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BLOOD

Anemia

Degradation of heme

- **Around 100–200 million aged erythrocytes/hour are broken down.**
- **The degradation process starts in reticuloendothelial cells in the spleen, liver, and bone marrow.**

[1] The tetrapyrrole ring of heme is oxidatively cleaved between rings A and B by heme oxygenase. This reaction requires molecular oxygen and $NADPH^{+}H^{+}$, and produces green

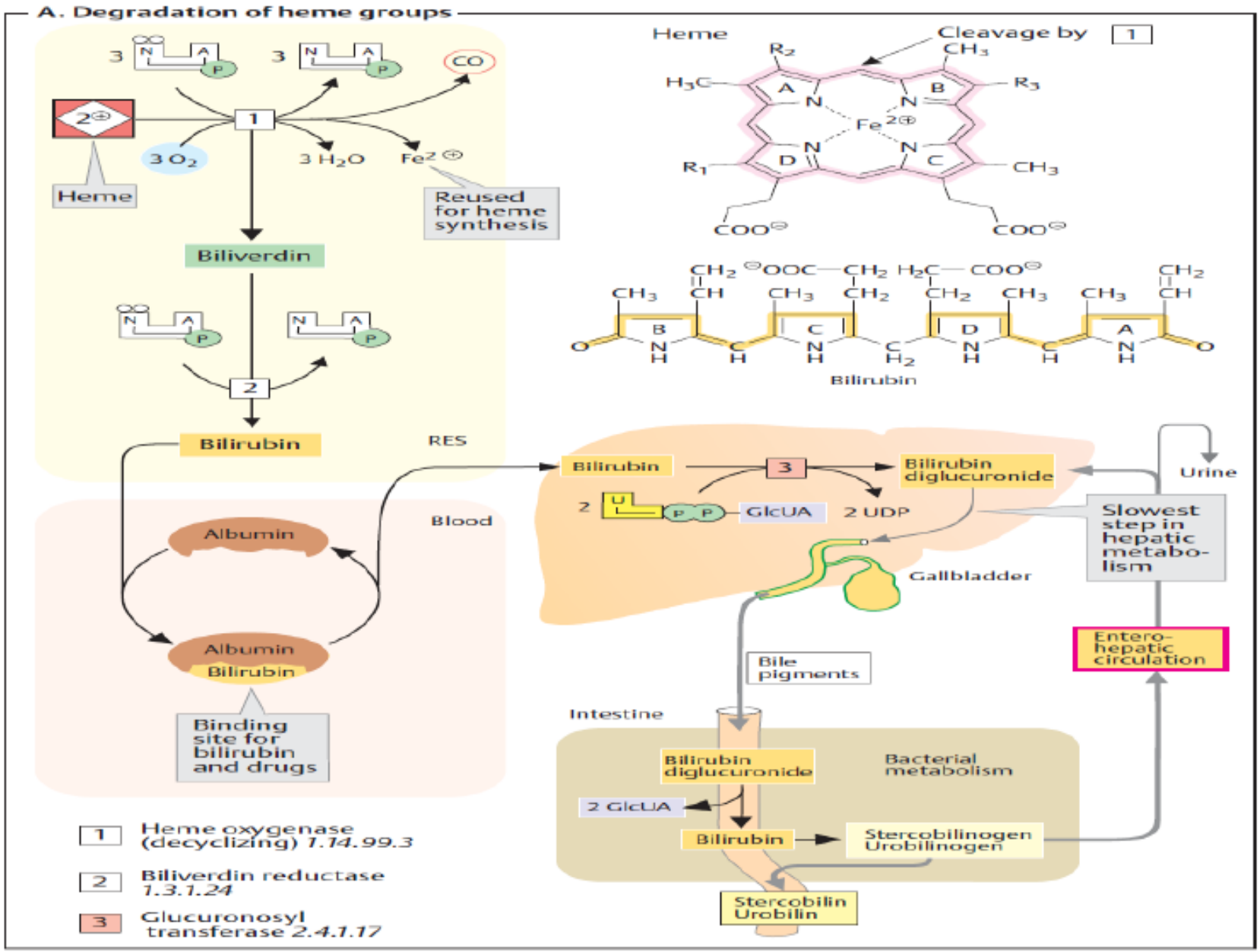
biliverdin, as well as CO (carbon monoxide) and Fe^{2+}, which remains available for further use.

[2] Biliverdin is reduced by biliverdin reductase to the orange colored bilirubin. For further degradation, bilirubin is transported to the liver via the blood. As bilirubin is poorly soluble, it is bound to albumin for transport. Some drugs that also bind to albumin can lead to an increase in free bilirubin.

[3] The hepatocytes take up bilirubin from the blood and conjugate it in the endoplasmic reticulum with the help of UDP-glucuronic acid into the more easily soluble bilirubin monoglucuronides and diglucuronides.

UDP glucuronosyltransferase forms ester type bonds between the OH group at C-1 of glucuronic acid and the carboxyl groups in bilirubin. The glucuronides are then excreted by active transport into the bile, where they form what are known as the bile pigments. Some of the bilirubin conjugates are broken down further in the intestine by bacterial γ-glucuronidases. The bilirubin released is then reduced further via intermediate steps into colorless stercobilinogen, some of which is oxidized again into orange to yellow-colored stercobilin.

The end products of bile pigment metabolism in the intestine are mostly excreted in feces, but a small proportion is resorbed (enterohepatic circulation). When high levels of heme degradation are taking place, stercobilinogen appears as urobilinogen in the urine, where oxidative processes darken it to formurobilin.


A. Degradation of heme groups
Heme
Cleavage by 1
CO
Heme
Reused for heme synthesis
Biliverdin
Bilirubin
RES
Blood
Albumin
Albumin
Bilirubin
Binding site for bilirubin and drugs
Bilirubin
Bilirubin diglucuronide
GlcUA
2 UDP
Slowest step in hepatic metabolism
Urine
Gallbladder
Entero-hepatic circulation
Bile pigments
Intestine
Bilirubin diglucuronide
Bacterial metabolism
2 GlcUA
Bilirubin
Stercobilinogen Urobilinogen
Stercobilin Urobilin
1 Heme oxygenase (decyclizing) 1.14.99.3
2 Biliverdin reductase 1.3.1.24
3 Glucuronosyl transferase 2.4.1.17

Hyperbilirubinemias. **An elevated bilirubin level (> 10 mg/L) is known as hyperbilirubinemia. When this is present, bilirubin diffuses from the blood into peripheral tissue and gives it a yellow color (jaundice). The easiest way of observing this is in the white conjunctiva of the eyes.**

Causes of jaundice:

- **If increased erythrocyte degradation (hemolysis) produces more bilirubin, it causes hemolytic jaundice.**

- **If bilirubin conjugation in the liver is impaired e. g., due to hepatitis or liver cirrhosis it leads to hepatocellular jaundice, which is associated with an increase in unconjugated (indirect) bilirubin in the blood.**
- **If there is a disturbance of bile drainage (obstructive jaundice, due to gallstones or pancreatic tumors), then conjugated (direct) bilirubin in the blood increases.**
- **Neonatal jaundice (physiologic jaundice) usually resolves after a few days by itself. In severe cases, however, unconjugated bilirubin can cross the blood–brain barrier and lead to brain damage (kernicterus).**

- **Up to the time of birth, fetal hemoglobin then predominates (HbF, $\alpha_2\gamma_2$), and it is gradually replaced by HbA during the first few months of life. Embryonic and fetal hemoglobins have higher O_2 affinities than HbA, as they have to take up oxygen from the maternal circulation.**

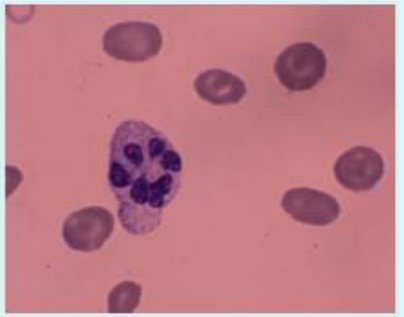
Erythrocyte Abnormalities (Anemia):

Deficiency in the oxygen-carrying capacity of the blood due to a diminished erythrocyte mass.

Normal Peripheral Smear

Due to:

- **Erythrocyte loss (bleeding)**
- **Decreased Erythrocyte production:**
  - **low erythropoietin**
  - **Decreased marrow response to erythropoietin**
    - **Iron-Deficiency**
    - **Vitamin B12 Deficiency**
    - **Folate Deficiency**
    - **Anemia of Chronic Disease**
- **Increased Erythrocyte destruction (hemolysis)**



Vitamin B12 Deficiency

Hematopoietic precursor cells are particularly sensitive to any insult that impairs DNA synthesis. This leads to appearance of characteristic megaloblasts - corresponds to normoblasts (characterized by increased ratio of RNA to DNA). The cause can be deficiencies in metal traces, folic acid & vitamin B12.

Iron-deficiency: Lack of dietary iron or excess blood loss (e.g menstruation)

Folic acid deficiency: Its deficiency leads to megaloblastic anemia as it is a co-factor for a variety of reactions to 1-carbonmetabolism(synthesis of purines & thymines).

Vitamin B12 deficiency: Leads to pernicious anemia. Based on malabsorption of Vitamin B12 due to failure of the gastric mucosa to secrete adequate intrinsic factors.

Anemia due to Decreased marrow response

Thalassemia: Microcytic anemia. Defects in either the alpha or beta chains of hemoglobin, leading to ineffective erythropoiesis and hemolysis α-thalassemia: Prevalent in Africa, Mediterranean, Middle East, Asia. β-thalassemia, Prevalent in Mediterranean, South East Asia, India, Pakistan.

Anemia due to Destruction of Red Blood Cells

Sickle Cell Anemia:

Characterized by the sickle-cell or crescent shape of the erythrocytes when the oxy HBS is converted to deoxy HbS at low PO_2. At intracellular concentrations, molecules of deoxy HbS aggregate to form filaments on tubules of indeterminately high molecular weight The sickle-cell causes severe anemia since they have increased mechanical fragility. Sickle cells also impede blood flow through capillaries. It is genetically transmitted.

Effects of Anemia

Due to decrease O2 supply to tissues.

1- Fatigue, muscle weakness

2- Mental effects: lack of concentration and dizziness , even Faintining

3- CVS effects: tachycardia, palpitation, heart failure if not treated

4- Nausea & anorexia

5- Retarded growth in children

Polycethemia

Abnormal increase of RBC in the circulation.

Polycethemia Vera: **Tumerous or cancerous production causes highly engorged blood. Genetic mutation in the hemocytoblastic cell line that increases RBC production. Hematocrit values can reach 70%.**

Secondary Polycethemia: **Mostly Physiologic. Increase in RBC production due to hypoxic tissues, e.g. high altitudes.**

Treatment: **Remove RBC by phlebotomy, blood donation.**

Effect of polycethemia on the circulatory system

1. Increased viscosity causes sluggish blood movement.

2. Thrombosis and obstruction of different blood vessels.

3. Decreased blood flow to tissues and Decreased delivery of O_2 to tissues.

4. Hct increases and so blood volume, blood pressure and work of the heart increases.