PERIPHERAL CYTOPENIAS
differential diagnosis

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BLOOD COUNT

leukocytes		4,0-10,0·10^9/l
erytrocytes	♂	4,2-5,9·10^{12}/l
	♀	3,9-5,2·10^{12}/l
hemoglobin	♂	140-180 g/l
	♀	120-160 g/l
hematocrite	♂	42-50 %
	♀	35-47 %
MCV		80-100 fl
MCH		28-34 pg
MCHC		320-360 g/l
RDW		11,0-14,5 %
thrombocytes		150-400·10^9/l

differential count (relative):	
neutrophils	45-70 %
lymphocytes	20-45 %
monocytes	3-10 %
eosinophils	0-7 %
basophils	0-2 %
differencial count (absolute):	
neutrophils	1,5-7,5·10^9/l
lymphocytes	1,0-3,5·10^9/l
monocytes	0,1-1,0·10^9/l
eosinophils	0,04-0,5·10^9/l
basophils	0,01-0,1·10^9/l

ANEMIAS

CLASSIFICATION OF ANEMIAS

PATOPHYSIOLOGICAL CRITERIAS

- **anemias from insufficient or defected RBC production:** decreased proliferation, proliferation of abnormal clone, defect of hemoglobin production, shortage of substances necessary for normal proliferation and differentiation
- **anemia from increased RBC destruction:** hemolysis, bleeding

MORPHOLOGICAL CRITERIAS

- **according to MCV:** microcytic, normocytic and macrocytic
- **according to MCHC:** normochromic and hypochromic
- **according to number of reticulocytes:** anemia with low, normal and high reticulocytes count

MICROCYTIC ANEMIA

- **MCV < 80 fl**
- **usually hypochromic**
- **reticulocytes count is not increased**

<u>laboratory examination:</u>

serum iron		6,0-26,6 µmol/l
ferritin	♂	20-230 µg/l
	♀	10-180 µg/l
TIBC		44-72 µmol/l
TRF saturation		23-28 %
solubile TRF receptor		1,7-3,7 mg/l
RDW		12-15 %

MICROCYTIC ANEMIA

- iron defficiency anemia
  - excessive loss: GIT, urogenital tract, dialysis, blood donors
  - insufficient intake: composition of diet, defect in absorption
  - higher consumption: gravidity, growth
- anemia of chronic disease
  - chronic infection
  - chronic inflammation
  - tumors
- thalassemias: most common is β–thalassemia minor
- sideroblastic anemias
  - inborn
  - acquired: RARS, RCMD
  - temporary: alcoholism, drugs (isoniaside, chloramphenicol, azathioprine)

MICROCYTIC ANEMIA

DIFFERENTIAL DIAGNOSIS

	Fe	TIBC	satTRF	ferritin	TRF receptor	RDW
iron defficiency anemia	↓	↑	↓	↓	↑	↑
anemia of chronic disease	↓	↓	N	N	N	N
thalassemia	N or ↑	N or ↓	N or ↑	N or ↑	↑	N or ↑

MACROCYTIC ANEMIA

- **MCV > 100 fl**
- **reticulocytes count is not increased**
- **megaloblastic anemias: deficiency of vitamin B_{12} or folic acid**
  - **defect of absorption: intrinsic factor, bowel diseases etc.**
  - **defect of transportion**
  - **increased consumption: pregnancy, growth**
  - **increased loss: dialysis**
  - **drugs: methotrexate, pyrimethamine, mercaptopurine**
- **macrocytic anemia without presense of megaloblasts**
  - **liver diseases, hypothyreosis, alcoholism**

<u>laboratory examination:</u>

vitamin B_{12}	190-660 ng/l
folic acid	3,1-17,5 µg/l

ANEMIAS WITH INCREASED RETICULOCYTES COUNT

POSTHEMORRHAGIC ANEMIA

HEMOLYTIC ANEMIA

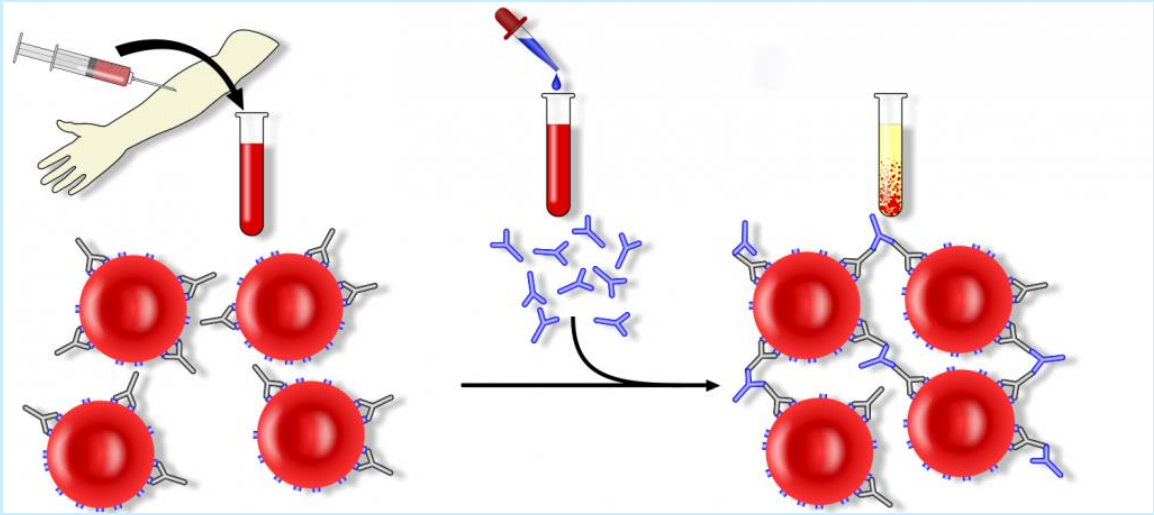
- corpuscular
  - altered composition of ery membrane: hereditary spherocytosis
  - enzymatic defect: deficit of PK and G6PD
  - defected globine synthesis: thalassemias, sickle cell anemia
- extracorpuscular
  - immune: primary vs. secondary (lymphoprolifferative disorders)
    - AIHA with warm antibodies
    - AIHA with cold antibodies
  - non-immune:
    - mechanical causes: MAHA → schistocytes (!!)
    - metabolic causes: liver diseases
    - chemic causes: venoms
    - infectious causes: sepsis, malaria

LABORATORY MARKERS OF RBC DESTRUCTION AND PRODUCTION

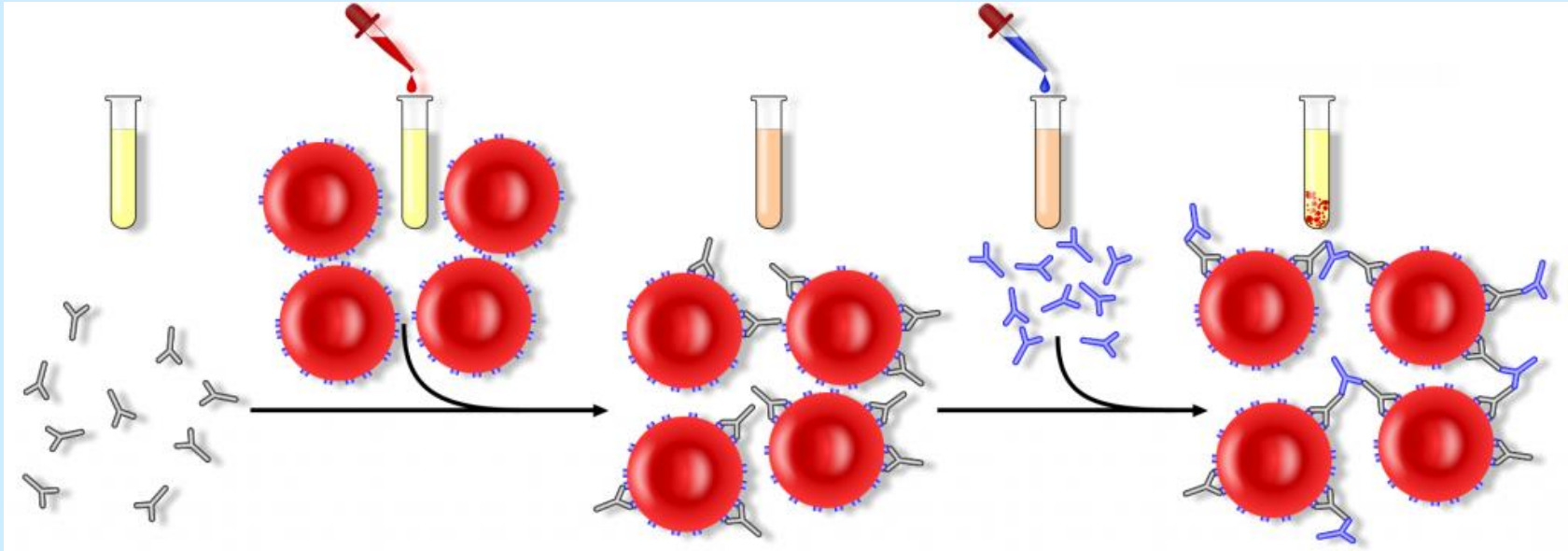
parameter	normal	hemolysis
plasma/serum: indicators of increased destrucion of erythrocytes		
free hemoglobin haptoglobin bilirubin LDH	< 100 mg/l 0,3-2,0 g/l 2,0-17,0 µmol/l 2,2-3,8 µkat/l	high (in intravascular hemolysis) low indirect is high high
urine: indicators of increased destruction of erythrocytes		
hemoglobinuria bilirubin urobilinogen	negative negative negative	positive (in intravascular hemolysis) positive (in intravascular hemolysis) positive
blood: indicators of escalated erythropoesis		
reticulocytes	$0,025\text{-}0,075 \cdot 10^{12}$/l 5-15 ‰	high
bone marrow: indicator of escalated erythropoesis		
erytropoesis	normal	high

COOMBS TEST

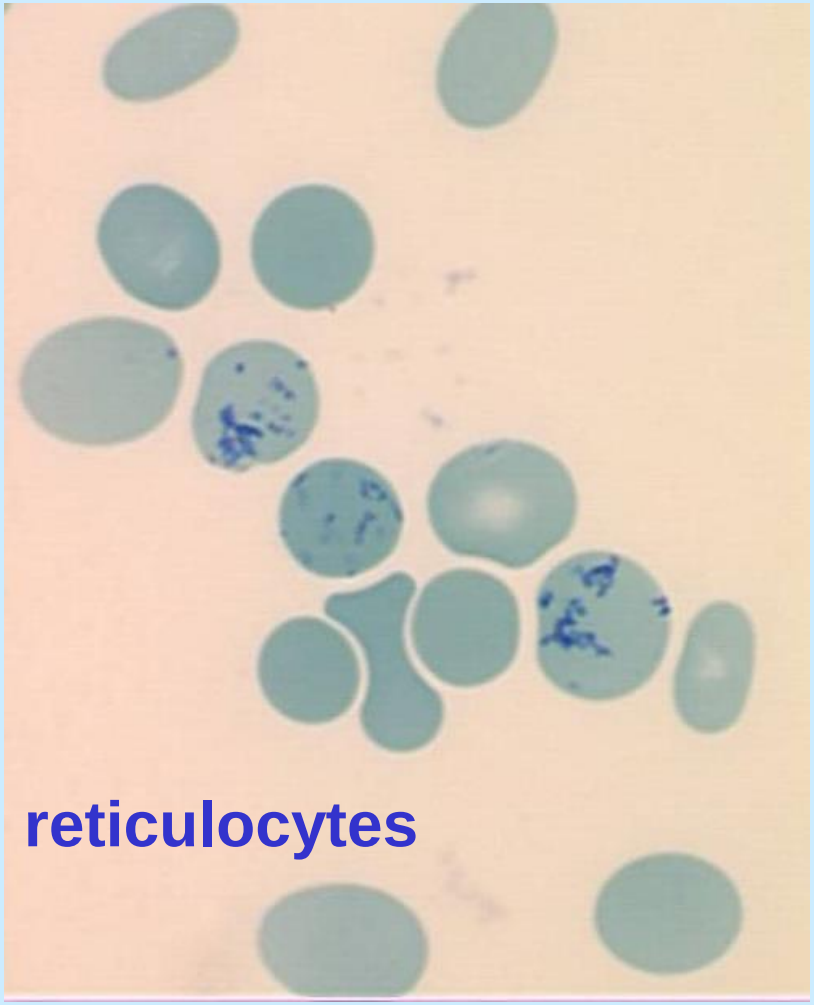
direct

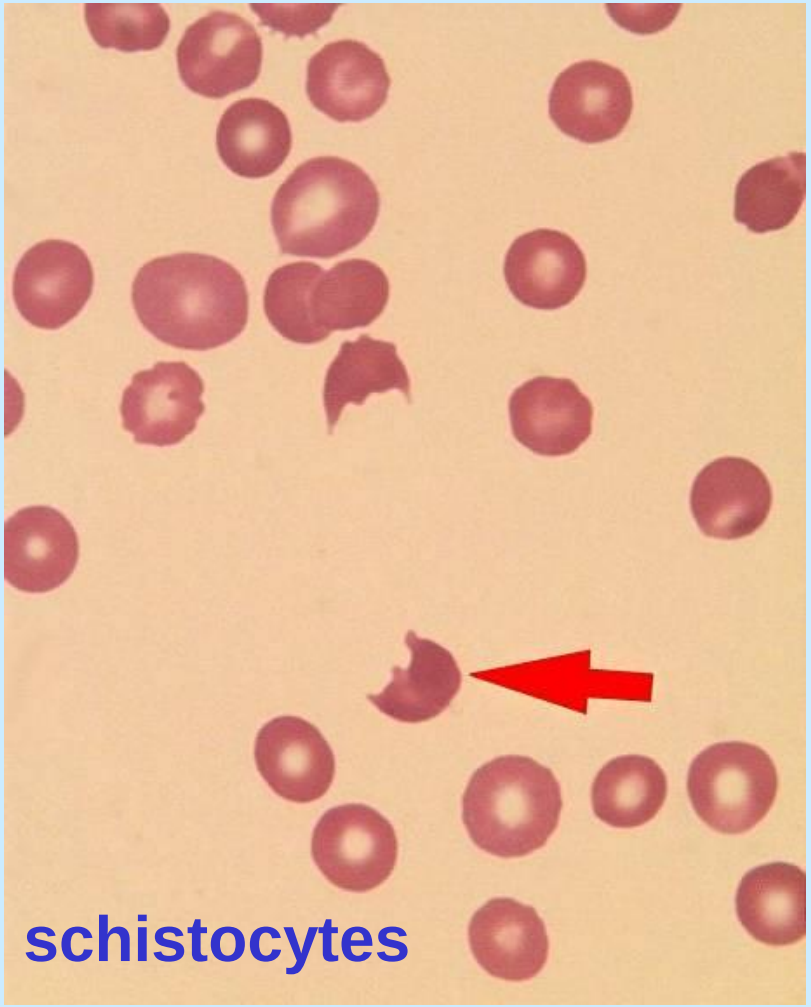


indirect



HEMOLYSIS: MICROSCOPIC FINDINGS

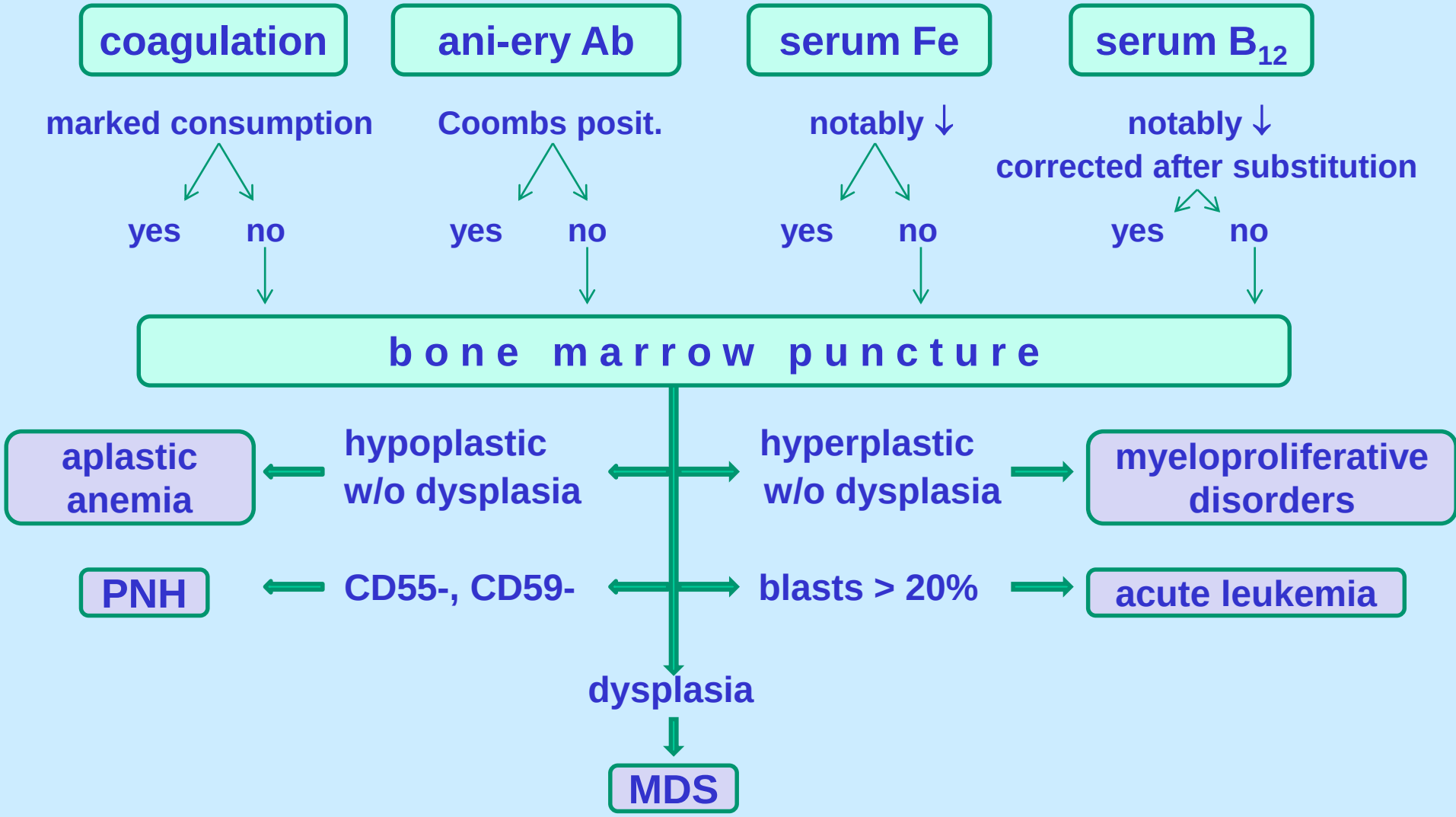




NORMOCYTIC ANEMIAS

- **MCV = 80-100 fl**
- **reticulocytes count is not increased**
- **defect of hematopoetic stem cell**
  - **aplastic anemia**
  - **poor red cell aplasia (PRCA):** thymoma, parvovirus B19
  - **myelodysplastic syndrome (early phase)**
    cytopenia in peripheral blood, hypercellular and dysplastic bone marrow: RA, RARS, RCMD
  - **paroxysmal nocturnal hemoglobinuria:** clone CD55-, CD59-
- **secondary defect of bone marrow**
  - **bone marrow infiltration (hematologic malignancies, metastases)**
  - **anemia of chronic disease**

MDS vs. OTHER CAUSES OF ANEMIA



NEUTROPENIAS

NEUTROPENIA

- neutrophils < $1,5 \cdot 10^9$/l
  mild: $1,0\text{-}1,5 \cdot 10^9$/l intermediate: $0,5\text{-}1,0 \cdot 10^9$/l severe: < $0,5 \cdot 10^9$/l

acquired:

- pseudoneutropenia: relocation of neutrophils to the marginating pool
- postinfectious
- drug induced and toxic
- nutritive
- immune based (eg. Felty syndrome)
- chronic benign neutropenia
- autoimmune neutropenia

inborn:

- severe congenital neutropenia (Kostman syndrome)
- cyclic neutropenia

LYMPHOPENIAS

LYMPHOPENIA

- lymphocytes < $1{,}0 \cdot 10^9$/l

  manifestation mainly in dominant population of CD3+/CD4+ T-lymphocytes

<u>acquired:</u>

- infection: AIDS, TBC, typhoid fever, etc.
- iatrogenic: radiotherapy, chemotherapy, immunosupressive agents
- autoimmune disorders: SLE, sarcoidosis
- nutritive

<u>inborn:</u>

- severe combined immunodeficiency (SCID)
- Wiskott–Aldrich syndrome etc.

THROMBOCYTOPENIAS

CAUSES OF THROMBOCYTOPENIA

1. SEQUESTRATION

→ clarify the cause of splenomegaly

- infection, inflammation, portal vein thrombosis, tumors, hemolysis, tesaurismoses

2. LOW PRODUCTION

→ bone marrow examination

- infiltration
- inefective megakaryopoesis (eg. MDS)
- selective disorder of platelets production

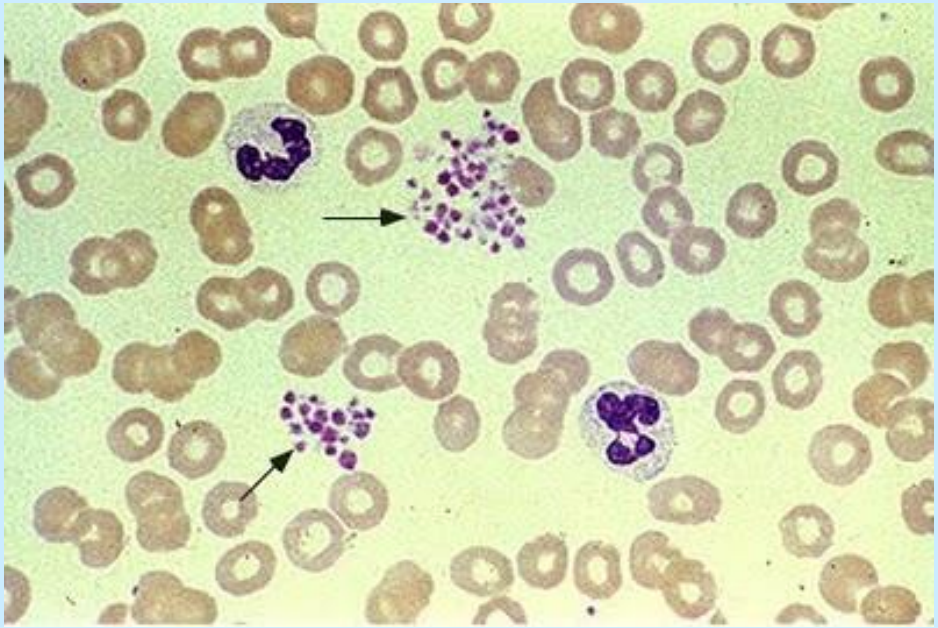
3. HIGH DESTRUCTION

→ search for the primary disease

- immune: autoimunity (ITP, SLE), drugs, infection, aloimmune reaction
- consumption: DIC, TTP/HUS, HELLP syndrome

PSEUDOTHROMBOCYTOPENIA

- false thrombocytopenia diagnosed in vitro not corresponding to the real platelet count
- 15-20 % of all isolated thrombocytopenias
- always perform confirmatory blood count test
  - repeated sampling
  - microscopic exam: thrombocytes in the smear
  - get another sample in different anticoagulant: citrate



ISOLATED vs. RELATED THROMBOCYTOPENIA

ISOLOVATED THROMBOCYTOPENIA

- most often **ITP**
  - examine antithrombocytic antibodies (serology), Ab bound on thrombocytes (flow cytometry)
  - clinical finding: purpura-like bleeding manifestaions
- in case of abnormal finding in other blood elements, full hematological examination is indicated

THROMBOCYTOPENIA RELATED WITH ANEMIA

- Coombs positive: Evans syndrome
- Coombs negative + clinical finding: **TTP/HUS**
  - pentade of signs: consumptive thrombocytopenia + MAHA + fluctuating neurological status + impairment of renal function + fever

DRUG INDUCES THROMBOCYTOPENIA

- time relation to the start of new therapy
- exclusion of other causes of thrombocytopenia
- normalisation of thrombocyte count after discontinuation

antibody induced thrombocytopenia:	aspirin, cimetidine, ranitidine, digoxin, furosemide, heparin, vaccines, β-lactam ATB (penicillin)
drug induced inhibition of trombocytopoesis:	thiazide diuretics, estrogens
drug induced consumptive microangiopathic thrombocytopenia:	ciclosporin, ticlopidin

HEPARIN INDUCED THROMBOCYTOPENIA (HIT)

- production of antibodies against complex heparin + platelet factor 4 (PF4)
- dg: thrombocytopenia + thrombotic complications + time relation to the start of heparin therapy

POSTTRANSFUSION PURPURA

- severe acute thrombocytopenia 5-10 days after transfusion (erythrocytes, plasma)
- antithrombocytic aloantibodies: most often after the first transfusion in multiparous women
- clinical findings: cutaneous/mucosal hemorhage, bleeding to GIT or urogenital tract, often with fever

PANCYTOPENIA

PANCYTOPENIA

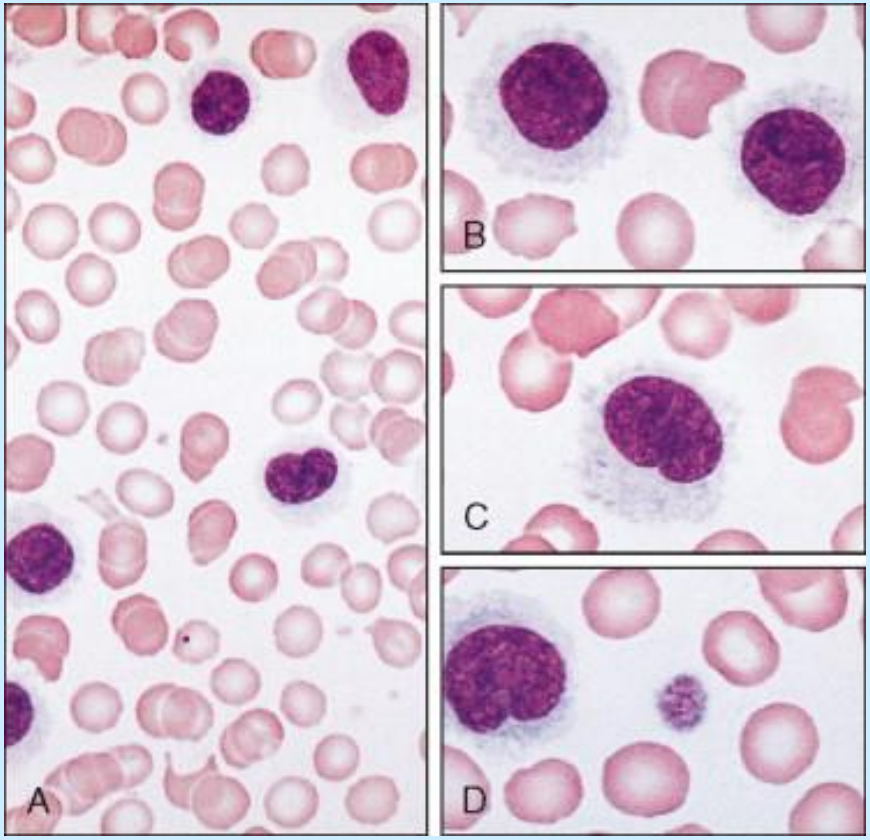
- reduction of blood elements in all 3 lineages
- necessary to exclude increased destruction in the periphery:
  - autoimmune process (reticulocytes ?)
  - disseminated intravascular coagulopathy
  - hypersplenismus
- exclude secondary ethiology
  - infection: TBC, legionella, brucella, sepsis, mycobacteria
  - endokrinne disorders: hypothyresis
  - autoimmune diseases: SLE, sarcoidosis
- bone marrow examination is indicated

PANCYTOPENIA: BONE MARROW FINDINGS

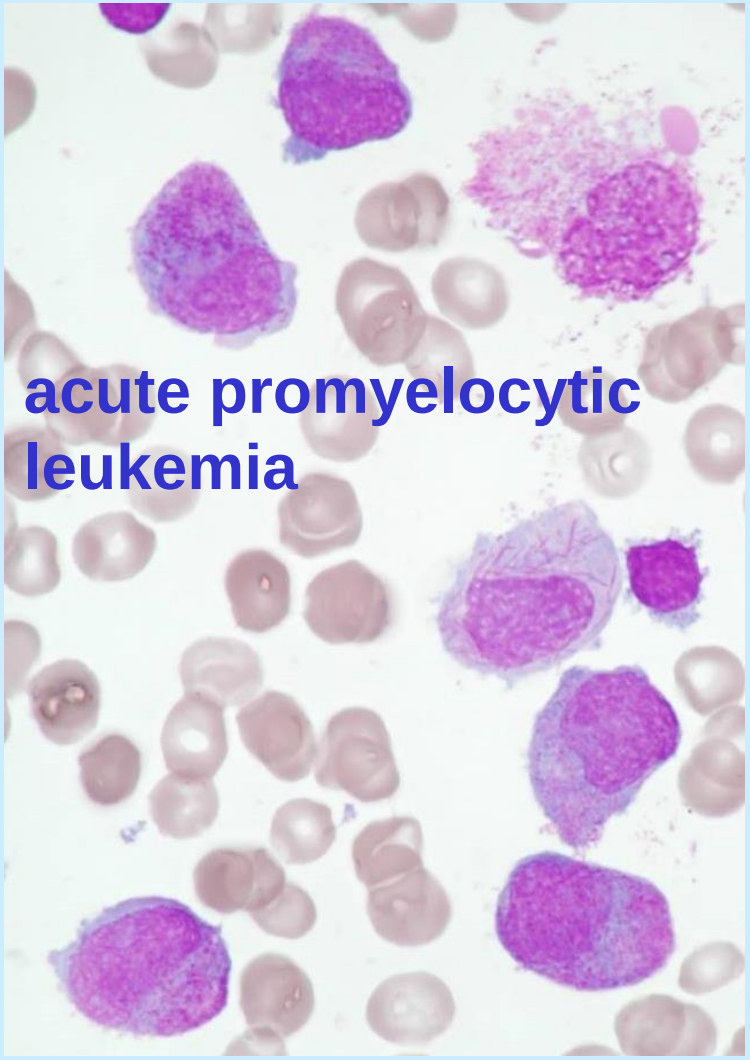
- **hypocellular marrow**
  - aplastic anemia: acquired vs. inborn
  - MDS (hypoplastic form)
- **punctio sicca**
  - myelofibrosis
  - hairy cell leukemia
  - secondary fibrosis in metastatic tumors
- **hypercellular marrow**
  - leukemias (aleukemic forma, acute promyelocytic leukemia)
  - MDS (late phases: RAEB, CMML)
  - paroxysmal nocturnal hemoglobinuria
- **infiltration by other tumors**
  - lymphoma
  - metastasising carcinoma
  - myeloma

HCL and APL: MICROSCOPIC FINDINGS

hairy cell leukemia



acute promyelocytic leukemia



SEVERE APLASTIC ANEMIA

- bone marrow cellularity < 30%
- blood count:

reticulocytes	< 1‰
neutrophils	< $0,5 \cdot 10^9$/l
thrombocytes	< $20 \cdot 10^9$/l

- bone marrow: hypocellular, no fibrosis, no dysplasia, no tumor infiltration
- idiopatic (70 %)
- known cause
  - infection: viruses (EBV, hepatitis, parvovirus, HIV)
  - radiation
  - drugs: chloramphenicol, antiepileptics, gold
  - cytostatics
  - chemic agents: benzene

THANK YOU FOR YOUR ATTENTION