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## Goldmine to Crack Exam

### Based on Recall MCQs from 2022 to 2026 with Detailed Explanations

**Dissect | Discuss | Dominate**

2nd Edition




R Rajamahendran
Madhu Choudhary

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# How to Study this Book?

This book is designed specifically for NEET PG aspirants who want to revise and consolidate their knowledge through past year questions (PYQs) from 2022 to 2026. The content is carefully organized both subject-wise and year-wise, making it easy to focus on individual topics or track trends across exams.

**Step 1: Build Your Foundation**

- Complete your theory study first.
- Focus on conceptual understanding before attempting PYQs.

**Step 2: Approach PYQs Strategically**

- Use this book after theory revision.
- PYQs are organized subject-wise and year-wise for easy navigation.
- Review questions in context of the concepts you've learned.

**Step 3: Study and Analyze Each Question**

- Read the question carefully.
- Refer to detailed explanations to understand reasoning.
- Note exam pearls, mnemonics, and flash facts for memory reinforcement.

**Step 4: Reinforce and Recall**

- Focus on high-yield topics and repeated questions.
- Use remember points and tips for rapid last-minute revision.
- Revisit volatile one-liners to boost retention.

**Step 5: Integrate and Revise**

- Combine PYQs with your concept notes.
- Practice active recall by attempting questions without looking at answers.
- Focus on weak areas highlighted during PYQ analysis.

By following below approach, aspirants can strengthen their conceptual clarity, reinforce memory of high-yield topics, and gain confidence for last-minute exam preparation:

Theory Study → Concept Building → PYQs (Subject and Year-wise) → Read Question → Understand Explanation → Note Mnemonics/Exam Pearls → Reinforce High-yield Concepts → Active Recall and Revision → Confidence for Exam

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CHAPTER 3

# Biochemistry

## NEET PG 2026

**Q1. A diabetic patient on adequate insulin has blood glucose persistently >250 mg/dL, with high cortisol levels. What explains the persistent hyperglycemia?**

A. Inhibition of hepatic glycogenolysis
B. Translocation of GLUT4 in skeletal muscle
C. Compensatory action of hormones
D. Increased insulin receptor sensitivity

**Ans. C. Compensatory action of hormones**

Insulin is the primary **hypoglycemic** hormone in the body, whereas **cortisol, glucagon, epinephrine, and growth hormone** act as **hyperglycemic (counter-regulatory/compensatory) hormones**.

Cortisol opposes the action of insulin by:

- Enhancing hepatic **gluconeogenesis** (increasing expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase).
- Promoting muscle protein breakdown to supply amino acid precursors for gluconeogenesis.
- Decreasing peripheral glucose uptake and inducing **post-receptor insulin resistance** in peripheral tissues.

In a diabetic patient with elevated cortisol levels (e.g., secondary to stress, Cushing's syndrome, or exogenous glucocorticoids), the **compensatory/counter-regulatory actions** of cortisol override the peripheral effects of administered insulin, resulting in persistent hyperglycemia (>250 mg/dL).

**Other Options**

(A) **Inhibition of hepatic glycogenolysis:** Cortisol promotes (or acts permissively with glucagon and epinephrine to maintain) hepatic glucose output and gluconeogenesis rather than inhibiting it. Inhibiting glycogenolysis would lower blood glucose levels.

(B) **Translocation of GLUT4 in skeletal muscle:** Translocation of GLUT4 vesicles to the cell membrane is the primary mechanism by which **insulin lowers blood glucose**. Cortisol inhibits or impairs GLUT4 translocation in skeletal muscle and adipose tissue, driving insulin resistance.

(D) **Increased insulin receptor sensitivity:** Cortisol causes **insulin resistance** (decreased receptor sensitivity and impaired downstream post-receptor signalling), which prevents insulin from effectively clearing glucose from the blood.

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## EXAM PEARL

### Hormonal Control of Blood Glucose

| *Hormone* | *Primary glycemic action* | *Biochemical effects on glucose metabolism* |
|---|---|---|
| **Insulin** | Hypoglycemic | Promotes GLUT4 translocation, glycogen synthesis, glycolysis; inhibits gluconeogenesis and glycogenolysis |
| **Cortisol** | Hyperglycemic | Increases **gluconeogenesis**, promotes amino acid mobilization from muscle, decreases peripheral glucose utilization (induces insulin resistance) |
| **Glucagon** | Hyperglycemic | Promotes hepatic glycogenolysis and gluconeogenesis via cAMP pathway |
| **Epinephrine** | Hyperglycemic | Stimulates glycogenolysis in liver and muscle; inhibits insulin secretion |

*Ref:* Vasudevan DM, Sreekumari S, Vaidyanathan K. Textbook of Biochemistry for Medical Students. 10th ed. p. 115-125.

**Q2. A patient with bronchogenic carcinoma has elevated heat-stable alkaline phosphatase isoenzyme. This tumor-associated isoenzyme resembles ALP normally found in which tissue?**

A. Bone
B. Liver
C. Placenta
D. Kidney

**Ans. C. Placenta**

The heat-stable Alkaline Phosphatase (ALP) isoenzyme elevated in patients with bronchogenic carcinoma (as well as ovarian, cervical, and gastrointestinal cancers) is known as the **Regan Isoenzyme**.

It is an ectopic, tumor-associated isoenzyme that is **heat-stable** (resists denaturation when heated to 65°C for 30 minutes) and inhibited by L-phenylalanine.

**Tissue Resemblance:** It is structurally, immunologically, and genetically identical to normal **Placental Alkaline Phosphatase (PLAP)**, which is synthesized by trophoblastic cells of the placenta.

**Oncofetal Markers:** The Regan isoenzyme is a classic example of an **oncofetal protein/antigen,** a protein produced normally during embryonic/fetal life (by placenta) that is abnormally re-expressed by malignant cells in adult life.

**Other Options**

(A) **Bone:** Bone ALP is **heat-labile** (easily inactivated by heat at 56°C; remember: ***"Bone burns, Liver lives"***).
(B) **Liver:** Liver ALP is moderately heat-stable at 56°C (more stable than bone, but destroyed at 65°C). It is not identical to the ectopic Regan isoenzyme found in bronchogenic carcinoma.
(D) **Kidney:** Renal ALP is heat-labile and cleared rapidly, contributing negligibly to serum ALP elevations in malignancy.

**MNEMONIC ALP - Heat Stability:**
*Bone Burns, Liver Lives, Placenta Prevails*
Bone is most heat-labile, Placenta/Regan is most heat-stable

## EXAM PEARL

### Alkaline Phosphatase (ALP) Isoenzymes

| *Isoenzyme* | *Source/associated conditions* | *Heat stability* | *L-phenylalanine inhibition* |
|---|---|---|---|
| **Placental (PLAP)** | Normal 3rd trimester placenta | Highly Heat-Stable (resists 65°C) | Inhibited |
| **Regan isoenzyme** | Ectopic tumor marker (Bronchogenic Ca, Ovarian Ca) | Highly Heat-Stable (resists 65°C) | Inhibited |
| **Nagao isoenzyme** | Ectopic variant (Testicular germ cell tumors/Seminoma) | Highly Heat-Stable | Inhibited (also inhibited by L-leucine) |
| **Liver ALP** | Biliary obstruction, hepatic disease | Moderately Stable (56°C) | Not inhibited |
| **Bone ALP** | Rickets, Paget's disease, osteoblastic bone metastases | Heat-Labile (destroyed at 56°C) | Not inhibited |

*Ref:* Vasudevan DM, Sreekumari S, Vaidyanathan K. Textbook of Biochemistry for Medical Students. 10th ed. p. 182-186.

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**Q3. A patient presents with severe abdominal pain for few hours. He was on a weight loss diet with less of carbohydrates. These was no abdominal distension or tenderness. The symptoms improve after hemin administration. Which enzyme is deficient?**

A. Ferrochelatase
B. ALA synthase
C. Porphobilinogen deaminase
D. ALA dehydratase

**Ans. C. Porphobilinogen deaminase**

The classic presentation of severe, colicky abdominal pain without abdominal distension, rigidity, or tenderness (severe neurovisceral abdominal pain without significant abdominal findings) is a hallmark of **Acute Intermittent Porphyria (AIP)**.

**Precipitating Factors:** Low-carbohydrate diets (caloric restriction/fasting) induce hepatic ALA **synthase 1 (ALAS1)** expression, precipitating an acute porphyric attack.

**Response to Hemin:** Administering IV **hemin (heme arginate)** restores the intrahepatic regulatory heme pool, which downregulates ALAS1 via negative feedback and rapidly alleviates symptoms.

**Enzyme Deficiency:**

- AIP is an autosomal dominant disorder caused by a deficiency of **Porphobilinogen Deaminase** (also known as **Hydroxymethylbilane Synthase** or **HMBS**).
- This deficiency leads to the accumulation of toxic heme precursors, specifically **δ-aminolevulinic acid (ALA)** and **Porphobilinogen (PBG)**, which cause neurovisceral symptoms.

**Diagnostic Test:** Urinary elevation of **Porphobilinogen (PBG)** and ALA during an acute attack. Urine darkens upon exposure to air and light (port-wine urine).

**Treatment of Acute Attack:**

- High-carbohydrate load (IV glucose/dextrose) for mild attacks (glucose suppresses ALAS1 transcription through heme regulatory pathways).
- **IV Hemin/Hematin** for moderate-to-severe attacks (gold standard treatment).

**Other Options**

(A) **Ferrochelatase:** Deficient in **Erythropoietic Protoporphyria (EPP)**, which manifests primarily as cutaneous photosensitivity rather than acute visceral abdominal pain.
(B) **ALA synthase:** The rate-limiting enzyme of heme synthesis. Its deficiency causes **X-linked sideroblastic anemia**, not acute intermittent porphyria or acute abdominal pain.
(D) **ALA dehydratase:** Deficient in **ALA Dehydratase Deficiency Porphyria (ADP)** (also known as Doss porphyria), an extremely rare autosomal recessive disorder.

**EXAM PEARL**

**Pathway & Enzyme Defects in Major Porphyrias**

| *Enzyme deficient* | *Disease* | *Key presentation* |
|---|---|---|
| **Porphobilinogen deaminase (HMBS)** | Acute intermittent porphyria (AIP) | Neurovisceral attacks (Abdominal pain, psychiatric, neuropathy), no skin lesions |
| **Uroporphyrinogen decarboxylase (UROD)** | Porphyria cutanea tarda (PCT) | Cutaneous photosensitivity, blistering, hyperpigmentation |
| **Ferrochelatase** | Erythropoietic Protoporphyria (EPP) | Painful solar urticaria/photosensitivity |
| **Uroporphyrinogen III synthase (UROS)** | Congenital erythropoietic porphyria (CEP) | Red urine, extreme cutaneous photosensitivity, erythrodontia |

*Ref:* Vasudevan DM, Sreekumari S, Vaidyanathan K. Textbook of Biochemistry for Medical Students. 10th ed. p. 290-296.

**Q4. A child has increased blood ammonia, increased urinary orotic acid, and decreased citrulline. The disorder is X-linked. Which enzyme is deficient?**

A. Carbamoyl phosphate synthetase I (CPS-I)
B. Carbamoyl phosphate synthetase II (CPS-II)
C. Argininosuccinate synthetase (ASS)
D. Ornithine transcarbamylase (OTC)

**Ans. D. Ornithine transcarbamylase (OTC)**

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Ornithine transcarbamylase (OTC) deficiency is the **only X-linked recessive** disorder of the urea cycle (all other urea cycle enzyme deficiencies are autosomal recessive).

**Pathophysiology and Biochemical Markers:**

1. **Hyperammonemia:** Blockade at the OTC step prevents conversion of carbamoyl phosphate and ornithine to citrulline, causing severe **hyperammonemia** and **decreased serum citrulline**.
2. **Orotic Aciduria:** The accumulated **carbamoyl phosphate** in the mitochondria leaks into the cytoplasm, where it enters the pyrimidine synthesis pathway, leading to massive production and urinary excretion of **orotic acid**.

**Biochemical Pathway Linkage**

$$\text{Ammoni} + HCO_3^- \xrightarrow{\text{CPS–I}} \text{Carbamoyl Phosphate} \xrightarrow[\textbf{OTC Defect}]{\text{OTC}} \text{Citrulline}$$

$$\downarrow \text{(Accumulation \& leakage into cystosol)}$$

$$\text{Carbamoyl Phosphate} \xrightarrow{\text{CPS-II}} \text{Orotidylate pathway} \rightarrow \textbf{Urinary Orotic Acid}$$

**Urea Cycle Disorders**

| *Enzyme deficient* | *Disease* | *Plasma citrulline* | *Urinary orotic acid* | *Inheritance* |
|---|---|---|---|---|
| **CPS-I** | Hyperammonemia Type I | Decreased | Low/Normal | Autosomal recessive |
| **OTC (most common)** | Hyperammonemia Type II | Decreased | Markedly increased | X-linked recessive |
| **ASS** | Citrullinemia Type I | Markedly Increased | Variable/Normal | Autosomal recessive |
| **ASL** | Argininosuccinic aciduria | Moderately increased | Normal | Autosomal recessive |
| **Arginase** | Hyperargininemia | Normal/Mild | Normal | Autosomal recessive |

**EXAM PEARL**

**Urea Cycle Defect**

**Most Common Urea Cycle Defect:** Ornithine Transcarbamylase (OTC) deficiency.

**Key Differentiating Feature:** High ammonia + low citrulline + **High Orotic Acid = OTC deficiency** vs. High ammonia + low citrulline + **Low Orotic Acid = CPS-I deficiency**.

**Clinical Presentation:** Neonatal lethargy, poor feeding, vomiting, tachypnea (hyperventilation due to cerebral edema), seizures, and coma.

*Ref:* Vasudevan DM, Sreekumari S, Vaidyanathan K. Textbook of Biochemistry for Medical Students. 10th ed. p. 248-254.

**Q5. A certain bioactive phospholipid marker is increased in the background of a tumor and promotes tumor growth by supressing oxidative phosphorylation and enhancing glycolysis. Which among the following is that phopspholipid?**

A. Phosphatidylcholine
B. Cardiolipin
C. Lysophosphatidic acid
D. Phosphatidylserine

**Ans. C. Lysophosphatidic acid**

**Lysophosphatidic Acid (LPA)** is a potent, extracellular **bioactive glycerophospholipid** that is significantly elevated in tumor microenvironments (particularly in ovarian, breast, prostate, and gastrointestinal cancers). It is produced extracellularly primarily by the lysophospholipase D enzyme, **Autotaxin**.

**Metabolic Reprogramming (Warburg Effect):** LPA signals through G protein-coupled receptors (LPAR1–6) and downstream **Akt-mTOR-HIF-1**α pathways. It drives the metabolic shift characteristic of cancer cells by:

- **Suppressing mitochondrial oxidative phosphorylation (OXPHOS)**.
- **Enhancing aerobic glycolysis** (upregulating hexokinase, glucose transporters [GLUTs], and lactate production).

**Tumor Promotion:** By promoting the Warburg phenotype, LPA supplies rapid ATP and metabolic precursors required for cell proliferation, survival, invasion, and tumor-associated angiogenesis.

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**Other Options**

(A) **Phosphatidylcholine:** The primary structural phospholipid component of eukaryotic cell membranes and pulmonary surfactant; it does not function as an elevated tumor bioactive signalling lipid driving the Warburg metabolic switch.

(B) **Cardiolipin:** A structural phospholipid localized almost exclusively in the **inner mitochondrial membrane**, crucial for maintaining electron transport chain complex integrity. Loss/oxidation of cardiolipin impairs OXPHOS, but it is not a tumor-secreted bioactive driver of glycolysis.

(D) **Phosphatidylserine:** An inner plasma membrane phospholipid. Flip-flop of phosphatidylserine to the outer leaflet serves as a **signal for phagocytosis** during apoptosis.

*Ref:* Vasudevan DM, Sreekumari S, Vaidyanathan K. Textbook of Biochemistry for Medical Students. 10th ed. p. 142-148.

## NEET PG 2025

**Q6. A mother brings her 18-month-old child to the clinic due to progressive motor weakness and recent onset of seizures. Physical examination reveals a characteristic cherry-red spot on the macula during fundoscopy. The mother gives a history of a spontaneous abortion during her second trimester. Diagnostic testing confirms a profound deficiency of the enzyme Hexosaminidase A. Which of the following substances is most likely accumulating in the lysosomes of this patient's neuronal cells?**

A. Ganglioside GM2
B. Galactocerebroside
C. Sphingolipids
D. Ganglioside GM1

**Ans. A. Ganglioside GM2**

The child is presenting with the classic triad of **Tay-Sachs Disease**, an autosomal recessive lysosomal storage disorder **(neurodegeneration + cherry-red spots on macula + hexosaminidase A deficiency)**.

**Pathophysiology**

The enzyme hexosaminidase A is responsible for the degradation of GM2 gangliosides within the lysosomes. When this enzyme is deficient, the GM2 gangliosides cannot be broken down.

They accumulate to toxic levels specifically in the neuronal cells of the brain and the retinal ganglion cells.

The cherry-red spot occurs because the retinal ganglion cells around the fovea swell with these lipids and turn opaque/white, while the fovea itself (which lacks these ganglion cells) remains transparent, allowing the red color of the underlying choroid to shine through.

**MNEMONIC** **Cherry red spot in medicine: Cherry Trees Never Grow Tall**
**C**entral Retinal Artery Occlusion
**T**ay-Sachs Disease
**N**iemann-Pick Disease
**G**M1 Gangliosidosis
**S**ialidosis/**S**andhoff Disease

**Other Options**

(B) **Galactocerebroside:** This accumulates in Krabbe disease (deficiency of galactocerebrosidase). It presents with peripheral neuropathy and globoid cells, but usually no cherry-red spot.

(C) **Sphingolipids:** While GM2 is a type of sphingolipid, the above question asks for the specific molecule. Sphingomyelin specifically accumulates in Niemann-Pick disease.

(D) **Ganglioside GM1:** This accumulates in GM1 Gangliosidosis (deficiency of beta-galactosidase). While it also features a cherry-red spot, the specific enzyme deficiency mentioned (hexosaminidase A) points to ganglioside GM2.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 235-238.

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**Q7. A man is rescued after being trapped in a tunnel for five days without access to food. Upon examination, he is conscious and hemodynamically stable. At this stage of prolonged fasting, which of the following metabolic processes serves as the primary source of fuel for his brain?**

A. Gluconeogenesis
B. Ketosis
C. Lipolysis
D. Glycogenolysis

**Ans. B. Ketosis**

Following prolonged fasting/starvation, the body undergoes significant metabolic shifts to preserve muscle mass and maintain brain function.

**Metabolic Timeline of Fasting**

**0–24 hours (Post-absorptive):** The brain relies on glucose provided by glycogenolysis. Liver glycogen stores are usually exhausted within 12–24 hours.

**Days 1–3 (Early starvation):** Gluconeogenesis becomes the primary source of glucose.

**Days 4 and beyond (Prolonged starvation):** If the body continues relying solely on gluconeogenesis, muscle wasting would occur rapidly. To prevent this, the body shifts to lipolysis. These fatty acids are converted in the liver into ketone bodies. By day 5, the brain adapts to use ketone bodies for approximately 60–70% of its energy requirements, drastically reducing the need for glucose and sparing muscle protein.

**Other Options**

(A) **Gluconeogenesis:** While this process still occurs at day five to provide the minimum glucose required for RBCs, it is no longer the ***primary*** source for the brain.
(C) **Lipolysis:** This provides fatty acids for the brain to synthesis ketones. However, the brain itself cannot effectively oxidize long-chain fatty acids because they do not cross the blood-brain barrier efficiently.
(D) **Glycogenolysis:** This is the sprint phase. These stores are long gone by day five.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 450-452.

**Q8. A patient presents with anaemia, ataxia and neuropathy and positive Romberg sign. Lab investigations reveal elevated total homocysteine and methylmalonic acid levels. Production of which of the following amino acids could be affected?**

A. Glutamine
B. Cysteine
C. Methionine
D. Tyrosine

**Ans. C. Methionine**

This clinical presentation describes Vitamin $B_{12}$ deficiency, which results in **subacute combined degeneration of the spinal cord (SCD)** and **megaloblastic anemia.** The biochemical findings of elevated methylmalonic Acid (MMA) and homocysteine are the "Gold Standard" for confirming vitamin $B_{12}$ deficiency.

**Vitamin $B_{12}$ (Cobalamin) acts as a co-factor for only two enzymes.**

**Methionine synthase:** This enzyme converts homocysteine into methionine. It requires vitamin $B_{12}$ (as methylcobalamin) and methyl-tetrahydrofolate. In vitamin $B_{12}$ deficiency, homocysteine cannot be converted to methionine. Therefore, methionine production is decreased, and homocysteine levels rise.

**Methylmalonyl-CoA mutase:** This enzyme converts methylmalonyl-CoA to succinyl-CoA. In vitamin $B_{12}$ deficiency, MMA accumulates. This is unique to vitamin $B_{12}$ deficiency and is not seen in folate deficiency.

**Other Options**

(A) **Glutamine:** Not directly dependent on vitamin $B_{12}$-mediated methionine cycle.
(B) **Cysteine:** While homocysteine can be converted to cysteine via the cystathionine pathway, this requires vitamin $B_6$, not $B_{12}$. Elevated homocysteine usually results in increased cysteine levels if vitamin $B_6$ is available.
(D) **Tyrosine:** Produced from phenylalanine via phenylalanine hydroxylase; this requires tetrahydrobiopterin.

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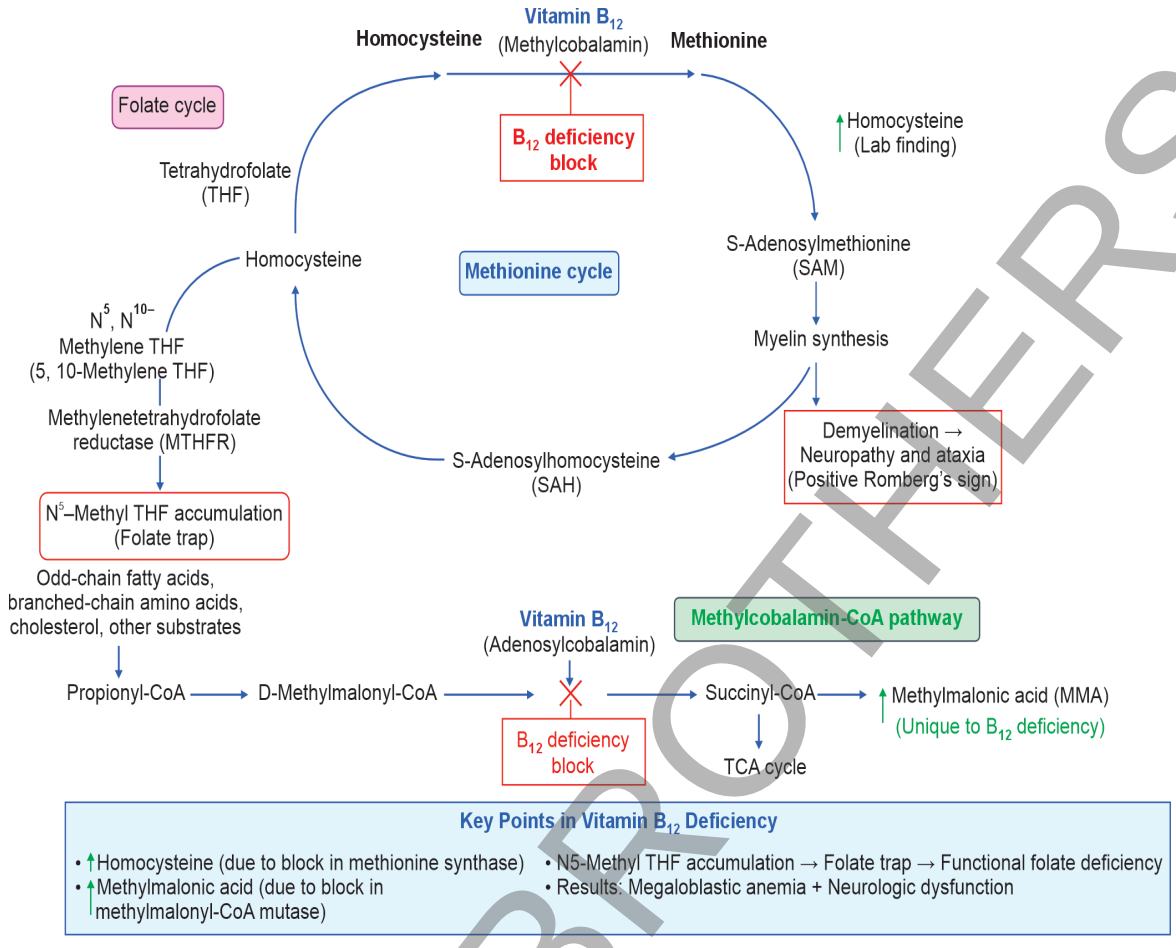


*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 320-324.

**Q9. A male child presents with fractured arm. Additional findings include bleeding from his gums and perifollicular haemorrhages. Which of the following enzymes is deficient in this child?**

A. Galactosyl transferase
B. ALA synthase
C. Prolyl hydroxylase
D. Glutathione reductase

**Ans. C. Prolyl hydroxylase**

The clinical presentation describes **scurvy**. In children, scurvy (also called Barlow's disease) presents with features of connective tissue weakness:

- **Perifollicular hemorrhages:** Bleeding around hair follicles due to capillary fragility.
- **Bleeding gums:** Collagen is essential for the integrity of the periodontal ligament and gingival capillaries.
- **Fractured arm/bone pain:** Vitamin C is crucial for the formation of the osteoid matrix. In children, deficiency leads to weakened bone mineralization and subperiosteal hemorrhages, making them highly prone to fractures.

**Biochemical Role of Vitamin C**

The synthesis of collagen requires a specific post-translational modification called hydroxylation. Prolyl hydroxylase and lysyl hydroxylase require vitamin C (ascorbic acid) and $Fe^{2+}$ (ferrous iron) as co-factor.

Proline and lysine residues on the alpha-chains of collagen are hydroxylated. This allows for the formation of hydrogen bonds, which are necessary to align with three alpha-chains into a stable triple helix.

***Vitamin C deficiency*** results in collagen that is unstable and quickly degraded by the body, leading to the permeable vessels and weak bones.

**MNEMONIC 4-H" of Scurvy**
**H**emorrhage (Perifollicular, subperiosteal, gingival)
**H**yperkeratosis (Rough skin, "corkscrew" hairs)
**H**ypochondriasis (Irritability and malaise)
**H**ematologic abnormalities

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**Other Options**

(A) **Galactosyl transferase:** This enzyme is involved in the glycosylation of collagen, but its deficiency is not a standard clinical presentation for these symptoms.

(B) **ALA synthase:** This is the rate-limiting enzyme in heme synthesis. A deficiency would lead to sideroblastic anemia, not connective tissue defects.

(D) **Glutathione reductase:** This enzyme helps protect red blood cells from oxidative stress. Deficiency (related to Vitamin $B_2$ or G6PD issues) leads to hemolysis, not bleeding gums or bone fractures.

## EXAM PEARL

### Scurvy – Classical Features

- **Frog-leg position:** Due to intense bone pain (subperiosteal hemorrhage), infants often lie with their hips and knees flexed and abducted
- **Hemorrhagic signs:** Perifollicular hemorrhages**;** swollen, spongy, purple gums; petechiae and ecchymoses
- **Scorbutic rosary:** Palpable beads at the costochondral junctions
- **Irritability:** Extreme tenderness upon handling or moving the limbs
- **White line of Frankel:** A dense, white band at the zone of provisional calcification
- **Wimberger's ring sign:** A thin, circular white rim surrounding a pale, demineralized centre of the epiphysis
- **Pelkan spur:** Bony outgrowths (spurs) at the edges of the metaphysis
- **Trummerfeld zone:** A dark, lucent band (scurvy line) just below the White Line of Frankel, representing a zone of crushed, weak bone

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 310-313.

**Q10. A baby presents with low phenylalanine levels. An apparent tyrosine deficiency was seen. But phenylalanine hydroxylase levels were normal. The deficiency of which of the following coenzymes can lead to this manifestation?**

A. SAM
B. Biopterin
C. Tetrahydrofolic acid (or Tetrahydrofolate).
D. Pyridoxal phosphate

**Ans. B. Biopterin**

The case scenario looks like **phenylketonuria (PKU)** because of the apparent tyrosine deficiency. However, phenylalanine hydroxylase (PAH), is functioning normally. This points to a deficiency in the coenzyme rather than the enzyme itself.

Phenylalanine hydroxylase requires tetrahydrobiopterin ($BH_4$) as a vital co-factor to catalyze the conversion of phenylalanine to tyrosine.

$$\textbf{Phenylalanine} + O_2 + BH_4 \rightarrow \textbf{Tyrosine} + H_2O + BH_2$$

If $BH_4$ is deficient (either due to a synthesis defect or a recycling defect via dihydropteridine reductase), phenylalanine cannot be processed even if the PAH enzyme is present in abundance.

Because the conversion is blocked, tyrosine levels decrease, leading to a deficiency of downstream neurotransmitters like dopamine, norepinephrine, and serotonin.

## EXAM PEARL

### Malignant Hyperphenylalaninemia

Also known as **atypical phenylketonuria** or **PKU Types IV and V**, it is a severe variant of PKU that occurs even when the phenylalanine hydroxylase (PAH) enzyme is perfectly functional. The cause is a deficiency of tetrahydrobiopterin ($BH_4$). This co-factor is essential for three critical hydroxylation reactions in the body:

- Phenylalanine → Tyrosine (via phenylalanine hydroxylase)
- Tyrosine → L-DOPA (via tyrosine hydroxylase)
- Tryptophan →5-hydroxytryptophan (via tryptophan hydroxylase)

Malignant PKU presents with progressive neurological deterioration despite controlled phenylalanine levels.

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**Other Options**

(A) **SAM (S-adenosylmethionine):** Involved in methylation reactions (e.g., converting norepinephrine to epinephrine), not hydroxylation.
(C) **Tetrahydrofolate ($FH_4$):** Involved in one-carbon metabolism (transferring methyl, methylene, or formyl groups). It is not the co-factor for Phenylalanine Hydroxylase.
(D) **Pyridoxal phosphate (B6):** Involved in transamination and decarboxylation reactions (e.g., the synthesis of heme or GABA).

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 248-251.

**Q11. If a frameshift mutation is introduced in a coding gene at the 4th nucleotide of a 900-nucleotide mRNA, what will be the most likely outcome?**

A. No biological change
B. Complete loss of protein function
C. Partial function of altered protein
D. No change in function due to post-translational modification

**Ans. B. Complete loss of protein function**

A **frameshift mutation** occurs when nucleotides are inserted or deleted in a number that is not a multiple of three. This shifts the reading frame of the genetic code, which is read in triplets (codons).

- **Early disruption:** The mutation occurs at the 4th nucleotide. Since the first codon consists of nucleotides 1, 2, and 3 (usually the start codon, AUG), the mutation happens immediately after the very first amino acid.
- **Downstream alteration:** From the 4th nucleotide all the way to the 900th, every single subsequent codon will be misread. This results in a completely different amino acid sequence than the one intended by the original gene.
- **Premature stop codons:** Frameshift mutations almost inevitably create a premature stop codon (UAA, UAG, or UGA) shortly after the mutation site. This leads to Nonsense-Mediated Decay (NMD) of the mRNA or the production of a severely truncated, non-functional protein fragment.

**Other Options**

(A) **No biological change:** This only happens with silent mutations (where the amino acid remains the same despite a base change). A frameshift is the most destructive type of point mutation.
(C) **Partial function:** This might occur if the frameshift happened at the very end of the 900-nucleotide sequence (e.g., at the 890th nucleotide), leaving most of the protein intact. At the 4th nucleotide, virtually 0% of the original protein is synthesized correctly.
(D) **No change due to post-translational modification:** Post-translational modifications (like phosphorylation or glycosylation) can only occur on a properly folded protein. If the primary sequence is entirely wrong, the protein will never reach the stage where these modifications could happen.

**Comparison of Mutation Types**

| *Mutation* | *Type* | *Molecular mechanism* | *Effect on protein* | *Clinical example* |
|---|---|---|---|---|
| **Point Mutation (Substitution)** | Silent | Single base change; same amino acid | None | Polymorphisms |
| | Missense | Single base change; different amino acid | Altered function or stability | Sickle cell anemia (Glu → Val) |
| | Nonsense | Single base change; codon becomes a stop codon | Premature termination; truncated protein | beta-thalassemia |
| **Frameshift** | Insertion/ deletion | Addition or loss of bases not in a multiple of 3 | Shifts reading frame; all downstream amino acids change | Duchenne Muscular Dystrophy |
| **Splicing** | Splice site | Mutation at intron-exon junctions | Exon skipping or intron retention | Tay-Sachs disease |
| **Dynamic** | Triplet repeat | Amplification of a 3-nucleotide sequence | Variable; often toxic gain of function | Huntington's disease |

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 395-398.

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**Q12. A 10-year-old child presents with enlarged orange-colored tonsils. Laboratory investigations show total cholesterol = 80 mg/dL, triglycerides = 300 mg/dL, HDL <5 mg/dL. There is a history of death of a family member due to cardiovascular disease. Which of the following is the most likely diagnosis?**

A. Abetalipoproteinemia
B. Familial hypercholesterolemia
C. Niemann Pick Disease
D. Tangier's disease

**Ans. D. Tangier's disease**

This case is a classic presentation of **Tangier's Disease** (hypoalphalipoproteinemia), a rare autosomal recessive disorder of lipid metabolism.

**Enlarged orange-colored tonsils:** This is the pathognomonic sign. It occurs because cholesterol esters accumulate in the reticuloendothelial system (macrophages), specifically in the tonsils, giving them a distinct orange hue.

**Profoundly low HDL (< 5 mg/dL):** In Tangier's, HDL is nearly absent. This is the defining laboratory feature.

**Low total cholesterol & high triglycerides:** Total cholesterol is low because HDL is low, and VLDL/Triglycerides often rise as a secondary effect.

**Family history of CVD:** Despite having low total cholesterol, the lack of HDL leads to premature atherosclerosis and early cardiovascular death in family members.

**Tangier's Disease:** The root cause is a mutation in the **ABCA1 (ATP-Binding Cassette A1) transporter gene**. ABCA1 helps move cholesterol and phospholipids out of cells and onto empty ApoA-I particles to form mature HDL.

In Tangier's disease, the ABCA1 transporter is broken. Cholesterol gets trapped inside cells (like macrophages in the tonsils). Since the cholesterol can't be loaded onto ApoA-I, the body rapidly clears the empty ApoA-I from the blood, leading to near-zero HDL levels and cholesterol-laden tissues (orange tonsils, enlarged liver/spleen, and peripheral neuropathy).

**Other Options**

(A) **Abetalipoproteinemia:** This involves a deficiency of ApoB-48 and ApoB-100. Lab results would show near-zero LDL and Triglycerides, not high triglycerides. Patients present with malabsorption and acanthocytosis.
(B) **Familial hypercholesterolemia:** This presents with extremely high LDL and total cholesterol (often >300–600 mg/dL) and physical signs like xanthomas or xanthelasma.
(C) **Niemann-Pick Disease:** While this involves lipid storage and can cause an enlarged spleen, it is characterized by sphingomyelin accumulation, not low HDL, and does not present with orange tonsils.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 192-195.

**Q13. A 10-year-old girl is brought to the dermatology clinic with extensive freckles across her face, neck, and dorsal surfaces of her hands. Her parents report that she is extremely photosensitive, developing severe sunburns after minimal sun exposure. Clinical evaluation reveals two biopsy-confirmed basal cell carcinomas on her malar region. Which of the following molecular mechanisms is most likely defective in this patient?**

A. DNA mismatch repair
B. Base excision repair
C. Nucleotide excision repair
D. Non-homologous end joining

**Ans. C. Nucleotide excision repair**

The patient presents with the classic triad of **xeroderma pigmentosum**, an autosomal recessive disorder characterized by an extreme inability to repair damage caused by ultraviolet **(UV light photosensitivity + early freckling + early malignancy)**.

**Nucleotide Excision Repair (NER)**

UV light (specifically UV-B) causes the formation of pyrimidine dimers (usually thymine-thymine dimers) in the DNA, where two adjacent bases on the same DNA strand become covalently bonded.

In healthy cells, the NER pathway identifies these lesions. An endonuclease complex cuts the DNA strand on both sides of the damage, the segment is removed, and DNA polymerase and ligase fill the gap.

Patients with xeroderma pigmentosa have mutations in the genes (XP-A through XP-G) that code for these repair proteins. The dimers remain in the DNA, leading to high mutation rates during cell division, which eventually triggers the formation of carcinomas.

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**Other Options**

(A) **DNA mismatch repair:** This is defective in Lynch Syndrome (hereditary nonpolyposis colorectal cancer). It corrects the mismatched base pairs (e.g., G paired with T) that occur during DNA replication.
(B) **Base excision repair:** This pathway fixes small, non-bulky damage (like deaminated bases or oxidized bases). It uses glycosylases to remove a single base.
(D) **Non-homologous end joining (NHEJ):** This is a way to repair double-strand breaks. A defect in this or related pathways is seen in ataxia-telangiectasia or SCID.

**DNA Repair Defects**

| *Disease* | *Defective repair pathway* | *Associated pathologies* |
|---|---|---|
| **Xeroderma pigmentosum** | Nucleotide excision repair (NER) | Skin cancers (BCC/SCC) |
| **Lynch syndrome (HNPCC)** | Mismatch repair (MMR) | Colorectal, endometrial, and ovarian cancers |
| **Ataxia-telangiectasia** | Non-homologous end Joining (NHEJ) | Cerebellar ataxia, telangiectasia, IgA deficiency |
| **BRCA1/2 mutations** | Homologous recombination | Breast and ovarian cancers |
| **MUTYH-associated polyposis** | Base excision repair (BER) | Polyposis and colon cancer |

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 408-411.

**Q14. A 2-year-old child is brought to the outpatient department due to developmental delay and progressive physical changes. Clinical examination reveals hepatosplenomegaly, coarse facial features, and significant corneal clouding. Neurological assessment confirms generalized muscle weakness. An enzyme assay demonstrates a profound deficiency of alpha-L-iduronidase. Which of the following substances is most likely to accumulate in this patient's lysosomes?**

A. Heparan sulfate and dermatan sulfate
B. Heparan sulfate
C. Keratan sulfate
D. Sphingomyelin

**Ans. A. Heparan sulfate and dermatan sulfate**

The patient is presenting with **Hurler Syndrome** (Mucopolysaccharidosis Type IH), the most severe form of MPS I. Alpha-L-iduronidase is responsible for the lysosomal degradation of specific glycosaminoglycans (GAGs). Both heparan sulfate and dermatan sulfate require alpha-L-iduronidase for their catabolism. Deficiency of this enzyme results in accumulation of the above substances within the lysosomes, causing cellular dysfunction.

**Dermatan sulfate** accumulation is largely responsible for the coarse facial features, corneal clouding, and valvular heart disease. **Heparan sulfate** accumulation is primarily associated with central nervous system involvement and developmental delay.

**Other Options**

(B) **Heparan sulfate:** Accumulates in Sanfilippo syndrome. Presents primarily with CNS symptoms; lacks the severe physical "coarsening" and corneal clouding.
(C) **Keratan sulfate:** Accumulates in Morquio syndrome; presents with distinctive skeletal dysplasia; typically no intellectual disability.
(D) **Sphingomyelin:** Seen in Niemann-Pick disease; presents with neurodegeneration and cherry-red spot on macula; no corneal clouding.

**Hurler vs. Hunter**

| *Feature* | *Hurler syndrome (MPS I)* | *Hunter syndrome (MPS II)* |
|---|---|---|
| Enzyme deficient | α-L-iduronidase | Iduronate sulfatase |
| Inheritance | Autosomal recessive | X-linked recessive |
| Corneal clouding | Present | Absent |
| Accumulated GAGs | Heparan and dermatan sulfate | Heparan and dermatan sulfate |

**MNEMONIC** **The Hunter needs clear vision to aim at the X**
**Hunter** Syndrome = **No** corneal clouding (clear vision)
**Hunter** Syndrome = **X**-linked recessive inheritance

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 105-108.

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**Q15. A 55-year-old male who has been on long-term hydrochlorothiazide therapy for hypertension presents to the OPD with neurological and cardiac symptoms. Physical examination reveals cerebellar ataxia, horizontal nystagmus, and a bilateral, sensory and motor peripheral neuropathy. Additionally, he shows signs of right-sided heart failure. He has no history of alcohol consumption. Which of the following vitamin deficiencies is most likely responsible for this clinical presentation?**

A. Thiamine B. Selenium C. Zinc D. Vitamin $B_{12}$

**Ans. A. Thiamine**

The patient presents with a combination of **Dry beriberi** (neurological symptoms) and **Wet beriberi** (cardiac symptoms).

Chronic use of diuretics, particularly **loop diuretics and thiazides**, can significantly increase the urinary excretion of thiamine. If the patient's dietary intake is marginal, drug-induced depletion can lead to clinical deficiency.

- **Dry beriberi:** Characterized by symmetric peripheral neuropathy involving both sensory and motor nerves, leading to muscle wasting and ataxia.
- **Wet beriberi:** Characterized by high-output heart failure. The deficiency leads to systemic vasodilation, increased venous return, and eventually right-sided heart failure (edema, JVD).
- **Wernicke-Korsakoff overlap:** The presence of nystagmus and ataxia suggests early CNS involvement, even in the absence of the classic alcohol history.

**EXAM PEARL**

**Thiamine Deficiency**

To confirm a thiamine deficiency in the lab, the most reliable test is measuring the **erythrocyte transketolase activity (ETKA)**. If the activity increases significantly after adding TPP in vitro, the patient is thiamine-deficient.

**Other Options**

(A) **Pyridoxine (B6):** Deficiency can cause peripheral neuropathy, but it is typically associated with isoniazid therapy and does not cause heart failure or nystagmus.

(C) **Niacin (B3):** Deficiency causes pellagra (the 3 D's: Dermatitis, Diarrhea, and Dementia), not heart failure or peripheral neuropathy.

(D) **Vitamin $B_{12}$ (Cobalamin):** Causes subacute combined degeneration of the spinal cord and megaloblastic anemia but is not linked to diuretic-induced heart failure.

**Vitamin B Complex: High-yield Summary**

| *Vitamin* | *Classic clinical trigger* | *Pathognomonic signs* | *Biochemical pearl* |
|---|---|---|---|
| **B1 (Thiamine)** | Chronic diuretics, polished rice diet, alcoholism | Wernicke's triad; high-output heart failure (Wet beriberi) | Cofactor for transketolase (HMP Shunt) |
| **B2 (Riboflavin)** | General malnutrition | Cheilosis, glossitis, corneal neovascularization | Precursor to FAD and FMN |
| **B3 (Niacin)** | Corn-based diet (low Tryptophan), Hartnup disease, Carcinoid syndrome | Pellagra; Casal's necklace | Precursor to NAD+/NADP+ |
| **B5 (Pantothenate)** | Rarely isolated | Burning foot syndrome | Essential component of Coenzyme A (CoA) |
| **B6 (Pyrodoxine)** | Isoniazid (INH) therapy for TB, oral contraceptives | Sideroblastic anemia, peripheral neuropathy, seizures | Required for ALT/AST and Heme synthesis |
| **B7 (Biotin)** | Excessive consumption of raw egg whites (Avidin) | Dermatitis, alopecia, lactic acidosis | Cofactor for carboxylase enzymes (ABC enzymes) |
| **B9 (Folate)** | Alcoholism, pregnancy, methotrexate use | Megaloblastic anemia, neural tube defects | Needed for one-carbon metabolism (dTMP synthesis) |
| **B12 (Cobalamin)** | Vegan diet, Pernicious anemia (Anti-IF antibodies), terminal ileum resection | Subacute Combined Degeneration (SCD) of spinal cord | Required for methionine synthase |

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 314-317.

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**Q16. A 10-year-old boy is brought to the outpatient clinic after his mother noticed firm, yellowish nodules over his elbows. Physical examination confirms the presence of subcutaneous xanthomas. The family history is significant for his father, who possessed similar skin lesions and suffered a fatal myocardial infarction at the age of 38. Laboratory results are as follows:**

- **Total Cholesterol: 480 mg/dL (High)**
- **LDL-C: 300 mg/dL (Severely High)**
- **Triglycerides: 146 mg/dL (Normal)**
- **HDL-C: 26 mg/dL (Low)**

**Based on the above findings, which type of hyperlipoproteinemia is the most likely diagnosis?**

A. Type I
B. Type IIa
C. Type IIb
D. Type III

**Ans. B. Type IIa**

This case describes **Familial hypercholesterolemia (Type IIa)**, an autosomal dominant disorder usually caused by a defect in the LDL receptor.

The combination of extremely high LDL, normal triglycerides, and tendon/subcutaneous xanthomas is classic. The premature death of the father from a myocardial infarction (MI) strongly suggests a genetic inability to clear LDL from the blood.

When LDL levels are chronically and severely elevated, macrophages in the skin and tendons take up the excess oxidized LDL, becoming "foam cells." These accumulate to form the visible yellowish nodules known as xanthomas.

A mutation in the *LDLR* gene (or less commonly APOB or PCSK9) leads to reduced clearance of LDL particles from the plasma by the liver.

**Fredrickson Classification**

| *Type* | *Elevated lipoprotein* | *Elevated lipid* | *Clinical associations* |
|---|---|---|---|
| **I** | Chylomicrons | Triglycerides | Eruptive xanthomas, pancreatitis |
| **IIa** | LDL | Cholesterol | Tendon xanthoma, premature CAD |
| **IIb** | LDL & VLDL | Cholesterol and triglycerides | Combined hyperlipidemia |
| **III** | IDL | Cholesterol and triglycerides | Palmar xanthomas |
| **IV** | VLDL | Triglycerides | Common, linked to diabetes/obesity |

**EXAM PEARL**

Thickening of the **Achilles tendon** is one of the earliest and most specific physical signs of **Type IIa hyperlipidemia**.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 188-191.

## NEET PG 2024

**Q17. A female presents with choreoathetoid movements, dysarthria, dystonia and eye findings shown below. Which of the following investigations is most effective for confirming the diagnosis?**

A. Serum ceruloplasmin
B. MRI
C. Urine copper excretion
D. Hepatic parenchymal copper estimation

**Ans. D. Hepatic parenchymal copper estimation**

The patient is presenting with a classic triad of neurological symptoms (choreoathetosis + dysarthria + dystonia) and Kayser-Fleischer (KF) rings. These are caused by the abnormal accumulation of copper in the brain (basal ganglia) and the cornea.

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**Wilson Disease** is an autosomal recessive disorder caused by a mutation in the *ATP7B* gene. The liver cannot incorporate copper into ceruloplasmin or excrete excess copper into the bile. Once the liver's storage capacity is exceeded, copper spills into the blood and deposits in the basal ganglia (causing movement disorders), the cornea (KF rings), and the kidneys.

**Diagnosis**

- Serum ceruloplasmin is not definitive, normal in ~10% of cases and low in 20% of carriers.
- Kayser-Fleischer rings appear in >99% of neurological cases but only 30–50% of hepatic or asymptomatic cases; their absence doesn't exclude diagnosis.
- Urine copper: >1.6 µmol/24 h in symptomatic, <1.3 µmol/24 h in carriers, and 0.9–1.6 µmol/24 h in presymptomatic patients.
- *ATP7B* gene testing confirms diagnosis in 50–75% of patients.
- Liver biopsy measuring copper >3.1 µmol/g dry weight is the gold standard; copper staining may be unreliable.

**Other Options**

(A) **Serum Ceruloplasmin:** Often low in Wilson disease, not specific.
(B) **MRI:** May show changes in basal ganglia but findings are not specific.
(C) **Urine Copper Excretion:** 24-hour urinary copper excretion is elevated in Wilson disease. Useful screening tool, but not always definitive (can be normal in asymptomatic/liver-predominant cases).

**EXAM PEARL**

**Neurological Rule in Wilson Disease**

**If a patient has neurological symptoms of Wilson disease, they MUST have Kayser-Fleischer rings.**
If a patient presents with tremors or dystonia but a slit-lamp exam shows **no KF rings**, you should strongly consider an alternative diagnosis.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 438-441.

**Q18. A child experiences recurrent abdominal pain, vomiting, and diarrhea after consuming a milk-based product. Which enzyme is most likely to be deficient?**

A. Lactase
B. Maltase
C. Amylase
D. Lipase

**Ans. A. Lactase**

The child's symptoms of abdominal pain, vomiting, and diarrhea immediately following the consumption of milk products are classic indicators of **lactose Intolerance**.

Lactose is a disaccharide (double sugar) found in milk. To be absorbed by the body, it must be broken down into the monosaccharides, glucose and galactose. This process is catalyzed by the enzyme **lactase**, which is located on the brush border of the small intestinal enterocytes.

When lactase is deficient, undigested lactose remains in the intestinal lumen, leading to:

1. **Osmotic diarrhea:** Lactose is osmotically active; it draws water into the intestines, causing bloating and watery stools.
2. **Bacterial fermentation:** Bacteria in the colon ferment the undigested lactose, producing gases (hydrogen, methane, carbon dioxide) and short-chain fatty acids. This results in flatulence and abdominal cramping.

**Comparison of Digestive Enzymes**

| *Enzyme* | *Substrate* | *Primary source* | *Product* |
|---|---|---|---|
| **Lactase** | Lactose | Small intestine | Glucose + Galactose |
| **Maltase** | Maltose | Small intestine | Glucose + Glucose |
| **Amylase** | Starch/polysaccharides | Saliva/pancreas | Maltose/oligosaccharides |
| **Lipase** | Fats | Pancreas | Fatty acids + Glycerol |

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## EXAM PEARL

**Lactase Deficiency:**
**Lactose digestion:** Minimal to none in the small intestine
**Colonic byproduct:** High Hydrogen and organic acids
**Hydrogen breath test:** Hydrogen spike > 20 ppm
**Stool pH:** Often acidic (due to fermented fatty acids)

**Secondary Lactase Deficiency:**
**Secondary Lactose Intolerance** can occur after a viral bout of gastroenteritis (like Rotavirus). The virus "shaves off" the microvilli where the lactase enzyme lives, leading to temporary milk intolerance until the intestinal lining heals.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 78-81.

**Q19. A 2.5-month-old infant shows signs of hypotonia, floppiness, difficulty feeding, failure to thrive, and macroglossia. On examination, hepatomegaly is noted, and the infant's weight is 2.8 kg with a length of 48 cm. Chest x-ray done is shown below. What is the most likely diagnosis?**



A. Transposition of great arteries
B. Ebstein's anomaly
C. Pompe's disease
D. Von Gierke disease

**Ans. C. Pompe's disease**

The infant's presentation is consistent with **Pompe's Disease,** a glycogen storage disorder caused by a deficiency of the enzyme acid α-glucosidase (GAA). This enzyme deficiency leads to glycogen accumulation in lysosomes, particularly affecting muscle tissue, including cardiac and skeletal muscles.

**Pompe's disease (Glycogen Storage Disease Type II)** manifests within the first few months after birth.

**Symptoms**

- Hypotonia and muscle weakness, giving a "floppy baby" appearance
- Difficulty feeding and poor weight gain (failure to thrive)
- Macroglossia

**Physical Signs**

- Hepatomegaly
- Hypertrophic cardiomyopathy, which can be seen on chest X-rays

**Complications**

- ECG may show a large QRS complex and shortened PR interval due to thickened ventricular walls
- Respiratory failure is a common cause of death
- Some infants may experience hearing problems

**Other Options**

(C) **Transposition of great arteries:** A cyanotic congenital heart disease presenting with severe cyanosis in newborns. There is no macroglossia or hepatomegaly, and typically no hypotonia.
(B) **Ebstein's anomaly:** A congenital heart defect with displaced tricuspid valve, causing cyanosis and heart murmur; does not cause macroglossia, hypotonia, or hepatomegaly.
(D) **Von Gierke disease (Glycogen storage disease type I):** Presents with severe hypoglycemia, hepatomegaly, lactic acidosis.

## EXAM PEARL

**Infantile-onset Pompe disease** (Glycogen Storage Disease Type II). It is unique because it is the only glycogen storage disease that is also a **lysosomal storage disorder**.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 115-118.

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**Q20. A 45-year-old patient undergoing treatment for hypertriglyceridemia presents with facial flushing, elevated blood glucose levels, and mildly raised liver enzymes. Which of the following lipid-lowering agents is likely to be responsible for these adverse effects?**

A. Niacin B. Fenofibrate C. Atorvastatin D. Ezetimibe

**Ans. A. Niacin**

Niacin is a potent agent used to treat hypertriglyceridemia and raise HDL levels, but it is notorious for a specific profile of side effects that matches this patient's presentation:

- **Facial flushing:** This is the most common side effect of niacin. It is mediated by prostaglandins (specifically $PGD_2$ and $PGE_2$), which cause peripheral vasodilation due to activation of GPR109A (HM74A) receptors. Patients are often advised to take aspirin 30 minutes before their dose to inhibit prostaglandin synthesis and reduce this effect.
- **Elevated blood glucose:** Niacin can cause insulin resistance, leading to hyperglycemia. Hence it should be used with caution in patients with diabetes.
- **Raised liver enzymes:** Niacin is associated with hepatotoxicity, which often manifests as a mild elevation in transaminases.
- **Hyperuricemia:** Niacin also competes with uric acid for excretion, which can potentially trigger gout in susceptible patients. Niacin can also worsen insulin resistance.

**Niacin (Vitamin $B_3$)**

Niacin = Nicotinic acid + Nicotinamide; originally known as the pellagra-preventing factor.

*Sources:* Liver, meat, fish, cereal husk, nuts, pulses.
*Synthesized* from tryptophan (60 mg tryptophan = 1 mg niacin).
*Chronic alcoholics* are at risk due to dietary deficiency and impaired absorption.

**Other Options**

(B) **Fenofibrate:** While fibrates are used for lowering triglycerides, they do not typically cause facial flushing or hyperglycemia. Their primary risks include muscle pain and an increased risk of cholesterol gallstones.
(C) **Atorvastatin:** Statins primarily lower LDL. While they can rarely cause a slight increase in blood glucose (new-onset diabetes) and elevated liver enzymes, they never cause the classic prostaglandin-mediated flushing seen with niacin.
(D) **Ezetimibe:** This drug inhibits cholesterol absorption in the small intestine. It is generally well-tolerated and is not associated with flushing or significant glucose instability.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 328-330.

**Q21. A child with phenylketonuria has been on a controlled diet, yet neurological symptoms persist, and serum phenylalanine levels are normal. Which enzyme is deficient in this case?**

A. Phenylalanine hydroxylase B. DOPA decarboxylase
C. Tyrosine hydroxylase D. Tetrahydrobiopterin synthase

**Ans. D. Tetrahydrobiopterin synthase**

This child has phenylketonuria (PKU) but is experiencing persistent neurological symptoms despite normal serum phenylalanine levels. This scenario suggests a tetrahydrobiopterin (BH4) deficiency, which is a rare variant of PKU caused by a defect in BH4 synthesis or recycling. BH4 is a critical cofactor for several enzymes, including phenylalanine hydroxylase (PAH), tyrosine hydroxylase, and tryptophan hydroxylase.

**Phenylketonuria:** Classical PKU results from a deficiency of phenylalanine hydroxylase, while non-classical PKU is caused by a defect in BH4 synthesis.

**Role of Tetrahydrobiopterin (BH4)**

- Acts as a cofactor for phenylalanine hydroxylase, enabling the conversion of phenylalanine to tyrosine.
- Essential for neurotransmitter production by supporting tyrosine hydroxylase (dopamine synthesis) and tryptophan hydroxylase (serotonin synthesis).
- BH4 deficiency can cause neurological problems due to dopamine and serotonin shortages, even if phenylalanine intake is low

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**Clinical Features**

- Intellectual disability
- Growth retardation
- Seizures
- Fair complexion
- Mousy odor

**Diagnostic Tests**

- Guthrie test: phenylalanine detection via bacterial growth
- Ferric chloride: urine phenylketone screening
- Tandem mass spectrometry detects hyperphenylalaninemia
- Molecular testing: gene probes for enzyme defects
- Blood phenylalanine: >20 mg/dL indicates PKU
- Enzyme assay: dry blood spot analysis

**Other Options**

(A) **Phenylalanine hydroxylase:** This is classic PKU in which a controlled diet and normal serum phenylalanine would typically prevent or stop neurological symptoms.
(B) **DOPA decarboxylase:** This enzyme converts DOPA to dopamine.
(C) **Tyrosine hydroxylase:** A deficiency here would cause "Infantile Parkinsonism" (low dopamine), but it would not affect phenylalanine levels or lead to the diagnosis of PKU.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 248-251.

**Q22. Which of the following conditions is most commonly diagnosed using the measurement of urine coproporphyrin levels?**

A. Anthracosis B. Asbestosis C. Lead poisoning D. Silicosis

**Ans. C. Lead poisoning**

Urine coproporphyrin is increased in lead poisoning due to a defect in the heme synthesis pathway.

**Lead poisoning (plumbism)** interferes with several enzymes in the heme synthesis pathway, leading to the accumulation of various precursors that are then excreted in the urine.

- **Mechanism:** Lead inhibits the enzyme coproporphyrinogen oxidase. This blockage causes accumulation of coproporphyrin III, which is then excreted in high amounts in the urine.
- **Diagnosis:** Measuring urinary coproporphyrin is a classic screening test for lead exposure. While measuring blood lead levels is the gold standard for diagnosis, elevated urinary coproporphyrin remains a significant indicator of lead's toxic effect on heme metabolism.
- **Other markers:** Lead also inhibits ALAD (aminolevulinic acid dehydratase) and ferrochelatase, leading to elevated urinary ALA and zinc protoporphyrin (ZPP) in red blood cells.

**Other Options**

(A, B, and D): These are all forms of pneumoconiosis (occupational lung diseases caused by inhaling inorganic dusts). They are primarily diagnosed through occupational history and imaging (Chest X-rays/CT) to visualize lung parenchymal changes, rather than biochemical urine tests.

**MNEMONIC Lead Poisoning: "LEAD"**

**L**ines (Burton lines on gums, Lead lines on epiphyses of long bones)
**E**ncephalopathy/**E**rythrocyte basophilic stippling
**A**bdominal colic/**A**LA (urinary) elevated
**D**rop (wrist/foot drop)/**D**iagnose with coproporphyrin in urine

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 288-291.

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**Q23. Which of the following food items is the primary source of thiamine for Indians?**

A. Chapati and rice
B. Curd
C. Cucumbers and onions
D. Vegetable curry

**Ans. A. Chapati and rice**

In the Indian diet, chapati (whole wheat flatbread) and unpolished rice serve as the primary foundational sources of **thiamine (Vitamin $B_1$)**. Because these grains are consumed in large quantities, they provide a significant portion of the population's daily nutritional requirement.

### Sources of Thiamine

The distribution of thiamine in grains is not uniform; it is concentrated in specific layers that can be lost during processing.

- **Grains:** The aleurone layer of cereals is the richest source of thiamine.
- **Nutritional value:** Whole wheat flour and unpolished, hand-pounded rice offer superior nutrition compared to fully polished or refined grains.
- **The effect of polishing:** Modern milling and polishing typically remove the nutrient-dense aleurone layer.
- **Other sources:** Yeast is considered an excellent source of the vitamin.
- **Cooking sensitivity:** Thiamine is sensitive to heat and can be partially destroyed during the cooking process.

### Deficiency

A lack of thiamine leads to various clinical syndromes, most notably *Beriberi*.

- **Wet Beriberi:** Primarily affects the cardiovascular system.
- **Dry Beriberi:** Characterized by neurological impairment and muscle wasting.
- **Infantile Beriberi:** Occurs in infants, often due to thiamine-deficient breast milk.
- **Wernicke-Korsakoff syndrome:** A severe neurological disorder often associated with chronic alcoholism.
- **Polyneuritis:** General inflammation of the peripheral nerves.

### Biochemical Indicators

When thiamine levels are low, specific metabolic changes occur that can be measured in a clinical setting:

1. **Reduced activity:** Blood thiamine levels drop, and erythrocyte transketolase activity decreases.
2. **Metabolite accumulation:** Because thiamine is a cofactor for carbohydrate metabolism, levels of pyruvate, alpha-ketoglutarate, and lactate increase in the blood.
3. **Measurement:** Accurate thiamine levels can be determined using High-Performance Liquid Chromatography (HPLC).

### Requirements and Clinical Use

- **Daily intake:** The standard daily requirement is 2–3 mg. Intake should be adjusted based on energy expenditure at a rate of 0.5 mg per 1,000 calories.
- **Increased demand:** Requirements rise to 3 mg during pregnancy and lactation.
- **Therapeutic use:** Thiamine supplementation is the definitive treatment for beriberi and various forms of neuritis.

**Other Options**

(B) **Curd:** Dairy products are excellent sources of Calcium and Riboflavin (B2), but they are relatively poor sources of Thiamine.
(C) **Cucumbers and onions:** These vegetables have high water content but provide negligible amounts of B-complex vitamins.
(D) **Vegetable curry:** While certain legumes or green peas in a curry might provide some thiamine, the heat used in typical Indian cooking often degrades this heat-sensitive vitamin. Furthermore, the volume of vegetables consumed is generally lower than the volume of staples like rice or wheat.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 314-317.

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**Q24. A 10-year-old boy presents with fingernail abrasions, excessive lip biting, and intellectual disability. What is the most likely diagnosis?**

A. Von Gierke syndrome
B. Lesch-Nyhan syndrome
C. Hunter syndrome
D. Hurler syndrome

**Ans. B. Lesch-Nyhan syndrome**

The combination of self-mutilation (lip biting, fingernail abrasions), intellectual disability, and neurological symptoms in a young boy is a classic presentation of **Lesch-Nyhan syndrome**.

- **Self-mutilating behaviour:** This is the hallmark of the condition. Patients often compulsively bite their lips, fingers, and cheeks.
- **Neurological impairment:** Symptoms include intellectual disability, spasticity, and dystonia (involuntary muscle contractions).
- **Hyperuricemia:** The underlying biochemical defect leads to a massive overproduction of uric acid. This often results in "orange sand" (uric acid crystals) in the diaper of infants, gouty arthritis, and urate kidney stones.

**Pathophysiology**

Lesch-Nyhan syndrome is an X-linked recessive disorder caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT).

1. **Defective purine salvage:** HGPRT normally recycles hypoxanthine and guanine back into the purine nucleotide pool.
2. **Increased de novo synthesis:** To compensate for the lack of recycling, the body ramps up *de novo* purine synthesis.
3. **Uric acid excess:** The excess purines are eventually broken down into uric acid, leading to severe hyperuricemia.

**Other Options**

(A) **Von Gierke syndrome:** This is a glycogen storage disease. While it causes growth failure and hepatomegaly, it does not cause self-mutilating behavior.

(C & D) **Hunter/Hurler syndromes:** These are mucopolysaccharidoses. While they involve intellectual disability and skeletal deformities, they are characterized by the accumulation of GAGs (glycosaminoglycans), not self-biting or hyperuricemia.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 344-345.

**Q25. A 3-year-old child is brought to the outpatient department with persistent delays in developmental milestones, along with macular lesions on the body that are hyperpigmented and more pronounced with sunlight exposure. What type of DNA repair error is likely involved?**

A. DNA mismatch repair
B. Nucleotide excision repair
C. Homologous recombination
D. Base excision repair

**Ans. B. Nucleotide excision repair**

The child's symptoms specifically the hyperpigmented macular lesions that worsen with sunlight exposure are hallmark signs of **Xeroderma Pigmentosum**. This condition is often accompanied by neurodevelopmental delays in some subtypes.

- **UV sensitivity:** Patients with XP have an extreme inability to repair damage caused by ultraviolet (UV) light.
- **Lesion:** UV light typically causes the formation of pyrimidine dimers (usually thymine dimers), where two adjacent bases on a DNA strand become covalently linked.
- **Defect:** In healthy individuals, these dimers are removed via nucleotide excision repair (NER). In XP, a mutation in the genes responsible for NER prevents this repair, leading to DNA mutations, skin "freckling," and a massive increase in skin cancer risk.

**Other Options**

(A) **DNA mismatch repair:** This system corrects errors that escape the "proofreading" of DNA polymerase during replication. It is not primarily associated with UV damage or photosensitivity.

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(C) **Homologous recombination:** This is used for high-fidelity repair of double-strand breaks, often associated with ionizing radiation rather than UV-induced surface lesions.
(D) **Base excision repair:** This pathway removes a single incorrect base (using a glycosylase). While vital, it is not the pathway used to clear the bulky pyrimidine dimers caused by the sun.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 385-388.

**Q26. A patient presents severe abdominal pain, elevated serum amylase and lipase levels, and imaging shows a stone in the common bile duct. Which enzyme is likely to be elevated in this condition?**

A. ALT
B. CPK
C. GGT
D. LDH

**Ans. C. GGT**

The patient's presentation of severe abdominal pain, elevated amylase and lipase (markers of pancreatic injury), and a choledocholithiasis indicates gallstone pancreatitis.

When a stone obstructs the common bile duct, it prevents the flow of both bile and pancreatic enzymes. This cholestasis (bile duct obstruction) triggers a specific pattern of enzyme elevation.

**Gamma-glutamyl transferase (GGT)** is a sensitive marker for diseases of the biliary tract.

- **Biliary obstruction:** GGT is found in the membranes of cells lining the biliary ducts. When a stone causes an obstruction, pressure increases and the biliary epithelial cells are irritated, causing GGT to leak into the bloodstream.
- **Specific for bile ducts:** While Alkaline Phosphatase (ALP) is also elevated in these cases, GGT is often used to confirm that the origin of the ALP elevation is the liver/bile ducts rather than bone.

In the presence of a known common bile duct stone, GGT (along with ALP and Bilirubin) will almost certainly be elevated.

**Other Options**

(A) **ALT:** It is raised primarily due to hepatocellular injury.
(B) **CPK:** It is an indicator of muscle or cardiac damage.
(D) **LDH:** It indicates non-specific tissue breakdown; is elevated in many conditions (hemolysis, cancer, infarcts); too non-specific for biliary diagnosis.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 552-555.

**Q27. A patient has neutropenia, along with depigmented hair and nails, suggesting a specific micronutrient deficiency. Which nutrient is most likely to be deficient based on these clinical and radiographic signs?**

A. Iron
B. Copper
C. Zinc
D. Fluoride



**Ans. B. Copper**

The symptoms of neutropenia, anaemia, depigmented hair, and nails indicate copper deficiency.

The X-ray shows classic "scorbutic-like" changes often seen in copper deficiency, such as metaphyseal cupping and fraying. One can also see **Menkes disease (kinky hair disease)** like bone changes.

**Menkes Disease (Kinky Hair Disease)**

- An X-linked disorder caused by mutations in the *ATP7A* gene.
- Copper is absorbed from the gut but cannot enter the bloodstream due to the lack of functional intracellular copper-transporting ATPase.
- Copper accumulates inside cells but is unavailable for metabolic use, resulting in impaired connective tissue cross-linking that affects vascular and connective tissues.

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**Other Options**

(A) **Iron:** While it causes anemia and nail changes (koilonychia), it does not cause neutropenia or the specific metaphyseal fraying seen in these X-rays.
(C) **Zinc:** Zinc deficiency causes severe skin rashes (periorificial) and impaired wound healing, but the skeletal "cupping" and neutropenia are much more specific to copper.
(D) **Fluoride:** Primarily affects the mineral density of teeth and bones; it does not lead to hair depigmentation or bone marrow suppression (neutropenia).

*Ref:* Harper's Illustrated Biochemistry. 32nd ed. p. 655-657.

**Q28. A mother came home to find her child having difficulty breathing after exposure to rotenone while bathing their pet. The child was taken urgently to the emergency room. What is the most probable cause of the child's symptoms?**

A. Cytochrome oxidase inhibition
B. NADH ubiquinone oxido-reductase inhibition
C. Cytochrome c reductase inhibition
D. Succinate dehydrogenase inhibition

**Ans. B. NADH ubiquinone oxido-reductase inhibition**

The most likely cause of the child's respiratory distress after exposure to rotenone is NADH ubiquinone oxido-reductase inhibition at Complex I.

**Rotenone** poisoning usually occurs through accidental or deliberate ingestion, but inhalation or skin absorption are also possible routes. Its toxicity primarily results from inhibiting mitochondrial complex I (NADH: ubiquinone oxidoreductase).

This inhibition disrupts the electron transport chain, decreasing oxidative phosphorylation and cellular ATP production. To compensate for the energy shortage, cells ramp up glycolysis, leading to increased lactate production. The buildup of lactic acid contributes to metabolic acidosis.

Symptoms of acute poisoning include nausea, vomiting, diarrhea, impaired coordination, cardiorespiratory issues, and can advance to hypoxemia, hypercapnia, and shock.

**Other Options**

(A) **Cytochrome oxidase inhibition:** This refers to Complex IV. While this also causes rapid respiratory failure and death, it is the classic mechanism for cyanide or carbon monoxide poisoning, not rotenone.
(C) **Cytochrome c reductase inhibition:** This refers to Complex III, which is inhibited by substances like antimycin A.
(D) **Succinate dehydrogenase inhibition:** This refers to Complex II, which is inhibited by malonate.

*Ref:* Harper's Illustrated Biochemistry. 32nd ed. p. 115-118.

**Q29. A 30-year-old female presents with multiple yellowish raised spots on the eyelids and xanthomas on the Achilles tendon. What is the most likely cause of these symptoms?**

A. Familial hypercholesterolemia
B. Fabry disease
C. Tangier disease
D. Xanthomatosis

**Ans. A. Familial hypercholesterolemia**

The symptoms described are classic physical markers of severely elevated low-density lipoprotein (LDL) cholesterol:

- **Xanthelasma palpebrarum:** These are the yellowish raised spots on the eyelids caused by localized deposits of cholesterol.
- **Tendon xanthomas:** The presence of nodules on the Achilles tendon is a highly specific finding for familial hypercholesterolemia (FH).
- **Early Onset:** Presenting at age 30 with these findings strongly suggests a genetic (familial) predisposition rather than purely lifestyle-related hyperlipidemia.

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**Familial hypercholesterolemia (Type IIa hyperlipoproteinemia)** is an autosomal dominant disorder typically caused by a mutation in the LDL receptor gene.

1. **Receptor deficiency:** The liver cannot effectively clear LDL from the blood because the LDL receptors are either absent or dysfunctional.
2. **Cholesterol accumulation:** This leads to extremely high levels of serum LDL and total cholesterol from birth.
3. **Tissue deposition:** Excess cholesterol leaks into macrophages in the skin and tendons (forming xanthomas) and the walls of arteries, leading to premature atherosclerosis and early myocardial infarction (heart attack).

**Other Options**

(B) **Fabry Disease:** This is a lysosomal storage disorder. While it involves lipid accumulation, it manifests as skin rashes (angiokeratomas), decreased sweating, and kidney issues, not tendon xanthomas.

(C) **Tangier disease:** This rare condition is characterized by near-zero HDL levels and pathognomonic enlarged, orange tonsils due to cholesterol ester accumulation, quite the opposite of the high-LDL profile of FH.

(D) **Xanthomatosis:** This is a descriptive clinical term for the condition of having multiple xanthomas, but it is not the underlying cause or specific diagnosis.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 188-191.

**Q30. A 48-year-old male presents with altered sensorium and a plasma glucose level of 45 mg/dL. His wife gives a history of binge alcohol consumption about him. What is correct about the treatment required?**

A. Thiamine only
B. 25% dextrose
C. Thiamine followed by dextrose
D. Vit $B_{12}$ supplementation

**Ans. C. Thiamine followed by dextrose**

The patient presents with hypoglycemia (45 mg/dL) and altered sensorium in the context of chronic or binge alcohol consumption. This scenario is a medical emergency where the sequence of treatment is as important.

- **Hypoglycemia:** The low plasma glucose requires immediate correction with dextrose (glucose).
- **Chronic alcohol** consumption leads to a deficiency of **Thiamine (Vitamin $B_1$)**. Thiamine is an essential cofactor for the enzyme pyruvate dehydrogenase, which is required to metabolize glucose.

Giving glucose (dextrose) before thiamine in a thiamine-deficient patient is dangerous:

1. **Metabolic demand:** Administering a large glucose load forces the body to ramp up carbohydrate metabolism.
2. **Cofactor exhaustion:** This process rapidly consumes the remaining tiny stores of thiamine.
3. **Wernicke encephalopathy:** The acute depletion of thiamine can trigger or worsen Wernicke encephalopathy, characterized by the triad of ophthalmoplegia, ataxia, and confusion.

Giving glucose before thiamine in a deficient patient can acutely precipitate or worsen Wernicke's encephalopathy. But in severe hypoglycemia, dextrose should not be delayed. Give glucose immediately; thiamine should be administered before or along with glucose in patients at risk of deficiency.

**MNEMONIC** **Clinical Triad of Wernicke's Encephalopathy: "CAN" symptoms**

**C**onfusion: Global encephalopathy, disorientation, or altered sensorium.
**A**taxia: Gait instability or difficulty with balance.
**N**ystagmus/Ophthalmoplegia: Involuntary eye movements or paralysis of the extraocular muscles.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 506.

**Q31. A patient with a family history of coronary artery disease presents with tendon xanthomas, elevated serum LDL, and high cholesterol levels. What is the likely defect?**

A. LDL receptor defect
B. Insulin receptor defect
C. Apolipoprotein A1 deficiency
D. Chylomicron overproduction

**Ans. A. LDL receptor defect**

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The defect lies in LDL receptors, reducing their ability to clear LDL from the blood. This results in high LDL, cholesterol, and tendon xanthomas (Familial hypercholesterolemia).

**Familial Hypercholesterolemia**

- **Elevated LDL cholesterol:** Serum appears clear.
- **Genetic causes:** Mainly LDL receptor defects or Apo B mutations. Caused by reduced number/function of LDL receptors in liver and tissues, raising plasma LDL. Apo B mutation (glutamine for arginine at position 3500) impairs LDL-receptor binding (familial defective Apo B). Sometimes LDL-receptor complex fails to internalize properly, worsening clearance.
- **Symptoms:** Atherosclerosis, coronary artery disease, tuberous xanthomas.
- **Treatment:** Low-cholesterol diet, reduce saturated fats, increase PUFAs, statins. Untreated cases often develop early-onset atherosclerosis and coronary artery disease.

**Other Options**

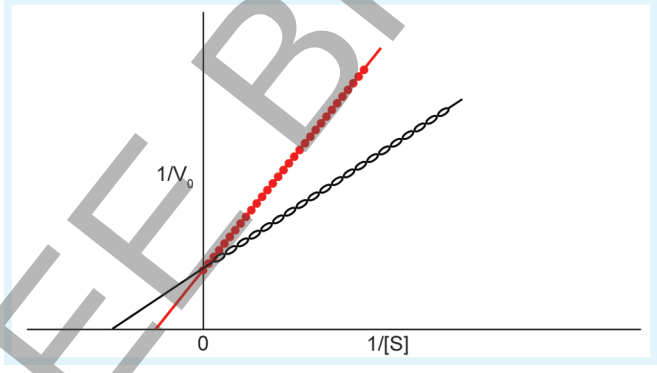
(B) **Insulin receptor defect:** This causes severe insulin resistance and diabetes, not the specific isolated elevation of LDL and tendon xanthomas.

(C) **Apolipoprotein A1 deficiency:** Apo A1 is the main protein for HDL. Deficiency would lead to very low "good" cholesterol, not primarily high LDL.

(D) **Chylomicron overproduction:** This (type I hyperlipidemia) leads to high triglycerides rather than high cholesterol and typically presents with pancreatitis and eruptive (skin) xanthomas rather than tendon xanthomas.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 188-191.

**Q32. In the provided Lineweaver-Burk plot, the black line indicates normal enzyme activity, while the red line represents the action of an inhibitor. What type of inhibition is depicted?**




A. Allosteric inhibition
B. Uncompetitive inhibition
C. Noncompetitive inhibition
D. Competitive inhibition

**Ans. D. Competitive inhibition**

The given graph shows competitive inhibition, in which $V_{max}$ remains constant and the $K_m$ value increases. The intercept on the y-axis remains unchanged while the intercept on the shifts close to zero forming a steeper slope.

**Competitive Inhibition**

- The inhibitor resembles the substrate and competes for binding at the enzyme's active site.
- This competition reduces the availability of enzyme molecules for the substrate, decreasing the reaction rate at low substrate concentrations.
- Competitive inhibition is reversible; increasing substrate levels can overcome the inhibition.
- In Lineweaver-Burk plots, competitive inhibitors raise the apparent $K_m$ (indicating lower substrate affinity) without affecting $V_{max}$.
- Example: Malonate acts as a competitive inhibitor of succinate dehydrogenase.

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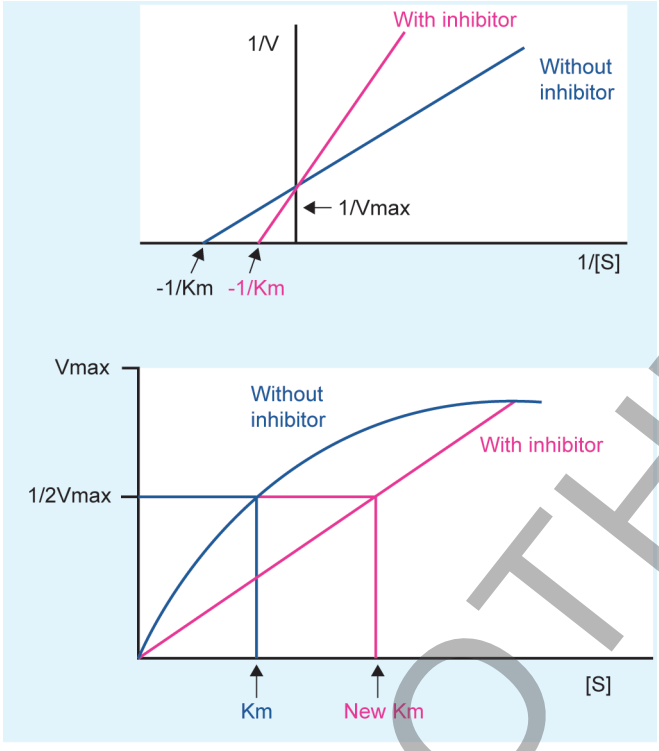
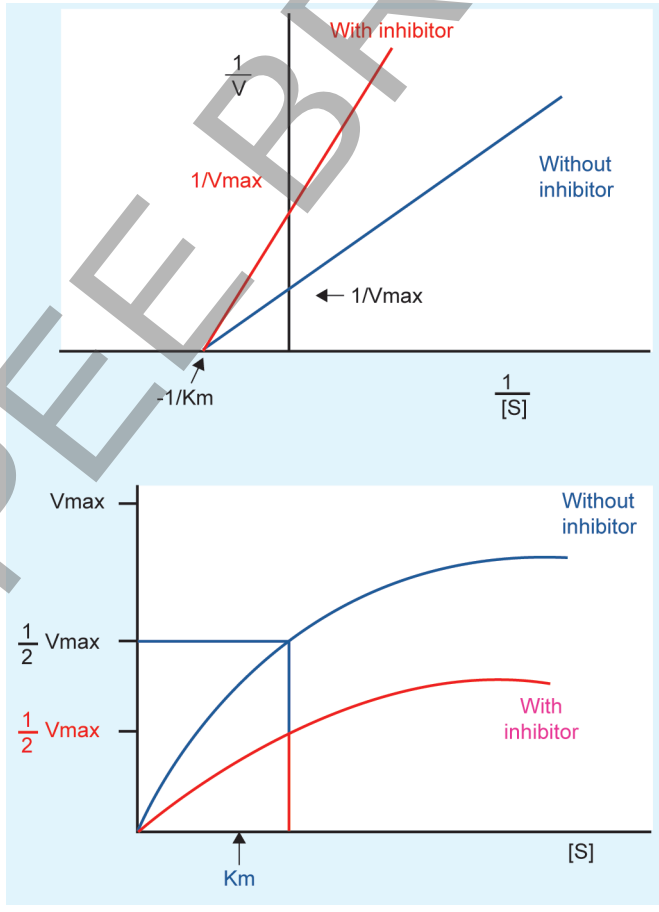



Figure showing substrate saturation curve in presence and absence of competitive inhibitor




Saturation curve of non-competitive inhibition

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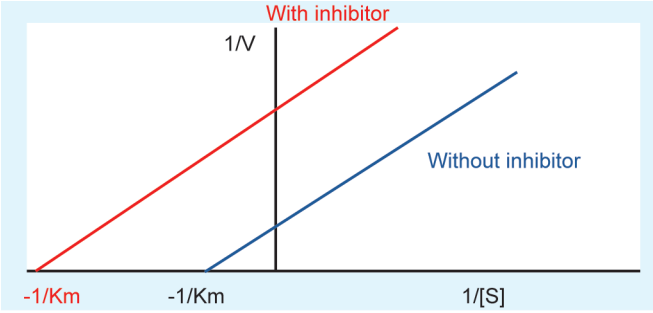


Figure showing competitive inhibition

**Other Options**

(A) **Allosteric inhibition:** Not typically represented by classic Lineweaver-Burk plot changes; usually shows sigmoidal kinetics, not Michaelis-Menten linear plots.
(B) **Uncompetitive inhibition:** Both $V_{max}$ and $K_m$ decrease, so lines are parallel with different intercepts.
(C) **Noncompetitive inhibition:** $V_{max}$ decreases (Y-intercept increases) but $K_m$ remains unchanged (X-intercept stays the same).

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 62-65.

**Q33. A 1-month-old neonate was brought to the OPD by her parents, complaining of lethargy and poor oral intake. Upon investigation, cataract is noted in both eyes, and the urine Benedict's test was positive, but glucose was not detected. Which enzyme deficiency is likely responsible for this condition?**

A. Hexokinase
B. Galactosyl-1 uridyl phosphatase
C. Galactokinase
D. Phosphofructokinase

**Ans. B. Galactose-1-phosphate uridyltransferase (GALT)**

The presentation of a neonate with lethargy, poor feeding, bilateral cataracts, and a specific urine profile is a classic "emergency" presentation of **classic galactosemia**.

**Galactosemia**

Galactosemia is a hereditary metabolic disorder where the body is unable to metabolise galactose. The condition manifests in two primary forms depending on the specific enzyme deficiency.

The severity of the disease is determined by which step of the metabolic pathway is blocked:

- **Classic galactosemia:** This results from a deficiency of galactose-1-phosphate uridyl transferase (GALT). It is a severe condition because it causes the toxic accumulation of galactose-1-phosphate in various tissues.
- **Galactokinase deficiency:** A less severe variant where only the first step of metabolism is impaired. This primarily leads to the formation of cataracts without the life-threatening systemic complications seen in the classic form.

**Diagnosis**

- **Screening:** Diagnosis is typically based on clinical symptoms such as cataracts and confirmed by detecting galactosuria and elevated blood galactose levels.
- **Prenatal testing:** Amniocentesis can be used to analyze fetal cells for the enzyme defect before birth.
- **Carrier testing:** Heterozygous parents (carriers) may exhibit abnormal blood galactose elevations during a "galactose challenge" test.

**Management and Prognosis**

- **Dietary restriction:** The primary treatment is the immediate and lifelong restriction of lactose intake.
- **Early intervention:** Starting a lactose-free diet early can stop the progression of symptoms. However, any intellectual impairment that occurs prior to treatment is irreversible.
- **Age-related improvement:** In some cases, GALT enzyme activity may naturally increase after the age of four, which can improve the child's tolerance to small amounts of lactose.

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**Other Options**

(A) **Hexokinase:** This enzyme is involved in the first step of glycolysis. Deficiency would typically cause non-spherocytic hemolytic anemia, not cataracts or neonatal lethargy.
(C) **Galactokinase:** While this *does* cause cataracts and a positive Benedict's test, it does not cause the systemic "sick baby" symptoms (lethargy, poor intake) seen in this case.
(D) **Phosphofructokinase:** This is the rate-limiting enzyme of glycolysis. Deficiency (Tarui disease) leads to exercise-induced muscle cramps and hemolytic anemia.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 110-113.

**Q34. An adolescent child from a southern Indian state from a poor family, comes to the OPD with rough and scaly skin. The child's diet lacks vegetables and fruits. After treatment with linseed oil, and vitamins A and B, the symptoms improve. What is the most likely diagnosis?**

A. Keratosis pilaris
B. Erythroderma
C. Phrynoderma
D. Lichen planus

**Ans. C. Phrynoderma**

**Phrynoderma (Toad skin)** is a type of follicular hyperkeratosis associated with severe nutritional deficiencies. The description of "rough and scaly skin" in an adolescent from a poor background with a diet lacking fruits and vegetables is a classic presentation.

**Nutritional basis:** It was historically linked primarily to vitamin A deficiency, but current understanding shows it is a multi-deficiency disorder involving essential fatty acids (EFAs), vitamin B-complex, and vitamin E.

The significant improvement after treatment with linseed oil is pathognomonic for an essential fatty acid deficiency (specifically alpha-linolenic acid), as linseed oil is a rich source of these fats.

***Physical appearance:*** The skin develops papules (bumps) that give it a dry, firm, "toad-like" appearance, typically on the elbows, knees, and extensor surfaces of the limbs.

**Other Options**

(A) **Keratosis pilaris:** A common benign condition caused by keratin plugging hair follicles. Seen in normal healthy individuals, especially on arms and thighs
(B) **Erythroderma:** Generalized redness and scaling over entire body. Usually seen in severe dermatitis, psoriasis, lymphoma, or drug reactions
(D) **Lichen Planus:** It is an autoimmune skin disorder; features include purple, polygonal, pruritic, planar papules (the 5 P's)

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 165-168.

**Q35. A 28-year-old woman presents with an erythematous, scaly rash on her forearm, neck, and face, along with loose stools and cognitive difficulties. She also states that she is having problems with remembering things lately. Her recent diet has shifted to being primarily corn-based due to financial constraints, and her electrolyte levels are normal. Which treatment is most likely to relieve her symptoms?**

A. High-dose IV thiamine
B. High-dose vitamin C
C. Oral nicotinamide supplementation
D. Discontinuing the corn diet

**Ans. C. Oral nicotinamide supplementation**

The patient's symptoms represent the classic "3 Ds" of **Pellagra**, which is caused by a deficiency of vitamin $B_3$ (niacin) or its precursor, the amino acid tryptophan.

- **Dermatitis:** The erythematous, scaly rash on sun-exposed areas (forearm, neck, and face) is characteristic. On the neck, this is often referred to as a Casal necklace.
- **Diarrhea:** Often due to atrophy of the gastrointestinal columnar epithelium.
- **Dementia:** Presented as cognitive difficulties.

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The shift to a primarily corn-based diet is a major diagnostic clue.

- **Low tryptophan:** Corn is naturally low in tryptophan, which the body normally uses to synthesize niacin.
- **Bound niacin:** The niacin found in corn is in a bound form (niacytin) that cannot be easily absorbed by the human gut unless the corn is treated with an alkali (like lime).

**Treatment**

The definitive treatment for Pellagra is the administration of niacin or nicotinamide.

- **Oral nicotinamide (250–500 mg/day):** This is the preferred treatment because it does not cause the "flushing" side effect associated with nicotinic acid.
- **Dietary modification:** While discontinuing the corn diet is a helpful long-term strategy, it will not provide the rapid, high-concentration replacement of the vitamin needed to resolve acute neurological and dermatological symptoms.

**Other Options**

(A) **IV Thiamine:** Used for Beriberi or Wernicke's, not for scaly rashes/corn-based deficiency.
(B) **Vitamin C:** Deficiency causes scurvy (bleeding gums, petechiae), not the 3 Ds of Pellagra.
(D) **Discontinue corn diet:** Supportive; but supplemental nicotinamide is required for recovery.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 328-331.

**Q36. A woman brings her child to the clinic with fatigue and muscle weakness during exercise. Laboratory tests show impaired long-chain fatty acid (LCFA) oxidation, and a muscle biopsy reveals fat vacuoles. What is the most likely diagnosis?**

A. LPL defect
B. LDL defect
C. FA synthase deficiency
D. Carnitine deficiency

**Ans. D. Carnitine deficiency**

The child's symptoms of fatigue and muscle weakness during exercise, combined with impaired long-chain fatty acid (LCFA) oxidation and the presence of fat vacuoles in muscle biopsy, strongly point to carnitine deficiency.

**Carnitine deficiency:** Primarily seen in newborns and premature infants due to inadequate synthesis or increased renal loss of the enzyme.

**Types**

- CPT-I Deficiency: Mainly impacts the liver, leading to decreased fatty acid oxidation and ketone production, resulting in hypoglycemia. Sulfonylurea drugs (e.g., glyburide, tolbutamide) can inhibit CPT-I, worsening fatty acid metabolism issues.
- CPT-II Deficiency: Primarily affects muscles causing rhabdomyolysis and, in severe cases, the liver.

**Clinical Features**

- Metabolic crisis usually occur between 3 months and 2 years of age, often triggered by catabolic stress such as fasting or illness.
- Symptoms include poor feeding, lethargy, irritability, hepatomegaly.
- Lab evaluation reveal hypoglycemia without ketone production (nonketotic or hypoketotic), raised liver enzymes (ALT, AST), hyperammonemia, lactic acidosis.

**Other Options**

(A) **LPL defect:** Lipoprotein Lipase (LPL) breaks down triglycerides in chylomicrons and VLDL in the blood. A defect causes massive hypertriglyceridemia but does not directly impair the intracellular oxidation of fatty acids within the mitochondria.
(B) **LDL defect:** Seen in Familial hypercholesterolemia, this involves cholesterol transport and leads to xanthomas and early heart disease, not exercise-induced muscle weakness or impaired fatty acid oxidation.
(C) **FA synthase deficiency:** FA synthase is involved in fatty acid synthesis, not breakdown.

*Ref:* Harper's Illustrated Biochemistry. 32nd ed. p. 210-213.

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**Q37. A patient comes with severe abdominal pain, vomiting, and loss of appetite, with serum triglyceride levels greater than 2000 mg/dL. Which apolipoprotein is most likely deficient?**

A. Apolipoprotein AL
B. Apolipoprotein B48
C. Apolipoprotein B100
D. Apolipoprotein CII

**Ans. D. Apolipoprotein CII**

The combination of severe abdominal pain (highly suggestive of acute pancreatitis) and massive hypertriglyceridemia (levels > 2000 mg/dL) points to **Type I hyperlipoproteinemia (Familial Chylomicronemia Syndrome)**.

When serum triglycerides exceed 1000 mg/dL, the risk of acute pancreatitis increases significantly. This explains the patient's abdominal pain, vomiting, and loss of appetite. In this condition, the body cannot clear chylomicrons from the blood. This is usually due to a deficiency in either the enzyme lipoprotein lipase (LPL) or its essential cofactor, apolipoprotein CII (Apo CII).

**Apolipoprotein CII** acts as the essential cofactor that activates LPL.

**Enzyme activation:** LPL is located on the walls of blood capillaries in muscle and adipose tissue.

**Hydrolysis:** Once activated by Apo CII, LPL breaks down the triglycerides inside chylomicrons and VLDL into free fatty acids.

**Deficiency:** Without Apo CII, LPL remains inactive even if the enzyme itself is present. Chylomicrons (which are mostly triglycerides) accumulate to extreme levels in the plasma, leading to the clinical symptoms described.

**Other Options**

(A) **Apolipoprotein AL**: This option does not correspond to a known apolipoprotein deficiency related to triglyceride metabolism.
(B) **Apolipoprotein B48**: This is essential for the synthesis of chylomicrons in the intestines and is not directly involved in the metabolism of triglycerides in the blood.
(C) **Apolipoprotein B100**: This apolipoprotein is involved in the synthesis of VLDL and is implicated in cholesterol metabolism but does not directly relate to the severe hypertriglyceridemia seen in this scenario.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 185-188.

**Q38. A patient presents with a rare autosomal recessive metabolic disorder characterized by ectopia lentis (dislocation of the lens). Peripheral blood smears show no evidence of megaloblastic anemia, and biochemical testing reveals low levels of methionine. Based on these findings, which nutritional supplement is the most effective treatment?**

A. Biotin
B. Pyridoxine
C. Thiamine
D. Riboflavin

**Ans. B. Pyridoxine**

The patient's presentation suggests a diagnosis of classical homocystinuria, a rare autosomal recessive disorder caused by a deficiency of the enzyme **cystathionine beta-synthase (CBS)**. This enzyme requires **pyridoxine (vitamin $B_6$)** as a cofactor for the metabolism of homocysteine to cystathionine.

**Homocystinuria** is mainly caused by a deficiency of Cystathionine β-Synthase enzyme. This deficiency disrupts the conversion of homocysteine to cystathionine, resulting in increased homocysteine and decreased cysteine levels in the bloodstream. Additionally, methionine levels rise due to impaired remethylation of homocysteine.

**Clinical Features**

- Ectopia lentis, or lens dislocation, is a key characteristic
- Skeletal abnormalities resembling Marfan syndrome are common
- Intellectual disability may be present
- Elevated homocysteine levels increase the risk of thromboembolic events

**Treatment**

- **Pyridoxine supplementation:** High doses of pyridoxine may help some patients by boosting residual CBS enzyme activity.

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- **Methionine-restricted diet:** Reducing methionine intake and supplementing with cysteine aids in managing homocystinuria.
- **Betaine treatment:** For patients who do not respond to vitamin $B_6$, betaine is used to enhance the remethylation of homocysteine back to methionine.

**Other Options**

(A) **Biotin ($B_7$):** Cofactor for carboxylase enzymes; used for multiple carboxylase deficiency, not homocystinuria.
(C) **Thiamine ($B_1$):** Cofactor for PDH, alpha-KGDH, and transketolase; used for Beriberi and Wernicke-Korsakoff syndrome.
(D) **Riboflavin ($B_2$):** Precursor for FAD and FMN; used for MTHFR mutations occasionally, but not the primary treatment for CBS-related ectopia lentis.

**EXAM PEARL**

**Homocystinuria**

Patients with homocystinuria are at an extremely high risk for **premature atherosclerosis** and life-threatening **thrombosis**. Lowering homocysteine levels through vitamin $B_6$, $B_{12}$, and folate is a life-saving intervention.

**MNEMONIC Homocystinuria: The "C" checklist**

**C**ystathionine β-synthase deficiency
**C**ysteine becomes essential
**C**harlie **C**haplin gait
**C**ardiovascular risk
**C**rystalline lens dislocation

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 256-259.

## NEET PG 2023

**Q39. A child presents with dementia, diarrhea and dermatitis. Which of the following is suspected deficiency?**

A. Vitamin $B_3$
B. Vitamin $B_6$
C. Vitamin C
D. Vitamin $B_{12}$

**Ans. A. Vitamin $B_3$**

The 3 Ds (**dermatitis, diarrhea, and dementia**) are the hallmark signs of **Pellagra**. The correct answer is **Vitamin $B_3$ (niacin)**.

Pellagra is caused by a severe deficiency of **niacin** (Nicotinic acid) or its precursor amino acid, tryptophan.

1. **Dermatitis:** This is a characteristic photosensitive rash. It appears on areas exposed to sunlight, such as the face, the "V" of the neck (known as **Casal's necklace**), and the back of the hands and feet. The skin becomes red, scaly, and eventually thickened and pigmented.
2. **Diarrhea:** Niacin is essential for the high-turnover cells of the gastrointestinal tract. Deficiency leads to inflammation of the tongue (glossitis) and the entire GI lining, resulting in chronic, often foul-smelling diarrhea.
3. **Dementia:** Neurological symptoms start with irritability, headaches, and insomnia, progressing to memory loss, confusion, and full-blown hallucinations or delirium.
4. **Death:** If left untreated, the metabolic failure becomes systemic and fatal.

**Pellagra: Common Causes**

- **Corn-based Diets:** Maize (corn) is low in Tryptophan, and the Niacin it does contain is in a bound form (niacytin) that the human gut cannot absorb unless treated with an alkali (like lime).
- **Hartnup disease:** A genetic disorder affecting the absorption of neutral amino acids (including tryptophan), leading to Pellagra-like symptoms.
- **Carcinoid syndrome:** Tryptophan is diverted toward the massive production of serotonin, leaving none for Niacin synthesis.
- **Isoniazid (INH) therapy:** An anti-tubercular drug, depletes Vitamin $B_6$, which is a necessary cofactor for making niacin from tryptophan.

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**EXAM PEARL**

**Niacin-tryptophan Connection**

- **60:1 Rule:** It takes approximately **60 mg of dietary tryptophan** to synthesize **1 mg of niacin**
- **Essential cofactors:** This conversion requires **vitamin $B_6$ (pyridoxine)**, **vitamin $B_2$ (riboflavin)**, and **iron**.

**Other Options**

(B) **Vitamin $B_6$:** While its deficiency can cause secondary niacin deficiency, vitamin $B_6$ deficiency itself typically presents with sideroblastic anemia, peripheral neuropathy, and convulsions.

(C) **Vitamin C:** Deficiency causes scurvy, characterized by bleeding gums, easy bruising, and corkscrew hairs, but not the 3 Ds.

(D) **Vitamin $B_{12}$ (D):** Deficiency leads to megaloblastic anemia and subacute combined degeneration (SCD) of the spinal cord, but not the photosensitive dermatitis of pellagra.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 328-331.

**Q40. A 4-year-old child presents with easy fatigability and frequent hunger between meals, with improvement after eating. On examination, the liver shows absence of glycogen. What is the most likely enzyme deficiency?**

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

**Ans. D. Glycogen synthase**

**Glycogen synthase deficiency (GSD Type 0)** is unique among glycogen storage disorders because it is a failure of **glycogen synthesis** rather than breakdown. Glycogen synthase is the rate-limiting enzyme that adds glucose molecules to a growing glycogen chain. As a result of deficiency of this enzyme, the liver cannot store glucose as glycogen.

Between meals, the body normally depends on liver glycogen to maintain blood sugar. Because this child has no stores, they experience fatigability and hunger very quickly after eating. GSD Type 0 is characterized by **low liver glycogen stores, fasting ketotic hypoglycemia, and postprandial hyperglycemia.**

**Post-prandial hyperglycemia:** After a meal, the blood sugar rises sharply because the liver cannot utilize the excess glucose into glycogen storage. This often leads to elevated lactate after eating as the body shunts excess glucose into glycolysis instead.

**Other Options**

(A) **Glucose-6-Phosphatase:** Deficiency leads to massive hepatomegaly because glycogen is stored but cannot be converted back to glucose.

(B) **Debranching enzyme:** Results in the accumulation of limit dextrins (partially broken down glycogen) in the liver, leading to hepatomegaly.

(C) **Branching enzyme:** Leads to the production of an abnormal, insoluble form of glycogen (amylopectin-like) that causes severe liver scarring and cirrhosis.

**Glycogen Storage Disorders (GSD)**

| *Type* | *Name* | *Deficient enzyme* | *Primary organ* |
|---|---|---|---|
| **Type 0** | – | Glycogen synthase | Liver |
| **Type I** | Von Gierke | Glucose-6-phosphatase | Liver and kidney |
| **Type II** | Pompe | α1,4-glucosidase (acid maltase) | Heart and muscle |
| **Type III** | Cori / Forbes | Debranching enzyme | Liver and muscle |
| **Type IV** | Andersen | Branching enzyme | Liver |
| **Type V** | McArdle | Muscle phosphorylase | Skeletal muscle |
| **Type VI** | Hers | Liver phosphorylase | Liver |
| **Type VII** | Tarui | Phosphofructokinase-1 | Muscle and RBCs |

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## EXAM PEARL

**GSD and Various Clinical Presentations**

- Hepatomegaly: GSDs (Types I–VI)
- No hepatomegaly: Type 0
- Limit dextrin: Type III (Cori disease)
- Hypoglycemia: Types I, III, VI
- Muscle cramps/weakness: Types V, VII

**Diagnostic Differentiators**

- **Doll-like facies + lactic acidosis** - Type I (Von Gierke)
- **Massive Heart/cardiomyopathy** - Type II (Pompe)
- **Cirrhosis/liver scarring** - Type IV (Andersen)
- **Myoglobinuria after exercise** - Type V (McArdle)

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 102-105.

**Q41. A family consuming a diet predominantly consisting of polished rice is most likely to develop which of the following vitamin deficiencies, and which associated enzyme activity is used to assess it?**

A. Pyridoxine with xanthurenic acid
B. Riboflavin with glutathione reductase
C. Thiamine and transketolase
D. Riboflavin with transketolase

**Ans. C. Thiamine and transketolase**

Thiamine is primarily located in the **outer layer (husk and germ)** of cereal grains. **Polishing (milling)** removes the bran and germ to make white rice, effectively stripping away the thiamine.

Populations that rely almost exclusively on polished rice as their primary calorie source are at high risk for **beriberi**. Since thiamine is a required cofactor for carbohydrate metabolism, a diet high in carbohydrates (like rice) increases the body's demand for the very vitamin it is missing.

**Diagnostic Assessment: Erythrocyte Transketolase Activity (ETKA)**

To confirm a thiamine deficiency, we look at the activity of enzymes that require thiamine pyrophosphate (TPP) as a cofactor.

**Transketolase** is a key enzyme in the pentose phosphate pathway (HMP Shunt) found in RBCs. It is measured by the activity of transketolase in the patient's RBCs before and after adding TPP in the test tube.

If the enzyme activity increases significantly (usually >25%) after adding TPP, it proves the patient was deficient. This is known as the TPP Effect.

## EXAM PEARL

**Three TPP-dependent Enzymes**

- **Pyruvate dehydrogenase (PDH):** Link between glycolysis and the TCA cycle
- α-**Ketoglutarate dehydrogenase:** Key step in the TCA cycle
- **Transketolase:** Key enzyme in the HMP shunt

**Other Options**

(A) **Pyridoxine with xanthurenic acid:** High levels of xanthurenic acid in the urine after a tryptophan load test is a marker for Vitamin $B_6$ (pyridoxine) deficiency. Vitamin $B_6$ is needed to convert kynurenine (a tryptophan metabolite) into niacin; without it, the pathway shunts toward xanthurenic acid.
(B) **Riboflavin with glutathione reductase:** While erythrocyte glutathione reductase activity is the standard way to assess riboflavin (Vitamin $B_2$) status, riboflavin deficiency is typically associated with a lack of dairy and meat, not specifically a polished rice diet.
(D) **Riboflavin with transketolase:** This is an incorrect pairing. Transketolase requires thiamine, not riboflavin.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 314-317.

**Q42. A patient presents with bleeding gums and easy bruising. Which of the following biochemical defects is most likely responsible for these symptoms?**

A. Inhibition of clotting factors
B. Increased keratinization of epithelium
C. Low calcium
D. Impaired collagen synthesis

**Ans. D. Impaired collagen synthesis**

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The clinical presentation of **bleeding gums**, **easy bruising**, and petechiae is the classic triad for **scurvy**, which is caused by a deficiency of **vitamin C (ascorbic acid)**.

Vitamin C acts as a reducing agent (keeping iron in the $Fe^{2+}$ state) for two critical enzymes: prolyl hydroxylase and lysyl hydroxylase. These enzymes add hydroxyl (-OH) groups to the amino acids proline and lysine within the collagen precursor chain. These hydroxyl groups are essential for forming hydrogen bonds that stabilize the collagen triple helix.

In cases of vitamin C deficiency, the collagen produced is structurally weak and unstable. It cannot support the walls of capillaries, leading to leakage of blood into the skin (bruising) and mucous membranes (bleeding gums).

**Other Options**

(A) **Inhibition of clotting factors:** This would typically be caused by vitamin K deficiency or anti-coagulants. While it causes bleeding, it does not specifically affect the integrity of the gums or produce the perifollicular skin changes seen in scurvy.

(B) **Increased keratinization of epithelium:** This is a hallmark of **vitamin A deficiency** (leading to Bitot's spots and Phrynoderma), not a cause of bleeding.

(C) **Low calcium:** While calcium is required for the clotting cascade (factor IV), clinical deficiency usually manifests as tetany and bone weakness before it causes significant bleeding.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 336-339.

**Q43. A child experiences fatigue after physical activity. Post-exercise blood tests reveal low levels of both glucose and lactate. What is the most likely diagnosis?**

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

**Ans. B. McArdle disease**

McArdle disease is caused by a deficiency of muscle phosphorylase (PYGM), impairing glycogen breakdown. After exercise, patients show fatigue with low blood lactate due to blocked glycolysis in muscles.

**McArdle disease** is caused by mutations in the *PYGM* gene, responsible for producing muscle glycogen phosphorylase (GSD Type V). More than 65 different mutations in PYGM have been identified in affected individuals.

Symptoms usually begin around age 5 and include reduced exercise tolerance, muscle cramps and fatigue during physical activity, elevated muscle glycogen levels (2.5–4%) due to impaired breakdown and low blood lactate levels after exercise. The limited availability of glucose to muscles leads to weakness and decreased endurance. **Second-wind phenomenon** is characteristic of McArdle disease.

**Other Options**

(A) **Tarui (GSD VII):** Causes normal glucose but low lactate (PFK deficiency).

(C) **Von Gierke (GSD I):** Causes high lactate (glucose-6-phosphatase deficiency).

(D) **Anderson (GSD IV):** Causes systemic disease, not isolated exercise intolerance.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 102-104.

**Q44. A child's urine darkens when left to stand. What is the most likely cause?**

A. Alkaptonuria
B. Type I tyrosinemia
C. Type II tyrosinemia
D. Congenital erythropoietic porphyria

**Ans. A. Alkaptonuria**

The characteristic darkening of urine upon standing (or when exposed to an alkaline environment) is the hallmark of **alkaptonuria**.

Alkaptonuria is an autosomal recessive disorder of **tyrosine** and **phenylalanine** catabolism. There is a deficiency of the enzyme homogentisate oxidase. This leads to a massive buildup of homogentisic acid (HGA) in the blood, which is then excreted in the urine. When HGA is exposed to air (oxygen), it undergoes oxidation and polymerization into a pigment called alkapton (similar to melanin), which turns the urine black.

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**Clinical Progression**

While the urine darkening is visible from infancy (often noted by parents as dark stains on diapers), the systemic complications usually appear in the 3rd or 4th decade of life:

- **Ochronosis:** This is the deposition of the dark pigment (homogentisic acid polymers) in connective tissues, such as the cartilage of the ears (which may appear bluish), the sclera of the eyes (black spots), and heart valves.
- **Ochronotic arthritis:** The pigment deposition in large joints and the spine leads to severe, debilitating arthritis and calcification of intervertebral discs.

**Other Options**

(B) **Type I tyrosinemia:** Caused by fumarylacetoacetate hydrolase deficiency. It is a very severe disease leading to liver failure, cabbage-like odor, and renal tubular defects, but not black urine.

(C) **Type II tyrosinemia:** Caused by tyrosine aminotransferase deficiency. It primarily affects the eyes (corneal ulcers) and skin (palmoplantar keratosis).

(D) **Congenital erythropoietic porphyria:** This condition causes the urine to turn red or dark brown (port-wine color) due to porphyrin excretion, and it is associated with extreme photosensitivity, but not the specific HGA-related darkening.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 248-250.

**Q45. A child presents with dermatitis, hair thinning, and alopecia. On further questioning, the family reports regular consumption of raw egg whites over a prolonged period. Which nutrient deficiency is the most likely cause?**

A. Iron
B. Biotin
C. Vitamin A
D. Vitamin $B_{12}$

**Ans. B. Biotin**

The association between **raw egg whites** and skin/hair issues is a definitive clue for **biotin (vitamin $B_7$)** deficiency.

A specific protein found in the egg white called **avidin**, a tetrameric glycoprotein that has a very strong affinity for biotin.

When a person consumes raw egg whites, the avidin binds to the biotin present in the digestive tract. This forms a complex that the human body cannot break down or absorb.

Heat denatures avidin. This is why cooked eggs do not cause biotin deficiency; the high temperature breaks the protein's structure, rendering it unable to bind biotin.

Biotin is an essential cofactor for several carboxylase enzymes (such as pyruvate carboxylase and acetyl-CoA carboxylase). A deficiency leads to dermatitis, alopecia and neurological symptoms.

**Other Options**

(A) **Iron:** While iron deficiency causes fatigue and koilonychia, it does not typically present with the specific periorificial dermatitis seen here.

(C) **Vitamin A:** Deficiency leads to night blindness (nyctalopia), Bitot's spots, and rough "toad skin" (phrynoderma), but it is not linked to raw egg white consumption.

(D) **Vitamin $B_{12}$:** Deficiency causes megaloblastic anemia and neurological issues (SCD of the spinal cord). It is usually seen in strict vegans or those with malabsorption, not as a result of eating eggs.

**EXAM PEARL**

**Raw Eggs and Biotin Deficiency**

It is estimated that one would need to consume about **12 to 24 raw egg whites per day** for several weeks to develop a clinically significant biotin deficiency. However, for any exam, any mention of raw eggs is an immediate pointer to biotin.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 333-335.

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**Q46. A 14-month-old infant presents with perioral erythematous, scaly, and pustular skin lesions along with persistent diarrhea. Which mineral deficiency is the most likely cause?**

A. Zinc
B. Copper
C. Iron
D. Calcium

**Ans. A. Zinc**

The clinical description describes a condition known as **acrodermatitis enteropathica**, which is the hallmark of severe **zinc deficiency**. In infants, this often manifests shortly after weaning from breast milk, as cow's milk and cereal-based diets have lower zinc bioavailability.

**Zinc** is an essential trace element required for the function of over 300 enzymes, including those involved in DNA synthesis, cell division, and protein metabolism. It is particularly critical for high-turnover tissues like the skin and the intestinal lining.

**Acrodermatitis enteropathica:** This is a rare genetic disorder caused by a mutation in the ZIP4 transporter (SLC39A4), which is responsible for absorbing zinc in the small intestine.

**Acquired deficiency:** More commonly, a similar presentation occurs due to malnutrition, chronic diarrhea, or malabsorption syndromes where zinc is lost faster than it can be replaced.

**Triad:** The clinical triad of this deficiency is the triad of **dermatitis, alopecia, and diarrhea**.

**Other Options**

(B) **Copper:** Deficiency leads to Menkes disease (kinky hair disease), characterized by brittle, silver-colored hair, neurological regression, and skeletal issues, but not the specific perioral pustular rash.
(C) **Iron:** Primarily causes microcytic hypochromic anemia, fatigue, and pica. While it can cause skin changes like koilonychia, it does not cause acute periorificial dermatitis.
(D) **Calcium:** Deficiency leads to rickets in children or tetany, but it does not present with a scaly, pustular skin rash.

**EXAM PEARL**

**Diarrhea and Zinc Supplementation**

Zinc supplementation is now a standard part of the WHO protocol for treating acute diarrhea in children. It reduces the duration and severity of the episode and helps prevent future recurrences for up to three months.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 432-434.

**Q47. A 6-month-old infant is brought in for evaluation of poor visual tracking and increased startle response to sounds. On examination, a cherry-red spot is noted on the macula. The child also has hypotonia and progressive neurodegeneration. Which of the following is the most likely diagnosis?**

A. Tay-sach disease
B. Hunter disease
C. Gaucher disease
D. Niemann Pick disease

**Ans. A. Tay-sach disease**

The cherry-red spot on the macula in an infant with neurodegeneration is a high-yield diagnostic hallmark of **Tay-Sachs disease**. It is an autosomal recessive disorder caused by a deficiency of the enzyme **hexosaminidase A**.

*For more on Tay-Sachs disease, Refer to Q6 of Biochemistry.*

**Other Options**

(B) **Hunter disease:** This is a mucopolysaccharidosis (MPS Type II). It presents with coarse facial features, clear corneas, and hepatosplenomegaly, but no cherry-red spot.
(C) **Gaucher disease:** The most common lysosomal storage disease. It features Gaucher cells (crinkled paper appearance), bone pain, and massive splenomegaly, but typically no cherry-red spot.
(D) **Niemann-Pick disease:** As noted above, the presence of hepatosplenomegaly is the definitive sign that points to Niemann-Pick over Tay-Sachs.

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**Differentiating Tay-Sachs from Niemann-Pick**

| *Feature* | *Tay-Sachs disease* | *Niemann-Pick disease* |
|---|---|---|
| **Enzyme defect** | Hexosaminidase A | Sphingomyelinase |
| **Accumulated lipid** | $GM_2$ ganglioside | Sphingomyelin |
| **Hepatosplenomegaly** | Absent | Present |
| **Cherry-red spot** | Present | Present |
| **Foam cells** | Not prominent | Classic finding on biopsy |

**EXAM PEARL**

**Tay-Sachs Disease**

Tay-Sachs is particularly prevalent in the **Ashkenazi Jewish** population. Genetic screening for carrier status has significantly reduced the incidence of this fatal condition in these communities.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 192-194.

**Q48. When there is low insulin: glucagon ratio, which of the following enzymes is stimulated?**

A. Phosphofructokinase I
B. Glycogen synthase
C. Hormone sensitive lipase
D. Lipoprotein lipase

**Ans. C. Hormone sensitive lipase**

A **low ratio** (high glucagon, low insulin) signifies a **fasting or stressed state**, where the body must mobilize stored energy to maintain blood glucose and provide fuel for tissues.

**Pathophysiology**

**When the insulin:** glucagon ratio is low, the body transitions from energy storage (anabolism) to energy mobilization (catabolism). This is primarily mediated by cyclic AMP (cAMP) and protein kinase A (PKA), which phosphorylate and activate specific fasting state enzymes.

**Hormone-sensitive lipase (HSL)** is such enzyme and is found in adipose tissue. Glucagon binds to its receptor, increasing cAMP, which activates PKA. PKA then phosphorylates HSL, and activating it.

HSL breaks down stored triglycerides into free fatty acids (FFAs) and glycerol. The FFAs are released into the blood to be used by muscles and the liver as an alternative fuel source to glucose.

**Enzyme Regulation – Comparison**

| *Enzyme* | *Stimulus* | *Metabolic state* | *Action* |
|---|---|---|---|
| **Hormone-sensitive lipase** | Low insulin: glucagon | Fasting/exercise | Lipolysis |
| **Lipoprotein lipase (LPL)** | High insulin: glucagon | Fed state | Lipogenesis |
| **Glycogen synthase** | High insulin: glucagon | Fed state | Glycogen synthesis (liver, muscle) |
| **Phosphofructokinase-I** | High insulin: glucagon | Fed state | Rate-limiting step of glycolysis |

**EXAM PEARL**

**Hormone-sensitive Lipase**

During **diabetic Ketoacidosis (DKA)**, the insulin: glucagon ratio is extremely low. This leads to massive, uncontrolled activation of **hormone-sensitive lipase**, increasing the levels of fatty acids, which are then converted into ketones, leading to acidosis.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 162-165.

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**Q49. A child was brought with pedal edema and cheilosis. On investigating, cardiomegaly was also present. Which vitamin deficiency is associated with this presentation?**

A. Thiamine
B. Pyridoxine
C. Niacin
D. Riboflavin

**Ans. A. Thiamine**

This clinical presentation is a classic description of **wet beriberi**, which is the cardiovascular manifestation of **thiamine (vitamin $B_1$)** deficiency. The combination of pedal edema and cardiomegaly are the hallmark signs of high-output heart failure associated with this condition.

Thiamine, in its active form thiamine pyrophosphate (TPP), is a vital cofactor for several key enzymes in carbohydrate metabolism, most notably pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase.

When thiamine is deficient, cells cannot efficiently convert pyruvate into acetyl-CoA to enter the TCA cycle. This leads to a severe deficit in ATP production. The lack of ATP and the accumulation of metabolites cause peripheral vasodilation. This leads to a high-output heart failure and hence pedal edema. Over time, the heart muscle (myocardium) weakens and dilates, leading to cardiomegaly.

**Clinical Variants of Beriberi**

| *Type* | *Primary system affected* | *Key features* |
|---|---|---|
| Wet beriberi | Cardiovascular | Edema, cardiomegaly, tachycardia, high-output heart failure |
| Dry beriberi | Neurological | Peripheral neuropathy, muscle wasting, "wrist drop" or "foot drop" |
| Infantile beriberi | Both/acute | Occurs in infants of thiamine-deficient mothers; aphonia (silent cry), heart failure |
| Wernicke-Korsakoff | CNS | Ataxia, ophthalmoplegia, confusion, memory loss |

**Other Options**

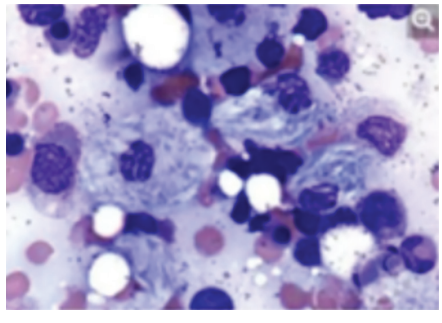
(B) **Pyridoxine (vitamin $B_6$):** Deficiency typically causes sideroblastic anemia, peripheral neuropathy, and convulsions. While it can cause cheilosis, it does not cause the cardiomegaly or edema.

(C) **Niacin (vitamin $B_3$):** This leads to pellagra (dermatitis, diarrhea, dementia). It can cause glossitis but not heart failure.

(D) **Riboflavin (vitamin $B_2$):** Deficiency leads to ariboflavinosis, which is characterized by cheilosis, glossitis, and corneal vascularization, but it is not cardiovascular issues like cardiomegaly.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 314-317.

**Q50. A child with refractory anemia undergoes a bone marrow biopsy. Based on the smear findings, which is the most likely enzyme deficiency?**



A. 1,4 α-glucosidase
B. β-glucocerebrosidase
C. Hexosaminidase A
D. Hexosaminidase B

**Ans. B. β-glucocerebrosidase**

The bone marrow smear provided shows characteristic **Gaucher cells**. These are large macrophages with a fibrillar, crinkled paper or crumpled silk appearance in the cytoplasm, which is pathognomonic for **Gaucher disease**.

Gaucher disease is the most common lysosomal storage disorder. It is an autosomal recessive condition characterized by deficiency in β-**glucocerebrosidase**.

The enzyme breaks down glucocerebroside (glucosylceramide) and its deficiency results in accumulation of glucocerebroside within the lysosomes of macrophages. This gives them the distinct, wrinkled-looking cytoplasm seen in the image.

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**Clinical features:** Patients often present with refractory anemia and thrombocytopenia because the marrow is being filled by these large Gaucher cells.

The most common radiological sign is the **Erlenmeyer flask deformity** of the distal femur. Bone pain and bone crises are common due to marrow expansion. Massive splenomegaly and hepatomegaly are also noted.

**Other Options**

(A) **1,4 α-glucosidase:** Also known as acid maltase. Its deficiency causes Pompe disease (GSD Type II), which presents with severe cardiomegaly and muscle weakness, not Gaucher cells in the marrow.

(C) **Hexosaminidase A:** Deficiency causes Tay-Sachs disease. While it is a lipid storage disorder, it presents with a cherry-red spot on the macula and neurodegeneration but lacks the specific Gaucher cell morphology.

(D) **Hexosaminidase B:** Deficiency causes Sandhoff disease, which is clinically similar to Tay-Sachs (cherry-red spot) but also involves systemic organ involvement.

**EXAM PEARL**

**Gaucher Disease vs. Niemann-Pick Disease**

**Crinkled paper** or **crumpled silk** cytoplasm = **Gaucher disease** (β-glucocerebrosidase)

**Foamy** or **soap bubble** cytoplasm = **Niemann-Pick disease** (Sphingomyelinase)

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 192-195.

**Q51. Which of the following zymogens require gamma-glutamyl carboxylase?**

A. Factors II, VII, IX and X
B. Factors II, VII, IX, XI
C. Factors II, VIII, IX, X
D. Factors II, VIII, X, XI

**Ans. A. Factors II, VII, IX, X**

**Vitamin K Cycle**

The enzyme **γ-glutamyl carboxylase** is responsible for adding a carboxyl group (-COOH) to specific glutamic acid residues on certain clotting factors. This process is essential for their function.

This carboxylation creates **γ-carboxyglutamate (Gla)** residues. These "Gla" residues act as high-affinity binding sites for **calcium**. Once calcium is bound, these clotting factors can then bind to the negatively charged phospholipids on the surface of activated platelets. Without this binding, the coagulation cascade cannot proceed efficiently.

**Vitamin K Dependent Factors**

There are six primary proteins in the coagulation system that require this specific Vitamin K-dependent modification:

- **Pro-coagulants:** Factors II (Prothrombin), VII, IX, and X
- **Anti-coagulants:** Protein C and Protein S

**MNEMONIC** **Pro-coagulant factors – 1972**

**1972** – Factors X, IX, VII, II

**Other Options**

(C, D) **Factor VIII:** This is part of the intrinsic pathway, but it is a glycoprotein co-factor, not a vitamin K-dependent protease. It does not undergo γ-carboxylation.

(B, D) **Factor XI:** This factor is part of the contact activation (intrinsic) pathway, but it is synthesized in its active form without the need for vitamin K-dependent modification.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 308-311.

**Q52. A chronic alcoholic shows a high NADH: $NAD^+$ ratio and normal urea. What change would you most likely expect in this person?**

A. Low urate
B. High urate
C. High glucose
D. Low lactate

**Ans. B. High urate**

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The metabolic profile of a chronic alcoholic is dominated by the massive production of **NADH** during ethanol metabolism. This shifts the internal redox state of the liver, shifting several key equilibrium reactions in directions that favor metabolic distress.

Alcohol is metabolized in two steps: Ethanol → acetaldehyde → acetate. Both steps, catalyzed by alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH), reduce $NAD^+$ to NADH.

This high NADH:$NAD^+$ ratio has several downstream consequences:

**Lactic acidosis:** To regenerate $NAD^+$, the liver shunts pyruvate into lactate. This leads to high blood lactate levels.

**Hypoglycemia:** Because pyruvate is being converted to lactate, it is no longer available for gluconeogenesis. This is why alcoholics are prone to low blood sugar, especially if they haven't eaten.

**Secondary hyperuricemia:** High levels of lactate in the blood compete with urate for excretion in the renal tubules of the kidney. The kidney prioritizes excreting the excess lactate, causing urate to be reabsorbed back into the blood. Additionally, alcohol consumption increases the breakdown of ATP, which provides more purine precursors for uric acid synthesis.

**Other Options**

(A) **Low urate:** As explained above, urate levels rise because its renal excretion is blocked by high lactate. Chronic alcoholism is a major trigger for gout for this reason.

(C) **High glucose:** Alcoholics typically present with fasting hypoglycemia. High NADH inhibits the conversion of lactate to pyruvate and glycerol to dihydroxyacetone phosphate (DHAP), both of which are required to synthesize glucose.

(D) **Low lactate:** Lactate levels will be high, not low. The high NADH pushes the pyruvate ↔ lactate equilibrium strongly toward lactate.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 158-160.

## NEET PG 2022

**Q53. Which of the following molecules is primarily responsible for the compaction of DNA within the nucleus?**

A. Nucleic acids
B. Histones
C. Helicases
D. Glycoproteins

**Ans. B. Histones**

The architectural organization of deoxyribonucleic acid (DNA) within the eukaryotic nucleus necessitates a sophisticated hierarchical packaging system to reconcile the extreme length of the genome with the microscopic dimensions of the nuclear envelope.

The primary mechanism for DNA compaction involves the association of the double helix with a class of small, highly basic proteins termed **histones**. These proteins are characterized by a high concentration of positively charged amino acids, specifically **lysine** and **arginine**.

**Electrostatic interaction:** The polyanionic nature of the DNA phosphate backbone facilitates a high-affinity electrostatic bond with the polycationic histone proteins.

**Nucleosome core:** This represents the fundamental structural unit of chromatin. It consists of approximately 146 base pairs of DNA wound in 1.75 left-handed superhelical turns around a discoidal protein octamer. The octamer is composed of two copies each of the core histones: **H2A, H2B, H3, and H4**.

**Linker histone (H1):** Histone H1 associates with the linker DNA between nucleosome cores. Its primary function is to stabilize the point where DNA enters and exits the core particle, promoting the folding of the nucleosomal chain into the higher-order 30-nm chromatin fibre.

**Genetic Regulation**

The compaction process is not merely a storage solution but a critical regulatory mechanism for gene expression:

- **Euchromatin:** Characterized by a more relaxed, open conformation (often mediated by histone acetylation), allowing the transcriptional machinery (RNA Polymerases) access to the genetic template.

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- **Heterochromatin:** A highly condensed, transcriptionally silent state where DNA is rendered inaccessible to regulatory proteins.

**Other Options**

(A) **Nucleic acids:** While DNA and RNA are the constituents of the genetic material, they lack the intrinsic structural capacity to achieve higher-order compaction without proteinaceous scaffolds.
(C) **Helicases:** These are ATP-dependent motor proteins responsible for the dissociation of the double-stranded DNA helix during replication and repair; their role is antagonistic to compaction.
(D) **Glycoproteins:** These molecules typically function in cellular recognition, signaling, and extracellular matrix integrity; they play no recognized role in the intranuclear packaging of the genome.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 458-460.

**Q54. Which of the following molecules facilitates the transport of mobilized fatty acids into the mitochondria for β-oxidation?**

A. LCAT
B. Cholesterol transporter
C. Acyl carrier protein
D. Carnitine

**Ans. D. Carnitine**

The translocation of long-chain fatty acids across the inner mitochondrial membrane is the rate-limiting step of lipid catabolism. Because the inner membrane is impermeable to polar molecules, a specialized "shuttle" system is required.

**Carnitine Shuttle**

Long-chain fatty acids (LCFAs) mobilized from adipose tissue enter the cytosol, but their oxidation occurs exclusively within the mitochondrial matrix. The transport process involves four distinct stages:

1. **Activation:** Fatty acids are first converted into fatty acyl-CoA by the enzyme acyl-CoA synthetase in the outer mitochondrial membrane.
2. **Transesterification (CPT-I):** The enzyme carnitine palmitoyltransferase-I (CPT-I), located on the outer membrane, replaces the coenzyme A group with carnitine, forming fatty acyl-carnitine.
3. **Translocation:** A specific carrier protein, carnitine-acylcarnitine translocase, shuttles the acyl-carnitine into the matrix while simultaneously moving a free carnitine molecule back out to the intermembrane space.
4. **Re-activation (CPT-II):** Once inside the matrix, CPT-II converts the acyl-carnitine back into fatty acyl-CoA, releasing free carnitine to repeat the cycle.

**EXAM PEARL**

**Malonyl-CoA Inhibition**

The carnitine shuttle is a critical site of metabolic regulation. **Malonyl-CoA**, the first intermediate in fatty acid synthesis, acts as a potent allosteric inhibitor of **CPT-I**.

- **Fed state:** High levels of Malonyl-CoA prevent newly synthesized fatty acids from immediately entering the mitochondria to be burned.
- **Fasting state:** Malonyl-CoA levels drop, lifting the inhibition on CPT-I and allowing mobilized fatty acids to undergo β-oxidation for energy.

**Other Options**

(A) **LCAT:** Lecithin-cholesterol acyltransferase is an enzyme associated with high density lipoproteins (HDL). It catalyzes the esterification of cholesterol in the plasma, playing a role in reverse cholesterol transport, not fatty acid oxidation.
(B) **Cholesterol transporter:** These proteins (such as ABCA1 or NPC1L1) facilitate the movement of cholesterol across cellular or lysosomal membranes and are unrelated to the mitochondrial transport of fatty acids.
(C) **Acyl carrier protein:** ACP is a critical component of the fatty acid synthase (FAS) multi-enzyme complex. It holds the growing fatty acid chain during synthesis in the cytosol, rather than participating in its breakdown in the mitochondria.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 166-169.

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**Q55. A patient reports muscle pain during physical activity and a history of dark-colored urine. McArdle's disease was diagnosed. What enzyme deficiency is likely to be responsible?**

A. Glucose-6-phosphatase
B. Hexokinase
C. Glycogen phosphorylase
D. Myophosphorylase

**Ans. D. Myophosphorylase**

McArdle's disease (Glycogen storaged Disease Type V) is a classic metabolic myopathy. The dark-colored urine mentioned is a critical clinical sign of **myoglobinuria**, which occurs when muscle fibres break down due to severe energy deprivation during exercise.

**Myophosphorylase** (the muscle-specific isoform of glycogen phosphorylase) is responsible for breaking the α-1,4-glycosidic bonds in glycogen to release glucose-1-phosphate. During the onset of exercise, muscles normally rely on this rapid release of glucose to fuel contraction. Patients experience painful cramps and fatigue shortly after beginning strenuous activity.

If the patient rests or slows down, they often feel a "second wind." This happens because the body begins to deliver alternative fuels, free fatty acids and glucose from the liver to the muscle.

Intense exertion can cause rhabdomyolysis. The released muscle protein, myoglobin, is excreted in the urine, turning it a dark, "ola or tea color. This can lead to acute kidney injury if severe.

**Other Options**

(A) **Glucose-6-phosphatase:** Deficiency causes Von Gierke's disease (Type I). Deficiency leads to severe fasting hypoglycemia and lactic acidosis, not muscle-specific exercise intolerance.
(B) **Hexokinase:** This enzyme traps glucose inside cells by phosphorylating it. A total deficiency would be incompatible with life in most tissues; it is not the cause of McArdle's.
(C) **Glycogen phosphorylase:** While technically correct in name, myophosphorylase is the better option.

*Further reading on Glycogen storage disorders, Refer to Q40 of Biochemistry.*

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 102-104.

**Q56. A person of Mediterranean descent was treated with primaquine for malaria and subsequently developed haemolytic anaemia. Which metabolic pathway is affected due to the enzyme deficiency in this condition?**

A. Gluconeogenesis
B. HMP pathway
C. Kreb cycle
D. Glycolysis

**Ans. B. HMP pathway**

The clinical scenario of drug-induced hemolytic anemia following **primaquine** administration, particularly in a patient of **Mediterranean descent**, is the classic presentation of **glucose-6-phosphate dehydrogenase (G6PD) deficiency**.

The **hexose monophosphate (HMP) shunt**, also known as the pentose phosphate Pathway, is the sole source of NADPH in mature red blood cells (RBCs). Unlike other cells, RBCs lack mitochondria and cannot generate reducing equivalents.

**G6PD** is the rate-limiting enzyme of the oxidative phase of the HMP pathway. NADPH is essential for maintaining a pool of reduced glutathione (GSH).

Reduced glutathione is the primary antioxidant that neutralizes reactive oxygen species (ROS), such as hydrogen peroxide ($H_2O_2$), which are generated by oxidative stressors like the anti-malarial drug **primaquine**.

**Mechanism of Hemolysis**

In G6PD deficiency, the HMP pathway cannot generate sufficient NADPH to keep up with oxidative stress. Oxidants (like primaquine, fava beans, or infections) cause the denaturation of hemoglobin.

The denatured hemoglobin precipitates into insoluble granules called **Heinz bodies**. As these RBCs pass through the splenic sinusoids, splenic macrophages pluck out the Heinz bodies, leaving behind "bite cells" (degmacytes). This damage to the RBC membrane leads to premature destruction and acute hemolytic anemia.

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**Other Options**

(A) **Gluconeogenesis:** This pathway occurs primarily in the liver and kidneys to synthesize glucose from non-carbohydrate precursors. It is not involved in the oxidative protection of red blood cells.

(C) **Krebs cycle:** Mature red blood cells lack mitochondria and therefore do not utilize the citric acid (Krebs) cycle for energy or metabolite production.

(D) **Glycolysis:** While RBCs depend entirely on glycolysis (the Embden-Meyerhof pathway) for ATP production, a defect here (such as pyruvate kinase deficiency) causes chronic non-spherocytic hemolytic anemia, not the acute, drug-induced hemolysis seen with G6PD.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 108-111.

**Q57. When a protein codon is changed to a terminating codon after a single mutation in a nucleotide base pair, then it is called as?**

A. Missense mutation
B. Stop codon mutation
C. Silent mutation
D. Nonsense mutation

**Ans. D. Nonsense mutation**

A single nucleotide substitution that results in the premature termination of a protein chain is a significant event with severe functional consequences for the cell. This a **nonsense mutation**, a point mutation (the substitution of a single base pair) changes a codon that previously specified an amino acid into one of the three **stop codons** (UAA, UAG, or UGA).

When the ribosome reaches this new stop codon during translation, it recruits release factors rather than a transfer RNA (tRNA) carrying an amino acid. This causes the translation process to end prematurely. The cell produces a truncated (shortened) protein that is almost always non-functional. These incomplete proteins are often rapidly degraded by the cell's quality-control systems.

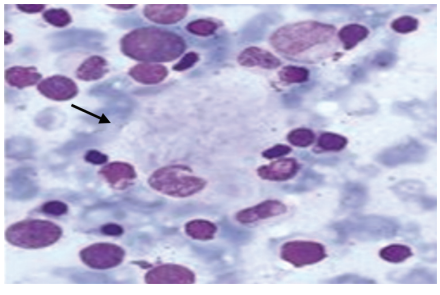
**Point Mutations**

| *Mutation type* | *Nature of the base change* | *Effect on protein structure* |
|---|---|---|
| Nonsense | Amino acid codon → stop codon | Truncated, usually non-functional protein |
| Missense | Amino acid codon → different amino acid | Protein may be functional, partially active, or inactive (e.g., sickle cell anemia) |
| Silent | Amino acid codon → same amino acid | No change in protein sequence (due to the degeneracy of the genetic code) |

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 488-490.

**Q58. The following histological image is seen in the patient who is complaining of growth failure and abdominal distension. The signs found were anemia, thrombocytopenia, and body pain. Which enzyme is deficient in this patient?**

A. Glucose-6-phosphatase
B. Hexosaminidase
C. β-glucocerebrosidase
D. Sphingomyelinase



**Ans. C. β-glucocerebrosidase**

*For more details, Refer to Q50 of Biochemistry.*

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**Q59. Which vitamin deficiency causes the following condition?**



A. Vitamin A B. Vitamin B
C. Vitamin C D. Vitamin E

**Ans. A. Vitamin A**

The image provided shows a **Bitot's spot**, which is a triangular, foamy, or cheesy-looking patch of keratinized epithelium on the bulbar conjunctiva. This is a characteristic clinical sign of **xerophthalmia** caused by vitamin A deficiency.

Vitamin A (retinol) is essential for maintaining the health of epithelial tissues and for production of rhodopsin in the retina.

1. Vitamin A is required for the differentiation of mucus-secreting goblet cells in the conjunctiva
2. When Vitamin A is deficient, these goblet cells are lost and replaced by keratinizing squamous epithelium. This causes the surface of the eye to become dry (**xerosis**).
3. The foamy appearance of these spots (Bitot's spots) is caused by the accumulation of keratin debris and the overgrowth of gas-producing bacteria, such as Corynebacterium xerosis, on the dry surface.

The World Health Organization (WHO) classifies the ocular signs of vitamin A deficiency in a specific order of severity.

| *Classification* | *Clinical sign* |
|---|---|
| **X1A** | Conjunctival xerosis (dryness) |
| **X1B** | Bitot's spots (foamy patches) |
| **X2** | Corneal xerosis |
| **X3A/X3B** | Keratomalacia |
| **XN** | Night blindness |
| **XF** | Xerophthalmic fundus |

**EXAM PEARL**

**Vitamin A Deficiency**

**Earliest SYMPTOM:** Night blindness (Nyctalopia)
**Earliest objective clinical SIGN:** Conjunctival xerosis (X1A)
**Most characteristic clinical SIGN:** Bitot's spots (X1B)
**END STAGE:** Keratomalacia

**Other Options**

(B) **Vitamin B:** Deficiencies in the B-complex group (like B2 or B3) typically affect the mouth (cheilosis, glossitis) or skin (pellagra), but they do not cause these specific keratinized plaques on the eye.
(C) **Vitamin C:** Deficiency causes scurvy, characterized by bleeding gums, petechiae, and poor wound healing due to defective collagen synthesis. It does not cause conjunctival keratinization.
(D) **Vitamin E:** This is a potent antioxidant. Deficiency is rare but can lead to hemolytic anemia or neurological issues (posterior column loss), but it has no direct link to Bitot's spots.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 296-299.

**Q60. Which of the following inhibits complex IV of the electron transport chain?**

A. Cyanide B. Carbon dioxide C. Antimycin D. Oligomycin

**Ans. A. Cyanide**

Complex IV, also known as **cytochrome c oxidase**, is the final enzyme in the respiratory chain that transfers electrons to oxygen.

**Complex IV** contains heme groups (iron) and copper centres that are essential for its catalytic activity. Cyanide ($CN^-$) has an extremely high affinity for the ferric iron ($Fe^{3+}$) in the heme $a_3$ component of cytochrome c oxidase.

By binding to this site, cyanide prevents the final transfer of electrons to oxygen ($O_2$). Because electrons can no longer move to oxygen, the entire ETC backs up. The proton gradient collapses, ATP synthesis stops, and the cell shifts to anaerobic metabolism, leading to severe lactic acidosis and rapid cell death.

**MNEMONIC** **ETC: Sites of inhibition - R-A-C-O (Complex I to V)**

**R**otenone → Complex **I**
**A**ntimycin A → Complex **III**
**C**yanide/CO → Complex **IV**
**O**ligomycin → Complex **V** (ATP Synthase)

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**Comparison of ETC Inhibitors**

| *Inhibitor* | *Target complex* | *Mechanism/consequence* |
|---|---|---|
| **Rotenone/amytal** | Complex I | Blocks NADH dehydrogenase; prevents electron entry from NADH |
| **Antimycin A** | Complex III | Blocks cytochrome $bc_1$ complex; prevents electron flow to cytochrome c |
| **Cyanide/CO/$H_2S$** | Complex IV | Blocks cytochrome c oxidase; prevents the reduction of $O_2$ to $H_2O$ |
| **Oligomycin** | ATP Synthase (CV) | Inhibits the $F_0$ subunit; physically blocks the flow of protons back into the matrix |

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 248-251.

**Q61. An alcoholic patient on anti-TB drugs for the past 2 months complains of numbness, tingling and burning sensation in all the extremities. What could be the vitamin deficiency?**

A. Vitamin A B. Vitamin $B_6$ C. Vitamin $B_{12}$ D. Vitamin D

**Ans. B. Vitamin $B_6$**

The patient is experiencing **peripheral neuropathy**, which is a well-documented side effect of the anti-tuberculosis drug **isoniazid (INH)**.

Isoniazid interferes with Vitamin $B_6$ metabolism through two primary mechanisms:

1. **Chemical complex formation:** Isoniazid reacts with the active form of the vitamin, pyridoxal-5-phosphate (PLP), to form a hydrazone complex. This complex is rapidly excreted by the kidneys, depleting the body's stores.
2. **Enzymatic inhibition:** Isoniazid also inhibits the enzyme pyridoxine kinase, which is responsible for converting dietary pyridoxine into its active PLP form.

PLP is a vital cofactor for several enzymes in the nervous system, including those responsible for synthesizing inhibitory neurotransmitters like GABA. When vitamin B6 levels are low, nerve function is impaired, leading to the "stocking-and-glove" distribution of paresthesia described by the patient.

**Other Options**

(A) **Vitamin A:** Deficiency primarily causes ocular issues (night blindness, Bitot's spots) and skin keratinization, not peripheral neuropathy.

(C) **Vitamin $B_{12}$:** While vitamin $B_{12}$ deficiency does cause neuropathy (subacute combined degeneration), it is not directly induced by anti-TB medications. It is more commonly associated with malabsorption or vegan diets.

(D) **Vitamin D:** Deficiency leads to rickets in children or osteomalacia in adults, affecting bone mineralization rather than peripheral nerve conduction.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 320-323.

**Q62. A 10-year-old boy was brought by his father to the ER in a drowsy state, giving history that his son was having rice water diarrhea for the past 3 days. What receptor is involved for the toxin responsible for this condition?**

A. GM-1 ganglioside receptor B. GM-2 ganglioside receptor
C. GM-3 ganglioside receptor D. GD 1 alpha ganglioside receptor

**Ans. A. GM-1 ganglioside receptor**

The clinical presentation of **rice water diarrhea** is the classic pathognomonic sign of **cholera**, caused by the bacterium *Vibrio cholerae*. The resulting dehydration and electrolyte imbalance explain the child's drowsy state.

The cholera toxin (CT) is an A-B type enterotoxin consisting of one A-subunit and five B-subunits. Its mechanism of action is a cornerstone of medical biochemistry:

The five B-subunits of the toxin act as the targeting mechanism. they specifically recognize and bind to **GM-1 ganglioside receptors** on the enterocytes. Once bound, the A-subunit is internalized into the cell. The A-subunit catalyzes the ADP-ribosylation of the $G_s$ α-subunit of the G-protein.

This modification locks the G-protein in its active state, keeping the enzyme adenylate cyclase permanently activated raising the intracellular levels of cyclic AMP (cAMP).

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High cAMP levels activate protein kinase A, which opens the CFTR (chloride) channels. This leads to the massive secretion of $Cl^-$, $Na^+$, and water into the intestinal lumen, resulting in profuse, watery diarrhea.

**Other Options**

(B) **GM-2 ganglioside receptor:** This molecule is associated with Tay-Sachs disease, where a deficiency in hexosaminidase A leads to its accumulation in the brain. It is not the target for cholera toxin.

(C) **GM-3 ganglioside receptor:** While GM-3 is a precursor in the synthesis of more complex gangliosides, it does not serve as a high-affinity receptor for the cholera toxin B-subunits.

(D) **GD 1 alpha ganglioside receptor:** This is a more complex disialoganglioside. While it exists in neural tissues, it is not the primary mediator for the secretory diarrhea seen in *Vibrio cholerae* infections.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 612-615.

## Q63. What is the mechanism of action of botulinum toxin?

A. Inhibits synthesis of acetyl choline
B. Inhibits reuptake of acetyl choline
C. Inhibits NM receptor
D. Inhibits release of acetyl choline from lower motor neurons

**Ans. D. Inhibits release of acetyl choline from lower motor neurons**

Botulinum toxin, produced by the bacterium *Clostridium botulinum*, is one of the most potent biological neurotoxins known. It targets the neuromuscular junction, leading to a state of **flaccid paralysis**.

### Pathophysiology

Under normal conditions, vesicles filled with acetylcholine (ACh) fuse with the presynaptic membrane of the motor neuron to release their contents into the synaptic cleft. This fusion is mediated by a set of proteins called **SNARE proteins** (including synaptobrevin, SNAP-25, and syntaxin). These proteins act like a winch, pulling the vesicle toward the membrane.

Botulinum toxin is a heavy-chain/light-chain complex. The heavy chain binds to the neuron, allowing the light chain (a zinc-dependent protease) to enter the cytosol. Once inside, the light chain acts as an enzyme and **cleaves the SNARE proteins**. Without functional SNARE proteins, the ACh vesicles cannot dock or fuse with the membrane. Even though the neuron may be activated, no acetylcholine is released into the synapse.

### Botulism

The lack of acetylcholine at the neuromuscular junction means the muscle fibres never receive the signal to contract. This results in:

- **Symmetric descending paralysis:** Usually beginning with the cranial nerves (diplopia, dysphagia, ptosis).
- **Autonomic dysfunction:** Dry mouth and blurred vision.
- **Respiratory failure:** If the toxin affects the diaphragm and intercostal muscles.

**EXAM PEARL**

**Botulinum vs. Tetanus**

**Botulinum toxin:** Acts on lower motor neurons → No ACh release → flaccid paralysis

**Tetanus toxin:** Acts on inhibitory interneurons (Renshaw cells) in the spinal cord → no GABA/Glycine release → unchecked ACh firing → spastic paralysis (lockjaw)

**Other Options**

(A) **Inhibits synthesis:** The toxin does not prevent the production of acetylcholine; the vesicles are fully formed and ready to go, but they are physically locked inside the neuron.

(B) **Inhibits reuptake:** Inhibiting reuptake would actually increase the amount of ACh in the synapse (similar to the effect of some antidepressants on serotonin). This is not the mechanism of botulinum.

(C) **Inhibits NM receptor:** Blocking the nicotinic acetylcholine (NM) receptor is the mechanism of curare and non-depolarizing neuromuscular blockers. Botulinum acts by preventing the ligand from ever reaching it.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 614-616.

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**Q64. A woman on anti-depressants presents with bleeding. She gives a history of bulky stools which stick to the pan. Which of the following vitamin deficiency can cause bleeding in this condition?**

A. Vitamin A
B. Vitamin D
C. Vitamin B
D. Vitamin K

**Ans. D. Vitamin K**

This clinical scenario describes a classic case of **steatorrhea**, which indicates the malabsorption of fats. When fat absorption is impaired, the absorption of **fat-soluble vitamins** (A, D, E, and K) is also compromised.

**Fat Malabsorption and Coagulopathy**

Vitamin K is a fat-soluble vitamin that requires bile salts and dietary lipids for efficient absorption in the small intestine.

In conditions causing steatorrhea (such as chronic pancreatitis, celiac disease, or biliary obstruction), fats are not digested or absorbed correctly. Vitamin K remains is hence excreted. Vitamin K is a necessary cofactor for the enzyme γ-glutamyl carboxylase. This enzyme performs the post-translational modification (carboxylation) of glutamic acid residues on specific clotting factors.

The factors affected are **II (Prothrombin), VII, IX, and X**, as well as **proteins C and S**. Without γ-carboxylation, these factors cannot bind calcium or associate with phospholipid membranes. This leads to a functional deficiency in the coagulation cascade, manifesting as easy bruising, mucosal bleeding, or prolonged bleeding from minor wounds.

Use of **anti-depressants** is a distractor as SSRIs can increase bleeding risk by inhibiting serotonin uptake into platelets, which impairs platelet aggregation. However, the primary cause of bleeding due to the nutritional deficiency of Vitamin K due to the underlying malabsorption.

**Other Options**

(A) **Vitamin A:** While fat-soluble and likely deficient in this patient, its primary symptoms involve the eyes (night blindness, Bitot's spots) and skin, not a bleeding disorder.
(B) **Vitamin D:** Also fat-soluble and likely deficient, but deficiency leads to bone-related issues such as osteomalacia (bone pain and fractures) and hypocalcemia, rather than coagulopathy.
(C) **Vitamin B:** Most B vitamins are water-soluble. Their absorption is generally not affected by fat malabsorption or steatorrhea. Deficiencies typically cause glossitis, anemia, or neurological symptoms.

*Ref:* DM Vasudevan Textbook of Biochemistry for Medical Students. 10th ed. p. 308-311.

**Q65. Which of the following enzyme activities can be estimated in RBCs to diagnose vitamin $B_2$ deficiency?**

A. Pyruvate dehydrogenase
B. Transketolase
C. Glutathione reductase
D. Kynenurinase

**Ans. C. Glutathione reductase**

The laboratory diagnosis of specific vitamin deficiencies often relies on measuring the activity of "marker enzymes" within red blood cells (RBCs) that require those vitamins as essential cofactors.

**Vitamin $B_2$ and FAD**

Vitamin $B_2$ (riboflavin) is the precursor for two major coenzymes: **Flavin mononucleotide (FMN)** and **flavin adenine dinucleotide (FAD)**. These coenzymes are vital for various oxidation-reduction reactions.

**Marker enzyme: Glutathione Reductase (GR)** is an FAD-dependent enzyme found in erythrocytes. Its primary role is to reduce oxidized glutathione (GSSG) back to reduced glutathione (GSH), which is critical for protecting the cell against oxidative stress.

**Diagnostic test:** To diagnose riboflavin deficiency, the activity of glutathione reductase in an RBC lysate is measured both with and without the addition of exogenous FAD.

**EXAM PEARL**

**Three RBC Markers**

- Vitamin $B_1$ (thiamine) – Transketolase
- Vitamin $B_2$ (riboflavin) - Glutathione reductase
- Vitamin $B_6$ (pyridoxine) - AST/ALT (transaminases)

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# Master Class *for* NEET PG

## Goldmine to Crack Exam

With the popularity of the first edition within its 1 month of release, the second edition is an updated comprehensive guide containing explanations and discussions of recall-based NEET PG MCQs from the years 2022 to 2026, for all NEET PG aspirants who study and revise the topics smartly, focusing on high-yield and must-know topics, building confidence before the examination. Recall MCQs of 2021 are given in online platform for easy references along with high-yield topics.

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