Physiology of the Blood II. Red Blood Cells (Erythrocytes)

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1. Number, structure, physical properties
Erythrocytes

- **number**: 4-5 million/µl, **life**: 120 days
- **diameter**: 7-8 µm
- **genesis**: bone marrow, facilitated by **ERYTHROPOIETIN** (produced by kidney, trigger: hypoxia)
- **mature form**: in humans no nucleus, mitochondria, endoplasmatic reticulum; metabolism: glycolysis
- **RETICULOCYTE**: young form with endoplasmatic reticulum (protein synthesis)
High altitude, etc. → PO$_2$ ↓ → Kidney → PO$_2$ ↑ → Erythropoietin ↑ → Erythrocytes → Bone marrow
Parameters of red blood cells

- **MCH** – mean corpuscular hemoglobin (29 pg)
- **MCHC** – mean corpuscular hemoglobin concentration (330 g/L)
- **MCV** – mean corpuscular volume (94 fL)
Distribution of the size of red blood cells:
PRICE-JONES curve

Small size, narrow variance

Normal

Large size, wide variance

Normal
Blood sedimentation

- inhibited coagulation (e.g. citrate, EDTA), **Westergren tube**
- red blood cells aggregate with plasma globulins
- the distance taken by the aggregates from the top of the tube during 1 hour
- 3-10 mm/hour, higher in women

**Increased:**
- inflammation, infection
- tumors
- gravidity
- anaemia
  (decreased red blood cell number)

Very non-specific method!
The osmotic resistance of the red blood cells

Hypotonic solution → H₂O in → spheroid shape → membrane rupture → **hemolysis**

**Minimal resistance**: hemolysis not yet (0.44%)

**Maximal resistance**: full hemolysis (0.3%)

Anemia, old red blood cells, membrane diseases (e.g., spherocytosis) – decrease of osmotic resistance
Membrane proteins of the erythrocytes

Proteins: aquaporin-1, Na⁺/K⁺ and Ca²⁺ ATP-ase, Cl⁻/HCO₃⁻, Na⁺/H⁺, Na⁺/K⁺/2Cl⁻ transporter, integrin/laminin binding adhesion molecules, nitrogen monoxide (NO) and hydrogen sulfide (H₂S) synthesis (vasodilatation), antigens (AB0 and Rh)
2. Genesis: iron and vitamins
The genesis of erythrocytes

IRON
- **uptake**: 1-2 mg/day (total need: 10-15 mg/day)
- better **absorption**: Fe$^{2+}$ (vitamin C and gastric acid: Fe$^{3+} \rightarrow$ Fe$^{2+}$) and **heme-bound iron** (from meat)
- duodenum - proximal jejunum (inhibited by cereals, oxalic acid [sorrel, spinach], tannic acid [tea])
- **intestine**: binding to **ferritin**; **circulation**: to **transferrin**
- **store**: liver, spleen, bone marrow’s macrophages in the form of **hemosiderin**
- **ferroportin**: release of iron from storage cells, inhibited by **hepcidin** produced in liver (e.g. infection, tumors)
- iron deficiency: **microcyter hypochrom anaemia**

Accessory minerals
- copper, nickel, cobalt (facilitates iron absorption)
Fe storage and Fe recycling

- Bone marrow
  - Ferritin
  - Hemosiderin
  - Fe stores

- Liver
  - Ferritin
  - Hemosiderin

- Systemic blood
  - Transferrin
  - Fe
  - Heme
  - Hemopexin
  - Haptoglobin
  - Hb

- Erythrocytes
  - Already in bone marrow

- Macrophages in spleen, liver, and bone marrow (extravascular)
  - Ferritin
  - Hemosiderin

- Hepcidin
  - Ferroportin
VITAMIN B12/FOLIC ACID
- DNA-synthesis
- **B12** bound to **R-protein** (saliva) and then to **intrinsic factor** (apoeritein, produced by stomach) in intestine
- **absorption**: ileum
- in blood bound to **transcobalamin**
- deficiency: macrocyter hyperchrom anaemia (anaemia perniciosa)

HORMONES
**Stimulation:** growth hormone, testosterone, thyroxin
**Inhibition:** estrogens

ERYTHROPOIETIN
- produced by kidney due to hypoxia
- stimulation of the erythroid line in bone marrow
3. Hemoglobin structure and function: gas transport
Hemoglobin (Hb) – Gas transport

- β-globin + heme (= [Fe$^{2+}$] porphyrin)
- Fe$^{3+}$: methemoglobin (loss of function)
- 4 subunits, 4 oxygen binding
- mainly HbA, α2β2 subunit-composition
- artery: 97% saturation
- Hüffner-number: 1.3 ml oxygen/1 g Hb

Oxygen-affinity decreased:
1. Temperature
2. H$^+$ (CO$_2$↑, pH↓) - Bohr-effect
3. 2,3-bis-phosphoglycerate (2,3-BPG, byproduct of glycolysis)

Oxygen-affinity increased:
1. Fetal hemoglobin (HbF, α2γ2 – no 2,3-BPG binding)
2. Carboxy-hemoglobin (CO-Hb, unable to let oxygen to tissue)
Decreased $P_{50}$ (increased affinity)
- ↓ Temperature
- ↓ PCO$_2$
- ↓ 2,3-DPG
- ↑ pH

Increased $P_{50}$ (decreased affinity)
- ↑ Temperature
- ↑ PCO$_2$
- ↑ 2,3-DPG
- ↓ pH
Changes of globin-chains with age

Pregnancy (months) | Age (months)
--- | ---
0 | BIRTH

- **Alpha-chain**
- **Gamma-chain (fetal)**
- **Epsilon-chain (embrional)**
- **Beta-chain (adult)**
- **Delta-chain**
CO₂ in tissue:

1. Carbonic acid is produced by carbonic anhydrase enzyme

2. Hb lets oxygen and takes up proton (H⁺) dissociated from the acid

3. Bicarbonate is exchanged for chloride (Hamburger shift)

4. Non-enzymatic solution and binding to proteins
4. Degradation of hemoglobin: the question of bilirubin
Degradation of hemoglobin 1.

1. Old erythrocytes: extraction from blood by macrophages (liver, spleen)

2. Haptoglobin transiently binds hemoglobin in circulation (hemopexin: heme-binding protein in blood)

3. Fe$^{2+}$ dissociation (used again or stored) & proteolysis of β-globin

4. Porphyrin degradation: CO + biliverdin (green), then bilirubin (yellow)

Circulation: bilirubin binds to albumin – indirect bilirubin
6. Liver takes up bilirubin and conjugates that with glucuronide – direct bilirubin

7. From liver to gut with bile where further transformation occurs (urobilinogen - urobilin, stercobilinogen - stercobilin; oxidoreductive process mediated by bacteria)

8. Some of them are reabsorbed to liver with bile acids via the portal vein: Enterohepatic circulation

9. Secretion with faces (gives its color) and urine
The image depicts the metabolism of bilirubin, a breakdown product of heme. The process begins with heme, which is converted to biliverdin by heme oxygenase (spleen). Biliverdin is then reduced to bilirubin by biliverdin reductase (spleen), utilizing NADPH and NADP+.

Bilirubin is transported to the liver where it is glucuronosylated by UDP-glucuronosyl transferase, using UDP-glucuronic acid. The UDP-glucuronate is then excreted in the bile and travels through the enterohepatic circulation.

In the intestine, bilirubin undergoes deconjugation and reduction, forming urobilinogens (uncolored). These are oxidized to urobilins (brown) and excreted in the feces.

The diagram shows the chemical structures of heme, biliverdin, bilirubin, and bilirubin diglucuronide, along with the enzymes and reactions involved in the process.
Bone marrow

RBC formation

Life span: 120 days

Blood

Breakdown

Spleen

Phagocytosis by macrophages in:
- Bone marrow
- Lymph nodes
- Spleen
- Liver, etc.

Test

"Still good"

"Too old"

Pulpal arteriole

Spenic pulp

Sinus
Urobilinogen in urine:
- ↑ degradation of red blood cells
- hepatic disease with icterus
5. Blood groups
The AB0 blood group

In the membrane of erythrocytes: glycolipid antigens

0 blood group: basic H-antigen
A and B groups: additional sugars are bound to H-antigen (e.g. galactose)

A (44%) – A1: many antigens, A2: few antigens
Circulating antibody (IgM): anti-B
Genotype: AA/A0

B (10%)
Circulating antibody: anti-A
Genotype: BB/BO

0 (42%) – „universal graft”
Circulating antibody: anti-A+B
Genotype: 00

AB (4%)
Circulating antibody: none
Genotype: AB

Bombay: H-antigen misses terminal sugar (fucose) → no more sugars can bind to it (0 group with other genotype)
Determination of blood groups

Cross reactions:

**Major test**: donor cell, host serum

**Minor test**: donor serum, host cell

Transfusion of non-compatible blood group: **HAEMOLYSIS**
(degradation of erythrocytes caused by the antigen-antibody reaction, release of hemoglobin, kidney dysfunction and multiple organ failure)
Rh (Rhesus) blood group

- Protein antigens, 3 alleles: c/C, d/D, e/E
- D is the only strong antigen – Rh+ blood group
- there is no spontaneous immunization (antibodies) only if:
  a. Rh- receives Rh+ blood
  b. Rh- mother has Rh+ baby
  (Rh prophylaxis by giving incomplete Rh-antibodies that suppress production, unless danger of erythroblastosis fetalis)