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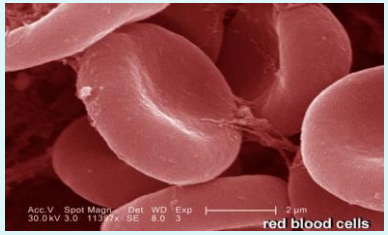
BLOOD

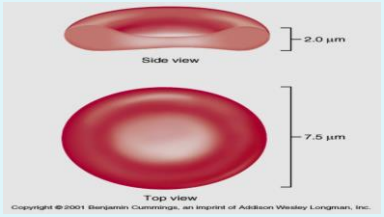
Red blood cells

Erythrocytes

- Circulating erythrocytes are derived from erythropoietic cells (the precursors of erythrocytes). RBCs arise from mesenchymal cells present in bone marrow.
- RBCs lack nucleus & other organelles, utilizes an aerobic metabolism.



- Anucleate – they lack a nucleus.
- RBCs have a biconcave disc shape (6 – 9 µm in diameter; 1 µm, thick; 2 - 2.25 µm at the periphery)



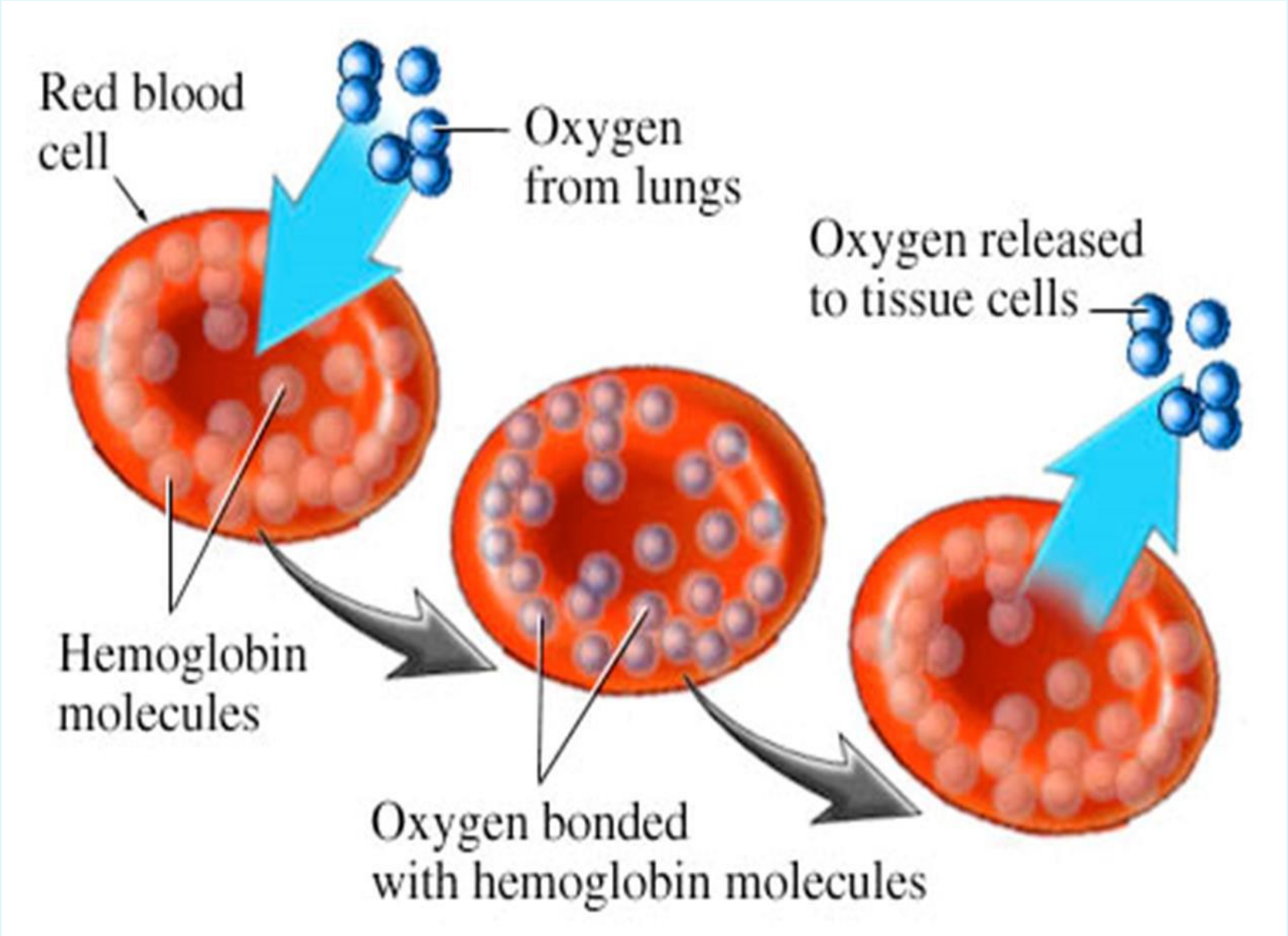
Normal RBC count

- **Male 5.4 million / drop**
- **Female 4.8 million / drop**
- **New RBCs enter circulation at 2 million / second**

Functions

- **Transport of oxygen from the lungs to the tissues by hemoglobin.**
- **Controls blood pH (CO2) is converted to bicarbonate by carbonic anhydrase = major buffering system).**

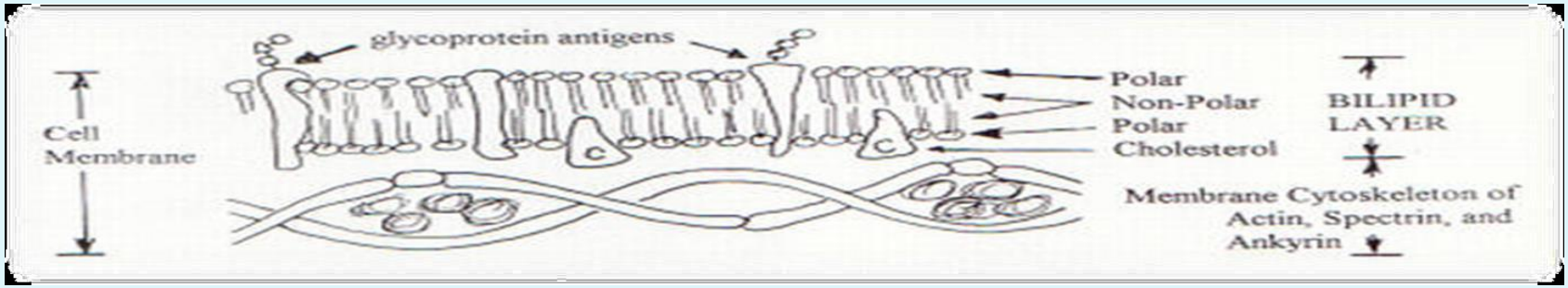
$$CO_2 + H_2O \longrightarrow H_2CO_3 = HCO^-_3 + H^+$$


Red blood cell
Oxygen from lungs
Oxygen released to tissue cells
Hemoglobin molecules
Oxygen bonded with hemoglobin molecules

Most of the solid matter is hemoglobin (the conjugated protein responsible for the red color of the blood)

The Erythrocyte Membrane

Composed largely of protein (49%) & lipid (43%) with a small amount of carbohydrate (8%). Has a cytoskeleton which controls the shape of the membrane & limits the lateral mobility of some intrinsic proteins. Some of the protein is glycoprotein covalently linked to CHO (Sialic acid)



Erythropoiesis

During gestation, erythrocytes are formed in various tissues occurring successively in:

- **Yolk sac – main site for the 1st weeks of gestation**
- **Liver & Spleen – from 6 weeks to 6 – 7 months & can continue to produce until about 2weeks after birth**
- **Lymph Nodes**
- **Infants (5 years old): Red cells of all bone marrow.**
- **Adults: Membranous bones like ribs, sternum, vertebrae and pelvic bones. But not in long bones like femur or tibia.**

Stem cells differentiate to produce committed stem cells called hematocytoblasts that in turn produce:

1. Proerythroblast: where Hb synthesis begins, big nucleus.

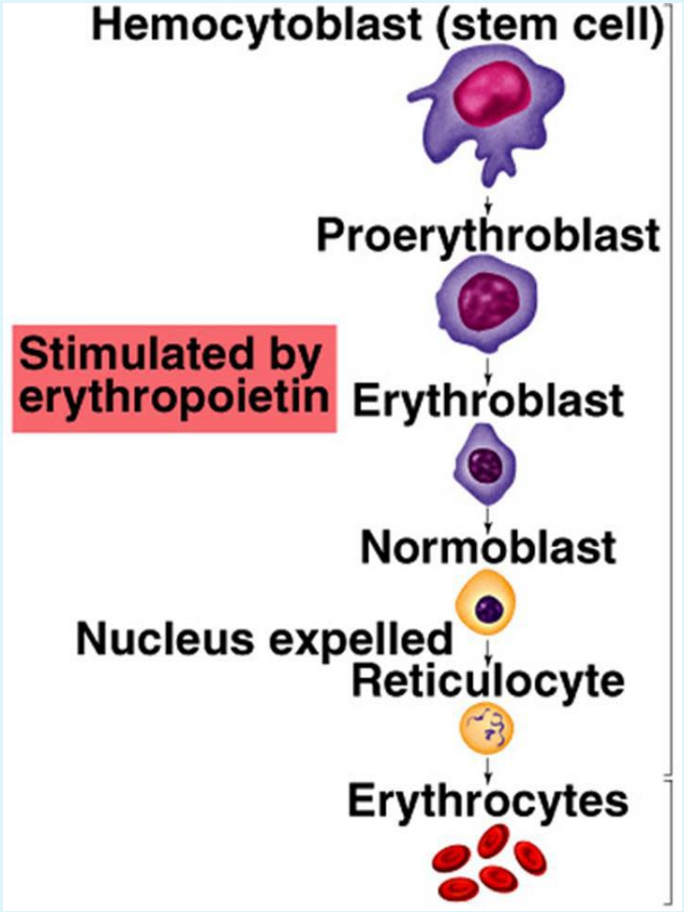
2. Basophile erythroblast: cell divide, continues

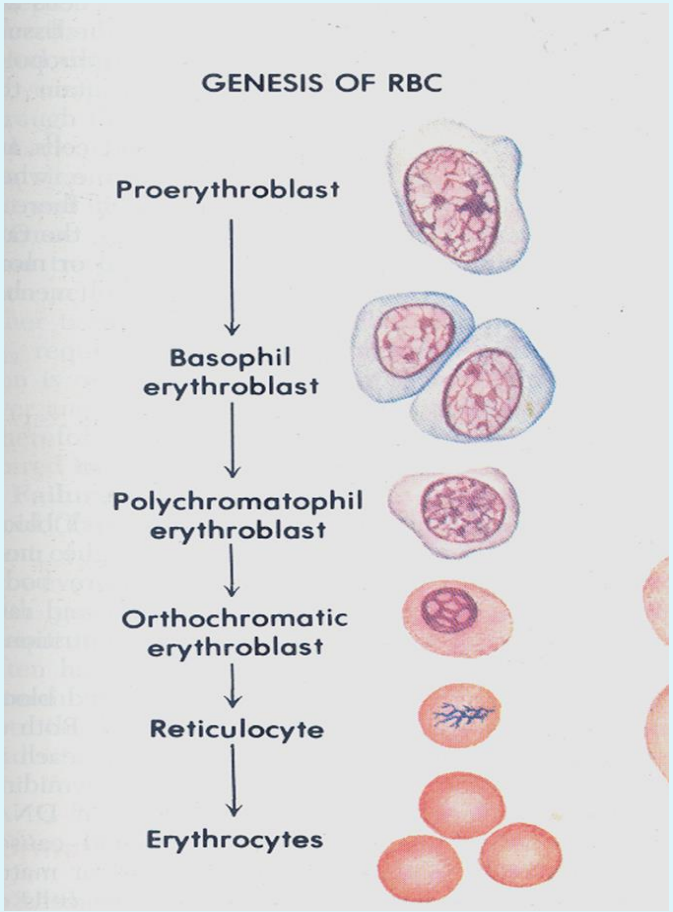
3. Polychromatophil erythroblast: Hb synthesis increases and fills the cytoplasm, nucleus size decreases.

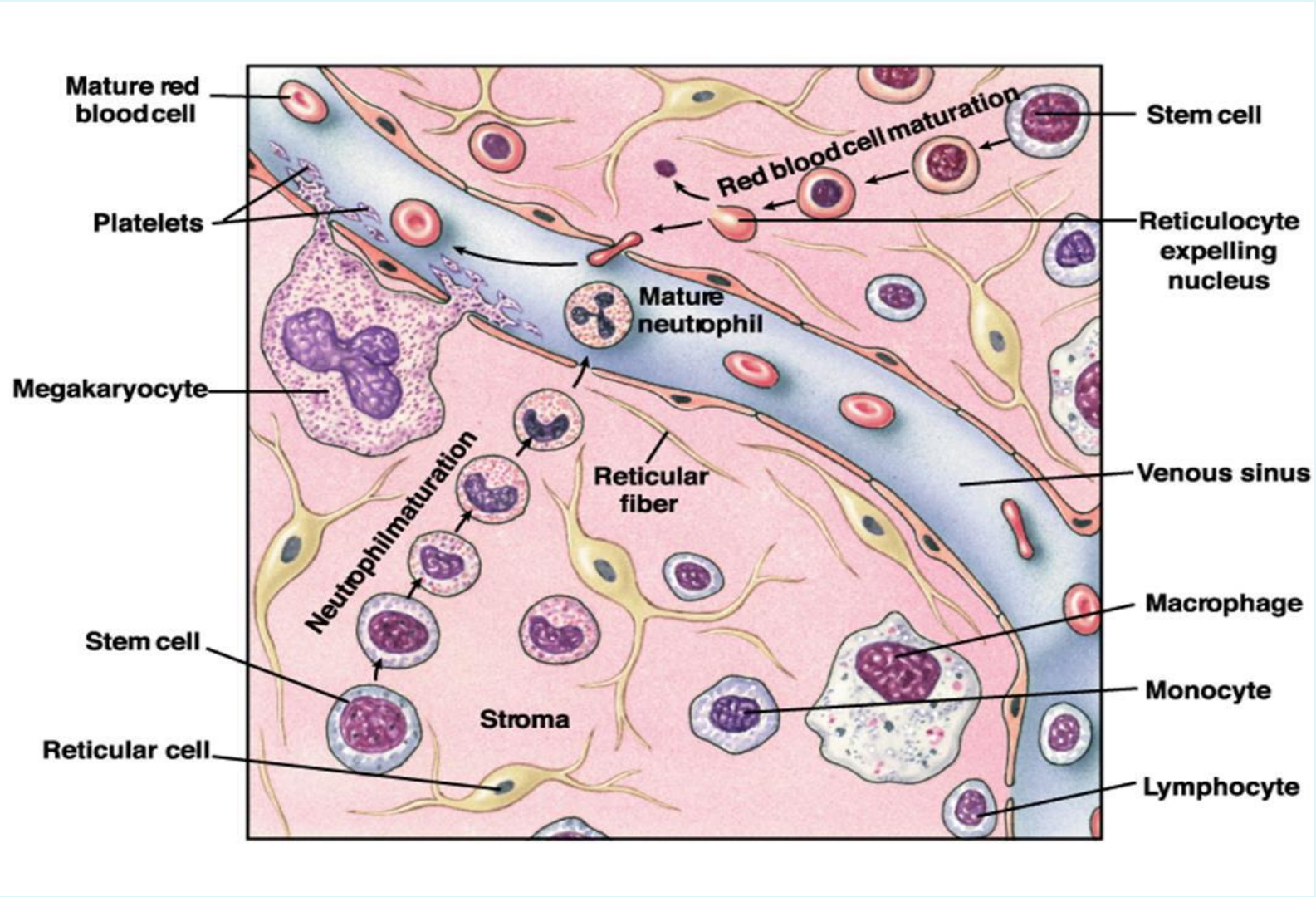
4. Ortochromatic erythroblast: Nucleus decreases.

5. Reticulocytes: Contains Hb, no nucleus and the cell is expelled from the bone to circulation. In 1 – 2 days, they eject the remaining organelles to become a mature RBC

6. Erythrocytes: Mature form of RBC without nucleus, filled with Hb.

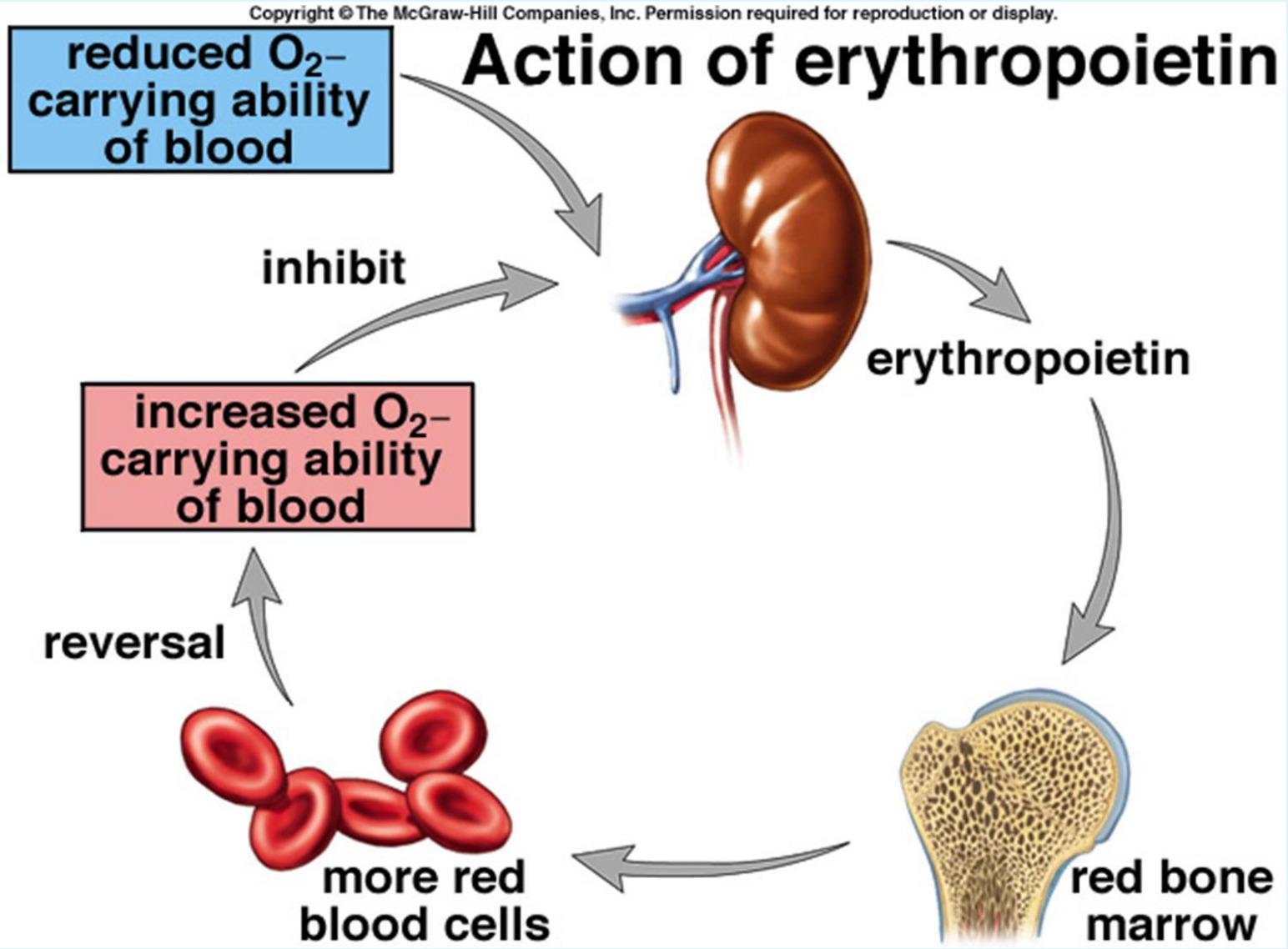





Mature red blood cell
Platelets
Megakaryocyte
Stem cell
Reticular cell
Stroma
Neutrophil maturation
Reticular fiber
Mature neutrophil
Red blood cell maturation
Stem cell
Reticulocyte expelling nucleus
Venous sinus
Macrophage
Monocyte
Lymphocyte

Physiological Mechanism

- Low oxygen (Hypoxia) that occurs in the kidney cells.
- Kidney then produce a hormone called erythropoietin.
- Erythropoietin is transported by the blood to the bone marrow.
- Bone marrow produces and releases RBC.
- Increased or adequate O_2 then blocks the formation of more RBC.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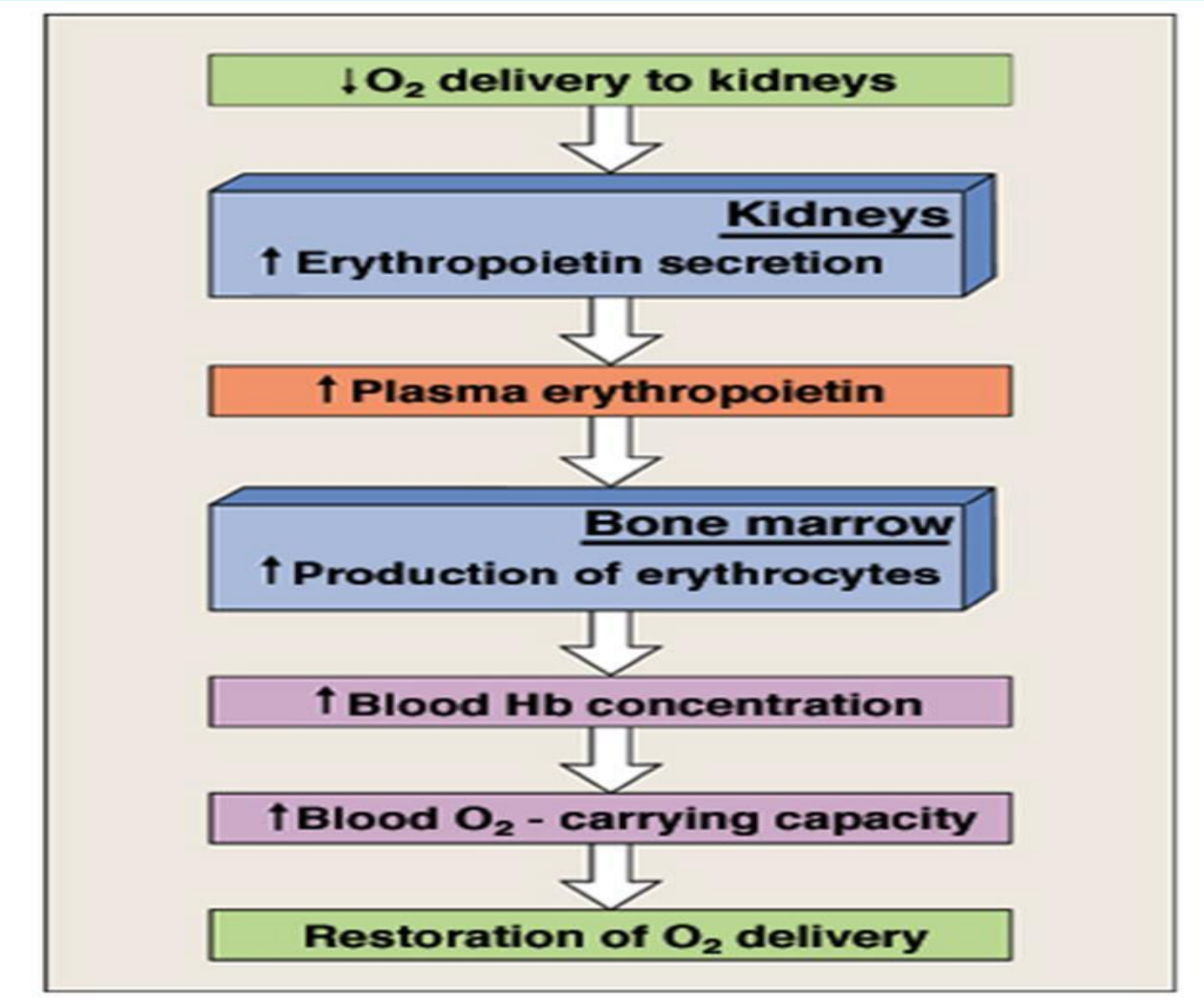
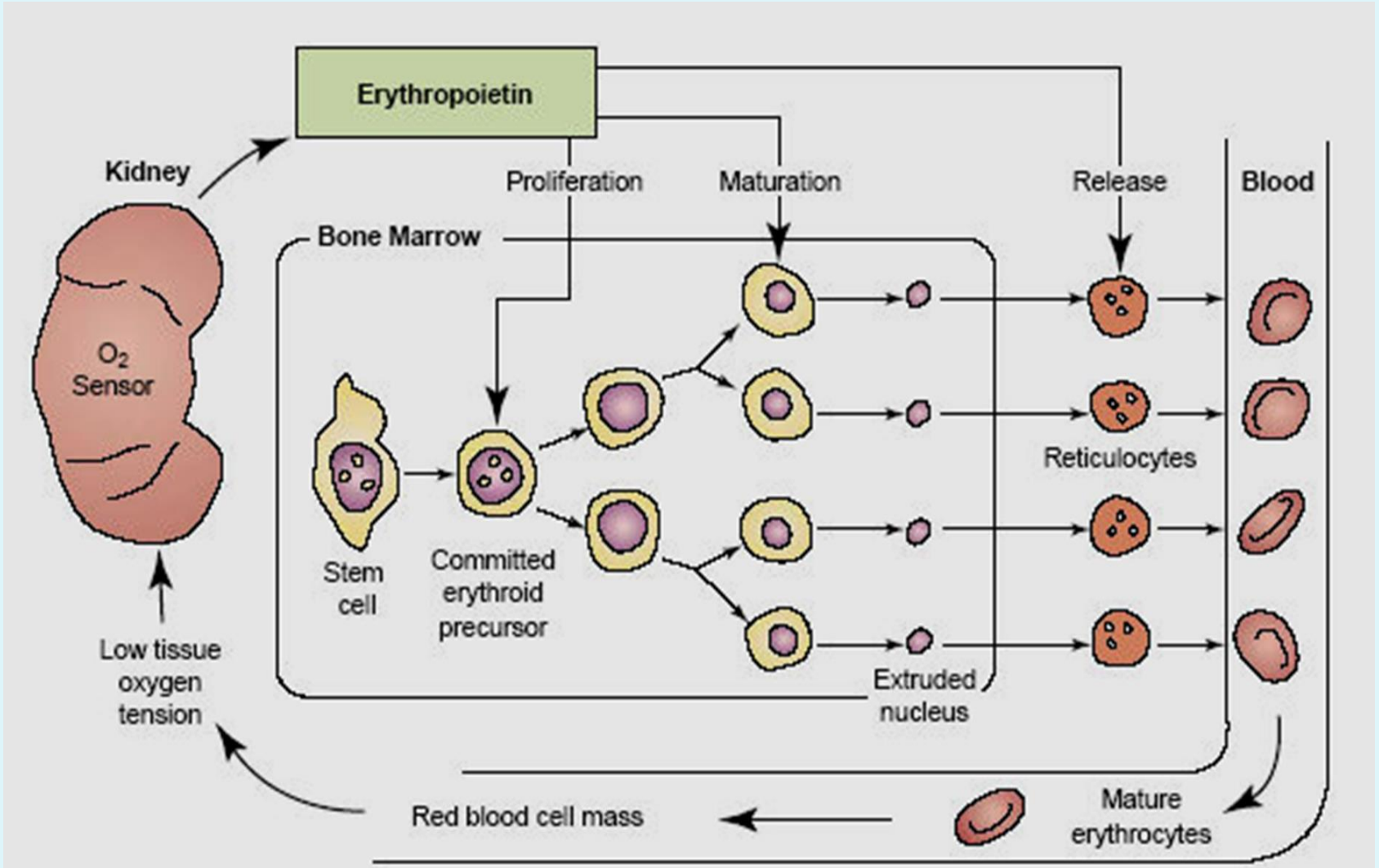
Action of erythropoietin
reduced O_2–carrying ability of blood
inhibit
erythropoietin
increased O_2–carrying ability of blood
reversal
more red blood cells
red bone marrow


↓O_2 delivery to kidneys
Kidneys
↑ Erythropoietin secretion
↑ Plasma erythropoietin
Bone marrow
↑ Production of erythrocytes
↑ Blood Hb concentration
↑ Blood O_2 - carrying capacity
Restoration of O_2 delivery



■ FIGURE 13-4 ■ Red blood cell development.

Organs involved in erythropoiesis

- **The bone marrow requires many precursors to synthesize new cells: Metals (Iron, manganese and cobalt), vitamins (B12, folate and ascorbic acid), amino acids and hormones.**
- **Kidney: Erythropiotein**
- **Liver: Store protein, vit. B12 & folic acid, synthesize globin, produce 10 % erythropiotein.**
- **Bone Marrow: Site of RBCs formation**
- **Stomach: intrinsic factor.**
- **Small Intestine: absorption of Iron, vitamins, and amino acids.**

Hemolysis

Hemolysis is the destruction (breakage) of the red blood cell's (RBC's) membrane, causing the release of the hemoglobin and other internal components into plasma fluid. Hemolysis is visually detected by showing a pink to red tinge in serum or plasma.

Causes of hemolysis

- **May be produced by substances that dissolve or change the state of membrane lipids (ether, chloroform, bile salts & soaps).**
- **Certain biological toxins (venomous snakes & hemolytic bacteria).**
- **Physical forces (UV rays, freezing, thawing).**
- **Aging – this is why whole blood can not be used after 5 – 7 days.**

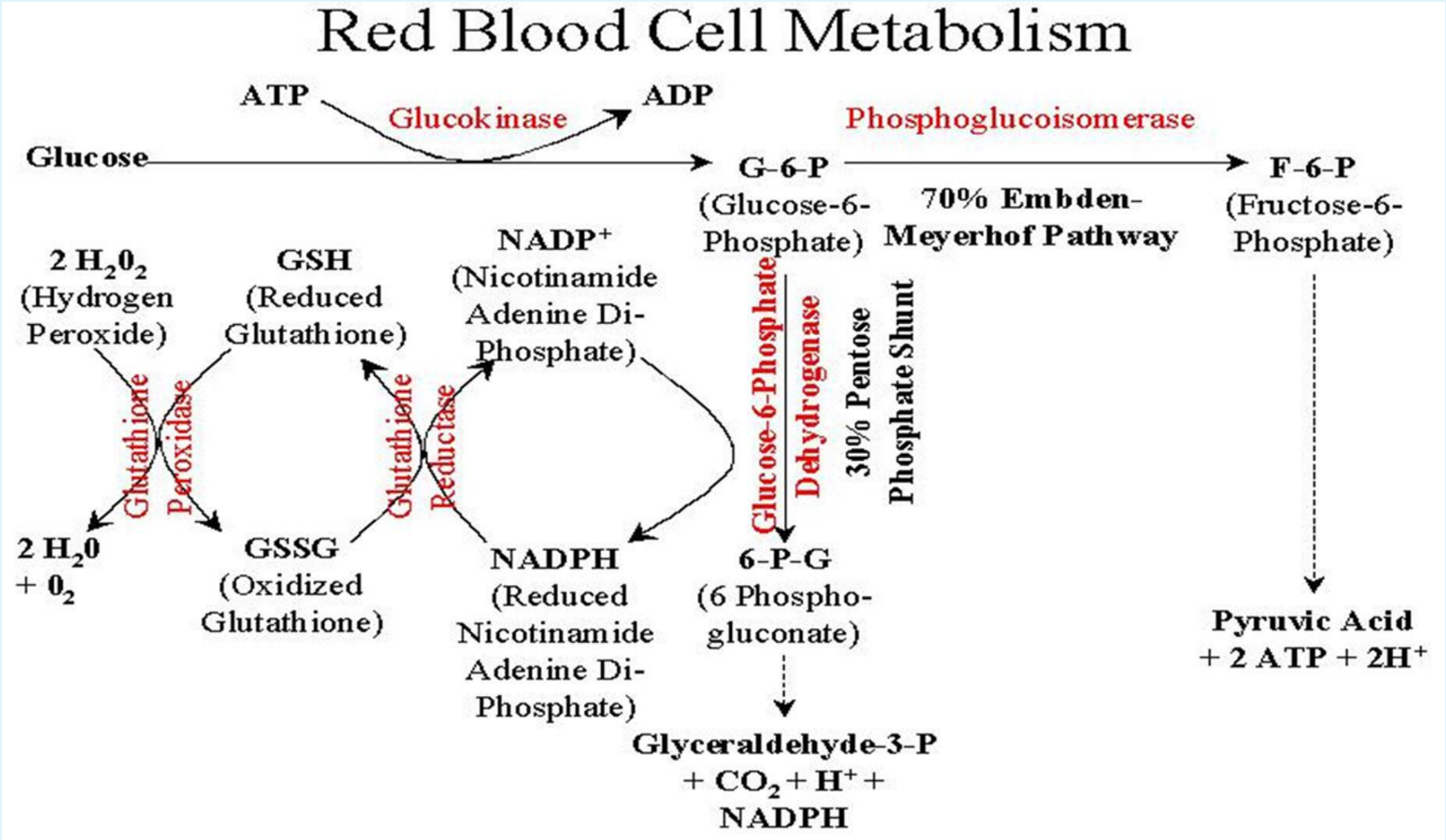
Erythrocyte metabolism

- Energy production by aerobic pathways depend on O_2.
- On the other hand, O_2 constantly gives rise to small quantities of toxic substances known as reactive oxygen species (ROS).
- ROS are powerful oxidation agents (reactive free radicals), which damage cellular structures and functional molecules.
- The erythrocytes are exposed to high concentrations of O_2 therefore particularly at risk from ROS.

- **Erythrocytes can inactivate ROS (superoxide dismutase, catalase, GSH) and repair damage caused by ROS.**
- **Products that are supplied by the erythrocytes maintenance metabolism, (anaerobic glycolysis and the pentose phosphate pathway, PPP).**
- **The ATP formed during glycolysis serves to supply Na^+/K^+-ATPase, which maintains the erythrocytes' membrane potential. Failure to produce enough ATP results in an ability to maintain ionic balance leading to accumulation of Ca^{2+} and shape change.**

- **2,3 BPG is a metabolite unique to the RBC derived from glycolysis. At a concentration of 4–5 mM, it is almost equimolar to Hb. 20–25 % of 1,3 DPG pass to 2,3 DPG by mutase, therefore ATP yield decreases from glucose. 2,3 DPG depends on the relative rates of the mutase & phosphatase reactions.**
- **The PPP supplies $NADPH^+ H^+$, which is needed to regenerate glutathione (GSH) from GSSG with the help of glutathione reductase.**

- **GSH, the most important antioxidant in the erythrocytes.**



- **GSH, tripeptide (sequence: Glu–Cys–Gly) contains an atypical γ-peptide bond between Glu and Cys. The thiol group of the cysteine residue is redox-active.**
- **GSH occurs in high concentrations as the most important antioxidant in the erythrocytes, serves as a coenzyme for glutathione peroxidase.**
- **Glutathione peroxidase: Selenium-containing enzyme detoxifies H_2O_2 and hydroperoxides, which arise during the reaction of ROS with unsaturated fatty acids in the erythrocyte membrane.**
- **The reduction of methemoglobin ($HbFe^{3+}$) to Hb ($HbFe^{2+}$) is carried out by GSH or ascorbate by a non-enzymatic pathway; however, there are also NAD(P) H-dependent Met-Hb reductases.**

- **Enzyme deficiencies affecting red cell metabolism (Hereditary hemolytic anemia): Phosphopyruvate hydratase (enolase) catalyzes the elimination of water from2-phosphoglycerate to form Phosphoenol-pyruvate.**
- **Enolase deficiency leads to decreased ATP required to maintain the biconcave shape of RBC (Hemolyticanemia).**
- **Glucose 6-P-Dehydrogenase (G6PDH) catalyzes the formation of 6-Phosphogluconolactone and NADPH from Glucose-6-phosphate and $NADP^+$.**

- **Glucose-6-P Dehydrogenase deficiency may result in increased hemolysis & severe hemolytic anemia.**
- **Pyruvate Kinase catalyze the transfer of a phosphate group from phosphoenol pyruvate (PEP) to ADP, yielding one molecule of pyruvate and one molecule of ATP.**
- **Pyruvate Kinase deficiency may lead to red blood cells become deficient in ATP, extremely fragile and hemolyzed.**
- **Deficiency in other enzymes in glycolysis such as hexokinase, glucose–phosphoisomerase, phosphofructokinase, triose phosphate isomerase,2-3 diphosphoglycerate dismutase leads to hemolytic anemia**.

Destruction of erythrocytes

- Senescent erythrocytes are engulfed primarily in the reticuloendothelial cells of the spleen.
- Free hemoglobin is released and binds to plasma proteins (e.g. haptoglobin) and transported to liver where Hb portion is split.
- Heme is transported to plasma & converted to bilirubin; excreted in the bile.
- Iron is released & stored in the liver for reuse.