Anemias

- 1. In general
- 2. Decreased erythrocyte production
- 3. Increased erythrocyte loss

Anemias

1. Anemias in general

Definition
- traditional ↓RBC or ↓Hb or ↓HTC
- alternative ↓ Erythron (M)

$$M = I * T,$$

where I = amount of new RBC produced per unit of time
T = red blood cell life span
Example (extreme compensation): M = 8 * 1/8 = 100%

Symptoms: under 80g Hb/L
Hemolysis → jaundice, splenomegaly, cholelithiasis
↓ O_2 diffusion → vasoconstriction of skin and kidneys
Pulmonary and cardiac function ↑
Medullary erythropoiesis ↑
2,3 diphosphoglycerate ↑ → shift of the Hb curve to the right → ↑ O_2 delivery to the tissues

Acute blood loss:
30% of volume (1500 mL) → circulatory colaps, shock
> 50% loss → death
↓ Hb after 2-3 days
No "emergency" pool of RBC, premature release of reticulocytes only
The marrow RBC production can rise up to 8times, if there is Fe enough

Classification of anemias (Fig. 14 a,b)

Decreased erythrocyte production, due to:		
Decreased proliferation of new erythrocytes, due to:		
Decreased erythropoietin, due to:	Impaired production by the kidneys	Anemia of renal failure
	Low oxygen requirements	Anemia of endocrine disease
	Impaired stem cell response to erythropoietin	Anemia of chronic disease
Bone marrow damage or defect, due to:	Replacement of marrow by tumor	Myelophthisic anemia
	Replacement of normal marrow by cancerous cell line	Anemia associated with myeloproliferative disease
	Damage to bone marrow by physical or chemical agents, or infections	Aplastic anemia
	Inherited bone marrow defect	Fanconi's anemia
Impairment in the maturation of new erythrocytes, resulting in:		
Macrocytic-normochromic erythrocytes, due to:	Folic acid deficiency	Megaloblastic anemia
	Vitamin B_{12} deficiency	Megaloblastic anemia
Microcytic-hypochromic erythrocytes, due to:	Iron deficiency	Iron deficiency anemia
	Unavailability of iron to blast cells	Anemia of chronic disease
	Impairment of heme synthesis	Sideroblastic anemia
	Impairment of globin synthesis	Thalassemia syndromes

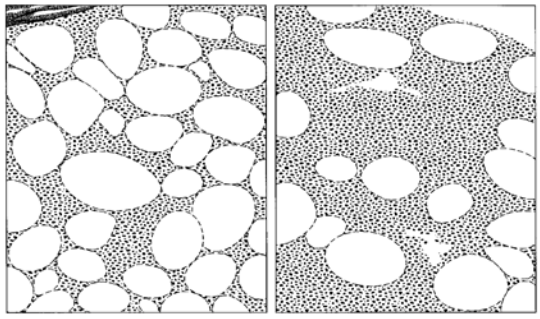
14a

Increased erythrocyte loss, due to:		
Hemorrhage		
Acute		
Chronic		
Intravascular hemolysis, as a result of:		
Hereditary factors, resulting in:	Defects in the erythrocyte membrane	Hereditary spherocytosis
		Hereditary elliptocytosis
	Defects in erythrocyte metabolism	G-6-PD deficiency anemia
	Abnormal hemoglobin production	Sickle-cell anemia
		HbC disease, HbD disease
		HbE disease
Acquired accelerated hemolysis, due to:	Activation of the immune system	Immunohemolytic anemia
	Physical factors	Red cell fragmentation syndromes
	Chemical agents	Various forms of hemolytic anemia
	Microorganisms	Various forms of anemia (e.g., anemia of malaria)
	Secondary to other diseases	Various forms of anemia (e.g., anemia of hepatic failure)
	Sensitivity to complement	Paroxysmal nocturnal hemoglobinuria

14b

2 Decreased erythrocyte production

21 Decreased proliferation of new erythrocytes = aplastic anemia s.l. = hypoproliferative anemia (Fig. 15)



a. aplastic (hypoplastic) anaemia iliac crest bone marrow trephine b. normal iliac crest bone marrow trephine

15

Reticulocyte index ↓. Hypoplasia of the red cell line in the marrow ⇔ inability to react to anemia
Name: in fact, the anemia is hypoplastic only (never complete aplasia)
Symptomatology: pancytopenia always present (white cells, platelets), infections, bleeding, reticulocytes↓, plasma Fe↑, total binding capacity↓
Prognosis not very good. Ther.: bone marrow transplantations and immunosuppression (cyclosporine and antilymphocyte serum)

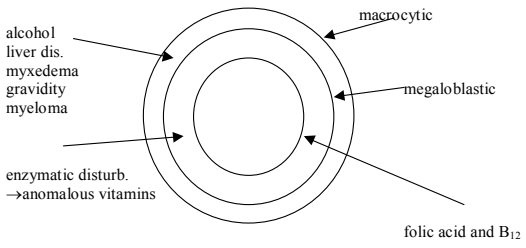
Etiology
- "**idiopathic**" – most often, probably caused by so far unknown pollutants
- known causes
  - **primary** (= inborn) – Fanconi´s
  - **secondary** (= acquiered):

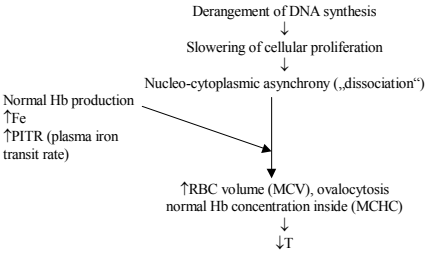
211 Decreased erythropoietin
Impaired production by the kidneys - **anemia of renal failure**
Low oxygen requirements - **anemia of endocrine disease** (hypothyreoidism)
Impaired stem cell response to erythropoietin - anemia of chronic diseases (see later)

212 Bone marrow damage or defect
Replacement of marrow by tumor (crowding out) - **myelophthisic anemia**
Replacement of normal marrow by cancerous cell line - **anemia associated with myeloproliferative disease**
Local competition for nutrients, secretion of inhibitory substances
Damage to bone marrow by physical or chemical agents, or infections – **aplastic anemia s.s.**
Benzene, chloramphenicol, analgesics, anticonvulsants, antianxiety drugs
Inherited bone marrow defect - **Fanconi's anemia:** multiple congenital abnormalities, recessive gene

22 Impairment in the maturation of new erythrocytes ⇔ **ineffective erythropoiesis**
Subcellular pathology → defective erythroblasts → intramedullary hemolysis (>50%). *The marrow is hypercellular, in spite of this, the reticulocytes are scanty, however ⇔ ineffective erythropoiesis*

221 Macrocytic-normochromic erythrocytes

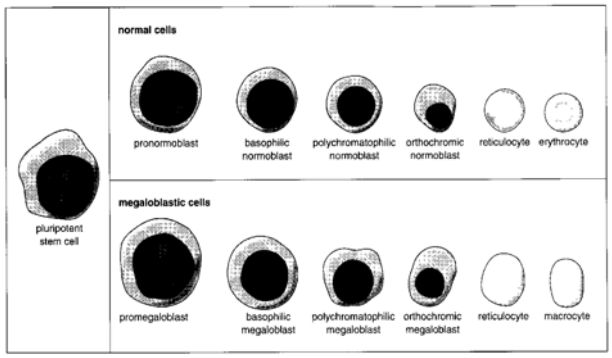




↓RBC, ↓HTC, anisocytosis and poikilocytosis always present, ↓leucocytes and platelets, hypersegmented neutrophils
Atrophic glossitis, purpura

Folic acid deficiency (**Megaloblastic anemia**, Fig. 16)

Folate compounds widely distributed in nature, rich in the dietbut small body stores.



16

Folate compounds widely distributed in nature, rich in the diet, but small body stores. Fig. 17.

	Vitamin B_{12}	Folate
Normal dietary intake	7–30 μg	600–1,000 μg
Main sources	Animal produce	Liver, greens, and yeast
Cooking effect	Minimal	Easily destroyed
Minimal daily requirement	1–2 μg	100–200 μg
Body stores	2–3 mg (sufficient for 2–4 years)	10–12 mg (sufficient for 4 months)
Absorption site	Ileum	Duodenum and jejunum
Mechanism	Intrinsic factor	Conversion to methyltetrahydrofolate
Limit	2–3 μg daily	50–80% of dietary content
Intracellular physiological forms	Methyl- and adenosylcobalamin	Reduced polyglutamate derivatives
Therapeutic form	Hydroxycobalamin	Folic (pteroylglutamic) acid

17

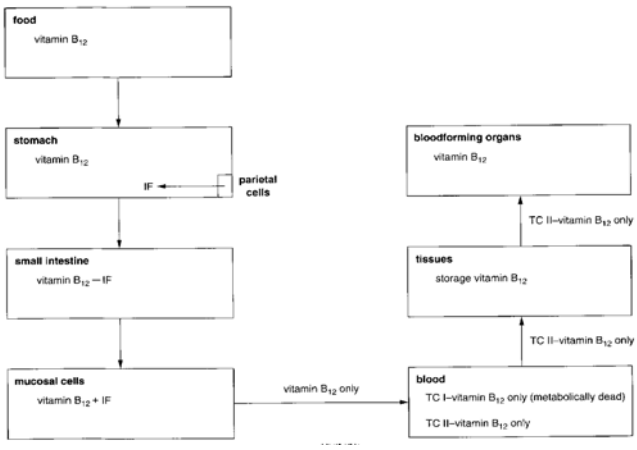
Decreased intake: alcoholism, hepatic diseases, tropical sprue (←coliform bacteria), malabsorption, resections. Increased requirements: gravidity, growth, ↑hematopoiesis. Folic acid antagonists: cytostatics, chemotherapeutics, antiparasitic and anticonvulsive drugs

Function of tetrahydrofolate: coenzyme for single-carbon transfers → necessary for thymidylate synthase → rate limiting for DNA synthesis

Vitamin B_{12} deficiency (Megaloblastic anemia)

Synthetized by microbes only → in foods of animal origin. Requirements small, stores large.

Absorption of B_{12} Fig. 18



18

Function of B_{12}: myelin (→**funicular myelosis**) and folate synthesis

Deficiency:

- total vegetarianism
- malabsorption syndromes (jejunal bacterial overgrowth, enteritis, intestinal parasites)
- lack of intrinsic factor ⇔ **pernicious anemia**
  - adults: genetic, autoantibodies against parietal cells or IF→ chronic atrophic gastritis
  - children: rare, inherited, abnormalities of IF

<u>222 Microcytic-hypochromic erythrocytes</u>

Iron deficiency (**Iron deficiency anemia**)

Fe absorption

in animal food – in hem

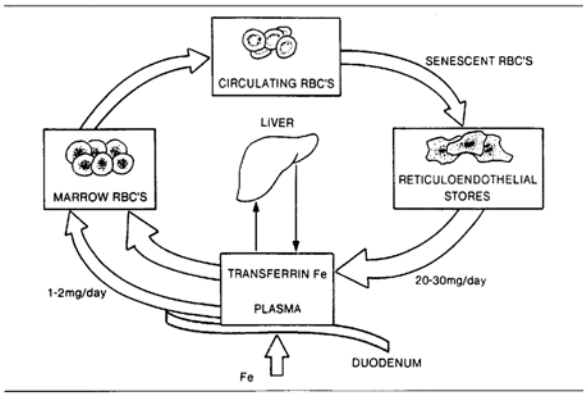
in plant food – inorganic

- Fe^{2+} } easily absorbable
- Fe^{3+} presupposes low pH in the stomach for solubilization

Absorption is regulated by the needs (i.e., by hematopoiesis) – by the Fe content in the mucosal gut cells

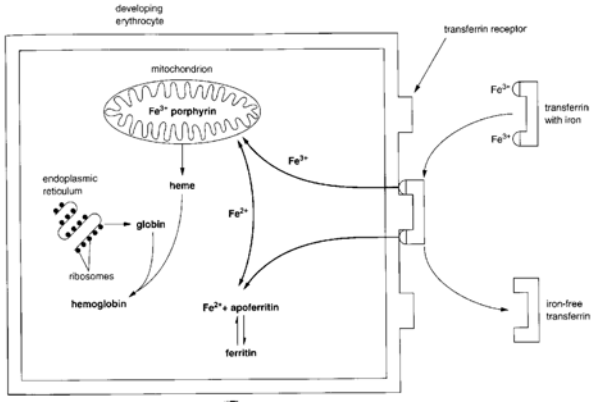
Etiology of Fe deficiency: blood losses, ↑need, malabsorption

Iron metabolism (Fig. 19)



19

Incorporation of Fe into the erythroblasts only from transferrin
Fig. 20



20

Ferritin: a protein envelope surrounds a microcrystalic core of inorg. Fe

Fe overload: disturbance of the gut mucosal cells.

Hemosiderosis = RES cell containing hemosiderin,

hemochromatosis = various organs contain hemosiderin

Clinic: angular stomatitis, glossitis, koilonychia, dysphagia, pica, no sideroblasts, typical serum composition (Fig. 21)

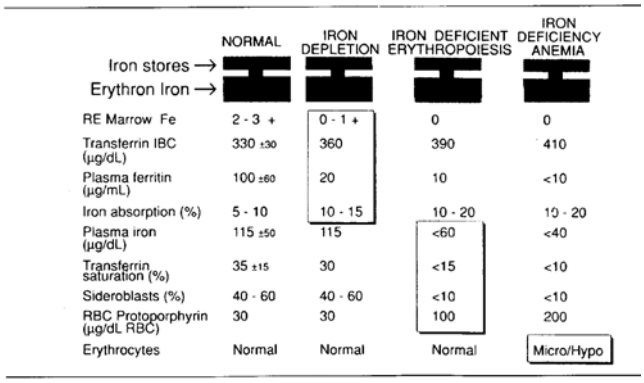
Plasma iron, total iron binding capacity and ferritin in anemias

	Plasma iron	Total iron binding capacity	Ferritin
Iron deficiency anemias	↓	↑	↓
Megaloblastic anemias	↑	−↓	−
Hemolytic anemias	↑	−	−↑
Hypoproliferative sideroblastic anemias	↑	−	↑
Anemia of chronic disease	↓	↓	−↑

− norm, ↑increased, ↓decreased

21

Development of microcytic anemia (Fig. 22)



22

Other microcytic-hypochromic anemias

Abnormalities of the heme or globin synthesis →

↓Hb production → more than 4 divisions →

microcytosis and hypochromia

Unavailability of iron to blast cells - Anemia of chronic disease (ACD)

Block of Fe metabolism: macrophages degrading Hb of the decayed RBC are activated, proliferate and retain Fe for themselves

↓ hepatic syntheses → ↓transferrin together with plasma Fe

(Fig. 23)

Plasma iron, total iron binding capacity and ferritin in anemias

	Plasma iron	Total iron binding capacity	Ferritin
Iron deficiency anemias	↓	↑	↓
Megaloblastic anemias	↑	–↓	–
Hemolytic anemias	↑	–	–↑
Hypoproliferative sideroblastic anemias	↑	–	↑
Anemia of chronic disease	↓	↓	–↑

– norm, ↑increased, ↓decreased

23

Fe storage normal or ↑

Besides

- ↓ EPO production or its binding to the stem cells (loss of EPO receptors, disturbed coupling)
- ↓ RBC life span

Etiopathogenesis: foreign antigenes pertaining to the inflammatory process → activation of macrophages →

Il-1 and TNF production: → Fe metabolism in MF disturbed; direct inhibition of EPO production

Conditions: chronic inflammations (e.g. hepatitis), some malignancies, collagen-vascular diseases

Impairment of heme synthesis (**Sideroblastic = sidero-achrestic anemia**)

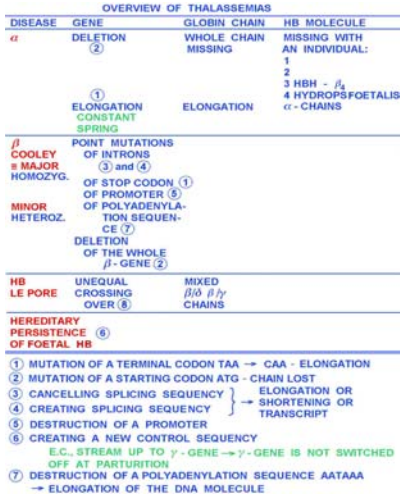
Fe into mitochondrias → ring erythroblasts

Etiology:

- inherited – aminolevulate synthetase – rate limiting
- acquiered – somatic mutation – cell clone

Impairment of globin synthesis (**Thalassemia syndromes**)

Fig. 24



24

3 Increased erythrocyte loss

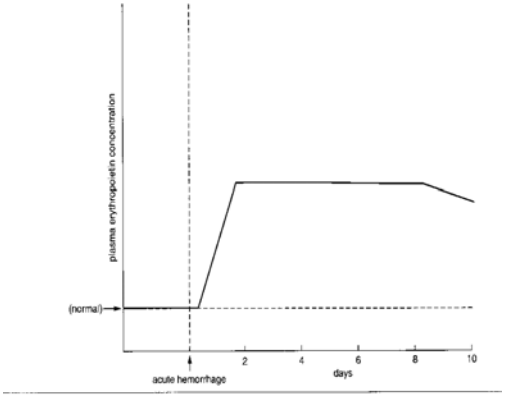
31 Hemorrhage ⇔ **hemorrhagic anemia**

Acute: influx of interstitial fluid into the circulation (several days) → progressive fall of Hb, HTC, RBC

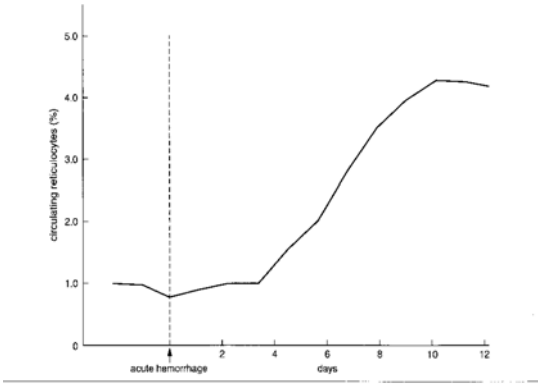
EPO and reticulocyte response (Fig. 25 and 26)

Chronic: GI ulcers and malignancies, menstruation.

Iron stores ↓



25



26

32 Intravascular hemolysis or premature phagocytosis ⇔ **hemolytic anemia**

321 Hereditary factors

Defects in the erythrocyte membrane

Hereditary spherocytosis

RBC flexibility is conditioned by the unique structure of the RBC membrane, and this is maintained by actin, spectrin, and ankyrin. Spectrin gene mutates most often

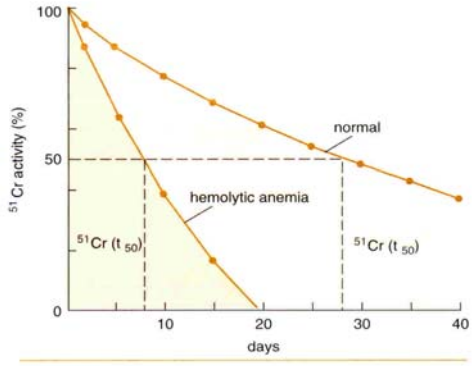
a) Mutated RBC → loss of flexibility → pitting in the splenic sinuses → RBC shrinking → getting spherical → loss of flexibility → destruction in the spleen

b) Mutated RBC → slowering of the Na/K-ATPase → Na into RBC → water into RBC → getting spherical etc.

c) Mutated RBC → enhanced need of glucose → lowered glucose concentration in the spleen → enhanced trapping of the microspherocytes

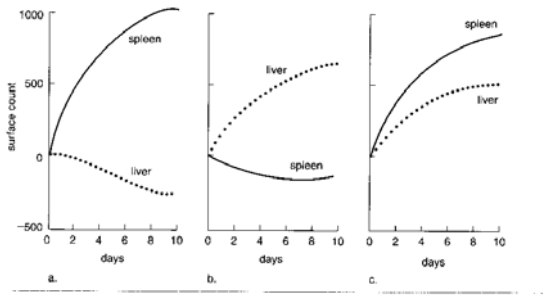
Symptomatology:
Mild anemia only
Bilirubin gale stones
Osmotic fragility test - series of salt solutions of increasing concentration
↑ sensitivity of RBC to a medium without glucose

Survival time by ^{51}Cr (Fig. 27)



27

Surface counting patterns of ^{51}Cr-labeled RBC (Fig. 28)
Splenectomy!



28

Hereditary elliptocytosis

Mild anemia, in combination with other anemizing factors only
Again a membrane defect of actin-spectrin-ankyrin skeleton
No therapy

Defects in erythrocyte metabolism

G6-PD deficiency anemia

95% of all glucose metabolism enzyme deficiencies
Triggering factors: oxidizing drugs, infections (→ activation of leucocytes producing active oxygen radicals)
Favism is a unique phenomenon – fava beans (contain an oxidant L-dopa)

Measuring of the G6-PD activity in the RBC → changing of the eating habits

Pyruvate kinase deficiency anemia

Embden-Meyerhof pathway, decline of ATP production, symptoms may be severe, specific enzyme assays (no other specific features), drugs not implicated in pathogenesis

Abnormal hemoglobin production

Point mutations of Hb are mostly innocent, a small fraction is pathogenic: ↓ solubility and precipitation, ↑↓ affinity to oxygen, unstability of quaternal structure and Hb denaturation

Sickle-cell anemia, HbC disease, HbD disease, HbE disease

See lecture on genetics

322 Acquired accelerated hemolysis

Approximately:

hereditary hemolysis ⇔ factors intrinsic to the RBC

acquiered hemolysis ⇔ factors extrinsic to the RBC

Physiological aging of RBC → their defense mechanisms↓ → *intravascular hemolysis or phagocytosis in mononuclear phagocytes* (MF, reticular and endothelial cells). The environmental stressing factors shorten the RBC life span further. They are present to a degree already under physiologic conditions in most people.

These physiological/pathophysiological factors are of chemical, physical or immunological nature. The boundary between physiological and pathological is fuzzy here:

- AB0 incompatibility is present in 23% of all gestations (hemolysis is very uncommon here, however)
- Paroxysmal nocturnal hemoglobinuria is rather common (mild hemolysis)
- Metabolic stress is ubiquitous

3221 Activation of the immune system ⇔ **immuno-hemolytic anemia**

Classification of immunohemolytic anemia (IHA)

Alloantibodies ⇔ hemolytic disease of the newborn (HDN)

AB0

Rh

Autoantibodies

Warm-active antibodies

Cold-active antibodies

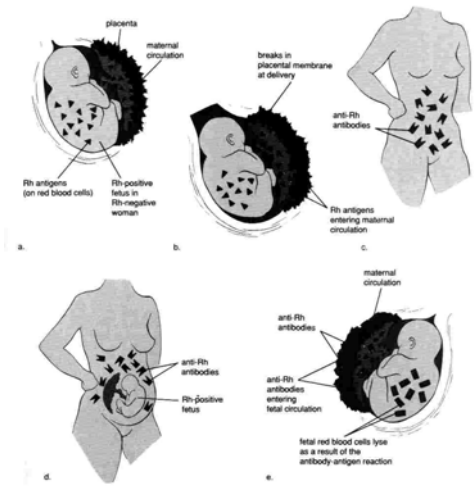
Alloantibodies

AB0 incompatibility

Mother 0 has antibodies against A and B already spontaneously (in contradisticition to Rh- mothers, in whom the antibodies not are formed before the first parturition), and these reach the foetus via placenta. Not easily, however – they are IgM, therefore large molecules, so the symptoms are mild

Antigen-antibody complexes → complement activation → premature lysis of RBC

Rh incompatibility – (Fig. 29)



<15% of Rh- mothers

At the first parturition, the RBC penetrate from the foetus into the mother → production of anti-Rh+-antibodies. The RBC having penetrated during the parturition could be killed by timely administration of anti Rh+ antibody (RhoGAM).

In the next gravidity, small numbers of the fetal RBC may get into the maternal circulation → anamnestic response → higher antibody titers of IgG (readily pass the placenta) → HDN in the foetus

Symptoms:

Hemolysis → erythroblastosis

Inability to conjugate bilirubin → jaundice (possibly s.c. kernikterus, into the basal ganglia)

Residual concentration of the mother´s antibody after birth → slowering of growth; exchange transfusion

Autoantibodies ⇔ autoimmune hemolytic anemias (AIHA)

Warm type AIHA

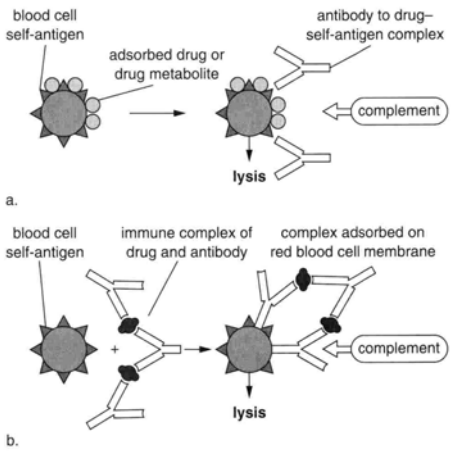
IgG against RBC membrane antigens

Types:

Idiopathic – antibodies against the proper RBC are formed. Common autoimmunity mechanisms could be considered:

- Molecular mimicry with some microbe
- Lowered function of T_S → production of antibodies
- Polyclonal B cell activation
- Enhanced presentation of antigens etc.

Drug induced (Fig. 30)



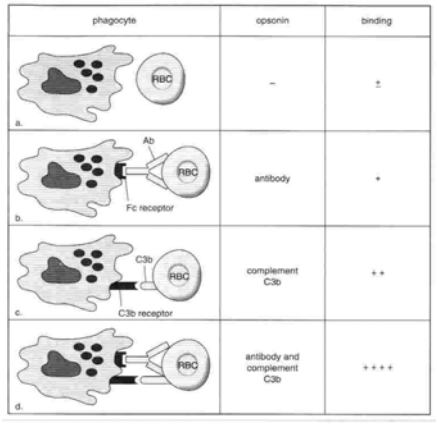
The drug is a hapten and in a complex with a carrier protein → production of antibodies. Three possibilities:

- a drug with a surface RBC antigen → neoantigen → production of antibodies and opsonization, e.g., penicillin
- a drug and serum protein (instead of RBC protein) → neoantigen → complexes are deposited on RBC membrane, e.g., antimalarics, sulfonamides, phenacetin

Alfa-methyldopa (antihypertensive drug) triggers the gene for the Rh factor

With other diseases: leukemias, SLE, inf. mononukleosis

Pathogenesis of warm type AIHA (Fig. 31):



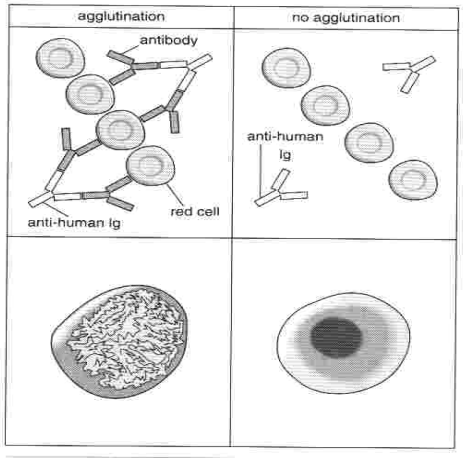
RBC coating with an antibody = opsonization → binding of MF on RBC → pitting by means of nipping of → RBC sphericity → loss of flexibility → trapping

Opsonization rarely leads to intravascular hemolysis

Symptoms of warm-type AIHA:
Are mild, hemolysis is compensated
Pitting → spherocytes, microcytes

Direct Coombs test (Fig. 32): Antiserum against anti-RBC antibodies is formed in rabbits → RBC agglutination. IgG alone cannot bridge the repulsive force between RBC (= zeta potential), IgG + anti-IgG antibody can do it → agglutination

Therapy: corticosteroids, immunosuppresive drugs



32

Cold type AIHA

IgM against s.c. **I antigen** on the RBC surface, present also normally. IgM bridge the zeta potential → they activate complement easily

Etiology:
Enhanced anti-I antibodies
- idiopathic
- in infectious diseases (cause unknown): mycoplasma, inf. mononucleosis, lymphoproliferative diseases

Patogenesis:
cooling → I antigens are better accessible to the antibodies

Complexes on RBC → complement activation → C3b fragment → intravascular hemolysis and agglutination

Symptoms:
Anemia only mild, but blocking of small extremity and acral vessels → painful blanching of the skin
The withdrawn blood agglutinates spontaneously in the room temperature

3222 Physical factors ⇔ **red cell fragmentation syndromes**

Etiology:
a) Long-distance running or marching (intravascular destruction of the RBC in the microcirculation of the feet due to the repeated crashes of the soles with hard surfaces – **march hemoglobinuria**)
b) Artificial heart valves - **traumatic cardiac hemolytic anemia. Schistocytes** often present (sickles)
c) Vasculitis or disseminated intravascular coagulation (DIC → production of multiple intravascular thrombi) → the blood is driven through the narrowed vessels → mechanical damage to RBC

3223 Chemical agents
Various forms of hemolytic anemia
Lead, copper salts, nitrobenzene, aniline, naphtalene
Aspirin, phenacetin, antimalarics, sulfonamides…
In high doses, they damage not only the G6-PD defective RBC, but also normal ones
Natural poisons (spiders, insects, snakes)

3224 Microorganisms
Various forms of anemia (e.g., anemia of malaria)
Multiply in the RBC – genus Plasmodium
Lyse the membrane – Clostridium welchii
Produce polysaccharides which are adsorbed to RBC → antibodies

3225 Secondary to other diseases
Various forms of anemia (e.g., anemia of hepatic failure)
Many inflammatory and malignant diseases

Renal failure – echinocytes (burr cells)
Hepatic diseases

3226 Sensitivity to complement ⇔ **paroxysmal nocturnal hemoglobinuria**
Unknown factor (somatic mution?) → complement activation in the RBC membranes (by the alternative way)
Pancytopenia
Loss of Fe via urine
Venous blood clots
Testing: a small quantity of complement lyses RBC