Final term

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Program:BS D.T

Biochemistry

DT and RAD

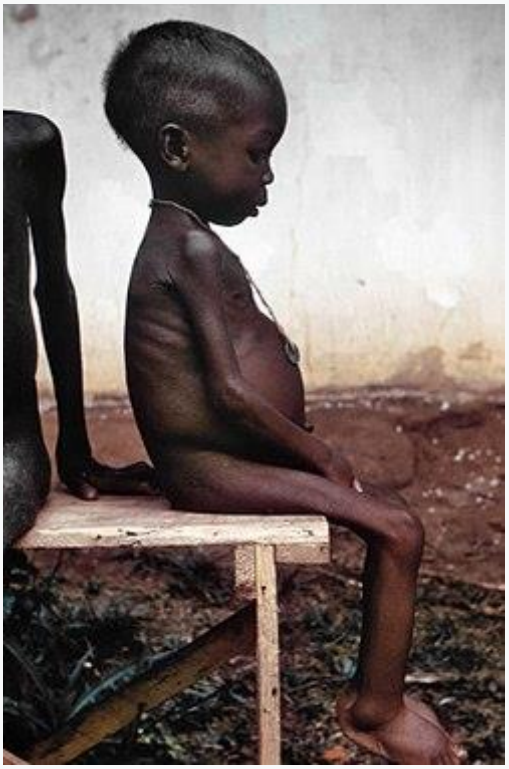
Marks 50

Q1) Define starvation and what are the metabolic changes takes places during starvation?

Ans: STARVATION :

Starvation is a severe deficiency in caloric energy intake, below the level needed to maintain an organism's life. It is the most extreme form of malnutrition. In humans, prolonged starvation can cause permanent organ damage and eventually, death. The term ***inanition*** refers to the symptoms and effects of starvation. Starvation may also be used as a means of torture or execution.

Starvation



A girl during the Nigerian Civil War of the late 1960s, shown suffering the effects of severe hunger and malnutrition.

Specialty	Critical care medicine
Symptoms	feeling weak or tired, lack of energy, loss of consciousness
Complications	Anemia, low blood sugar, dangerously low blood pressure, organ failure
Causes	Malnutrition

Diagnostic method	based on symptoms
Treatment	intensive care

According to the World Health Organization, hunger is the single gravest threat to the world's public health. The WHO also states that malnutrition is by far the biggest contributor to child mortality, present in half of all cases. Undernutrition is a contributory factor in the death of 3.1 million children under five every year. Figures on actual starvation are difficult to come by, but according to the Food and Agriculture Organization, the less severe condition of undernourishment currently affects about 842 million people, or about one in eight (12.5%) people in the world population. The bloated stomach represents a form of malnutrition called kwashiorkor. The exact pathogenesis of kwashiorkor is not clear, as initially it was thought to relate to diets high in carbohydrates (e.g. maize) but low in protein.] While many patients have low albumin, this is thought to be a consequence of the condition. Possible causes such as aflatoxin poisoning, oxidative stress, immune dysregulation and altered gut microbiota have been suggested. Treatment can help mitigate symptoms such as the pictured weight loss and muscle wasting, however prevention is of utmost importance.

- **Starvation metabolic changes:**

Animals, including humans, invoke a comprehensive programme of hormonal and metabolic adaptations that enable them to withstand prolonged periods of starvation. The brain is only capable of using glucose or ketone bodies as respiratory fuel. During prolonged starvation, the primary source of glucose is gluconeogenesis from amino acids arising from muscle proteolysis. To spare glucose use (and thus spare muscle protein) most tissues of the body utilise fat-derived fuels (fatty acid and ketone bodies). As starvation progresses ketone bodies also become the major fuel of the brain, again reducing the need for glucose. High concentrations of ketone bodies result in significant ketonuria with ketones excreted as ammonium salts. The ammonia is derived from the catabolism of glutamine in the kidney with the carbon skeleton being recovered as glucose. This well-orchestrated pattern of metabolism allows a consistent fuel supply to the brain and other tissues during prolonged starvation.

Key Concepts

- Circulating glucose concentrations do not drop below 3.5 mmol L^{-1} even in prolonged starvation.
- During starvation, the brain must be supplied with fuel in the form of glucose or ketone bodies.
- Carbohydrate reserves are depleted after 24 h of starvation.
- In prolonged starvation, gluconeogenesis provides the glucose oxidised by the brain.
- The major substrates for gluconeogenesis are amino acids derived from skeletal muscle protein breakdown.
- Circulating ketone body concentrations rise during prolonged starvation.
- During starvation, most tissues utilise fatty acids and/or ketone bodies to spare glucose for the brain.
- Glucose utilisation by the brain is decreased during prolonged starvation as the brain utilises ketone bodies as the major fuel.
- High concentrations of ketone bodies result in significant excretion of ketones.
- Urinary ketones are excreted as ammonium salts derived from the renal metabolism of glutamine with the carbon skeleton being recovered through renal gluconeogenesis

Q2) Write clinical significance of some of the enzymes?

a) Gamma-glutamyl transferase
b) Glucose -6-phosphate dehydrogenase

- Ans(A): **Useful For**
- Diagnosing and monitoring hepatobiliary disease, it is currently the most sensitive enzymatic indicator of liver disease

- Ascertaining whether observed elevations of alkaline phosphatase are due to skeletal disease (normal gamma-glutamyltransferase: GGT) or reflect the presence of hepatobiliary disease (elevated GGT)

- A screening test for occult alcoholism
- **Clinical Information**
- Gamma-glutamyltransferase (GGT) is primarily present in kidney, liver, and pancreatic cells. Small amounts are present in other tissues. Even though renal tissue has the highest level of GGT, the enzyme present in the serum appears to originate primarily from the hepatobiliary system, and GGT activity is elevated in any and all forms of liver disease. It is highest in cases of intra- or posthepatic biliary obstruction, reaching levels some 5 to 30 times normal. GGT is more sensitive than alkaline phosphatase (ALP), leucine aminopeptidase, aspartate transaminase, and alanine aminotransferase in detecting obstructive jaundice, cholangitis, and cholecystitis; its rise occurs earlier than with these other enzymes and persists longer. Only modest elevations (2-5 times normal) occur in infectious hepatitis, and in this condition, GGT determinations are less useful diagnostically than are measurements of the transaminases. High elevations of GGT are also observed in patients with either primary or secondary (metastatic) neoplasms. Elevated levels of GGT are noted not only in the sera of patients with alcoholic cirrhosis but also in the majority of sera from persons who are heavy drinkers. Studies have emphasized the value of serum GGT levels in detecting alcohol-induced liver disease. Elevated serum values are also seen in patients receiving drugs such as phenytoin and phenobarbital, and this is thought to reflect induction of new enzyme activity.

- Normal values are observed in various muscle diseases and in renal failure. Normal values are also seen in cases of skeletal disease, children older than 1 year, and in healthy pregnant women-conditions in which ALP is elevated.

- **Reference Values**
- Males
- 0-11 months: <178 U/L
- 12 months-6 years: <21 U/L
- 7-12 years: <24 U/L
- 13-17 years: <43 U/L
    - or =18 years: 8-61 U/L

- Females
- 0-11 months: <178 U/L
- 12 months- 6 years: <21 U/L
- 7-12 years: <24 U/L
- 13-17 years: <26 U/L
    - or =18 years: 5-36 U/L

- **Interpretation**
- An elevation of gamma-glutamyltransferase (GGT) activity is seen in any and all forms of liver disease, although the highest elevations are seen in intra- or posthepatic biliary obstruction. Elevated values can also indicate alcoholic cirrhosis or individuals who are heavy drinkers.

- The finding of increased GGT and alkaline phosphatase (ALP) activity is consistent with hepatobiliary disease.

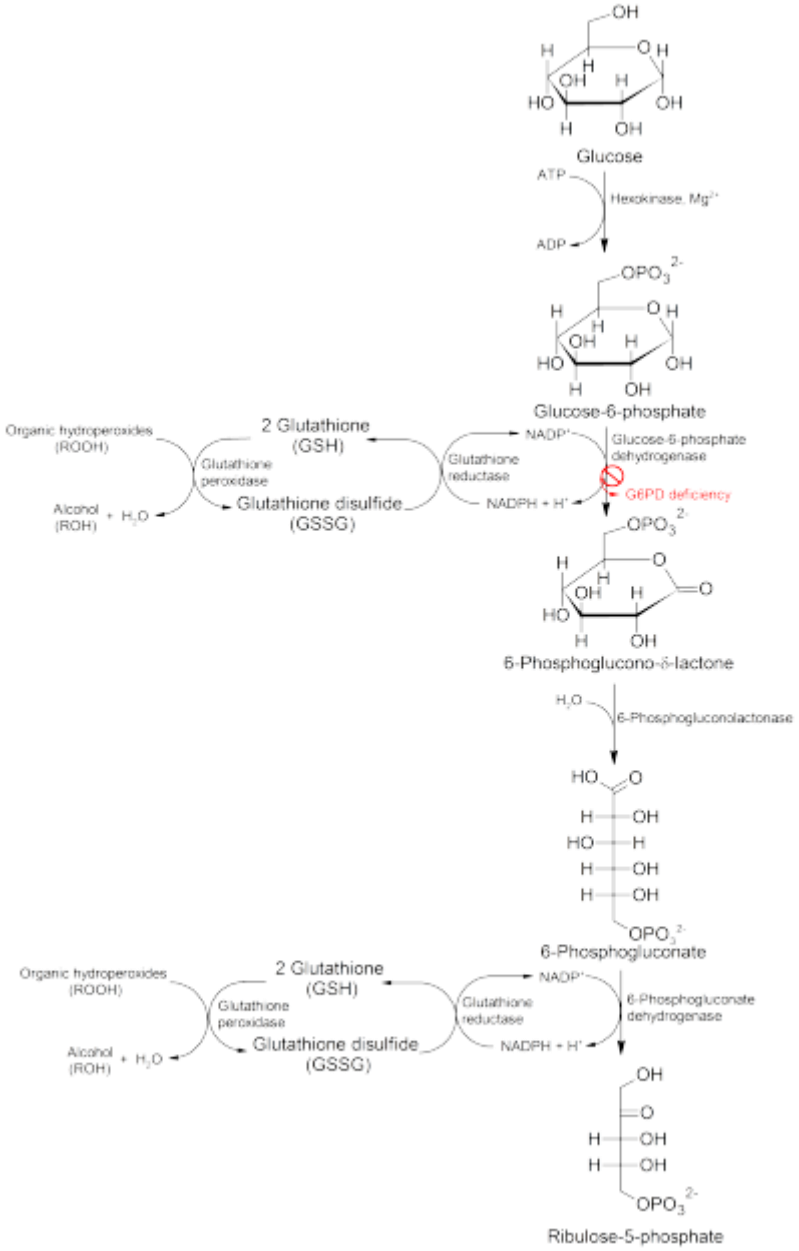
- The finding of normal GGT activity and increased ALP activity is consistent with skeletal disease.

- **Cautions**
- Gamma-glutamyltransferase activity is inducible by drugs such as phenytoin and phenobarbital and, therefore, elevations should not be considered indicative of liver disease until drug use is ruled out. Elevations are also seen after ingestion of alcoholic beverages.

- In very rare cases, gammopathy, in particular, type IgM (Waldenstrom macroglobinemia) may cause unreliable results.

- **Clinical Reference**
- Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company, Philadelphia, 1994
- Heiduk M, Page I, Kliem C, et al: Pediatric reference intervals determined in ambulatory and hospitalized children and juveniles. Clin Chim Acta 2009:406:156-161

Ans B: G6PD is remarkable for its genetic diversity. Many variants of G6PD, mostly produced from missense mutations, have been described with wide-ranging levels of enzyme activity and associated clinical symptoms. Two transcript variants encoding different isoforms have been found for this gene.
Glucose-6-phosphate dehydrogenase deficiency is very common worldwide, and causes acute hemolytic anemia in the presence of simple infection, ingestion of fava beans, or reaction with certain medicines, antibiotics, antipyretics, and antimalarials.



Cell growth and proliferation are affected by G6PD. G6PD inhibitors are under investigation to treat cancers and other conditions. *In vitro* cell proliferation assay indicates that G6PD inhibitors, DHEA (dehydroepiandrosterone) and ANAD (6-aminonicotinamide), effectively decrease the growth of AML cell lines. G6PD is hypomethylated at K403 in acute myeloid leukemia, SIRT2 activates G6PD to enhance NADPH production and promote leukemia cell proliferation.

Q3) How electrons transfer takes place in electron transport chain?

Ans: The electron transport chain is a series of electron transporters embedded in the inner mitochondrial membrane that shuttles electrons from NADH and $FADH_2$ to molecular oxygen. In the process, protons are pumped from the mitochondrial matrix to the intermembrane space, and oxygen is reduced to form water.

During the process, a proton gradient is created when the protons are pumped from the mitochondrial matrix into the intermembrane space of the cell, which also helps in driving ATP production. Often, the use of a proton gradient is referred to as the chemiosmotic mechanism that drives ATP synthesis since it relies on a higher concentration of protons to generate "proton motive force". The amount of ATP created is directly proportional to the number of protons that are pumped across the inner mitochondrial membrane.

The electron transport chain involves a series of redox reactions that relies on protein complexes to transfer electrons from a donor molecule to an acceptor molecule. As a result of these reactions, the proton gradient is produced, enabling mechanical work to be converted into chemical energy, allowing ATP synthesis. The complexes are embedded in the inner mitochondrial membrane called the *cristae* in eukaryotes. Enclosed by the inner mitochondrial membrane is the matrix, which is where necessary enzymes such as pyruvate dehydrogenase and pyruvate carboxylase are located. The process can also be found in photosynthetic eukaryotes in the thylakoid membrane of chloroplasts and in prokaryotes, but with modifications.

By-products from other cycles and processes, like the citric acid cycle, amino acid oxidation, and fatty acid oxidation, are used in the electron transport chain. As seen in the overall redox reaction,

$$2\,H^{+} + 2\,E^{+} + \tfrac{1}{2}\,O_2 \rightarrow H_2O + ENERGY$$

energy is released in an exothermic reaction when electrons are passed through the complexes; three molecules of ATP are created. Phosphate located in the matrix is imported via the proton gradient, which is used to create more ATP. The process of generating more ATP via the phosphorylation of ADP is referred to oxidative phosphorylation since the energy of hydrogen oxygenation is used throughout the electron transport chain. The ATP generated from this reaction go on to power most cellular reactions necessary for life.

Steps of the Electron Transport Chain

In the electron transfer chain, electrons move along a series of proteins to generate an expulsion type force to move hydrogen ions, or protons, across the mitochondrial membrane. The electrons begin their reactions in Complex I, continuing onto Complex II, traversed to Complex III and cytochrome c via coenzyme Q, and then finally to Complex IV. The complexes themselves are complex-structured proteins embedded in the phospholipid membrane. They are combined with a metal ion, such as iron, to help with proton expulsion into the intermembrane space as well as other functions. The complexes also undergo conformational changes to allow openings for the transmembrane movement of protons.

These four complexes actively transfer electrons from an organic metabolite, such as glucose. When the metabolite breaks down, two electrons and a hydrogen ion are released and then picked up by the coenzyme NAD^+ to become NADH, releasing a hydrogen ion into the cytosol.

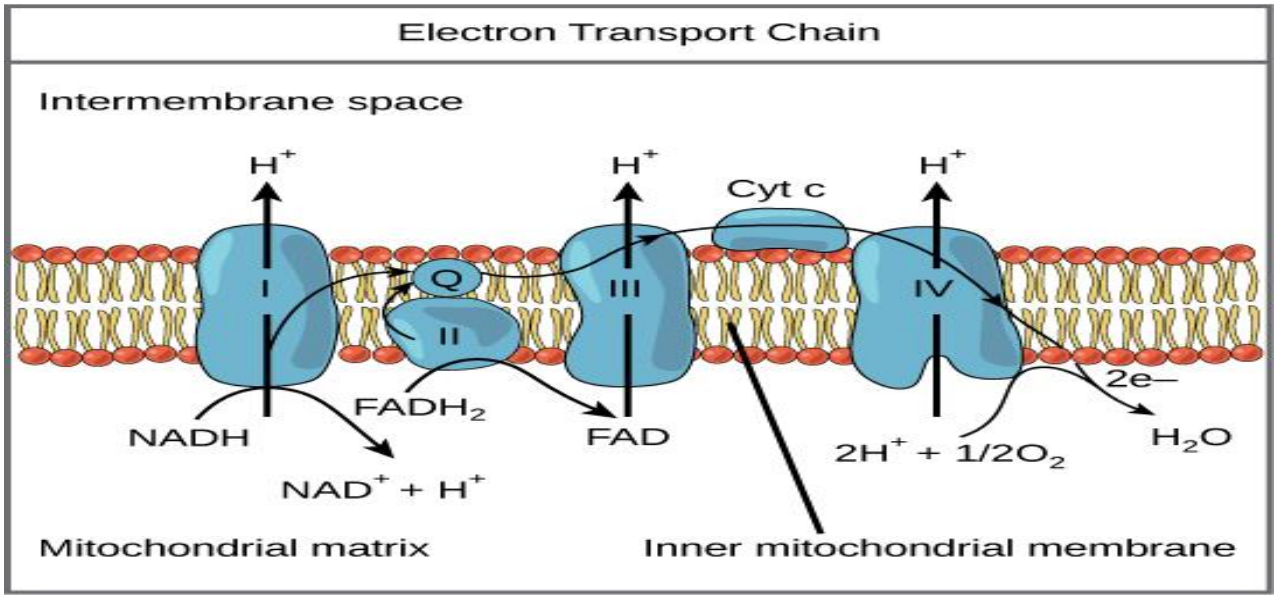
The NADH now has two electrons passing them onto a more mobile molecule, ubiquinone (Q), in the first protein complex (Complex I). Complex I, also known as NADH dehydrogenase, pumps four hydrogen ions from the matrix into the intermembrane space, establishing the proton gradient. In the next protein, Complex II or succinate dehydrogenase, another electron carrier and coenzyme, succinate is oxidized into fumarate, causing FAD (flavin-adenine dinucleotide) to be reduced to $FADH_2$. The transport molecule, $FADH_2$ is then reoxidized, donating electrons to Q (becoming QH_2), while releasing another hydrogen ion into the cytosol. While Complex II does not directly contribute to the proton gradient, it serves as another source for electrons.

Complex III, or cytochrome c reductase, is where the Q cycle takes place. There is an interaction between Q and cytochromes, which are molecules composed of iron, to continue the transfer of electrons. During the Q cycle, the ubiquinol (QH_2) previously produced donates electrons to ISP and cytochrome b becoming ubiquinone. ISP and cytochrome b are proteins that are located in the matrix that then transfers the electron it received from ubiquinol to cytochrome c1. Cytochrome c1 then transfers it to cytochrome c, which moves the electrons to the last complex. (Note: Unlike ubiquinone (Q), cytochrome c can only carry one electron at a time). Ubiquinone then gets reduced again to QH_2, restarting the cycle. In the process, another hydrogen ion is released into the cytosol to further create the proton gradient.

The cytochromes then extend into Complex IV, or cytochrome c oxidase. Electrons are transferred one at a time into the complex from cytochrome c. The electrons, in addition to hydrogen and oxygen, then react to form water in an irreversible reaction. This is the last complex

that translocates four protons across the membrane to create the proton gradient that develops ATP at the end.

As the proton gradient is established, F_1F_0 ATP synthase, sometimes referred to as Complex V, generates the ATP. The complex is composed of several subunits that bind to the protons released in prior reactions. As the protein rotates, protons are brought back into the mitochondrial matrix, allowing ADP to bind to free phosphate to produce ATP. For every full turn of the protein, three ATP is produced, concluding the electron transport chain.

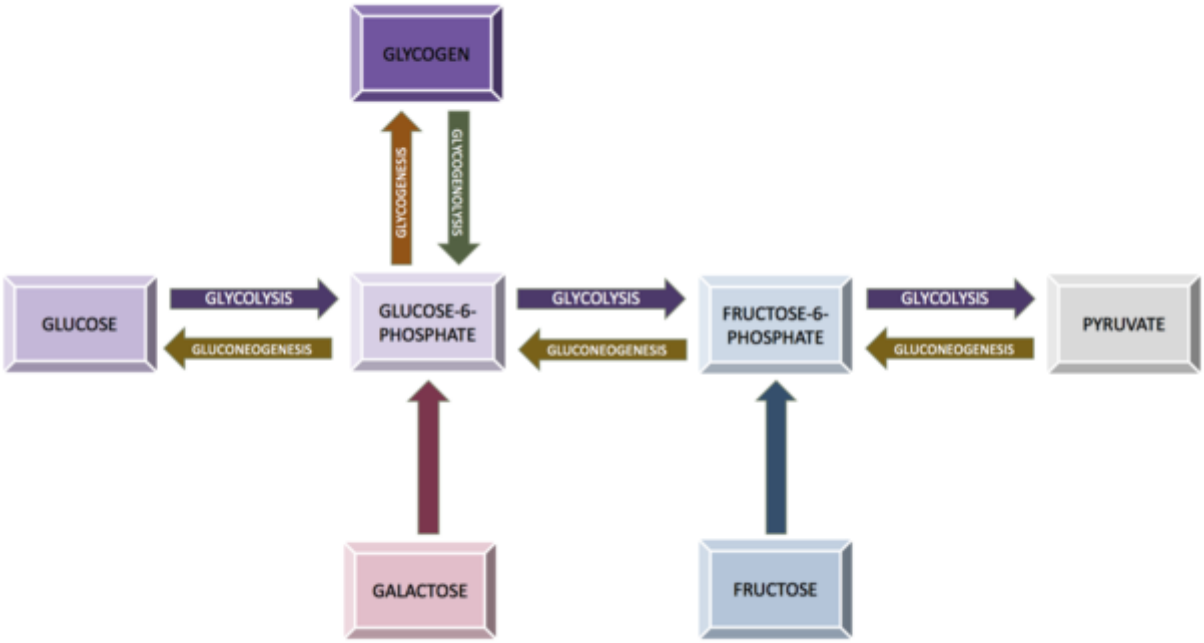


Q4) Write note on metabolism of carbohydrate?

Ans: **Carbohydrate metabolism** is the whole of the biochemical processes responsible for the metabolic formation, breakdown, and interconversion of carbohydrates in living organisms.
Carbohydrates are central to many essential metabolic pathways.[1] Plants synthesize carbohydrates from carbon dioxide and water through photosynthesis, allowing them to store energy absorbed from the sunlight internally. When animals and fungi consume plants, they use cellular respiration to break down these stored

carbohydrates to make energy available to cells. Both animals and plants temporarily store the released energy in the form of high-energy molecules, such as ATP, for use in various cellular processes.
Although humans consume a variety of carbohydrates, digestion breaks down complex carbohydrates into a few simple monomers (monosaccharides) for metabolism: glucose, fructose, and galactose. Glucose constitutes about 80% of the products and is the primary structure that is distributed to cells in the tissues, where it is broken down or stored as glycogen. In aerobic respiration, the main form of cellular respiration used by humans, glucose and oxygen are metabolized to release energy, with carbon dioxide and water as byproducts. Most of the fructose and galactose travel to the liver, where they can be converted to glucose.
Some simple carbohydrates have their own enzymatic oxidation pathways, as do only a few of the more complex carbohydrates.
The disaccharide lactose, for instance, requires the enzyme lactase to be broken into its monosaccharide components, glucose and galactose.

Metabolic pathways



Overview of connections between metabolic processes.

Glycolysis

Glycolysis is the process of breaking down a glucose molecule into two pyruvate molecules, while storing energy released during this process as ATP and NADH.[2] Nearly all organisms that break down glucose utilize

glycolysis. Glucose regulation and product use are the primary categories in which these pathways differ between organisms. In some tissues and organisms, glycolysis is the sole method of energy production. This pathway is common to both anaerobic and aerobic respiration.
Glycolysis consists of ten steps, split into two phases. During the first phase, it requires the breakdown of two ATP molecules. During the second phase, chemical energy from the intermediates is transferred into ATP and NADH. The breakdown of one molecule of glucose results in two molecules of pyruvate, which can be further oxidized to access more energy in later processes.
Glycolysis can be regulated at different steps of the process through feedback regulation. The step that is regulated the most is the third step. This regulation is to ensure that the body is not over-producing pyruvate molecules. The regulation also allows for the storage of glucose molecules into fatty acids. There are various enzymes that are used throughout glycolysis. The enzymes are what help upregulate, downregulate, and feedback regulate the process.

Gluconeogenesisl

Gluconeogenesis is the reverse process of glycolysis. It involves the conversion of non-carbohydrate molecules into glucose. The non-carbohydrate molecules that are converted in this pathway include pyruvate, lactate, glycerol, alanine, and glutamine. This process occurs when there are lowered amounts of glucose. The liver is the primary location of gluconeogenesis, but some also occurs in the kidney. The liver is the organ that breaks down the various non-carbohydrate molecules and sends them out to other organs and tissues to be used in Gluconeogenesis. This pathway is regulated by multiple different molecules. Glucagon, adrenocorticotropic hormone, and ATP encourage gluconeogenesis. Gluconeogenesis is inhibited by AMP, ADP, and insulin. Insulin and glucagon are the two most common regulators of gluconeogenesis.

Glycogenolysis

Glycogenolysis refers to the breakdown of glycogen. In the liver, muscles, and the kidney, this process occurs to provide glucose when necessary.[1]A single glucose molecule is cleaved from a branch of glycogen, and is transformed into glucose-1-phosphate during this process. This molecule can then be converted to glucose-6-phosphate, an intermediate in the glycolysis pathway.
Glucose-6-phosphate can then progress through glycolysis. Glycolysis only requires the input of one molecule of ATP when the glucose originates in glycogen.[1] Alternatively, glucose-6-phosphate can be converted back into

glucose in the liver and the kidneys, allowing it to raise blood glucose levels if necessary.
Glucagon in the liver stimulates glycogenolysis when the blood glucose is lowered, known as hypoglycemia. The glycogen in the liver can function as a backup source of glucose between meals. Adrenaline stimulates the breakdown of glycogen in the skeletal muscle during exercise. In the muscles, glycogen ensures a rapidly accessible energy source for movement.

Glycogenesis

Glycogenesis refers to the process of synthesizing glycogen. In humans, excess glucose is converted to glycogen via this process. Glycogen is a highly branched structure, consisting of glucose, in the form of glucose-6-phosphate, linked together. The branching of glycogen increases its solubility, and allows for a higher number of glucose molecules to be accessible for breakdown. Glycogenesis occurs primarily in the liver, skeletal muscles, and kidney.

Pentose phosphate pathway

The pentose phosphate pathway is an alternative method of oxidizing glucose. It occurs in the liver, adipose tissue, adrenal cortex, testis, milk glands, phagocyte cells, and red blood cells. It produces products that are used in other cell processes, while reducing NADP to NADPH. This pathway is regulated through changes in the activity of glucose-6-phosphate dehydrogenase.

Fructose metabolism

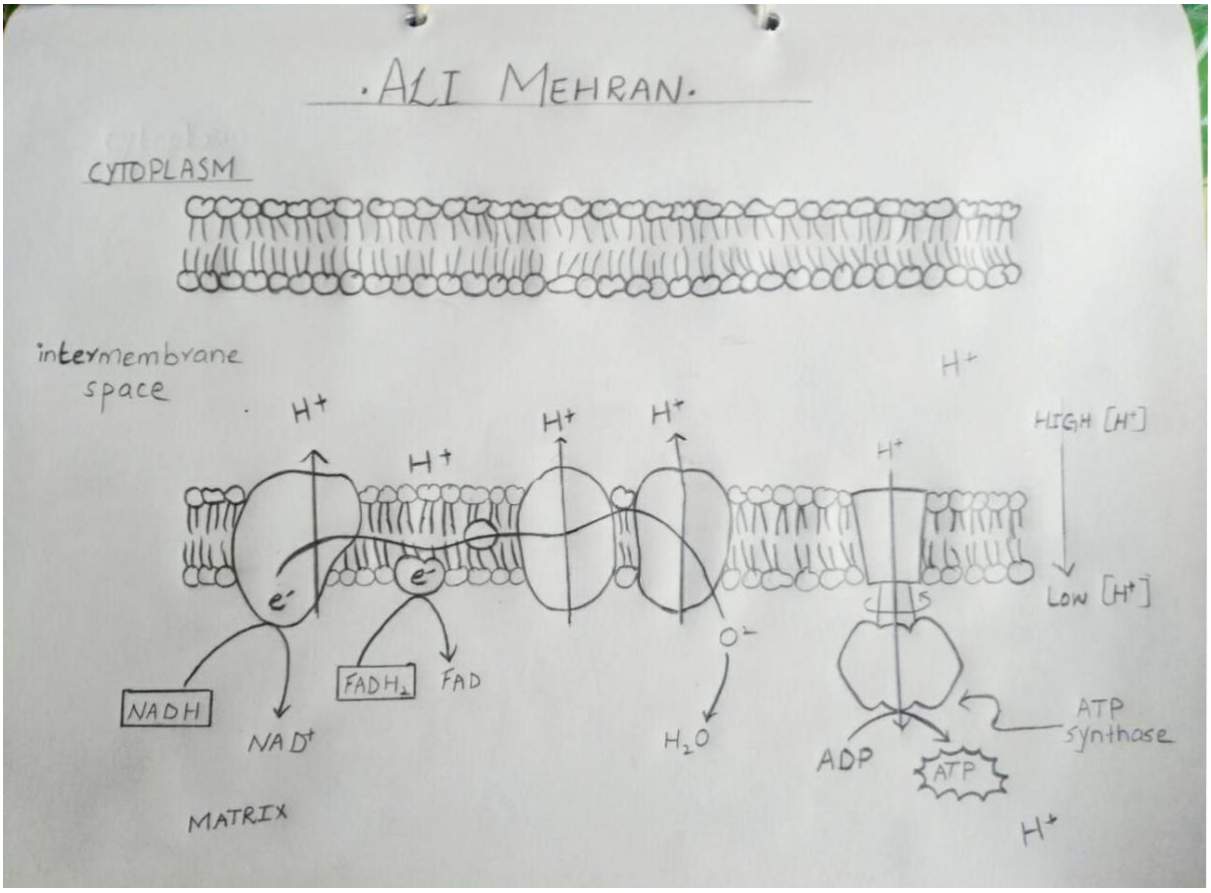
Fructose must undergo certain extra steps in order to enter the glycolysis pathway. Enzymes located in certain tissues can add a phosphate group to fructose. This phosphorylation creates fructose-6-phosphate, an intermediate in the glycolysis pathway that can be broken down directly in those tissues. This pathway occurs in the muscles, adipose tissue, and kidney. In the liver, enzymes produce fructose-1-phosphate, which enters the glycolysis pathway and is later cleaved into glyceraldehyde and dihydroxyacetone phosphate.

Galactose metabolism

Lactose, or milk sugar, consists of one molecule of glucose and one molecule of galactose. After separation from glucose, galactose travels to the liver for conversion to glucose. Galactokinase uses one molecule of ATP to phosphorylate galactose. The phosphorylated galactose is then converted to glucose-1-phosphate, and then eventually glucose-6-phosphate, which can be broken down in glycolysis

Q5) Draw diagram of oxidative phosphorylation?

Ans: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CYTOPLASM
intermembrane space
H+
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O2-
H2O
ADP
ATP
ATP synthase
MATRIX