Anaemias: classification and conservative treatment

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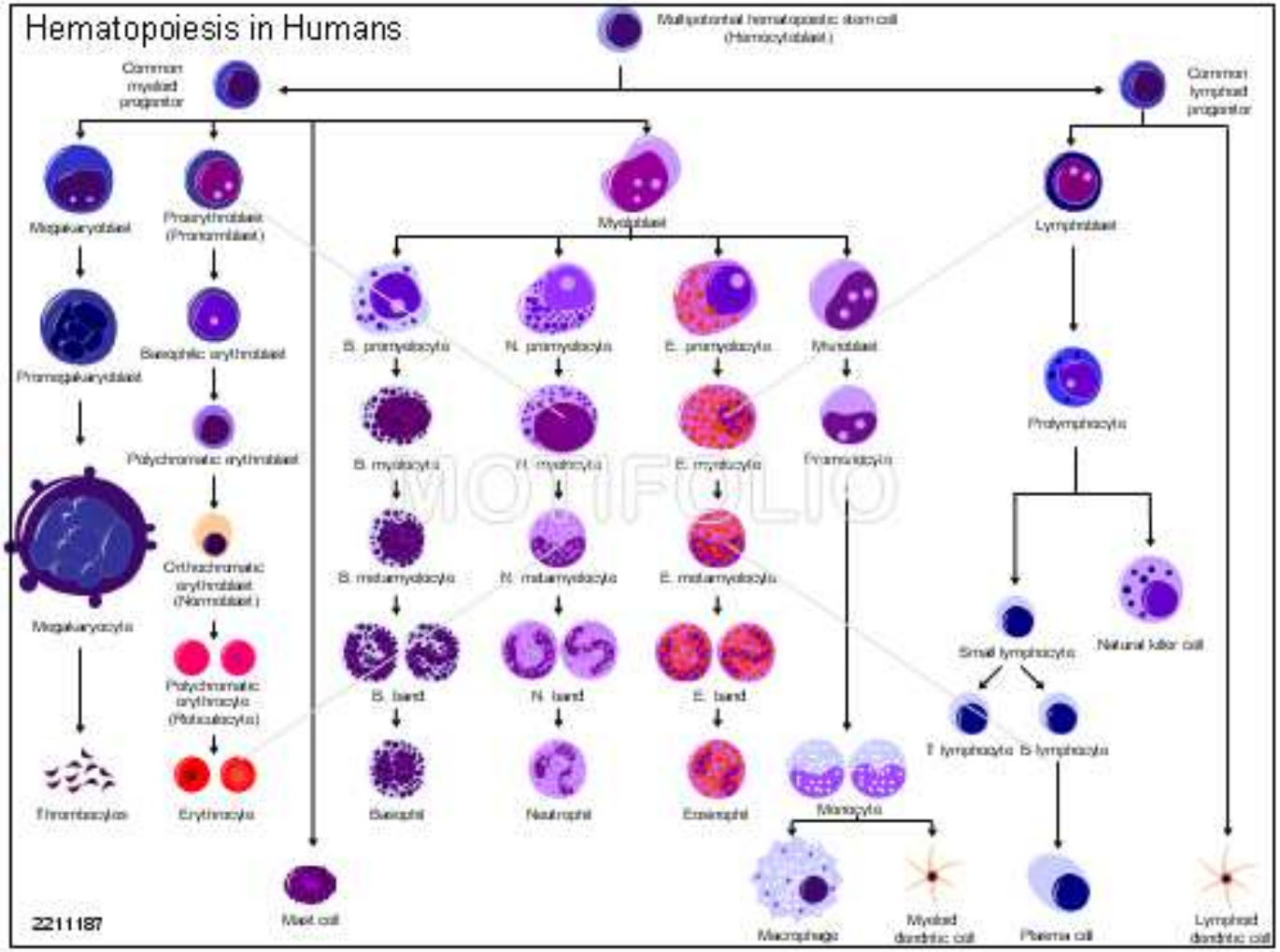
Haemopoesis



Contents

- Pathophysiology

- Iron metabolism and IDA
- ACD
- Renal anaemia
- B_{12} and folate deficiency

- Case reports

Anaemia is a symptom and not a diagnosis!

i.e.: consequence of something and not a disease per se

Erythropoesis – physiology

ερυθροζ (gr.): red; *ποιησιζ (gr.)*: production, generation

BFU_E

↓

CFU_E

↓

Proerythroblast (E1)

↓

Basophil macroblast (E2)

↓

Polychromatic macroblast (E3)

↓

Polychromatic normoblast (E4)

↓

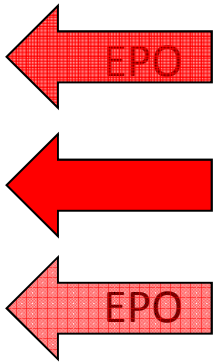
Orthochromatic normoblast (E5)

↓

Reticulocyte

↓

Red blood cell



- E1↑↑
- E1→ reticulocyte: 5 days, EPO effect: 2 days.

1 E1 → 16 RBC

Erythropoetin (EPO) I.

- Classic hormon: acts far from the site of its production, negative feed-back
- Produced by renal peritubular fibroblasts (90%) (in 10% it’s produced by the liver)
- 30.4 kD, 165 aminoacids and 4 CH chains, 60% of its is peptid, the rest is CH

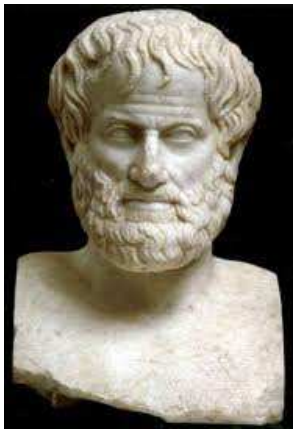
Erythropoetin (EPO) II.

- Production is increased by tissue hypoxia, this depends on:
  - O_2 tension of the sorrounding air (high altitude)
  - O_2 tension of the arterial blood (cardiorespiratory functions)
  - Haemoglobin concentration
  - Haemoglobin O_2 affinity
  - Renal arterial blood flow (polycystic kidney, hydronephrosis)
  - Renal O_2 consumption
- EPO level can increase by 2-3 logs!
- Effector cells: BFU_E , $CFU_E \rightarrow RBC\uparrow$, $Hb\uparrow$

Erythropoetin (EPO) III.

- Factors suppressing endogenous EPO production:
  - decrease of renal parenchyma:
    - renal failure
  - cytokin effect (TNF, IL-2, IFN):
    - inflammation
    - infection
    - tumor burden
  - direct deterioration of peritubular cells:
    - chemotherapy (platina-derivates)

Definition of anaemia



- αν | αιμα (*Aristotle, Historia Animalium*)
- Decrease of haemoglobin concentration, haematocrit or red blood cell count below the normal level
- Hgb: < 135 g/l (male); < 120 g/l (female)

  Htc: < 0.40 (male); < 0.37 (female)

WHO classification of anaemia based on haemoglobin level (g/l)

- Grade 0: ≥ 110 normal
- Grade 1: 95-109 mild
- Grade 2: 80-94 moderate
- Graed 3: 65-79 severe
- Grade 4: < 65 life-threatening

Anaemia – complaints and symptoms

- Complaints
  - weakness, intolerance for physical excercise
  - somnolence
  - effort dyspnoe, tachycardia, angina
  - dizziness, tinnitus
  - loss of appetite
- Symptoms
  - paleness (skin, mucous membranes)
  - tachycardia, hypotonia
  - heart failure
  - visual disturbances, psyhiatric symptoms

Tolerance for anaemia

- Level of anaemia
- Age
- Concomittant diseases (eg. cardiovascular, pulmonary)
- Speed of the development of anaemia (compensation: 2,3 DPG$\uparrow \rightarrow$ maintaining tissue oxigenisation)

Useful laboratory tests

- CBC (RBC, Hgb, Htc, WBC, PLT)
- Reticulocyte (ratio and absolute count)
- MCV, MCH
- Peripheral blood smear – cytomorphology
- SeBi, LDH
- ESR, CRP
- SeFe, Tf, Sat, SolTfR, Ferritin
- FOBT, urine sediment

- B_{12}, folic acid
- Direct Coombs test, irregular antibodies
- Haptoglobin, plasma free haemoglobin
- Erythropoetin
- Serum total protein, ELFO
- Bone marrow (cytology, Prussian-blue, FACS, cytogenetics)
- Hgb ELFO

Classification of anaemias based on etiology

- Aregenerative – decreased production
- Regenerative – increased destruction
- Bleeding
- Problems of distribution

Aregenerative – decreased production

- Erythropetic stem cell defect (aplastic anaemia, BM infiltration (precursor↓), myelodysplasia)
- Disordres of DNA synthesis (megaloblastic anaemia: deficiency of B_{12}, folic acid)
- Disorders of Hgb synthesis (iron deficient anaemia)
- Deficiency of erythropoetin (renal anaemia)

Regenerative – increased destruction

- Intrinsic RBC defects (corpuscular haemolytic anaemias)
  - Membrane defects
  - Enzime defects
  - Haemoglobinopathies
- Extrinsic causes (extracorpuscular haemolytic anaemias)
  - Allo-/autoantibodies
  - Drugs
  - Infections
  - Thrombotic microangiopathies (TTP/HUS, HELLP)
  - Physical-chemical harms
  - Metabolic disorders
  - Rare causes

Bleeding and distrubutional problems

- Acute blood loss
  - Anaemia due to bleeding
- Problems of distribution
  - Sequestration in enlarged spleen: hypersplenism
  - Pregnancy

Classification of anemias based on RBC size (MCV) and MCH

- Hypochrom microcytic (MCH↓, MCV↓)
- Normochrom normocytic (MCH→, MCV→)
- Hyperchrom macrocytic (MCH↑, MCV↑)

Hypochrom microcytic anaemias

- Iron (Fe) ↑/→
  - Thalassaemia
  - Myelodysplastic syndrome
  - ***ACD, anaemia of chronic disease***

- Iron (Fe) ↓, ferritin↓
  - ***Iron deficient anaemia***

Mentzer-index: MCV/RBC;
<12: Thalassaemia

Normochrom normocytic anaemia

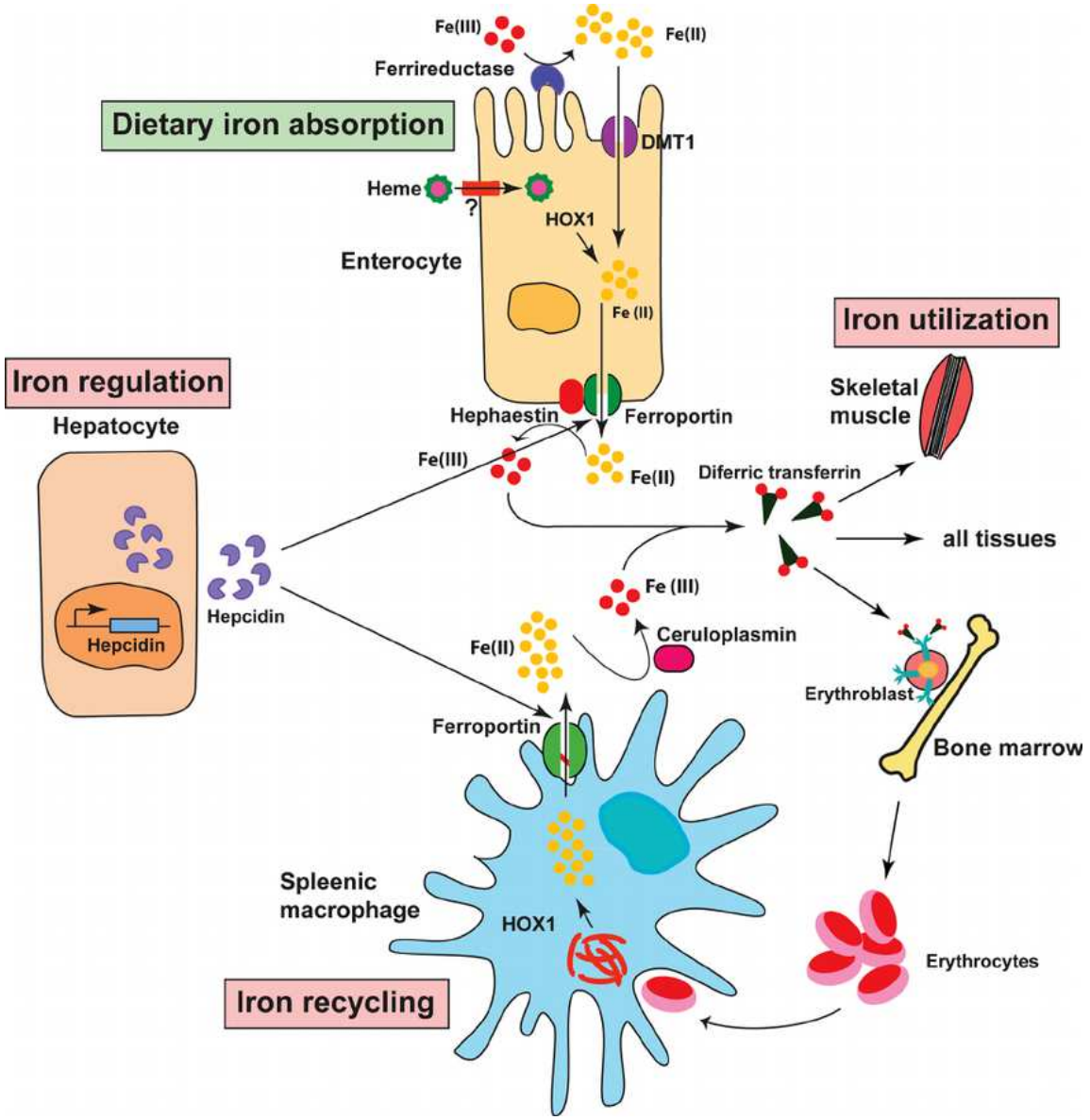
- <u>Reticulocyte ↑</u>
  - Haemolytic anaemia
  - Bleeding anaemia

  NB!: in case of high reticulocyte MCV ↑
- <u>Reticulocyte ↓</u>
  - Aplastic anaemia
  - BM infiltration (lymphoma, leukaemia, tumor)
  - ***Renal anaemia***
  - ***ACD, anaemia of chronic disease***

Hyperchrom macrocytic anaemia

- Reticulocyte $\rightarrow$/$\downarrow$
  - ***Megaloblastic anaemias (deficiency of B_{12}, folic acid)***
  - Myelodysplastic syndrome

Iron metabolism



Iron metabolism I.

- Daily iron loss: male 1 mg, young female 2 mg, pregnant/breast feeding female 3 mg
- Iron stores: **male 50 mg/bwkg**, female**: 35 mg/bwkg**
- Iron stores
  - Haem-iron – 70%
  - Storage iron (ferritin and haemosiderin) – 18%
  - Functional iron (myoglobin and enzymes) – 12%
  - Transport iron (binded to transferrin) – 0.1%
- 1 g hgb: 3,4 mg Fe; **1 ml blood: 0.5 mg Fe**

Iron metabolism II.

- Absorption
  - Proximal small intestine (<10% → 25%)
  - Fe^{2+}
  - Transport of iron: transferrin (approx. iron content 3 mg)
  - Hepcidin, ferroportin
- **Reutilisation** [RES; *reuse*: haem/myoglobin/enzymes]
  - Daily iron need of erythropoesis: 20-25 mg → volume of reutilisation is 90%!
- Storage
  - Intracellulary *ferritin* (water soluble: apoferritin + ferro-hydroxi-phosphate micells) and *haemosiderin* (non-water soluble, lysosomes developing due to autophagocytosis)
  - Liver, BM, other tissues

Iron deficient anaemia (IDA) I.

- Europe: 10% of reproductive females; developing countries: 50% of population; worldwide 25%
- 80% of all anaemias, 80% of IDA cases are females!
- Etiology:
  - *Primary:* long lasting disbalance between necessity and intake without underlying disease (infants, children, adolescents, pregnants, breast-feeders, elderly, vegans)
  - *Secondary:*
    - ***Chronic bleeding (80%!)***
    - Decreased absorbtion (resection of stomach, malabsorption (coeliac disease))
    - Problems of iron mobilisation and transport (ACD)

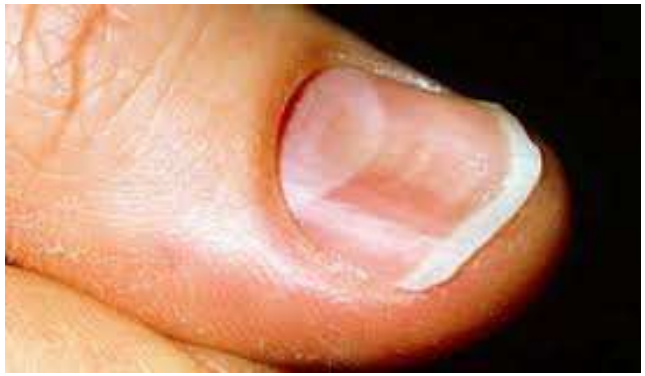
Iron deficient anaemia (IDA) II.

- Blood (haemoglobin) loss
  - Genital bleeding of females
  - GI tract
  - Other sources (urogenital, oropharynx, gums, nose, lung)
  - Bleeding due to surgery and trauma
  - Haemodialysis, frequent blood sampling, blood donation
  - Intravasal haemolysis → haemoglobinuria
  - Artefacts (Münchhausen sy.)

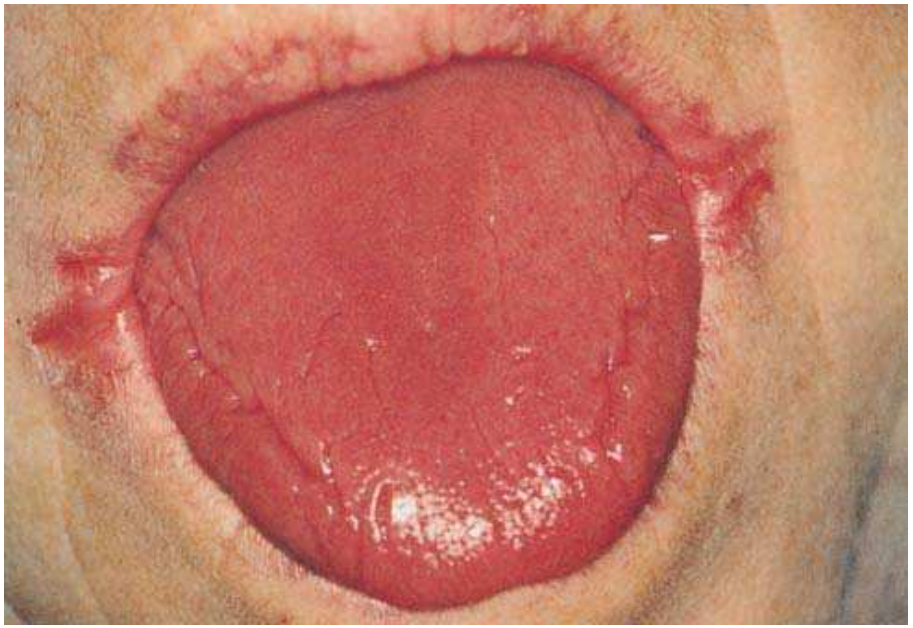
Iron deficient anaemia (IDA) III.

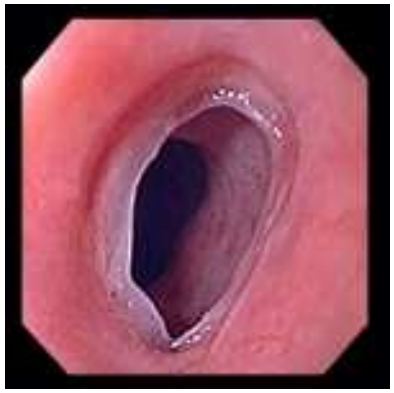
- Skin and mucous membrane symtoms: striated nails, koilonychia, fragile nails and hair, hair loss, dry skin, itching
- Plummer-Vinson sy.: iron deficient mucous membrane atrophy
- Aspecific neuro-psychiatric symptoms: headache, decreased ability to concentrate, irritability, „restless leg”, pica
- General anaemic symptoms

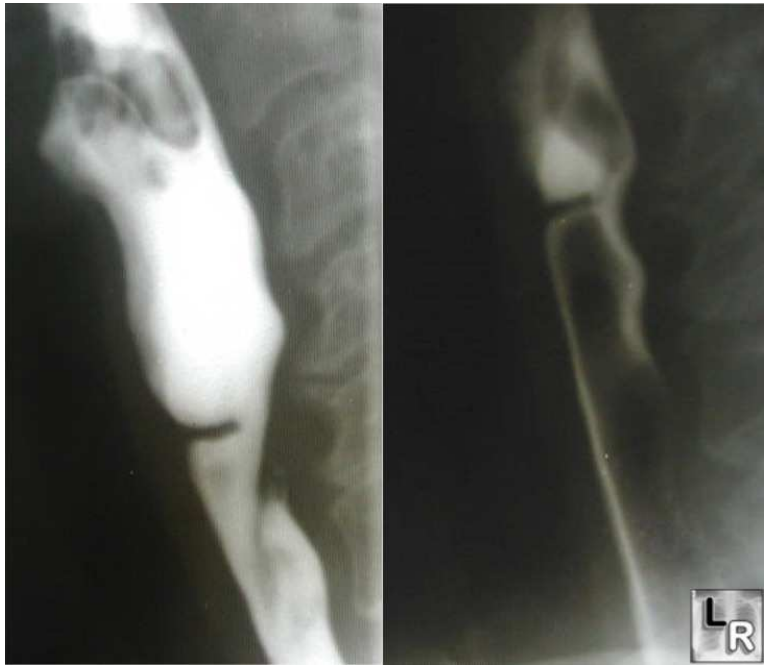
Koilonychia



Plummer-Vinson sy.







Iron deficient anaemia (IDA) IV.

- Prelatent iron deficiency
  - Ferritin↓ and BM iron storage ↓
- Latent iron deficiency (iron deficient erythropoesis)
  - + SeFe↓, TF↑, sTfR↑, Sat↓, >10% microcytes
- Overt iron deficiency = iron deficient anaemia (IDA)
  - + Hgb↓, Vvs↓, Htk↓, RBC morphology (aniso-poikilocytosis, microcytes), thrombocytosis!

Iron deficient anaemia (IDA) V.

- ***Not a disease per se, but a consequence $\rightarrow$ Search for the cause!***
- Therapy
  - Oral: 100-200 mg Fe^{2+}/die, fasting, 2$\times$ daily; overdosage impossible (haemochromatosis) – during 3-6 months; improvement of CBC after one week; GI toxicity – less with IPC (Fe^{3+})
  - Parenteral (IBD, malabsorption – test of iron absorption!, intolerance): irongluconate (Fe^{3+}) ; allergy, overdosage; ***does not act significantly faster!***

  Iron need (mg) = lack of Hgb (g/dl) $\times$ body weight (kg) $\times$ 3

  Profilactic iron supplementation during pregnancy, breast-feeding and for prematures

Anaemia of chronic disease (ACD) I.

- Normochrom (75%) or hypochrom (25%), RDW
- Underlying: inflammation, infection, tumor
- Macrophage activation
  - RBC lifetime decreases
  - Iron stored in macrophages
    (SeFe↓, TF↓, Ferritin↑)
- EPO↓ (absolute/relative) – cytokin effect
- BFU_E and CFU_E blockade – cytokin effect
- Blood loss

Anaemia of chronic disease (ACD) II.

- In case of malignant diseases:
  - BM infiltration
  - Chemotherapy
    - Suppression of EPO production
    - Direct myelotoxicity
  - Radiation therapy
    - Direct myelotoxicity

Renal anaemia

- Decreasing EPO production paralelly with the decreasing renal parenchyma
- Decrease of GFR resulting azotaemia (~BUN 20 mmol/l, ~creatinin 300 μmol/l, GFR 30 ml/min/m2)
- Normocytic, normochrom anaemia, generally moderate
- Additive effects of other factors:
  - Iron deficiency (haemodialysis)
  - ACD (uraemia is a chronic toxic condition!)
  - Infection (Cimino-fistule, CAPD)
  - Aluminium intoxication

Biochemical role of B_{12} and folic acid

- B_{12} (cobalamin)
  - catalyses: intramolecular rearrangement, methylation, reduction of ribonucleotids to desoxiribonucleotids
  - *5-desoxicobalamine* (methylmalonilCoA – succinilCoA); abnormal fatty acids↑ and incorporates to neural lipids
  - *metilcobalamine* (homocystein – methionin); disorder of folic acid synthesis: DNA synthesis, erythropoesis
- Folic acid
  - Coenzyme of C1 units; reduced to tetra- and dihidrofolates

B_{12} and folic acid metabolism

B_{12}

- Source: liver, meat, eggs
- Intrinsic factor (IF) is produced by parietal cells of stomach
- B12 + IF: absorption in terminal ileum
- Storage: 2 mg in liver, 2 mg outside of it; *enough for 3 years*
- Daily need: 5 μg

Folic acid

- Source: vegetables, liver
- Poliglutamate is deconjugated to monoglutamate in small intestine (difenilhidantoin, AC!)
- Absorbed from jejunum
- Storage: 5 mg in liver, *enough for 3 months*
- Daily need: 400 μg

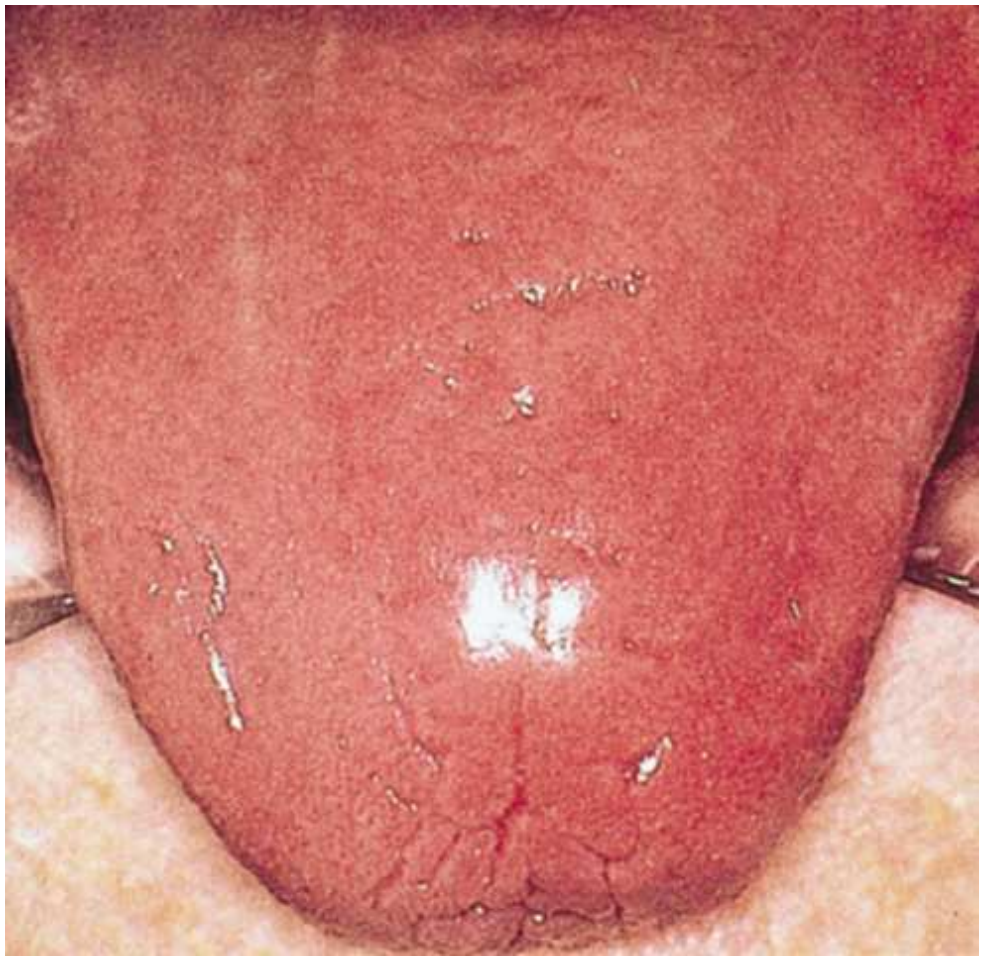
Causes of B_{12} deficiency

- Decreased intake (vegetarians)
- Lack of IF
  - After resection of stomach
  - Pernicious anaemia (PA): antibodies against parietal cells and IF, A-type atrophic gastritis
- Bowel diseases with malabsorption (M.Crohn, resection of ileum)
- Increased need (Diphyllobotrium latum)
- Bacterial overgrowth, „blind loop syndrome”

Causes of folic acid deficiency

- Malnutrition (alcoholists, old people, psychiatric patients)
- Increased need (haemolysis, pregnancy)
- Malabsorption
- Deconjugation problem caused by drugs (phenytoin)
- Folic acid antgonist therapy (methotrexat, pyrimethamin, trimethoprim, triamteren)

Hunter-glossitis; B_{12}-deficiency



Clinical aspects of B_{12} and folic acid deficiency

B12

- Macrocytic anaemia (MCV↑↑), pancytopenia, indirect SeBi↑, LDH↑↑↑, ovalo-macrocytosis, hypersegmented gr.
- GI tsymptoms
  - „A”-type atrophic gastritis in PA
  - Hunter glossitis
- Neurologic symptoms
  - Posterior tract: spinal ataxia
  - Pyramid pathway: spastic paresis
  - Psychotic symptoms

  May present without anaemia!

Folic acid

- Macrocytic anaemia (MCV↑↑), pancytopenia, indirect SeBi↑, LDH↑↑↑, ovalo-macrocytosis, hypersegmented gr.

Diagnostics of B_{12} and folic acid deficiency

B_{12}

- History, clinical features
- CBC, Lab
- B_{12} level
- BM: E hyperplasia, megaloblastic alteration, blocade of maturation, giant stab
- Schilling-test
- AB against parietal cells (>90%), AB against IF (70%), AB against thyroid (40%)
- Gastroscopy, biopsy

Folic acid

- History, clincal features
- CBC, Lab
- Folic acid level (serum and RBC)
- BM: E hyperplasia, megaloblastic alteration, bloclade of maturation, giant stab
- Schilling-test negative

Treatment of B_{12} and folic acid deficiency

B12

- Causal therapy
- 300 μg im. q.o.d. for 2 w, than 3×300 μg weekly for 2 w, than 1×300 μg monthly life long
- HD oral oral (2000 μg/die), for prevention (1% of it is absorbed)
- Potassium and iron supplementation!
- CBC will improve after 1 week: SeBi↓, LDH↓, reticulocyte↑↑; hgb/htc↑; thrombophilia!
- In PA yearly gastroscopy!

Folic acid

- Causal therapy
- 5-10 mg po. q.o.d.
- Potassium and iron supplementation!
- CBC will improve after 1 week: SeBi↓, LDH↓, reticulocyte↑↑; hgb/htc↑; thrombophilia!
- Prevention for pregnants!