an upper respiratory infection preceding development of symptoms.

Pathogenesis

- Likely mechanism thought to be an immune-complex mediated disease with deposits in the glomerular capillaries, dermal capillaries and GI tract.
- Mesangial deposits of IgA are the same as those seen in IgA nephropathy

Epidemiology

- More frequent in children than adults, with most cases occurring between 2 and 8 yr of age,
- Most frequently in the winter months.
- The overall incidence is estimated to be 9/100,000 population.
- Males are affected twice as frequently as females.

Clinical manifestations

- Rash (95-100%), especially involving the legs, may not be present on initial presentation
- Subcutaneous edema (20-50%)
- Abdominal pain and vomiting (85%)
- Joint pain (60-80%), especially involving the knees and ankles
- Scrotal edema (2-35%)
- Bloody stools

Clinical Presentation



Petechiae in Henoch-Schönlein purpura Clusters of palpable, pruritic petechiae on the thigh of a patient with Henoch-Schönlein purpura. These lesions could be mistaken for thrombocytopenic petechiae.

- Petechiae
- Purpura
- Ecchymoses



Arthritis

- Present in more than $\frac{2}{3}$ of children with HSP,
- Is usually localized to the knees and ankles and appears to be concomitant with edema.
- The effusions are serous, not hemorrhagic,
- Resolve after a few days without residual deformity or articular damage.
- They may recur during a subsequent reactive phase of the disease.

Gastrointestinal tract

- Intermittent abdominal pain that is often colicky in nature.
- There may be peritoneal exudate, enlarged mesenteric lymph nodes, segmental edema, and hemorrhage into the bowel.
- More than half of patients have occult heme-positive stools,
- Diarrhea (with or without visible blood), or hematemesis.
- Complete bowel obstruction or infarction with bowel perforation.

Renal involvement

- occurs in 25-50% of children

may manifest with:

- hematuria,
 - proteinuria, or both;
 - nephritis or nephrosis;
 - acute renal failure.
-
- Renal involvement at presentation may lead to chronic hypertension or end-stage renal disease in the future

The END

Have a wonderful day!