

PREP XI RR

STUDY NOTES

BIOCHEMISTRY

9

VIDEOS

157

PAGES

PREMIUM STUDY MATERIAL

PREP XI RR

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1. CELL, SUB ORGANELLES, TESTS, TYPES OF BLOOD COLLECTION TUBES

BIG QUESTION 1: What are the sites of various biochemical pathways and their importance?

Broad Answer:

Various biochemical pathways are compartmentalized within the cell. Some occur in the cytoplasm, some in mitochondria, and some across both. This spatial separation ensures proper regulation and efficiency of metabolism. It allows simultaneous yet distinct pathways to function without interference. Such compartmentalization is key to maintaining cellular homeostasis and metabolic balance.

DETAILED QUESTIONS

Q1.1: Which of the following pathways only takes place in a cell's cytoplasm?

- A. Glycolysis
- B. Beta Oxidation
- C. TCA
- D. Urea cycle

Answer: A. Glycolysis

Explanation

- Typically, the oxidation process requires oxygen, which occurs in the Mitochondria.
- Glycolysis- the only oxidation that happens even in the absence of Oxygen.
- So, it can happen in the Cytoplasm.
- Beta oxidation takes place in Mitochondria and Peroxisomes
- The TCA cycle occurs in the Mitochondria
- Urea cycle occurs partly in Mitochondria and partly in the Cytoplasm

Q1.2: What are the sites of different biochemical pathways?

Answer:

Pathways	Sub organelles
Glycolysis	Cytoplasm
PDH	Mitochondria
TCA cycle	Mitochondria
Glycogen metabolism: Glycogen synthesis and Glycogenolysis	Cytoplasm
Gluconeogenesis	Mitochondria, Cytoplasm, and ER
HMP shunt	Cytoplasm
Fatty acid synthesis	Cytoplasm

Broad Answer: The conversion of glucose into energy involves interconnected pathways like glycolysis, the pyruvate dehydrogenase (PDH) complex, and the TCA cycle. PDH forms the link between glycolysis and the TCA cycle by converting pyruvate to acetyl-CoA. In contrast, gluconeogenesis is essentially the reverse of glycolysis, beginning in mitochondria and completing in the cytoplasm.

DETAILED QUESTIONS

Q2. 1: What is glycolysis, and what are its major products under aerobic and anaerobic conditions?

Answer:

- Glycolysis is the process by which a 6-carbon glucose molecule is split into two 3-carbon products.
- The two products will differ depending on whether the process occurs aerobically or anaerobically
 - Aerobic process: Forms 2 pyruvate + 7 ATP.
 - Anaerobic process: Forms 2 lactate + 2 ATP.
- It's the only pathway that produces ATP in the absence of oxygen.

Q2.2: What is the function of the pyruvate dehydrogenase (PDH) complex?

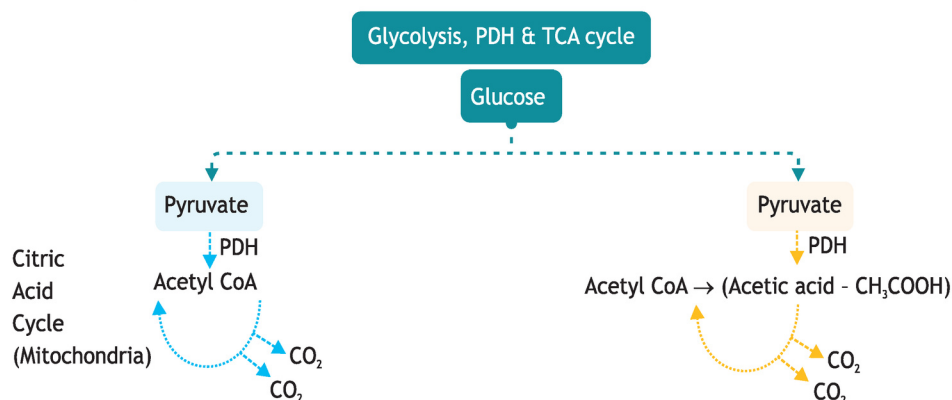
Answer:

- It serves as a link between glycolysis and the citric acid (TCA) cycle.
- Converts pyruvate (from glycolysis) into Acetyl-CoA.

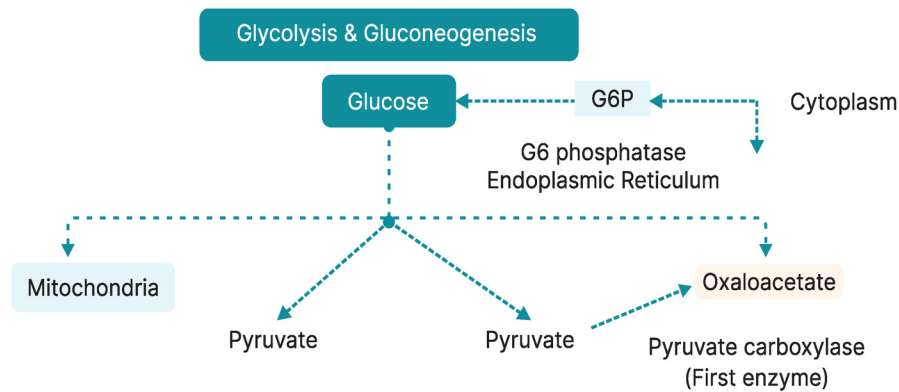
Q2.3: Where does the citric acid cycle occur, and what are its key inputs and outputs?

Answer:

- Occurs in the mitochondria.
- Acetyl-CoA will enter into Citric acid cycle and come out as CO_2 .
- Product of the Citric acid cycle: CO_2 .
- Every metabolic pathway has one aim: To push every fuel that we ingest into CO_2 .



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Q2.4: What is gluconeogenesis, and what are the steps that take place in mitochondria?**Answer:**

- Gluconeogenesis is the reversal of glycolysis.
- Starts with 2 molecules of pyruvate, which condense to form one molecule of glucose.
- Step 1: Pyruvate is converted to Oxaloacetate by Pyruvate carboxylase
- First enzyme: Pyruvate carboxylase
- Pyruvate carboxylase is present in Mitochondria
- So, the first step of Gluconeogenesis occurs in the Mitochondria

Q2.5: After oxaloacetate is formed in mitochondria, where does it go, and what happens next?**Answer:**

- Oxaloacetate reaches the cytoplasm.
- In the cytoplasm, gluconeogenesis continues until glucose-6-phosphate is formed.

Q2.6: Where is glucose-6-phosphatase located, and what is its role?**Answer:**

- Located in the endoplasmic reticulum.
- Converts glucose-6-phosphate to glucose.

Q2.7: What is the significance of glucose-6-phosphatase as an enzyme marker?**Answer:**

- It is a microsomal enzyme marker (indicating ER presence).

BIG QUESTION 3: What are the various metabolic functions of peroxisomes in human cells?

Broad Answer: Peroxisomes are cellular organelles that play essential roles in lipid metabolism, detoxification, and amino acid breakdown. They are involved in the oxidation of specific fatty acids, bile acid conjugation, and ketone body metabolism, and work in coordination with other organelles like the ER and mitochondria. These metabolic activities are crucial for maintaining cellular energy balance and removing toxic intermediates.

DETAILED QUESTIONS**Q3.1: What are the major functions of peroxisomes?****Answer:**

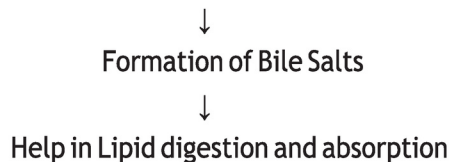
- Oxidation of very long-chain fatty acids (VLCFA)
- Oxidation of branched-chain fatty acids

- Glycine and taurine conjugation of bile acids
- Ether lipid synthesis

Q3.2: What is the origin of bile acids, and how are they conjugated?

Answer:

- All bile acids are derivatives of Cholesterol
- Bile acids undergo conjugation with Glycine and Taurine



Q3.3: What are the functions of the endoplasmic reticulum (ER)?

Answer:

- Smooth ER is involved in steroid synthesis.
 - Since Cholesterol is a steroid, it is synthesized partly in the Smooth ER and the Cytoplasm
- Rough ER is related to protein synthesis.

Q3.4: Where does ketone body production occur, and what is the role of peroxisomes?

Answer:

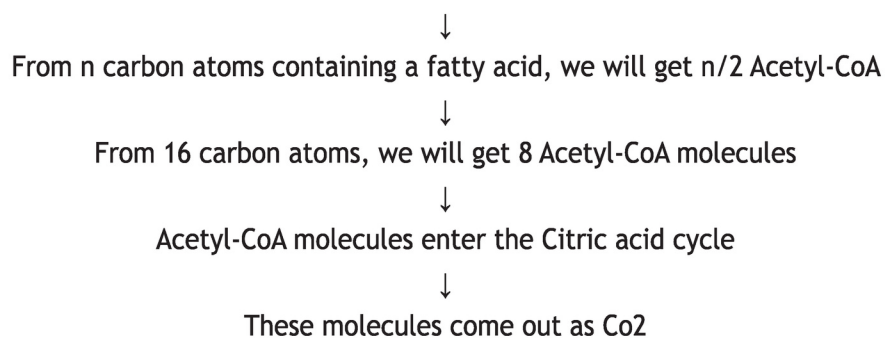
Peroxisomes are involved in ketone body production, especially through the incomplete oxidation of fatty acids.

Q3.5: What happens to fatty acids during β -oxidation?

Answer:

- Fatty acid oxidation: Suppose we take nCFA (Some carbon atoms containing Fatty acid); E.g., Palmitic acid(16 carbon atoms)

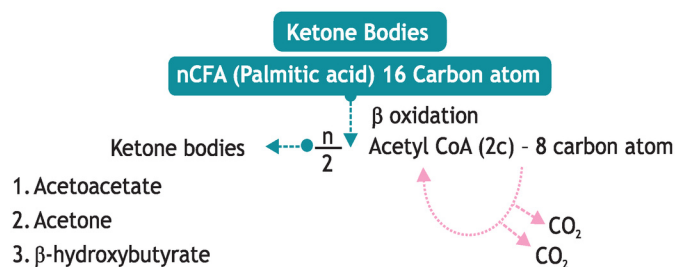
When this fatty acid is subjected to Beta oxidation, it is converted to acetyl-CoA (contains 2 carbon atoms)



- Fatty acid oxidation is known as Complete oxidation because CO₂ is formed, which is exhaled out

Q3.6: When does Acetyl-CoA enter ketone body formation instead of the Citric Acid Cycle?

Answer:



- If Acetyl-CoA cannot enter the TCA cycle, it forms ketone bodies.
- Ketone bodies include:
 - o Acetoacetate (2 molecules of Acetyl-CoA get condensed)
 - o Acetone (Acetoacetate undergoes decarboxylation)
 - o β -Hydroxybutyrate

Q3.7: What happens when amino acids undergo oxidation in the peroxisome?

Answer:

Whenever amino acids undergo oxidation
 ↓
 Amino group is released as Ammonia (Toxic)
 ↓
 Toxic ammonia is converted to non-toxic urea by the Urea cycle

BIG QUESTION 4: What are the marker enzymes of cell organelles, and what is the metabolic fate of pyruvate?

Broad Answer: Various cell organelles have specific marker enzymes that help identify their functions and location. These enzymes are important for biochemical reactions like glycolysis, gluconeogenesis, oxidative phosphorylation, and detoxification. Additionally, pyruvate, a crucial intermediate of glycolysis, can be directed into different metabolic pathways depending on the cellular requirements, including the TCA cycle, gluconeogenesis, or conversion into lactate.

DETAILED QUESTIONS

Q4.1: The marker enzyme of microsomes is:

- A. Galactosyl transferase
- B. Cathepsin
- C. Lactate dehydrogenase
- D. Glucose-6-Phosphatase

Answer: D. Glucose-6-Phosphatase

Explanation

- Glucose-6-phosphatase is the last enzyme of Gluconeogenesis
- Galactosyl transferase - a marker enzyme for the Golgi complex
- Cathepsin - a marker enzyme for Lysosomes
- Lactate dehydrogenase - a marker enzyme for the Cytoplasm

Q4.2: What are the various Marker enzymes?

 PYQ: FMGE 2020, 2023

Answer:

Sr. No.	Organelle	Marker Enzyme
1	Nucleus	DNA Polymerase / RNA Polymerase
2	Endoplasmic Reticulum	Glucose-6-Phosphatase
3	Golgi complex (related to Glycoprotein synthesis)	Glucosyl transferase / Galactosyl transferase

4	Mitochondria	Outer Membrane (OM)	Monoamine Oxidase (MAO)
		Inner Membrane	Complex 2 of ETC/SDH or Complex 5 of ETC/ATP synthase
5	Lysosome		Cathepsins
6	Cytoplasm (Glycolysis)		Lactate dehydrogenase
7	Peroxisome		Catalase

Q4.3: What is the role of the nucleus and its associated enzymes?

Answer:

- The nucleus is the site where chromosomes are present
- Chromosomes/DNA can undergo Replication/Transcription
- Replication is done by DNA Polymerase
- Transcription is done by RNA Polymerase

Q4.4: What is found in the inner membrane of mitochondria?

Answer:

Electron transport chain complexes are present along the inner side of the inner mitochondrial membrane

Q4.5: What is the fate of pyruvate in the cell?

Answer:

Three fates of Pyruvate:

1. Pyruvate can become Acetyl CoA by Pyruvate dehydrogenase complex (Citric acid cycle)
2. Pyruvate can enter into Gluconeogenesis
 - o Pyruvate carboxylase converts Pyruvate to Oxaloacetate
3. Pyruvate can become Lactate
 - o Lactate dehydrogenase converts Pyruvate to Lactate

Q4.6: What is the function of the peroxisome and the catalase enzyme?

Answer:

- Peroxisome is called so because Hydrogen peroxide is constantly generated in it.
- Catalase enzyme detoxifies Hydrogen peroxide

BIG QUESTION 5: What are the various abnormal constituents in urine and what are the biochemical tests to detect them?

Broad Answer: Abnormal constituents in urine can include proteins, glucose, ketone bodies, bile pigments, blood, and others. Simple biochemical tests such as Benedict's test, Rothera's test, sulfosalicylic acid test, and Hay's sulfur test help detect these substances. Their detection is important for diagnosing conditions like diabetes mellitus, liver disease, kidney disorders, and metabolic disturbances.

DETAILED QUESTIONS

Q5.1 On prolonged starvation, which of the following tests will be positive?

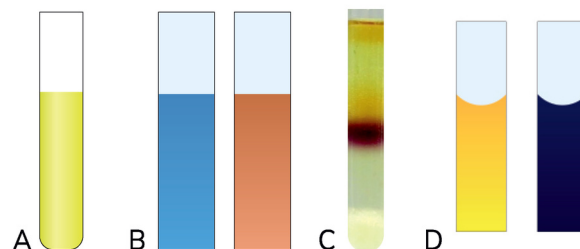
- A. Xanthoproteic acid test
- B. Benedict's test
- C. Rothera's test
- D. Benzidine test

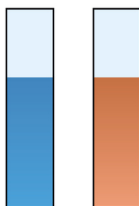
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Answer: C. Rothera's test

Explanation:

- On prolonged starvation → Ketoacidosis
- Ketone bodies in urine answer Rothera's test (purple ring)
- Rothera's test - done to detect Ketone bodies
- It is seen in Starvation and Diabetic patients



Choice	Image	Name of Test	Significance
A		Xanthoproteic acid test (Yellow colour reaction)	Answered by any aromatic amino acids: Phenylalanine, Tyrosine, Tryptophan
B		Benedict's test	To detect the presence of reducing substances in the urine sample
C		Rothera's test	Positive in Diabetic ketoacidosis or Starvation ketosis
D		Benzidine test	1. Alkaptonuria 2. Heme present in urine (haematuria or Hemoglobinuria)

Q5.2: What are the tests done in urine to detect Abnormal Constituents?

Answer:

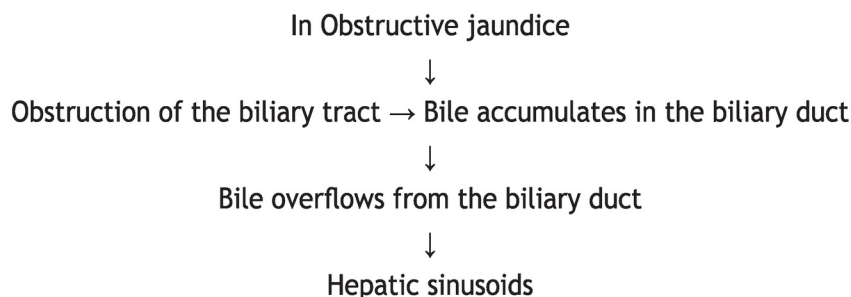
Sr. No.	Abnormal Constituents	Colour Reaction	Observation
1	Reducing substances	Benedict's test (Semi-quantitative test)	Blue → Green → Yellow → Orange → Red
2	Ketone bodies	Rothera's test	Purple ring
3	Protein	Sulphosalicylic acid test	White colour precipitate
4	Blood/Hemoglobin	Benzidine test	Yellow → Dark green/Black
5	Bile salts	Hay's test	Sulfur powder sinks to the bottom

6	Bile pigments	Fouchet's test	Bluish or Green precipitate on the filter paper
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Q5.3: What is the biochemical basis for the presence of bile salts and pigments in urine in obstructive jaundice?

Answer:

- Bile salts and pigments are seen in Obstructive jaundice



- Bile salts and pigments overflow into the hepatic sinusoids → Systemic circulation
- Thus, the blood has bile salts and pigments
- Anything present in the blood is filtered into the urine
- Urine will have bile salts and pigments

BIG QUESTION 6: The additive that is used in the given blood collection tube is?

- A. Sodium Fluoride
- B. K2EDTA
- C. Heparin
- D. Silica

Broad Answer:

Answer: D. Silica

Explanation:

- Red colour top
- RSS: Red top tube is used for Serum separation that has got Silica as additive (Clot activator)



DETAILED QUESTIONS

Q6.1: What is the difference between serum and plasma?

Answer:

Serum	Plasma
- If a blood sample is collected in a simple tube → negative charges of the tube will stimulate in vitro clotting. - The component that separates above after clotting is Serum	If an anticoagulant is placed in a blood sample, the component that separates above is Plasma
Does not have clotting factors, Fibrinogen	All clotting factors including Fibrinogen are present
- It is used for all biochemical estimation - For E.g.: Renal function test, Liver function tests, Amylase, Lipase, Hormone estimation - Tube top is red coloured: Serum	- Plasma is used for whole blood samples - For E.g.: CBC, HbA1C - K2EDTA is an anticoagulant used for CBC (Tube top is Lavender coloured)

Note:

- If by mistake K2 EDTA is used for biochemical estimation → If Potassium level is estimated → Potassium will be elevated
- In this case, if Calcium is estimated → Calcium level is low → All enzyme activities will be falsely low.
- Hence, K2EDTA tubes or lavender topped tubes are not be used for biochemical analysis

Q6.2: What are the different types of blood collection tubes?**Answer:**
🔍 PYQ: INICET 2023
🔍 PYQ: FMGE 2023

Tube	Description
Gray Colored Top Tube 	• Tube with gray coloured cap is used for Glucose estimation. • The additive used is Sodium Fluoride and Potassium Oxalate ◦ Fluoride inhibits enolase of RBCs ◦ As long as RBCs are in touch with plasma, it will continue to utilise glucose from plasma After sometime when plasma glucose estimated ↓ Left over glucose → False low values ↓ Fluoride is added in the tube (To avoid getting false low values) ↓ Fluoride does not allow RBCs to use glucose. ↓ Thus we get true values of plasma glucose
Lavender Coloured Top Tube 	• K2EDTA/K3EDTA • EDTA chelates Calcium • It acts as an Anticoagulant • So, we will get a plasma sample that is used for Whole blood samples • E.g.: CBC, HbA1c • It is also used for estimation of labile parameters (PTH, ACTH, Ammonia) → Degraded by Protease in the sample • Proteases are inhibited by chelating Calcium • Calcium is chelated by EDTA · • E.g.: Patient of CKD □ For estimation of PTH → Lavender top tube is used
Blue Coloured Top Tube 	• Citrated tube • Additive: 3.2% Sodium citrate • It is used for Coagulation assays ◦ For estimation of PT, aPTT, Fibrinogen • 3.8% Sodium citrated tube (Black top tube) - For estimation of ESR

Green Coloured Top Tube

- Heparinised tubes
- It is used for stat biochemical analysis
- For E.g.: Cardiac Trop T
- Also used for Molecular diagnostics and Cytogenetics
 - Where RNA and DNA need to be extracted

Yellow Coloured Top Tube

- Gel and a clot activated tube - Gel is present in the bottom
- Use:
 - For transportation of blood samples or storage of blood samples
 - Advantage: Even if the cell is contaminated, serum is not contaminated because of the presence of Intracellular fluid
 - On blood centrifugation, gel acts as a mechanical barrier between the cells and the serum

Q6.3: What are the differences between the red and yellow coloured top tube?**Answer:**

Red coloured top tube	Yellow coloured top tube
● Cells in the bottom after clotting will be in touch with the Serum ● In due course, when the cells undergo lysis, there will be contamination of Serum ● It cannot be used if the sample has to be transported or stored	● It is used by Private laboratory chains wherein multiple collection centres collect the blood samples and has to be transported to the main laboratory ● In the laboratory, if the sample has to be retaken for 24-48 hours we use Gel and clot activator tube.

Q6.4: What is the order of Draw?**Answer:**

- Dependent on two variables:
 - How sensitive is the parameter to contamination (collected first)
 - How notorious is the additive in the tube is to cause contamination (collected at last)
- **Order of Draw is as follows:**
 - Culture blood samples (Yellow bottles) - Collected first
 - Blue top tube - for coagulation assays
 - Red coloured top tube (clot activated tube)/ Yellow coloured top tube (gel and clot activated tube)
 - Green coloured top tube: Heparinised tube
 - Lavender top tube: CBC/HbA1c
 - Black top tube: ESR estimation
 - Gray top tube: Fluoride is too notorious because of inhibition of many assays

BIG QUESTION 7: The most widely used technique for HbA1C estimation?

PYQ: INICET 2021

- A. Ion Exchange Chromatography
- B. Affinity Chromatography
- C. Immunoassay
- D. Electrophoresis

Broad Answer:**Answer:** A. Ion Exchange Chromatography**Explanation**

- The most widely used technique for HbA1c estimation is **Ion exchange Chromatography**
 - o Because it was used since the parameter was introduced
 - o ADA treatment goal is based on the value estimated by ion exchange chromatography
- Affinity Chromatography, Immunoassay, Electrophoresis are also used for HbA1c estimation

DETAILED QUESTIONS**Q7.1: What is glycated hemoglobin? What are the methods to measure glycated hemoglobin?****Answer:**

- It is a measure of irreversible non enzymatic glycation of N terminal Valine of beta globin chain of Adult Haemoglobin
- Irreversible: Long term glycemic status of an individual needs to be estimated
- Non enzymatic: The variable that determines the proportion of glycated hemoglobin is only the glucose level in the blood
 - o Not affected by enzymatic activity
- Globin chain: Lifespan of RBCs is 120 days
 - o Once glycated, it remains glycated for the entire 120 days
 - o Not affected by short term glycemic changes of an individual
 - o It measures the latest 6-8 weeks glycemic control of an individual
- Methods used to measure glycated hemoglobin
 - o Ion exchange Chromatography
 - o Affinity Chromatography
 - o Electrophoresis based assays
 - o Immunoassays

Q7.2: What are the limitations of Glycated hemoglobin?**Answer:**

- In Iron deficiency anemia, the Iron level in the body is low
 - o Life span of RBC is prolonged
 - o Thus HbA1c value is falsely elevated
- In Hemolytic anemia, RBC lifespan is reduced
 - o Thus HbA1c value is falsely decreased
- In these scenarios, always estimate Complete blood count before analyzing HbA1c values
 - o If the patient has got Iron deficiency anemia, always interpret the value with a guard
- In these scenarios, Fructosamine can be used

Q7.3: Long term glycemic control in a person with hemolysis is assessed by estimating Fructosamine.**Fructosamine is a/an?**

- A. Glycosaminoglycan
- B. Urea
- C. Fructose
- D. Protein

Answer: D. Protein**Explanation**

- Irreversible non enzymatic glycation of Albumin (Since albumin is a protein, Fructosamine is Protein- Option.D)
- So, its not affected by Lifespan of RBCs
- Lifespan of Albumin is not as high as RBCs
- If glycated hemoglobin can give you information on glycemic status for the last 6-8 weeks, Fructosamine can give you information on glycemic status for the last 3-4 weeks only.
- Immunoassays are used for estimating Fructosamine

BIG QUESTION 8: The group present in Tryptophan is:

- A. Benzene
- B. Phenol
- C. Indole
- D. Imidazole

Broad Answer:**Answer:** C. Indole**Explanation**

Tryptophan indole has a ring that answers Aldehyde tests (Mnemonic: TIA)

Aminoacid Mnemonics:

- HIP: **H**istidine has a **I**midazole group and it answers **P**auly's test
- TIA: **T**ryptophan has an **i**ndole ring that answers **A**ldehyde tests
- AGS: **A**rginine has got **G**uanidinium group and it answers **S**akaguchi test
- MPS: **M**illon's test, **P**auly's test, **S**akaguchi test - These tests give red colour reaction

DETAILED QUESTIONS**Q8.1: Describe the groups and colour reactions of various Amino acids****Answer:**

Sr. No.	Aminoacid	Group	Color reaction	Color
1	Phenylalanine	Benzene	Xanthoproteic acid test	Yellow → Orange
2	Tyrosine	Phenol	• Xanthoproteic acid test • Millon's test	• Yellow → Orange • Millon's test gives red colour
3	Tryptophan	Indole group	Aldehyde test	Purple colour reaction
4	Histidine	Imidazole group	Pauly's test	Red colour reaction
5	Arginine	Guanidinium	Sakaguchi test	Red colour reaction
6	Proline (Iminoacid)	Pyrollidine	Ninhydrin test	Yellow colour reaction

- Phenylalanine on hydroxylation forms Tyrosine
- Benzene on hydroxylation forms a Phenol group.
- Proline is the only Iminoacid.
- All aminoacids react with Ninhydrin to give purple colour reaction
- But Iminoacids react with Ninhydrin to give yellow color reaction

BIG QUESTION 9: Which molecular method is used to detect RNA?

- A. Western blot
- B. RT PCR
- C. Sanger's method
- D. G banding

 PYQ: INICET 2021

Broad Answer:

Answer: B. RT PCR

Explanation:

RT PCR	qPCR
• Reverse Transcriptase PCR • Use - o To convert RNA to DNA - o To detect RNA	• Real-time PCR which is used for quantification of nucleic acids

DETAILED QUESTIONS

Q9.1: What is Western blot? What are its uses?

Answer:

- Generally blotting technique is used for identifying a specific substance amongst a group of similar substances
- To identify a specific DNA from a group of DNA - Southern blot is used
- Southern blot is named after the person who invented the technique
- To identify a specific RNA from a group of RNA - Northern blot is used
- To identify an unknown protein - Western blot is used

Q9.2: What is Sanger's sequencing?

Answer:

- DNA sequencing/Protein sequencing is first done by Sanger
- Method used is Dideoxy Nucleotide Triphosphate method/Termination method

Q9.3: What is G banding? What are its uses?

Answer:

- G banding (Giemsa staining of chromosome) is used for Karyotyping
- To detect copy number variations of DNA



2. INTRODUCTION TO METABOLISM

BIG QUESTION 1: What is metabolism and how is energy generated through catabolism?

Broad Answer: Metabolism refers to the process by which the body assimilates food and converts it into energy and building blocks for growth. It has two components: catabolism and anabolism. Energy from catabolism is trapped in the form of ATP either by substrate-level phosphorylation or oxidative phosphorylation.

DETAILED QUESTIONS

Q1.1: What are the components of metabolism?

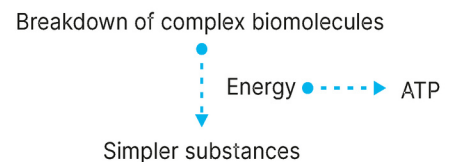
Answer:

- Catabolism
- Anabolism

Q1.2: What happens during catabolism?

Answer:

- Energy is trapped as ATP
- Trapping energy as ATP avoids its loss as unwanted heat



Q1.3: What are the types of catabolism based on ATP trapping?

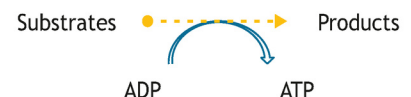
Answer:

1. Substrate-level phosphorylation
2. Oxidative phosphorylation

Q1.4: What is substrate-level phosphorylation?

Answer:

- ATP is generated directly at the substrate level
- Catalyzed by kinases



Q1.5: What are examples of substrate-level phosphorylation?

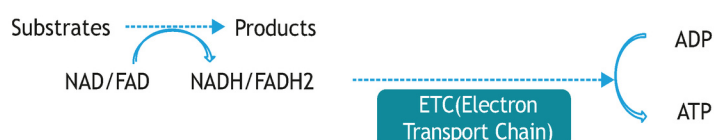
Answer:

- Phosphoglycerate kinase (glycolysis)
- Pyruvate kinase (glycolysis)
- Succinyl thiokinase (Citric Acid Cycle)
- Creatine kinase (muscle)

Q1.6: What is oxidative phosphorylation?

Answer:

- ATP is generated indirectly
- Catalyzed by dehydrogenases
- More common due to aerobic nature of humans



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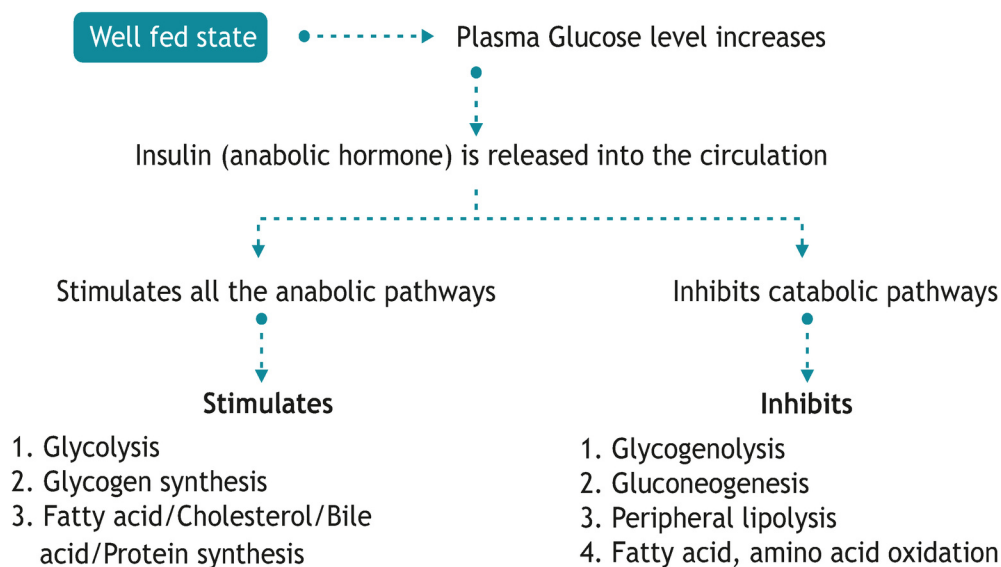
BIG QUESTION 2: How is metabolism integrated and influenced by energy status and hormones?

Broad Answer: Metabolism is integrated by the influence of hormonal signals (insulin and counter-regulatory hormones) and energy states (low vs high energy). It modulates anabolic and catabolic pathways accordingly.

DETAILED QUESTIONS**Q2.1: What are the effects of insulin on metabolism?**

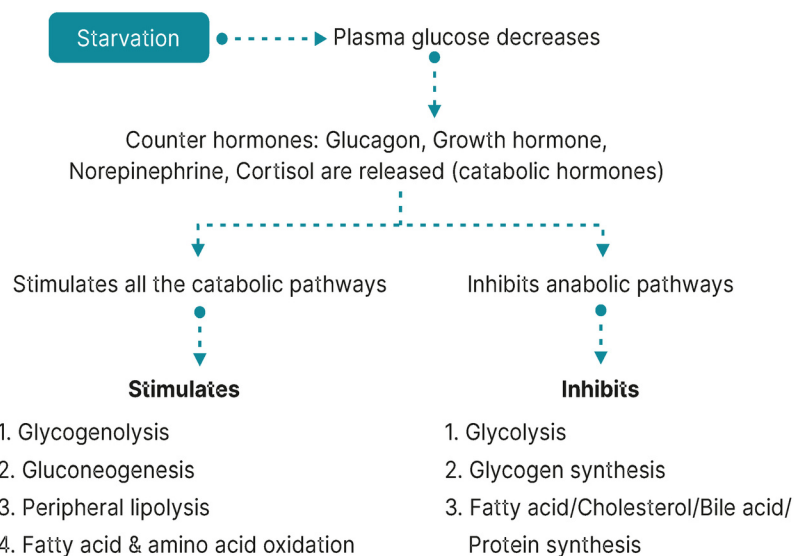
Answer:

- Stimulates anabolic pathways:
 - o Glycolysis
 - o Glycogen synthesis
 - o Fatty acid/Cholesterol/Bile acid/Protein synthesis
- Inhibits catabolic pathways:
 - o Glycogenolysis
 - o Gluconeogenesis
 - o Peripheral lipolysis
 - o Fatty acid/amino acid oxidation

**Q2.2: What are the effects of catabolic hormones (glucagon, cortisol, GH, norepinephrine)?**

Answer:

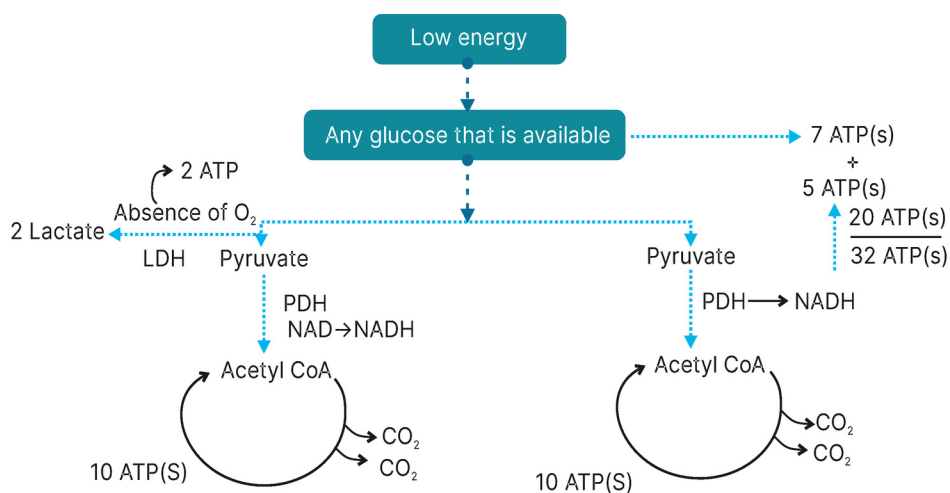
- Stimulates catabolic pathways:
 - o Glycogenolysis
 - o Gluconeogenesis
 - o Peripheral lipolysis
 - o Fatty acid/amino acid oxidation
- Inhibits anabolic pathways:
 - o Glycolysis
 - o Glycogen synthesis
 - o Fatty acid/Cholesterol/Protein synthesis



Q2.3: What happens in low energy state?

Answer:

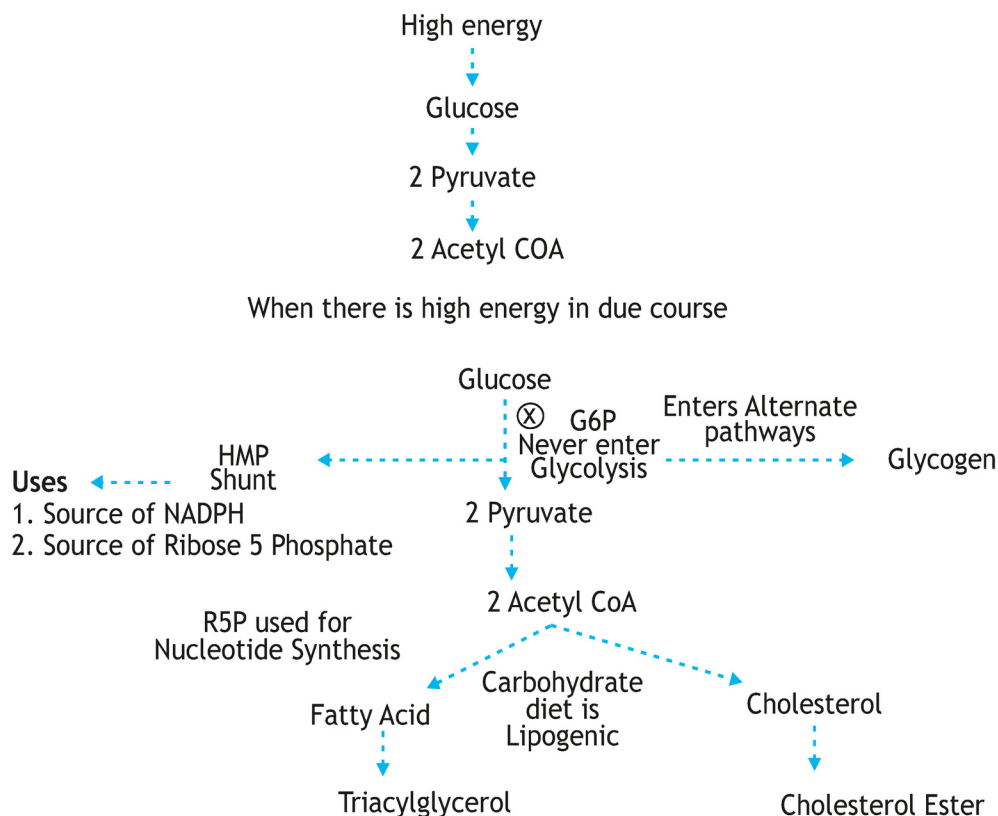
- Glucose enters glycolysis → 2 pyruvates → 7 ATPs
- Absence of O₂: Pyruvate → Lactate (via LDH), yields 2 ATPs
- Presence of O₂: Pyruvate → Acetyl CoA (via PDH), yields NADH
 - o 2 NADH → 5 ATP
 - o Acetyl CoA enters TCA cycle → 10 ATP per cycle
 - o Total ATP: 7 (glycolysis) + 5 (NADH) + 20 (TCA) = 32 ATPs



Q2.4: What happens in high energy state?

Answer:

- Glucose → G6P → Glycogen synthesis or HMP Shunt
- HMP shunt functions:
 - o Produces NADPH
 - o Produces Ribose-5-Phosphate (R5P)
- Acetyl CoA used for lipid synthesis:
 - o Fatty acids → Triacylglycerol
 - o Cholesterol → Cholesterol ester



Q2.5: What is the difference between NADH and NADPH?

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Answer:

Property	NADH	NADPH
Use	Enters ETC and acts as a source of ATP	Cannot enter ETC 1. Used for fat synthesis 2. Required for glutathione regeneration (antioxidant in RBCs) 3. Required for Cytochrome P450 enzymes 4. Required for Ribonucleotide reductase
Sources	1. Glycolysis 2. Pyruvate dehydrogenase complex 3. Citric acid cycle 4. Fatty acid oxidation 5. Amino acid oxidation	1. HMP shunt pathway (major source) 2. Cytoplasmic isocitrate dehydrogenase 3. Malic enzyme

BIG QUESTION 3: What is the significance of NADPH in RBCs and how does its deficiency cause hemolytic anemia?

Broad Answer: NADPH plays a crucial role in maintaining red blood cell (RBC) integrity by supporting the detoxification of reactive oxygen species (ROS), especially hydrogen peroxide (H_2O_2). This is done through regeneration of reduced glutathione (GSH), an antioxidant that neutralizes H_2O_2 . NADPH is produced via the HMP shunt pathway, primarily through glucose-6-phosphate dehydrogenase (G6PD). Deficiency of G6PD leads to impaired NADPH generation, reduced glutathione regeneration, accumulation of H_2O_2 , oxidative damage to RBC membrane, and consequent hemolytic anemia.

DETAILED QUESTIONS

Q3.1: Why are RBCs a major source of oxidative stress?

Answer:

- RBCs carry oxygen.
- Oxygen transport increases the probability of generating superoxide radicals.

Q3.2: What happens to the superoxide radical inside RBCs?

Answer:

- It is detoxified into hydrogen peroxide (H_2O_2).

Q3.3: How is hydrogen peroxide detoxified in RBCs?

Answer:

- Detoxified by reduced glutathione (GSH).
- GSH donates a hydrogen atom to $\text{H}_2\text{O}_2 \rightarrow$ converts H_2O_2 to H_2O .

Q3.4: What is the fate of glutathione (GSH) after neutralizing H_2O_2 ?

Answer:

- Becomes oxidized to GS-SG (glutathione disulfide).
- Reaction catalyzed by glutathione peroxidase.

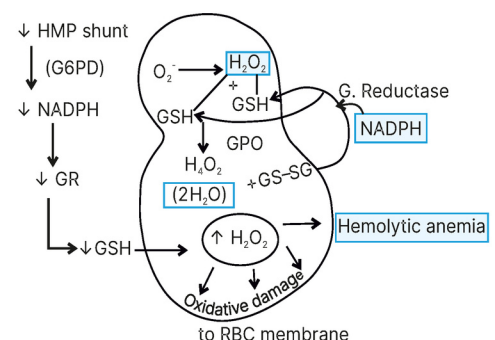
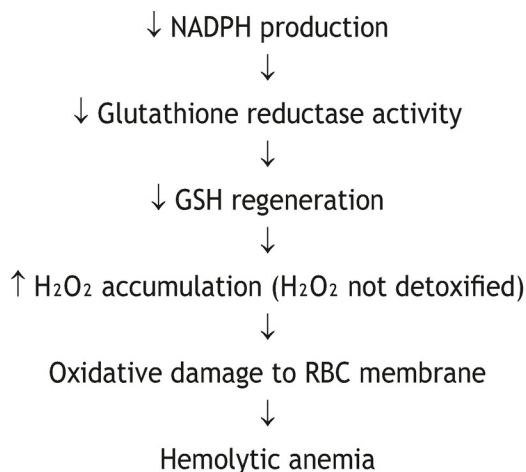
Q3.5: How is glutathione (GSH) regenerated in RBCs?

Answer:

- Glutathione reductase regenerates GSH from GS-SG.
- This process requires NADPH as a hydrogen donor.

Q3.6: What happens if the HMP shunt is defective (e.g., G6PD deficiency)?

Answer:



Q3.7: What can precipitate hemolysis in G6PD deficiency?

Answer:

- Primaquine
- Fava beans (oxidative stress inducers)

Q3.8: What is the role of Ribose-5-Phosphate?

Answer:

- Used in Purine & Pyrimidine synthesis:

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- o Adenosine → AMP
- o Guanine → GMP
- o Cytosine → CMP

Q3.9: Why are RBCs prone to oxidative stress?

Answer:

- RBCs carry oxygen → Superoxide radical generation → Converted to H₂O₂

BIG QUESTION 4: What are the preferred fuels for different tissues in various metabolic states?

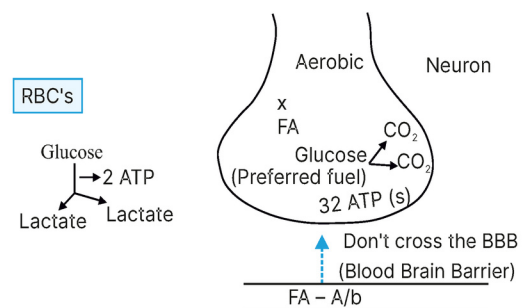
Broad Answer: Preferred fuel varies based on cell type and oxygen availability. Anaerobic cells rely only on glucose. Aerobic cells prefer fatty acids, except neurons, which always use glucose.

DETAILED QUESTIONS

Q4.1: Which cells rely exclusively on glucose (anaerobic)?

Answer:

- RBCs
- Retinal and Corneal cells
- White muscle fibers
- Renal medulla



Q4.2: Which cells prefer fatty acids in aerobic conditions?

Answer:

- Cardiac muscle fibers
- Red muscle fibers

Q4.3: Why do neurons prefer glucose even though they are aerobic?

Answer:

- Fatty acids cannot cross the BBB (bound to albumin)

Q4.4: What is the preferred fuel of hepatocytes?

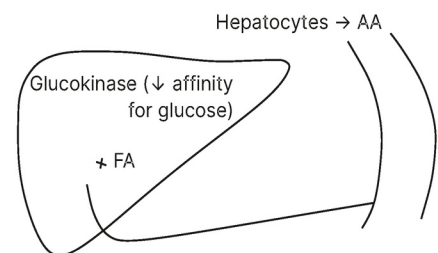
Answer:

- Amino acids

Q4.5: Why doesn't liver use glucose or fatty acids as primary fuel?

Answer:

- Glucokinase has low affinity for glucose
- FA enter as chylomicrons via lymphatics → bypass portal vein → liver doesn't get dietary fat directly



Q4.6: Why doesn't the liver use dietary glucose for its own energy needs?

Answer:

- Glucokinase's low affinity prevents excessive uptake of glucose
- Conserves glucose for peripheral tissues to prevent hypoglycemia

Q4.7: How does dietary glucose reach the liver?**Answer:**

- Diet → Intestine → Absorption → Portal vein → Liver

Q4.8: Why doesn't the liver use dietary fatty acids as an energy source?**Answer:**

- Dietary fatty acids → Chylomicrons → Lymphatics → Systemic circulation (bypasses liver)
- Dietary fatty acids are absorbed as chylomicrons
- Chylomicrons are large and drain via lymphatics, not capillaries
- Lymphatics drain into systemic circulation (extrahepatic), not portal circulation

Q4.9: Which fatty acids can be used by the liver?**Answer:**

- Only those drained by capillaries that reach the portal vein

BIG QUESTION 5: What are the metabolic causes of hemolytic anemia and how are glycolytic enzyme defects involved?

Broad Answer: Hemolytic anemia can occur due to metabolic defects such as G6PD deficiency and glycolytic enzyme defects. G6PD deficiency impairs NADPH production, while glycolytic enzyme defects impair ATP production in RBCs, leading to cell swelling and rupture. Tarui disease (PFK1 defect) and pyruvate kinase deficiency are examples of glycolytic defects. RBCs and white muscle fibers depend on anaerobic glycolysis. Hence, their malfunction leads to hemolysis or exercise intolerance, respectively.

DETAILED QUESTIONS**Q5.1: What are the main metabolic causes of hemolytic anemia?****Answer:**

- G6PD deficiency (↓ NADPH → oxidative stress)
- Glycolytic enzyme defects:
 - PFK1 defect (Tarui disease / GSD Type 7)
 - Pyruvate kinase deficiency

Q5.2: What are the clinical features of glycolytic enzyme defects?**Answer:**

- Hemolytic anemia
- Exercise intolerance (especially anaerobic exercise)

Q5.3: What is the enzyme defect in Tarui disease?**Answer:**

- Phosphofructokinase-1 (PFK1)

Q5.4: Which metabolic pathway is affected in Tarui disease?**Answer:**

- Glycolysis

Q5.5: Why is glycolysis significant for RBCs?

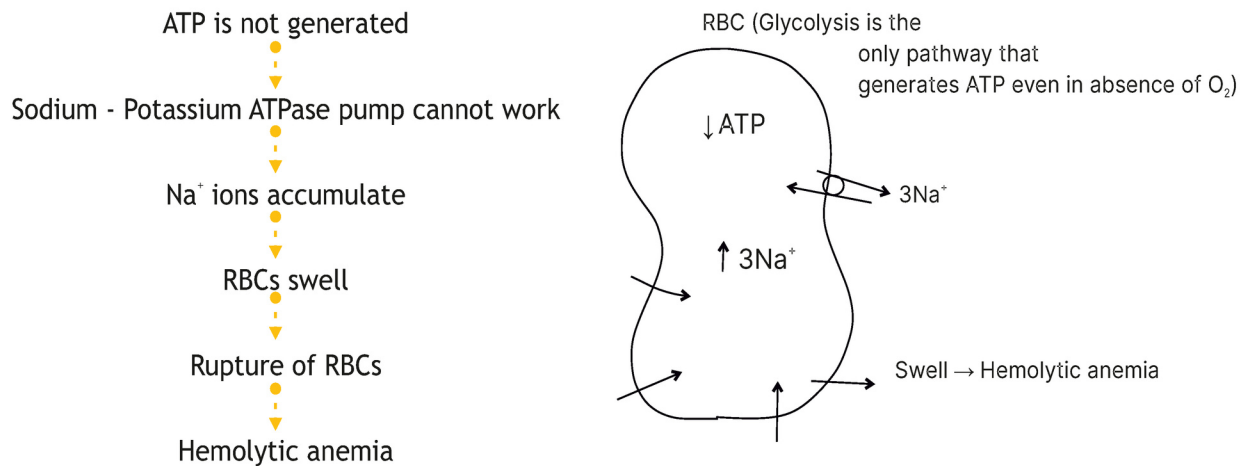
Answer:

- Only pathway to generate ATP in absence of oxygen
- RBCs lack mitochondria → rely entirely on glycolysis

Q5.6: What happens when RBCs are affected by glycolytic defects?

Answer:

- ↓ATP → Na^+/K^+ ATPase pump fails → Na^+ accumulates → RBCs swell and rupture → Hemolytic anemia



Q5.7: What are the consequences of glycolytic enzyme defects in white muscle fibers?

Answer:

- Exercise intolerance, particularly during anaerobic (isometric) exercise

Q5.8: What are examples of isometric and isotonic exercises?

Answer:

Isometric (Anaerobic)	Isotonic (Aerobic)
Clenching fist	Walking
Lifting weights	Running
Pushing against resistance	Swimming

Q5.9: What is the preferred fuel for aerobic exercise?

Answer:

- Fatty acids

Q5.10: Which pathway is used for aerobic exercise?

Answer:

- Fatty acid oxidation

Q5.11: What is the metabolic fuel for RBCs during starvation?

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Answer:

- Glucose
- RBCs rely on glucose under both well-fed and starvation states (anaerobic glycolysis)

Q5. 12: What are the preferred fuels in different tissues during starvation?**Answer:**

Tissue	Preferred Fuel - Well Fed	Preferred Fuel - Starvation
RBCs	Glucose (anaerobic)	Glucose (anaerobic)
Neurons	Glucose (aerobic)	Ketone bodies
Cardiac & Red muscle	Fatty acids	Ketone bodies
White muscle fibers	Glucose (anaerobic)	Glucose (anaerobic)

Metabolic Summary:

- Glycolysis is essential for cells without mitochondria.
- ATP production failure in such cells leads to hemolysis (RBCs) or fatigue (white muscle fibers).
- Fatty acid oxidation fuels aerobic activity.



3. CARBOHYDRATE METABOLISM

BIG QUESTION 1: How is glucose maintained during starvation, and what is the role of peripheral lipolysis?

Broad Answer:

- During starvation, the body maintains glucose levels by shifting between glycogenolysis and gluconeogenesis.
 - o 0-2.5 hours after eating: Dietary glucose
 - o 2.5-12 to 18 hours: Liver glycogenolysis
 - o 6 hours to 2-3 weeks: Gluconeogenesis
 - o This shift requires substrate and energy, which comes primarily from peripheral lipolysis.
 - o Lipolysis supplies glycerol (substrate for gluconeogenesis) and fatty acids (for energy).
 - o Hormone-sensitive lipase regulates this process and is controlled by insulin and catabolic hormones like glucagon and cortisol.

DETAILED QUESTIONS

Q1.1: What are the key energy sources during different phases of starvation?

Answer:

Time After Meal	Primary Energy Source
0 - 2.5 hours	Dietary glucose
2.5 - 12 to 18 hours	Liver glycogenolysis
6 hours - 2-3 weeks	Gluconeogenesis (from glycerol, lactate, alanine)

Q1.2: What is gluconeogenesis and what does it require?

Answer:

- **Definition:** Anabolic reversal of glycolysis; synthesizes glucose from non-carbohydrate precursors.
- **Substrates:**
 - o Glycerol
 - o Lactate
 - o Alanine
- **Energy Requirement:**
 - o 11 ATPs for 2 pyruvate → 1 glucose
 - o 6 high-energy phosphates for 2 lactate → 1 glucose
- **Dependency:** Requires both substrate + energy → relies on peripheral lipolysis.

Q1.3: What is peripheral lipolysis and how is it hormonally regulated?

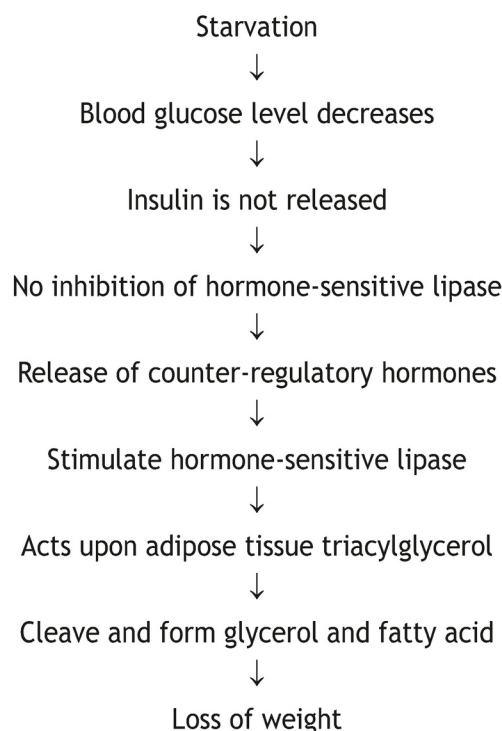
Answer:

- Occurs in adipose tissue; triacylglycerols → glycerol + fatty acids

- Enzyme: Hormone-sensitive lipase (catabolic)
- Inhibited by: Insulin (anabolic hormone)
- Stimulated by catabolic hormones:
 - o Glucagon
 - o Growth hormone
 - o Norepinephrine
 - o Cortisol

Q1.4: What is the hormonal sequence during starvation leading to lipolysis?

Answer:



- Glycerol → Substrate for gluconeogenesis in liver
- Fatty Acids → Oxidized in liver to supply energy for gluconeogenesis
- Leads to weight loss

Q1.5: What are the consequences of defective fatty acid oxidation during starvation?

Answer:

- If fatty acid oxidation fails → gluconeogenesis cannot proceed (no ATP)
- Results in fasting hypoglycemia

Q1.6: How do anaerobic tissues contribute to gluconeogenesis?

Answer:

- Tissues like RBCs, white muscle fibers, retinal cells, corneal cells produce lactate
- Lactate enters circulation → used by liver in Cori cycle for gluconeogenesis

Q1.7: How does prolonged starvation lead to use of alanine and muscle loss?

Answer:

- During prolonged fasting:

- o Muscle protein breakdown occurs
- o Alanine released into circulation
- o Used by liver for gluconeogenesis
- **Consequence:** Emaciation and reduced muscle mass

Q1.8: What are the ATP yields from major metabolic pathways (comparison)?

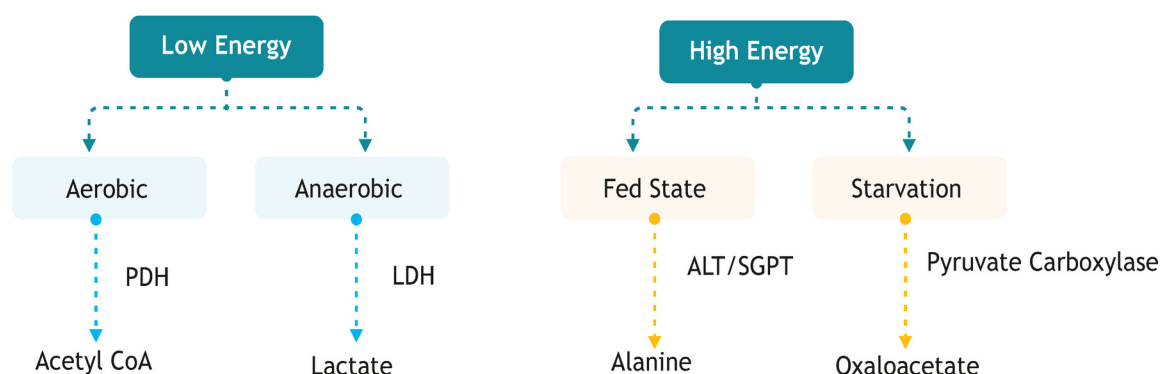
Answer:

Pathway	ATP Yield
Aerobic glycolysis	7 ATP
Anaerobic glycolysis	2 ATP
TCA cycle (per turn)	10 ATP
Complete oxidation of glucose	32 ATP
Palmitic acid (complete oxidation)	106 ATP
Stearic acid	120 ATP
Gluconeogenesis	Utilizes 11 ATP (- 11)

BIG QUESTION 2: What are the metabolic fates of pyruvate, and how do they relate to the cell's energy state?

Broad Answer:

- Pyruvate is a crucial metabolic crossroad whose fate depends on the cell's energy and oxygen status.
- In low-energy aerobic conditions, it fuels the TCA cycle via conversion to Acetyl-CoA.
- Under anaerobic conditions, it becomes lactate to regenerate NAD^+ .
- In high-energy states, pyruvate shifts toward anabolic processes like forming alanine for protein synthesis or oxaloacetate for gluconeogenesis.
- Transaminases mediate its amino conversion and require vitamin B₆ as pyridoxal phosphate.



DETAILED QUESTIONS

Q2.1: What determines pyruvate's fate in the cell?

Answer:

- Depends on:
 - o Energy status (low vs. high)
 - o Oxygen availability (aerobic vs. anaerobic conditions)

Q2.2: What happens to pyruvate in low-energy aerobic cells?

Answer:

- Pyruvate enters the citric acid cycle.
- Converted to Acetyl-CoA by **pyruvate dehydrogenase complex (PDH)**.

Q2.3: What happens to pyruvate in low-energy anaerobic cells?

Answer:

- Anaerobic glycolysis becomes the only ATP-producing route.
- Pyruvate is converted to **lactate** via lactate dehydrogenase.

Q2.4: What happens to pyruvate in a high-energy well-fed state?

Answer:

- Used in anabolic processes:
 - Converted to **alanine** by alanine transaminase (ALT).

Q2.5: What happens to pyruvate during starvation if cellular energy remains high?

Answer:

- Starvation ≠ energy deficiency but = fuel deficiency.
- Cells oxidize fatty acids/ amino acids.
- Pyruvate is converted to **oxaloacetate (OAA)** via pyruvate carboxylase for gluconeogenesis.

Q2.6: What is the role of transaminases in pyruvate metabolism?

Answer:

- All transaminases require **pyridoxal phosphate (Vitamin B₆ active form)**.
- They transfer amino groups:



Q2.7: Which of the following is not a fate of pyruvate?

- Acetyl-CoA
- Lactate
- Alanine
- Valine

Answer: D. Valine:

- Pyruvate converts into:
 - Lactate (Lactate dehydrogenase)
 - Acetyl-CoA (Pyruvate dehydrogenase complex)
 - Alanine (Alanine transaminase)
 - OAA (Pyruvate carboxylase)
- Valine is not derived from pyruvate.

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BIG QUESTION 3: How does the Pyruvate Dehydrogenase Complex regulate the link between glycolysis and the TCA cycle?**Broad Answer:**

- The Pyruvate Dehydrogenase (PDH) complex is a mitochondrial enzyme complex that catalyzes the irreversible oxidative decarboxylation of pyruvate to form Acetyl-CoA, connecting glycolysis to the citric acid cycle.
- Acetyl-CoA generated from PDH is not gluconeogenic, which means even-chain fatty acids that produce only Acetyl-CoA cannot contribute to gluconeogenesis.
- The PDH complex consists of 3 enzyme subunits and requires 5 coenzymes.
- Its activity is inhibited by compounds like arsenite.

**DETAILED QUESTIONS****Q3.1: Where is the Pyruvate Dehydrogenase complex located, and what is its primary role?****Answer:**

- Located in the mitochondria.
- Links glycolysis to the TCA cycle by converting pyruvate to Acetyl-CoA.

Q3.2: Why is the reaction catalyzed by PDH considered irreversible?**Answer:**

- The conversion of pyruvate to Acetyl-CoA releases CO₂, making the reaction energetically and chemically irreversible.
- Hence, Acetyl-CoA cannot be converted back to glucose.

Q3.3: Why can Acetyl-CoA not participate in gluconeogenesis?**Answer:**

- Acetyl-CoA enters the TCA cycle but cannot regenerate pyruvate or other gluconeogenic intermediates.
- All even-chain fatty acids break down only into Acetyl-CoA, so they cannot contribute to gluconeogenesis.

Q3.4: Describe the oxidative decarboxylation reaction catalyzed by PDH.**Answer:**

- PDH simultaneously:
 - Removes hydrogen from pyruvate, transferring it to NAD to form NADH.
 - Releases CO₂ via decarboxylation.
- Overall reaction:
 - $\text{Pyruvate} + \text{NAD} + \text{CoA} \rightarrow \text{Acetyl-CoA} + \text{NADH} + \text{Co}_2$

Q3.5: What are the subunits and coenzymes of the PDH complex?**Answer:**

- **3 Subunits:**
 - E1: Pyruvate Dehydrogenase / Pyruvate Decarboxylase
 - E2: Dihydrolipoyl transacetylase
 - E3: Dihydrolipoyl dehydrogenase

- **5 Coenzymes:**

- o E1 → Thiamine pyrophosphate (Vitamin B1)
- o E2 → Lipoamide and Coenzyme A
- o E3 → FAD (Riboflavin) and NAD (Niacin)

Q3.6: What are the substrates and products of the PDH complex reaction?

Answer:

Substrates (Input)	Products (Output)
Pyruvate	Acetyl-CoA
NAD	NADH
Coenzyme A	CO ₂

Q3.7: Which compound can inhibit the PDH complex, and how?

Answer:

- Arsenite inhibits the PDH complex by binding to lipoamide groups in the E2 subunit, preventing proper enzyme function.

Q3.8: All the following are coenzymes of pyruvate dehydrogenase complex except:

- A. Thiamine
- B. Riboflavin
- C. Niacin
- D. Biotin

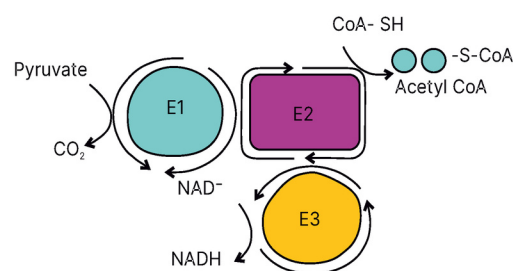
Answer: D. Biotin

- Biotin is required for carboxylases, not for PDH.

Q3.9: Identify E1 and E2 subunits:

- A. Pyruvate decarboxylase, Dehydrogenase
- B. Pyruvate decarboxylase, Transacetylase
- C. Transacetylase, Dehydrogenase
- D. Dehydrogenase, Decarboxylase

Answer: B. Pyruvate decarboxylase, Transacetylase



Q3.10: Which of the following is not a glucogenic substrate?

- A. Acetyl-CoA
- B. Glycerol
- C. Lactate
- D. Alanine

Answer: A. Acetyl-CoA

- Acetyl-CoA cannot generate glucose because its conversion to CO₂ in the TCA cycle is irreversible.

BIG QUESTION 4: How is galactose metabolized in the human body, and what disorders are associated with its metabolism?

Broad Answer:

- Galactose metabolism involves its conversion into usable forms via key enzymes.
- Defects in these enzymes can lead to metabolic diseases such as galactosemia, cataracts, and hypophosphatemia.

DETAILED QUESTIONS

Q4.1: How does galactose enter cells and what happens to it initially?

Answer:

- Galactose enters cells via GLUT transporters using passive diffusion, moving from high to low concentration regardless of intra- or extracellular fluid.
- The first step:
 - Galactose → Galactose-1-Phosphate
 - Enzyme: Galactokinase

Q4.2: What is the pathway of galactose metabolism after forming galactose-1-phosphate?

Answer:

- Galactose-1-phosphate → UDP-Galactose
 - Enzyme: Galactose-1-phosphate uridyl transferase (GalPUT)
 - UDP-Galactose is used in anabolic processes, e.g.:
 - Keratan sulfate synthesis
 - Myelin synthesis
 - Ganglioside synthesis
- Excess UDP-galactose → converted to UDP-glucose via epimerase → enters glycogen synthesis.

Q4.3: What happens in galactokinase deficiency?

Answer:

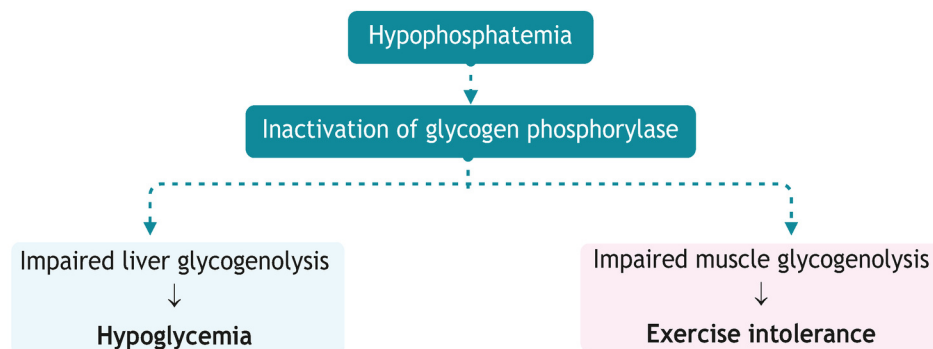
- Galactose cannot be trapped in the cell → effluxes back into circulation.
- Results in elevated blood galactose → galactosemia.
- Excess galactose filtered into urine → positive Benedict's test.
- Enters the lens → converted by aldose reductase into galactitol (dulcitol):
 - Causes osmotic water movement → lens fiber swelling → oil drop cataract.

Q4.4: What happens in GalPUT deficiency (Classical Galactosemia)?

Answer:

- Galactose-1-phosphate accumulates.
- Inhibits galactokinase → further raises galactose levels.
- Leads to:
 - Positive Benedict's test.
 - Cataract formation due to galactitol accumulation.
 - Hypophosphatemia because trapped galactose-1-phosphate reduces cellular phosphate.
 - ATP deficiency → affects hepatocytes → jaundice, hepatomegaly.
 - Excess ADP → uric acid formation → lactic acidosis.

- o E. coli neonatal sepsis risk.
- o Female infants may develop premature ovarian failure.



Q4.5: What is the role of aldose reductase in cataract formation?

Answer:

- Converts galactose → galactitol (dulcitol) in lens fibers.
- Galactitol cannot leave the lens → water influx → swelling → **oil drop cataracts**.

Q4.6: A breast-fed infant begins to vomit frequently and lose weight. Several days later she is jaundiced, her liver is enlarged and cataracts are noticed in her lenses. She is diagnosed with classical galactosemia. The enzyme responsible for cataract in this condition is?

- Galactose-1-phosphate uridyl transferase
- Lactase
- Aldose reductase
- Aldolase B

Answer: C. Aldose reductase

- Breast milk has lactose.
 - o Lactose is a Disaccharide: Galactose + Glucose.
 - o Hence, Galactose metabolism disorder in the mother-fed baby.
 - o Galactose metabolism disorder causes cataractous changes in lens because of aldose reductase converting galactose into dulcitol.
 - o As the question is about the enzyme responsible for cataract, the answer is choice C (Aldose reductase)
- Lactase deficiency causes Lactose intolerance.
- Aldolase B defect causes Hereditary fructose intolerance.

BIG QUESTION 5: What are mucopolysaccharides, and what are their biochemical properties, locations, and clinical significance?

Broad Answer:

- Mucopolysaccharides (glycosaminoglycans) are long, unbranched polysaccharides composed of repeating disaccharide units containing uronic acids and amino sugars.
- They play structural and functional roles in connective tissues, extracellular matrix, and biological processes like anticoagulation.
- They may undergo modifications like sulfation or acetylation to carry strong negative charges, affecting their biochemical behavior and interactions.

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DETAILED QUESTIONS

Q5.1: What are the structural components of mucopolysaccharides, and which exceptions exist?

Answer:

PYQ: AIIMS 2020

- All mucopolysaccharides are:
 - o Long, straight, unbranched chains.
 - o Composed of repetitive units of:
 - Uronic acid
 - Amino sugar
- Exception 1: Keratan sulfate
 - o Instead of uronic acid, it has galactose in repeating units.
 - o Structure: Repetitive units of galactose and amino sugar.
- Exception 2: Dermatan sulfate
 - o Both exceptions:
 - Contains iduronic acid instead of glucuronic acid.
 - Contains galactosamine instead of glucosamine.
- Hyaluronic acid:
 - o Follows all structural rules.
 - o Composed of:
 - Glucuronic acid
 - Glucosamine
 - o Not sulfated or acetylated.
- Most mucopolysaccharides get:
 - o Sulfated or acetylated to carry more negative charges.
 - o Hyaluronic acid is the only one neither sulfated nor acetylated.

Q5.2: Which uronic acids and amino sugars are found in mucopolysaccharides, and what are their exceptions?

Answer:

- Uronic acid:
 - o Mostly glucuronic acid in most mucopolysaccharides.
 - o Instead, iduronic acid is found in:
 - Heparin
 - Heparan sulfate
 - Dermatan sulfate
- Amino sugar:
 - o Mostly glucosamine in most mucopolysaccharides.
 - o Instead, galactosamine is found in:
 - Chondroitin sulfate
 - Dermatan sulfate

Q5.3: Where are different mucopolysaccharides located in the body?

PYQ: FMGE 2019

Answer:

Mucopolysaccharide	Location
Hyaluronic acid	Synovium, vitreous
Keratan sulfate type 1	Cornea

Keratan sulfate type 2	Loose connective tissue
Heparin (natural anticoagulant)	Mast cells
Heparan sulfate (holds enzymes within vascular tree)	Glomerular basement membrane (GBM), large vessel walls like aortic wall
Chondroitin sulfate	Cartilages and bones
Dermatan sulfate (widest distribution)	Skin, extracellular matrix of every tissue

Q5.4: What is the functional significance of heparan sulfate?

Answer:

- Heparan sulfate:
 - o Anchors enzymes to vessel walls.
 - o Example:
 - Lipoprotein lipase acts on blood lipoproteins but must be tethered to vessel walls via heparan sulfate for enzymatic action.

Q5.5: All the following are components of mucopolysaccharides except?

- A. Uronic acid
- B. Amino sugar
- C. Sulphate
- D. NANA

Answer: D. NANA (N-acetylneuraminic acid)

- NANA is a component of glycolipids, specifically gangliosides—not mucopolysaccharides.

Q5.6 The mucopolysaccharide present in the glomerular basement membrane is?

- A. Hyaluronic acid
- B. Heparan sulfate
- C. Dermatan sulfate
- D. Keratan sulfate

Answer: B. Heparan sulfate

BIG QUESTION 6: What are the rate-limiting enzymes in key pathways of carbohydrate metabolism?

Broad Answer:

Pathway	Rate Limiting Enzyme
Glycolysis	Phosphofructokinase-1
TCA Cycle	Isocitrate dehydrogenase
Gluconeogenesis	Fructose-1,6-bisphosphatase
Glycogen Synthesis	Glycogen synthase
Glycogenolysis	Glycogen phosphorylase
HMP Shunt	Glucose-6-phosphate dehydrogenase

BIG QUESTION 7: How is glycogen metabolized, and what are the glycogen storage disorders?**Broad Answer:**

PYQ: FMGE 2021 PYQ: NEET PG 2022

- Glycogen is the storage form of glucose, kept in the liver and skeletal muscle.
- Glycogen metabolism involves synthesis (glycogenesis) and breakdown (glycogenolysis), regulated by specific enzymes.
- Enzyme deficiencies cause glycogen storage disorders (GSDs), each with unique biochemical and clinical features.
- GSDs may cause fasting hypoglycemia, exercise intolerance, or organ damage due to abnormal glycogen accumulation.

Type	Name	Enzyme Defect
Type 0	Glycogen synthase deficiency	Glycogen synthase (called as Type 0 Glycogen storage disorder because it is a glycogen storage disorder without glycogen storage)
Type I	Von Gierke's Disease	Glucose-6-phosphatase
Type II	Pompe's Disease	Acid maltase/ alpha glucosidase
Type III	Cori's Disease	Debranching enzyme
Type IV	Anderson's Disease	Branching enzyme
Type V	McArdle's Disease	Muscle Phosphorylase
Type VI	Her's Disease	Liver phosphorylase
Type VII	Tauri's Disease	Phosphofructokinase-1

DETAILED QUESTIONS**Q7.1: Where is glycogen stored, and what are its structural features?****Answer:**

- Glycogen is stored only in:
 - o Liver – raises blood glucose during fasting.
 - o Skeletal muscle – uses glycogen locally for contraction energy.
- Structure:
 - o Most highly branched polysaccharide.
- Linkages:
 - α -1,4 linkages → along straight chains.
 - α -1,6 linkages → at branch points.

Q7.2: Which enzymes are involved in glycogen metabolism, and what are their roles?**Answer:**

- Glycogen Synthase
 - o Rate-limiting enzyme of glycogenesis.
 - o Forms α -1,4 linkages.
- Branching Enzyme
 - o Creates α -1,6 branches.
- Glycogen Phosphorylase

- o Rate-limiting enzyme of glycogenolysis.
- o Breaks α -1,4 linkages.
- Debranching Enzyme
 - o Breaks α -1,6 linkages.
- Glucose-6-phosphatase
 - o Converts glucose-6-phosphate $\rightarrow$ glucose in the liver.
 - o Absent in muscle; thus muscle glycogen does not contribute to blood glucose.

Q7.3: How does glucose-6-phosphatase deficiency affect glycogen metabolism?

Answer:

- Deficiency of glucose-6-phosphatase leads to:
 - o Both gluconeogenesis and glycogenolysis failing to raise blood glucose.
 - o Severe fasting hypoglycemia.
- Clinical example:
 - o Von Gierke's Disease (GSD Type I).
 - o First discovered glycogen storage disorder.

Q7.4: How are glycogen storage disorders categorized based on symptoms?

Answer:

Type of Defect	Manifestation
Liver glycogenolysis defect	Fasting hypoglycemia
Muscle glycogenolysis defect	Exercise intolerance
Both defects	Both fasting hypoglycemia and exercise intolerance
Neither defect	No fasting hypoglycemia or exercise intolerance

Q7.5: Which GSD types cause fasting hypoglycemia?

Answer:

- **Type 0 – Glycogen Synthase deficiency**
 - o Fasting hypoglycemia
 - o Exercise intolerance
 - o Liver biopsy $\rightarrow$ 0 glycogen
- **Type I – Von Gierke's Disease**
 - o Severe fasting hypoglycemia
 - o Does not respond to counter-regulatory hormones.
- **Type III – Cori's Disease**
 - o Fasting hypoglycemia
 - o Exercise intolerance
 - o Liver biopsy shows abnormal glycogen with multiple branch points $\rightarrow$ limit dextrinosis.
- **Type VI – Her's Disease**
 - o Fasting hypoglycemia
 - o Responds to counter-regulatory hormones.

YOURWISH

Q7.6: Which GSD types cause exercise intolerance?**Answer:**

- **Type 0** – Glycogen Synthase deficiency
- **Type III** – Cori's Disease
- **Type V** – McArdle's Disease
 - o Exercise intolerance, especially to anaerobic activities (e.g. weightlifting).
 - o No lactate rise in exercising arm.
 - o Low glucose after exercise (not fasting hypoglycemia).
- **Type VII** – Tarui's Disease
 - o Affects RBCs → hemolytic anemia.
 - o Affects white muscle fibers → exercise intolerance.

Q7.7: Which GSD types cause neither hypoglycemia nor exercise intolerance?**Answer:**

- **Type II – Pompe's Disease**
 - o Only lysosomal storage + glycogen storage disorder.
 - o Enzyme defect: Acid maltase (α -glucosidase).
 - o Features:
 - Cardiomegaly
 - Cardiomyopathy
 - Hypotonia (floppy baby)
 - Respiratory distress
 - Death within 2 years
 - o Enzyme replacement therapy is available.
- **Type IV – Anderson's Disease**
 - o Defect in branching enzyme.
 - o Accumulation of abnormal glycogen lacking branches.
 - o Leads to hepatomegaly → cirrhosis.

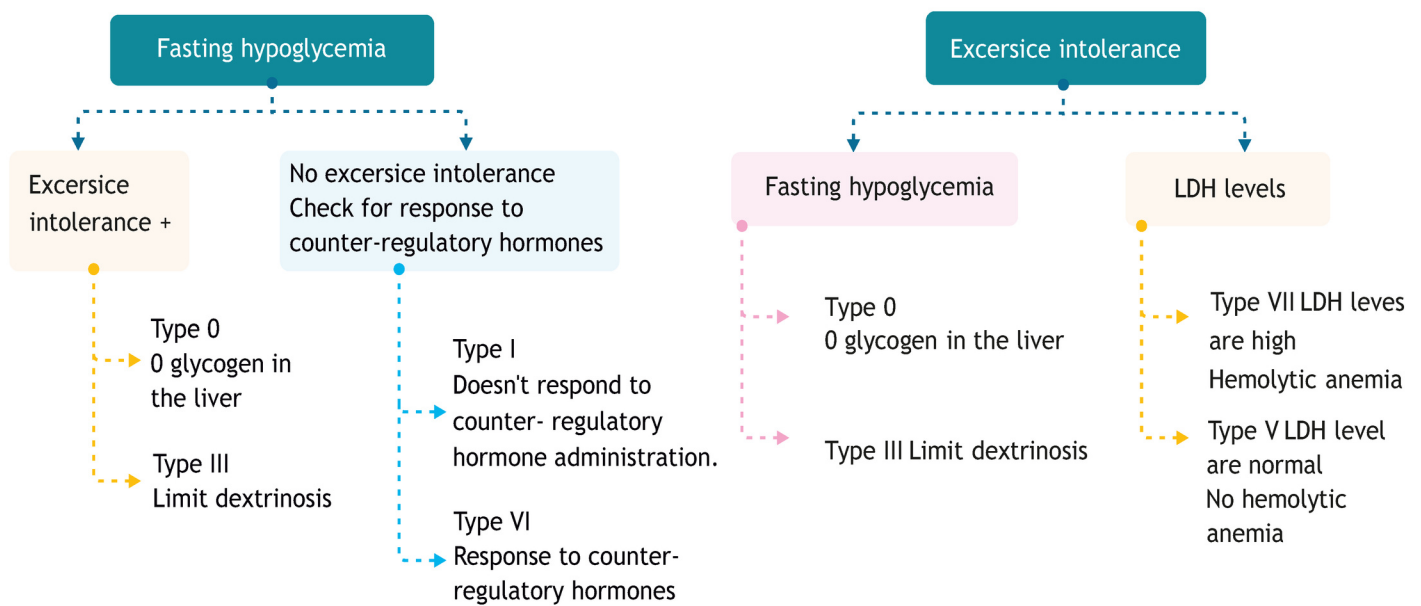
Q7.8: What are counter-regulatory hormones, and what do they do in GSD?**Answer:**

- Increase gluconeogenesis when glycogenolysis fails.
- Hormones:
 - o Glucagon
 - o Growth hormone
 - o Nor-epinephrine
 - o Cortisol

Q7.9: Describe diagnostic features and algorithms for GSDs.**Answer:**

- **Diagnostic Clues:**
 - o Type 0 → no glycogen in liver biopsy.
 - o Type I → severe hypoglycemia, no response to hormones.
 - o Type III → abnormal glycogen with many branches (limit dextrinosis).

- o Type VI → responds to hormones.
- o Type V → low glucose + lactate in exercise.
- o Type VII → hemolytic anemia + high LDH.



Q7.10: A child was fatigued after exercise and the blood sample collected soon after exercise showed low glucose and lactate level. The probable diagnosis is?

- A. McArdle's disease
- B. Von Gierke's disease
- C. Tarui's disease
- D. Anderson's disease

Answer: A. McArdle's disease

- In McArdle's disease, muscle cannot utilize glycogen during exercise, extracts glucose from blood → low glucose and lactate after exercise.

Q7.11: A 4-year-old child has easy fatiguability. The mother also complained that the child was more hungry between meals, but the child recovers after food. Liver examination revealed no glycogen.

- A. Branching enzyme
- B. Debranching enzyme
- C. Glucose-6-phosphatase
- D. Glycogen synthase

Answer: D. Glycogen synthase

- Type 0 GSD. Liver biopsy shows zero glycogen.

BIG QUESTION 8: How Does the Electron Transport Chain (ETC) Function, and What Are Its Key Features and Inhibitors?

Broad Answer:

- The electron transport chain (ETC) in mitochondria is a series of redox reactions transferring electrons from reduced coenzymes (NADH, FADH₂) to oxygen.

- This creates a proton gradient driving ATP synthesis.
- ETC involves 5 stationary complexes and 2 mobile electron carriers.
- Certain toxins inhibit specific complexes, while uncouplers disrupt ATP formation despite normal electron flow.

DETAILED QUESTIONS

Q8.1: What are the stationary and mobile complexes of the electron transport chain?

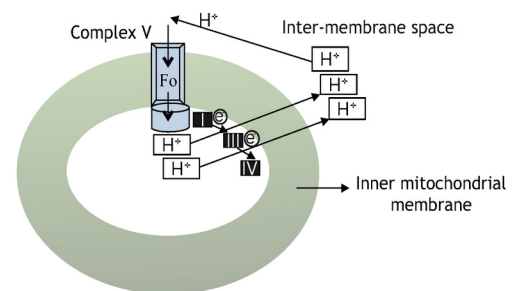
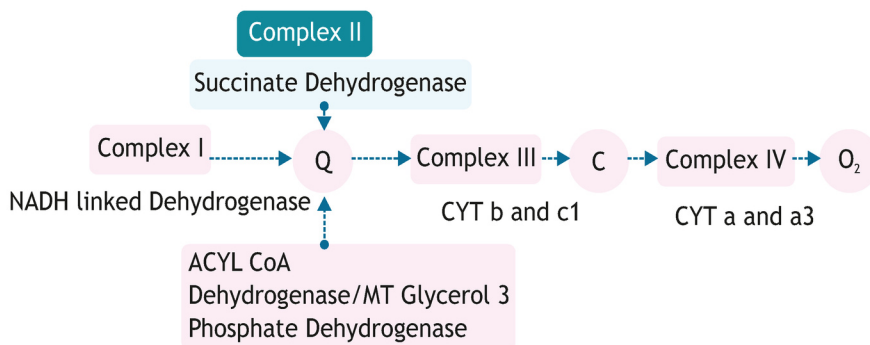
Answer:

- **5 Stationary complexes (numbered I to V):**
 - o Complex I → NADH-linked dehydrogenase
 - o Complex II → Succinate dehydrogenase
 - o Complex III → Cytochrome b and c_1
 - o Complex IV → Cytochrome a and a_3
 - o Complex V → ATP synthase complex
- **2 Mobile complexes:**
 - o Ubiquinone (CoQ) → Between Complex I and III
 - o Cytochrome c → Between Complex III and IV

Q8.2: How do electrons enter and move through the ETC?

Answer:

- Electrons from NADH enter via Complex I.
- Electrons from FADH_2 enter via Complex II.
- Complexes funnel electrons through mobile carriers (CoQ and Cyt c) to oxygen at Complex IV.
- Other FAD-linked enzymes also feed directly into CoQ:
 - o Acyl-CoA dehydrogenase
 - o Mitochondrial glycerol-3-phosphate dehydrogenase



Q8.3: What are specific inhibitors of the ETC and where do they act?

Answer:

Site of Block	Inhibitors
Complex I → CoQ	Rotenone, Piericidin A, Amobarbital
Complex II	Malonate
Complex II → CoQ	TTFA, Carboxin
Complex III → Cyt c	Antimycin, BAL
Complex IV → O_2	Cyanide, Carbon monoxide, Hydrogen sulfide

Q8.4: What is the function of uncouplers in oxidative phosphorylation?

Answer:

- Uncouplers separate electron transport from ATP synthesis.
- Electrons still flow → fuels oxidized → energy released as heat instead of ATP.
- Consequences:
 - o No ATP production
 - o Increased oxygen consumption
 - o Heat production
- Examples:
 - o Physiological:
 - Thyroxine → raises BMR via uncoupler proteins
 - Brown adipose tissue → non-shivering thermogenesis
 - o Artificial:
 - 2,4-Dinitrophenol
 - Valinomycin
 - Nalinomycin
 - Nigericin

Q8.5: How does thyroxine act as a physiological uncoupler?

Answer:

- Increases uncoupler proteins in the mitochondrial membrane.
- Hydrogen ions bypass ATP synthase → heat generation.
- Leads to:
 - o Heat intolerance (thyrotoxicosis)
 - o Cold intolerance (hypothyroidism)
 - o Raised BMR

Q8.6: What happens in brown adipose tissue related to uncoupling?

Answer:

- Rich in mitochondria containing uncoupler proteins.
- Generates heat instead of ATP.
- Role in:
 - o Neonates
 - o Hibernating animals
- Called non-shivering thermogenesis.

Q8.7: What are the consequences and dangers of artificial uncouplers?

Answer:

- Increase fuel oxidation → no ATP formed → energy released as heat.
- Used as anti-obesity agents historically.
- Side effects:
 - o Dangerous hyperthermia
 - o Posterior subcapsular cataracts

YOURWISH

Q8.8: How does oligomycin affect oxidative phosphorylation?**Answer:**

- Inhibits Fo component of ATP synthase.
- Blocks proton flow → no ATP synthesis.
- Differs from uncouplers (which allow proton flow but block ATP formation).

Q8.9. Which of the following is a complex IV inhibitor?

- A. Cyanide
- B. Carbon dioxide
- C. BAL
- D. Antimycin

Answer: A. Cyanide

- Complex IV inhibitors: Cyanide, CO, Hydrogen sulfide

Q8.10. You are conducting an experiment on mitochondrial respiration. You add malate/pyruvate and respiration is normal. You add succinate and respiration is normal. In the presence of malate/pyruvate/succinate, another substance is added, and respiration is inhibited. What is the likely substance?

- A. Rotenone
- B. Antimycin A
- C. Oligomycin
- D. 2,4 Dinitrophenol

Answer: B. Antimycin A

- Respiration means oxidation is normal.
 - Malate and pyruvate form NADH.
 - NADH enters ETC through Complex I.
 - Since oxidation of malate and pyruvate is normal, Complex I is normal.
- Complex II is also normal as oxidation is normal with succinate.
- Rotenone - Acts between Complex I and Q
- 2,4 Dinitrophenol - Uncoupler, oxidation should be unaffected.
- Antimycin - Acts between Complex III and C
- Oligomycin - Inhibits Complex V (last complex)



4. HEME SYNTHESIS AND PORPHYRIAS/ LIPIDS

BIG QUESTION 1: Explain the Structure, clinical significance, and disorders of Heme synthesis.

Broad Answer: Heme synthesis is a multi-step process that occurs partly in the mitochondria and partly in the cytosol, producing heme, an essential component of hemoglobin and various enzymes. Disorders of heme synthesis, called porphyrias, result from enzyme deficiencies in this pathway. These disorders lead to the accumulation of toxic intermediates. Clinical features vary depending on the site of the enzyme defect and the type of porphyria.

DETAILED QUESTIONS

Q1.1: What is the structure of Heme?

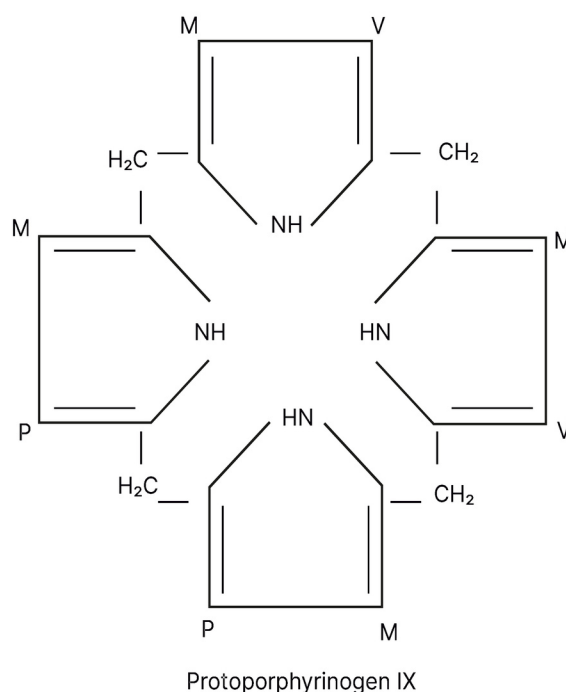
Answer:

- Heme is a metal-containing Protoporphyrin ring
- It consists of a metal ion (Fe^{2+}) at the center, surrounded by four Pyrrole rings

Q1.2: What is the structure of Porphyrinogen?

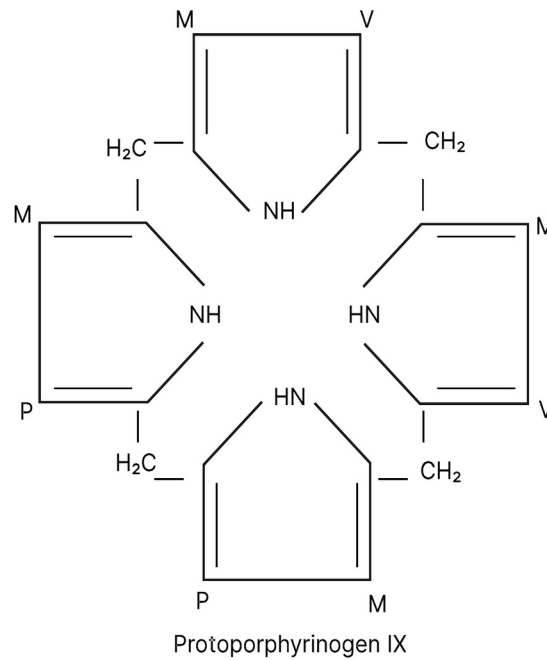
Answer:

- All the pyrrole rings are connected by single-bond methylene bridges
- This structure is called Porphyrinogen



Q1.3: What is the structure of Porphyrin?

Answer: Instead of single-bond bridges, if the pyrrole rings are connected by double-bond bridges, it is called a Porphyrin.



Note: All the features seen in Porphyria are due to Porphyrin accumulation

Q1.4: What is the clinical significance of double-bond bridges?

Answer:

Double bond bridges:

- Absorbs light at 400 nm and emits light at 600 nm
- Absorption at 400 nm is responsible for the Soret band
- All the features of Porphyria are due to a double bond bridge absorbing light of wavelength 400 nm and emitting light of wavelength 600 nm.

Q1.5: What is a simple test to detect the presence of Porphyrin in a patient with Porphyria?

Answer:

- Urine can be collected in a test tube and placed in front of a source of white light.
- When white light goes through the urine sample, if the sample has Porphyrin, it absorbs a photon of 400 nm.
- The emitted light misses a 400 nm photon.
- When emitted light is viewed through a Spectroscope, a dark band corresponding to 400 nm is seen, and that is called the **Soret band**
- It emits light at 600 nm, and it corresponds to the red color

Q1.6: What is Vampire disease?

Answer:

- Congenital erythropoietic Porphyria is the most severe photosensitive porphyrias
- Also known as “**Vampire disease**”
- **Clinical features:**
 - o Nocturnal behavior due to fear of photosensitivity
 - o Facial Blistering followed by atrophic scarring occurs when exposed to sun
 - o Hair distribution is peripherally seen

- o Erythrodontia: The red fluorescence of teeth
- o In teeth, porphyrins are deposited that absorb light of 400 nm and emit light at 600 nm, which corresponds to a red color.
- o Port wine urine - Urine that looks like red wine. They emit light at 600 nm.

Q1.7: What is the relationship between Energy and wavelength?

Answer: Porphyrins absorb light of shorter wavelengths and emit light of longer wavelengths.

Energy and wavelength are inversely proportional.

$$E = h\nu$$

$$E = \frac{hc}{\lambda}$$

Q1.8: What is the mechanism of Photosensitivity in Porphyrins?

Answer:

Porphyrins absorb photons of higher energy and emit photons of lower energy.



The energy difference will be liberated as free energy.



That free energy excites the oxygen present in the medium to form superoxide radicals.



These superoxide radicals cause photooxidative damage.



Photooxidative damage is responsible for Photosensitivity.

BIG QUESTION 2: What are the various Heme synthesis disorders, and their clinical features?

Broad Answer: Disorders of heme synthesis, known as porphyrias, are caused by specific enzyme defects in the heme biosynthetic pathway. These lead to the accumulation of intermediate compounds, which can cause neurovisceral or cutaneous symptoms. The presentation depends on the site of accumulation. Management is based on identifying and avoiding triggers.

DETAILED QUESTIONS

Q2.1: Which enzyme defect in the heme synthesis pathway results in a complete defect?

Answer:

- The only defect that is a complete defect is the first enzyme defect - **ALA synthase 2**
- Most of the defects of the Heme synthetic pathways are partial defects

Q2.2: What happens when there is a complete defect of ALA synthase 2?

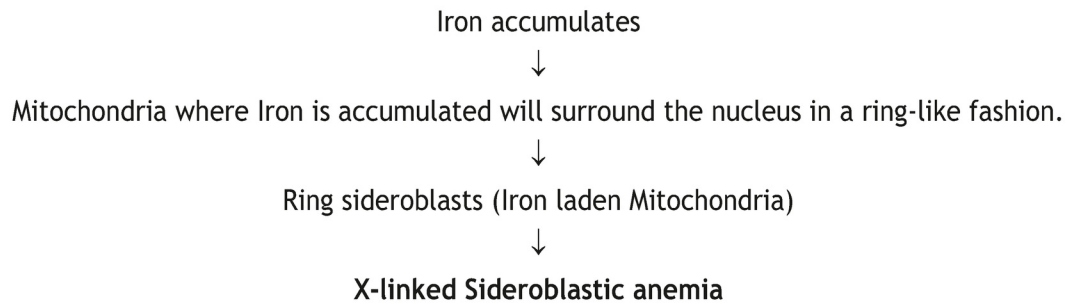
Answer:

Complete defect of ALA synthase 2



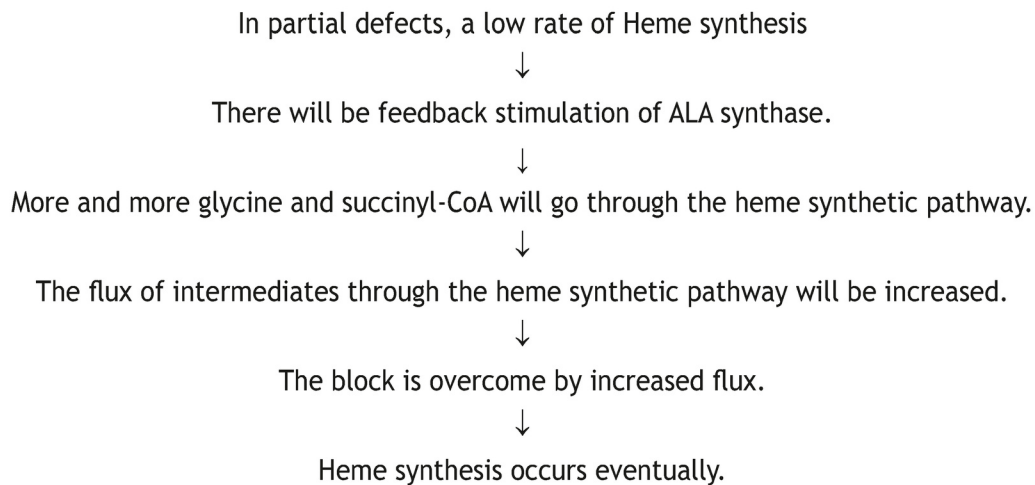
There is no Protoporphyrin ring.





Q2.3: What is the compensatory mechanism that takes place in partial defects?

Answer:



Q2.4: In which Porphyria is anemia seen?

Answer:

- Anemia is seen only in the complete defect of ALA synthase 2
- Anemia is not a feature of other Porphyrins

Q2.5: What is the mechanism of clinical manifestations in Heme synthesis disorders?

Answer:

- The body tries to make heme, but due to an enzyme deficiency, the process is blocked at a certain step.
- The steps before the block keep producing intermediates.
- Since the pathway is blocked, these intermediates cannot proceed further, so they accumulate.
- Depending on which intermediate accumulates, different clinical symptoms (e.g. neurovisceral symptoms, photosensitivity) occur.

Q2.6: What symptoms result from the accumulation of ALA/ PBG/both?

Answer:

- Accumulation of ALA/PBG/Both (Toxic to neurons) → Neuropsychiatric manifestations
 - o Sensory neuropathy
 - o Recurrent abdominal pain
 - o Cyclical bizarre behavior.
 - o Normal imaging and exploratory laparotomy

Q2.7: What symptoms are seen if Porphyrins accumulate?**Answer:**

Accumulation of porphyrins results in photosensitivity

Q2.8: What happens when both ALA/PBG and porphyrins accumulate?**Answer:**

- Photosensitivity
- Neuropsychiatric manifestation

Q2.9: What are the three clinical categories of Porphyrins?**Answer:**

Porphyrins are classified into three categories:

- Porphyrins present with only neuropsychiatric manifestations
- Porphyrins present with only photosensitivity
- Porphyrins present with both neuropsychiatric manifestations and Photosensitivity

BIG QUESTION 3: How are Porphyrins classified, what is the basis for their classification, and what are the enzyme defects seen in porphyrins?

Broad Answer: Porphyrins are classified based on the predominant site of enzyme defect and the type of symptoms. Clinically, they are grouped into acute porphyrins (with neurovisceral or neuropsychiatric symptoms), cutaneous porphyrins (with photosensitivity), or mixed types (showing both). This helps guide diagnosis and management.

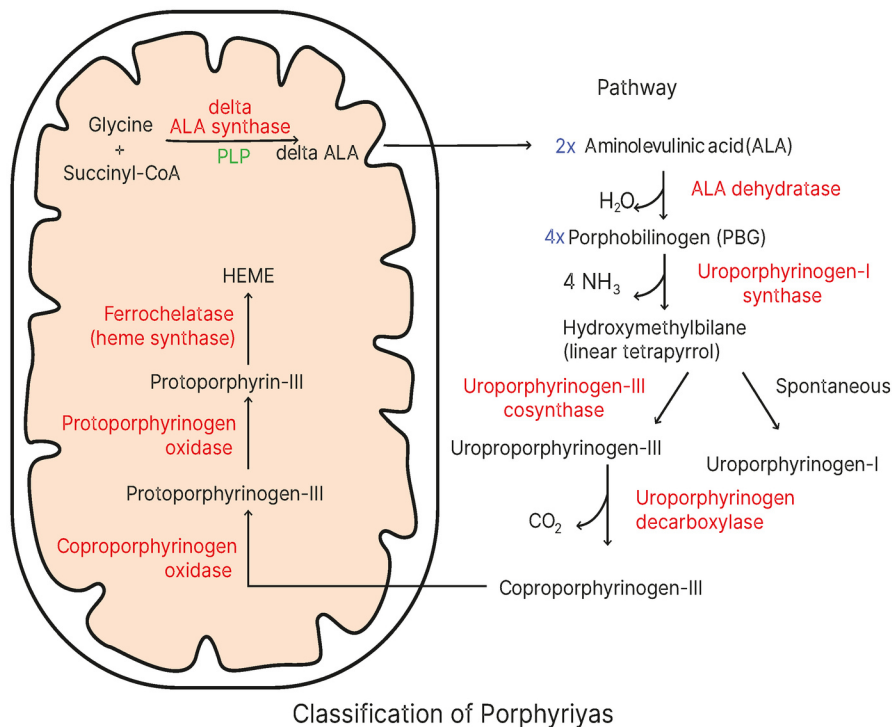
DETAILED QUESTIONS**Q3.1: Classify porphyrins.****Answer:**

Classification of Porphyrins:

- **With Neuropsychiatric manifestations**
 - o ALA Dehydratase Deficient Porphyrin (ADP) - ALA accumulates
 - o Acute Intermittent Porphyrin (AIP) - ALA & PBG accumulate
- **With Photosensitivity**
 - o Congenital Erythropoietic Porphyrin (CEP)
 - o Porphyrin Cutanea Tarda (PCT)
 - o Hereditary Erythropoietic Protoporphyrin (HEP)
- **Both**
 - o Hereditary Coproporphyrin (HCP)
 - o Variegated Porphyrin

Q3.2: Describe the classification of Porphyrins in the form of a schematic diagram

Answer:



Q3.3: What are the enzyme deficiencies in Porphyrins?

Answer:

Enzyme deficiency	Disorder
ALA synthase	X-linked Sideroblastic anemia (XLSA)
ALA dehydratase	ALA dehydratase defective Porphyria (ADP)
Porphobilinogen deaminase/ Hydroxymethylbilane synthase/ Uroporphyrinogen-1 synthase	Acute intermittent Porphyria (AIP)
Uroporphyrinogen 3 synthase	Congenital Erythropoietic Porphyria (CEP)
Uroporphyrinogen decarboxylase	Porphyria Cutanea Tarda (PCT)
Coproporphyrinogen oxidase	Hereditary Coproporphyria
Protoporphyrinogen oxidase	Variegate Porphyria
Ferrochelatase (heme synthase)	Erythropoietic protoporphyria (EPP)

Q3.4: What are the consequences of Defective ALA Dehydratase?

Answer:

- Defective ALA Dehydratase → ALA accumulates
- ALA is toxic to neurons
- This presents with Neuropsychiatric manifestations

Q3.5: What are the features of Acute Intermittent Porphyria?

Answer: In Acute Intermittent Porphyria,

- When there is a defect of Uroporphyrinogen -1 synthase
- There will be accumulation of both ALA and PBG
- This presents with Neuropsychiatric manifestations because ALA and PBG are toxic to neurons
- No porphyrin ring is formed yet
- They do not present with Photosensitivity

Q3.6: What are the enzymes of heme synthesis inhibited by Lead?

Answer:

Lead inhibits three enzymes in heme synthesis

- ALA Dehydratase - ALA accumulates
- Coproporphyrinogen oxidase - Coproporphyrinogen levels are high
- Ferrochelatase - Zinc protoporphyrin levels are high

Q3.7: What is the most sensitive marker for lead poisoning?

Answer:

Elevation of Zinc Protoporphyrin levels

Q3.8: A paint shopkeeper presents with anemia. Which of the following enzyme inhibition causes anemia?

- A. ALA synthase
- B. Uroporphyrinogen 111 synthase
- C. Uroporphyrinogen 1 synthase
- D. Ferrochelatase

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Answer: D. Ferrochelatase

Explanation:

- Paint suggests Lead poisoning
- Lead inhibits Ferrochelatase & ALA dehydratase & Coproporphyrinogen oxidase

BIG QUESTION 4: What are the pathways involved in Lipid metabolism, and their significance?

Broad Answer:

Lipid metabolism involves several key pathways: digestion and absorption of dietary lipids, synthesis of fatty acids and triglycerides, β -oxidation of fatty acids for energy, and lipoprotein metabolism for transport. These pathways ensure lipid storage, mobilization, and utilization throughout the body.

DETAILED QUESTIONS

Q4.1: What are the rate-limiting steps of different pathways of lipid metabolism?

Answer:

Pathways	Rate limiting enzyme	Miscellaneous points
Fatty acid synthesis	Acetyl CoA carboxylase	The precursor of fatty acid is Acetyl-CoA
Fatty acid oxidation	Carnitine acyl transferase 1	Carnitine is the carrier
Cholesterol synthesis	HMG CoA Reductase	Statins reduce blood cholesterol levels by inhibiting HMG-CoA reductase

YOURWISH

Ketone body synthesis	HMG COA Lyase or HMG COA synthase	-
Bile acid synthesis	7- α hydroxylase	-

Q4.2: Which of the following helps in transporting fatty acids across the inner mitochondrial membrane, for them to be utilized in Mitochondria?

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- A. Acyl carrier protein
- B. LCAT
- C. Malate
- D. Carnitine

Answer: D. Carnitine

Explanation:

- Fatty acids cannot cross the inner mitochondrial membrane
- They need a carrier - Carnitine
- Fatty acids must be transported into mitochondria so that they can be oxidized.
- The rate-limiting enzyme of fatty acid oxidation is Carnitine acyl transferase 1

Q4.3: What is the relationship between Cholesterol and Ketone body synthesis?

Answer:

- The first few steps of Cholesterol and Ketone body synthesis are the same
- Until HMG COA is formed, the steps involved in both these pathways are identical
- After HMG COA is formed, depending on the pathways it is acted upon by different enzymes.

Q4.4: What happens when HMG COA reductase acts on HMG COA?

Answer: When HMG COA reductase acts on HMG COA → Committed to cholesterol synthesis

Q4.5: What happens when HMG COA synthase or HMG COA lyase acts on HMG COA?

Answer: When HMG COA synthase or HMG COA lyase acts on HMG COA → Committed to Ketone body synthesis

BIG QUESTION 5: Classify Hyperlipoproteinemias.

Broad Answer: Hyperlipoproteinemias are disorder characterized by abnormal levels of lipoproteins in the blood, leading to elevated cholesterol and/or triglyceride levels. They can be primary (genetic) or secondary (acquired) and are classified based on the type of lipoprotein that is elevated. These conditions increase the risk of atherosclerosis, pancreatitis, and other cardiovascular complications.

DETAILED QUESTIONS

Q5.1: A 25-year-old male presents with an episode of Pancreatitis. His Cholesterol is 190 mg/dl and his Triglyceride level is 1180mg/dl. His post heparinized Lipoprotein lipase activity is low. Which of the following is true about his condition?

- A. The diagnosis is Familial Chylomicronemia syndrome
- B. It is a defect of Hormone-sensitive lipase
- C. It is a defect of apo C111
- D. It is an autosomal dominant condition

Answer: A. The diagnosis is Familial Chylomicronemia syndrome

Explanation:

- The given cholesterol level is 190 mg/dl (Normal level of cholesterol is <200 mg/dl)
- Triglyceride level is 1180 mg/dl (Normal triglyceride level < 150 mg/dl) → Triglyceride is massively elevated
- Isolated hypertriglyceridemia is present in this condition- Familial chylomicronemia syndrome
 - o Massive elevation of Triglycerides
 - o Post-heparinized lipoprotein lipase activity is low
 - o Autosomal recessive condition
 - o Due to a defect of Lipoprotein lipase
 - o It is a defect of Apo C-II

Q5.2: What is Friedrickson's Classification?

Answer:

- Based on electrophoretic patterns and lipid profile, classified into Six types :
 - o Type I
 - o Type II a
 - o Type II b
 - o Type III
 - o Type IV
 - o Type V

Q5.3: Classify hyperlipoproteinemia based on the type of lipoprotein elevated.

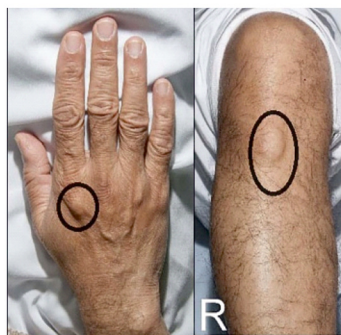
Answer:

- Based on the type of lipoprotein elevated, classified into three categories:
 - o Hypercholesterolemia
 - o Hypertriglyceridemia
 - o Both

Q5.4: What are the clinical features of Hypercholesterolemia?

Answer:

- Tendon Xanthomas: Small eruptive lesions present along the line of attachment of Tendons
 - o More pronounced along Knuckles or Ankles
- Accelerated Atherosclerosis



Tendon Xanthomas

Q5.5: What are the clinical features of Hypertriglyceridemia?**Answer:**

- Eruptive xanthomas: These are tinier than tendon xanthomas
 - o These are present along the extensive surfaces of the limb
 - o More present along the elbows
- Recurrent pancreatitis
- On examination, Lipemia retinalis present

Q5.6: What are the clinical features of hyperlipoproteinemia where both triglycerides and cholesterol are elevated?

Answer: A mix-up of features of Hypertriglyceridemia and Hypercholesterolemia is present.

Q5.7: What type of hyperlipoproteinemia presents with only elevation of Cholesterol?**Answer:**

- The hyperlipoproteinemia that presents with only elevation of Cholesterol is Type II a
- Type IIa is otherwise called Familial Hypercholesterolemia

Q5.8: What is the defect in Familial Hypercholesterolemia?

Answer: LDL receptor is defective → cannot accept LDL → LDL will not be cleared from the circulation → LDL stays back within the circulation → LDL carries Cholesterol → Hypercholesterolemia

Q5.9: A 25-year-old male presents with hypercholesterolemia. His elder brother has also died of a heart disease a few years ago. An LDL receptor defect was observed. What is the most probable cause?

- A. Abetalipoproteinemia
- B. Familial hypercholesterolemia
- C. Familial combined hyperlipidemia
- D. Apo E deficiency

Answer: B. Familial hypercholesterolemia

Explanation:

- It is caused by the defect of the LDL receptor
- It is an autosomal dominant condition because both siblings are affected

Q5.10: What are the examples of autosomal dominant hyperlipoproteinemias?

Answer: The autosomal dominant hyperlipoproteinemias are as follows:

- Type IIA
- Type IV
- Type V

Q5.11: In which hyperlipoproteinemias isolated elevation of triglycerides seen?

Answer: Isolated elevation of Triglycerides is seen in:

- Type I
- Type IV
- Type V

Q5.12: Which types of hyperlipoproteinemia show an elevation of both cholesterol and triglycerides?**Answer:**

- Type I
- Type II

Q5.13: What is the diagnosis?

- A. Wolman's disease
- B. Gaucher's disease
- C. Tangier's disease
- D. Tay-Sachs disease

**Answer:** C. Tangier's disease**Explanation:**

- Orange-colored tonsil is a characteristic feature of Tangier's disease (Orange is a famous flavor in Tang juice)
- **Pathogenesis**
 - It is caused by the mutation of **ABC1 (ATP Binding Cassette transporter 1)**
 - ABC 1 is a protein involved in HDL metabolism

When this protein is defective, → HDL is not formed



HDL level will be very low (HDL normally collects Cholesterol esters and Phospholipids from Extrahepatic tissue membranes and reaches the Liver)



When no HDL is synthesized, Cholesterol esters cannot be removed from extrahepatic tissues.



Cholesterol esters accumulate everywhere.

- When cholesterol esters accumulate in the tonsils, → Grayish Orange tonsils are seen.
- Cholesterol esters, when accumulated in the Liver and spleen, → Hepatosplenomegaly
- They also present Mononeuritis Multiplex.

Other options:

- **Wolman's disease** - It is caused by a defect in Acid lipase
- It is characterized by adrenal calcification
- The **acid maltase** defect causes Pompe's disease.

**BIG QUESTION 6: What are the features, underlying mechanisms, and diagnostic methods of type I hyperlipoproteinemia?**

Broad Answer: Type I Hyperlipoproteinemia is a lipid disorder caused by a defect in the metabolism of chylomicrons. It leads to lipid accumulation and presents with specific clinical features. Understanding this condition involves knowing the pathway of chylomicron transport, the key proteins involved, and how diagnosis is confirmed.

DETAILED QUESTIONS**Q6.1: What is the defect in Type I Hyperlipoproteinemia?****Answer:**

- Also called Familial Chylomicronemia Syndrome.
- Caused by the defect of Apo CII/LPL defect

YOURWISH

Q6.2: How do chylomicrons transport lipids, and why do they use the lymphatics?**Answer:**

- Chylomicrons transport exogenous/dietary triacylglycerol from the intestine to extrahepatic tissues.
- Because of their large size, they are not drained by capillaries, but instead by lymphatics.
- From lymphatics → Thoracic duct → Systemic circulation → Extrahepatic tissues.

Q6.3: What apoproteins do chylomicrons carry and when are they released?**Answer:**

- Chylomicrons are formed in the intestine and released into circulation.
- They have few apoproteins:
 - o Apo CII
 - o Apo E
 - o Apo B48

Q6.4: What is the function of Apo CII, and how does it activate LPL?**Answer:**

- Apo CII activates lipoprotein lipase (LPL).
- LPL binds to the vessel wall and is held by Heparan sulfate.
- LPL acts on chylomicrons to cleave triacylglycerol → glycerol + fatty acid.

Q6.5: How do fatty acids reach extrahepatic tissues, and where is glycerol utilized?**Answer:**

- Fatty acids cross the endothelium into extrahepatic tissues.
- Only the liver can utilize glycerol
- Extrahepatic tissues store fatty acids as triacylglycerol.

Q6.6: What happens to chylomicrons after the loss of triacylglycerol?**Answer:**

- It becomes a chylomicron remnant.
- Taken up by the liver using the remnant receptor or LDL receptor.
- Remnant receptor accepts Apo E.

Q6.7: What is the role of the LDL receptor?

Answer: LDL receptor is a receptor that can accept any lipoprotein that has Apo B100 or Apo E

Q6.8: What happens when there is a defect in Apo CII or LPL?**Answer:**

- Triacylglycerol from chylomicrons cannot be metabolized.
- Chylomicrons accumulate in circulation → Type I Hyperlipoproteinemia.

Q6.9: What are the features of Familial Chylomicronemia Syndrome?**Answer:**

- Massive hypertriglyceridemia due to the accumulation of triacylglycerol.
- Clinical signs:

- o Hypertriglyceridemia
- o Recurrent pancreatitis
- o Eruptive xanthomas
- o Lipaemia retinalis

Q6.10: How is type I hyperlipoproteinemia diagnosed?

Answer:

- Diagnosis is by checking lipoprotein lipase enzyme activity
- Heparin is injected into the individual, and a blood sample is collected
- Heparin is injected because Lipoprotein lipase is not floating in the blood
- Lipoprotein lipase is clinging to the vessel wall, held in place by Heparan sulfate
- When heparin is injected, Heparin in the circulation will compete with Heparan sulfate of the vessel wall to hold the enzyme
- The enzyme will get detached from the vessel wall and is now floating in the blood, and acts as a source for Lipoprotein Lipase
- If this blood sample shows low lipoprotein lipase activity → then the diagnosis is confirmed (Post-heparinised lipoprotein lipase activity is low)

BIG QUESTION 7: What are the features, pathogenesis, and diagnostic markers of type III hyperlipoproteinemia?

Broad Answer: Type III Hyperlipoproteinemia is a lipid disorder involving defective clearance of remnant lipoproteins. It is associated with specific protein defects, characteristic lipid profile changes, and pathognomonic dermatological and electrophoretic findings.

DETAILED QUESTIONS

Q7.1: What is the primary defect in Type III Hyperlipoproteinemia?

Answer: Caused by a defect in Apo E.

Q7.2: What is the key metabolic abnormality in this condition?

Answer: It is a remnant disease - remnant lipoproteins are not cleared from circulation.

Q7.3: What lipid profile changes are seen in Type III Hyperlipoproteinemia?

Answer: There is an elevation of both cholesterol and triglycerides (TGL).

Q7.4: What are the alternate names for this condition?

Answer:

- Broad Beta Disease
- Familial Dysbetalipoproteinemia

Q7.5: What is the pathognomonic finding on electrophoresis in this condition?

Answer: Broad Beta Band seen on Lipoprotein Electrophoresis.

Q7.6: What is the genetic cause of this disorder?

Answer: Caused by a Homozygous E2 mutation.

Q7.7: What are the dermatological pathognomonic features?

Answer:

- Palmar eruptive xanthomas
- Xanthoma palmaris striae



Q7.8: A 38-year-old male presents with yellowish discoloration of the Palmar creases as shown in the image. His cholesterol is 300 mg/dl, and his Triglyceride level is 280 mg/dl. What is expected in his lipoprotein electrophoresis ?

- A. A band at the site of application
- B. Broad alpha band
- C. Broad beta band
- D. Absent alpha band



Answer: C. Broad beta band

Explanation:

- Mixed dyslipidemia is seen in Type IIb and Type III
- Mixed dyslipidemia with Xanthoma striae is seen in Type III hyperlipoproteinemia
- Type 3 hyperlipoproteinemia is associated with a broad beta band

BIG QUESTION 8: What is the structure and composition of Glycolipids? Describe the features of Sphingolipidosis.

Broad Answer: Glycolipids are lipid molecules with attached carbohydrate groups, playing key roles in cell membrane structure and signaling. Inherited defects in lysosomal enzymes responsible for degrading these glycolipids lead to their accumulation, causing a group of disorders known as sphingolipidoses. These include conditions like Gaucher, Tay-Sachs, Niemann-Pick, and Fabry disease. The clinical features vary but often involve neurological, visceral, or skeletal involvement. Diagnosis and management depend on the specific enzyme defect and disease severity.

DETAILED QUESTIONS

Q8.1: Glycolipids are derivatives of which basic molecule?

Answer:

- All glycolipids are derivatives of Ceramide
- Ceramides = Fatty acid + Sphingosine
- Glycolipids are esters containing a Carbohydrate group, in addition to a fatty acid and an alcohol.

Q8.2: Give examples of Glycolipids with their composition.

Answer:

- Ceramide + Monosaccharide (Glucose/Galactose) = Cerebroside.

- Ceramide + Oligosaccharide = **Globoside**.
 - Eg: Ceramide + (Glucose & Galactose) = Lactosylceramide (Globoside)
- Ceramide + Oligosaccharide with NANA (N-acetyl Neuraminic Acid) = **Ganglioside**.
 - Eg: Ceramide + Glucose-Galactose-NANA = GM3 Ganglioside.
 - GM3 Ganglioside is the simplest Ganglioside.

Q8.3: How are GM2 Ganglioside and GM1 Ganglioside formed?

Answer:

- If Galactose in GM3 Ganglioside attaches to N-Acetyl Gal NH₂ (N-acetyl Galactose Amine) produces **Gm2 Ganglioside**
- If N-Acetyl Gal NH₂ in GM2 Ganglioside is attached to Galactose produces **GM1 Ganglioside**.

Q8.4: What happens when GM1 ganglioside is undergoing metabolism?

Answer:

- If GM1 ganglioside is given for metabolism, galactose is removed first
- Galactose is in Beta form
- The first enzyme to begin the metabolism of GM1 ganglioside is Beta-galactosidase.

 PYQ: NEET PG 2021

Q8.5: A young boy is having difficulty breathing while running and is unable to rise from a squatting position. His fundus examination image is provided below. What is the probable condition?

- A. Tay-Sachs disease
- B. Gaucher's disease
- C. Fabry's disease
- D. Krabbe's disease



Answer: A. Tay Sachs disease

Explanation:

- Difficulty in breathing while running and unable to rise from the squatting position - suggests Neurological manifestation.
- Fundus examination reveals Cherry red spots.
- Neurological manifestation with cherry red spot without Organomegaly - Tay Sachs disease
- Cherry red spots are absent in KGF (Krabbe's disease, Gaucher's disease, and Fabry's disease)
- The lipid that accumulates in Fabry's disease - Globozyme
- The disorder caused by the defect of Hexosaminidase A - Tay-Sachs disease/GM2 gangliosidosis
- The beta-galactosidase defect causes GM1 gangliosidosis

Q8.6: What are the enzyme defects seen in gangliosidosis?

Answer:

GM1 Gangliosidosis	• Beta Galactosidase removes Galactose in GM1 Ganglioside and converts it to GM2 Ganglioside. • The absence of Beta Galactosidase causes GM1 Gangliosidosis.
GM2 Gangliosidosis	• Hexosaminidase A (Galactosaminidase) removes N-Acetyl Gal NH₂ in GM2 Ganglioside and converts it to GM3 Ganglioside. • The absence of Hexosaminidase A leads to GM2 Gangliosidosis, also known as Tay-Sachs' Disease.

YOURWISH

GM3 Gangliosidosis or Sialidosis	• Neuraminidase removes NANA in GM3 Ganglioside and converts it to Globoside. • The absence of Neuraminidase leads to GM3 Gangliosidosis or Sialidosis
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Q8.7: What are the enzyme defects and clinical features of various glycosphingolipidoses?**Answer:**

Disorder	Enzyme Defect	Clinical features
GM1 gangliosidosis	Beta-galactosidase	Neurological manifestations, Organomegaly (Hepatosplenomegaly), Skeletal manifestations
Fabry's disease	Alpha galctosidase	Angiokeratomas, Massive proteinuria, CKD, Early Myocardial infarction
Tay-Sachs disease	Hexosaminidase A	Neurological manifestations, Cherry red spot, No organomegaly - GM2 ganglioside accumulation only
Sandhoff disease	Hexosaminidase A and B	Neurological manifestations, cherry red spots, no organomegaly - GM2 ganglioside and Globoside accumulation
Sialidosis	Neuraminidase	Generalized swelling, Neurological manifestation, Organomegaly
Gaucher's disease	Beta glucosidase	Anemia, Thrombocytopenia, Hepatosplenomegaly, Crumpled Tissue paper cells appearance, Bony pain, Erlenmeyer flask deformity
Farber's disease	Ceramidase	Granulomatous disorder - Painful subcutaneous nodules and CKD

Note: Tay-Sachs & Sandhoff can be collectively called GM2 gangliosidosis**Q8.8: What are the features of Fabry's disease?****Answer:**

- X-linked recessive inherited disorder
- Alpha Galactosidase removes Galactose in Globoside and converts it to Cerebroside.
- The absence of Alpha Galactosidase leads to Fabry's disease
- Globoside gets accumulated in Fabry's disease
- It presents with reddish-purple spots/Angiokeratomas
- Other features include Proteinuria, CKD, and early Myocardial infarction

Q8.9: What are the features of Gaucher's disease?

PYQ: FMGE 2021

Answer:

- Beta Glucosidase removes Glucose from Cerebroside and converts it to Ceramide.
- The absence of beta-glucosidase causes Gaucher's disease.
- The lipid that accumulates is Glucosyl ceramide/Glucosyl cerebroside
- Glucosyl cerebroside is present in the RBC membrane and/or platelet membrane
- Both RBCs and platelets have abnormal membranes that get engulfed by macrophages
- This causes Refractory anemia and Thrombocytopenia
- Refractory anemia causes compensatory erythropoiesis → Bony erosions and bone pain
 - **Ehrlen Mayer flask deformity** (distal end of the femur looks like a conical flask)
- Compensatory extramedullary erythropoiesis causes Hepatosplenomegaly.
- The macrophages within which the membranes accumulate like fibrils - Tissue paper cells appear on the bone marrow biopsy.
- **Treatment:** Enzyme replacement therapy

**Q8.10: What are a few differentiating features of sphingolipidosis?****Answer:**

- No mental retardation in GF (Gaucher's disease and Fabry's disease)
- No Cherry red spot - KGF (Krabbe's disease, Gaucher's disease and Fabry's disease)
- No organomegaly - Tay Sach's and Krabbe's disease

Q8.11: A child presents with anemia and thrombocytopenia. On examination, hepatosplenomegaly is observed. The child also complains of bony pain. Light microscopy reveals a crumpled tissue paper appearance. The enzyme defect is:

- Alpha-glucosidase
- Beta-glucosidase
- Alpha-galactosidase
- Beta-galactosidase

Answer: B. Beta-glucosidase

Explanation:

- The condition described in the question is Gaucher's disease
- The enzyme deficiency is Beta-glucosidase (Beta-glucosyl cerebroside)



5. GENETICS

BIG QUESTION 1: What are the different types of nitrogenous bases found in nucleic acids, and what are the sources of atoms in their structure?

Broad Answer: Nitrogenous bases are classified as purines (adenine, guanine) and pyrimidines (cytosine, thymine, uracil). Purines have a double-ring structure, while pyrimidines are single-ringed. Their atoms are derived from amino acids (glycine, aspartate, glutamine), CO_2 , and tetrahydrofolate derivatives.

DETAILED QUESTIONS

Q1.1: Pyrimidine ring is derived from all except:

- A. Carbon dioxide
- B. Glutamine
- C. Aspartate
- D. Glycine

Answer: D. Glycine

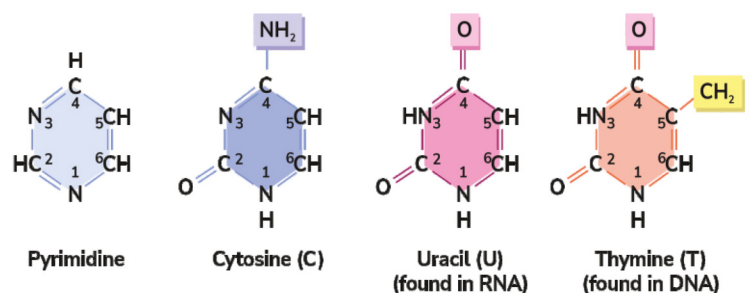
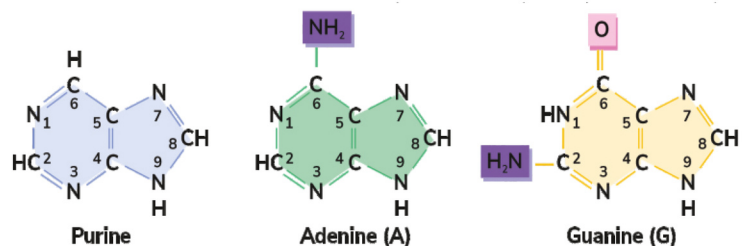
- Glycine is necessary for purine ring formation, not pyrimidine.
 - Glycine contributes to the purine ring at positions C4, C5, C6, and N7.
- Carbon dioxide forms C2 of the pyrimidine ring.
- Glutamine forms N3 of the pyrimidine ring.
- Aspartate forms N1, C4, C5, and C6 of pyrimidine rings.

Q1.2: What are the types of nitrogenous bases?

Answer:

- Two types:
 - **Purines:**
 - Bigger structure with two rings and nine atoms.
 - Adenine and Guanine.
 - **Pyrimidines:**
 - Smaller structure with a single ring and six atoms.
 - Cytosine, Uracil, Thymine. (Mnemonic: CUT)

PYQ: FMGE 2019



Q1.3: What is the source of atoms in the purine ring?

Answer:

- N1: Aspartate.
- C2 & C8: Tetrahydrofolate derivative.
- N3 & N9: Glutamine.
- C4, C5, and N7: Glycine.
- C6: Carbon dioxide.
- **Rate-limiting enzyme for the de novo synthesis of purine:** Glutamine PRPP Amidotransferase.

Q1.4: What is the source of atoms in the pyrimidine ring?

Answer:

- N1, C4, C5, C6: Aspartate.
- N3: Glutamine.
- C2: Carbon dioxide.
- **Rate-limiting enzyme:** Carbamoyl phosphate synthetase II.

BIG QUESTION 2: How are nitrogenous bases organized into nucleosides, nucleotides, and polynucleotides, and what is the clinical relevance of defects in this organization?

Broad Answer: Nitrogenous bases attach to pentose sugar to form nucleosides, which combine with phosphate to form nucleotides. Nucleotides join via 3'→5' phosphodiester bonds, forming polynucleotides. This organization ensures stable genetic storage and transfer. Defects in base excision repair enzymes can lead to the accumulation of mutations and hereditary colon cancer

DETAILED QUESTIONS

Q2.1: How are the nitrogenous bases organized?

Answer:

- When a nitrogenous base is attached to a ribose or deoxyribose sugar: **Nucleoside**
- When a Nucleoside is attached to a phosphate: **Nucleotide**
- When many nucleotides are linked together: **Polynucleotide chain**
- When two polynucleotide chains interact with each other: **Double-stranded DNA**
- When a long double-stranded DNA gets condensed with the help of a protein: **Chromosome**
- Every chromosome has multiple genes
- A gene is a segment of a chromosome
- These genes, upon **transcription**, give rise to **mRNAs**
- These **mRNAs**, upon **translation**, give rise to **proteins**

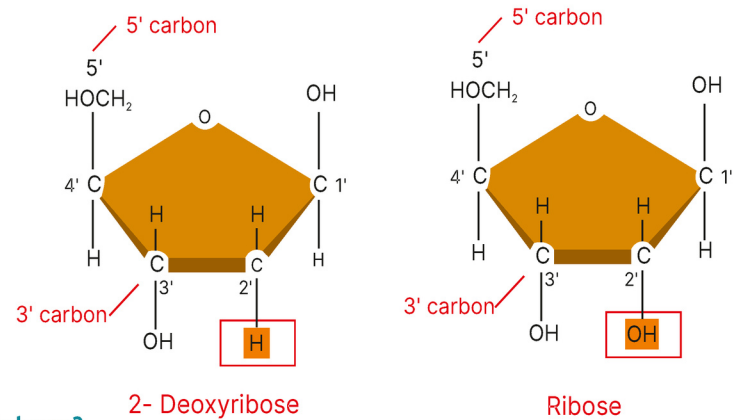
Q2.2: How are nucleosides formed?

Answer:

- Base + Ribose or Deoxyribose sugar → Nucleoside
- Both Ribose and Deoxyribose are pentoses with 5 carbon atoms.
- Ribose, being a carbohydrate, will have multiple hydroxyl groups
- Deoxyribose means the second carbon atom would have lost its oxygen (2-deoxyribose)
- A purine or pyrimidine base gets attached to a ribose or deoxyribose sugar to form a nucleoside

YOURWISH

- The first hydroxyl group of ribose or deoxyribose sugar gets attached to n-9 of purine or n-1 of pyrimidine to get nucleoside.
- The link between base and sugar is a **Beta-N-Glycosidic linkage**.



Q2.3: What are the features of the Beta-N-Glycosidic linkage?

Answer:

- It's called a glycosidic linkage because a linkage is formed with a carbohydrate.
- **N-Glycosidic linkage:** because the linkage is formed between a carbohydrate and a nitrogenous base.
- It's called Beta-N-Glycosidic linkage because the OH group in the ribose or deoxyribose sugar is above the plane of the ring.

Q2.4: A 39-year-old person presents with colon cancer. A tissue biopsy was sent to detect the presence of a mismatch repair defect and microsatellite stability index, which was high. The geneticist, however, detects multiple base excisions in the DNA. The linkage that is broken to cause a base excision is:

- Phospho ester
- Beta N glycosidic linkage
- 3'5'phosphodiester linkage
- 5'3' Phosphodiester linkage

Answer: B. Beta N glycosidic linkage

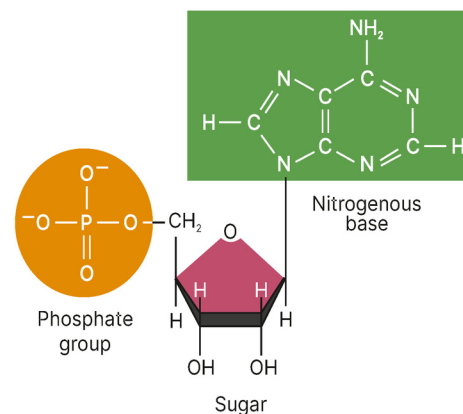
- The clinician suspects Hereditary Non-Polyposis Colon Cancer/Lynch syndrome caused by the defect of Mismatch Repair.
- In the above question, multiple base excisions are observed
- The linkage that is broken to cause a base excision is the **β-N-glycosidic linkage**
- Base excision means the backbone of the double-stranded DNA is maintained normally
- Backbone is made up of 3'5' phosphodiester linkages and Ribose or deoxyribose sugars
- The step is made up of a Nitrogenous base linked by hydrogen bonds
- Whenever hydrogen bonds are broken, a double-stranded DNA will undergo unwinding to form 2 single strands
- Breakage of hydrogen bonding results in denaturation or unwinding, which does not cause base excision
- Whenever there is a breakage of the linkage that links the base with the sugar, the base is lost
 - This is called base excision
- The linkage between the base and the sugar- β-N-glycosidic linkage
 - It is thermo-labile
 - Many times, this linkage is broken and the base gets lost, resulting in a base excision error.
- Base excision error is caused by the breakage of β-N-glycosidic linkages.

Q2.5: How is nucleoside converted to nucleotide?

Answer:

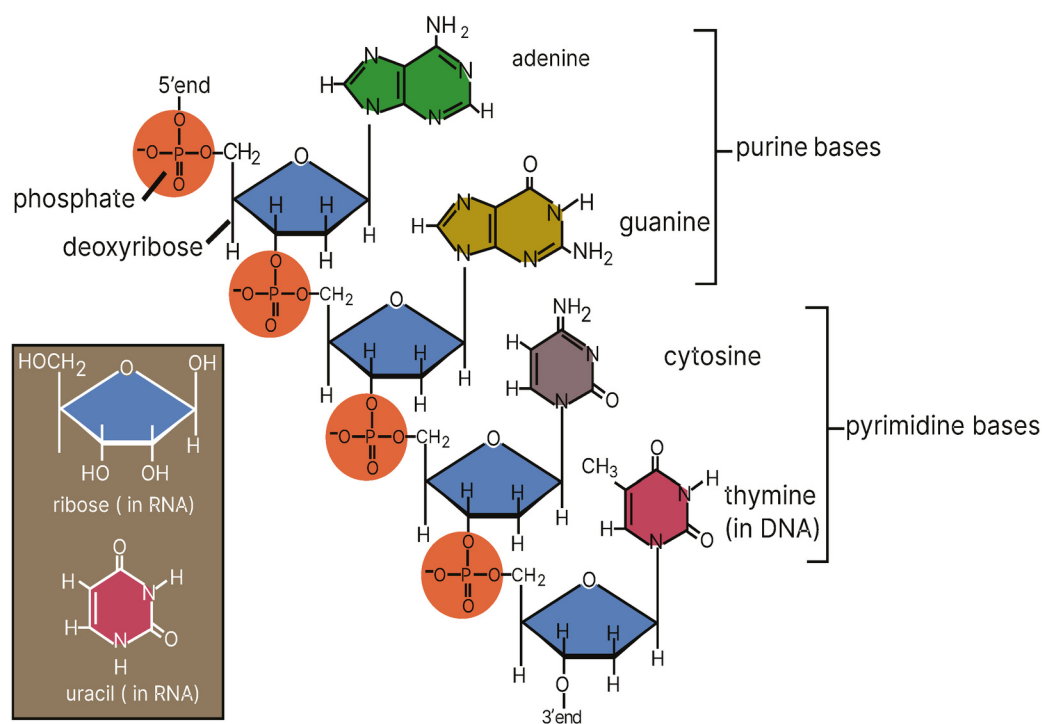
- Attaching the phosphate group to the 5' hydroxyl group of nucleosides to get a monophosphate nucleotide

- The linkage formed is a phosphoester linkage
- The linkage between the alcohol group and the acid group → ester linkage
- Monophosphate nucleotide (NMP) is converted into diphosphate nucleotide (NDP) by adding an additional phosphate group.
- $\text{NDP} + \text{Phosphate} = \text{NTP}$
- Out of these three forms, it is NMP that is present in any polynucleotide chain.



Q2.6: What is the role of hydroxyl and phosphate groups in polynucleotide formation, and how do they determine the directionality and ends of the chain?

Answer:

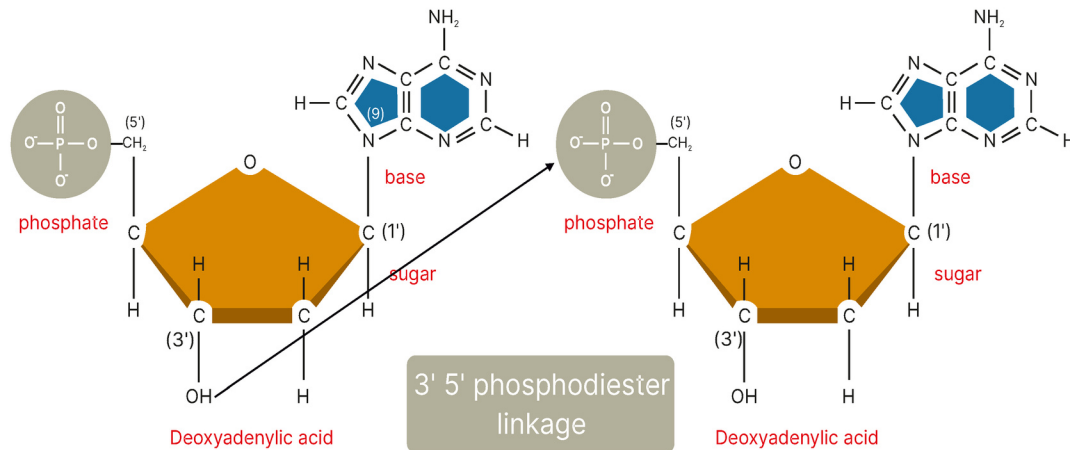


Structure of Polynucleotide Chain

- For any substance to get linked in a poly-form, there must be a free hydroxyl group
 - The first hydroxyl group in a monophosphate nucleotide is engaged in a beta-N-glycosidic linkage with the base
 - 2' hydroxyl group is not always present (missing in 2'deoxyribose)
 - The last hydroxyl group is involved in phosphoester linkage formation
 - Only the 3' prime hydroxyl group remains free.
- 3' prime hydroxyl group, which is free in monophosphate nucleotide, links with the following 5' phosphate group of the next nucleotide, forming a 3' 5' phosphodiester linkage.
- Every nucleotide has a 5' phosphate group and a 3' hydroxyl group
- In the first nucleotide, 3' hydroxyl group is involved in 3' 5' phosphodiester linkage formation
 - So the 5' phosphate group has to be free. The end where the 5' phosphate group is free is called the 5' end
- In the last nucleotide, the 5' phosphate group will be involved in linkage formation with the previous nucleotide
 - So the 3' hydroxyl group is free. The end where the 3' hydroxyl group is free is called the 3' end

Q2.7: How does the polynucleotide chain grow, and what are the enzymatic and strand-directional requirements for DNA/RNA synthesis?

Answer:



- The polynucleotide chain is synthesized only in the 5' 3' direction
- The linkage is always a 3' 5' phosphodiester linkage.
- All the polymerases (DNA and RNA Polymerases) can synthesize new strands only in the 5' 3' direction.
- DNA Polymerase and RNA Polymerases need a template strand to be already present
 - Only then can they synthesize a new strand that is complementary and antiparallel.
 - If a new strand is synthesized in the 5' 3' direction
 - Template strand is synthesized in 3' 5' direction
- All DNA and RNA polymerases have only one polymerase activity, which is 5' 3' polymerase activity.
- When two polynucleotide chains interact with each other, it results in double-stranded DNA.

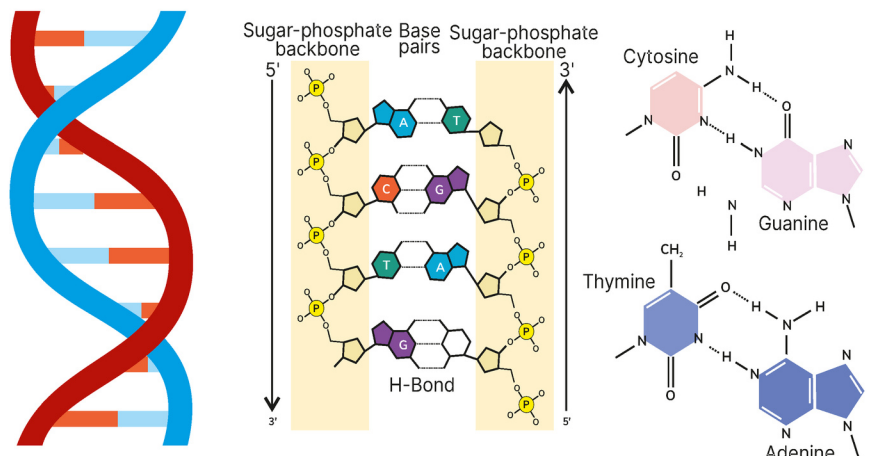
BIG QUESTION 3: How is DNA structurally organized to enable stable genetic storage, and what are the major conformational variants observed under different conditions?

Broad Answer: DNA is a double-stranded helical molecule composed of nucleotides joined by 3'→ 5' phosphodiester linkages. Each strand runs antiparallel, and bases pair through hydrogen bonds, A with T, and G with C, allowing complementary base pairing. The most common conformation under physiological conditions is B-DNA, which is right-handed with 10 base pairs per turn. A-DNA, also right-handed but more compact, is seen in dehydrated conditions and RNA-DNA hybrids. Z-DNA is a left-handed helix, seen in GC-rich regions, and is associated with gene regulation. These structural forms allow DNA to remain stable yet flexible for replication and transcription.

DETAILED QUESTIONS

Q3.1: Who proposed the structure of DNA?

Answer: The DNA structure was given by Watson and Crick.



Q3.2: What are the basic orientation features of the DNA?

Answer:

- Two strands are exactly **complementary** (A-T, G-C) and **anti-parallel**
 - **Complementarity:** If there is A on one strand, there should be T on the other strand
 - If there is G on one strand, there should be C on the other strand
- Strands are oriented in a ladder like fashion

Q3.3: What makes up the backbone and steps of the DNA double helix?

Answer:

- The backbone of the ladder is made up of 3' 5' phosphodiester linkages with ribose or deoxyribose sugars.
- Steps are made up of nitrogenous bases that are linked by hydrogen bonds.
- There are 2 hydrogen bonds between A and T and 3 hydrogen bonds between G and C.

Q3.4: What are the consequences of breaking different bonds and linkages in DNA?

Answer:

- When a hydrogen bond is broken, a double-stranded DNA will unwind to form 2 single strands.
- When the **B-N-glycosidic linkage** is broken, the base will be excised. This is called a **base excision error**.
- When a **3' 5' phosphodiester linkage** is broken on both strands, this is called a **double-stranded DNA break**.

Q3.5: What are the features of the B type of DNA?

Answer:

- The most common physiological form of DNA is B-type DNA
- It is a right handedly coiled helix
- 10 base pairs for every full turn
- Each base pairing raises the height by 3.4Å
- One full turn measures 34Å
- Width is 20Å
- Every full turn has one major and one minor groove

Q3.6: What are the characteristics of A type of DNA?

Answer:

- It forms after DNA undergoes Dehydration
- Whenever there is a hybrid between DNA and RNA, or an RNA-RNA hybrid
- It is a right handedly coiled helix
- 11 base pairs for every full turn
- All grooves are of the same dimension

Q3.7: What is Z-type DNA, and its significance?

Answer:

- It is seen in GC-rich sequences of chromosomes
- It is the only left-handedly coiled confirmation
- Every complete turn has 12 base pairs

YOURWISH

Q3.8: DNA is extracted from a blood sample and is subjected to dehydration. The form of DNA that is expected is:

- A. B DNA
- B. A DNA
- C. Z DNA
- D. C DNA

Answer: B. A DNA

- As soon as the DNA is extracted, it is B type
- On dehydration, it becomes an A type

BIG QUESTION 4: How is DNA organized into chromosomes, and how does this structural organization relate to its function?

Broad Answer: DNA, being long and double-stranded, is condensed into chromosomes using positively charged histone proteins. These histones interact electrostatically with negatively charged DNA to initiate the first level of compaction—nucleosomes. Further folding produces 10 nm and 30 nm fibrils that loop onto chromosome scaffolds, ultimately forming a condensed chromosome. For replication and transcription to occur, chromosomes must temporarily uncoil and unbind.

DETAILED QUESTIONS

Q4.1: Why does long double-stranded DNA need to be condensed, and what enables this condensation?

Answer:

- Long double-stranded DNA is condensed with the help of proteins.
- To enable packaging, they are condensed into chromosomes with the help of proteins called histones.

Q4.2: What are histones? How do they interact with DNA, and how do they help initiate chromosome formation?

Answer:

- Histones are basic proteins and are positively charged.
- DNA is negatively charged.
- There is an electrostatic attraction between positively charged histones and negatively charged DNA.
- This allows a segment of double-stranded DNA to wind around histones.
- Winding gives the first level of compactness to form chromosomes.
- Histone sits in the center and attracts double-stranded DNA that gets wound around.
- The resulting structure has a **string-on-bead appearance**, known as a **nucleosome**.

Q4.3: What are the five types of histones involved in DNA packaging?

Answer:

- H1
- H2A
- H2B
- H3
- H4

Q4.4: Which histones form the histone octamer, and which one does not?**Answer:**

- Except for H1, the remaining four (H2A, H2B, H3, H4) form dimers.
- These dimers combine to form an octamer.
- H1 histone is not part of the octamer.
- H1 histone is absent in nucleosomes but is present in the linker fragment that connects nucleosomes.

Q4.5: What are the successive levels of DNA compaction after nucleosome formation?**Answer:**

- After nucleosome formation, the DNA-histone complex appears as a 10-nanometer fibril (based on its width).
- This 10 nm fibril further folds upon itself to form a thicker 30-nanometer fibril – the second level of compaction.
- The 30 nm fibril is then organized into loops by attaching to chromosome scaffolds.

Q4.6: What are chromosome scaffolds and what do they do?**Answer:**

- Chromosome scaffolds are tubular proteins that sit in the center.
- 30 nm fibrils form loops on all chromosome scaffolds.

Q4.7: What is the final outcome of all these levels of compaction?

Answer: On several such condensations, a highly condensed chromosome is formed with a centromere, a short arm, and a long arm.

Q4.8: The process of gene regulation involves condensation and uncondensation of chromosomes. This occurs by the binding of a variety of proteins to DNA by charge interactions. At physiological pH, the charge on DNA is:

- A. Positive charge
- B. Negative charge
- C. Both
- D. No charge

Answer: B. Negative charge

Explanation:

- DNA has a negatively charged phosphate backbone at physiological pH
- This negative charge allows the binding of positively charged histone during condensation.

Q4.9: What are the two key functions of chromosomes?

Answer: All chromosomes perform two functions:

- Replication
- Transcription.

Q4.10: What structural changes occur in chromosomes during replication and transcription?

Answer: When the chromosomes are performing replication and transcription, there will be uncondensation first and then unbinding.

BIG QUESTION 5: What are genes, and how are they expressed, modified, and regulated in cells?

Broad Answer: Genes are functional units of DNA that undergo transcription to form RNA. The primary transcript undergoes post-transcriptional modifications like capping, tailing, and splicing. Some genes lack introns or don't follow the standard expression pathway (e.g., non-coding RNAs). These exceptions and modifications ensure regulated gene expression in both normal and special contexts.

DETAILED QUESTIONS

Q5.1: What are transcription units and the structural features of a gene?

Answer: **Gene:** Older term; **Transcription unit:** Newer term

- A transcription unit is a segment of a chromosome that codes for a protein or RNA
- Within a gene, **coding and non-coding** intervening sequences are present
- Non-coding sequence can be called an **Intron** when interspersed within a gene

Q5.2: What is the primary transcript, and what is its fate?

Answer:

- When transcription is performed, the first product is not called functional mRNA (intervening non-coding sequences) but called as primary transcript.
- Primary transcript: Also called **Heteronuclear RNA** → Formed in the nucleus → Then enters the **nucleolus** → **Post-transcriptional modification happens.**

Q5.3: What are the steps of post-transcriptional modifications?

Answer: The three types of Post transcriptional modifications are:

- **7-Methyl guanosine cap** gets added to 5 prime ends.
- **Poly-A tail** gets added to the 3 prime ends.
 - o Cap and tail are added because the nucleus is rich in exonucleases
 - o Endonucleases make a cleavage in between (site-specific)
 - o Exonuclease breaks an oligonucleotide or polynucleotide from the exterior (either from the 3' or 5' ends)
 - If they break from the 5' end, then it is called a 5'3' exonuclease
 - If they break from the 3' end, then it is called 3'5' exonucleases
 - o The nucleus is rich in exonucleases
 - o These exonucleases should not attack our own RNAs
 - o To protect endogenous RNA from their attack, the cap and tail are added to the 5' end and 3' end, respectively.
- **Removal of non-coding intervening sequence** or introns. And joining the coding sequences or exons in a process called splicing.
- Introns are removed by **endonucleases**, and all exons are connected.

Note: Not all three post-transcriptional modifications mentioned above are universal

Q5.4: What are the events that occur after the post-transcriptional modification?

Answer:

After the three post-transcriptional modifications, a functional mRNA is formed.

Functional mRNA comes out of the nucleus and reaches the cytoplasm.



In the cytoplasm, the ribosome starts reading mRNA from the 5' end to the 3' end.



Once the AUG codon is identified, ribosomes start translating it.



Depending on the AUG codon, the ribosome recruits a complementary anti-codon containing tRNA.



That tRNA drags along with it an amino acid (Methionine)

Q5.5: How does the ribosome elongate the polypeptide chain during translation?

Answer:

When the ribosome moves along the mRNA from the 5' end to the 3' end, it reads every codon one by one.



Depending upon the codon that is present, the ribosome recruits a complementary anti-codon containing tRNA



tRNA drags along with it a second amino acid



Between Methionine and a second amino acid, a Peptide linkage is formed.



The polypeptide chain grows from the amino terminal end to the carboxy terminal end.



This is called **Translation**.

Q5.6: What is gene expression?

Answer: A gene giving rise to an RNA or a protein

Q5.7: What are the exceptions in histone mRNA formation?

Answer:

- Histone genes are like prokaryotic genes
- They don't have Introns
- Splicing need not happen during histone mRNA formation
- It does not involve a Poly A tail addition
- The histone mRNA 3' end is protected by a stem-loop structure

Q5.8: Which of the following is not associated with post-transcription modification?

 PYQ: INICET 2024

- A. Methylation
- B. Endonuclease cleavage
- C. 5' capping
- D. Glycosylation

Answer: D. Glycosylation

- Glycosylation means glycosylating a protein (carbohydrate residues are added to proteins, forming a glycoprotein or a proteoglycan)
- This is a post-translational modification.

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Q5.9: A patient who has been diagnosed with multiple colonic polyps and carcinoma with a positive family history of HNPCC has a defect of which of the following repair mechanisms?

 PYQ: NEET PG 2021

- A. Mismatch repair
- B. Nucleotide excision repair
- C. Base excision repair
- D. Point mutation

Answer: A. Mismatch repair

- HNPCC is caused by a defect in the Mismatch Repair (MMR)
- Nucleotide excision repair defect causes Xeroderma pigmentosa and Cockayne syndrome

BIG QUESTION 6: What are DNA errors, and how are they repaired in the cell?

Broad Answer: DNA errors can occur spontaneously or due to external agents, leading to mutations. To maintain genetic integrity, cells have evolved several repair mechanisms. These include mismatch repair, base excision repair, nucleotide excision repair, and double-strand break repair. Each pathway detects and corrects specific types of damage to ensure faithful DNA replication and cellular function.

DETAILED QUESTIONS

Q6.1: What are the various DNA errors?

Answer:

- Base excision error - most common
- Mismatch error
- Pyrimidine dimerization
- Double-stranded DNA break

Q6.2: What is a base excision error?

Answer:

- It is the most common error in DNA
- Beta N-glycosidic linkage, which links the base with sugar, is very weak.

Q6.3: What are the features of a mismatch error?

Answer:

- Mismatch error is common during replication
- During replication, the parent double-stranded DNA undergoes unwinding
- After unwinding, each of these strands acts as a template, based on which two new strands are synthesized
- When these two strands are synthesized by DNA Polymerases,
 - o If they find A on the template strand, the DNA Polymerase must attach T
 - o If they find G on the template strand, it is the responsibility of DNA Polymerase to attach C
- But DNA Polymerases are not error-proof
- They can introduce defects during replication
 - o When they find G, DNA Polymerases can sometimes attach to T
 - o That causes a mismatch error

Q6.4: What is pyrimidine dimerization?

Answer: UV light causes adjacent pyrimidines to dimerise.

Q6.5: What happens in a double-stranded DNA break?

Answer:

- The backbone of both strands is broken
- The backbone is made up of 3' 5' phosphodiester linkage
- When this is broken, it is called Double stranded DNA break
- This happens in the presence of ionizing radiation
- Gamma rays are called ionizing radiation
- Ionizing radiation causes ionization of water
 - o Ester and ether linkages can be broken by adding water.

Q6.6: What are the various DNA repair mechanisms?

Answer:

- **Base excision repair mechanism:** For Base excision error
- **Mismatch repair mechanism:** For a mismatch error
- **Nucleotide excision repair:**
 - o Whenever there is UV light-mediated Pyrimidine dimerization, it creates a kink that is abnormal
 - o The repair is done by a special enzyme called UV-specific endonuclease
 - o UV-specific endonuclease makes two 2 nicks adjacent to the kink
 - o It excises the whole nucleotide away
 - o Because a segment of nucleotide is excised away, it is called Nucleotide excision repair
 - o The enzyme is called Excinuclease
- **Double-stranded DNA break repair**

BIG QUESTION 7: What are the DNA errors and their repair mechanisms?

Broad Answer: Disorders caused by DNA repair mechanisms include Mismatch repair (Hereditary Non-polyposis Colon cancer), Nucleotide Excision repair (Xeroderma pigmentosa/Cockayne syndrome), and Double-stranded DNA break repair. Double-stranded DNA break repair can happen through two mechanisms—Non-homologous end joining (NHEJ) and Homologous DNA repair (HDR). Various diseases are linked to defects in these pathways.

DETAILED QUESTIONS**Q7.1: What are some disorders caused by DNA repair mechanisms?**

 PYQ: AIIMS 2020

 PYQ: INICET 2020

Answer:

- Mismatch repair causes Hereditary Non-Polyposis Colon Cancer.
- Nucleotide Excision repair defect causes Xeroderma pigmentosa/Cockayne syndrome.
- Double-stranded DNA break repair mechanism

Q7.2: What are the ways the double-stranded DNA repair mechanism can be brought out?

Answer: The repair mechanism can be brought out in 2 ways:

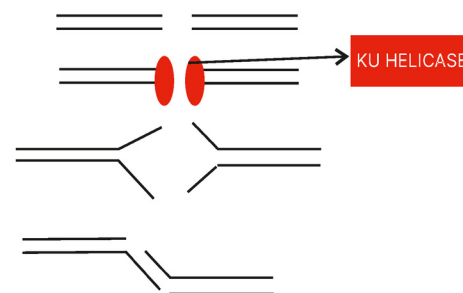
- Non-homologous end joining (NHEJ)
- Homologous DNA repair (HDR)

Q7.3: What is Non-homologous end joining?

PYQ: NEET PG 2018

Answer:

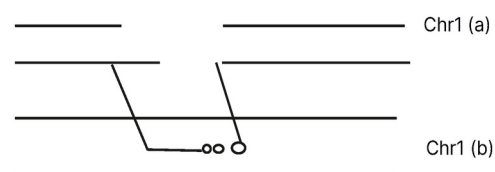
- NHEJ is more common than HDR.
- NHEJ is mediated by **Ku Helicase**, a dimer; each of the two units goes and binds with both ends
- Ku Helicase will cause unwinding of both ends and approximation.
- Approximation continues until they find the base pairing, and the excess strand will be removed.
- Now, DNA ligase will unite the ends.
- There is a loss of some nucleotide sequences
 - o This causes detrimental mutations



Q7.4: What is Homologous DNA repair?

Answer:

- When a double-stranded DNA that has undergone a double-stranded DNA break
- A homologous DNA sequence will be the other copy of the same chromosome
- When the homologous DNA sequences are brought into alignment with each other, DNA Polymerase Epsilon or Beta has a proofreading and repair mechanism
- These DNA polymerases are brought into action
- They remove a part of one of the two strands
- When these are removed, overhanging edges are produced
 - o The overhanging edge has a very high strand invasion ability
- Thus, it invades the double-stranded homologous DNA sequence
- This strand acts as a template, based on which DNA Polymerase epsilon or beta will substitute the right sequence
- Once the right sequence is substituted, this end also invades the double-stranded DNA, and Ligase will unite the ends
- This is the best form of a repair mechanism whenever there is double stranded DNA break



Q7.5: What are the defects of the double-stranded DNA repair and their associated disorders?

Answer:

- It causes many disorders.
- Mnemonic: **ABF**

Disorder	Associated Repair Mechanism
Ataxia Telangiectasia	Non-Homologous End Joining (NHEJ)
Bloom's Syndrome	Non-Homologous End Joining (NHEJ)
Fanconi's Anaemia	Homology-Directed Repair (HDR)
HBOC (Human Breast and Ovarian Cancer Syndrome)	Homology-Directed Repair (HDR)
Severe Combined Immunodeficiency (SCID)	Non-Homologous End Joining (NHEJ)

Q7.6: What is the significance of the BRCA1 protein in DNA repair and cancer risk?**Answer:**

- The BRCA1 protein is involved in homologous DNA repair
- Mutations of BRCA1 cause a person to be susceptible to developing breast and ovarian cancer
- These mutations are inherited in an autosomal dominant pattern

BIG QUESTION 8: What are the different types of chromatin found in the nucleus, and how do they differ in their function and structure?

Broad Answer: Chromatin exists in two main forms—euchromatin and heterochromatin—depending on its level of condensation and transcriptional activity. Heterochromatin is further divided into constitutive heterochromatin, which is permanently inactive and found in repetitive DNA regions, and facultative heterochromatin, which can switch between active and inactive states. Euchromatin remains loosely packed and is generally transcriptionally active, allowing gene expression. The balance between these forms plays a crucial role in gene regulation, cellular differentiation, and genome stability.

DETAILED QUESTIONS**Q8.1: What are the types of chromatin?****Answer:**

There are two types

1. Euchromatin
2. Heterochromatin

Q8.2: What are the differences between Euchromatin and heterochromatin?**Answer:**

 PYQ: AIIMS 2018

Euchromatin	Heterochromatin
Active transcriptionally	Inactive transcriptionally
Uncondensed	Highly condensed
Less densely stained	More densely stained

Q8.3: What are the types of heterochromatin?**Answer:**

1. Constitutive heterochromatin
2. Facultative heterochromatin

Q8.4: What is the location and significance of constitutive heterochromatin during the mitotic phase?**Answer:**

- Constitutive heterochromatin is found in the Centromere and Telomeric ends
- It is found in the Centromere because, in the M phase (Mitotic phase), there is a phase called Metaphase
- In Metaphase, the mitotic spindle is formed and is attached to the centromere
- In the next phase, Anaphase, the mitotic spindle contracts
- When the mitotic spindle contracts, the centromere breaks longitudinally
- The one long and short arm goes to one pole, and the other long and short arm goes to the other pole

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- Centromere is a region which is subjected to repeated breakage
- Breakage will never be perfect
- There will be a tendency for one of the two chromosomes to gain sequences, and there will tendency for the other chromosomes to miss sequences.

Q8.5: Why are centromeric regions composed of non-coding sequences, and how does this relate to the type of chromatin found there?

Answer:

- If the centromeric region has coding sequences, every time there is breakage and segregation, one daughter chromosome would have undergone duplication of gene sequences, and the other one would have undergone deletion of detrimental DNA sequences.
- This is the reason why Centromeric regions are provided with non-coding sequences.
- It's a heterochromatin type
- It is marked as a dark dot

Q8.6: Why is constitutive heterochromatin present in the telomeric ends?

Answer: Because:

- Every time the chromosome undergoes replication, or the cells undergo cell division, the telomeric end undergoes progressive shortening.
- If Telomeric ends are provided with coding sequences, every time a cell divides, the daughter cell would undergo deletion of gene sequences, which is dangerous.

Q8.7: What are the examples of constitutive heterochromatin?

Answer: Centromere and Telomeres

Q8.8: What is facultative heterochromatin? Give examples.

Answer:

- Example: Female X chromosome
- Every female somatic cell has two X chromosomes, but only one X chromosome is transcriptionally active (other one is transcriptionally inactive).
- Since it is transcriptionally inactive, it is highly condensed and stains more densely as a Barr body
- It is called as Facultative heterochromatin because if you compare two somatic cells and X chromosome which is active in one cell will be inactive in another cell and vice versa
- That's why it is called random inactivation of the X chromosome
- *In germ cells, both X chromosomes will be transcriptionally active*

Q8.9: Barr body is an example of:

- A. Euchromatin
- B. Constitutive heterochromatin
- C. Facultative heterochromatin
- D. Hypersensitive heterochromatin

Answer: C. Facultative heterochromatin

Explanation:

- The Barr body is used for sex determination
- A female is supposed to have a barr body
- Barr body is an example of facultative heterochromatin

BIG QUESTION 9: What are the functions, requirements, and enzymatic activities of DNA Polymerases, including the Klenow Fragment?

Broad Answer: DNA Polymerases synthesize DNA in the 5' to 3' direction using a 3' to 5' template. They require a primer, deoxyribonucleotides, magnesium or manganese as cofactors, and a buffer to maintain pH. DNA Polymerases also possess proofreading functions via 3'→5' exonuclease activity, and some have 5'→3' exonuclease activity as well. The Klenow Fragment, a fragment of DNA Polymerase I, retains 5'→3' polymerase and 3'→5' exonuclease activity but lacks 5'→3' exonuclease activity, making it useful in applications like PCR.

DETAILED QUESTIONS

Q9.1: In which direction can DNA polymerases synthesize a new strand?

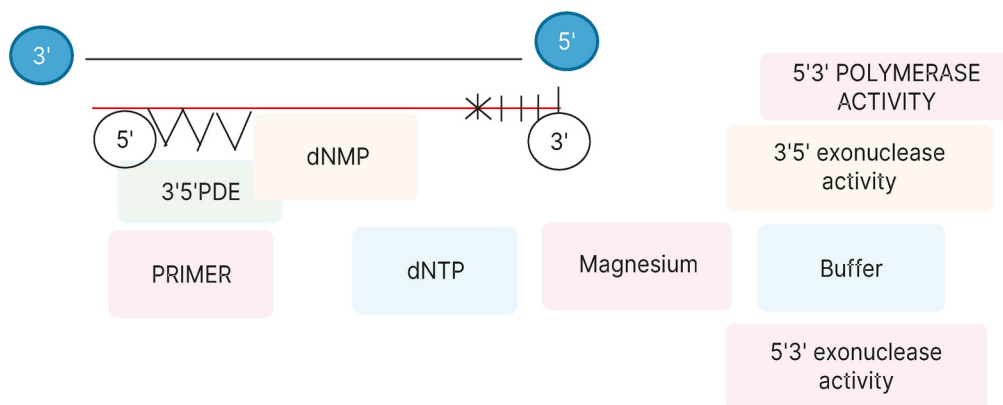
Answer:

- DNA Polymerases can synthesize a new strand (complementary and antiparallel) only in the 5' to 3' direction.
- They always need a template strand.

Q9.2: What should be the direction of the template strand for DNA Polymerase?

Answer: The template strand should always be in a 3' to 5' direction.

Q9.3: What are the requirements of DNA Polymerase for synthesizing DNA?

Answer:

- Every DNA Polymerase needs a 3' to 5' strand to act as a template.
 - Only then can they synthesize a 5' to 3' strand continuously.
- They always need a primer.
 - Only then they can elongate a new strand.
- They always need all four deoxyribonucleoside triphosphates.
 - DNA Polymerases can only recruit complementary deoxyribonucleotides and cannot synthesize those nucleotides.
 - So all the nucleotides have to be provided for the DNA Polymerases.
 - That's why deoxyribonucleoside triphosphates are needed.

- o The form of nucleotide that is present in a polynucleotide chain is a Monophosphate nucleotide.
- o However, they need all nucleotide triphosphates.
- o The reason for this discrepancy is that they recruit complementary nucleotide triphosphate and link adjacent nucleotides by forming 3'→5' phosphodiester linkages.
- o This requires energy, which is obtained by recruiting complementary nucleotide triphosphate instead of recruiting monophosphate nucleotides directly.
- o The last two linkages are broken, and energy is used for forming 3'→5' phosphodiester linkages.

Q9.4: What cofactors and conditions are required for DNA Polymerase activity?

Answer:

- They need Magnesium or Manganese to act as a catalyst.
- They need a buffer to maintain the pH.

Q9.5: What are the properties of DNA Polymerases?

Answer:

- Proofreading and repair activity
 - o Synthesis of a new strand occurs in the 5' to 3' direction.
 - o As they synthesis a new strand, they also proof read the strand.
 - o When they proofread a strand, when they find a defect at one place, they start removing defective strands from the other end
- Proofreading and repair activity needs a 3' to 5' exonuclease activity.
- All DNA Polymerases have 5'3' Polymerase activity and 3'5' exonuclease activity
- **Exception:**
 - o DNA Polymerase 1 has both 3'5' exonuclease activity and 5'3' exonuclease activity

Q9.6: What is the Klenow Fragment, and what are its enzyme activities?

Answer:

- Klenow Fragment is a fragment of Taq DNA polymerase type I used in PCR.
- The enzymatic activities of DNA Polymerase I are as follows:
 - o 5'→3' polymerase activity
 - o 3'→5' exonuclease activity
 - o 5'→3' exonuclease activity
- Out of all these three enzymatic activities, the DNA Polymerase used in PCR should not have 5'→ 3' exonuclease activity.
- If the enzyme has 5' → 3' polymerase activity and the enzyme has 5'→3' exonuclease activity, as it synthesizes and removes the same strand
- 5'3' polymerase activity and 3' → 5' exonuclease activity is in the same subunit, and 5'3'exonuclease activity is in the other subunit, which has to be removed
- The removal is done by Subtilisin
- Subtilisin enzyme acts on Taq DNA Polymerase and it removes 5' → 3' exonuclease activity alone.
- The remaining fragment is known as the Klenow fragment.

Q9.7: DNA Polymerase requires all except?

A. RNA Primer

- B. 3' to 5' strand to act as a template
- C. dNTP
- D. 5' to 3' strand act as a template

Answer: D. 5' to 3' strand acts as a template

Explanation: The template for DNA Polymerase should always be in 3' 5' direction

Q9.8: All of the following are true about Klenow fragment except:

- A. It is a product of DNA polymerase I.
- B. It has 5'3' polymerase activity.
- C. It has 5'3' exonuclease activity.
- D. It has 3'5' exonuclease activity.

Answer: C. It has 5'3' exonuclease activity.

BIG QUESTION 10: What are the key differences between DNA replication and RNA transcription?

Broad Answer: Replication is the process by which the double-stranded DNA undergoes unwinding and both strands act as templates for new DNA strands. In transcription, only the 3'-5' strand acts as a template to synthesize single-stranded RNA. Transcription uses only one strand as a template, and the coding strand has the same sequence as RNA (except that T is replaced by U). Polarity plays a role in identifying template and coding strands.

DETAILED QUESTIONS

Q10.1: What are the sequence of events during replication and transcription in terms of unwinding and template usage?

Answer:

- **Replication**
 - o The parent double-stranded DNA undergoes unwinding
 - o After unwinding, each of the two strands will act as templates based on which two new strands are synthesized
- **Transcription**
 - o The transcription unit undergoes unwinding
 - o After unwinding, the 3 '5' strand acts as a template, based on which a new RNA in 5' to 3' direction is synthesized.

Q10.2: Which strand takes part in transcription?

Answer:

- The 5'3' strand formed after unwinding does not take part in transcription because transcription aims to synthesize a single-stranded RNA
- The strand that acts as a template is called a Template strand
- Based on this template strand, a new RNA is synthesized that is complementary and anti-parallel

Q10.3: What is a coding strand, and how is it related to the synthesized RNA?

Answer:

- The other strand that does not take part in transcription is called a coding strand.

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- Coding strand- has the same polarity and same sequence as newly synthesized strand, except T in coding strand replaced by U in RNA.

Q10.4: What steps should be followed to find the RNA sequence when the template strand sequence is provided?

Answer

- Step 1: Check the polarity
 - o Irrespective of the polarity in which they have given you the template strand
 - o The template is written in 3'5' direction
 - o Complementary sequence is written in 5'3' direction
- If the template strand sequence is provided, but polarity is not mentioned
 - o Polarity should be considered in the 5'3' direction.
- Rule: Any strand sequence should be written in 5'3' direction.

10.5: What steps should be followed to find the RNA sequence when the coding strand sequence is provided?

Answer:

- Maintain polarity and retain the sequence.
- Replace T by U.
- The gene sequence is the coding strand sequence.
- If the coding strand sequence is given, the RNA sequence can be understood

Q10.6: The strand of DNA used as the template for transcription has the base sequence GATCTAC. What is the base sequence of the RNA product?

- A. CTAGATG
- B. GTAGATC
- C. GAUCUAC
- D. GUAGAUC

Answer: D. GUAGAUC

Explanation:

- The template strand sequence is given: GATCTAC
- The polarity is 5'3' direction since the polarity is not given
- The template strand sequence is 5' GATCTAC 3'
 - o Then it should be written as 3' CATCTAG 5'
 - o Complementary sequence should then be written: 5' GUAGAUC 3'

BIG QUESTION 11: What is the role of miRNA and siRNA in gene regulation, and how do they differ from gene knock-out and knock-in?

Broad Answer: miRNA is a precursor of siRNA, and both miRNA and siRNA bring about gene knockdown by interfering with gene expression at the translational level. In contrast, gene knock-out and gene knock-in are methods of gene editing, usually mediated by CRISPR and DNA repair mechanisms like NHEJ and HDR.

DETAILED QUESTIONS

Q11.1: miRNA is used for?
 PYQ: INICET 2021

- A. Gene knock down
- B. Gene knock out
- C. Gene knock in
- D. RNA editing

Answer: A. Gene knock down

Explanation

- miRNA is a precursor of siRNA
- miRNA and siRNA bring about Gene knockdown

Q11.2: What is siRNA, and what is its primary function in gene expression?

Answer:

- siRNA: It is a small interfering RNA
- It interferes with gene expression.

Q11.3: How does gene expression occur, and how does siRNA interfere with it?

Answer:

- Gene expression is the genes' transcription, giving rise to mRNA
- These mRNAs on translation will give rise to proteins
- SiRNAs interfere with gene expression at the translational level

Q11.4: How does siRNA recognize and bind to its target?

Answer:

- siRNAs have their sequences
- When siRNAs find complementary sequences on any of the full-length mRNAs, they hybridize with the mRNAs in the 3' untranslated regions of the mRNAs

Q11.5: How does the ribosome respond to siRNA-mRNA hybridization?

Answer:

- Not knowing that such a structure is formed in the 3' untranslated region, the ribosome reads the mRNA and translates it until it reaches the double-stranded RNA structure.
- It tells the ribosome that something is wrong and stops translation
- The ribosome recruits the endonuclease, and it makes multiple nicks in the mRNA
- Once the mRNA is fragmented, no more translation is down - It has down regulated the gene expression

Q11.6: Why is the interference by siRNA termed as gene knockdown?

Answer: Since it has downregulated the gene expression, it is called gene knockdown

Q11.7: What are Gene Knock Down & Knock Out & In?
 PYQ: INICET 2021

 PYQ: FMGE 2020

Answer:

- Gene knockdown: Downregulation of gene expression mediated by siRNA
- Knockout and Knock-in are two ways of gene editing
- Gene knock-out: Removal of a defective gene.

- Gene knock-in: Replacement of a defective gene with a normal gene.

Q11.8: What is the difference between Knock out/in and Gene knock down?

Answer:

Knock out/in	Gene knock down
Gene sequences are edited • Removal of defective gene: Knock out • Replacement of defective gene with normal gene: Knock in • Knock in is the better editing mechanism	Gene sequence is not edited but gene expression is down regulated at the translation level

Q11.9: How does CRISPR facilitate gene editing through knock-in and knock-out?

 PYQ: AIIMS 2019

Answer:

 PYQ: INICET 2021

- CRISPR-mediated gene editing causes a double-stranded DNA break
- After there is a double-stranded DNA break, the repair mechanism is done by
 - o Non-homologous end joining (NHEJ).
 - o Homologous DNA repair (HDR).
- NHEJ mediated by leading to loss of gene sequence- Gene knock-out.
- HDR mediated by homologous DNA sequences- Gene knock-in.
- Replacing the defective gene with a normal gene

Q11.10: What is the Nobel-prize winning contribution of Emmanuel Charpentier in CRISPR technology?

Answer: Emmanuel Charpentier was given a Nobel price because she repurposed the CRISPR-CAS enzyme system that is present in E.coli for gene editing.

- CAS enzyme makes double-stranded DNA breaks at sites complementary to its guide RNA. Hence, when the CAS enzyme can be synthesised with a guide RNA, which is complementary to mutation sites, the CAS enzyme makes double-stranded nicks at mutation sites, causative of disease.

Q11.11: What determines whether a CRISPR-induced DNA nick leads to knock-in or knock-out?

Answer:

- Following the nick, if Non-Homologous End Joining is mediated, it results in gene knock out, wherein the defective gene is removed.
- Following the nick, if Homologous DNA repair is mediated, it results in gene knock-in, wherein the defective gene is replaced by a normal gene.

Q11.12: miRNA binds to?

 PYQ: INICET 2021

- A. 5' UTR
- B. 3' UTR
- C. Gene promotor
- D. Gene exons

Answer: B. 3' UTR

Explanation:

- miRNA binds to the 3' UTR of target mRNA to regulate gene expression.
- This binding leads to inhibition of translation or degradation of the mRNA.

Q11.13: Following CRISPR-mediated gene nicks, which of the following can result in gene knock-in?

- A. Non-homologous end joining.
- B. Homologous DNA repair.
- C. Interference.
- D. Ku helicase-mediated repair.

PYQ: INICET 2022

Answer: B. Homologous DNA repair.**Explanation:**

- The interference phenomenon causes gene knockdown.
- Non-homologous end joining and Ku helicase-mediated repair can cause a knockout.

BIG QUESTION 12: What are the key steps, conditions, and enzymes involved in PCR and isothermal DNA amplification techniques?

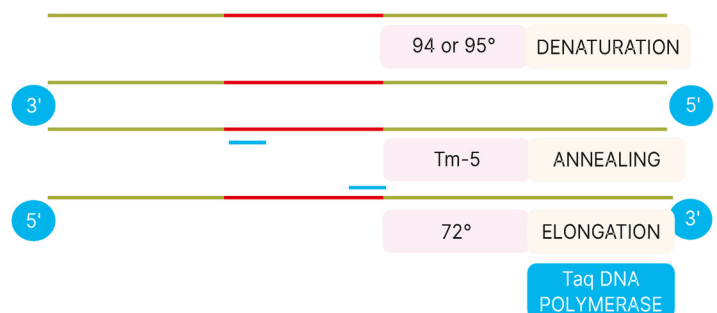
Broad Answer: PCR (Polymerase Chain Reaction) is an in vitro method used to amplify specific DNA fragments using primers complementary to flanking regions. It involves three main steps—denaturation, annealing, and elongation—each requiring specific temperatures and enzymes. PCR relies on thermocycling and thermostable enzymes like Taq polymerase. Isothermal techniques like the LAMP assay simplify amplification without cycling by using strand invasion-capable enzymes such as BSM or BST DNA polymerases.

DETAILED QUESTIONS**Q12.1: What is PCR used for, and how is it achieved?****Answer:**

- PCR is a replication process
- PCR is used for in vitro amplification of a desired fragment of DNA.
- This is achieved by constructing Primers.
- Primers are constructed in such a way that these are complementary to the flanking or terminal sequences of the desired fragment.

Q12.2: What are the steps of PCR?**Answer:**

- For every replication, the first step is unwinding
 - o DNA is unwound into two single strands
 - o Unwinding is otherwise known as Denaturation
- Annealing
- Elongation

**Q12.3: What happens during denaturation?****Answer:**

- 1st step of PCR.
- It is brought about by breaking hydrogen bonds
- These hydrogen bonds are broken at higher temperature

constructed two primers - the melting temperature of the forward primer is 64 °C, and that of the reverse primer is 60 °. He uses *Bacillus smithii* DNA polymerase enzyme. The elongation step temperature that he would use for this setup is:

- A. 62 °
- B. 72 °
- C. 57 °
- D. 60 °

Answer: D. 60 °

- Since the person uses *Bacillus smithii* polymerase enzyme, elongation should be done at 60 degrees.

BIG QUESTION 13: How do Microarray and Comparative Genomic Hybridisation help identify genetic abnormalities in tumour tissues?

Broad Answer: Microarray and Comparative Genomic Hybridisation (CGH) are diagnostic technologies used to analyse genetic differences between tumour and normal tissues. Microarray identifies gene expression levels using labelled cDNA, while CGH reveals chromosomal amplifications or deletions by comparing fluorescently labelled tumour and normal DNA.

DETAILED QUESTIONS

Q13.1: What is Microarray technology used for?

Answer:

- Chip technology
- It is used to understand the pathogenesis of a particular disorder
- It is used to understand differences in the level of gene expression between tumor tissue and normal tissue

Q13.2: How is cDNA prepared and used in microarray analysis?

Answer:

- mRNAs from tumor tissue and normal tissue are extracted, converted to cDNA.
- They are then labeled with fluorescent labels differentially and added to a microarray chip.
- This chip has multiple spots /wells → Wells have oligonucleotides that are complementary to the mRNAs of interest to that particular disease.

Q13.3: How does microarray technology detect gene expression in diseases like breast cancer?

Answer:

- Breast cancer is caused by overexpression or underexpression of 15-20 genes
- These 15-20 mRNAs will be expressed on all these spots
- mRNAs from tumor tissues are converted to cDNAs and labelled with red fluorescent DNA (example)
- mRNAs from normal tissues are converted to cDNA and labeled with green fluorescent dye (example)
- They are mixed, and they compete with each other to go and bind with microarray oligonucleotides

Q13.4: How is gene expression interpreted based on microarray spot colors?

Answer:

- **Yellow fluorescence (green and red mix equally):** Gene is equally expressed in both normal and tumour tissue.
- **One spot has red fluorescence:** mRNA in tumor tissue is over expressed
- **One spot shows green fluorescence:** mRNA in the tumor tissue is not expressed at all
- **Conclusion:** In this patient, breast cancer is caused by over expression of one gene and under expression of other gene
- Based on which gene is overexpressed or under expressed, particular modality of treatment can be chosen

Q13.5: The metaphase chromosome in comparative genomic hybridisation painted purple represent:

- A. Balanced DNA content
- B. Amplification in tumour DNA
- C. Under expression in tumour DNA
- D. Overrepresentation of the whole chromosome in tumour DNA

Answer: B. Amplification in tumor DNA

- **Purple color:** Tumor DNA
- **Aqua blue colour:** Normal DNA
- **Dark blue colour (purple and aqua blue color is mixed equally):** A segment of chromosome is expressed equally both in reference DNA and tumour DNA.
- **Purple colour alone-** That segment of the chromosome is amplified in the tumour DNA
- **Aqua blue color alone-** It means that there is no representation from the tumor DNA
 - That segment of the chromosome has undergone deletion in the tumor DNA

Q13.6: What is Comparative Genomic Hybridisation (CGH)?

Answer: A cytogenetic version of a microarray, where we try to understand chromosomal aberrations

Q13.7: What are the steps involved in CGH?

Answer:

- Chromosomes from the diseased individuals are extracted
- After extraction, Chromosomes are digested using restriction enzymes
- Multiple fragments of chromosomes are present
- These fragments are denatured and labeled with a particular fluorescent dye.
- Only when they are single-stranded can they bind with Oligonucleotide probes on the CGH chip and be labeled with a particular fluorescent dye.

Q13.8: How are tumor and normal DNA labeled in CGH?

Answer:

- Tumour DNA is labeled with a red fluorescent dye
- Simultaneously, standard chromosome fragments are taken
- Those standard chromosome fragments are also denatured
- It is labeled with a different fluorescent dye -green colour

Q13.9: How are CGH results interpreted?

Answer:

- Both the tumour DNA fragment and normal DNA fragment are mixed and spread on the microarray chip (CGH CHIP)

- If a particular segment of DNA is equally present on tumour DNA and NORMAL DNA, green and red will mix equally to give yellow colour fluorescence.
- **Green colour:** That segment is not present in tumour DNA, called a Microdeletion
- **Red color:** That segment is overexpressed in the tumor tissue (Amplification)
- In this way, all the chromosomes are painted → Helps to understand which chromosomal aberration has caused this particular disease in that individual.

BIG QUESTION 14: How is VNTR analysis used to determine biological paternity in forensic cases?

Broad Answer: VNTR (Variable Number of Tandem Repeats) analysis, based on satellite DNA, is used to compare the microsatellite repeat patterns between a child, mother, and putative father. A match in inherited alleles across multiple loci indicates biological parentage.

DETAILED QUESTIONS

Q14.1: What are the applications of satellite DNA?

Answer:

- It is called a highly repetitive sequence because the number of times satellite DNA is repeated in the whole human genome is more than one lakh times.
- Not all the lakh repeats are concentrated at a single locus
- It will be distributed at various loci
- The number of times the satellite DNA is repeated at a particular locus is unique to a particular person.
- E.g.: If the CAG repeat is used, we check the number of times the CAG is repeated at a particular locus.
- The satellite DNA can be used for personal identification

Q14.2: What are the types of satellite DNA?

Answer:

- Satellite DNA is of two types:
 - o Microsatellite
 - o Minisatellite repeats/VNTR
- It is used to clear off paternal dispute cases - forensic application
 - o A mother with a child claims that X is the father of the child
 - o We find out whether X could be the father of the child - paternal dispute cases

Q14.3: What are the steps involved in paternal dispute cases?

Answer:

- For any molecular diagnostic techniques, Step number 1 is sample collection.
- Blood samples from the mother, the child, and the suspected father are collected.
- DNA from all three samples is extracted
- Three sets of DNA are present
- In all the DNA samples, we have to analyse the inheritance of at least 5 microsatellite repeats at 5 loci each.
- For eg: CAG repeat at rs7903146
 - o When the child's DNA shows 8/8
 - o There are two numbers because we have two copies of every chromosome
 - o In the one chromosome, it is repeated 8 times and in the other chromosome also, it is repeated 8 times

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- o Suppose in the maternal DNA, it is repeated 11/8
- o One of the eight of the child has come from the mother
- o The other 8 must come from the father
- o Suppose the father shows 11/12, 11/10 (other than 8)
- o This means that the person is not the biological father of the child

Q14.4: A paternal dispute case was filed by a mother. The forensic center checked 5 VNTR systems

Individual	VNTR1	VNTR2	VNTR3	VNTR4	VNTR5
Child	9/10	8/11	10/12	9/8	6/7
Mother	7/9	8/9	11/10	9/11	6/9

Which of the following repeats should be observed in the putative father's DNA for him to be considered as the biological father of the child?

- A. 7/8, 9/11, 11/12, 8/10, 6/8
- B. 7/8, 9/11, 10/12, 8/10, 6/8
- C. 10/11, 11/10, 12/11, 8/7, 7/9
- D. 10/11, 11/10, 11/10, 11/9, 9/10

Answer: C. 10/11, 11/10, 12/11, 8/7, 7/9

- VNTR is a Variable Number of Tandem Repeats
- It is a type of Satellite DNA
- DNA fingerprinting or person identification can be done by VNTR analysis or Satellite DNA analysis

BIG QUESTION 15: What are the correct steps involved in molecular diagnosis of sickle cell anemia in a suspected individual with a known family history?

Broad Answer: Molecular diagnosis of sickle cell anemia involves DNA-level analysis targeting the 6th codon of the β -globin gene, using techniques like PCR and RFLP. The correct steps start from sample collection, followed by DNA extraction, PCR amplification, and finally mutation detection using RFLP.

DETAILED QUESTIONS

Q15.1: What is the first step in molecular diagnosis of a known mutation site?

Answer:

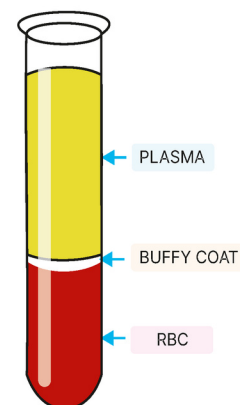
- Sample collection
- Preferred sample is blood.

Q15.2: How is DNA extracted from blood samples?

Answer:

- **Centrifugation** of blood sample.
- Extraction of the buffy coat to extract the DNA
 - o Plasma and RBCs do not have a nucleus or DNA
- After Centrifugation, the plasma is discarded, and the buffy coat
- Transfer the extract of the buffy coat alone into a test tube containing WBCs (Nucleus and DNA)

- To mediate cell and nuclear lysis, a salt method is employed
- The high salt method is used to employ cell lysis
 - **6M NaCl or guanidinium isothiocyanate.**
 - This causes osmotic lysis of cells and the nucleus, and then the DNA comes out.
- Now the DNA is ready to take part in Molecular diagnostics
- This means that all 46 chromosomes containing 25000 genes are extracted



Q15.3: How is PCR used in the molecular diagnosis of sickle cell anemia?

Answer:

- DNA is subjected to PCR
- Primers specific for fragments that include the β -globin gene 6th codon.
- Now we have a fragment with the 6th codon.
- To know whether the 6 codon is normal or abnormal, RFLP or sequencing is used.
- Next step may be sequencing or RFLP.

Q15.4: What is the role of sequencing in this diagnostic process, and what are its limitations?

Answer:

- Determine whether the fragment is normal or abnormal.
- It is not a cost-effective option
- They are not always available

Q15.5: What is RFLP, and how is it used to detect mutations?

Answer: Restriction fragment Length Polymorphism

- A restriction enzyme is used for this method
- It cuts at specific sites
- There are thousands of Restriction enzymes available in the market
- If we decide to use RFLP for diagnosis, we should choose a specific restriction enzyme that cuts the codon if its normal
- Restriction enzyme should be chosen in such a way that it cuts the site of mutation only when it is normal
- Depending upon whether it is cut or uncut, we will be able to give the diagnosis

Q15.6: How is Mst II restriction enzyme used in sickle cell diagnosis?

Answer:

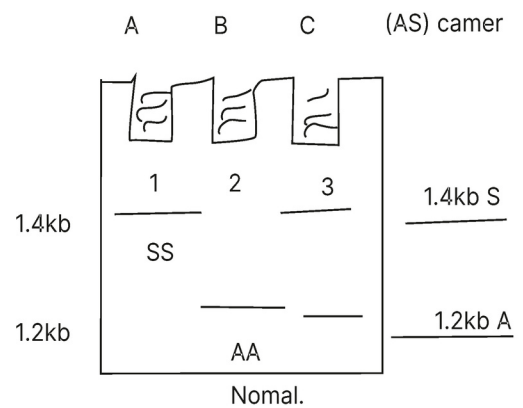
- A restriction enzyme should be chosen in such a way that it cuts the site of mutation only when it is normal.
- Depending upon whether it is cut or uncut, we will be able to give the diagnosis.
 - E.g.: We have constructed primers in such a way that a 1.4 kb fragment of the Beta globin gene that includes the sixth codon.
 - Sixth codon is the restriction site of the enzyme- Mst II
 - Mst II will cut it if the sixth codon is normal
 - If its normal, it will give rise to two fragments: One of length 1.2 kb and the other of length 0.2 kb.
 - If it is mutated, the entire length will remain the same

- o To find out whether it is cut or uncut, after PCR, PCR tube is taken
- o The PCR tube has 1.4 kb of the Beta globin gene
- o Mst II is added to the PCR tube
- o Mst II is allowed to try and cut it by incubating the enzyme there

Q15.7: How are electrophoresis results interpreted in the diagnosis of sickle cell anemia?

Answer:

- When the fragments are allowed to run on Electrophoresis (Polyacrylamide gel)
- Gel has three wells
- Well A, B, C - Restriction digest of person A, B, C are added respectively
- Longer fragments cannot move and they stay close to the point of application
- Shorter fragments move faster
- If the length is 1.4 kb, it is uncut (mutated) - S
- If the length is 1.2 kb, it is cut (normal) - A
- Person C - Two bands are seen (corresponding to 1.4 kb and the other corresponding to 1.2 kb) - Carrier (AS)
- Person B - Both are cut; Normal (AA)
- Person A - Both are uncut; Genotype is SS (the patient has Sickle cell disease)



Q15.8: A 21-year-old man wants a molecular diagnosis of sickle cell anemia, as three of his maternal cousins are diagnosed with sickle cell anemia. The intern knows a few steps involved in molecular diagnostics in a jumbled way. Help him choose appropriate steps and arrange them in the right sequence.

1. RT-PCR
 2. Sample collection
 3. FISH
 4. RFLP
 5. Cytogenetics
 6. Conventional PCR
 7. DNA extraction.
- A. 2, 7, 1, 3
 - B. 2, 7, 6, 4
 - C. 7, 2, 1, 3
 - D. 2, 6, 7, 3

Answer: B. 2, 7, 6, 4

- **Reverse transcriptase-PCR (RT-PCR)** is a molecular diagnostic test done for RNA estimation.
 - o This is used for Reverse transcription (RNA → DNA)
 - o Whenever the nucleic acid of interest is RNA
- **Real-time PCR/Quantitative PCR (qPCR)**
 - o This is used for quantifying the nucleic acid
- Cytogenetics is done to detect chromosomal aberrations
- Molecular diagnostics is done to see the differences in the nucleotide sequencing level

BIG QUESTION 16: What are the different cytogenetic techniques used to detect chromosomal aberrations, and what are their diagnostic applications and limitations?

Broad Answer: Cytogenetics is done to detect chromosomal aberrations. There are three types of cytogenetic techniques: Karyotyping, FISH (Fluorescent In Situ Hybridization), and Comparative Genomic Hybridization (Chromosome Painting). FISH cannot detect point mutations and is useful only when the target abnormality is already suspected, as it requires a specific probe to be synthesized.

DETAILED QUESTIONS

Q16.1: What are the types of cytogenetic techniques?

Answer:

- Cytogenetics: It is done to detect chromosomal aberrations
- There are three types of Cytogenetics techniques:
 - o Karyotyping
 - o FISH
 - o Comparative Genomic Hybridization/Chromosome painting

Q16.2: What is the role of karyotyping in cytogenetics?

Answer:

- It is done by Giemsa staining of chromosomes
- It helps to identify copy number variations at the chromosomal level
- It cannot be used to detect structural alterations like translocations or to detect microdeletions

Q16.3: What is FISH?

Answer: FISH (Fluorescent Insitu Hybridization)

- Specific probes which are directed against segments of chromosomes that are supposed to be altered to cause a disease
- We label it with a fluorescent dye and then we give a report
- Copy number variations can be detected by this method

Q16.4: How is FISH used to diagnose trisomy 21?

Answer:

- If Trisomy 21 is suspected, a polynucleotide or oligonucleotide probe is synthesized that is complementary to chromosome 21 sequences, and it is labeled with a fluorescent dye.
- This probe is added to the metaphase arrest of the chromosome of the individual
- This is viewed through a fluorescence microscope
- Normal individuals: 2 signals are seen → Two copies of chromosome number 21.
- Individual with three signals → Got 3 copies of chromosome number 21 → Trisomy 21.

Q16.5: What is the role of FISH in diagnosing structural alterations?

Answer:

- Structural alterations, like Translocation, can be detected
- E.g.: A patient with Leukemia is treated to know whether the individual has BCR-ABL translocation
- Two probes are synthesized → One will be complementary to BCR sequences, and the other complementary to ABL

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sequences → Probes complementary to BCR and ABL sequences will carry different fluorescent dyes.

- Spread it on the metaphase arrest of the chromosome and looked through a fluorescent microscope.
- Normal individual: Two red and two green signals are seen emanating from four different chromosomes.
- If BCR and ABL signals are coming from two different chromosomes, and BCR and ABL signals is coming from a single chromosome, → BCR-ABL translocation

Q16.6: How is FISH used to detect microdeletions?

Answer:

- Microdeletions can be detected
- Suppose we are suspecting Prader -Willi syndrome or Angelman's syndrome
- Synthesize a polynucleotide or oligonucleotide probe that is complementary to those segments that are suspected to have undergone Microdeletions.
- Label it with a fluorescent dye and spread it on the metaphase arrest chromosome of the individual.
- Allow it to hybridize with the chromosome of the individual and then wash it and look through a microscope.
- If the signal is not seen at all, it means that the segment of chromosome is deleted in the individual.

Q16.7: What are the limitations of FISH?

Answer:

- FISH cannot be used to detect point mutations at the molecular level
- FISH is a cytogenetic technique that can detect at the chromosomal level
- We will be able to use the FISH technique if we know what we are looking for → Cannot detect unknown defects
 - o Suppose you're a family physician and a newborn presents with multiple neurodevelopmental defects (facial dysmorphism and cardiac abnormalities) despite no prior family history of such syndromic features → **Cannot be detected by FISH.**

Q16.8: What are the applications of Comparative Genomic Hybridization/Chromosome painting?

Answer:

- It is a technique that is used to check every segment of all 46 chromosomes.
- Wherever the aberration is, it will give you a signal

Q16.9: FISH is used to detect all of the following except?

 PYQ: INICET 2024

- A. Translocation
- B. Amplification
- C. Deletion
- D. Point mutation

Answer: D. Point mutation

- FISH cannot detect a point mutation at the molecular level
- To detect point mutation, PCR/RFLP, and PCR/Sequencing are used



6. VITAMINS AND AMINOACID METABOLISM

BIG QUESTION 1: Which vitamin deficiencies cause neurological manifestations?

Broad Answer: Neurological symptoms can result from deficiencies in specific B-complex vitamins, particularly those involved in glucose metabolism and neuronal function. These include Thiamine (B1), Niacin (B3), Pyridoxine (B6), and Cobalamin (B12).

DETAILED QUESTIONS

Q1.1: Which vitamin deficiencies are known to cause neurological manifestations?

PYQ: FMGE 2022

Answer:

- B1 (Thiamine deficiency): Dry beri beri (neuropathy)
- B3 (Niacin deficiency): Pellagra (Dementia is a neurological feature)
- B6 (Pyridoxine deficiency and hypervitaminosis): Both cause neurological symptoms
- B12 (Cobalamin deficiency): Peripheral neuropathy and Subacute Combined Degeneration

Q1.2: Which vitamin deficiency causes tingling sensation (neuropathy)?

Answer: Thiamine (B1)

Q1.3: Why does thiamine deficiency cause lactic acidosis?

PYQ: FMGE 2020

Answer: Thiamine is essential for the activity of Pyruvate Dehydrogenase (PDH). In its deficiency, PDH is inhibited, leading to accumulation of pyruvate, which is then converted to lactate, causing lactic acidosis.

Q1.4: Which enzyme's inhibition leads to lactic acidosis in thiamine deficiency?

Answer: Pyruvate Dehydrogenase (PDH)

Q1.5: What are the metabolic fates of pyruvate?

Answer:

- Pyruvate → Acetyl-CoA (via PDH)
- Pyruvate → Lactate (via Lactate Dehydrogenase)

Q1.6: What happens when PDH is inactive due to thiamine deficiency?

Answer: Pyruvate is shunted to lactate pathway, causing lactic acidosis.

Q1.7: What are the effects of lactic acidosis in thiamine deficiency?

Answer:

- Causes vasodilation
- Leads to hypotension, tachycardia
- Increases hydrostatic pressure in capillaries
- Results in peripheral edema and high-output cardiac failure

Q1.8: Which other enzymes are thiamine-dependent?**Answer:**

1. Pyruvate Dehydrogenase (PDH)
2. α -Ketoglutarate dehydrogenase
3. Branched-Chain Ketoacid Dehydrogenase
 - o Deficiency: Maple Syrup Urine Disease (responds to thiamine)
4. Transketolase (HMP shunt)
 - o RBC Transketolase activity is measured to confirm deficiency

BIG QUESTION 2: What is the diagnosis in an alcoholic who avoids alcohol for 2 days and presents with confusion, hallucination, and autonomic hyperactivity?

Broad Answer: Delirium tremens is the most likely diagnosis. It occurs 2-10 days after alcohol withdrawal and presents with global confusion, hallucination, fever, diaphoresis, hypertension, and tachycardia.

DETAILED QUESTIONS**Q2.1: What is Delirium Tremens?**

Answer: A severe form of alcohol withdrawal seen 2-10 days post-cessation, with neuropsychiatric and autonomic symptoms.

 PYQ: FMGE 2021

Q2.2: What are the key features of Delirium Tremens?**Answer:**

- Global confusion
- Hallucinations
- Fever
- High BP
- Diaphoresis
- Autonomic hyperactivity

Q2.3: Why not Wernicke's Encephalopathy?**Answer:**

- Wernicke's presents with GOA: Global confusion, Ophthalmoplegia, Ataxia
- No autonomic hyperactivity, hallucinations, or fever

Q2.4: Why not Korsakoff Syndrome?**Answer:**

- Presents with amnesia, confabulation
- Occurs in chronic thiamine deficiency

Q2.5: Why not Pancreatitis?**Answer:**

- Does not present with confusion, hallucinations, or autonomic hyperactivity

Q2.6: How does alcohol contribute to thiamine deficiency?

Answer: Alcohol is a source of empty calories. It interferes with thiamine and magnesium absorption, and disrupts thiamine phosphorylation due to magnesium deficiency, leading to functional thiamine deficiency.

Q2.7: How does alcohol affect nutrient intake?

Answer:

- Causes high ATP/ADP ratio
- Suppresses hunger
- Leads to meal skipping and micronutrient deficiency

Q2.8: What does 'empty calorie' mean?

Answer: Alcohol provides energy without essential nutrients

Q2.9: Why do chronic alcoholics have functional Thiamine deficiency?

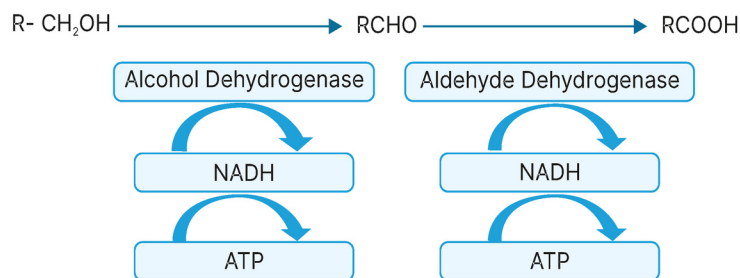
Answer:

- Alcohol interferes with **Thiamine and Mg^{2+}** absorption
- Thiamine $\rightarrow$ Thiamine pyrophosphate via **Thiamine kinase**
- Thiamine kinase is **Mg^{2+}** dependent
- **Hypomagnesemia** $\rightarrow$ inactive Thiamine kinase $\rightarrow$ no TPP $\rightarrow$ functional deficiency

Q2.10: What is the metabolic status of a chronic alcoholic?

Answer:

- High **NADH/NAD⁺** ratio $\rightarrow$ inhibits normal metabolism
- High **ATP/ADP** ratio $\rightarrow$ "High energy" state
- $\downarrow$ Appetite $\rightarrow$ **micronutrient deficiency** $\rightarrow$ "empty calories"

**BIG QUESTION 3: What are the neurological consequences of thiamine deficiency?**

Broad Answer: Thiamine deficiency severely affects neurons due to impaired glucose oxidation, causing peripheral neuropathy (Dry beri beri), and acute/chronic encephalopathies (Wernicke's and Korsakoff syndrome).

DETAILED QUESTIONS**Q3.1: Why are nerves affected in thiamine deficiency?**

Answer:

- Neurons depend on aerobic glucose metabolism
- PDH converts pyruvate to Acetyl CoA
- PDH needs thiamine
- Without it, energy production fails

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Q3.2: What is Dry Beri Beri?**Answer:** Peripheral neuropathy due to thiamine deficiency**Q3.3: What is the acute form of Thiamine Deficiency?****Answer:** Wernicke's Encephalopathy (metabolism gets affected)

- Global confusion
- Ophthalmoplegia (CN 3, 4, 6 involvement)
- Ataxia (cerebellar involvement)

Q3.4: Which brain areas are most affected in Wernicke's encephalopathy?**Answer:**

- Mammillary bodies (Papez circuit): Global confusion
- CN 3,4,6: Ophthalmoplegia
- Cerebellar neurons: Ataxia

Q3.5: What is the consequence of chronic thiamine deficiency?**Answer:** Korsakoff Syndrome (nerves undergo atrophy).

- **Cause:** Chronic alcoholic → Always in Thiamine deficiency status → No Treatment → Korsakoff Syndrome
- Retrograde and anterograde amnesia
- Confabulation
- Sensory agnosia

BIG QUESTION 4: What is the diagnosis in a patient presenting with diarrhea, dermatitis, and dementia?**Broad Answer:** The classic triad of diarrhea, dermatitis, and dementia is seen in Pellagra, which is due to Niacin (Vitamin B3) deficiency.**DETAILED QUESTIONS****Q4.1: What is the most probable diagnosis for diarrhea, dementia, and dermatitis?** **PYQ: FMGE 2021****Answer:** Pellagra**Q4.2: What causes Pellagra?****Answer:** Niacin (B3) deficiency**Q4.3: Why not Cystinuria?****Answer:**

- Caused by defect in transporter for COLA: Cysteine, Ornithine, Lysine, Arginine
- Presents with recurrent renal stones (hexagonal)
- No neuro or GI features

Q4.4: Why not Alkaptonuria?**Answer:**

- Defect in Homogentisate oxidase
- Urine turns black on standing
- No diarrhea/dementia/dermatitis

Q4.5: Why not Porphyrria?**Answer:**

- Presents with neuropsychiatric symptoms or photosensitivity
- These symptoms not mentioned

Q4.6: What are the effects of thiamine deficiency on cardiovascular function?

Answer: Thiamine deficiency leads to lactic acidosis which acts as a vasodilator, causing arteriolar dilation and venoconstriction. This results in hypotension, tachycardia, edema, and high-output cardiac failure.

Q4.7: What causes cardiovascular symptoms in thiamine deficiency?

Answer: Lactic acidosis

Q4.8: What is the mechanism of edema in thiamine deficiency?**Answer:**

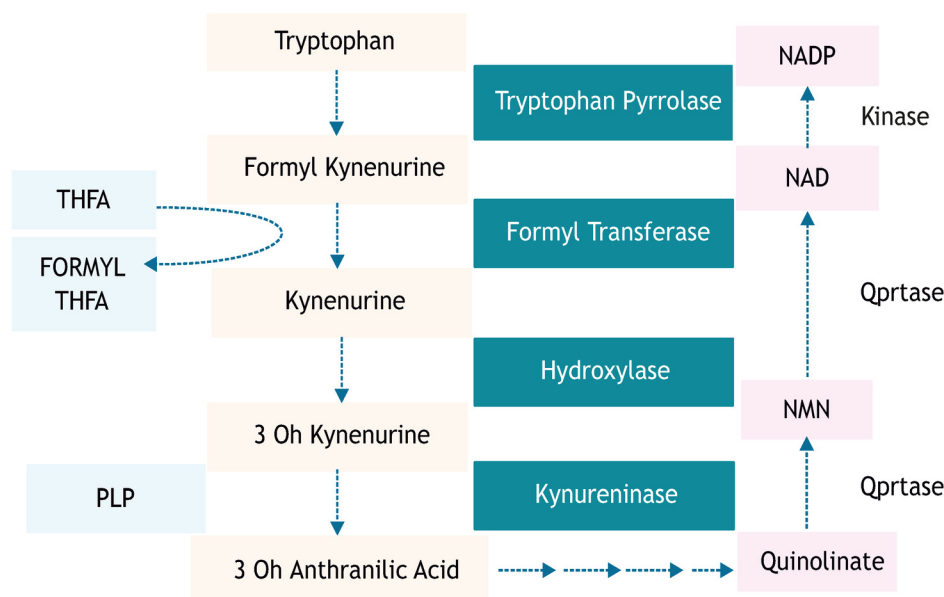
- Arteriolar dilation
- Hypotension & tachycardia
- Increased capillary hydrostatic pressure
- Peripheral edema

Q4.9: What is Wet Beri Beri?**Answer:**

- Cardiovascular form of thiamine deficiency
- Presents with edema and high-output cardiac failure

BIG QUESTION 5: How is tryptophan converted into niacin? (size 13, bold)

Broad Answer: Tryptophan undergoes a multi-step metabolic conversion to form niacin, involving enzymes such as tryptophan pyrrolase, formyltransferase, kynureninase (B6-dependent), and quinolinate phosphoribosyl transferase (QPRTase). Niacin is then converted into coenzyme forms: NMN, NAD, and NADP.

**DETAILED QUESTIONS****Q5.1: Which enzyme catalyzes the first step in the tryptophan to niacin pathway?**

Answer: Tryptophan → Formylkynurenine

- Enzyme: **Tryptophan Pyrrolase**

Q5.2: What enzyme catalyzes the conversion of Formylkynurenine to Kynurenine?**Answer:**

- Formyltransferase
- It converts Tetrahydrofolate (THFA) to N10-formyl THFA, contributing to the one-carbon pool

Q5.3: What happens to Kynurenine in the next step?**Answer:** Kynurenine → 3-Hydroxy Kynurenine

- Enzyme: Hydroxylase

Q5.4: What is the role of B6 in the tryptophan-niacin pathway?**Answer:**

- Enzyme: Kynureninase (requires Vitamin B6 / Pyridoxal phosphate)
- Catalyzes:
 - o 3-OH Kynurenine → 3-OH Anthranilic Acid
 - o Also acts in other step
- B6 deficiency leads to accumulation of precursors and failure to synthesize niacin

Q5.5: What happens to 3-OH Anthranilic Acid?**Answer:**

- Undergoes a series of non-enzymatic reactions
- Forms a ring structure called Quinolate

Q5.6: How is Quinolate converted to Niacin Mono Nucleotide (NMN)?**Answer:**

- Quinolate + Ribose 5 Phosphate → Niacin Mono Nucleotide
- Enzyme: Quinolate Phosphoribosyl Transferase (QPRTase)

Q5.7: How is Niacin Mono Nucleotide (NMN) further converted into NAD?**Answer:**

- Via action of another phosphoribosyl transferase
- Forms Nicotinamide Adenine Dinucleotide (NAD)

Q5.8: How is NAD converted into NADP?**Answer:**

- Enzyme: Kinase
- Converts NAD → NADP

Q5.9: What are the coenzyme forms of niacin?**Answer:**

- NMN (Niacin Mono Nucleotide)
- NAD (Nicotinamide Adenine Dinucleotide)
- NADP (Nicotinamide Adenine Dinucleotide Phosphate)

BIG QUESTION 6: What are the causes of Pellagra and how do they relate to tryptophan and niacin metabolism?

Broad Answer: Pellagra is caused by deficiencies or disruptions in niacin synthesis, tryptophan availability, or cofactor involvement (especially B6). It can also result from enzymatic inhibition by certain amino acids or diversion of tryptophan in specific diseases.

DETAILED QUESTIONS

Q6.1: What are the causes of Pellagra?

Answer:

1. **Dietary deficiency of Niacin**
2. **Dietary deficiency of Tryptophan** (e.g., maize-based diet)
3. **Tryptophan malabsorption**
 - o Seen in **Hartnup's disease**
 - o Presents with Pellagra-like symptoms
4. **Carcinoid syndrome**
 - o Tryptophan diverted to **serotonin synthesis**
 - o Depletes tryptophan for niacin production
5. **Vitamin B6 (Pyridoxine) deficiency**
 - o Kynureninase is B6-dependent
 - o Deficiency leads to **block in conversion** → Pellagra
6. **Excess Leucine**
 - o Inhibits **QPRTase**
 - o Seen in **Sorghum-based diet** (rich in Leucine)
 - o Results in **Leucine-induced Pellagra**

Q6.2: How does B6 deficiency contribute to Pellagra?

Answer:

- **Kynureninase** becomes inactive
- Kynurenine is diverted to **Xanthurenic acid**
- Elevated **Xanthurenic acid in urine** after tryptophan load
- Indicates **B6 deficiency** affecting tryptophan-niacin pathway

Q6.3: What lab investigations are useful in vitamin deficiency disorders?

Answer:

 PYQ: FMGE 2020, 2021

Vitamin Deficiency	Special Investigation	Condition
B1	RBC Transketolase activity	Wet Beriberi
B2	RBC Glutathione Reductase activity	Riboflavin
B6	Xanthurenic acid level after Tryptophan load	Pyridoxine
Folate	FIGLU level after Histidine load	Folate status
B12	Methylmalonic acid in urine after overnight fasting	B12 deficiency

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BIG QUESTION 7: What are the clinical manifestations of niacin deficiency (Pellagra)?

Broad Answer: Niacin deficiency presents with the classical triad of **diarrhea, dermatitis (photosensitive), and dementia**, known as the 3 D's of Pellagra. It may be seen in various nutritional or metabolic disorders.

DETAILED QUESTIONS**Q7.1: What is Cassal's necklace and what causes it?**

Answer:

- Hyperpigmented skin lesion in photo-exposed areas (neck)
- Pathognomonic of **niacin deficiency (Pellagra)**
- Called **Cassal's necklace**

Q7.2: A patient presents to the OPD with complaints of diarrhoea. The patient was later diagnosed with dementia and photosensitive dermatitis in sun-exposed areas. Which Vitamin deficiency is responsible for this condition?

Answer:

- **Niacin**
- Classical triad of Pellagra
- Diarrhea, Dementia, Dermatitis = **Niacin deficiency**

Q7.3: Given picture depicts the deficiency of?

🔍 PYQ: INICET 2022

🔍 PYQ: FMGE 2021

🔍 PYQ: NEET PG 2022



Answer:

Niacin

The picture depicts **Cassal's necklace**, a pathognomonic skin finding in **niacin deficiency**

Q7.4: A known patient of Tuberculosis on INH for six months presents with tingling sensation and paraesthesia. Deficiency of which of the following vitamins is the most probable cause?

Answer:

🔍 PYQ: NEET PG 2022

Vitamin B6

- **Isoniazid (INH)** inhibits **B6 metabolism**
- B6 deficiency causes **neuropathy (tingling, paresthesia)**

BIG QUESTION 8: What are the B6-dependent enzymes and the clinical consequences of their deficiency?

Broad Answer: Vitamin B6 (Pyridoxal Phosphate or PLP) is a coenzyme involved in numerous enzymatic reactions including transamination, decarboxylation, and glycogen breakdown. Deficiency leads to neurological symptoms, anemia, Pellagra-like features, and homocystinuria.

DETAILED QUESTIONS

Q8.1: Name the key B6-dependent enzymes.

Answer:

- Glycogen phosphorylase
- Transaminases → Breakdown of Ornithine (e.g., Ornithine aminotransferase)
- Decarboxylases → Gamma glutamate semialdehyde (e.g., Glutamate decarboxylase)
- Kynureninase (Tryptophan → Niacin pathway)
- Cystathionine beta synthase (Homocysteine → Cysteine)

Q8.2: What is the role of Ornithine aminotransferase and its clinical consequence?

Answer:

- Breaks down Ornithine → Glutamate semialdehyde → Glutamate → α -ketoglutarate → TCA cycle
- Derived from Arginine metabolism via Arginase
- Deficiency causes **Ornithine accumulation**, which is **toxic to retinal pigment epithelium** → **Gyrate Atrophy of Retina**

Q8.3: How is Gyrate Atrophy of Retina managed?

Answer: Ornithine is avoided from accumulation by:

- Arginine-restricted diet
- Ornithine-restricted diet
- **B6 supplementation**

Q8.4: What is the role of Glutamate decarboxylase (GAD) in seizures?

Answer:

- Converts Glutamate → GABA (inhibitory neurotransmitter)
- B6 deficiency → ↓ GABA and ↑ Glutamate → **Seizures**

Q8.5: How is neonatal seizure treated when calcium gluconate fails?

Answer:

- Consider structural/metabolic causes
- A shot of vitamin **B6** → Glutamate (present in synapse) becomes GABA → Reduced seizure.

Q8.6: What is the role of B6 in heme synthesis?

Answer:

- First step: Glycine + Succinyl CoA → ALA via **ALA Synthase** (B6-dependent)
- Deficiency leads to impaired heme synthesis → **Anemia**
- **Responsive to B6 therapy**

Q8.7: How does B6 deficiency cause Pellagra?

Answer:

- Kynureninase (B6-dependent) is involved in Tryptophan → Niacin
- Deficiency → Pellagra
- **Pellagra responds to B6 administration**

Q8.8: What is the role of B6 in homocysteine metabolism?**Answer:**

- Homocysteine + Serine → Cystathionine via **Cystathionine β-synthase** (B6-dependent)
- Cystathionine → Cysteine via Cystathioninase
- Deficiency causes **Homocystinuria**
 - o Causes accelerated atherosclerosis and thrombosis.

Q8.9: What are the types and features of Homocystinuria?**Answer:**

- **Type 1 (Major fate defect):** Cystathionine β-synthase deficient
 - o Low Cysteine, High Methionine
 - o Responds to **B6**
- **Type 2 (Minor fate defect):** Methionine synthase (B12-dependent)
 - o Low Methionine, High Cysteine
 - o Responds to **B12 + Folate**

Q8.10: A 4-year-old child with mental retardation, Charley Chaplin gait, ectopia lentis, ↑Homocysteine & Methionine, ↓Cysteine. Likely diagnosis?**Answer:** Homocystinuria type 1**Q8.11: Sideroblastic anemia is treated with?****Answer:** Vitamin B6
 PYQ: INICET 2021
Q8.12: Twins with chorioretinal atrophy were diagnosed with Gyrate atrophy. True about the disorder?

- A. Responds to Arginine supplementation
- B. Responds to PLP supplementation
- C. Low ornithine levels
- D. Enzyme defective is Ornithine transcarbamylase

Answer: B. Responds to PLP supplementation

- Gyrate atrophy of the choroid and retina is caused by the defect of Ornithine aminotransferase and elevated Ornithine levels

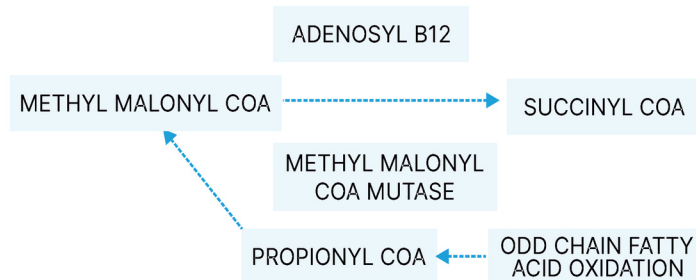
Q8.13: A woman with tingling and numbness taking vitamin supplements. Cause?**Answer:** Hypervitaminosis B6**BIG QUESTION 9: What are the biochemical and clinical features of B12 and folate deficiency?**

Broad Answer: Vitamin B12 has two forms (Methyl and Adenosyl B12) involved in homocysteine metabolism and fatty acid degradation. Its deficiency leads to neurologic deficits, methylmalonic aciduria, and megaloblastic anemia. Folate deficiency impairs DNA synthesis and causes macrocytic anemia.

DETAILED QUESTIONS**Q9.1: What is the role of Adenosyl B12?****Answer:**

- Coenzyme for **Methylmalonyl-CoA Mutase**

- Odd chain fatty acids → Propionyl CoA → Succinyl CoA
- Deficiency → **Methylmalonic aciduria** → Abnormal myelin → Neuropathy (Demyelination - Starts from peripheral nerves)



Q9.2: What is the clinical progression of B12 deficiency?

Answer:

- Starts with **peripheral sensory neuropathy** (tingling)
- Then affects **posterior column + spinothalamic**
- Ends in **Subacute combined degeneration of spinal cord**

Q9.3: What is the role of Methyl B12 in methylation?

Answer:

- Coenzyme for **Methionine synthase**: Homocysteine → Methionine → SAM
 - B12 deficiency → No Methyl B12 & Methionine synthase → Homocysteine accumulates (Homocystinuria).
- SAM used for transmethylation: **Creatine, Choline, Epinephrine**

Q9.4: What is the Methyl Folate Trap?

Answer:

- B12 deficiency → low activity of Methionine synthase → THFA trapped as **Methyl THFA** → Functional deficiency of THFA
- THFA not available for Purine/Pyrimidine synthesis → Functional folate deficiency

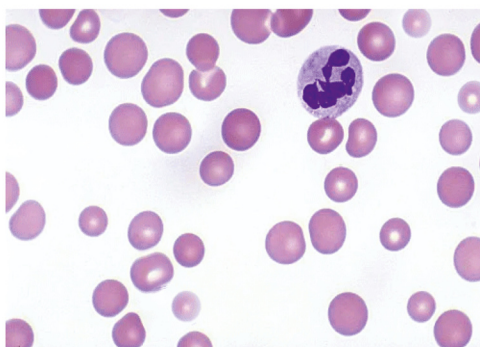
Q9.5: What is the effect of Folate deficiency?

Answer:

- No THFA → Uridine → Thymidine
- No Purine ring (C2, C8)
- No Purine & Pyrimidine → No Replication → No cell division → **Macrocytic anemia**

Q9.6: Vegetarian with anemia and hypersegmented neutrophil. Likely diagnosis?

Answer: Megaloblastic anemia



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Q9.7: Which vitamin deficiency causes Methyl THFA accumulation?

PYQ: INICET 2021

Answer: B12**Q9.8: Which of the following enzyme activities can be estimated in RBCs to diagnose Vitamin B2 deficiency?**

- A. Transketolase
- B. Glutathione reductase
- C. Kynureninase
- D. Pyruvate dehydrogenase

Answer: B. Glutathione reductase

- Vitamin B2 is otherwise called as Riboflavin
- Enzyme activity that can be estimated - RBC Glutathione reductase (Ribbon and Glue)

Q9.9: Which enzyme activity is low in Riboflavin deficiency?

PYQ: FMGE 2021

- A. Transketolase
- B. Glycogen phosphorylase
- C. Propionyl CoA carboxylase
- D. Glutathione reductase

Answer: D. Glutathione reductase

- Transketolase activity is low in Thiamine deficiency
- Glycogen phosphorylase activity is low in B6 deficiency
- All carboxylases need Biotin
- Propionyl CoA carboxylase activity will be low in Biotin deficiency

Q9.10: Which nutrients play a role in collagen maturation?**Answer:** Copper and Ascorbic acid**BIG QUESTION 10: What are the structural components, maturation steps, and clinical relevance of Collagen?**

Broad Answer: Collagen is a triple helical protein composed of three polypeptide chains. It undergoes essential post-translational modifications—particularly hydroxylation and cross-linking—that require vitamins C and copper. Deficiencies in these nutrients disrupt collagen maturation and result in clinical manifestations like bleeding.

DETAILED QUESTIONS**Q10.1: What is the basic structural composition of collagen?****Answer:**

- Collagen is a **triple helix**
- Made of **three polypeptide chains**
- Each chain has **~ 1000 amino acids**
- Composed of repetitive **(Glycine-X-Y)_n** sequences
- **Glycine** makes up **1/3rd of amino acids**
- **X and Y** positions often contain **Proline or Lysine**

Q10.2: What are the post-translational modifications that collagen undergoes?**Answer:**

- **Hydroxylation of Proline and Lysine:**
 - Enzymes: **Prolyl hydroxylase** and **Lysyl hydroxylase**
 - Require **Vitamin C** as a cofactor
- **Oxidation of hydroxylysine residues:**
 - Enzyme: **Lysyl oxidase**
 - Forms **aldemine cross-linkages** for collagen maturation
 - Requires **Copper** as a cofactor

Q10.3: What is the clinical effect of Vitamin C deficiency on collagen?**Answer:**

- Weak collagen cross-linking
- Leads to **weak subendothelial tissue**
- Causes **bleeding disorders**

BIG QUESTION 11: What is the structure, function, and clinical relevance of Vitamin A and its deficiency?

Broad Answer: Vitamin A exists in several forms: retinol, retinal, and retinoic acid. It is essential for vision, epithelial maintenance, and immune function. Its deficiency causes xerophthalmia, Bitot's spots, and keratomalacia.

DETAILED QUESTIONS**Q11.1: What are the different forms of Vitamin A and their significance?****Answer:**

Form	Type	Function
Retinol	Alcohol	Absorption, transport, storage
Retinal	Aldehyde	Vision (present in rhodopsin)
Retinoic Acid	Acid	Cell growth and differentiation

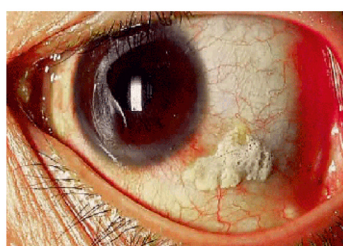
- **All-trans retinoic acid** → Growth & differentiation
- **13-cis retinoic acid** → Suppresses keratinization, induces apoptosis of sebaceous glands

Q11.2: What are the clinical manifestations of Vitamin A deficiency?**Answer:**

- Loss of **13-cis retinoic acid** → **Phrynoderma** (follicular hyperkeratosis)
- Conjunctival **xerosis** due to keratinization
- **Bitot's spots** → keratin debris on conjunctiva
- **Keratomalacia** → corneal softening → ulcer → scar

Q11.3: Which of the following Vitamin deficiencies causes the condition shown in the image?

Answer: Vitamin A as Bitot's spots are pathognomonic of Vitamin A deficiency.



? PYQ: NEET PG 2022

? PYQ: FMGE 2021

Q11.4: Which condition is treated using 13-cis retinoic acid?**Answer:** Resistant Acne**Q11.5: Vitamin A deficiency leads to?**

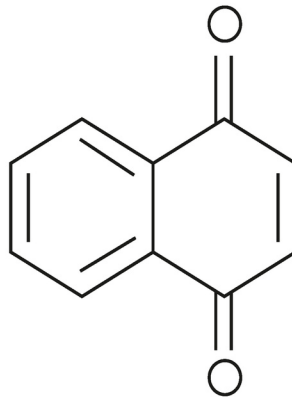
- A. Xerophthalmia
- B. Beri- Beri
- C. Pellagra
- D. Neuropathy

Answer: A. Xerophthalmia

- Beri Beri is caused by Thiamine deficiency
- Pellagra is caused by Niacin deficiency
- Neuropathy is caused by B1/B3/B6/B12 deficiency

BIG QUESTION 12: What are the structure, forms, and clotting-related functions of Vitamin K?

Broad Answer: Vitamin K is a lipid-soluble vitamin with different side chain lengths (K1, K2). It is essential for γ -carboxylation of clotting factors and bone proteins. Warfarin inhibits its recycling.

**DETAILED QUESTIONS****Q12.1: What are the forms of Vitamin K and how are they classified?****Answer:**

- **Vitamin K1 (Phylloquinone)** → 20-carbon isoprenoid side chain
- **Vitamin K2 (Menaquinone)** → 30-carbon isoprenoid side chain
- **Menadione** → No side chain; water-soluble
 - o Can be prescribed to bleeding due to fat malabsorption

Q12.2: What is the functional role of Vitamin K?**Answer:**

- Acts as **coenzyme** for γ -carboxylase
- Required for:
 - o Clotting factors: II, VII, IX, X
 - o Proteins: C, S, Osteocalcin
- **Hydroquinone** form is active
- Gets oxidized to **epoxide** form
- Regenerated by **epoxide reductase**

Q12.3: How does Warfarin act on Vitamin K metabolism?

Answer:

- Warfarin **inhibits epoxide reductase**
- Prevents regeneration of **hydroquinone form**
- Inhibits **γ -carboxylase activity** → Clotting factors remain inactive

Q12.4: Which vitamin deficiency is associated with fat malabsorption and bleeding? A woman with antidepressant use presents with bleeding and bulky stools sticking to the pan. Which deficiency is the likely cause?

Answer:

Vitamin K

Fat malabsorption leads to vitamin K deficiency → bleeding

BIG QUESTION 13: What are the key metabolic pathways and disorders of Tyrosine metabolism?

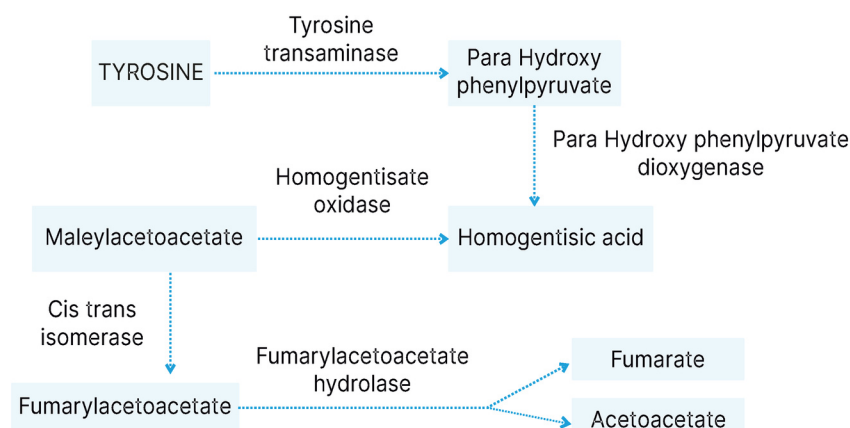
Broad Answer: Tyrosine metabolism involves a series of enzymatic reactions leading to the formation of fumarate and acetoacetate. Defects in these enzymes result in specific metabolic disorders like Tyrosinemia types I, II, III and Alkaptonuria, each with distinct clinical presentations and enzymatic deficiencies.

DETAILED QUESTIONS

Q13.1: What are the initial steps and enzymes in Tyrosine metabolism?

Answer:

- Tyrosine is acted upon by **Tyrosine transaminase** to form para-hydroxyphenylpyruvate.
- Para-hydroxyphenylpyruvate is converted to homogentisic acid by **para-hydroxyphenylpyruvate dioxygenase**.
- Homogentisic acid is converted to maleylacetoacetate by **homogentisate oxidase**.
- Maleylacetoacetate is converted to fumarylacetoacetate by **cis-trans isomerase**.
- Fumarylacetoacetate is broken down to fumarate and acetoacetate by **fumarylacetoacetate hydrolase**.



Q13.2: What is the cause and clinical presentation of Type I Tyrosinemia?

Answer:

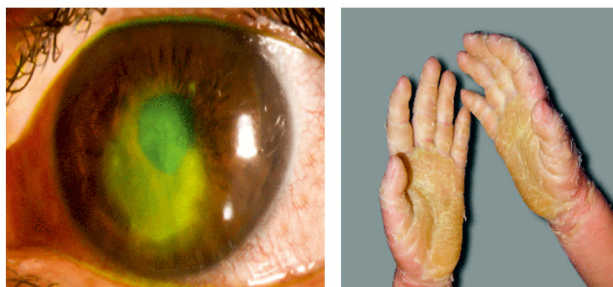
- **Cause:** Deficiency of **Fumarylacetoacetate hydrolase**.
- **Accumulated metabolite:** Fumarylacetoacetate → converted to **Succinylacetone**.
- **Effects:**
 - o Hepatorenal syndrome: Damaged liver and parenchymal cells → Jaundice, hepatomegaly, hypoglycemia, cirrhosis, HCC.
 - o Renal: Parenchymal cells damaged → Fanconi syndrome progressing to CKD.
 - o CNS: Succinylacetone inhibits ALA dehydratase → ALA accumulation (neurotoxic) → Porphyria-like features.

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Q13.3: What are the features and enzyme deficiency in Type II Tyrosinemia?

Answer:

- Also known as: Occulocutaneous syndrome / Richner-Hanhart syndrome.
- Deficiency: Tyrosine transaminase.
- Features:
 - Ocular: Painful corneal erosions.
 - Cutaneous: Palmar hyperkeratosis.



Q13.4: What are the features and enzyme defect in Type III Tyrosinemia?

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Answer:

- Deficiency enzyme: Para-hydroxyphenylpyruvate dioxygenase.
- Features: Recurrent seizures, intermittent ataxia.
- Cause: Loss of function mutation.
- Note: Gain of function mutation → Hawkinsinuria.

Q13.5: What drug is used in Type I Tyrosinemia and why?

Answer:

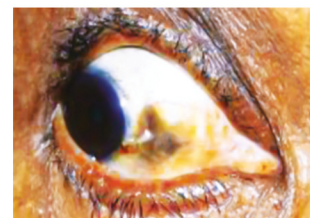
- Drug: Nitisinone
- Action: Inhibits para-hydroxyphenylpyruvate dioxygenase.
- Effect: Prevents formation of fumarylacetoacetate → no succinylacetone → no hepatocellular damage.

Q13.6: What is the defect and clinical presentation of Alkaptonuria?

PYQ: INICET 2023 PYQ: NEET PG 2022

Answer:

- Defect: Homogentisate oxidase deficiency.
- Accumulated metabolite: Homogentisic acid → oxidizes to benzoquinone acetate → polymerizes to melanin-like fibrils.
- Clinical Features:
 - Dark urine (turns dark on standing) → First symptom.
 - Pigmentation: Pinna, nose tip, thenar/hypothenar, mucus membrane.
 - Osler's sign: Pigmentation along medial/lateral rectus attachment → First sign
 - Joint/cartilage damage → Ochronosis, intervertebral disc bulges.
- Treatment: Nitisinone (prevents homogentisic acid accumulation).



Osler's sign

Q13.7: An infant presented with watering of the eye, incessant cry, and on observation, tiny corneal erosions. Rough palm was observed. The probable diagnosis is:

Answer:

Type II Tyrosinemia

Painful corneal erosions + palmar hyperkeratosis → Occulocutaneous syndrome → Type II Tyrosinemia

Q13.8: What is Hawkinsinuria?**Answer:**

- Caused by **gain of function** mutation in **para-hydroxyphenylpyruvate dioxygenase**.

Q13.9: What are the indications for Nitisinone?**Answer:**

- Type I Tyrosinemia
- Hawkinsinuria
- Alkaptonuria

Q13.10: Give a summary on Tyrosinemia Types and Alkaptonuria**Answer:**

Disorder	Enzyme Deficiency	Features	Treatment
Type I Tyrosinemia	Fumarylacetoacetate hydrolase	Hepatorenal syndrome, succinylacetone toxicity, neuro sx	Nitisinone
Type II Tyrosinemia	Tyrosine transaminase	Corneal erosions, palmar hyperkeratosis (Occulocutaneous syndrome)	Dietary management
Type III Tyrosinemia	Para-hydroxyphenylpyruvate dioxygenase	Seizures, ataxia	Nitisinone
Alkaptonuria	Homogentisate oxidase	Pigmented tissues, black urine, ochronosis, joint degeneration	Nitisinone

Q13.11: What are the key differences between adenosyl and methyl B12 deficiency and folate deficiency?**Answer:**

Adenosyl B12 deficient	Methyl B12 deficient
• Methyl malonic aciduria • Causes Neurological manifestations	• Methionine synthase is deficient • Causes Homocysteinuria • Methyl Folate Trap → Macrocytic anaemia due to functional deficiency of THFA

Q13.12: A person who follows a strict vegan diet presents with macrocytic anemia. Another individual, who consumes a predominantly non-vegetarian diet with inadequate fiber intake, also presents with macrocytic anemia. What could be the likely diagnoses in each of these two scenarios?

Answer: A person following a vegan diet presents with macrocytic anemia, likely due to vitamin B12 deficiency, while another individual on a non-vegetarian diet with inadequate fiber intake presents with macrocytic anemia, most likely caused by folate deficiency.

B12 deficiency	Folate deficiency
• Methyl Malonic aciduria • Presents with neurological manifestations • Common in Veganism	• FIGLU levels will be elevated in urine after Histidine load • Does not present with Neurological manifestations • Occurs when the person doesn't take adequate vegetables



7. CLINICAL BIOCHEMISTRY PART- 1

BIG QUESTION 1: Write briefly about ABG Interpretation.

Broad Answer: The underlying primary acid-base disorder is first identified by determining if the pH is low (acidic) or high (basic). Then, subsequently, we determine whether it is metabolic or respiratory in nature by interpreting the values of plasma HCO_3^- and pCO_2 . Finally, we calculate for compensation, if any.

DETAILED QUESTIONS

Q1.1: Identify the acid-base disorder in a patient with the following values:

PYQ: NEET PG 2022

- Blood pH: 7.2
- pO_2 : 90 mmHg
- pCO_2 : 80 mmHg
- Plasma HCO_3^- : 35 mEq/L

- A. Respiratory acidosis
- B. Respiratory alkalosis
- C. Metabolic acidosis
- D. Metabolic alkalosis

Answer: A. Respiratory acidosis

Explanation:

- Normal ranges:
 - o Normal blood pH: 7.36-7.44
 - o Normal pCO_2 : 36-44 mmHg
 - o Normal HCO_3^- : 21-27 mEq/L

Step 1: pH

- < 7.36 : Acidosis
- > 7.44 : Alkalosis
- The normal range does not exclude an acid-base disorder
- For example, mixed acid-base disorders like coexistence of metabolic acidosis and metabolic alkalosis can cause a normal pH, eg, a Type 2 diabetic individual dines out and presents with vomiting
 - o Outside eating causes vomiting
 - o Vomiting leading to metabolic alkalosis (dehydration-induced secondary hyperaldosteronism)
 - o GI distress causes Diabetic ketoacidosis, which causes metabolic acidosis

Step 2: Is it Metabolic or Respiratory?

- Interpret Bicarbonate and pCO_2 values
- Bicarbonate is a major plasma buffer that neutralises metabolic acids
 - o Low HCO_3^- levels lead to Metabolic acidosis
 - o High HCO_3^- levels lead to Metabolic alkalosis

- Carbon dioxide is a source of acid
 - High $p\text{CO}_2$ levels cause Respiratory acidosis
 - Low $p\text{CO}_2$ levels cause Respiratory alkalosis

Q1.2: Interpret ABG report

Blood pH: 7.30

$p\text{CO}_2$: 29 mmHg

Plasma HCO_3^- : 14 mEq/L

- A. Compensated metabolic acidosis
- B. Uncompensated metabolic acidosis
- C. Compensated respiratory acidosis
- D. Uncompensated respiratory acidosis

Answer: B. Uncompensated metabolic acidosis

Step 3: Basis of compensation

- If the primary defect is metabolic, compensation is done by the lungs
- For example, if the primary defect is Metabolic acidosis (low HCO_3^-), the lungs reduce $p\text{CO}_2$ levels
- In acidosis, Central chemoreceptors in the medulla are stimulated (by H^+ ions in CSF)
- Which activates the respiratory centre and hyperventilates
- CO_2 is washed out by hyperventilation, i.e Kussmaul breathing

Rule 1:

- Compensation is always parallel
- If the primary defect is a decrease in HCO_3^- , the compensation effect is a decrease in $p\text{CO}_2$ and Vice versa
- If the primary defect is an increase in $p\text{CO}_2$, the compensation effect is an increase in HCO_3^- and Vice versa

Rule 2:

- Only for respiratory disorders, there is always an **acute** and **chronic** compensation
- In respiratory acidosis, low pH, increased $p\text{CO}_2$, compensation is by an increase in HCO_3^-
- First response by **Chemical equilibrium shift** by Buffer system (Acute compensation)
 - $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-$
 - For every mole increase in CO_2 , there is a corresponding increase in HCO_3^-
- Second response by Kidneys (Chronic compensation):
 - In acidosis, the kidney reclaims more amounts of HCO_3^-

Q1.3: Describe the formulae for calculating compensation in metabolic disorders.

Answer:

Condition	pH	HCO_3^-	Compensation	Expected $p\text{CO}_2$
Metabolic acidosis	Low	Low	Reduce $p\text{CO}_2$	$p\text{CO}_2 = 1.5 \times \text{HCO}_3^- + 8$ (Winters formula)
Metabolic alkalosis	High	High	Increase $p\text{CO}_2$	$p\text{CO}_2 = 0.9 \times \text{HCO}_3^- + 16$

- For example, in a patient's ABG:
 - pH = 7.33 (acidosis)
 - $\text{HCO}_3^- = 18$ mEq/L (Metabolic)
 - Expected $p\text{CO}_2 = 1.5 \times 18 + 8 = 35$ mmHg

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- o If the actual $p\text{CO}_2$ in the ABG report is 40mmHg, it is 2 uncompensated
- o If the actual $p\text{CO}_2$ in the ABG report is 35mmHg, it is compensated
- o If the actual $p\text{CO}_2$ in the ABG report is 30mmHg, it is not overcompensation
 - There is a Hidden acid-base disorder (Respiratory alkalosis) due to washed-out CO_2 (Hyperventilation)
 - This condition has both Metabolic acidosis + Respiratory alkalosis
 - The body never overcompensates → Always in the Uncompensated or compensated stage.

Q1.4: Describe the formulae for calculating compensation in respiratory disorders.**Answer:**

- Acute and chronic compensation

Disorder	Acute	Chronic
Respiratory acidosis	1	3.5
Respiratory alkalosis	2	5

- In Respiratory acidosis, $p\text{CO}_2$ is increased
 - o For every 10 mmHg rise in $p\text{CO}_2$
 - o HCO_3^- value
 - Acute: Elevated by 1 mEq/L
 - Chronic: Elevated by 3.5 mEq/L
- In Respiratory alkalosis, $p\text{CO}_2$ is decreased
 - o For every 10 mmHg decline in $p\text{CO}_2$
 - o HCO_3^- value reduced by
 - Acute: 2 mEq/L
 - Chronic: 5 mEq/L

Q1.5: In a COPD patient (accumulation of CO_2) with $p\text{CO}_2 = 60$ mmHg and pH of 7.33. What is the type of compensation seen if the actual $p\text{CO}_2$ is:

- A. 24 mm Hg
- B. 30 mm Hg
- C. 35 mm Hg

Answer:

- Expected HCO_3^- = Increased by 7 = $24+7 = 31 \pm 1$ mEq/L (30-32)
- If actual $p\text{CO}_2$ is 24 mmHg: Uncompensated Chronic Respiratory acidosis
- If actual $p\text{CO}_2$ is 30 mmHg: Compensated Chronic Respiratory acidosis
- If actual $p\text{CO}_2$ is 35 mmHg: Hidden acid base disorder (Chronic Respiratory acidosis with Metabolic alkalosis)

Q1.6: Interpret the ABG report:

- Blood pH: 7.30
- $p\text{CO}_2$: 29 mmHg
- Plasma HCO_3^- : 14 mEq/L

- A. Compensated metabolic acidosis
- B. Uncompensated metabolic acidosis
- C. Compensated respiratory acidosis
- D. Uncompensated respiratory acidosis

Answer: A. Compensated metabolic acidosis

Explanation:

- Expected $pCO_2 = 1.5 \times HCO_3^- + 8 = 1.5 \times 14 + 8 = 29$ mmHg
- Step 1: Acidosis or alkalosis, Low pH
- Step 2: Primary metabolic disorder (Metabolic or respiratory), low HCO_3^-
- Step 3: Hidden disorder (calculate compensation), 29 mmHg
- Step 4: Only if Metabolic acidosis, calculate the Anion gap

Q1.7: Interpret the ABG report:

- Blood pH: 7.30
- pCO_2 : 29 mmHg
- Plasma HCO_3^- : 14 mEq/L
- Na^+ : 130 mEq/L
- Cl^- : 90 mEq/L

- A. Compensated increased anion gap metabolic acidosis
- B. Uncompensated increased anion gap metabolic acidosis
- C. Compensated normal anion gap metabolic acidosis
- D. Uncompensated normal anion gap metabolic acidosis

Answer: A. Compensated increased anion gap metabolic acidosis

Explanation:

Expected $pCO_2 = 1.5 \times HCO_3^- + 8 = 1.5 \times 14 + 8 = 29$ mmHg

- Step 1: Acidosis or alkalosis, Low pH
- Step 2: Primary metabolic disorder (metabolic or respiratory), low HCO_3^-
- Step 3: Hidden disorder (calculate compensation), 29 mmHg
- Step 4: Calculate the Anion gap (Only if Metabolic acidosis)

Step 4: Anion gap**BIG QUESTION 2: How do you calculate anion gap?****Broad Answer:**

- In any physiological solution, the sum of anions is equal to the sum of cations
- The anion gap is the difference between Unmeasured anions and unmeasured cations
- Anion gap = $[Na^+] - [(Cl^-) + (HCO_3^-)]$
- Normal anion gap : 12 ± 2 mEq/L
- It is used to find the cause of Metabolic acidosis

DETAILED QUESTIONS**Q2.1: What are the cations and anions of plasma?****Answer:**

- Cations of plasma:
 - o Na^+ (majority)
 - o K^+ (negligible)
 - o Unmeasured cations
- Anions in plasma:
 - o Cl^-

- o HCO_3^-
- o Unmeasured anions
- Cations $[(\text{Na}^+) + (\text{Unmeasured cations})] = \text{Anions } [(\text{Cl}^-) + (\text{HCO}_3^-)] (\text{Unmeasured anions})$

Q2.2: What is the equation for the anion gap?

Answer:

- Anion gap = $[\text{Na}] - [(\text{Cl}) + (\text{HCO}_3^-)]$

Q2.3: What is the normal anion gap?

Answer:

- Normal anion gap : $12 \pm 2 \text{ mEq/L}$

Q2.4: What is the purpose of finding the anion gap?

Answer:

It is used to find the cause of metabolic acidosis

Q2.5: Name the conditions in which an increased anion gap is seen.

Answer:

- Ketoacids
- Lactic acids
- Uric acids
- Alcohol (Methanol, Ethanol, Ethylene glycol)
- Salicylic acids
- Chronic kidney disease

Q2.6: Name the conditions in which a normal anion gap is seen.

Answer:

- Normal anion gap, due to GI or urinary loss:
 - o GI loss of HCO_3^-
 - Diarrhea
 - Ureterosigmoidostomy
 - o Urinary loss of HCO_3^-
 - Renal tubular acidosis (Type I, II, IV)
 - Anion gap = $\text{Na} - (\text{Cl} + \text{HCO}_3^-)$

BIG QUESTION 3: What is the underlying mechanism of metabolic acidosis?

Broad Answer: Metabolic acidosis, which is characterised by a decrease in bicarbonate, is because of two reasons: Increased utilisation of HCO_3^- , due to abnormal acid production and loss of HCO_3^-

DETAILED QUESTIONS

Q3.1: Explain how increased use of HCO_3^- in the body causes metabolic acidosis in the body.

Answer:

- Abnormal acids represented by HA

- $\text{HA} + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 + \text{A}^-$
- Every mole of Acid (HA) needs 1 mole of HCO_3^-
- Unmeasured anion (UMA) concentration increases

Q3.2: What are the sources of abnormal acids?

Answer:

- Ketoacidosis
 - DKA: increased acetoacetate concentration
 - Starvation ketosis: increased β -hydroxybutyrate concentration
- Lactic acidosis
- Uric acidosis
- Alcohol poisoning
 - Methanol: Formaldehyde $\rightarrow$ Formic acid $\rightarrow$ Formate anion
 - Ethanol: Acetaldehyde $\rightarrow$ Acetic acid $\rightarrow$ Acetate anions
 - Ethylene glycol (Antifreeze): Alcohol dehydrogenase $\rightarrow$ Aldehyde dehydrogenase $\rightarrow$ Oxalic acid $\rightarrow$ Oxalate anions
- Kidney failure, failure to secrete metabolic acids, and corresponding anions increase

Q3.3: Explain how loss of HCO_3^- results in metabolic acidosis.

Answer:

- Loss is by the GIT or the kidney
- GIT loss is due to
 - Diarrhea
 - $\rightarrow$ Intestinal mucus rich in HCO_3^- is lost (intestinal cells secrete more HCO_3^- into the intestinal lumen $\rightarrow$ through $\text{HCO}_3^- - \text{Cl}^-$ Antiporter)
 - $\rightarrow$ Loss of major plasma buffer causes metabolic acidosis
 - $\rightarrow$ The ureter is transplanted into the sigmoid colon
 - $\rightarrow$ Excess mucus production causes loss of bicarbonate through the GIT
- Renal loss is due to Renal tubular acidosis.
 - In PCT acidosis or Fanconi's syndrome, reclamation of HCO_3^- is absent, and Na^+ reabsorption also fails
 - To maintain osmotic balance, the body reclaims chloride anions along with Na^+ in the early DCT
 - Plasma Cl^- concentration increases
 - Hyperchloremic Metabolic Acidosis (GIT or kidney) is seen, anion gap is normal

Q3.4: What is Hyperchloremic Metabolic Acidosis?

Answer:

- Loss of HCO_3^- by the GIT or kidneys
- Metabolic acidosis is due to increased elimination of HCO_3^-
- Compensated by Chloride ions
- In the ABG report, the Anion gap is normal
 - Anion gap is considered only in Metabolic acidosis

Q3.5: Interpret the ABG report

- Blood pH: 7.30
- pCO_2 : 29 mmHg

YOURWISH

- Plasma HCO_3^- : 14 mEq/L
- Na^+ : 130 mEq/L
- Cl^- : 90 mEq/L

- A. Compensated increased anion gap metabolic acidosis
- B. Uncompensated increased anion gap metabolic acidosis
- C. Compensated normal anion gap metabolic acidosis
- D. Uncompensated normal anion gap metabolic acidosis

Answer: A. Compensated increased anion gap metabolic acidosis

Explanation:

Normal anion gap, 12 ± 2 , if K is not included

Anion gap = $130 - (90 + 14) = 26 \text{ mEq/L}$

$26 > 12 \pm 2$, increased anion gap

Q3.6: Severe vomiting leads to

- A. Hypokalemia
- B. Hypochloremia
- C. Metabolic alkalosis
- D. Respiratory alkalosis

 PYQ: INICET 2023

Answer: A, B, C

- A. Hypokalemia
- B. Hypochloremia
- C. Metabolic alkalosis

Vomiting-induced dehydration leads to low chloride delivery to DCT (hypochloremia), which activates RAAS, which leads to secondary hyperaldosteronism, which leads to reabsorption of sodium and water, and secretion of potassium (Hypokalemia) and hydrogen ions (metabolic alkalosis).

Q3.7: A 60-year-old diabetic patient with repeated vomiting following a recent dine-out. Her blood pressure was 90/60 mmHg

 PYQ: NEET PG 2022

- pH: 7.3
- HCO_3^- : 18 mEq/L
- pCO_2 : 35 mmHg

Identify the acid-base disorder:

- A. Metabolic Acidosis
- B. Metabolic Alkalosis
- C. Respiratory Alkalosis
- D. Respiratory Acidosis

Answer: A. Metabolic Acidosis

Explanation:

- Vomiting, metabolic alkalosis
- pH, acidosis
- Diabetic with stress, DKA

Q3.8: A 7-week-old baby was brought by the mother with complaints of repeated projectile vomiting and pellet stools. The probable metabolic disturbance is:

 PYQ: NEET PG 2022

- A. Normal anion gap metabolic acidosis
- B. Hypochloremic hypokalemic metabolic alkalosis
- C. Hyperchloremic hypokalemic metabolic alkalosis
- D. Respiratory acidosis

Answer: B. Hypochloremic hypokalemic metabolic alkalosis

Q3.9: The interpretation of the following ABG value is?

 PYQ: INICET 2024

pH-7.34

Na-135meq/L

Cl - 93 meq/L

HCO_3^- - 20meq/L

- A. Normal anion gap metabolic acidosis
- B. High anion gap respiratory acidosis
- C. Increased anion gap metabolic acidosis
- D. Normal anion gap respiratory acidosis

Answer: C. Increased anion gap metabolic acidosis

- Anion gap = $135 - (93 + 20)$
- $135 - 113 = 21$
- High anion gap

Q3.10: The interpretation of the following ABG value is:

pH: 7.5

pCO₂: 50mm Hg

HCO_3^- : 30meq/L

- A. Metabolic acidosis
- B. Metabolic alkalosis
- C. Respiratory acidosis
- D. Respiratory alkalosis

Answer: B. Metabolic alkalosis

Q3.11: A hyperventilating hysterical woman presents with carpopedal spasm. The cause is:

 PYQ: NEET PG 2022

- A. High total calcium
- B. Low total calcium
- C. Alkalosis
- D. Acidosis

Answer: C. Alkalosis

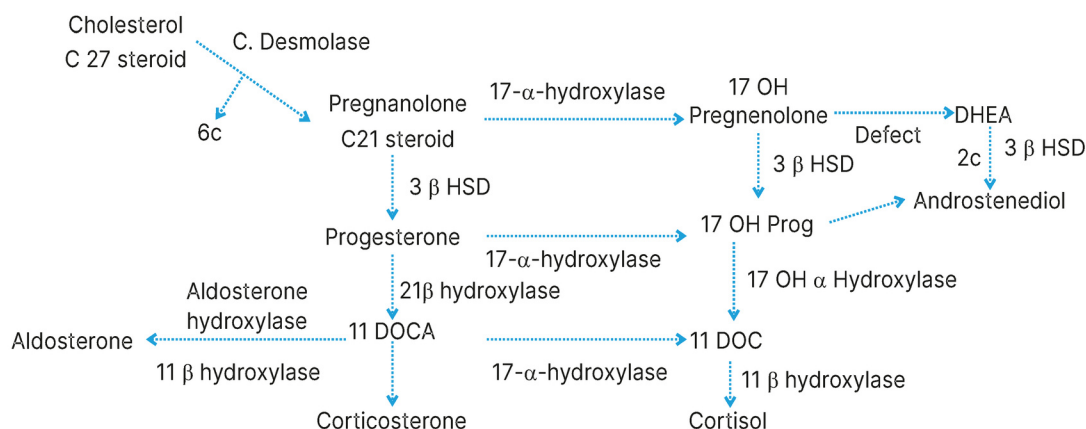
Explanation:

- Respiratory alkalosis is seen
- pH is high
- All plasma proteins buffer, neutralise alkaline pH
- Proteins lose H⁺, charged

- Calcium has bound or free-form
- Bound to either inorganic anions or plasma proteins
- Free calcium is the active form that stabilises the resting membrane potential
- In respiratory alkalosis, because all plasma proteins are negatively charged (because albumin is negatively charged) bind more calcium
- Free calcium concentration is reduced, and neurons are hyperstimulated
- This causes carpopedal spasm

Q3.12: What is Congenital Adrenal Hyperplasia?

Answer:

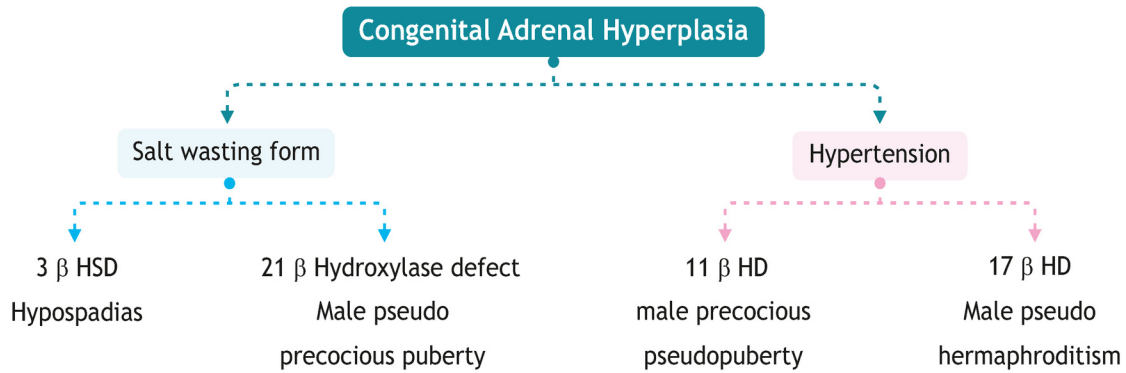


C21 steroids	C19 steroids	C18 steroids
• Progesterone • Aldosterone • Cortisol	• DHEA • Androstenedione • Testosterone • DHT	• Estrone • Estradiol • Estriol

Defects:

- Cholesterol desmolase defect: Death in utero.
- 3-Beta-hydroxy steroid dehydrogenase defect: Congenital adrenal hyperplasia and excess DHEA in a female fetus causes virilisation (Female pseudo-hermaphroditism)
- Defects in male external genitalia, like hypospadias, are seen in male fetuses.
- Salt wasting forms due to aldosterone absence.

3-β hydroxy steroid dehydrogenase defect	Salt wasting form of CAH + Female pseudo hermaphroditism + male hypospadias
21-β hydroxylase defect	Salt wasting form of CAH + female pseudohermaphroditism + male precocious pseudo puberty
11 β-hydroxylase defect	CAH (hypertensive) + female pseudohermaphroditism + male precocious pseudopuberty
17-hydroxylase defect	CAH (hypertensive) + Male pseudo hermaphroditism + female sexual infantilism



Q3.13: A 2-month-old boy presented with ambiguous genitalia. His blood pressure is normal. The DHT value was low. The probable diagnosis is:

PYQ: FMGE 2021

- A. 21 β-hydroxylase deficiency
- B. 11 β-hydroxylase deficiency
- C. 17 β-hydroxylase deficiency
- D. 3 β-hydroxy steroid dehydrogenase deficiency

Answer: C. 17 β-hydroxylase deficiency

Q3.14: A male with hyperpigmentation, Tanner stage 5, presents with hypertension and precocious puberty. The causative defect is:

PYQ: INICET 2024

- A. 21 β-hydroxylase deficiency
- B. 11 β-hydroxylase deficiency
- C. 17 β -hydroxylase deficiency
- D. 17 α-hydroxylase deficiency

Answer: B. 11 β-hydroxylase deficiency

- 1 beta-hydroxylase deficiency presents as the salt-wasting form
- 17 alpha-hydroxylase deficiency presents with male pseudohermaphroditism.

BIG QUESTION 4: What is Massive Blood Transfusion?

Broad Answer:

- More than 10 units of packed red blood cells in 24 hrs.
- More than 4 units of packed red blood cells in 4 hours with anticipation of further requirements in the next 24 hrs.
- More than 1 blood volume in 24 hrs or more than 50% of the blood volume in 4 hrs.

DETAILED QUESTIONS

Q4.1: Massive blood transfusion causes all of the following except?

- A. Hypokalemia
- B. Hypocalcemia
- C. Hypomagnesemia
- D. Alkalosis

Answer: A. Hypokalemia

YOURWISH

- RBCs in stored blood do not have oxygen, leading to reduced ATPs
- Low ATP impairs the $\text{Na}^+ \text{K}^+ \text{ATPase}$ pump, resulting in hyperkalemia
- Citrate, which is used as an additive, chelates calcium and magnesium, resulting in hypocalcemia and hypomagnesemia, respectively.
- Citrate is metabolised to produce HCO_3^- , resulting in alkalosis.

Q4.2: What are the other adverse reactions to Massive blood transfusion?

Answer:

1. Hypothermia
2. Dilutional coagulopathy
3. Hypocalcemia and hypomagnesemia
4. Hyperkalemia
5. Lactic acidosis
6. TRALI



8. SUBORGANELLES/ CLINICAL BIOCHEMISTRY PART- 2

BIG QUESTION 1: Write a short note on Mitochondria.

Broad Answer: Mitochondria are known as the *powerhouse of the cell* due to their role in ATP production through oxidative phosphorylation. This process occurs on the inner membrane, specifically involving the electron transport chain (ETC). Mitochondria also house all enzymes for the citric acid cycle, support fatty acid oxidation, and contribute to parts of heme synthesis and the urea cycle.

DETAILED QUESTIONS

Q1.1: Why are mitochondria known as the 'powerhouse of the cell'?

Answer: Mitochondria are known as the powerhouse of the cell due to their role in ATP production through oxidative phosphorylation

Q1.2: What are the functions of mitochondria?

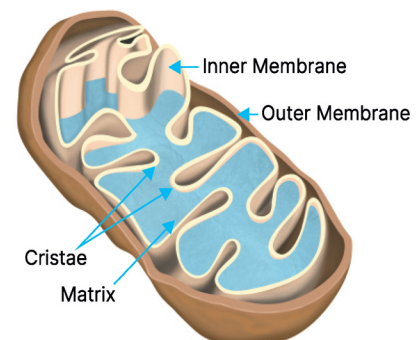
Answer:

- Electron transport chain-mediated oxidative phosphorylation in the inner side of the inner mitochondrial membrane.
- All citric acid cycle enzymes are present within mitochondria.
- Fatty acid oxidation
- A part of heme synthesis and the urea cycle happens in mitochondria.

Q1.3: What are the marker enzymes in the mitochondria?

Answer:

- Marker enzymes:
 - o Outer membrane (OM): Monoamine oxidase(MAO)
 - o Inner membrane:
 - Complex II of ETC: Succinate dehydrogenase (SDH)
 - Complex V of ETC: ATP synthase



BIG QUESTION 2: Write a short note on the Endoplasmic reticulum

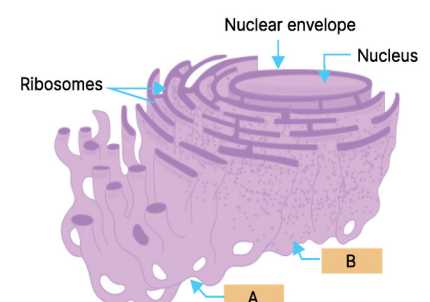
Broad Answer: The **endoplasmic reticulum (ER)** is a network of vesicles and tubules connected to the outer nuclear membrane, often referred to as the *microsome* in its isolated form. It plays a key role in protein and lipid synthesis.

DETAILED QUESTIONS

Q2.1: Describe the structure of the endoplasmic reticulum in brief.

Answer:

- A group of vesicles and tubules attached to the outer nuclear membrane.
- Also known as Microsome.
- Yellow dots in the image represent ribosomes.



Q2.2: What is the difference between smooth and rough endoplasmic reticulum?**Answer:**

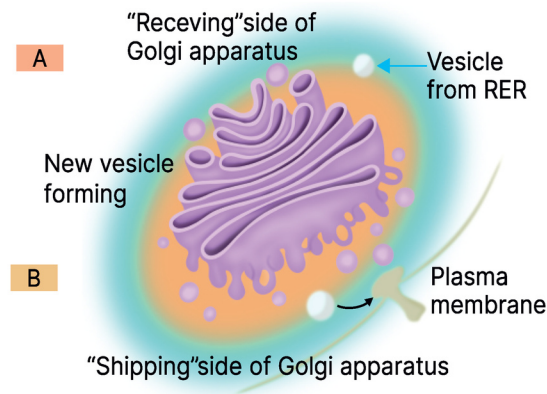
ER + Ribosomes	Rough endoplasmic reticulum (B)	Protein synthesis
ER without Ribosomes	Smooth endoplasmic reticulum (A)	Steroid synthesis: Cholesterol, bile acids, steroid compound

Q2.3: Name the marker enzymes for the endoplasmic reticulum?**Answer:** Marker enzymes: Glucose -6- phosphatase: Converts glucose-6-phosphate to glucose**BIG QUESTION 3: WRITE A SHORT NOTE ON THE GOLGI APPARATUS.****Broad Answer:**

The **Golgi apparatus** is a membrane-bound organelle involved in the modification, packaging, and transport of proteins and lipids synthesized in the endoplasmic reticulum. It consists of flattened, stacked pouches called cisternae and plays a key role in glycosylation, protein sorting, and the formation of lysosomes. It is especially prominent in secretory cells and functions as the cell's central delivery system.

DETAILED QUESTIONS**Q3.1: What are the 2 sides of the golgi apparatus?****Answer:**

- A - Cis Golgi
- B - Trans Golgi

**Q3.2: What are the functions of the golgi apparatus?****Answer:**

- Post-translational modifications
- Protein sorting

Q3.3: Name the marker enzyme for golgi apparatus**Answer:**

Marker enzymes:

- Glucosyl transferase
- Galactosyl transferase

BIG QUESTION 4: What is the structure and function of eukaryotic ribosomes in protein synthesis?

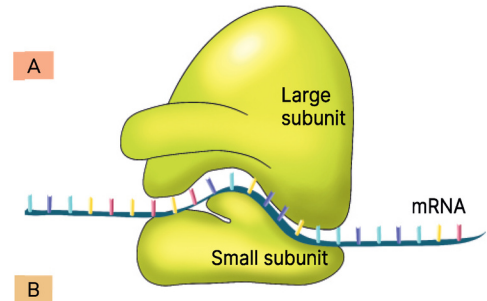
Broad Answer: Eukaryotic ribosomes play a central role in protein synthesis by reading and translating messenger RNA (mRNA). They are classified as **80S ribosomes**, consisting of two subunits: a **40S small subunit**, and a **60S large subunit**. Together, these subunits ensure accurate and efficient translation of genetic information into functional proteins.

DETAILED QUESTIONS

Q4.1: What are the subunits of 80S eukaryotic ribosomes?

Answer:

- 40s - Small subunit (B)
- 60s - Large subunit (A)



Q4.2: What is the function of ribosomes?

Answer: Ribosomes read and translate the mRNA-protein synthesis and translation

BIG QUESTION 5: What are the mechanisms of glucose transport across the intestinal epithelium?

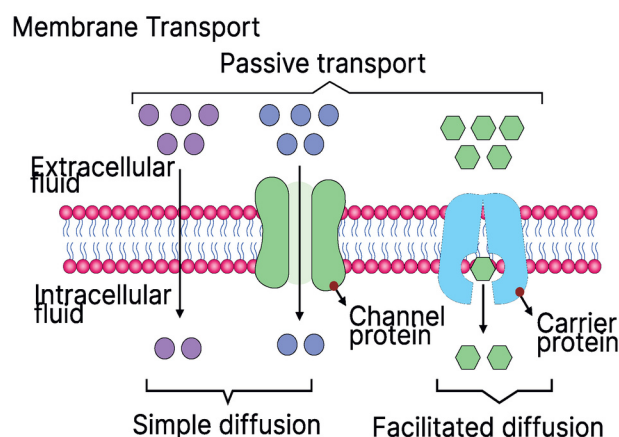
Broad Answer: Glucose transport involves both **facilitated passive diffusion** and **secondary active transport**. SGLT-1 on the apical membrane uses sodium co-transport for glucose uptake (secondary active transport), while GLUT2 on the basolateral membrane allows glucose to exit the cell via facilitated diffusion, following its concentration gradient.

DETAILED QUESTIONS

Q5.1: Write a short note on passive diffusion in glucose transport.

Answer:

- The substance moves from a higher concentration to a lower concentration
 - o Along the concentration gradient in passive diffusion.



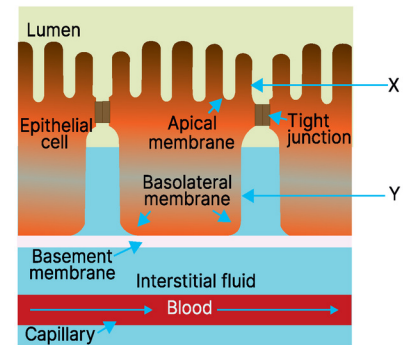
Q5.2: What is facilitated passive diffusion?

Answer: Whenever a carrier protein is used in a passive diffusion mechanism, it is called facilitated passive diffusion

YOURWISH

Q5.3: How is glucose transported across the apical and basolateral membranes of intestinal epithelial cells?**Answer:**

- X- moves glucose along the apical membrane (villi)
 - SGLT-1 (Sodium-Glucose Co-transporter -1)
 - Secondary active transport
- Co-transporter or counter-transporter of sodium other than Na K - ATPase pump
 - Secondary active transport
- Y - moves glucose along the basolateral membrane
 - GLUT 2: Facilitated passive diffusion mechanism

**BIG QUESTION 6: Write briefly about GLUT transporters.**

Broad Answer: GLUT (Glucose Transporter) proteins are a family of facilitative transporters that mediate the passive transport of glucose across cell membranes, following the concentration gradient. Among them, **GLUT2** is particularly important in the intestines, liver, and pancreas, enabling glucose to exit epithelial cells at the **basolateral membrane** after absorption. These transporters do not require energy (ATP) and are crucial for maintaining glucose homeostasis in the body.

DETAILED QUESTIONS**Q6.1: Write a note on the different GLUT transporters along with their functions.**

PYQ: FMGE 2020

Answer:

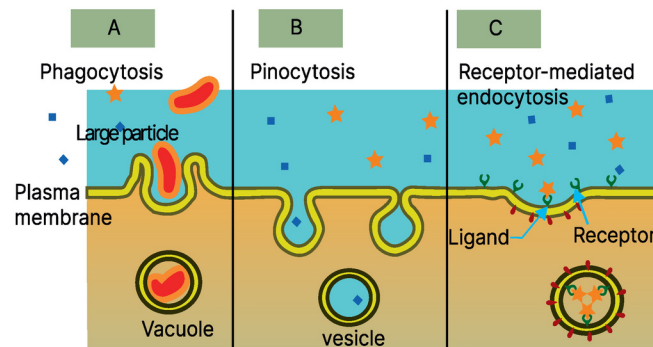
Glut Transporters	Locations
GLUT 1	Neurons, RBCs and Placentas
GLUT 2	Enterocytes, Hepatocytes, β - cells of pancreas, proximal convoluted tubule cell
GLUT 3	Neurons, RBCs and Placentas
GLUT 4	● Insulin Dependent Glucose Uptake ○ Skeletal Muscles, Cardiac Muscles, Adipose Tissues
GLUT 5	● Fructose absorption along the intestine (enterocytes) ● Also present in Seminal vesicle

Q6.2: Name the glucose transporters present in enterocytes that help in glucose uptake?**Answer:**

- Apical side - Sodium-Glucose co-transporter 1
- Basolateral side - GLUT 2 transporter

Q6.3: Name the transporters present in enterocytes that help in fructose uptake.**Answer:**

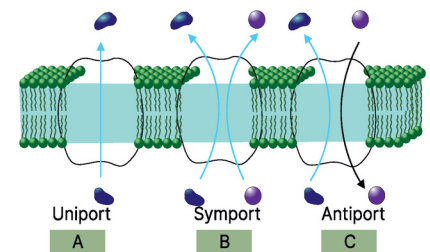
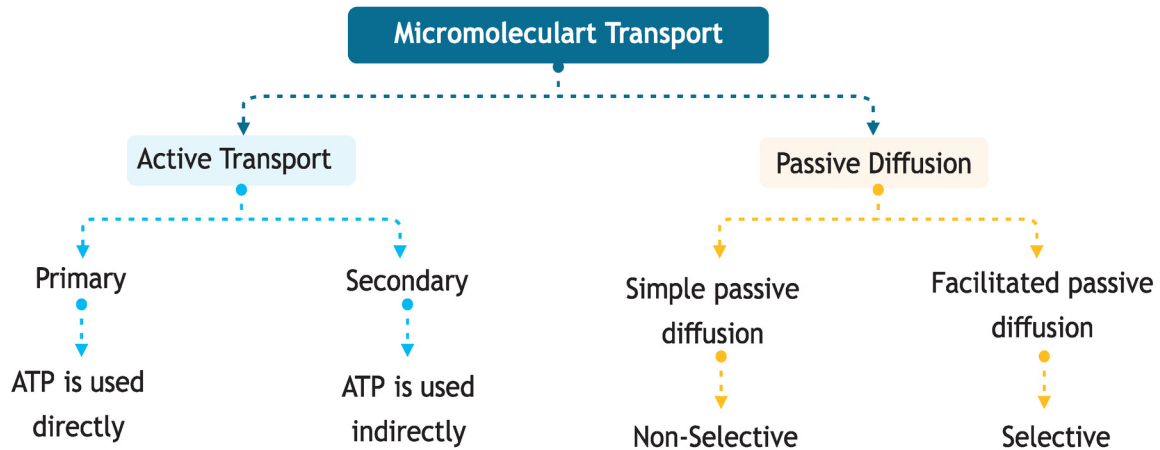
- Apical side - GLUT 5
- Basolateral side - GLUT 2

Q6.4: Illustrate phagocytosis, Pinocytosis and receptor-mediated endocytosis.**Answer:**

- (A) Phagocytosis - a cell engulfs a solid
- (B) Pinocytosis - the cell is taking up fluid
- (C) Receptor-mediated endocytosis - a receptor in the cell membrane accepts a ligand, and the ligand gets engulfed

Q6.5: What are the mechanisms of active transport?**Answer:** Active transport: Moving against the concentration gradient

- A - → One substance is transported Uniport
- B - → Two substances are transported in the same direction. Symport
- C - → Two substances are transported in opposite directions.

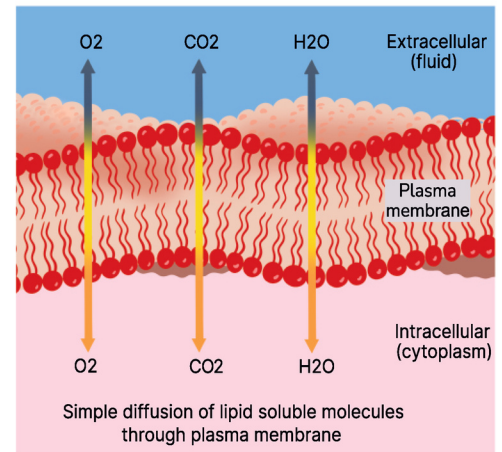
**BIG QUESTION 7: Classify the different types of micromolecular transport.****Broad Answer:****DETAILED QUESTIONS****Q7.1: Write a short note on passive diffusion.****Answer:**

- Along the concentration gradient
- Energy is liberated

Q7.2: Write a short note on simple non-selective passive diffusion.**Answer:**

- Non-selective: CO₂, O₂, urea diffusion

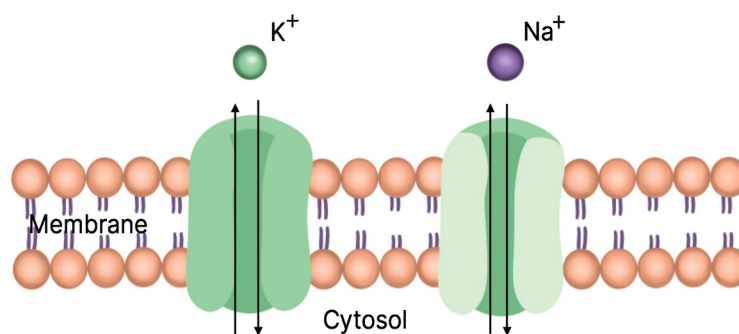
- o Anything that is lipid-soluble can move across any part of the lipid bilayer.
- o The part of the membrane across which transport happens is not selective
- o The substance being transported is not selective.



Q7.3: Draw a schematic diagram of selective passive diffusion and what is it used for ?

Answer:

Selective passive diffusion: Ion channels



Q7.4: What is facilitated passive diffusion? Give examples of the same.

Answer:

- Facilitated passive diffusion - A Carrier protein is used
 - o GLUT transporters
 - o Epithelial sodium channels

Mineralocorticoid acts on mineralocorticoid receptors on the basolateral side of the principal cells of late DCT and collecting duct



It causes the upregulation of Epithelial sodium channels (ENaC) along the apical side.

- Aquaporin 2 channels

Vasopressin acts on the V receptor present along the basolateral side of intercalated cells of late DCT and collecting duct cells.



Causes upregulation of Aquaporin 2 channels along the apical side.



Allow water movement along the concentration gradient

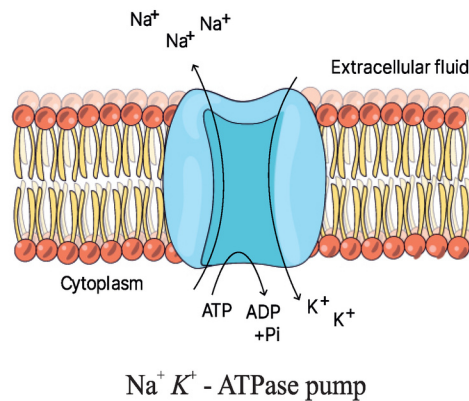
Q7.5: Write a short note on active transport.

Answer:

- Moving against the concentration gradient
- Energy is used.

Q7.6: What is Primary active transport ? Give examples of the same.**Answer:**

- Primary active transport: Carrier protein gets energy by directly hydrolyzing ATP.



Na⁺ K⁺ - ATPase pump.	• Pumps out 3 Na⁺ ions into extracellular fluid (rich in Na⁺) • Reciprocally, it takes in 2 K⁺ ions into intracellular fluid (rich in K⁺)
Calcium ATPase	• Present in the Sarcoplasmic reticulum (storage house of Ca²⁺) of muscle - o For excitation-contraction coupling, Ca²⁺ has to be released from the sarcoplasmic reticulum - o During relaxation, Ca²⁺ has to be pumped into the sarcoplasmic reticulum
K⁺/H⁺ ATPase	• Present in the gastric parietal cells. - o Secretes hydrogen ions into the gastric lumen - o Reciprocally, it takes in K⁺

Q7.7: What is Secondary active transport? Give examples of the same.**Answer:**

- Co-transporter or counter-transporter of sodium other than Na⁺ + K⁺ - ATPase pump.
 - o Sodium Glucose Cotransporter -1
 - o Sodium Amino Acid Cotransporter
 - o Sodium Bicarbonate Cotransporter
 - o Sodium H⁺ Antiporter
- Present along the apical side of enterocytes

Na⁺ K⁺ - ATPase pump pumps out 3 Na⁺ from enterocyte



Low sodium concentration within the enterocyte



Sodium ion movement will be initiated (from higher concentration to lower concentration)



Energy is liberated

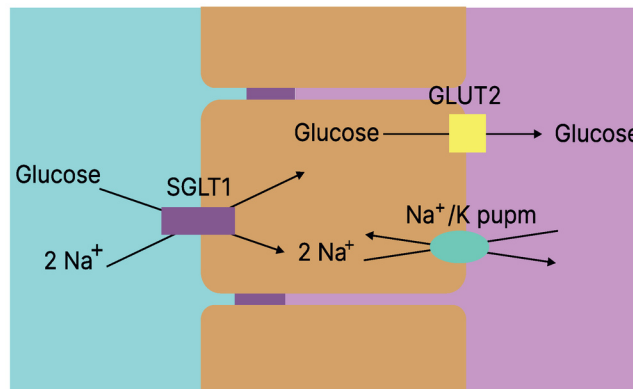


This energy is used for moving glucose.

- Glucose movement against the concentration gradient is facilitated by Sodium movement along a concentration gradient.

YOURWISH

- Sodium movement along a concentration gradient is facilitated by low sodium concentration within the enterocytes.
- Low sodium concentration within the enterocytes is supported by Na^+/K^+ -ATPase pump, which uses ATP.
- Hence, SGLT1 uses ATP indirectly through the functioning of Na^+/K^+ ATPase pump.

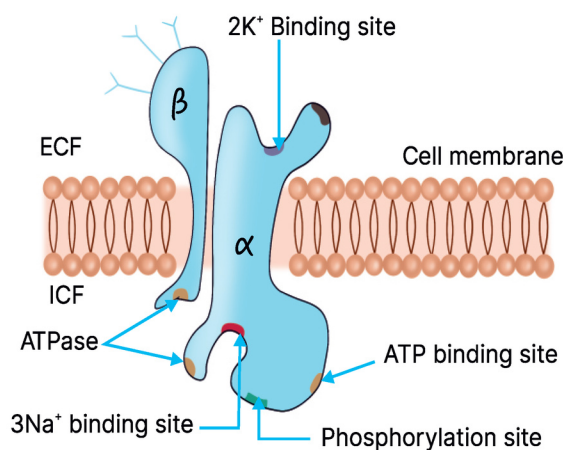


Q7.8: What are the different types of transport across the membrane, along with their examples?

Answer:

Sr. No.	Type of Transport	Example
1.	Non-selective simple passive diffusion	Oxygen, Carbon dioxide and Urea Diffusion
2.	Selective Simple passive diffusion	Ion channels
3.	Facilitated passive Diffusion	GLUT transporter, ENaC, Aquaporin-2
4.	Primary Active Transport	Sodium Potassium ATPase, Calcium ATPase, H^+/K^+ ATP
5.	Secondary active Transport	Sodium cotransporters and counter transporter

Q7.9: Identify the transporter and transport mechanism involved.



Answer: Sodium Potassium ATPase - Primary active transport

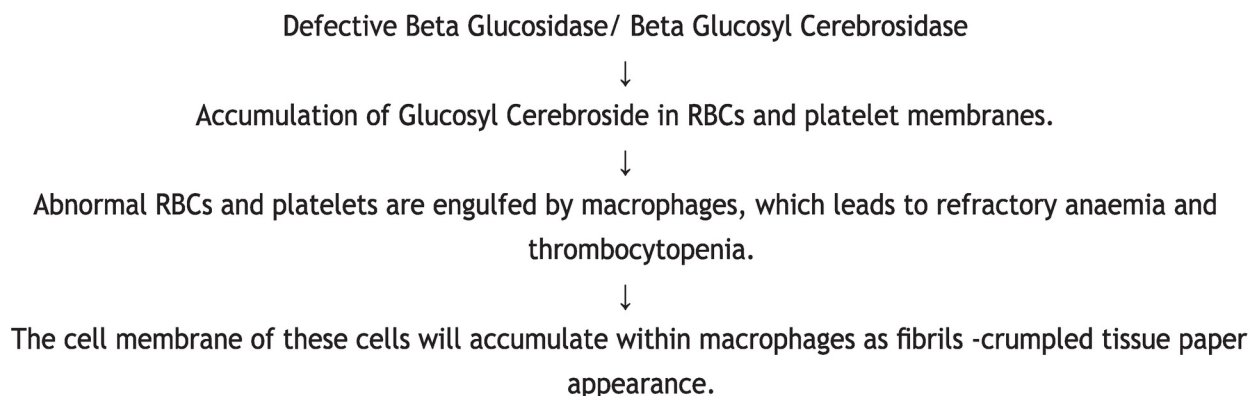
BIG QUESTION 8 Describe Gaucher's disease in brief.

Broad Answer: Gaucher's disease is a genetic lysosomal storage disorder caused by a deficiency of the enzyme glucocerebrosidase, leading to the accumulation of glucocerebroside in macrophages. This results in enlarged spleen and liver (hepatosplenomegaly), bone pain, anemia, and fatigue. It is inherited in an autosomal recessive pattern and is treatable with enzyme replacement therapy.

DETAILED QUESTIONS

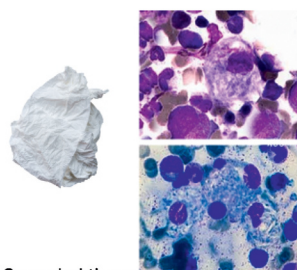
Q8.1: What is the pathophysiology of Gaucher's disease?

Answer:



Q8.2: What is the classical appearance of the cell in a bone marrow biopsy. PYQ: NEET PG 2021 PYQ: FMGE 2021

Answer: Crumpled tissue paper appearance - Blue color cell with fibrils on bone marrow biopsy



Crumpled tissue paper appearance

Q8.3: How does refractory anemia lead to skeletal deformities and hepatosplenomegaly?

Answer:

- Refractory anemia causes compensatory erythropoiesis
 - o In bone → Bony erosion and bony pain (Erlenmeyer flask deformity).
 - o In extramedullary tissues → Hepatosplenomegaly

PYQ: NEET PG 2021 PYQ: FMGE 2021



Erlenmeyer flask shaped bone

Q8.4: What is the treatment available for Gaucher's disease?

Answer: Enzyme replacement therapy

BIG QUESTION 9: Write a short note on Tay-Sachs Disease.

Broad Answer: Tay-Sachs disease is a rare autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme **hexosaminidase A**, leading to the accumulation of GM2 gangliosides in neurons. This results in progressive neurodegeneration, developmental delay, seizures, and a characteristic **cherry-red spot on the macula**. It is most commonly seen in infants and is typically fatal in early childhood.

DETAILED QUESTIONS

Q9.1: A young boy is having difficulty in breathing while running and is unable to rise from a squatting position. His fundus examination image is provided below. The probable condition?

- A. Tay-Sachs disease
- B. Gaucher's disease

- C. Fabry's disease
- D. Krabbe's disease

Answer: Tay-Sachs disease

- Progressive weakness, inability to rise, hypotonia, and a characteristic cherry-red spot on fundus examination.

Q9.2: What is GM2 gangliosidosis?

Answer: Tay Sachs disease + Sandhoff = GM2 gangliosidosis.

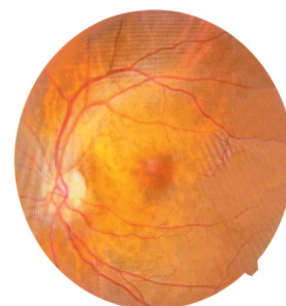
Q9.3: What is the characteristic appearance of the fundus in Tay-Sachs disease?

Answer:

Cherry red spot:

- Opacification of the entire macula, where the fovea remains transparent
- Lipid storage disorders - lipid accumulates in ganglion cells (the Fovea lacks ganglion cells)
- Feature of central retinal artery occlusion (Fovea is supplied by the choroid)

 PYQ: NEET PG 2022



Q9.4: In which lysosomal storage disorders are cherry-red spots typically absent?

Answer:

Cherry red spots are **absent** in KGF:

- Krabbe's disease
- Gaucher's disease
- Fabry's disease

BIG QUESTION 10: Write a short note on Phenylketonuria.

Broad Answer: Phenylketonuria (PKU) is an autosomal recessive metabolic disorder caused by a deficiency of the enzyme **phenylalanine hydroxylase**, leading to the accumulation of phenylalanine in the body. This can result in intellectual disability, seizures, a musty body odour, and developmental delays if not treated early. Management involves a strict **phenylalanine-restricted diet** to prevent neurological damage.

DETAILED QUESTIONS

Q10.1: A child presents with mental retardation, a characteristic odour and hypopigmentation along side is provided the result of Ferric chloride test that was done in his urine. The cause of the characteristic odour in the patient is:

- A. Benzoquinone acetate
- B. Phenyl pyruvate
- C. Phenyl Acetate
- D. Alpha-hydroxy butyrate

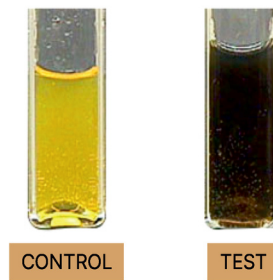
Answer: Phenyl Acetate

Q10.2: What is the Ferric chloride test used for?

PYQ: FMGE 2021

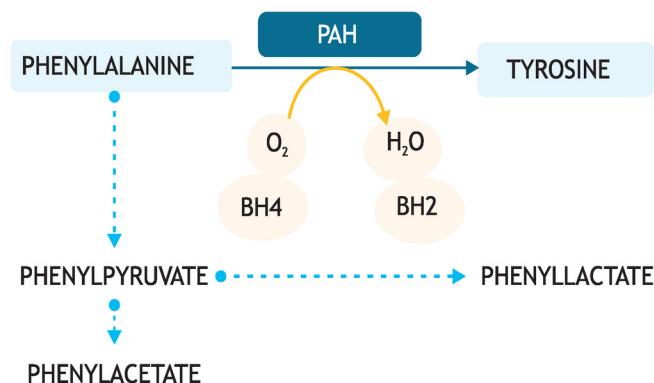
PYQ: NEET PG 2023

PYQ: INICET 2023

Answer: Ferric chloride test is positive - black color or dark green urine**Q10.3: What are the components of phenylketonuria****Answer:** Mental retardation + characteristic odour + hypopigmentation + ferric chloride positive → Phenylketonuria**Q10.4: What is the enzyme responsible for causing phenylketonuria****Answer:** Caused due to the deficiency of phenylalanine hydroxylase, causing accumulation of phenylalanine in the body**Q10.5: What are the functions of tyrosine****Answer:**

Tyrosine is used in:

- Melanin synthesis
- Neurotransmitters (Norepinephrine, epinephrine, dopamine)
- Thyroid hormone synthesis

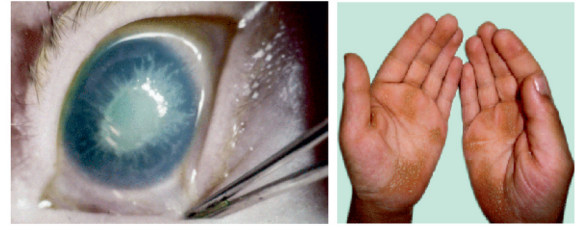
Q10.6: What is the transamination product of phenylalanine**Answer:** Phenylalanine, on transamination, forms Phenylpyruvate**Q10.7: What are the key biochemical findings and clinical features associated with phenylketonuria (PKU)?****Answer:**

Low Tyrosine	Hypopigmentation
Accumulation of Phenylpyruvate (phenyl ketone)	• Ferric chloride test positive • Mental retardation - competes with neutral amino acids to cross the Blood-brain barrier
Accumulation of Phenylacetate	Mousy odor

YOURWISH

Q10.8: An infant presented with watering of the eye, incessant cry and on observation tiny erosions were seen as shown in the image. The pediatrician also observed a rough palm in the infant. The probable diagnosis is:

- A. Type I Tyrosinemia
- B. Type II Tyrosinemia
- C. Type III Tyrosinemia
- D. Alkaptonuria



Answer:

- Type II Tyrosinemia
- Spontaneous corneal erosion (painful) and palmar hyperkeratosis
- Also Oculocutaneous syndrome
- Tyrosine Transaminase defect

Q10.9: A 20-year-old boy with severe mental retardation, mousy odour in body fluids, hypopigmentation. Patient has frequent episodes of seizures & aggressive behaviour. What is your diagnosis?

- A. Tyrosinemia
- B. Albinism
- C. MSUD
- D. Untreated PKU Phenylketonuria

Answer:

Untreated PKU Phenylketonuria

- Mental retardation + mousy odor + hypopigmentation + seizures = Untreated phenylketonuria



Q10.10: Name the characteristic urine odours and their diagnosis

🔍 PYQ: FMGE 2022 🔍 PYQ: NEET PG 2020, 2023

Answer:

Odor	Disorders
Mousy	PKU (phenylketonuria)
Fruity	DKA (diabetic ketoacidosis)
Cabbage	Tyrosinemia (type I)
Boiled cabbage	Hypermethioninemia
Oast house (urine and sweat smell as oasthouse)	Methionine malabsorption/ beer baby syndrome
Swimming pool	Hawkinsinuria

Sweaty feet	Isovaleric acidemia
Tom cat urine	Multiple carboxylase deficiency

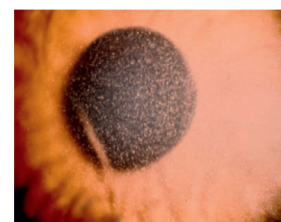
Q10.11: Write a short note on Hartnup's Disease.

Answer:

- A neutral amino acid transporter is present in both enterocyte and proximal convoluted tubular cells
- This transporter is responsible for reabsorbing tryptophan.
- Defect in transporter → Hartnup's disease
- Tryptophan will not be absorbed along the intestine in Hartnup's disease. It gets lost in feces
- 60 mg of Tryptophan = 1 mg of Niacin
- Niacin is one micronutrient that can be synthesized from tryptophan in the body
- In Hartnup's disease, there is:
 - o Tryptophan deficiency
 - o Niacin deficiency: Diarrhoea, Dermatitis, Dementia
- When reabsorption along PCT does not happen
 - o Aminoaciduria is also present

Q10.12: A 12-year-old boy presented with photophobia, short stature, polyuria and polydipsia. Slit lamp examination of the cornea is shown in the image. The probable diagnosis is:

- A. Cystinuria
- B. Cystinosis
- C. Homocystinuria
- D. Hartnup's disease



Answer: Cystinosis

Q10.13: Write a short note on Cystinuria

Answer:

- Caused by a defect of neutral amino acids, which is specific to reabsorbing 4 amino acids along PCT (Mnemonic: COLA)
 - o Cysteine
 - o Ornithine
 - o Lysine
 - o Arginine
- These 4 together get reabsorbed along Renal Tubule through a common transporter

Q10.14: What does Cystinuria present as.

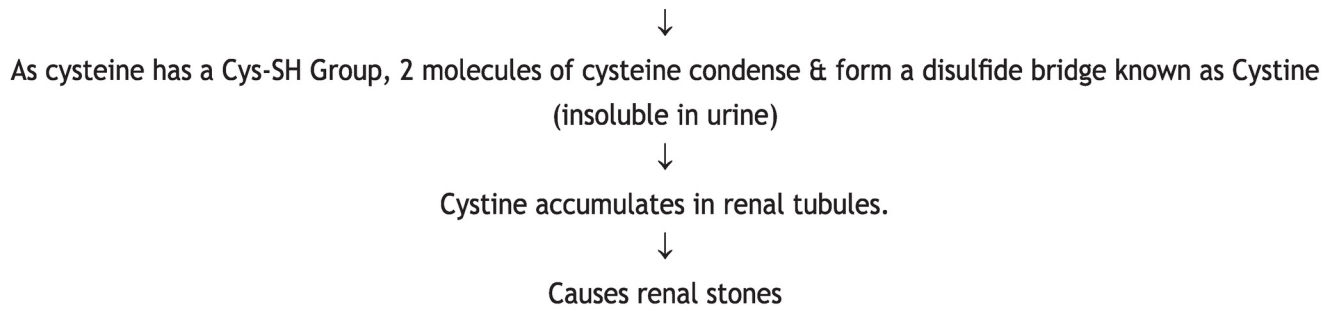
Answer:

- Recurrent renal stones (Hexagonal)
- Recurrent obstructive neuropathy

Q10.15: Explain how cystinuria causes renal stones.

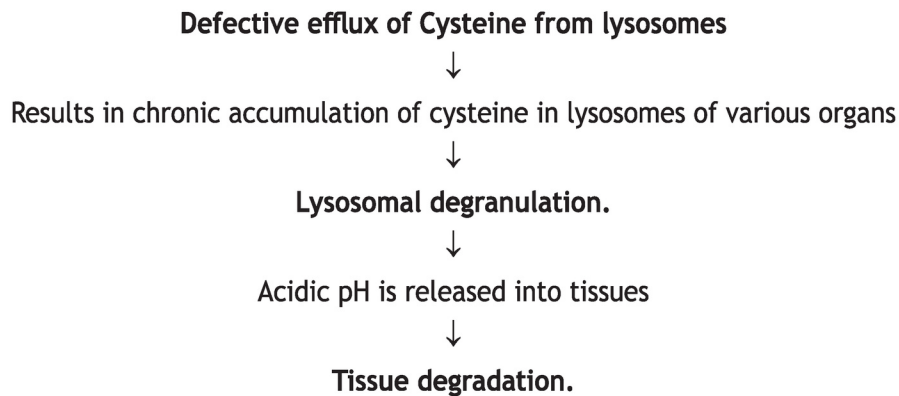
Answer:

When the common transporter is defective, all four amino acids are excreted in the urine. Supersaturation of Cysteine



Q10.16: Write a short note on cystinosis

Answer: Lysosomal storage disorder



Q10.17: Write a short note on Fanconi's syndrome

Answer:

- Fanconi syndrome is a rare disorder of the proximal renal tubules
 - Impaired reabsorption of various substances such as glucose, amino acids, phosphate, bicarbonate, and uric acid.
- Leads to polyuria, growth failure, rickets or osteomalacia (due to phosphate loss), metabolic acidosis, and electrolyte imbalances.
- It can be inherited (e.g., in **cystinosis** or Wilson's disease) or acquired (due to drugs like ifosfamide or heavy metals).

Q10.18: What are the iris features in cystinosis

Answer:

Local tissue damage on the iris causes:

- Iris depigmentation
- Photophobia

Q10.19: What are the slit lamp examination findings in cystinosis?

Answer: On slit lamp examination, there is characteristic cystine crystals (Shimmery-like crystals in the cornea).

BIG QUESTION 11: Write a short note on Pellagra

Broad Answer: Pellagra is a nutritional deficiency disease caused by a lack of niacin (vitamin B3) or its precursor **tryptophan**. It is classically characterized by the “3 Ds”: **dermatitis**, **diarrhea**, and **dementia**; if left untreated, it can lead to death. The dermatitis is typically photosensitive, affecting sun-exposed areas, and the condition is commonly seen in malnourished individuals or those with chronic alcoholism or Hartnup disease.

DETAILED QUESTIONS

PYQ: FMGE 2020

PYQ: NEET PG 2023

PYQ: INICET 2023

Q11.1: A 65-year-old man with alcohol use disorder, presented with insomnia, irritability and confusion. His son attributed the confusion to a probable dehydration caused by diarrhoea. On examination, there were erythematous non-itchy skin lesions in the sun exposed areas as shown in the image. The probable cause of confusion is:

- A. Wernicke's encephalopathy
- B. Delirium tremens
- C. Korsakoff syndrome
- D. Pellagra



Answer: D. Pellagra

- Deficiency of Niacin causes pellagra.
- Chronic alcoholics may skip meals, leading to deficiency of essential micronutrients
- Characterized by **3 D's**:
 - o Diarrhoea
 - o Dementia
 - o Dermatitis

Q11.2: Write a short note on Wernicke's Encephalopathy.

Answer:

PYQ: FMGE 2021

PYQ: NEET PG 2023

- Acute thiamine deficiency
- Common in chronic alcoholics
- Presents as:
 - o Global confusion
 - o Ophthalmoplegia
 - o Ataxia

Q11.3: Write a short note on Delirium Tremens.

Answer:

- One of the features of Alcohol withdrawal
- Presents between 2 (common) and 10 day of Alcohol withdrawal.

Mental Manifestations	Physical Manifestations
Global confusion	Tremors
Hallucinations	Hyperthermia
Nightmares	Tachycardia
Mnemonic: Government Hospital Nurse	Hypertension

Q11.4: What are the features of Chronic Thiamine Deficiency

Answer:

- Presents as Korsakoff syndrome.
- Characterized by:

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- o Amnesia (retrograde and anterograde).
- o Confabulation (framing stories).
- o Sensory agnosia

BIG QUESTION 12: How does Phrynoderma present, and what causes it?

Broad Answer: Phrynoderma is a skin condition from vitamin A or essential fatty acid deficiency, causing keratinised papules on limb extensor surfaces. Vitamin A forms include retinol (storage), retinal (vision), and retinoic acid (epithelial health). Deficiency leads to mental and physical symptoms, plus eye changes like Bitot's spots and keratomalacia.

DETAILED QUESTIONS

Q12.1: A 7-year-old girl presents with bilaterally symmetrical discrete papules with central keratinous plug localized to elbows as shown in the image. The probable cause is deficiency of:

- A. Retinol
- B. Retinal
- C. Retinoic acid
- D. Vitamin D



Answer: C. Retinoic acid

The bilaterally symmetrical discrete papules with central keratinous plug localized to elbows is known as **Phrynoderma**

- Caused by Vitamin A / essential fatty acid deficiency due to impaired suppression of keratinization of epithelium
- Also known as Follicular hyperkeratosis manifests as small papillary lesions in the extended surfaces of the limb with the keratin plug in the tip.

Q12.2: What are the different forms of vitamin A?

Answer:

- Retinol - Alcohol form
- Retinal - Aldehyde form
- Retinoic acid - Acid form

Q12.3: What is the Significance of Retinol ?

Answer: Form in which vitamin A is absorbed, transported, and stored

Q12.4: What is the Significance of Retinal ?

Answer:

- Present in Rods and Cones in the form of Rhodopsin and Conopsin
- As long as there is no light, Rhodopsin is 11 cis Retinal in the center attached to Opsin

Q12.5: What is the significance of Retinoic acid?

Answer:

- 2 forms of Retinoic Acid:
 - o All Trans Retinoic Acid: Helps in the growth and differentiation of epithelium.
 - o 13-Cis Retinoic Acid: Suppresses keratinization of epithelium

Q12.6: What is Conjunctival xerosis?**Answer:**

- Keratinization of conjunctiva in Vitamin A deficiency.
- Keratin accumulates as Bitot's spots

Q12.7: What is keratomalacia?

Answer: Corneal epithelium undergoes keratinization.

BIG QUESTION 13: Write in brief about Marfan's syndrome.

Broad Answer: Marfan syndrome is a genetic connective tissue disorder caused by mutations in the **FBN1 gene** encoding **fibrillin-1**. It affects multiple systems, including the **skeletal system** (tall stature, long limbs, arachnodactyly), **ocular system** (lens dislocation), and **cardiovascular system** (aortic root dilation, aneurysm, or dissection). It follows an **autosomal dominant** inheritance pattern and requires regular monitoring, especially of the heart and aorta.

DETAILED QUESTIONS**Q13.1: What is the most common sign in Marfan's syndrome****Answer:**

Spontaneous bilateral superotemporal dislocation of the lens

- The most common first sign of Marfan syndrome
- The most common cause is Marfan syndrome

Q13.2: What is the mode of inheritance?

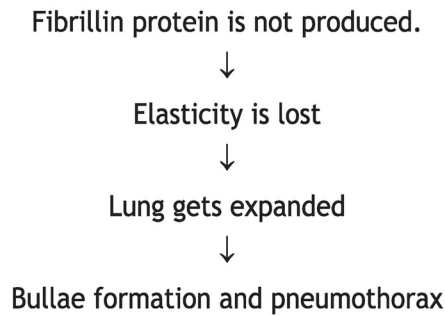
Answer: Autosomal dominant inheritance

Q13.3: Name the gene and chromosome affected in Marfan's.**Answer:**

- FBN1 gene mutation in chromosome 15
- FBN1 gene codes for fibrillin protein

Q13.4: What are fibrillins?**Answer:** Fibrillin:

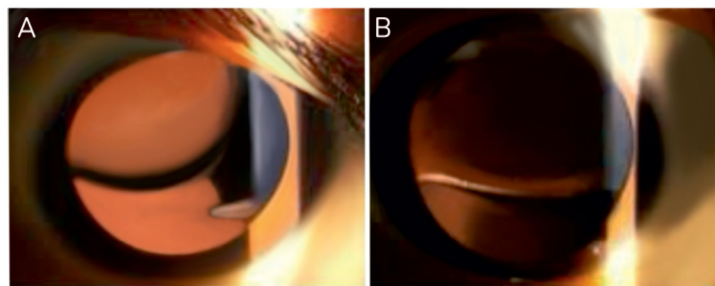
- Microfibrils in connective tissue.
- Either in association with elastin or without elastin
- With elastin- they increase the elasticity of tissues.
 - o Present in skin, lungs, and blood vessels
- Without elastin - increase tensile strength
 - o Present in tendons and suspensory ligaments of Linn
- Reduces TGF beta levels because it causes necrosis.

Q13.5: What is the pathophysiology of formation of pneumothorax in Marfans syndrome.**Answer:****Q13.6: What are the cardiac manifestations of Marfan's?****Answer:**

- Aortic regurgitation and mitral valve prolapse are due to loss of elasticity in the root of the blood vessels.
- TGF beta level increases → Necrosis → Cystic medial necrosis - Dissection of the aorta

Q13.7: What are the other manifestations of Marfans**Answer:**

- Arachnodactyly due to loss of tensile strength
- Dislocation of the lens due to loss of tensile strength in suspensory ligaments.

Q13.8: Why do we give beta blockers in Marfans syndrome?**Answer:** Beta blockers or losartan reduce TGF beta levels in Marfan syndrome.**Q13.9: A 15-year-old boy presented to the Ophthalmology department with an acute reduction in visual acuity in both the eyes. The direct observation of both the eyes is shown here.**

The ophthalmologist suspected a disorder and ordered for genetic testing, which revealed FBN1 gene mutation. Which of the following is true about the disorder and the protein involved?

- The protein reduces TGF-Beta levels
- Alpha 2 agonists delay the progression of the disorder
- It is an autosomal recessive disorder
- The protein involved reduces the elasticity of tissues normally

Answer: The protein reduces TGF-Beta levels

Q13.10: Tabulate the difference between Homocystinuria vs Marfan syndrome**Answer:**

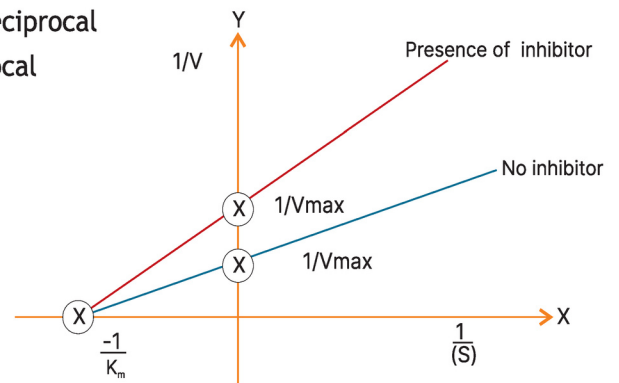
Sr. No.	Characteristic	Marfan	Homocysteinuria
1.	Inheritance	Autosomal Dominant	Autosomal Recessive
2.	Gene mutated	FBN1 gene of Chromosome 15	Cystathionine beta synthase of chromosome 21
3.	Lens dislocation	Superotemporal	Inferonasal
4.	Joints	Extensible	Restricted
5.	Blood vessels	Dilated	Vaso-occlusive
6.	Treatment	Beta blockers, Losartan (reduce TGF Beta)	Vitamin B6



9. IBQ- GRAPH, TESTS, CLINICAL BIOCHEMISTRY

BIG QUESTION 1: What is the Lineweaver-Burk Plot (Double Reciprocal Plot) and how is it used to find enzyme inhibition?

Broad Answer: The Lineweaver-Burk plot, also called the Double Reciprocal Plot, is used to find the type of enzyme inhibition by plotting reciprocal values of velocity and substrate concentration.



DETAILED QUESTIONS

Q1.1: What is the use of the Lineweaver-Burk plot?

Answer:

- It is used for finding the type of enzyme inhibition.

Q1.2: What are the axes in the Lineweaver-Burk plot?

Answer:

- Y-axis = $1/V$
- X-axis = $1/[S]$

Q1.3: How many lines are present in the plot and what do they represent?

Answer:

- Two lines are present:
 - o One line represents enzyme-based chemical reaction kinetics in the **absence** of an inhibitor.
 - o The other line represents the kinetics in the **presence** of an inhibitor.

Q1.4: What are the intercepts on the plot called?

Answer:

- If we extrapolate the lines, they cut:
 - o X-axis at **x-intercept** = $-1/K_m$
 - o Y-axis at **y-intercept** = $1/V_{max}$

BIG QUESTION 2: What are V_{max} and K_m in enzyme kinetics?

Broad Answer: V_{max} and K_m are key parameters representing the maximum velocity of an enzymatic reaction and the substrate concentration at half-maximal velocity, respectively.

DETAILED QUESTIONS

Q2.1: What is V_{max} ?

Answer: V_{max} is the maximum velocity achieved by an enzyme.

Q2.2: What is K_m ?

Answer: K_m is the substrate concentration at half-maximal velocity.

Q2.3: Explain with an example how K_m reflects substrate concentration.

Answer:

- If K_m is 100 micromol:
 - o Substrate concentration required to achieve $\frac{1}{2}$ maximal velocity is 100 micromol.
- If K_m is 1000 micromol:
 - o Substrate concentration required to achieve $\frac{1}{2}$ maximal velocity is 1000 micromol.

Q2.4: What does a high K_m indicate?

Answer:

- If K_m is high, more substrate has to be supplied to achieve half-maximal velocity.
- High K_m indicates low affinity of the enzyme for the substrate.

Q2.5: What is the relationship between K_m and affinity?

Answer: K_m and enzyme affinity are inversely proportional.

BIG QUESTION 3: What are the types of Enzyme Inhibition?

Broad Answer: Enzyme inhibition can be classified as reversible or irreversible. Reversible inhibition includes several pharmacologically important types, while irreversible inhibition permanently inactivates the enzyme.

DETAILED QUESTIONS

Q3.1: What are the broad categories of enzyme inhibition?

Answer:

- A. Reversible (Pharmacological agents - Reversible inhibitors)
- B. Irreversible

Q3.2: What are the types of reversible inhibition?

Answer:

- Competitive
- Uncompetitive
- Mixed
- Non-competitive is a special type of mixed inhibition

BIG QUESTION 4: What is Competitive Inhibition?

Broad Answer: In competitive inhibition, a substrate analog competes with the substrate for binding at the enzyme's active site, preventing product formation. Increasing substrate concentration can overcome this inhibition.

DETAILED QUESTIONS

Q4.1: How does competitive inhibition occur?

Answer:

- Enzymes react with substrate to form enzyme-substrate (ES) complex.
- Competitive inhibitor is a substrate analog that competes with the substrate.
- Binds to the active site of the enzyme.
- Forms enzyme-inhibitor complex.
- Prevents product formation.

Q4.2: How does competitive inhibition affect product formation?

Answer:

- Competitive inhibitor reduces the probability of the formation of enzyme-substrate complexes.
- Therefore, it reduces the probability of product formation.

Q4.3: How can competitive inhibition be overcome?

Answer:

- When substrate concentration is increased, the substrate wins the competition.
- Product formation occurs.

Q4.4: How does competitive inhibition affect V_{max} and K_m ?

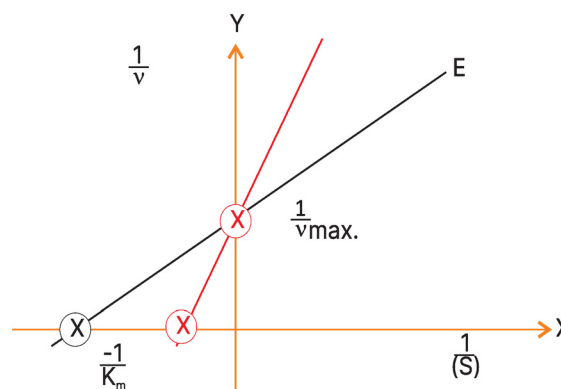
Answer:

- V_{max} is unaltered as inhibition can be overcome.
- K_m (substrate concentration at half-maximal velocity) is increased.

Q4.5: How does the Lineweaver-Burk plot appear in competitive inhibition?

Answer:

- The red line shows competitive inhibition.
- Effects of competitive inhibitor:
 - V_{max} is unaltered.
 - K_m is increased or $-1/K_m$ is decreased.



BIG QUESTION 5: What is Uncompetitive Inhibition?

Broad Answer: In uncompetitive inhibition, the inhibitor binds to the enzyme-substrate complex, preventing product formation. This type of inhibition cannot be overcome by increasing substrate concentration.

DETAILED QUESTIONS

Q5.1: How does uncompetitive inhibition occur?

Answer:

- The inhibitor binds to the enzyme-substrate complex.
- Forms enzyme-substrate-inhibitor complex.
- Does not allow product formation.

Q5.2: Can increasing substrate concentration overcome uncompetitive inhibition?

Answer:

- No.
- Increasing substrate concentration $\rightarrow$ more enzyme-substrate complex $\rightarrow$ more enzyme-substrate-inhibitor complex $\rightarrow$ inhibition persists.

Q5.3: How does uncompetitive inhibition affect $V_{\max}$ and K_m ?

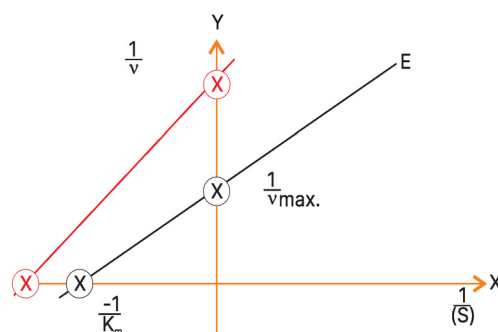
Answer:

- $V_{\max}$ is decreased.
- K_m is also decreased.

Q5.4: How does the Lineweaver-Burk plot appear in uncompetitive inhibition?

Answer:

- The red line shows uncompetitive inhibition.
- Both lines are parallelly shifted.
- $1/V_{\max}$ and $-1/K_m$ are high.



BIG QUESTION 6: What is Mixed Inhibition?

Broad Answer: In mixed inhibition, the inhibitor binds to both the free enzyme and the enzyme-substrate complex, preventing product formation. This type of inhibition cannot be overcome by increasing substrate concentration.

DETAILED QUESTIONS

Q6.1: How does mixed inhibition occur?

Answer:

- The inhibitor binds to both:
 - Free enzymes.
 - Enzyme-substrate complexes.
- Forms enzyme-substrate complex and enzyme-substrate-inhibitor complex.
- Product is not formed.

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Q6.2: Can increasing substrate concentration overcome mixed inhibition?

Answer:

- No.
- Increasing substrate concentration does not overcome the inhibition.

Q6.3: How does mixed inhibition affect V_{max} and K_m ?

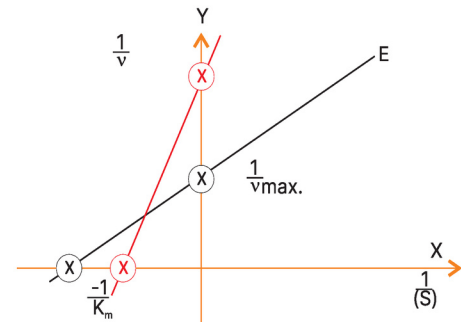
Answer:

- V_{max} is decreased.
- K_m is increased.

Q6.4: How does the Lineweaver-Burk plot appear in mixed inhibition?

Answer:

- The red line shows a mixed inhibitor.
- $1/V_{max}$ is increased.
- $-1/K_m$ is reduced.



BIG QUESTION 7: What is Non-competitive Inhibition?

Broad Answer: Non-competitive inhibition is a special type of mixed inhibition where the inhibitor binds to both the free enzyme and the enzyme-substrate complex with equal affinity. It prevents product formation and cannot be overcome by increasing substrate concentration.

DETAILED QUESTIONS

Q7.1: How does non-competitive inhibition occur?

Answer:

- It is a special type of mixed inhibition.
- The inhibitor binds to both:
 - o Free enzymes.
 - o Enzyme-substrate complexes.
- It binds with the **same affinity** to both forms.

Q7.2: How does non-competitive inhibition affect V_{max} and K_m ?

Answer:

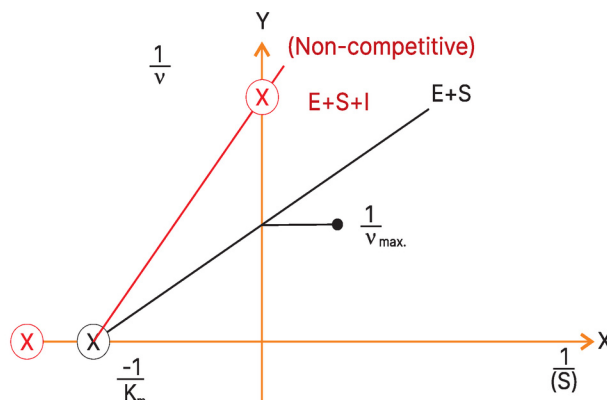
- V_{max} is decreased.
- K_m is normal.

Q7.3: How does the Lineweaver-Burk plot appear in non-competitive inhibition?

Answer:

- The red line shows a non-competitive inhibitor.
- $1/V_{max}$ is increased (high).

- $-1/K_m$ is normal.



BIG QUESTION 8: What are the effects of different types of enzyme inhibitors on K_m and V_{max} ?

Broad Answer: Different types of enzyme inhibitors have characteristic effects on V_{max} and K_m , which can be visualised using the Lineweaver-Burk plot.

DETAILED QUESTIONS

Q8.1: What is the summary of effects of different inhibitors on V_{max} and K_m ?

Answer:

Type of Inhibition	V_{max}	K_m
Competitive inhibition	Normal	Increased $\uparrow$
Uncompetitive inhibition	Decreased $\downarrow$	Decreased $\downarrow$
Mixed inhibition	Decreased $\downarrow$	Increased $\uparrow$
Non-competitive inhibition	Decreased $\downarrow$	Normal

BIG QUESTION 9: What is Lipoprotein Electrophoresis and how is it interpreted clinically?

Broad Answer:

Lipoprotein electrophoresis is a laboratory test performed on a glass slide to separate different lipoproteins based on their charge and size. It helps in diagnosing lipid disorders by observing band patterns.

DETAILED QUESTIONS

Q9.1: How is lipoprotein electrophoresis performed?

Answer:

- A glass slide is coated with a support medium (Agarose).
- Serum lipoprotein is applied near one end of the slide.
- The negatively charged electrode is connected close to the point of application.
- The positively charged electrode is connected to the opposite end.
- When electric current is applied:
 - o Lipoproteins migrate towards the positively charged electrode.

Q9.2: What factors affect the migration of lipoproteins?

Answer:

- Number of negative charges (more negative charge → faster movement).
- Size of the particle (larger particles move slower).

Q9.3: How do different lipoproteins migrate on electrophoresis?

Answer:

- **Alpha band / HDL:**
 - Moves farthest due to high phospholipid, high protein content, and more negative charges.
- **Chylomicron band:**
 - Moves closest because of its large size.

Q9.4: What is the significance of the Chylomicron band?

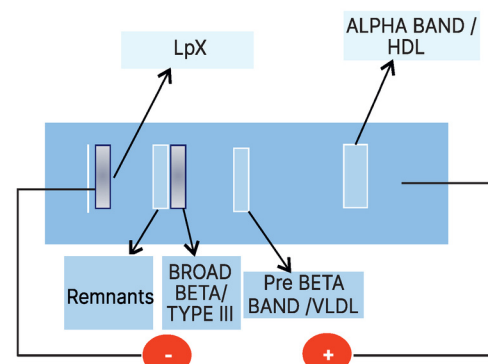
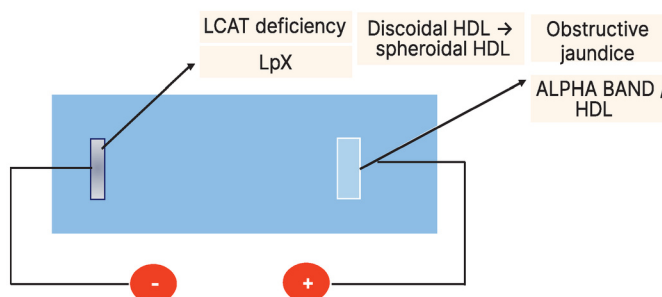
Answer:

- In a fasting sample, normally no chylomicron band is present.
- If present:
 - **If the patient is not fasting:** Chylomicron is elevated (dietary triglycerides).
 - **If patient is fasting:** Suggestive of Familial Chylomicronemia Syndrome.

Q9.5: What is Lipoprotein X (LpX) and when is it seen?

Answer:

- LpX appears as a band at the point of application.
- Seen in:
 - **LCAT deficiency:**
 - LCAT normally converts discoidal HDL to spheroidal HDL.
 - LCAT deficiency → Increase in discoidal HDL.
 - Discoidal HDL forms a lamellar structure = LpX band.
 - LpX accumulates in mesangium → Chronic kidney disease.
 - LCAT deficiency causes Hypo alpha lipoproteinemia.
 - HDL is involved in reverse cholesterol transport → Deficiency leads to cholesterol ester accumulation → Corneal opacity (Fish eye disease).
 - **Obstructive jaundice:**
 - Increased bile salt concentration in circulation.
 - Forms a lamellar structure = Band at the point of application.



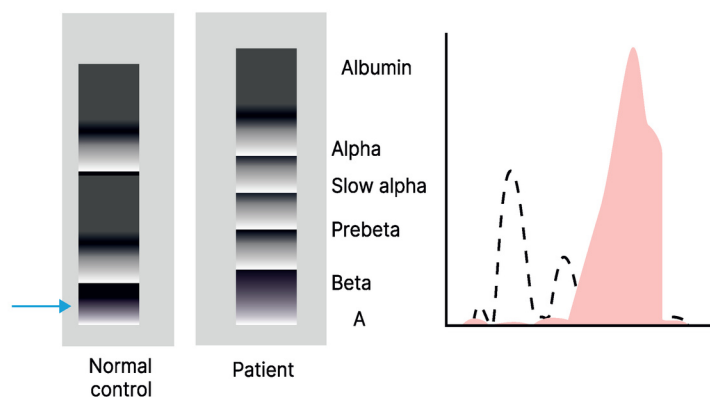
Q9.6: What are the other bands seen in lipoprotein electrophoresis?

Answer:

- **Beta band:** LDL
- **Pre-beta band:** VLDL
- **Remnant band:**
 - o Normally remnant concentration is too low to be detected.
 - o If present, seen after the beta band.
 - o Significant in Type III Hyperlipoproteinemia (Remnant disease) → Broad beta band.

 PYQ: FMGE 2021

Q9.7: Lipoprotein electrophoresis of a patient presenting with chronic kidney disease, corneal opacity, and low HDL is provided here. The band identified as A and the disorder is:



- A. M band and Multiple Myeloma
- B. Chylomicron and Type I Hyperlipoproteinemia
- C. LDL and Type II Hyperlipoproteinemia
- D. LpX and complete LCAT deficiency

Answer: D. LpX and complete LCAT deficiency

Explanation:

- The image is of lipoprotein electrophoresis.
- The arrow denotes the point of application.
- The farthest band from the arrow is the alpha band (HDL).
- A band seen at the point of application is present.
- Clinical clues:
 - o Low HDL → Hypo alpha lipoproteinemia.
 - o Corneal opacity → Fish eye disease.
- LCAT deficiency is characterised by:
 - o Lipoprotein X (band at point of application).
 - o Corneal opacity.
 - o Hypo alpha lipoproteinemia.
 - o Chronic kidney disease.

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BIG QUESTION 10: What is Type III Hyperlipoproteinemia and how is it diagnosed using Lipoprotein Electrophoresis?

Broad Answer: Type III Hyperlipoproteinemia, also called Remnant Disease, is characterised by the presence of significant remnant lipoproteins in the serum, which can be detected as a broad beta band on lipoprotein electrophoresis.

DETAILED QUESTIONS**Q10.1: What is the principle of Lipoprotein Electrophoresis?****Answer:**

- It is performed on a glass slide coated with a support medium (Agarose).
- Serum lipoprotein is applied near one end of the slide.
- Negative electrode is connected near the application point.
- Positive electrode is connected at the opposite end.
- Electric current causes migration of lipoproteins towards the positively charged electrode.
- Migration depends on:
 - o Number of negative charges ($\uparrow$ negative charge $\rightarrow$ more rapid movement).
 - o Size (larger particles migrate slower).

Q10.2: What are the normal bands seen in Lipoprotein Electrophoresis?**Answer:**

- **Alpha band (HDL):** Moves farthest due to high phospholipid and protein content.
- **Chylomicron band:** Moves closest due to large size.
- **Beta band:** LDL.
- **Pre-beta band:** VLDL.
- **Remnant band:** Normally undetectable in healthy serum.

Q10.3: What abnormality is seen in Type III Hyperlipoproteinemia?**Answer:**

- Presence of significant remnant lipoproteins.
- Seen as a **broad beta band** after the LDL (beta) band on electrophoresis.

BIG QUESTION 11: What is the Ninhydrin Test and how is it used to detect amino acids?

Broad Answer: The Ninhydrin Test is a chemical test that detects amino acids with free alpha-amino groups by producing a characteristic purple colour. It also reacts with imino groups producing a yellow colour.

DETAILED QUESTIONS**Q11.1: What is the principle of the Ninhydrin Test?****Answer:**

- Ninhydrin reagent reacts with:
 - o Any amino acid containing an **alpha-amino group** (e.g lysine) $\rightarrow$ produces a **purple colour**.
 - o **Imino groups** (e.g., Proline) $\rightarrow$ produce **yellow colour**.
 - o If neither alpha-amino nor imino groups are present $\rightarrow$ no colour change.

Q: 11.2 mL of Ninhydrin reagent was taken in 3 test tubes. Few drops of solutions A, B, and C were added to the three tubes and were kept in a boiling water bath. The resultant colour is shown. Solutions A, B, and C respectively are:

PYQ: FMGE 2022



- A. Arginine, Glucose, Lysine
- B. Lysine, Glucose, Arginine
- C. Lysine, Fructose, Proline
- D. Hydroxyproline, Fructose, Lysine

Answer: C. Lysine, Fructose, Proline

Explanation:

- Ninhydrin reagent reacts with:
 - o **Lysine** (alpha-amino group) → Purple colour.
 - o **Proline** (imino group) → Yellow colour.
 - o If no amino or imino group is present → no colour.

BIG QUESTION 12: What is Benedict's Test and what are the causes of reducing substances in urine?

Broad Answer: Benedict's Test is a chemical test that detects the presence of reducing substances in urine. It helps identify various physiological and pathological conditions associated with glycosuria or other reducing substances.

DETAILED QUESTIONS

Q12.1: What is the principle of Benedict's Test?

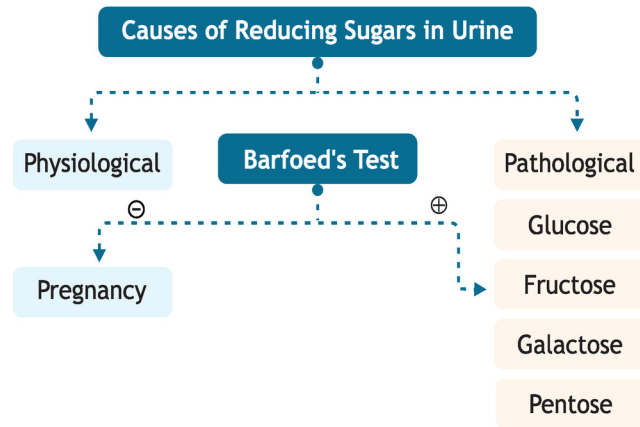
Answer:

- Benedict's solution is blue in colour.
- When a reducing substance is present in urine:
 - o The solution changes colour to **red**, indicating a positive Benedict's test.
- The test detects reducing sugars and other reducing substances in urine.

Q12.2: What are the causes of reducing substances in urine?

Answer:

Type	Cause
Physiological	Pregnancy and lactation: Presence of lactose (a reducing disaccharide made of galactose and glucose); prolactin excess. Barfoed's Test is negative.
Pathological	Glucose: Diabetes Mellitus, Renal glycosuria (e.g., Fanconi syndrome), Alimentary glycosuria (postprandial, thyrotoxicosis). Fructose: Essential fructosuria (fructokinase defect), Hereditary fructose intolerance (aldolase D defect). Galactose: Galactosemia (galactokinase deficiency), Classical galactosemia (GalPUT deficiency). Pentose: Essential pentosuria (Xylitol dehydrogenase defect).



Q12.3: What is Barfoed's Test and how does it help in diagnosis?

Answer:

- Barfoed's test differentiates between monosaccharides and reducing disaccharides.
- **Barfoed's positive (red precipitate)** → Monosaccharides (e.g., glucose, fructose, galactose, pentose).
- **Barfoed's negative with positive Benedict's** → Reducing disaccharides (e.g., lactose, maltose).

Q12.4: A person gives her urine sample for routine screening. Benedict's test result is shown. All of the following can be a cause EXCEPT:

- A. Multiple Myeloma
- B. Pregnancy
- C. Fanconi's syndrome
- D. Galactosemia



Answer: A. Multiple Myeloma

Explanation:

- Positive Benedict's Test → Red colour in urine.
- Indicates presence of reducing substance.
- **Multiple Myeloma:**
 - Bence Jones protein in urine → Not a reducing substance → Cannot cause positive Benedict's test.
- **Pregnancy:**
 - Lactose present → Reducing disaccharide → Positive test.
- **Fanconi syndrome:**
 - Proximal tubule defect → Renal glycosuria → Positive test.
- **Galactosemia:**
 - Galactose in urine → Reducing monosaccharide → Positive test.

BIG QUESTION 13: What is Barfoed's Test and how does it help differentiate reducing sugars in urine?

Broad Answer: Barfoed's Test is a chemical test used to differentiate monosaccharides from reducing disaccharides based on their ability to produce a red precipitate.

DETAILED QUESTIONS

Q13.1: What is the principle of Barfoed's Test?

Answer:

- Barfoed's test distinguishes monosaccharides from reducing disaccharides.
- The test result depends on the ability of sugars to reduce copper ions under acidic conditions.

Q13.2: What are the possible results of Barfoed's Test and their interpretation?

Answer:

- **Barfoed's Positive (Red precipitate):** Indicates presence of monosaccharides.
- **Barfoed's Negative with Positive Benedict's Test:** Indicates presence of reducing disaccharides.

Q13.3: Which substances give a positive Barfoed's Test?

Answer:

- Monosaccharides, which are strongly reducing, such as:
 - o Fructose
 - o Glucose
 - o Galactose
 - o Pentose

Q13.4: Which substances give a negative Barfoed's Test with a positive Benedict's Test?

Answer:

- Reducing disaccharides, such as:
 - o Maltose
 - o Lactose

Q13.5: What are the pathological causes of reducing sugars in urine?

Answer:

Reducing Sugar	Cause
Glucose	Diabetes Mellitus, Renal glycosuria (e.g., Fanconi syndrome), Alimentary glycosuria (postprandial, thyrotoxicosis).
Fructose	Essential fructosuria (fructokinase defect), Hereditary fructose intolerance (aldolase D defect).
Galactose	Galactosemia (galactokinase deficiency), Classical galactosemia (GalPUT deficiency).
Pentose	Essential pentosuria (Xylitol dehydrogenase defect).

Q13.6: A person gives her urine sample for a routine screening test. Benedict's test is positive. Below is the result of Barfoed's test. Which of the following is the most probable cause?

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- A. Diabetes Mellitus
- B. Pregnancy

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- C. Fanconi's syndrome
- D. Galactosemia

Answer: B. Pregnancy

Explanation:

- **Positive Benedict's Test:** Indicates presence of reducing substance.
- **Barfoed's Test interpretation:** Here, the Barfoed's test is negative.
 - If Barfoed's Test is **negative**, physiological cause is likely (e.g., Lactose from pregnancy).
 - If Barfoed's Test is **positive**, pathological monosaccharide is present.

Further Differentiation based on specific tests:

- **Glucose detection (Aldose):** Glucose Oxidase-Peroxidase (GOD-POD) strip test.
- **Fructose detection (Ketose):** Seliwanoff's Test → Cherry red colour indicates Fructose.
- **Galactose detection:** Mucic Acid Test → White crystals indicate Galactose.
- **Pentose detection:** Bial's Test.



Q13.7: A person's urine answers Benedict's Test. The biochemist runs a battery of urine tests to detect the reducing sugar present. Based on the images provided below, find out the substance found in urine. Which of the following is the most probable cause?



- A. Diabetes Mellitus
- B. Fructosuria
- C. Fanconi's syndrome
- D. Galactosemia

Answer: B. Fructosuria

BIG QUESTION 14: What is Rothera's Test and how is it used to detect ketone bodies in urine?

Broad Answer: Rothera's Test is a chemical test that detects the presence of ketone bodies in urine, producing a characteristic purple-coloured ring, especially in conditions like prolonged starvation.

DETAILED QUESTIONS

Q14.1: What is the principle of Rothera's Test?

Answer:

- Rothera's Test detects the presence of ketone bodies in urine.
- A positive test is indicated by the appearance of a **purple-coloured ring**.

Q14.2: When does Rothera's Test become positive?**Answer:**

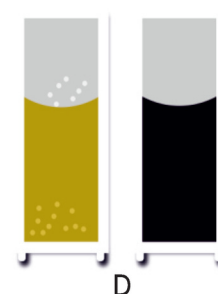
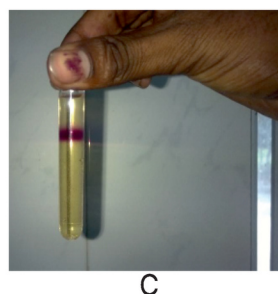
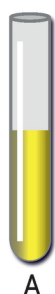
- During conditions associated with ketone body formation, such as:
 - Prolonged starvation → Ketosis.

Q14.3: What are other important urine tests and what do they detect?**Answer:**

Test Name	Detects
Xanthoproteic Acid Test	Aromatic amino acids
Benedict's Test	Reducing substances
Rothera's Test	Ketone bodies
Benzidine Test	Blood
Urine turning dark on standing	Alkaptonuria

Q14.4: What are the abnormal constituents of urine and their colour reactions?**Answer:**

Abnormal Constituent	Colour Reaction	Observation
Reducing substance	Benedict's test	Blue → Red
Ketone body	Rothera's test	Purple-coloured ring
Protein	Sulfosalicylic acid test	White precipitate
Blood	Benzidine test	Green/Black
Bile salt	Hay's test	Sulphur sinks to the bottom
Bile pigment	Fouchet's test	Green/Blue

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Q14.5: On prolonged starvation, which of the following tests will be positive?

- A. Xanthoproteic acid test
 B. Benedict's test
 C. Rothera's test
 D. Benzidine test

Answer: C. Rothera's test

Explanation:

- Prolonged starvation → Ketosis → Ketone bodies in urine.
- Rothera's Test is specific for detecting ketone bodies.
- Other options are unrelated to ketone detection.

BIG QUESTION 15: What are the types of blood collection tubes and their uses?

Broad Answer: Blood collection tubes contain different additives and are colour-coded based on their specific laboratory applications, such as biochemical analysis, coagulation studies, and storage.

DETAILED QUESTIONS

Q15.1: What additives are used in different coloured blood collection tubes?

Answer:

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Tube Colour	Additive	Use	Image
Grey	Sodium Fluoride, Potassium Oxalate	Glucose estimation	
Lavender	K2EDTA / K3EDTA	Whole blood samples (e.g., CBC, HbA1C) Estimation of labile parameters (PTH, ACTH, ammonia)	
Red	Silica (Clot activator)	Serum collection for biochemical tests	
Blue	3.2% Sodium Citrate	Coagulation assays (PT, aPTT, Fibrinogen)	
Black	3.8% Sodium Citrate	ESR estimation	

Green	Heparin	Stat biochemical analysis (eg. Cardiac troponin T), Molecular diagnostics, Cytogenetics	
Yellow	Gel and clot activator	Transport and storage of blood samples	

Q15.2: What is the significance of K2EDTA tubes?

Answer:

- K2EDTA chelates calcium, preventing clotting.
- Used for biochemical estimations requiring plasma or whole blood (e.g., CBC, HbA1C).
- Note:
 - If potassium is estimated from K2EDTA tube → Falsely elevated potassium levels.
 - If calcium is estimated → Falsely low calcium levels → Enzyme activities may appear falsely low.

Q15.3: How are serum and plasma differentiated based on blood collection tubes?

Answer:

- **Serum:**
 - Obtained from blood collected in a plain tube (Red-top).
 - Blood clots → Serum separates above clot.
 - Used for biochemical estimations (Renal function test, Liver function test, Hormone assays).
- **Plasma:**
 - Obtained from blood collected with anticoagulants (e.g., K2EDTA tube - Lavender-top).
 - Used for whole blood samples (e.g., CBC, HbA1C).

Q15.4: What is the use of Yellow coloured blood collection tubes?

Answer:

- Contains gel at the bottom.
- Used for transportation and storage of blood samples.
- **Advantage:**
 - Even if cells lyse, the serum is not contaminated due to separation by gel.
 - Gel acts as a mechanical barrier between cells and serum upon centrifugation.



Q15.5: What additive is used in the given blood collection tube?

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- A. Sodium Fluoride
- B. K2EDTA
- C. Heparin
- D. Silica

Answer: D. Silica

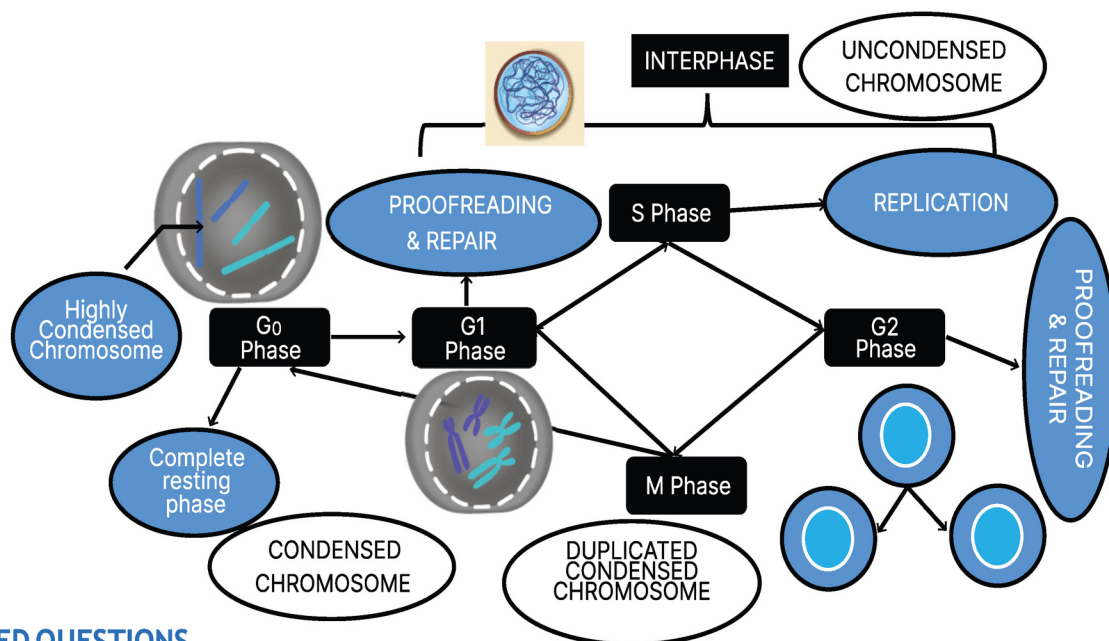
Explanation:

- Based on tube colour:
 - o **Sodium Fluoride:** Grey top (Glucose estimation).
 - o **K2EDTA:** Lavender top (CBC, HbA1C).
 - o **Heparin:** Green top (Stat biochemistry, molecular diagnostics).
 - o **Silica:** Red top (Clot activator for serum collection).



BIG QUESTION 16: What is the relationship between replication and chromosome condensation during the cell cycle?

Broad Answer: Chromosomes undergo phases of condensation and uncondensation during the cell cycle. Replication occurs during the uncondensed phases to allow access to DNA, while condensation ensures proper chromosome segregation during cell division.



DETAILED QUESTIONS

Q16.1: What is the structure of a chromosome?

Answer: One chromosome is a long double-stranded DNA molecule condensed with the help of proteins.

Q16.2: Why does a chromosome undergo condensation and uncondensation?

Answer:

- **Condensation:**
 - o For packaging the DNA.

- o Chromosomes are not actively performing replication or transcription.
- **Uncondensation:**
 - o Chromosomes become accessible for replication and transcription.

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Q16.3: What happens in different phases of the cell cycle regarding chromosome structure?

Answer:

Phase	Chromaosome State	Key Events
G ₀ phase	Condensed	Complete resting phase
G ₁ phase	Uncondensed	Pre-synthetic phase, proofreading and repair
S phase	Uncondensed	DNA replication occurs
G ₂ phase	Uncondensed	Post-synthetic phase, proofreading and repair of daughter DNA
M phase	Highly condensed	Cell division, chromosome segregation

Q16.4: What happens to chromosome arms during different phases?

Answer:

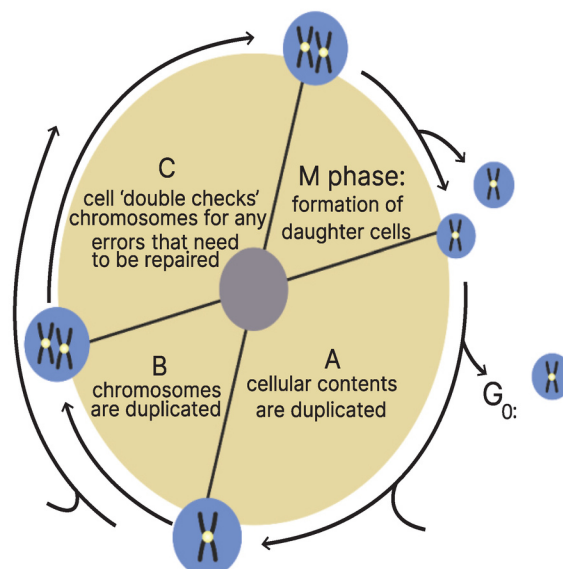
- **G₀ phase:**
 - o Each chromosome has one long and one short arm.
- **S phase:**
 - o Replication occurs, resulting in two long and two short arms per chromosome in M phase

Q16.5: What happens during the M phase of the cell cycle?

Answer:

- One diploid cell divides to give two diploid daughter cells.
- Events include:
 - o **Metaphase:** Mitotic spindle forms and attaches to the centromere.
 - o **Anaphase:** Mitotic spindle contracts, centromere breaks longitudinally, chromosomes segregate.
 - o Chromosomes are highly condensed throughout the M phase.

Q16.6: Which of the following statements is true regarding replication and chromosome structure?



- A. Replication happens in the B phase. In the B phase, the chromosome is highly condensed.
- B. Replication happens in the C phase. In the C phase, the chromosome is highly condensed.
- C. Replication happens in the B phase. In the B phase, the chromosome is uncondensed.
- D. Replication happens in the C phase. In the C phase, the chromosome is uncondensed.

Answer: C. Replication happens in the B phase. In the B phase, the chromosome is uncondensed.

Explanation:

- Replication occurs in the **S phase**, which corresponds to the **B phase** in this context.
- During replication, chromosomes are **uncondensed** to allow DNA access.

BIG QUESTION 17: What is Grave's Disease and how is it diagnosed clinically?

Broad Answer: Grave's disease is an autoimmune disorder directed against the TSH receptor, leading to hyperthyroidism, goitre, exophthalmos, pretibial myxoedema, and clubbing. It is mediated by stimulatory antibodies like Long-acting thyroid stimulator antibody (LATS).

DETAILED QUESTIONS

Q17.1: What is the underlying cause of Grave's Disease?

Answer:

- Autoimmune disorder directed against the TSH receptor.
- Leads to hyperfunctioning of the receptor and excessive thyroid hormone production.

Q17.2: What are the characteristic clinical features of Grave's Disease?

Answer:

- Hyperthyroidism.
- **Goitre** (thyroid hyperplasia).
- **Exophthalmos** (bulging eyes) due to retro-orbital tissue oedema.
- **Pretibial myxoedema** (localized skin thickening on the shins).
- **Clubbing**.

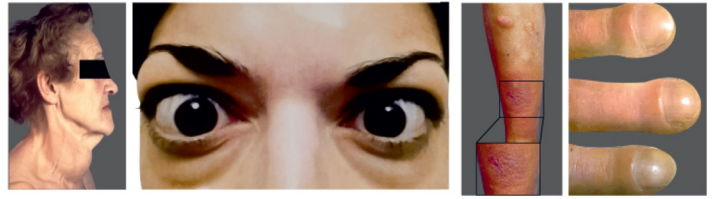
Q17.3: What is the role of Long-acting thyroid stimulator antibody (LATS) in Grave's Disease?

Answer:

- It is an autoantibody directed against TSH receptors.
- Stimulates the receptor, causing hyperthyroidism.
- Cross-reacts with TSH receptor analogs on preadipocyte fibroblasts.
- Induces cytokine release → Oedema in retro-orbital tissues → Exophthalmos.
- Responsible for pretibial dermatopathy.

Q17.4: The most probable antibody detected in this condition (Grave's Disease) is:

- A. Antithyroglobulin antibody
- B. Anti gliadin antibody
- C. Anti transglutaminase antibody
- D. Long-acting thyroid stimulator antibody



Answer: D. Long-acting thyroid stimulator antibody

Explanation:

- Image shows: A - Goitre B - Exophthalmos C - Pretibial myxoedema D - Clubbing
- Grave's Disease is associated with LATS (Long-acting thyroid stimulator antibody).
- Other options:
 - **Antithyroglobulin antibody:** Seen in Hashimoto's thyroiditis.
 - **Anti gliadin antibody:** Seen in Celiac disease.
 - **Anti transglutaminase antibody:** Seen in Celiac disease.

BIG QUESTION 18: What is Addison's Disease and what causes hyperpigmentation in this condition?

Broad Answer: Addison's disease is adrenal cortical failure, often due to autoimmune destruction or tuberculosis. It leads to low cortisol and mineralocorticoid levels, causing symptoms like hypotension, hypoglycemia, electrolyte imbalance, and characteristic hyperpigmentation.

DETAILED QUESTIONS

Q18.1: What is the underlying cause of hyperpigmentation in Addison's Disease?

Answer:

- Adrenal cortical failure leads to low cortisol and mineralocorticoid levels.
- Low cortisol removes negative feedback on ACTH.
- **Proopiomelanocortin (POMC)** is processed to produce:
 - ACTH.
 - **Gamma-MSH (Melanocyte-stimulating hormone).**
- Gamma-MSH causes hyperpigmentation.

Q18.2: What are the causes of Addison's Disease?

Answer:

- Autoimmune-mediated destruction of adrenal cortex.
- Tuberculosis affecting the adrenal glands.

Q18.3: What are the clinical features of Addison's Disease?

Answer:

- **Low cortisol:**
 - No counteraction of insulin → Hypoglycemia.
 - Dextrose infusion may cause water retention due to low cortisol hypo-osmotic circulation → Water enters the thermostat cells of hypothalamus → Causing thermal dysregulation → **Dextrose fever.**

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- **Low mineralocorticoids:**
 - o Sodium not reabsorbed → Hyponatremia.
 - o Hypotension.
 - o Hyperkalemia.
 - o Metabolic acidosis.
- Hyperpigmentation (due to increased MSH).

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Q18.4: A 42-year-old man presents with hypoglycemia. He is a known patient of tuberculosis with poor adherence to treatment. He was treated with dextrose and before discharge he wanted a dermatological opinion for hyperpigmentation of gums, dorsum of the tongue, and joints. The dermatologist suspected Addison's. The cause of hyperpigmentation in Addison's disease is:

- A. Glucocorticoid stimulates MSH
- B. ACTH has MSH activity
- C. ACTH and MSH are synthesised from proopiomelanocortin
- D. Autoimmune process stimulates pigmentation



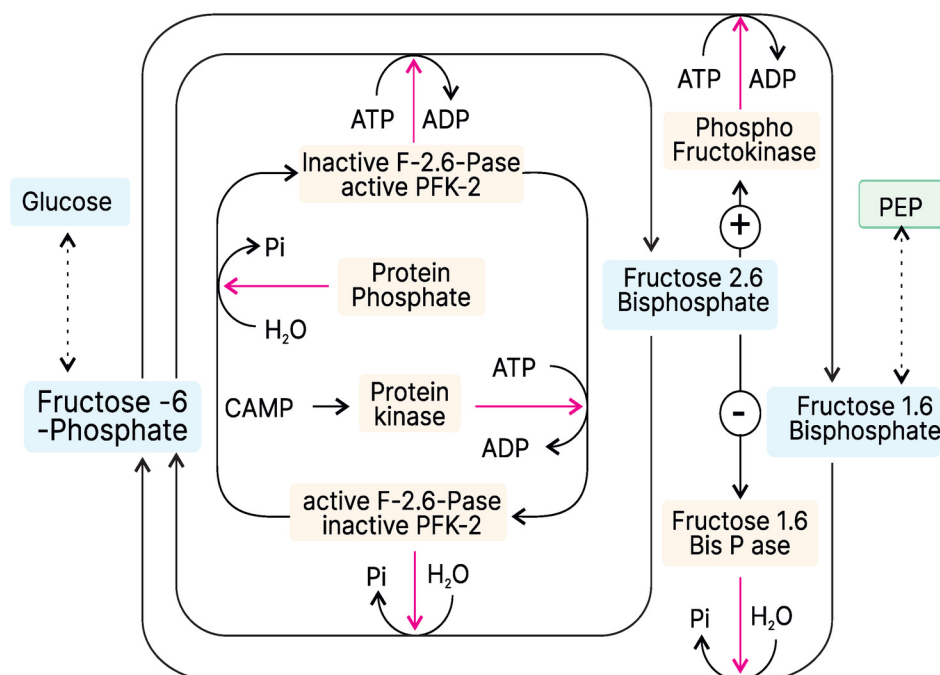
Answer: C. ACTH and MSH are synthesised from proopiomelanocortin

Explanation:

- In Addison's disease, adrenal cortical failure leads to low cortisol.
- Loss of feedback inhibition → Increased ACTH production.
- ACTH and MSH are derived from **Proopiomelanocortin (POMC)**.
- Increased MSH causes hyperpigmentation.

BIG QUESTION 19: How is glycolysis and gluconeogenesis regulated by Fructose 2,6-bisphosphate and related enzymes?

Broad Answer: Glycolysis and gluconeogenesis are reciprocal pathways regulated by Fructose 2,6-bisphosphate (F-2,6-BP), which stimulates glycolysis and inhibits gluconeogenesis. This prevents a futile cycle and ensures proper glucose homeostasis.



DETAILED QUESTIONS

Q19.1: What is the role of Fructose 2,6-bisphosphate in metabolism?

Answer:

- Fructose 2,6-bisphosphate is a common allosteric regulator.
- **Stimulates glycolysis** by activating Phosphofructokinase-1 (PFK-1).
- **Inhibits gluconeogenesis** by inhibiting Fructose 1,6-bisphosphatase.

Q19.2: How is Fructose 2,6-bisphosphate synthesized and degraded?

Answer:

- Fructose 2,6-bisphosphate is synthesised by the bifunctional enzyme PFK-2/FBPase-2 when it is dephosphorylated, activating PFK-2 activity.
- It is degraded by the same enzyme when it is phosphorylated, activating fructose 2,6-bisphosphatase (FBPase-2) activity.

Q19.3: What is a tandem enzyme and what are its activities?

Answer:

- Abi-functional enzyme with opposite enzymatic activities.
- When dephosphorylated:
 - Exhibits **PFK-2** activity → Produces Fructose 2,6-bisphosphate → Stimulates glycolysis.
- When phosphorylated:
 - Exhibits **Fructose 2,6-bisphosphatase** → Degrades Fructose 2,6-bisphosphate → Stimulates gluconeogenesis.

Q19.4: What happens during starvation to regulate these pathways?

Answer:

- Blood glucose decreases → Glucagon is released.
- Glucagon acts on **GS receptor** → Stimulates adenylyl cyclase → Produces cyclic AMP.
- cAMP activates protein kinase A.
- Protein kinase A phosphorylates tandem enzyme → Activates Fructose 2,6-bisphosphatase activity.
- Fructose 2,6-bisphosphate is cleaved →
 - Glycolysis is inhibited.
 - Gluconeogenesis is stimulated.
- Plasma glucose levels increase to maintain homeostasis.

Q19.5: What are the consequences if regulation fails (futile cycle)?

Answer:

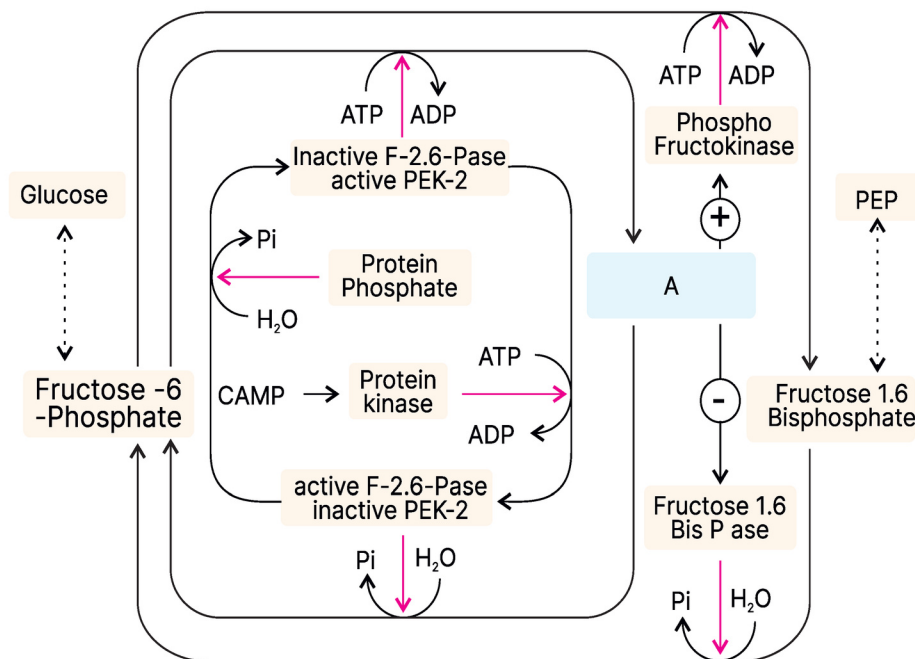
- Simultaneous activation of both pathways leads to:
 - Continuous conversion of intermediates without net gain.
 - ATP wastage.
 - Example:
 - A Starving person uses 11 ATP molecules for futile cycling between pyruvate and fructose 6-phosphate if regulatory enzymes fail.

Q19.6: What are the important facts to remember about Fructose 2,6-bisphosphate and Tandem Enzyme?

Answer:

- Fructose 2,6-bisphosphate:
 - o Activates PFK-1 → Stimulates glycolysis.
 - o Inhibits Fructose 1,6-bisphosphatase → Inhibits gluconeogenesis.
- Tandem enzyme:
 - o When **dephosphorylated**, acts as **PFK-2**, producing Fructose 2,6-bisphosphate → Stimulates glycolysis.
 - o When **phosphorylated**, acts as **Fructose 2,6-bisphosphatase**, degrading Fructose 2,6-bisphosphate → Stimulates gluconeogenesis.

Q19.7: Identify A in the following regulatory pathway diagram related to glycolysis and gluconeogenesis.



- A. Fructose 1,6-bisphosphate
- B. Fructose 2,6-bisphosphate
- C. PFK-1
- D. PFK-2

Answer: B. Fructose 2,6-bisphosphate

Explanation:

- The image depicts regulation of glycolysis and gluconeogenesis.
- **Fructose 2,6-bisphosphate** is the common regulator affecting both pathways.
- It stimulates glycolysis and inhibits gluconeogenesis.