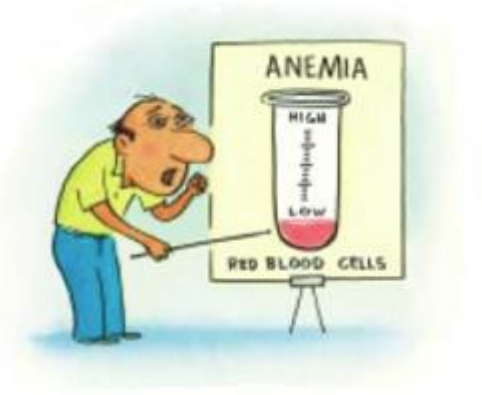
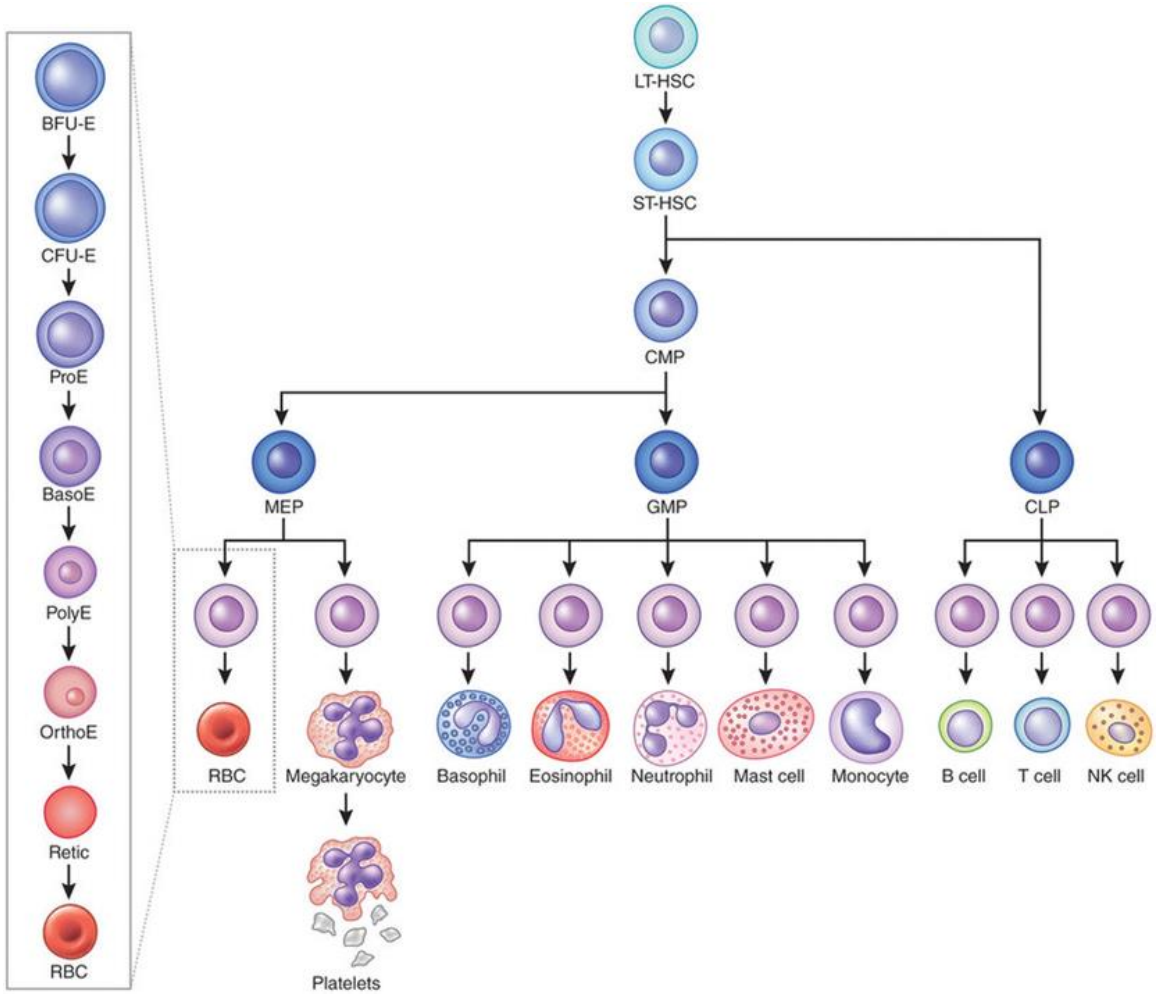
Anemia - tutorial



Hemopoiesis

- pluripotent stem cell
  - able to give rise to any blood cell
  - properties
    - self-renewal
    - proliferation and differentiation into progenitor cells



Hemopoietic growth factors

- glycoproteins
- act on the cytokine-receptor superfamily
- stimulating factors
  - erythropoietin
  - IL-3, 6, 7, 11, 12
  - thrombopoietin
    - produced in the kidney and liver
    - controls platelet production
- inhibiting factors
  - TNF-α, TGF-β
- use in treatment
  - G-CSF
    - accelerate recovery after chemotherapy and hemopoietic cell transplantation
  - EPO
  - thrombopoietin receptor agonist
    - treatment of immune thrombocytopenic purpura

The formation of blood cells

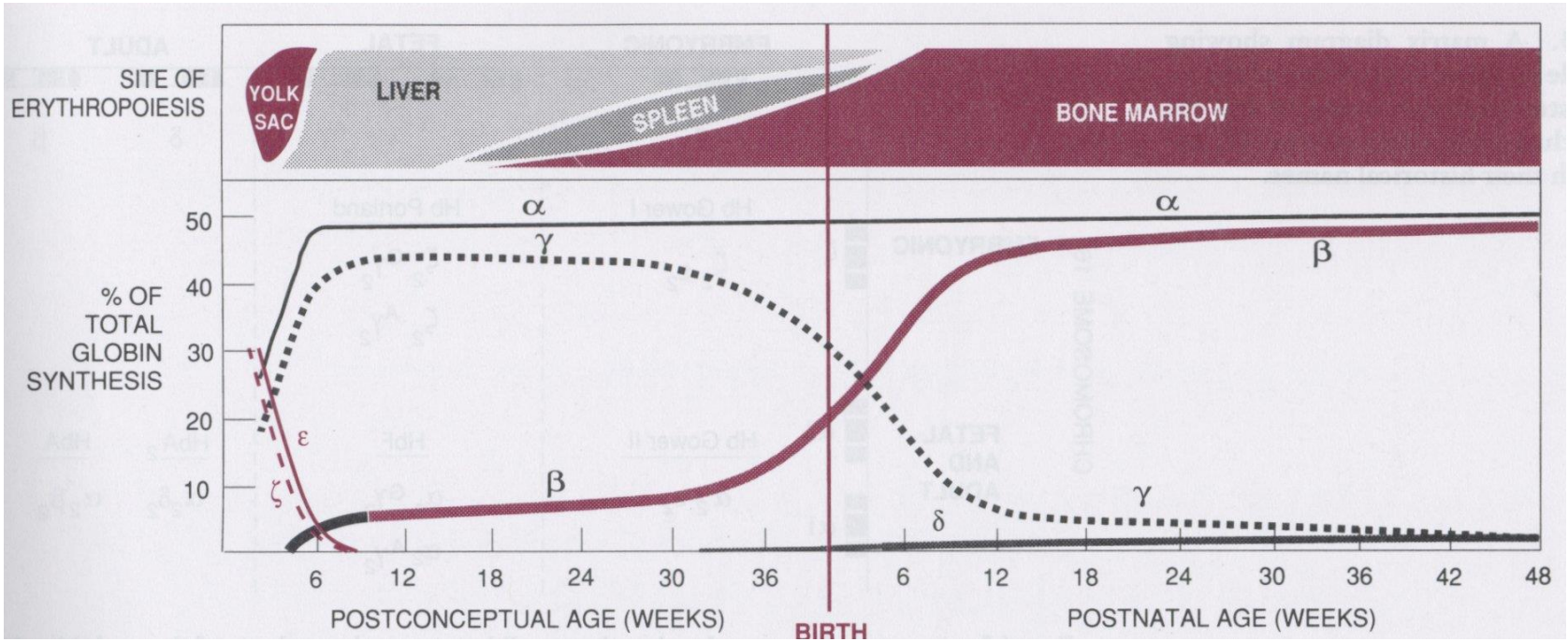
- hemopoietic system
  - bone marrow, liver
  - spleen, lymph nodes
  - thymus
- huge turnover of cells
  - tight regulation according to the needs of the body
- survival
  - RBC 120 days
  - platelets 7 days
  - granulocytes hours

- hemopoiesis during life
  - at birth
    - in the marrow of nearly every bone
  - as the child grows
    - gradually replaced by fat
  - in the adult
    - central skeleton
    - proximal ends of the long bones
  - extramedullary hemopoiesis
    - hemopoietic activity in the liver and spleen
      - pathological processes interfering with normal hemopoiesis

Erythropoiesis

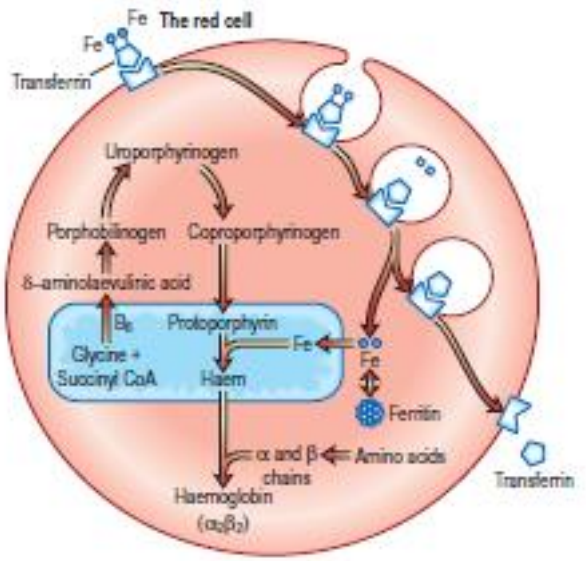
- several stages in the bone marrow
  - earliest recognizable is pronormoblast
  - smaller normoblasts result from cell division
  - precursors at each stage contain less DNA and more Hb in the cytoplasm
  - nucleus becomes more condensed and lost from the late normoblast
    - reticulocyte
      - residual ribosomal RNA
      - synthesize hemoglobin
      - in the marrow 1 – 2 days
      - into circulation
        - loose their RNA
        - become RBC after 1-2 days
- normoblasts
  - in peripheral blood
    - normally not present
    - present if there is extramedullary hemopoiesis
- physiologic erythropoiesis
  - 10 % of erythroblast may die in the bone marrow
- erythropoietin
  - polypetide, 175 AA, 30kDa
  - produced in the kidney (90 %) and liver (10 %)
  - production regulated by oxygen tension
    - hypoxia – HIF-1
    - increases proportion of bone marrow precursors committed to erythropoiesis

Erythropoiesis during ontogenesis

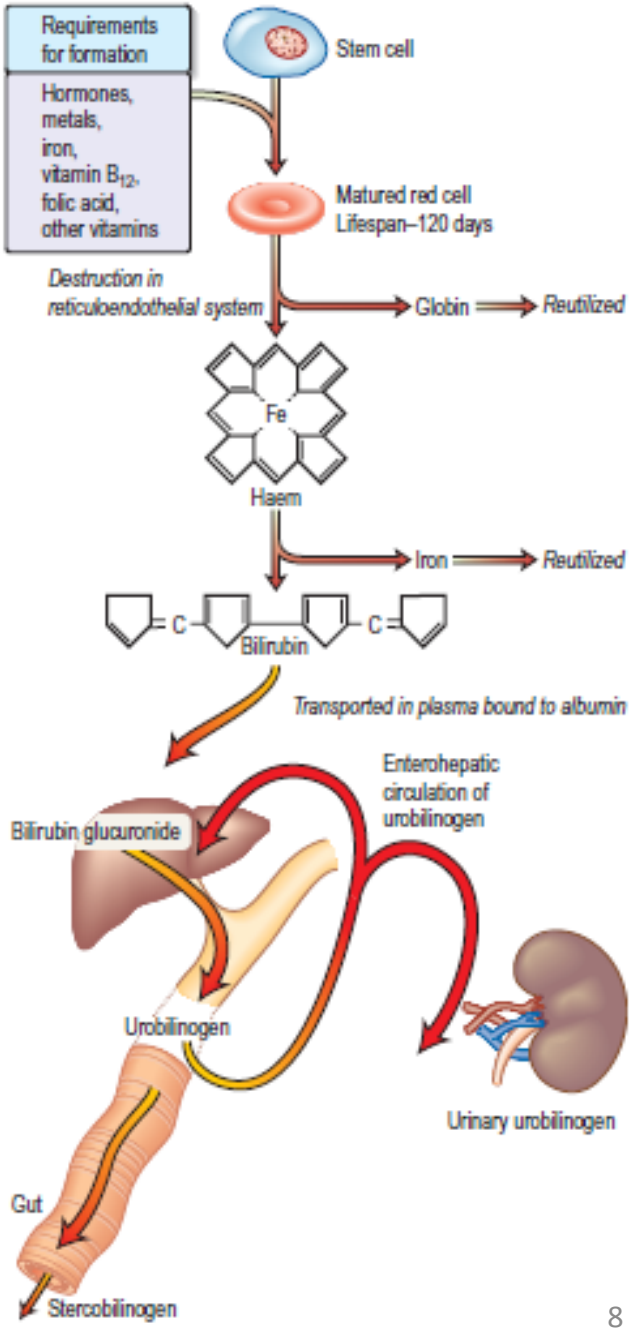


Hemoglobin synthesis

- performs main function of RBC
- adult Hb molecule (HbA)
  - 2 α chains, 2 β chains ($\alpha_2\beta_2$)
  - 97 % of the Hb in adults
- other types
  - HbA2 ($\alpha_2\delta_2$): 1.5 – 3.2 %
  - HbF ($\alpha_2\gamma_2$): < 1 %
- synthesis in the mitochondria
  - production of aminolevulinic acid
    - ALA synthase
    - rate-limiting step
    - coenzyme vitamin B_6
    - inhibited by heme
    - stimulated by EPO



RBC production and breakdown



Anemia

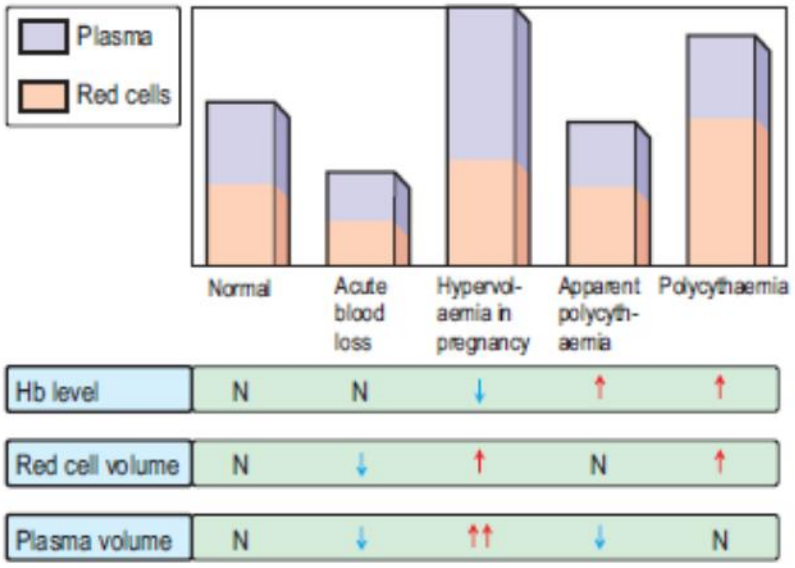
- decrease in Hb in the blood below the reference level for the age and sex of the individual
  - men 135 – 175 g/l
  - women 120 – 160 g/l

- classification by MCV
  - hypochromic microcytic with a low MCV
  - normochromic normocytic with a normal MCV
  - macrocytic with a high MCV

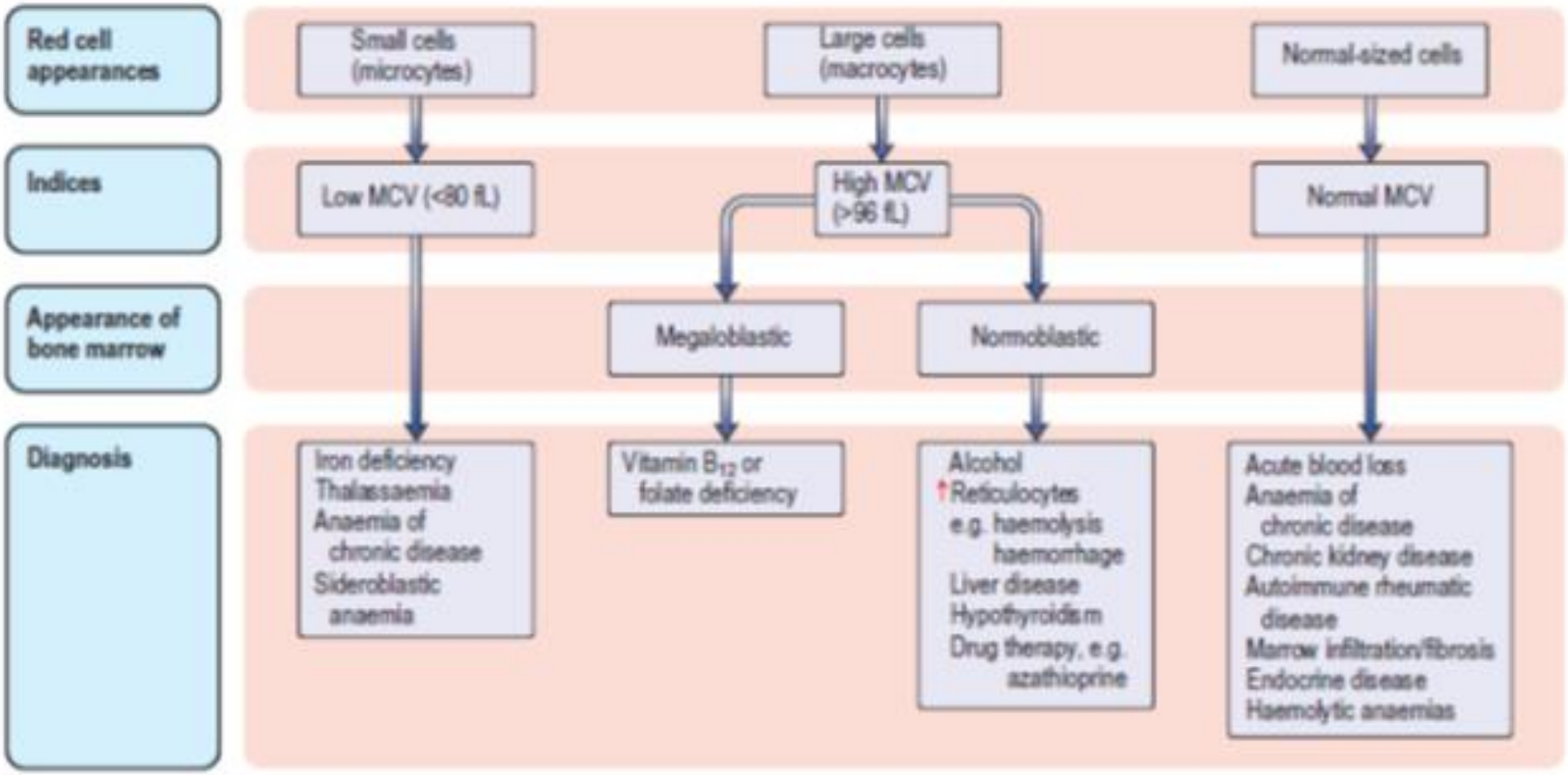
Table 8.1 Normal values for peripheral blood

	Male	Female
Hb (g/L)	135–175	115–160
PCV (haematocrit; L/L)	0.4–0.54	0.37–0.47
RCC (10^{12}/L)	4.5–6.0	3.9–5.0
MCV (fL)	80–96	
MCH (pg)	27–32	
MCHC (g/L)	320–360	
RDW (%)	11–15	
WBC (10^9/L)	4.0–11.0	
Platelets (10^9/L)	150–400	
ESR (mm/h)	<20	
Reticulocytes	0.5–2.5% (50–100×10^9/L)	

ESR, erythrocyte sedimentation rate; Hb, haemoglobin; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume of red cells; PCV, packed cell volume; RCC, red cell count; RDW, red blood cell distribution width; WBC, white blood count.



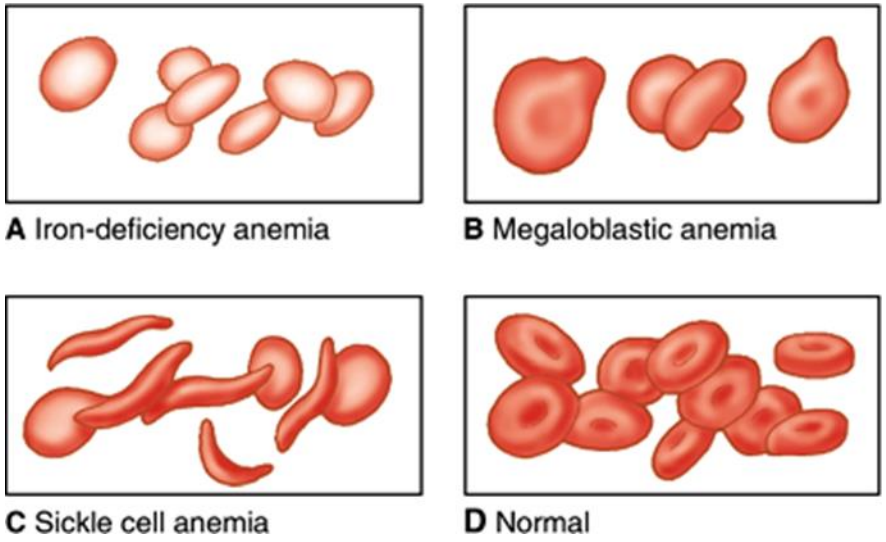
Classification of anemia



Anemia classification

- pathogenetic
  - increased RBC loss
    - bleeding
    - hemolytic anaemia
      - corpuscular
        - membrane
        - hemoglobinopathy
        - enzymopathy
      - extracorpuscular
        - toxic
        - autoimmune
  - insufficient RBC production
    - lack of erythropoietin
    - lack of essential factors
    - bone marrow disorder

- morphologic
  - RBC size
  - haemoglobin content
  - pathologic morphology



Abnormalities of RBC morphology

Red cell morphology	Nonhemolytic
Normal	
Macro-ovalocyte	Megaloblastic anemia
Microcyte	Iron deficiency, Thalassemia
Pencil cell	Iron deficiency
Tear-drop cell	Myelofibrosis, Extramedullary hemopoiesis
Target cell	Liver disease, Hemoglobinopathies, Post-splenectomy
Howell-Jolly body	Nuclear inclusion, Post-splenectomy

Red cell morphology	Hemolytic
	Polychromasia
Reticulocyte (supra-vital stain)	
Spherocyte	Hereditary spherocytosis, Autoimmune hemolytic anemia
Elliptocyte	Hereditary elliptocytosis
Stomatocyte	Liver disease, Hereditary stomatocytosis
Sickle cell	Sickle cell anemia
Fragments	Microangiopathy (DIC, TTP, HUS), and cardiac valve
Blister cell	G6PD deficiency
Spur cell	Severe liver disease

Symptoms

- symptoms
  - fatigue, headaches and faintness
  - breathlessness
  - angina
  - intermittent claudication
  - palpitations
- signs
  - pallor
  - tachycardia
  - systolic flow murmur
  - cardiac failure
- investigations
  - peripheral blood
    - RBC indices
    - WBC count
    - platelet count
    - reticulocyte count
    - blood film
  - bone marrow

Microcytic anemia

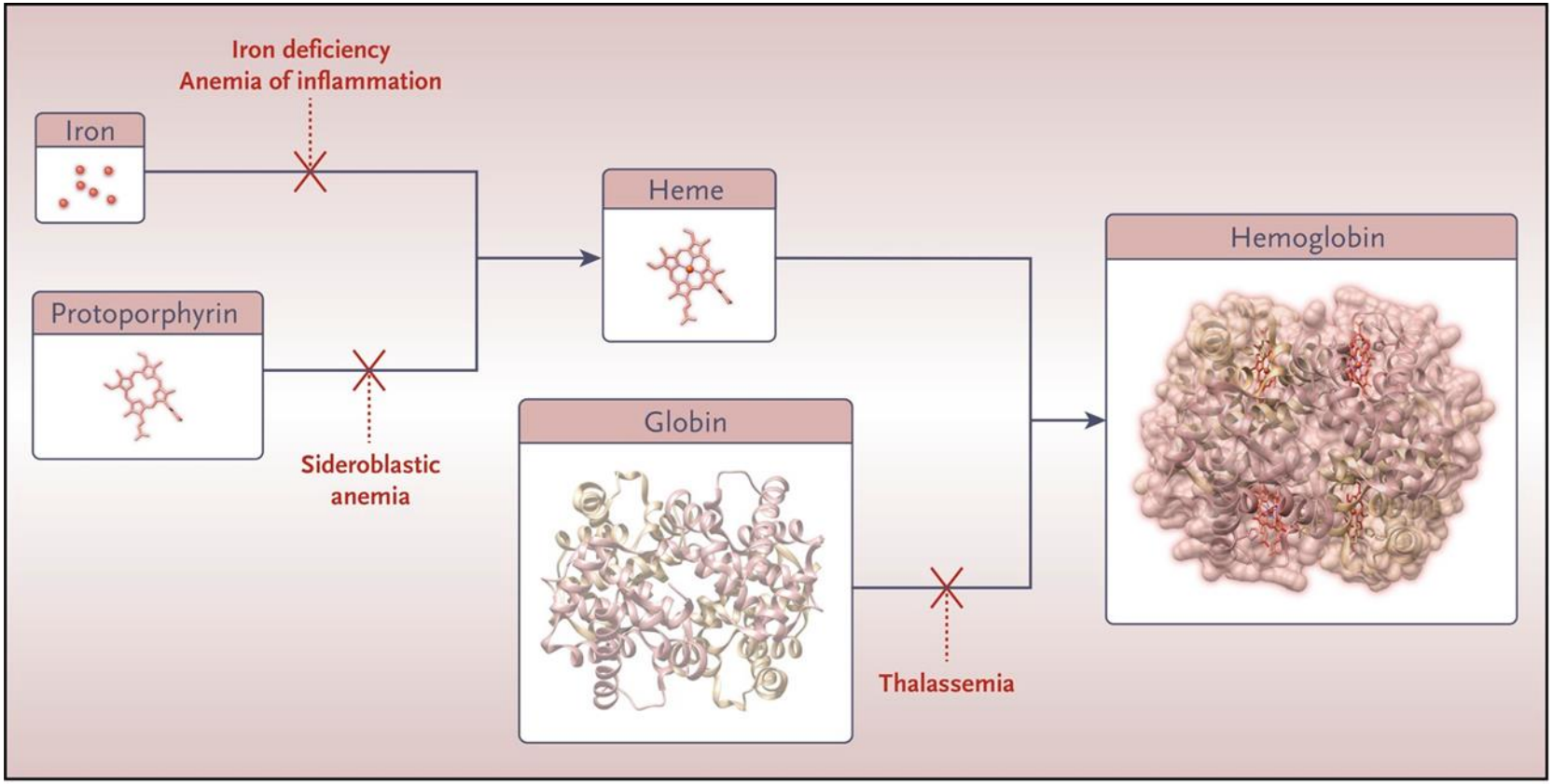
- causes
  - iron deficiency
    - most common cause affecting 30 % of world‘s population
  - anemia of chronic disease
  - sideroblastic anemia
  - thalassemia
    - defect in globin synthesis, other causes – defect in the synthesis of heme

Table 8.3 Microcytic anaemia: the differential diagnosis

	Iron deficiency	Anaemia of chronic disease	Thalassaemia trait (α or β)	Sideroblastic anaemia
MCV	Reduced	Low normal or normal	Very low for degree of anaemia	Low in inherited type but often raised in acquired type
Serum iron	Reduced	Reduced	Normal	Raised
Serum TIBC	Raised	Reduced	Normal	Normal
Serum ferritin	Reduced	Normal or raised	Normal	Raised
Serum soluble transfer receptors	Increased	Normal	Normal or raised	Normal or raised
Iron in marrow	Absent	Present	Present	Present
Iron in erythroblasts	Absent	Absent or reduced	Present	Ring forms

TIBC, total iron binding capacity.

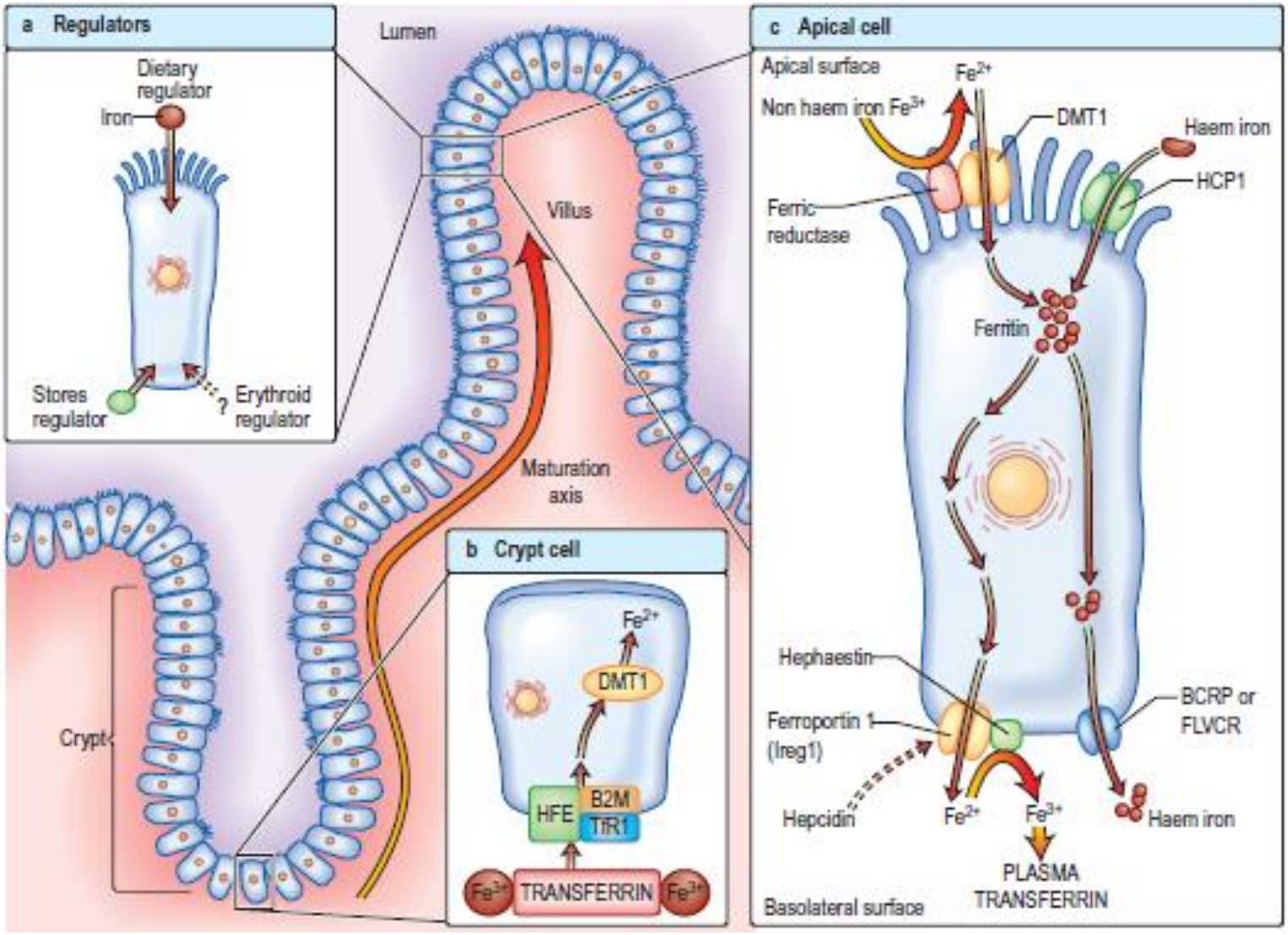
Disorders characterized by microcytosis



Iron metabolism

- 15 – 20 mg/day in the average diet in the UK
  - 10 % is absorbed
  - 20 – 30 % in iron deficiency and pregnancy
- source
  - non-haem iron
    - main part of dietary iron
    - cereals
      - commonly fortified with iron
  - haem iron
    - haemoglobin and myoglobin from meat
    - better absorbed than non-haem iron
- iron stores
  - 2/3 in the circulation
    - haemoglobin
    - 2.5 – 3 g in adult man
  - stored in cells
    - hepatocytes
    - reticuloendothelial cells
    - skeletal muscle cells
    - 500 – 1500 mg
    - 2/3 ferritin
    - 1/3 hemosiderin
  - small amounts
    - plasma
    - myoglobin
    - enzymes

Regulation of iron absorption



Iron metabolism

- free iron is toxic
  - ferritin
    - liver, spleen, bone marrow
    - plasma levels correlate with iron stores
  - hemosiderin
    - from degraded ferritin
    - usually only trace amount
    - ↑ in iron overload
- balance ensured by regulation of absorption
  - mechanism of excretion does not exist
  - absorption of haem and non-haem iron differs
  - regulation of absorption
    - hepcidine
      - produced in the liver
      - released when stores are ↑
      - effect on hepatocytes
      - supresses release of iron from macrophages
        - important in anaemia of chronic disease
        - proinflammatory madiators increase production of hedcidin
      - ↓ hepcidin in hemochromatosis

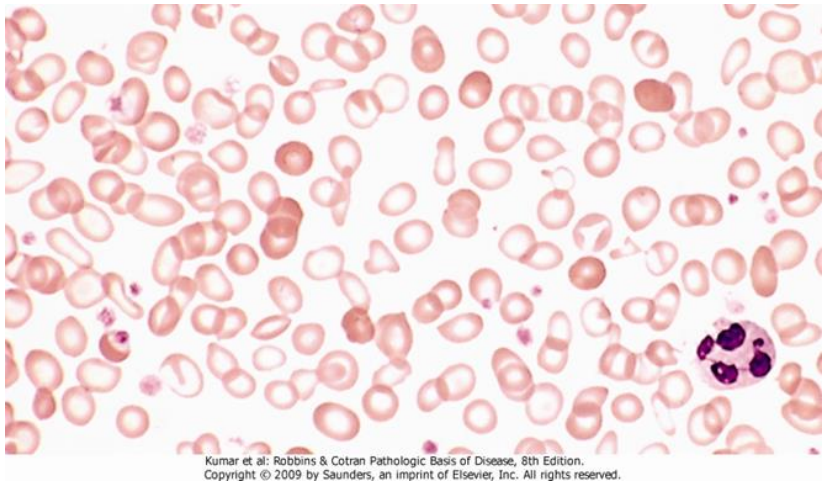
Iron deficiency anemia

- inadequate iron for haemoglobin synthesis
- cause
  - blood loss
  - increased demands
    - growth, pregnancy
  - decreased absorption
    - post-gastrectomy
  - poor intake

- etiology
  - food deficiency
    - infants
    - developing countries
  - ↓ absorption
    - absorption is supported by
      - ascorbic acid
    - supressed by
      - oxalates, phosphates, tanins
    - malabsorption syndrome
    - diarrhea
    - gastrectomy
  - ↑ demands
    - growth, pregnancy
  - ↑ losses
    - chronic
      - GIT bleeding

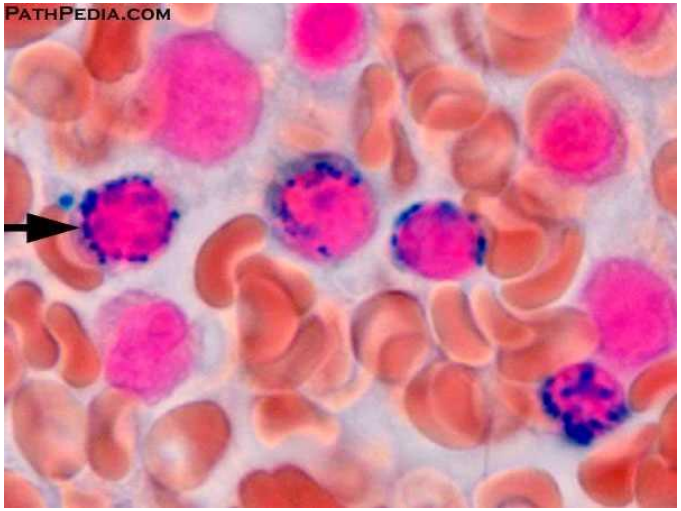
Iron deficiency anemia

- hypochromic microcytic anemia
  - after depletion of stores
    - ↓ serum iron, ferritin and transferin saturation
    - absence of stainable iron in the macrophages from bone marrow
- diagnostics
  - ↓ hemoglobin, hematocrit
  - ↓ iron, ferritin and transferrin saturation (< 15 %)
- iron supplementation
  - ↑ reticulocyte count after 5 – 7 days



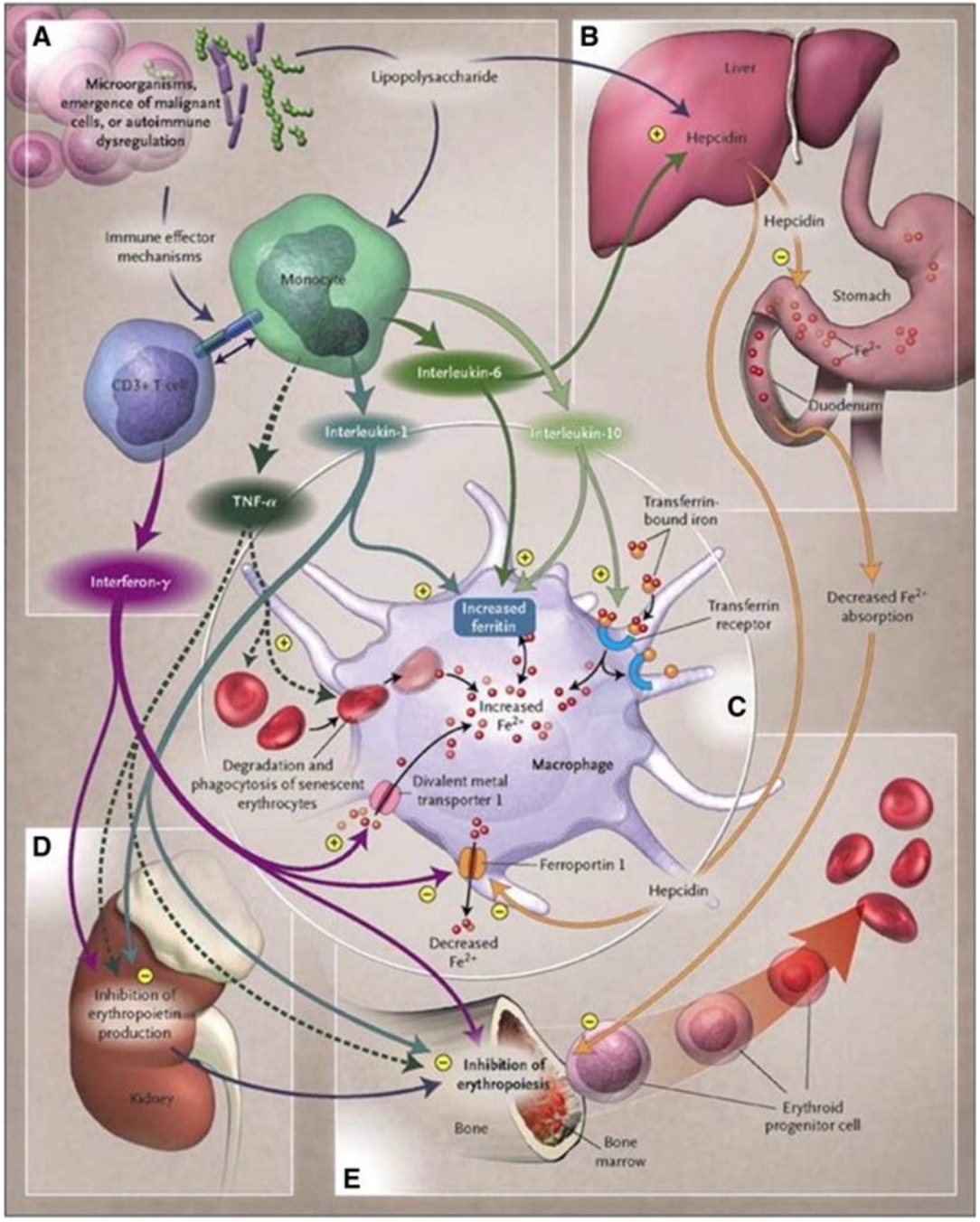
Sideroblastic anemia

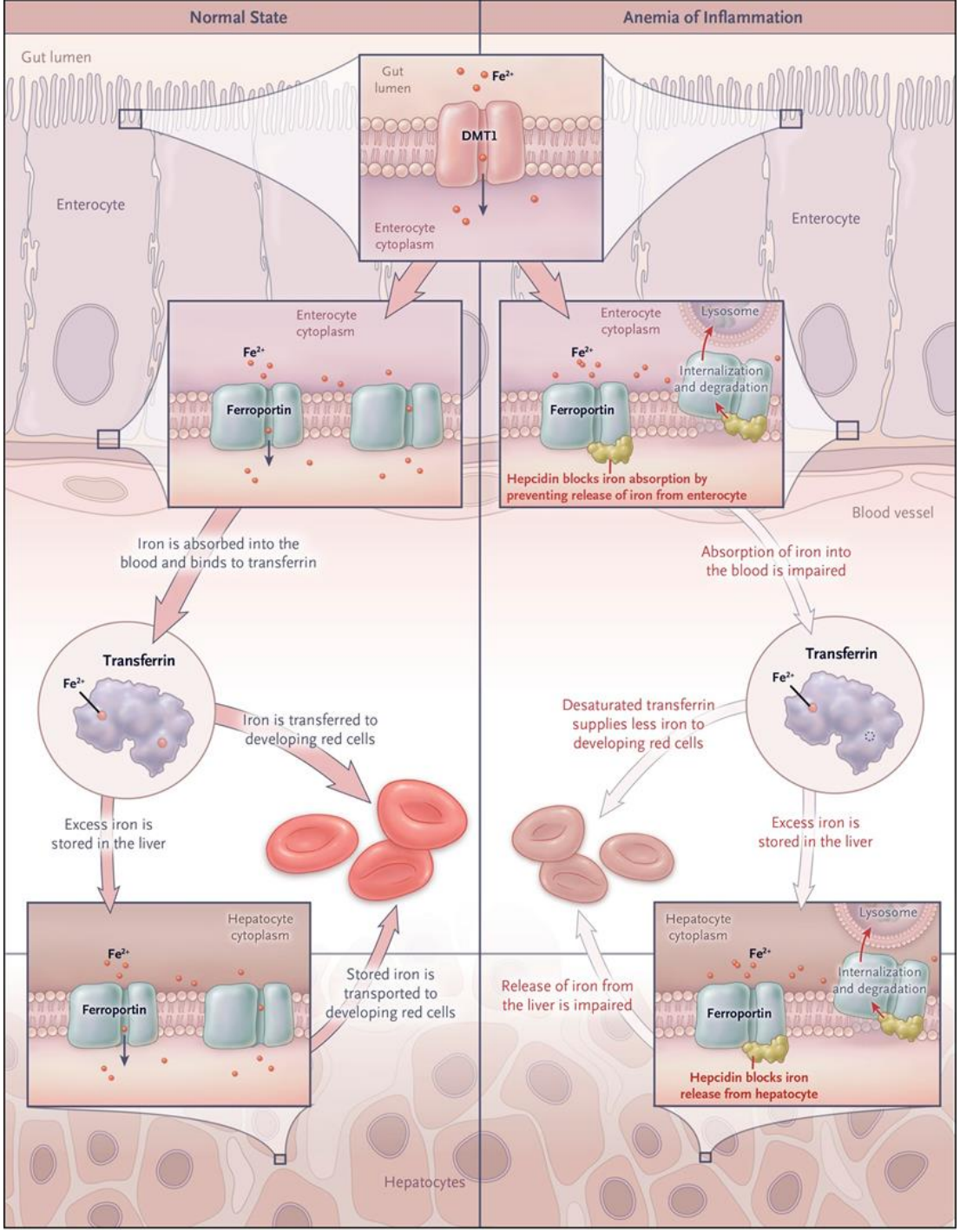
- inherited or acquired disorder
- inadequate use of iron
  - accumulation in mitochondria of erythroblasts
    - ring sideroblast
      - an erythroblast with stainable iron granules in its cytoplasm
  - defect of ALA-synthase
    - inherited form
  - excess iron in bone marrow
- acquired
  - alcohol, drugs
- mutations
  - protoporphyrine production is slow
- variable number of hypochromic microcytes



Anemia of chronic disease

- common
- ↓ proliferation of RBC precursors
- deteriorated utilization of iron
- causes
  - chronic microbial infection
  - autoimmune disease
    - rheumatoid arthritis
  - cancer
    - lung cancer
- systemic inflammation
  - hepcidin stimulation (IL-6)
    - supression of iron release from macrophages
      - ↓ supplementation of RBC precursors
    - defence from bacteries that utilize iron (H. influenza)
      - structural similarity between hepcidin and defensins
  - production of EPO is supressed
- anemia
  - mild
  - normochromic and normocytic or hypochromic microcytic
  - ↑ serum ferritin,
  - ↑ iron in macrophages
  - treatment
    - correction of the cause
    - possibly EPO


A
Microorganisms, emergence of malignant cells, or autoimmune dysregulation
Lipopolysaccharide
Immune effector mechanisms
Monocyte
CD3+ T cell
Interleukin-6
Interleukin-1
Interleukin-10
TNF-α
Interferon-γ
B
Liver
Hepcidin
Hepcidin
Stomach
Fe2+
Duodenum
Transferrin-bound iron
Transferrin receptor
Decreased Fe2+ absorption
Increased ferritin
Increased Fe2+
C
Macrophage
Degradation and phagocytosis of senescent erythrocytes
Divalent metal transporter 1
Ferroportin 1
Hepcidin
Decreased Fe2+
D
Inhibition of erythropoietin production
Kidney
Inhibition of erythropoiesis
Bone
Bone marrow
Erythroid progenitor cell
E


Normal State
Anemia of Inflammation
Gut lumen
Gut lumen
Fe2+
DMT1
Enterocyte cytoplasm
Enterocyte
Enterocyte
Enterocyte cytoplasm
Fe2+
Ferroportin
Enterocyte cytoplasm
Lysosome
Fe2+
Internalization and degradation
Ferroportin
Hepcidin blocks iron absorption by preventing release of iron from enterocyte
Blood vessel
Iron is absorbed into the blood and binds to transferrin
Absorption of iron into the blood is impaired
Transferrin
Fe2+
Iron is transferred to developing red cells
Desaturated transferrin supplies less iron to developing red cells
Transferrin
Fe2+
Excess iron is stored in the liver
Excess iron is stored in the liver
Hepatocyte cytoplasm
Fe2+
Ferroportin
Stored iron is transported to developing red cells
Release of iron from the liver is impaired
Hepatocyte cytoplasm
Lysosome
Fe2+
Internalization and degradation
Ferroportin
Hepcidin blocks iron release from hepatocyte
Hepatocytes

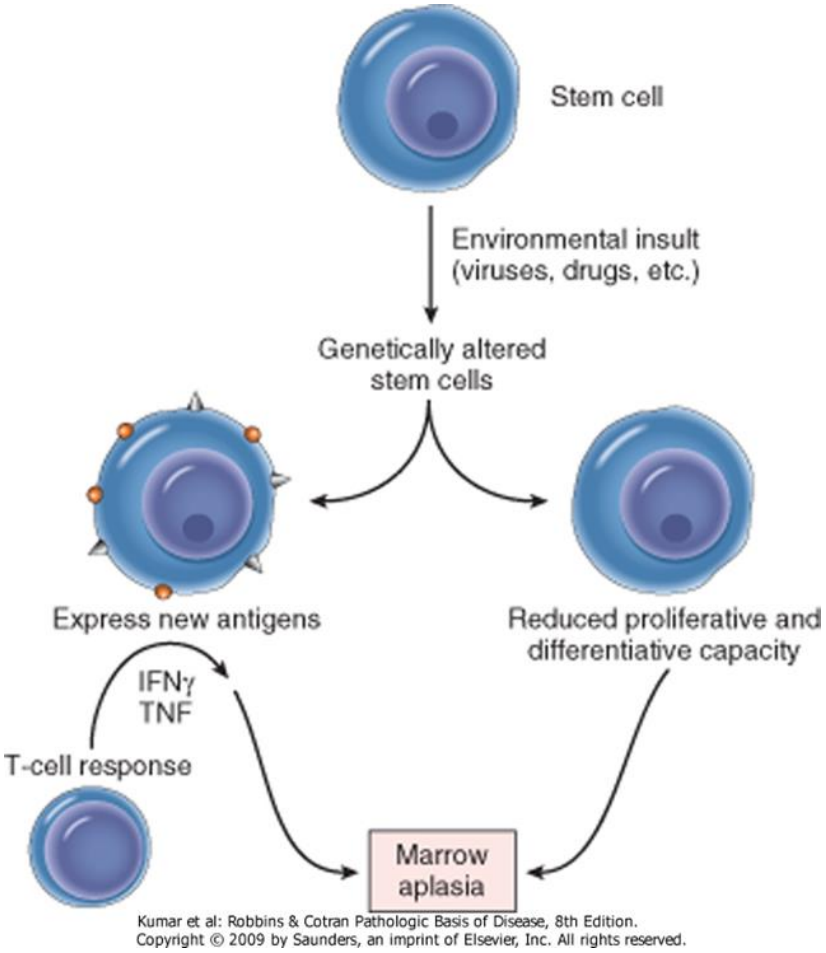
Normocytic anemias

Anemia due to blood loss

- acute
  - intravascular volume loss
    - amount is important
    - cardiovascular collapse, shock, death
  - volume repletion
    - water shift, ↓ hematocrite
  - ↑ EPO production
  - iron loss
  - blood pressure decrease
    - epinephrine release
    - granulocytes mobilization
      - leukocytosis
  - reticulocytosis
    - 10 – 15 % after 15 days
  - thrombocytosis
- chronic
  - less activated erythropoiesis
  - losses may exceeed regeneration capacity of bone marrow
  - iron stores depletion

Aplastic anemia

- chronic failure of hematopoiesis
- etiology
  - idiopathic (65 %)
  - chemicals
    - benzene
    - alkylation agents
    - antimetabolites
  - viral infection
    - hepatitis, CMV, EBV
  - radiation
  - hereditary defects
  - Fanconi anemia
    - DNA reparation disorder
    - defects of telomerase



Aplastic anaemia

- pathogenesis
  - extrinsic cause
    - change of stem cells‘ antigens
    - activation of Th1
      - cytokines, destruction of progenitors
    - up-regulation of proapoptotic genes
    - immunosupresive therapy
  - intrinsic cause
    - karyotype changes
    - short telomeres
- morphology
  - hypocellular bone marrow
  - common infection, bleeding
- signs
  - pancytopenia
    - anaemia, petechia, infection
    - reticulocytopenia
- treatment
  - transplantation

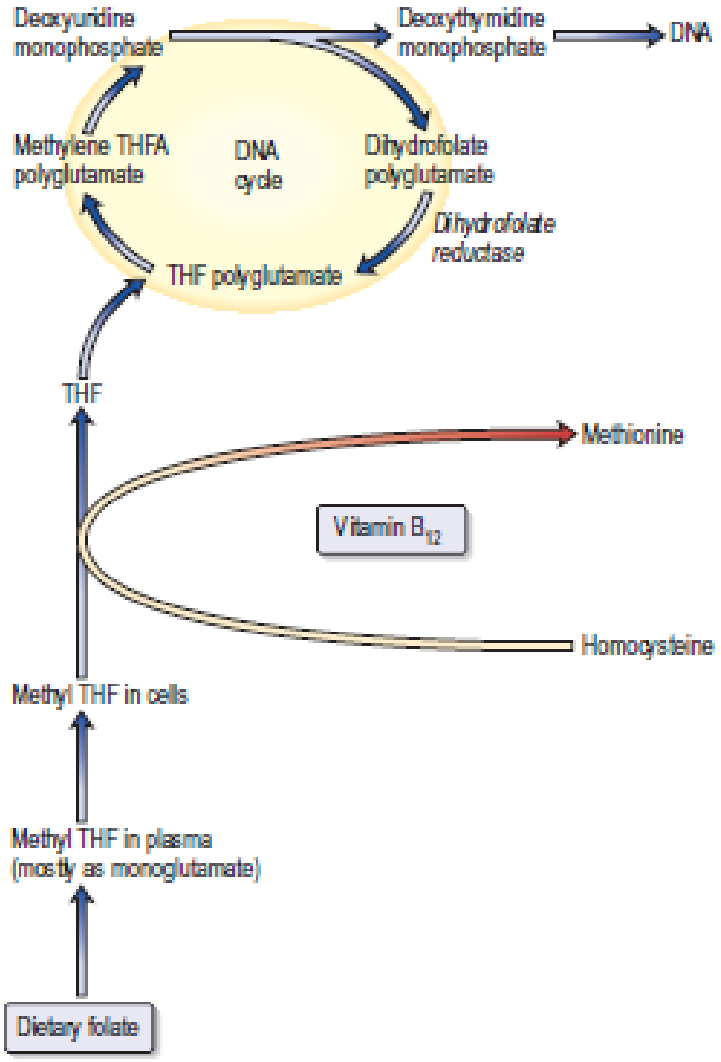
Macrocytic anemias

Megaloblastic anemia

- erytroblasts with delayed nuclear maturation in the bone marrow
- defective DNA synthesis
  - abnormally large RBC and their precursors
  - immature nuclei
- deficit of vitamin B_{12} or folic acid
  - thymidine synthesis
  - defects in nucleus maturation
    - delay or blocade of cell division
- morphology
  - macrocytes or macroovalocytes
    - central brightening is missing but MCHC is not increased
    - anisocytosis, poikilocytosis
    - ↓ reticulocytes
    - neutrophils
      - larger and hypersegmented
    - hypercellular bone marrow
    - maturation of cytoplasm and Hb accumulation is normal
    - ↑ growth factors
      - apoptosis of precursors in the bone marrow
    - mild hemolysis

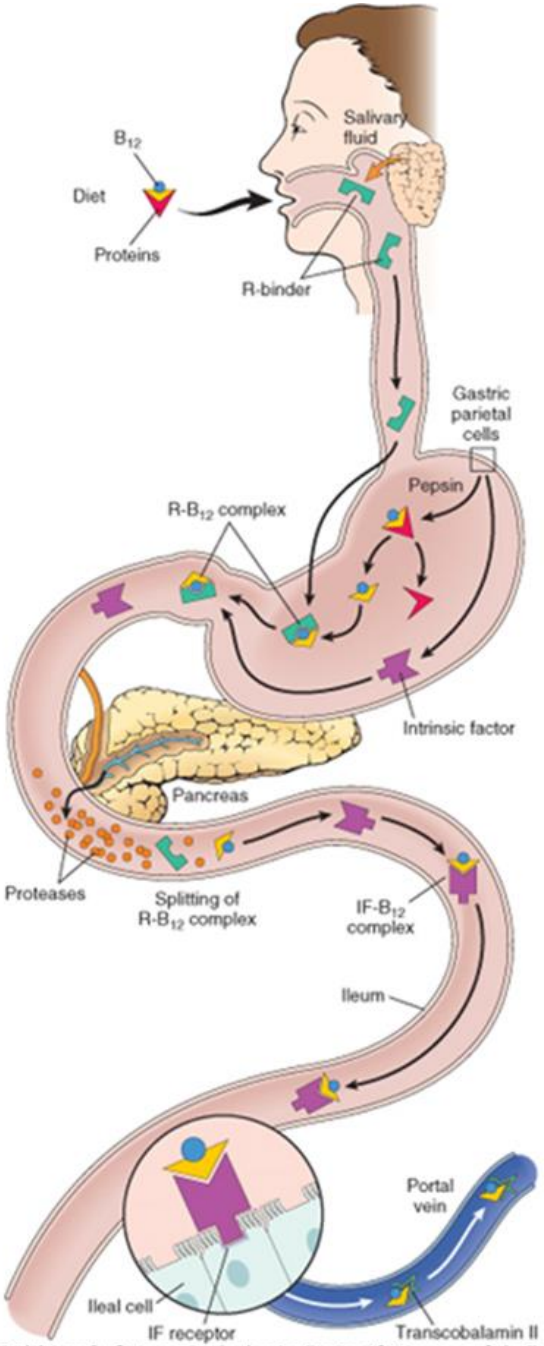
Biochemical basis of megaloblastic anemia

- key biochemical problem
  - block in DNA synthesis
    - inability to methylate deoxyuridine monophosphate to deoxythimidine monophosphate
    - folate deficiency
      - ↓ supply of methylene tetrahydrofolate
    - vitamin B_{12} deficiency
      - slowing the demethylation of methyl thetrahydrofolate
- other forms
  - interference with purine or pyrimidine synthesis causing an inhibition of DNA synthesis



Vitamin B_{12} metabolism

- vitamin B_{12} = cobalamin
- essential
- animal sources
  - meat, fish, egg, milk
  - not in plants
  - usually not destroyed by cooking
- stores in the liver
- alternative resorption
  - without IF
  - up to 1 % of its content in the diet

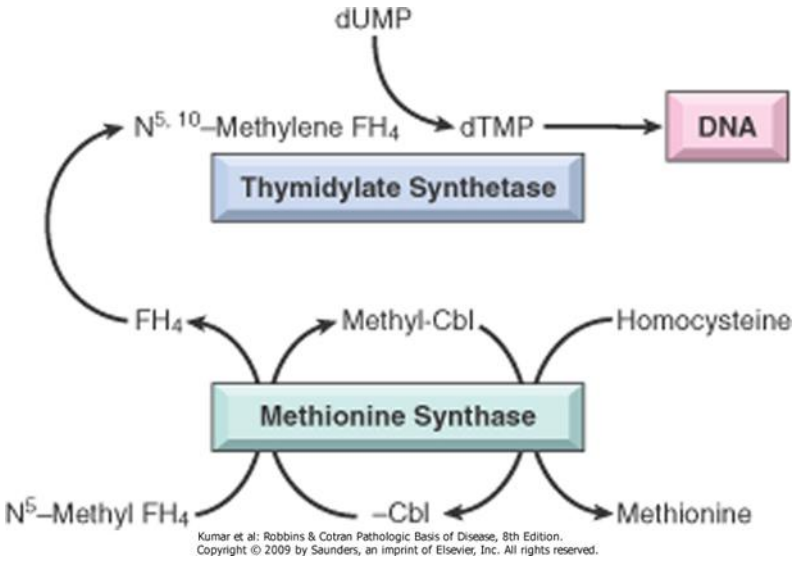


B_{12} deficit = pernicious anemia

- autoimmune gastritis
  - intrinsic factor deficit
- ocurrence
  - all races
  - older people (median 60 years)
- pathogenesis
  - autoimmunity
    - chronic atrofic gastritis
      - parietal cells loss
      - autoantibodies are not specific
    - autoreactive T cells
  - achlorhydria, ↓ pepsine
  - gastrectomy
  - exocrine pankreas dysfunction
  - ileum resection
  - tapeworm
  - ↑ demands on B_{12}
    - relative deficit
- diagnostics
  - megaloblasts
  - leucopenia
    - hypersegmented granulocytes
  - ↓ level of B_{12}
  - ↑ homocysteine and methylmalonyl acid
  - gastritis
    - ↑ risk of gastric carcinoma
  - homocysteine

Vitamin B_{12} functions

- 2 reactions dependent of B_{12}
  - methionine production
    - methyl group acceptor
    - formation of TH4
  - generation of sukcinyl CoA from methylmalonyl CoA
    - ↑ methylmalonyl acid in plasma and urine
    - abnormal fatty acids in neuronal lipids
    - neurologic complications



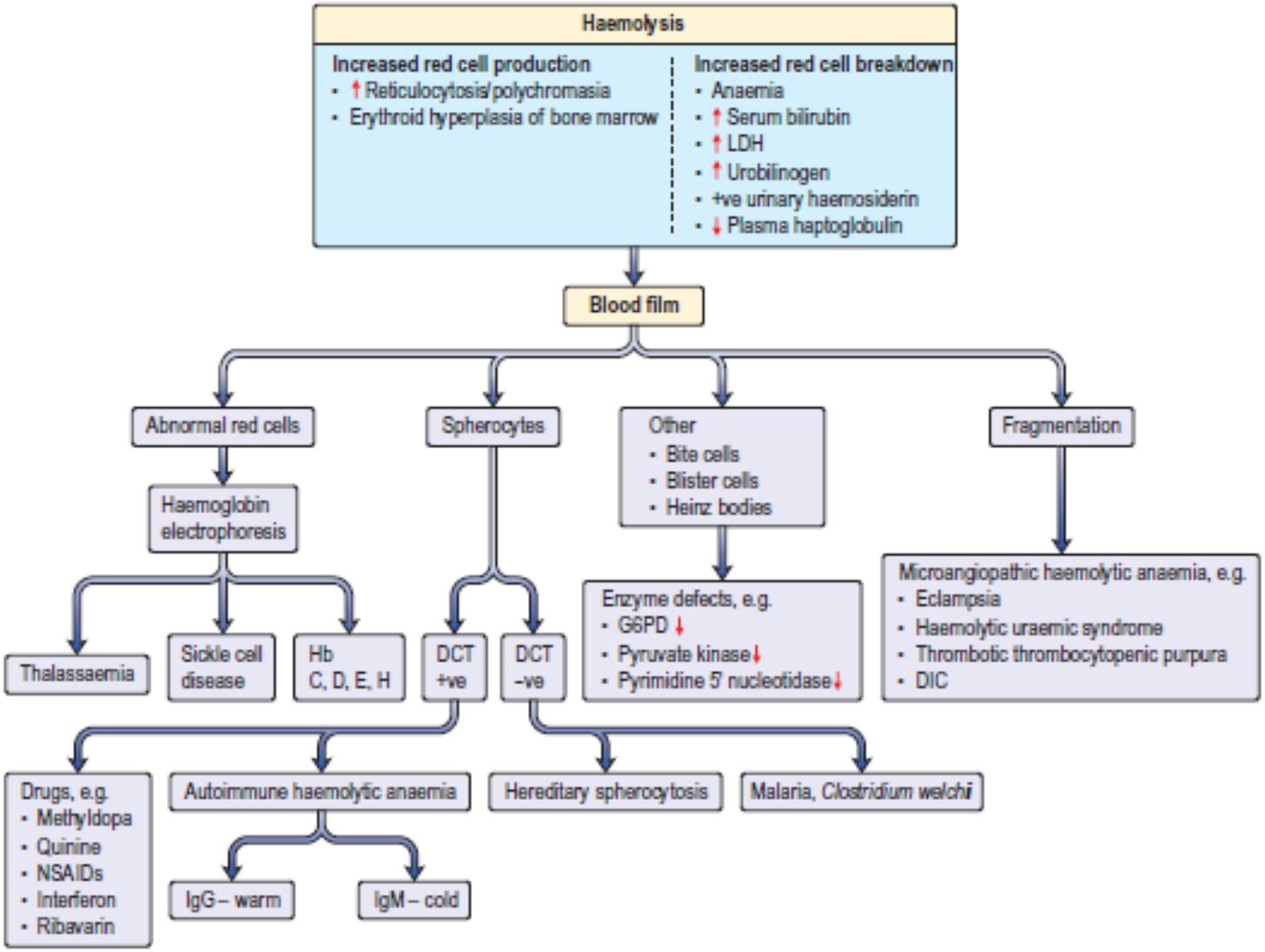
Folic acid deficiency anemia

- tetrahydrofolate (FH4)
  - transfer of 1 C groups
    - methyl, formyl
  - processes dependent on these tranfers
    - purines synthesis
    - homocysteine → methionine
    - synthesis of deoxythimidylate monophosphate

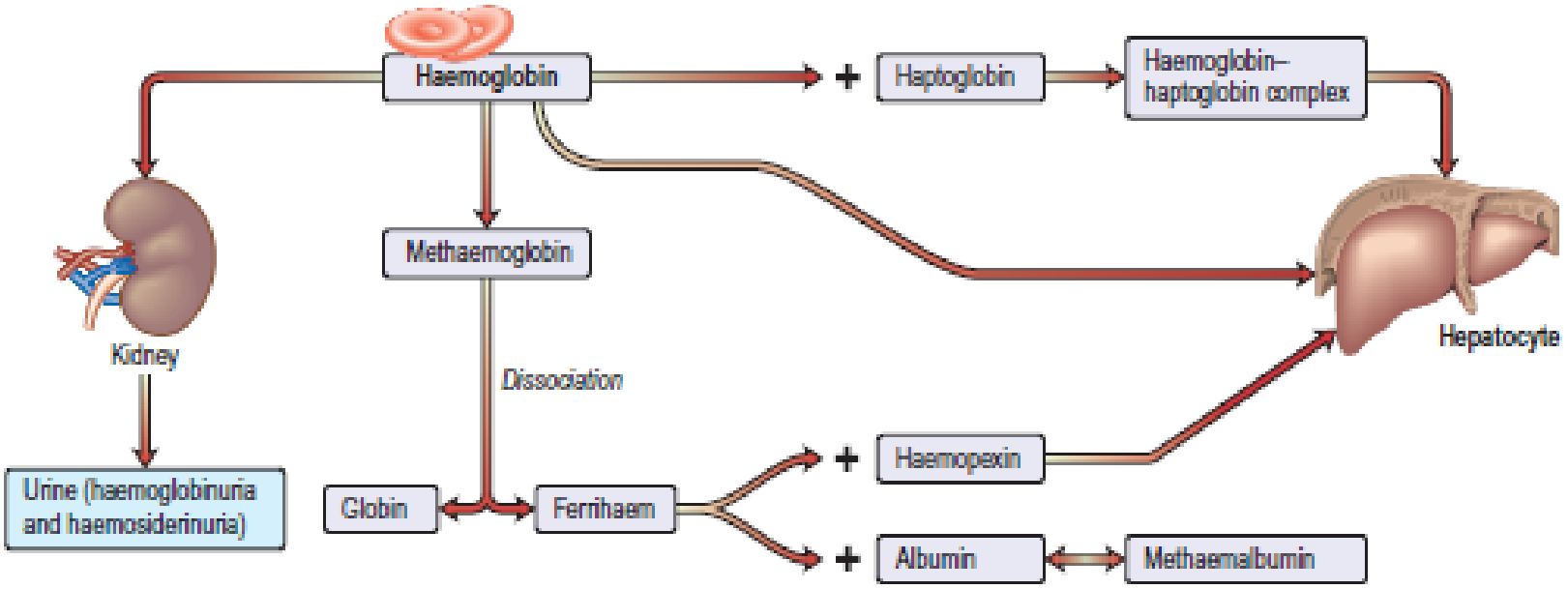
- etiology
  - decreased intake
    - essential, heat inactivation
    - small stores (weeks)
  - increased demands
    - pregnancy, growth, cancer
  - disturbed utilization
    - methotrexate
      - folic acid antagonist
        - dihydrofolate reductase

- distinction from pernicious anemia
  - ↓ folates in the blood
  - ↑ homocysteine but not methylmalonic acid

Hemolysis: diagnostic and hematological features



Fate of Hb following hemolysis



Hemolytic anemias

- common signs
  - premature RBC destruction
    - normally in mononuclear phagocytes
    - usually extravascular
      - phagocytes hyperplasia
        - splenomegalia
  - increased EPO and stimulation of erythropoiesis
  - accumulation oof hemoglobin degradation products
  - iron deficit is not present
- clinical signs
  - anaemia
  - splenomegalia
  - jaundice
- intravascular haemolysis
  - hemoglobinemia
  - hemoglobinuria
  - hemosiderinuria
  - splenomegalia is missing
  - ↓ haptoglobin

Classification of hemolytic anemias

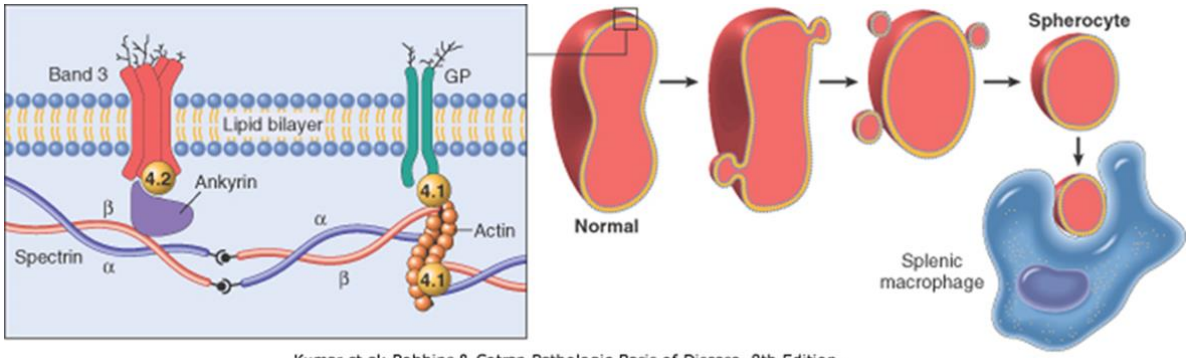
- corpuscular
  - membrane disorders
    - hereditary spherocytosis
    - eliptocytosis

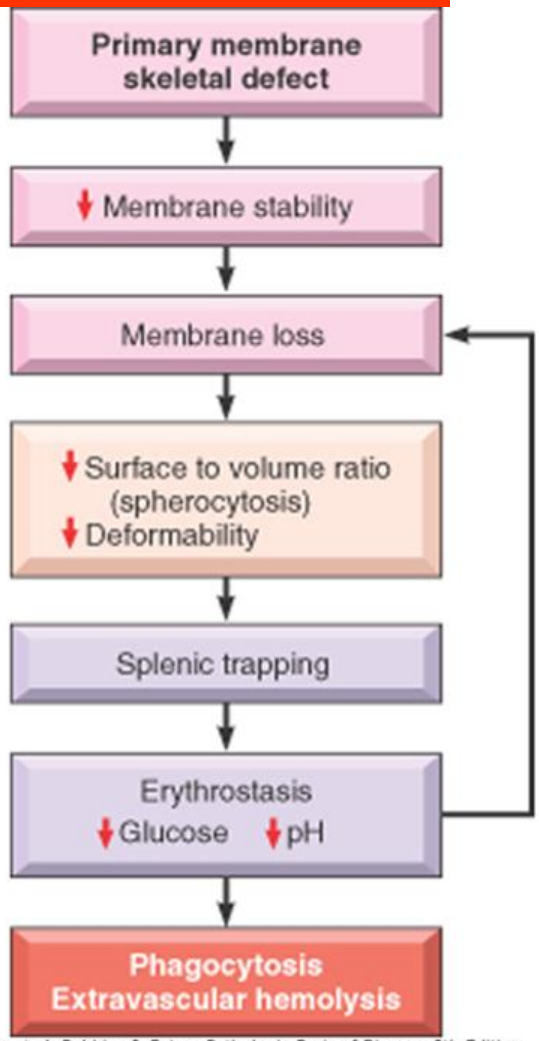
    paroxysmal nocturnal hemoglobinuria
  - metabolism disorders
    - glucose-6-phosphate dehydrogenase
    - pyruvate kinase
  - disorders of hemoglobinisation and hemoglobinopathies
    - thalassemia
- extracorpuscular
  - damage due to physical and toxic insults
    - mechanical
    - heat
    - bacterial toxins
    - changed lipid metabolism and membrane disorders
  - damage caused by autoantibodies

Hereditary spherocytosis

- most common inherited hemolytic anemia in Northern Europeans (1:5000)
- autosomal dominant
  - one defect (75 %)
- in 75 % neither parent is affected
  - spontaneous mutation
  - recessive?
- defect in RBC membrane
  - deficit of structural proteins
    - most commonly ankyrin
    - also band 3 or 4.2, spectrin
  - mutations
    - reading frame shift or premature stop codon
  - RBC lifespan 10 – 20 days
- changes
  - young RBC – normal shape
    - ↓ membrane stability with aging
    - ↓ deformability – trapping in the spleen
  - splenectomy
    - spherocytes remain
    - correction of anaemia
- clinical features
  - possible jaundice at birth
  - onset can be delayed for many years
  - some patients may go through life without symptoms

Hereditary spherocytosis



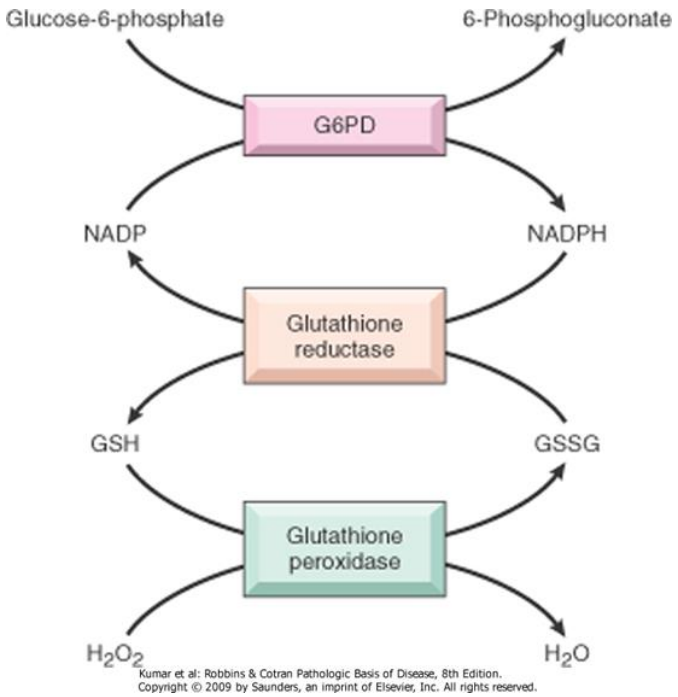


Another cell membrane defects

- hereditary elliptocytosis
  - inherited disorder
    - autosomal dominant
    - 1:2500 in Caucasians
  - deficiency of
    - protein 4.1
    - spectrin/actin/4.1 complex
  - membrane defect
  - similar to HS but milder
  - minority of patient have anemia
- hereditary stomatocytosis

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

- recessive X-linked disease (Xq28)
  - more common in males
  - affects millions of people
    - Africa, Mediterranean, Middle East (20 %)
    - South-East Asia (up to 40 % in certain areas)
- G6PD function
  - oxidation of G6P to 6-phosphoglycerate
    - production of NADPH
      - the only source of RBC
      - regeneration of glutathione
        - protection of oxidative damage

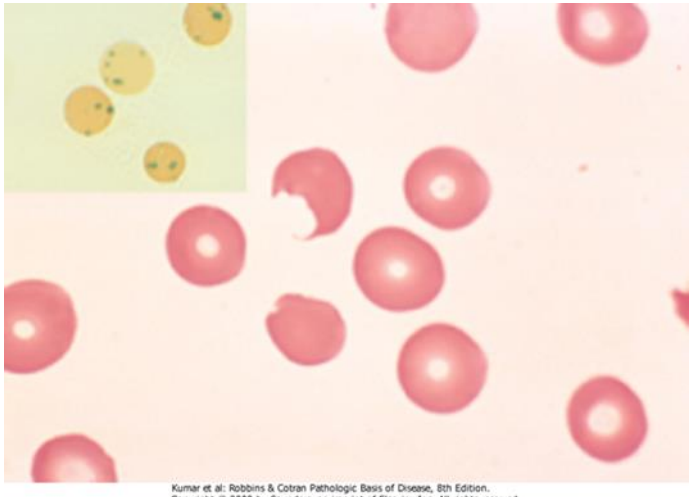


G6PD deficiency

- over 400 mutations identified
  - mostly amino acids substitutions
  - WHO classification
    - normal activity
      - **B+**
        - almost all Caucasians, 70 % of black Africans
      - **A+**
        - 20 % of black Africans
    - reduced activity
      - **A-**
        - mild deficiency, more marked in older cells, young cells have nearly normal activity
      - **Mediterranean type**
        - both young and old RBC have very low enzyme activity
        - after oxidant shock, Hb may fall precipitously, transfusion is needed
  - mutations provide protection from malaria
    - Plasmodium falciparum

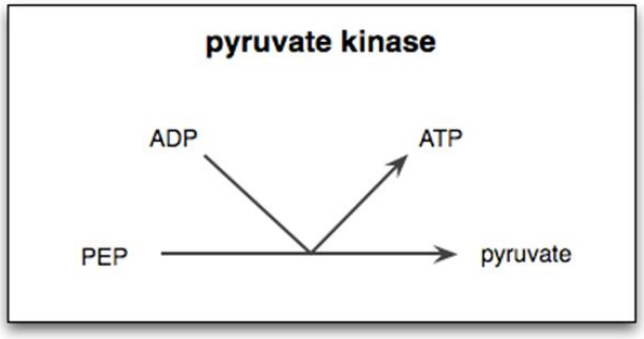
G6PD deficiency

- episodic hemolysis
  - ↑ oxidative stress
    - infection
      - viral hepatitis, pneumonia
    - drugs
      - antimalarics, sulfonamids
    - ingestion of fava beans
      - favism
  - denaturation of gobin chains
    - binding of sulfhydryl groups
    - precipitates bound to membrane
      - Heinz bodies
        - ↓ deformability
        - intravascular haemolysis
  - clinical features
    - anemia
    - jaundice
    - hemoglobinuria



Pyruvate kinase deficiency

- the most common defect of RBC metabolism after G6PD deficiency
  - affects thousands people
- autosomal recessive
  - variable severity
  - homozygotes have anemia and splenomegaly
- lower PK aktivity
  - reduced ATP production
  - energy deficit
    - ↓ resitance of membrane – rigid RBC
- diagnostics
  - lower enzymatic aktivity
    - 5 – 20 % in affected homozygotes

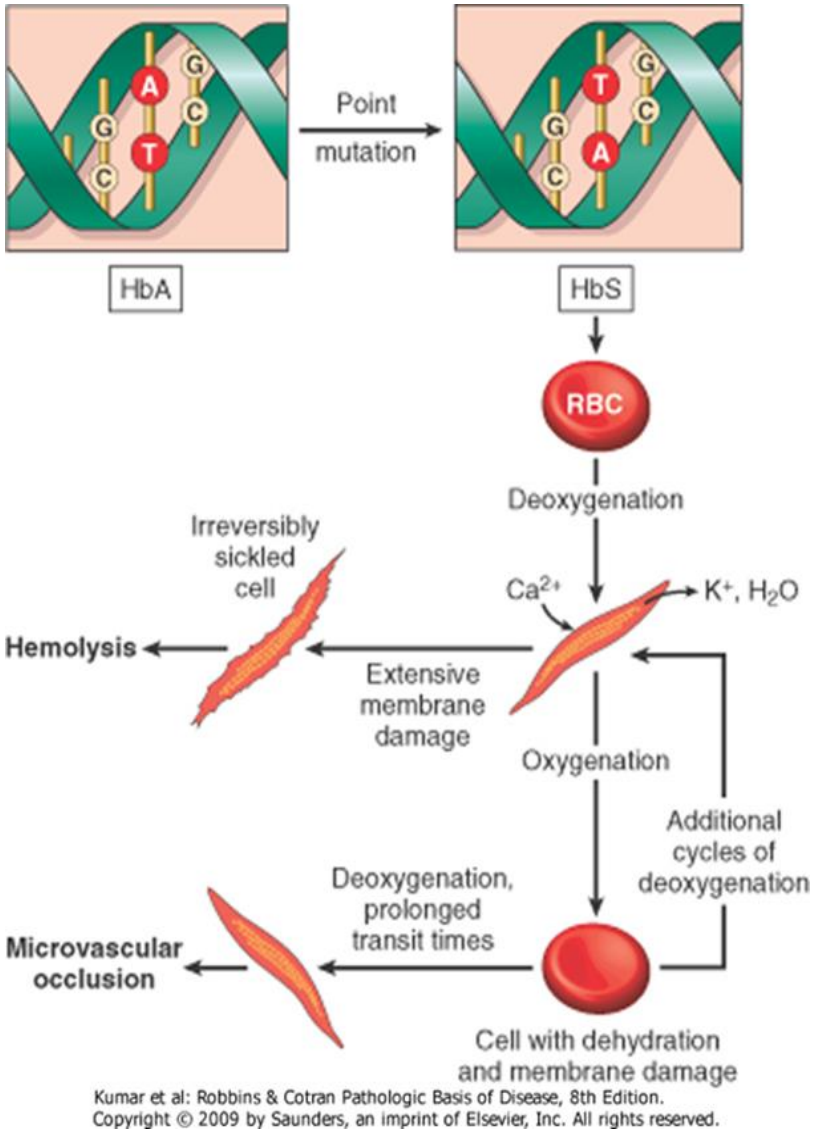


Hemoglobinopathies

- abnormalities occur in
  - globin chain production
    - thalassemia
  - structure of the globin chain
    - sickle cell disease
- change of aminoacid composition of globin chain or incorrect proportion of subunits
- highly variable clinical manifestations
  - mild hypochromic anemia
  - moderate hematological disease
  - severe, lifelong, transfusion-dependent anemia with multiorgan involvement

Sickle cell anemia

- common hereditary hemoglobinopathy
- point mutation in the codon 6
  - valin instead of glutamic acid
  - abnormal HbS
- 2 forms
  - homozygous
    - sickle cell anemia (HbSS)
  - heterozygous
    - sickle cell trait (HbAS)
- most common in
  - Africa
    - up to 25 % in some populations
  - India, Middle East, Southern Europe
- HbF synthesis is normal
  - manifestation when hbF decreases to adult levels
    - approx. 6 months of age



Sickle cell anemia

- deoxygenated HbS
  - polymerizes and becomes insoluble
  - flexibility of RBC is decreased
  - rigid, sickle appearance
  - change of shape
    - initially reversible
    - after repeated sickening membrane loses flexibility
      - irreversibly sicked cell
- sickling can produce
  - shortened RBC survival
  - impaired passage through microcirculation
- sickling precipitated by
  - infection, dehydration
  - cold, hypoxia
- clinical features
  - vaso-occlusive crisis
    - pain in the hands and feet
  - pulmonary hypertension
    - in 30 – 40 %
      - NO deficiency?
  - anemia
    - stable Hb 60 – 80 g/l
  - splenic sequestration

Thalassemias

- normally balanced production of α and β globin chains (1:1)
- defective synthesis of globin chains in thalassemia
  - imbalance
  - precipitation of globin chains
    - ineffective erythropoiesis
    - Hemolysis
- mutations causing ↓ synthesis of HbA
- heterogenous group
- endemic
  - Middle East, tropic Africa, India, Asia
  - one of the most common hereditary diseases
    - heterozygous forms
      - protection from malaria
- α-talassemia
  - deficit of α chain synthesis
- β-thalassemia
  - deficit of β chain
    - chromosome 11

Table 1. Features of the Thalassemias.*

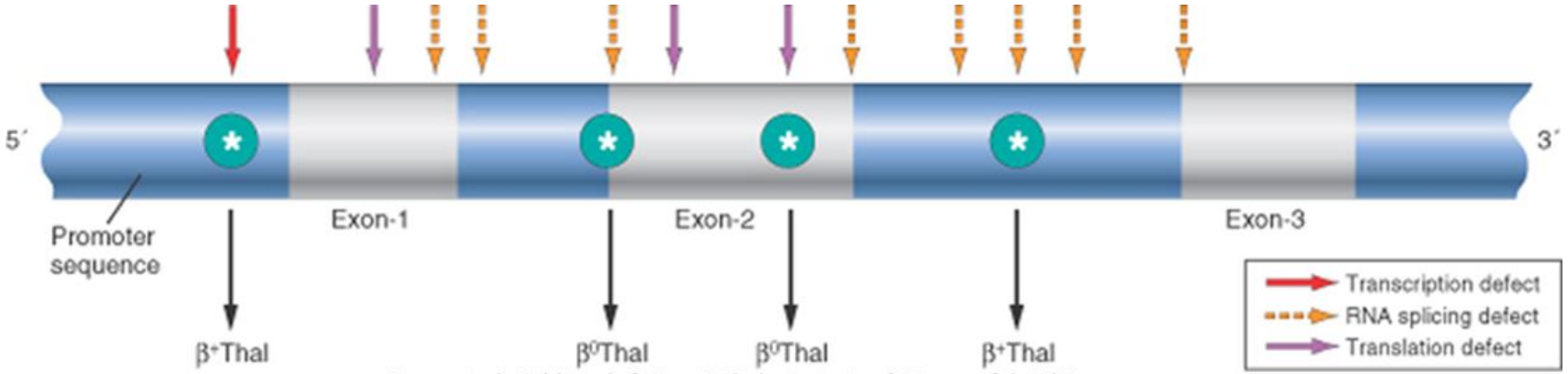
Type	Mean Corpuscular Volume *fl*	Hemoglobin *g/dl*	Findings on Electrophoresis	Other Features
β-Thalassemia				
Major	50–75	<7	Increased hemoglobin A_2	Severe anemia
Intermedia	50–75	<9	Increased hemoglobin A_2	Target cells on smear
Minor	65–75	9–10	Increased hemoglobin A_2	Target cells on smear
α-Thalassemia				
Trait 1 (α α/α–)	80–85	12–14	Normal	
Trait 2 (α–/α–) or (α α/–)	65–75	12–13	Normal	
Hemoglobin H disease (α–/–)	60–69	9–8	Hemoglobin H	Hemolysis, splenomegaly
Hemoglobin Bart's (– –/–)			Hemoglobin H, hemoglobin Bart's	Hydrops fetalis
Hemoglobin E disease				
Heterozygous	80–85	12	Hemoglobin E present	Rare target cells on smear
Homozygous	70–79	11–12	Hemoglobin E predominant	Target cells on smear

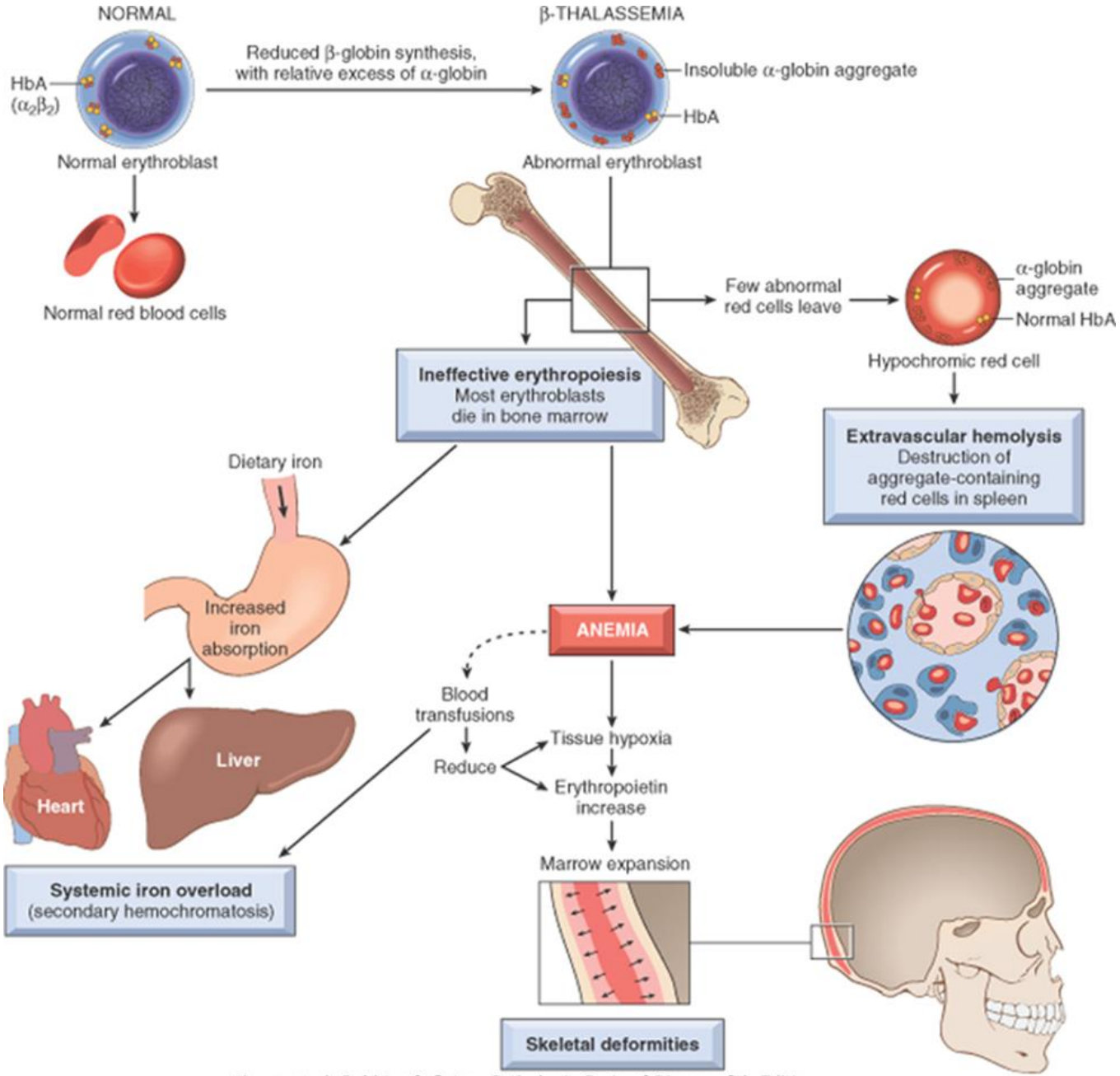
* The normal range for mean corpuscular volume is 80 to 100 fl. The normal range for hemoglobin level is 13.5 to 17.5 g per deciliter in men and 12 to 16 g per deciliter in women.

β-thalassemia

- homozygous β-thalassemia
  - β0 mutation
    - β-chain is missing
  - β+ mutation
    - β-chain production is reduced
- heterozygous β-thalassemia
  - usually symptomless
  - microcytosis with or without mild anemia

- ↓ lifespan of RBC and their precursors
- precipitation of α-chains – membrane damage
- ineffective erythropoiesis
  - destruction of some RBC in bone marrow
  - remaining RBC are prone to extravascular hemolysis





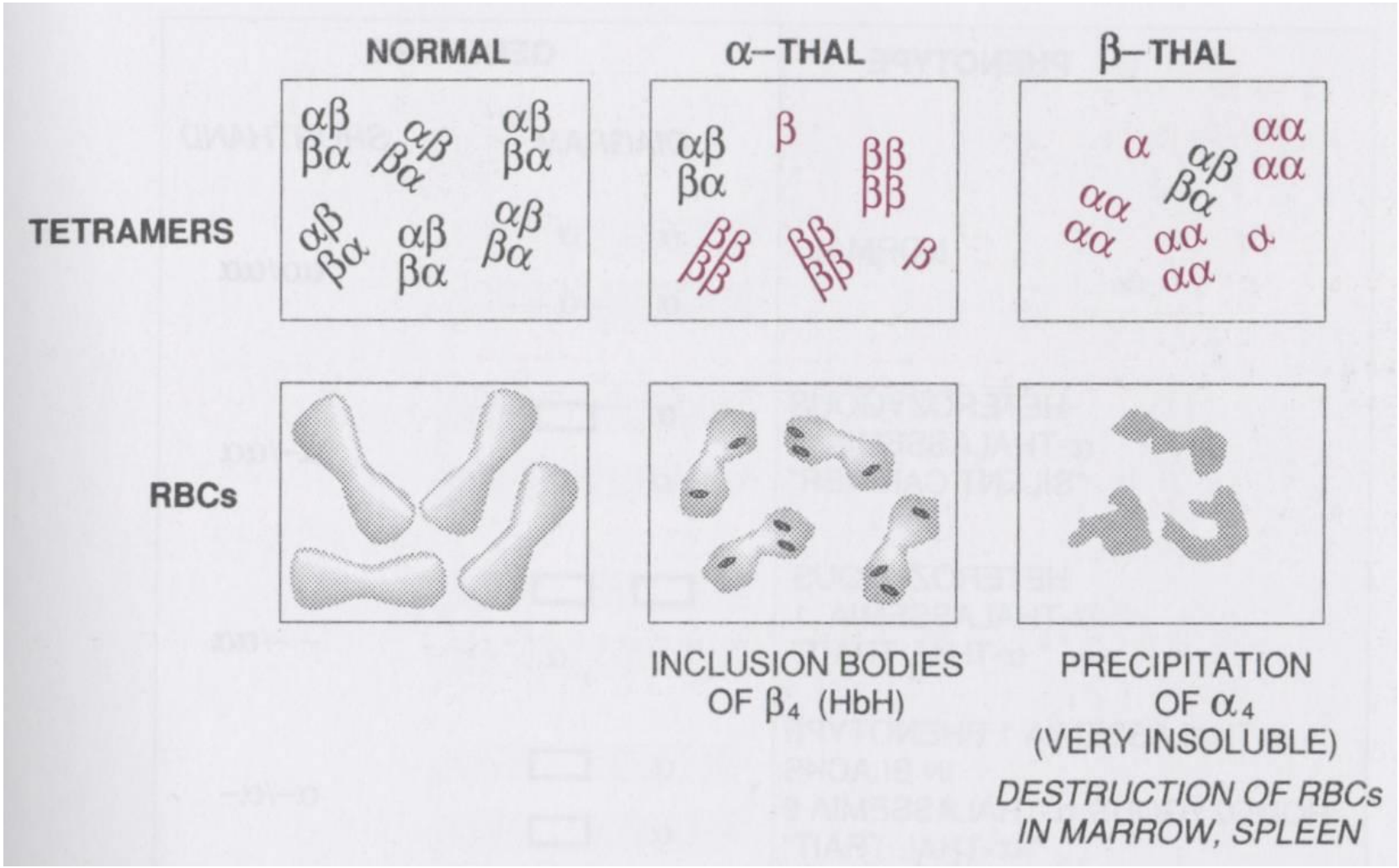
β-thalassemia

- > 200 genetic defects
  - mainly point mutations
  - highly unstable β-chain
- clinical classification
  - major
    - 2 alleles
    - severe anemia requiring regular transfusions
  - minor (thalasemia trait)
    - 1 allele, heterozygous carrier
    - without symptoms
  - intermedia
    - genetically heterogenous
    - moderate anemia not requiring regular transfusions
- serious β-thalassemia
  - erythroid hyperplasia, extramedullar hemopoiesis
  - bone damage
  - increased iron absorption
    - supressed hepcidin synthesis
    - iron from transfussions

α-thalassemia

- gene for α-globin chain is duplicated on both chromosomes 16
- normal person has 4 α-globin genes
  - deletion of 1 or both α-chain genes on each chromosome may occur
    - most common is deletion of 1
- decreased α-chain synthesis
  - excess of unmatched chains
- less severe than β-thalassemia

Thalassemias - summary



Extracorpuscular hemolytic anemias

- RBC damage
  - mechanical
  - toxins or parasites
  - antibodies and complement
  - antibodies against blood group antigens

Paroxysmal nocturnal hemoglobinuria

- rare form
  - mutation affecting hemopoietic stem cell
  - enzyme PIG-A
    - impaired synthesis of GPI
      - it anchors many proteins to the cell surface
    - synthesis of surface proteins
  - not only RBC
  - present in most healthy people
    - in small number of cells
  - deficit of proteins that regulate complement activity
    - intravascular hemolysis of deficient cells
- night lysis of cells
  - in 25 % of patients
  - pH
  - complement activity
- hemosiderinuria
- clinical signs
  - intravascular hemolysis
  - hemoglobinuria
  - vein thrombosis
- urinary iron loss
  - may cause deficiency
- treatment and prognosis
  - chronic
  - blood transfusions