Anemias

1. In general

- Decreased erythrocyte production
- Increased erythrocyte loss

2. Decreased erythrocyte production

- Decreased proliferation of new erythrocytes = aplastic anemia
- Increased erythropoiesis (Fig. 15)

Classification of anemias (Fig. 14 a,b)

- Decreased erythrocyte production, due to impaired production by the kidneys
- Decreased erythrocyte production, due to impaired marrow response to erythropoietin
- Decreased erythrocyte production, due to decreased marrow reserve
- Increased erythropoiesis
- Medullary erythropoiesis
- 2,3 diphosphoglycerate
- Pulmonary and cardiac function
- Acute blood loss:
  - 30% of volume (1500 mL) → circulatory colaps, shock
  - > 50% loss → death

Symptoms: under 80g Hb/L

Hemolysis → jaundice, splenomegaly, cholelithiasis

↓ O₂ diffusion → vasoconstriction of skin and kidneys

Pulmonary and cardiac function → ↑

Medullary erythropoiesis → ↑

2,3 diphosphoglycerate → shift of the Hb curve to the right → ↑O₂ delivery to the tissues

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No “emergency” pool of RBC, premature release of reticulocytes only

The marrow RBC production can rise up to 8 times, if there is Fe enough

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The marrow RBC production can rise up to 8 times, if there is Fe enough
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 transplantsations and immunosuppression (cyclosporine and antilymphocyte serum)

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

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

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 B₁₂ deficiency (Megaloblastic anemia)

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

Absorption of B₁₂, Fig. 18

Function of B₁₂: 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

222 Microcytic-hypochromic erythrocytes

Iron deficiency (Iron deficiency anemia)

Iron absorption in animal food - in hem Fe⁺⁺⁺ easily absorbable
in plant food - inorganic Fe⁺ 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)
Incorporation of Fe into the erythroblasts only from transferrin
Fig. 20

Ferritin: a protein envelope surrounds a microcrystalline 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)

Development of microcytic anemia (Fig. 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

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<th>Plasma iron</th>
<th>Total iron binding capacity</th>
<th>Ferritin</th>
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<tr>
<td>Iron deficiency anemias</td>
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<td>Megaloblastic anemias</td>
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<td>Hemolytic anemias</td>
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<td>Hypoproliferative anemic anemias</td>
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<td>Anemia of chronic disease</td>
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- norm, ↑ increased, ↓ decreased

- 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 antigens pertaining to the inflammatory process → activation of macrophages → II-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 = sideroachrestic anemia)

Fe into mitochondrias → ring erythroblasts

**Etiology:**
- inherited – aminolevulate synthetase – rate limiting
- acquired – somatic mutation – cell clone

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

Fig. 24

### 3 Increased erythrocyte loss

#### 3.1 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 ↓
32 Intravascular hemolysis or premature phagocytosis ⇔ hemolytic anemia

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 mutate 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 → slowing 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 gall 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)

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
See lecture on genetics

322 Acquired accelerated hemolysis
Approximately:
hereditary hemolysis ⇔ factors intrinsic to the RBC
acquired 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.

3221 Activation of the immune system ⇔ immunohemolytic anemia

Classification of immunohemolytic anemia (IHA)

Alloantibodies ⇔ hemolytic disease of the newborn (HDN)
AB0
Rh
Autoantibodies
Warm-active antibodies
Cold-active antibodies

Allantibodies

AB0 incompatibility

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

Mother 0 has antibodies against A and B already spontaneously (in contradistinction 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 titer of IgG (readily pass the placenta) → HDN in the foetus
Symptoms:
- Hemolysis → erythroblastosis
- Inability to conjugate bilirubin → jaundice (possibly s.c. kernicterus, into the basal ganglia)

Residual concentration of the mother’s antibody after birth → slowing 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, immunosuppressive drugs

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, naphthalene
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 mutation?) → 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