# BCM 317 LECTURE

BY

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# JAUNDICE

- Jaundice is yellowish discoloration of the skin, sclera and mucous membrane, resulting from an increased bilirubin concentration in the body fluid. It is usually detectable clinically when the plasma bilirubin exceeds (2mg/dl).

# TYPES OF JAUNDICE

**HEPATOCELLULAR JAUNDICE**

- Damage of the liver cells (as seen in Liver cirrhosis or hepatitis) reduces the liver's ability to metabolize bilirubin. This leads to a build up of unconjugated bilirubin in the blood.

- Primary biliary cirrhosis (destruction of small bile ducts of the liver) and swelling of liver cells may cause obstruction to the biliary canaliculi, this leads to an impairment of excretion of conjugated bilirubin into the bile. In such a case, blood levels of conjugated bilirubin is increased.

- Thus, in hepatocellular jaundice, Both conjugated and unconjugated bilirubin are increased in the blood

# HEMOLYTIC JAUNDICE

- This results from massive lysis of Red blood cells (as seen in patients with sickle cell anemia, or malaria). This leads to an increase in production of bilirubin from heme, so more bilirubin is excreted in the bile.

- Bilirubin is produced faster than it can be conjugated. Therefore,unconjugated bilirubin level in blood is increased.

# OBSTRUCTIVE JAUNDICE

- This results from obstruction of the bile duct (due to hepatic tumor or bile stone that may block the bile duct), preventing passage of bilirubin into the intestine.

- The liver regurgitates bilirubin into the blood. Thus the level of conjugated bilirubin in the blood is increased.

- Patients with obstructive jaundice suffer from gastrointestinal pain and nausea and produce stools that are a pale, clay coloured.

# NEONATAL JAUNDICE

Neonatal jaundice results from simultaneous occurrence of the following two phenomena:

- Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes and the higher erythrocyte mass in neonates.

- Hepatic excretory capacity of bilirubin is low in neonates both because of low concentrations of the binding protein 'ligandin' in the hepatocytes and because of low activity of glucoronyl transferase, the enzyme responsible for binding bilirubin to glucoronic acid.

# HEPATITIS

- Hepatitis is a disease characterized by inflammation of and injury to the liver. Hepatitis has many causes including misuse of alcohol and drugs, but viruses are the most common cause.

- Symptoms of viral hepatitis appear from two weeks to six months after exposure to the virus. The first symptoms are usually fatigue, poor appetite and nausea. Pain in the abdomen above the liver and a slight fever are also common. After a few days the person's urine becomes dark and jaundice appears.

- The jaundice and dark urine indicate the liver is not working properly in removing bilirubin from the blood

- Symptoms of viral hepatitis generally last two to six weeks. Severe cases can lead to liver failure and death.

- In some patients, the disease becomes persistent and is called chronic hepatitis.

- Chronic hepatitis can lead to a liver disease called cirrhosis, and it is also a major cause of liver cancer.

# TYPES OF VIRAL HEPATITIS

- There are six types of viral hepatitis:
- Hepatitis A (highly contagious and is also called infectious hepatitis)
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Hepatitis E
- Hepatitis G

- Hepatitis A,C,D,E and G are caused by viruses that have a core of ribonucleic acid (RNA). The hepatitis B virus has  a deoxyribonucleic (DNA) core.

# ERYTHROCYTES METABOLISM

## Major functions of the RBC

RBC are small cells (6-8µm in diameter)

- Transport $O_2$ from lungs to the peripheral tissues.
- Disposal of $CO_2$ and $[H^+]$ protons formed during tissue metabolism.
- Carry $CO_2$ to lungs for elimination by exhalation

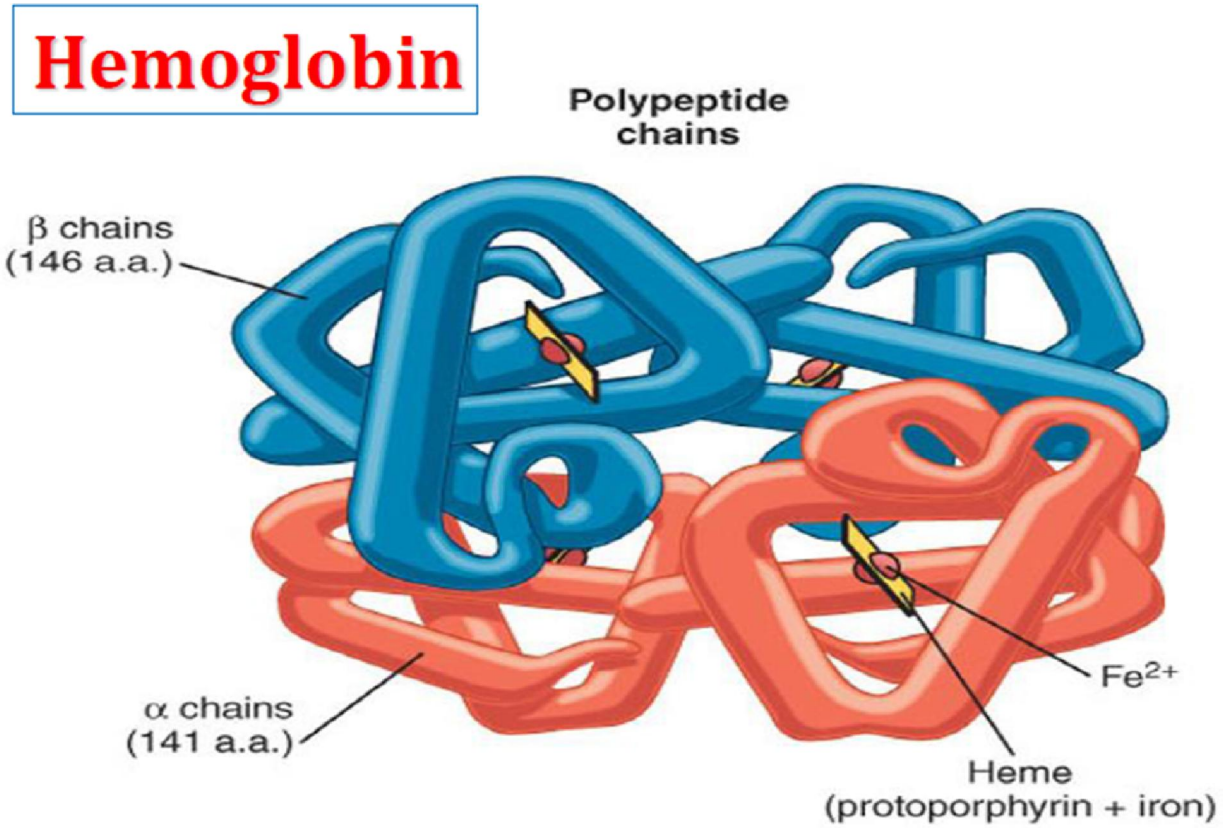
# Introduction to RBCs

- The red blood cells (RBCs) are not true cells.
- Composed of Membrane surrounding a solution of hemoglobin(95%). Bag filled with hemoglobin.
- RBCs contain no nucleus or nucleic acids, and thus, can not reproduce.

- RBCs contain no cell organelles (such as mitochondria, Golgi, ER or lysosomes) and thus possess no synthetic activities (no protein biosynthesis, no lipid synthesis & no carbohydrate synthesis).

- RBCs must be able to squeeze through some tight spots in micro-circulation. For that RBCs must be easily & reversibly deformable

# Structure of hemoglobin



# Metabolism of RBCs Introduction:

- RBCs contain no mitochondria, so there is no respiratory chain, no citric acid cycle, and no oxidation of fatty acids or ketone bodies.
- The RBC is highly dependent upon glucose as its energy source.
- Energy in the form of ATP is obtained ONLY from the glycolytic breakdown of glucose with the production of lactate (anaerobic glycolysis).

- ATP produced is being used for keeping the biconcave shape of RBCs and in the regulation of transport of ions, water in and out of RBCs

# 1. Glucose transport through RBC membrane

- Glucose is transported through RBC membrane by facilitated diffusion through glucose transporters, GLUT-1.
- Glucose transporter (GLUT-1) is independent on insulin i.e. insulin does not promote glucose transport to RBCs
- It functions by generating a gated pore in the membrane to permit passage of glucose

# 2.Glycolysis:

- Glucose is metabolized in RBCs through anaerobic glycolysis (that requires no mitochondria and no oxygen)

- One molecule of glucose yields 2 molecules of ATP by one anaerobic glycolytic pathway.
- In addition, 2 molecules of lactate are produced.

- Lactate is transported to blood & in the liver it is converted to glucose.

# Glucose metabolism in RBC

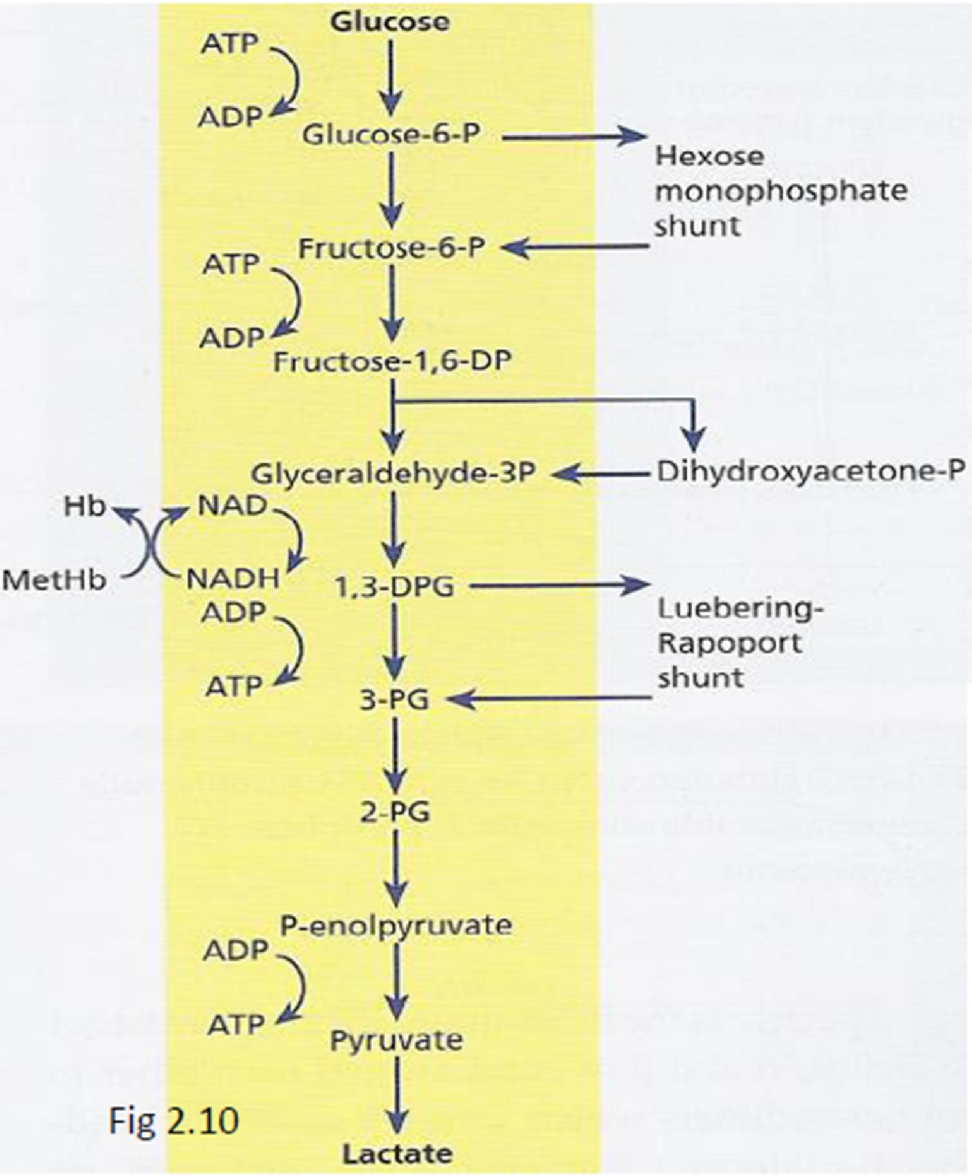
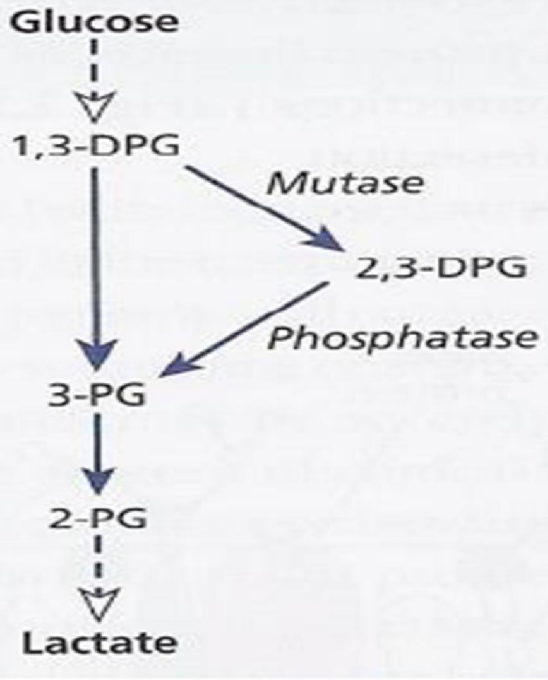


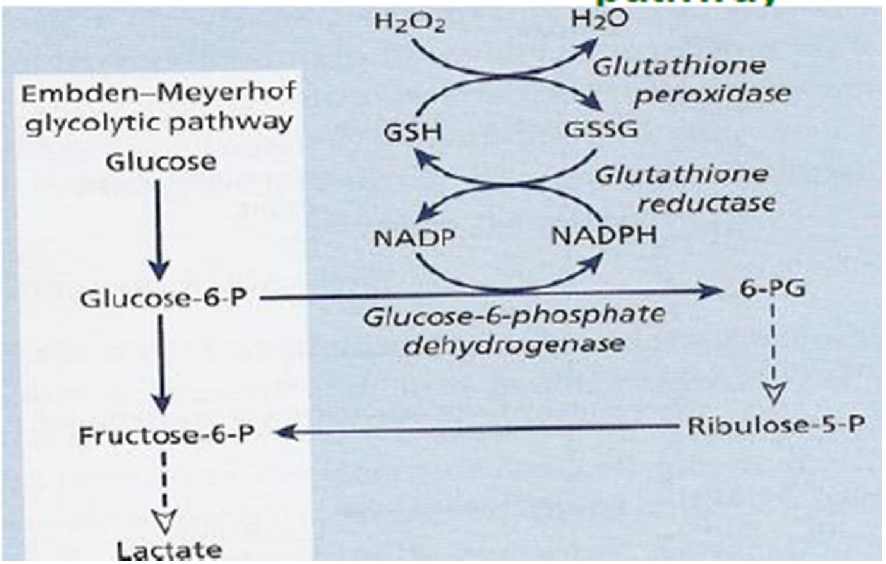

Fig 2.10

**Embden-Meyerhof glycolytic pathway**




**Luebering -Rapoport shunt**

**Hexose monophos phate shunt pathway**



# Genetic defects in enzymes of glycolysis

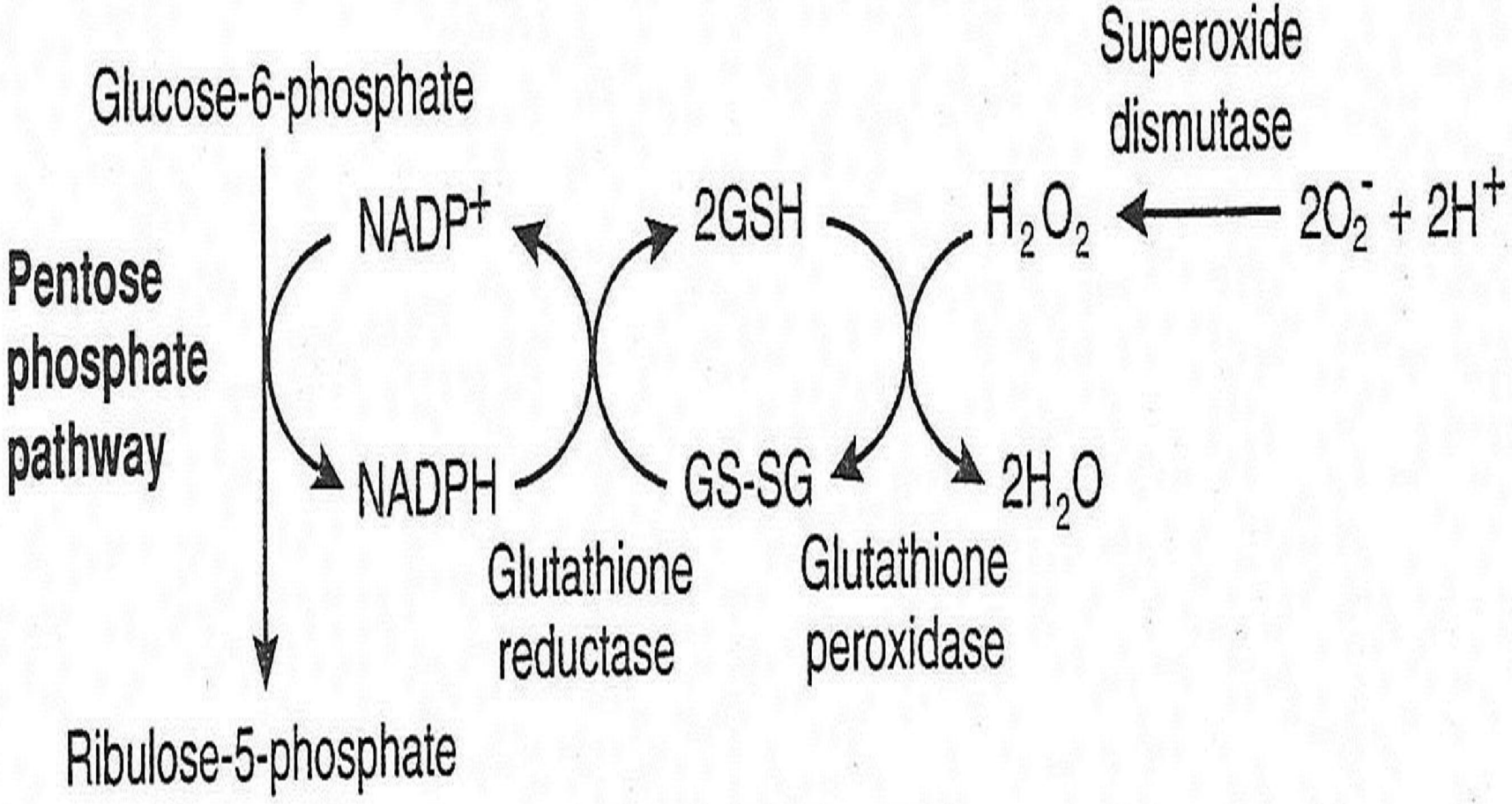
- Genetic defects of one of the enzymes of glycolysis in RBCs results in a reduce rate of glycolysis in RBCs & by this way deprive RBCs of the only means for producing energy.
- As a result, hemolytic anemia will be a consequence as RBCs will not be able to keep the biconcave flexible shape which allows it to squeeze through narrow capillaries with an end result of hemolysis (destruction of RBCs) .

- 95% of cases of genetic defects in glycolytic enzymes is caused by pyruvate kinase deficiency.

- About 5% is caused by phosphoglucose isomerase deficiency

# 4.Pentose phosphate pathway (HMP-SHUNT)

- RBCs contain an active pentose phosphate pathway (PPP) for glucose that supplies NADPH.
- NADPH is important in keeping glutathione in the reduced form.
- Reduced glutathione plays a very important role in the survival of the red blood cells. (prevents oxidation of membrane)


Glucose-6-phosphate
Superoxide dismutase
$2O_2^- + 2H^+$
$H_2O_2$
2GSH
$NADP^+$
Pentose phosphate pathway
NADPH
GS-SG
$2H_2O$
Glutathione reductase
Glutathione peroxidase
Ribulose-5-phosphate

# Glucose 6-phosphate dehydrogenase deficiency (G6PD Deficiency)

- Glucose 6-phosphate dehydrogenase is the first enzyme of pentose phosphate pathway & its deficiency leads to reduced production of NADPH ending in **acute hemolytic anemia.**

# FATE OF RBCs

- When RBCs reach the end of their lifespan, the globin is degraded to amino acids (which are reutilized in the body), the iron is released from heme and also reutilized, and the tetrapyrrole component of heme is converted to bilirubin, which is mainly excreted into the bowel via the bile.