1. RAPID REVISION PART 1

PATHWAY

00.02.45

<table>
<tr><th>Pathway</th><th>Site</th><th>Others</th></tr>
<tr><td>GLYCOLYSIS</td><td>Cytoplasm</td><td>

A process in which a 6C compound called Glucose is split to form 2 products
Products are different in both aerobic and anaerobic cell

<table>
<tr><th>Aerobic</th><th>Anaerobic</th></tr>
<tr><td>2 molecules of pyruvate
7 ATP</td><td>2 molecules of lactate
2 ATP</td></tr>
</table>

Significance- Generates ATP in the absence of oxygen

</td></tr>
<tr><td>TCA CYCLE- Pyruvate Dehydrogenase Complex</td><td>Mitochondria</td><td>

Links glycolysis and the TCA cycle

2 molecules of Pyruvate
↓ Pyruvate dehydrogenase
Acetyl CoA
↓ Citric acid cycle
CO_2

Citric acid cycle is the final oxidative pathway, through which every fuel in the body gets oxidised as CO_2

</td></tr>
<tr><td>GLYCOGEN METABOLISM</td><td>Cytoplasm</td><td>

It includes

Glycogen synthesis
Glycogenolysis

</td></tr>
<tr><td>GLUCO-NEOGENESIS</td><td>Mitochondria, Endoplasmic Reticulum/ Microsomes</td><td>

Reversal of Glycolysis
2 molecules of pyruvate are used to synthesize 1 molecule of Glucose
Pyruvate carboxylase converts Pyruvate to OAA
OAA diffuses to cytoplasm, and the reversal of glycolysis occurs to form Glucose 6 phosphate
Glucose 6 phosphatase

It converts Glucose 6 phosphate to Glucose
Endoplasmic Reticulum / Microsomes

</td></tr>
</table>

HMP SHUNT	Cytoplasm	• Glucose 6 phosphate enters HMP shunt • Enzyme involved is Glucose 6 phosphate dehydrogenase • Microsomal enzyme marker - Glucose 6 Phosphatase
FATTY ACID SYNTHESIS	Cytoplasm	
FATTY ACID OXIDATION	Mitochondria	• Exception: VLCFA/BCFA oxidation occurs in Peroxisomes • Functions of Peroxisomes ○ Oxidation of Very long-chain fatty acid & Branched-chain fatty acid ○ Conjugation of glycine and taurine with Bile acids to form bile salts that help in lipid digestion- Bile acids are derivatives of cholesterol ○ Ether lipid synthesis **DISORDERS OF PEROXISOMES** • Zellweger syndrome ○ AKA Cerebrohepatorenal syndrome ○ Peroxisomal biogenesis disorder ○ Peroximes is not generated ○ Clinical features → Rapidly progressive → Presents with severe hypotonia at birth → All the functions of peroxisomes are impaired • Refsum Disease ○ Defect in branched-chain fatty acid oxidation ○ Mainly the Phytanic acid ○ Deficiency of an enzyme is Phytanic acid oxidase ○ Clinical features- Retinitis pigmentosa
KETONE BODY SYNTHESIS	Mitochondria	• Products of incomplete oxidation of fatty acid **Complete oxidation of fatty acids** nCFA (E.g. Palmitic acid- 16C, Stearic acid- 18C) ↓ Beta Oxidation ↓ n/2 acetyl CoA ↓ Citric acid cycle ↓ CO_2 **Incomplete oxidation of fatty acids** Diabetes, starvation ↓ Acetyl CoA will not be able to enter the Citric acid cycle

		Accumulation of Acetyl CoA ↓ Accumulation of Acetyl Condensation of Acetyl CoA molecules to form ketone bodies ↓ Acetone acetate — β-hydroxybutyrate — Acetone
CHOLESTEROL SYNTHESIS	Cytoplasm and SER	• Cholesterol and Bile acids are steroids which are synthesized in Endoplasmic reticulum • Endoplasmic reticulum ○ RER with Ribosomes- Protein synthesis ○ SER- Steroid synthesis
BILE ACID SYNTHESIS	SER	
UREA CYCLE	Mitochondria, Cytoplasm	• Organ → Liver • Function ○ Amonia formed by oxidation of amino group of amino acids is detoxifed to urea
HEME SYNTHESIS	Mitochondria, Cytoplasm	• Heme synthesis for ○ Haemoglobin ○ Myoglobin ○ Cytochrome P450 enzyme

MARKER ENZYME

00.30.04

Organelle	Functions	Marker enzyme
Nucleus	• Have chromosomes • Chromosomes has centromere, short and long arm • Visualized as long double-stranded DNA • DNA condensed with protein • Function ○ Replication - DNA polymerase ○ Transcription - RNA polymerase	• DNA polymerase • RNA polymerase
Endoplasmic Reticulum/ Microsomes	Glucose 6 phosphate → Glucose By the enzyme Glucose 6-phosphatase	Glucose 6-phosphatase
Golgi complex		Glucosyl / Galactosyl transferase
Mitochondria		
Outer membrane		Monoamine oxidase
Inner membrane	Electron transport chain is present in inner side of the inner mitochondrial membrane	Complex II- Succinate dehydrogenase Complex V- ATP Synthase

Matrix	TCA cycle occurs	Citrate synthase
Lysosomes		Cathepsin
Cytoplasm	Glycolysis occurs both aerobic and anaerobic • In presence of oxygen - 2 molecules of pyruvate is formed from 1 glucose • In absence of oxygen - 2 molecules of lactate is formed from pyruvate	Lactate dehydrogenase
Peroxisomes	Generation of hydrogen peroxide. For its detoxification catalase is present	Catalase

ESTIMATION & TEST

00.36.10

Types of Blood Collection Tubes

COLOUR CODED TUBE	COMPONENT	ESTIMATION

Red
 
	• Clot activator present- Silica
	  ○ Serum is separated
	  ○ No clotting factors
	• Clot activator absent
	  ○ Plasma is separated
	  ○ Have all clotting factors, including fibrinogen
		• RFT (S.urea, S.creatinine)
		• Serum electrolytes
		• LFT (bilirubin, SGOPT, SGPT, ALP)
		• Serum amylase, lipase
		• Cardiac function test (CK-MB)
		• Hormonal analysis (TFT)

Gray
 
	• Sodium fluoride
	  ○ Inhibits Enolase of RBC
	  ○ Glycolysis is inhibited
	  ○ Prevents false low values
	• Potassium oxalate
	  ○ Inhibits microbes
		• Glucose estimation
		• Lactate estimation
		• Blood alcohol estimation
		  ○ Quantitative estimation
		  ○ An ideal tube should contain sodium fluoride and potassium dichromate ($k_2Cr_2O_7$)

Lavender
 
	• K_2EDTA/K_3EDTA
	  ○ Chelates calcium
	  ○ Clotting does not occur
	  ○ Inactivates protease
	  ○ Plasma is separated
		• CBC
		• HbA1c
		  ○ With the addition of hemolysate
		• Labile parameter
		  ○ PTH/ACTH- these are small peptides degraded by protease
		  ○ A false low value is observed
		• Ammonia
		  ○ False high value in the presence of protease

Light blue 	• 3.2% sodium citrate	• Coagulation assays • PT • aPTT • Fibrinogen • Factor assay

Green
 
	• Sodium heparin
	• Lithium heparin
		• Stat biochemical analysis
		  ○ Plasma electrolyte
		  ○ Trop T
		  ○ Intraoperative PTH
		• Molecular diagnosis and cytogenetics

Yellow
 
	• Clot activator
	• Gel
	  ○ Due to the difference in co efficient of sedimentation
	  ○ Gel forms a mechanical barrier between the cells (bottom) and serum (top) after centrifugation
	  ○ Prevent contamination of serum
		• RFT (S.urea, S.creatinine)
		• Serum electrolytes
		• LFT (bilirubin, SGOPT, SGPT, ALP)
		• Serum amylase, lipase
		• Cardiac function test (CK-MB)
		• Hormonal analysis (TFT)
		• Tumor markers
		
		Especially used when a sample has to be transported over a long distance and stored for a longer duration

Important Information

- Serum electrolyte estimation - Red/yellow-topped tube
- Plasma electrolytes - Green-topped tube
- The range for both serum and plasma electrolytes varies

Order of draw

00:55:28

INICET May 2023

- To avoid contamination
- Tube which measure analyte, which is sensitive to contamination, is collected first
- Tube containing the additive, which is notorious for causing contamination, is collected last
- Order of collection: Culture tube (yellow) > Blue > Red > Gold (Gel & clot factor) > Green > Lavender > Gray

METHODS FOR ESTIMATION OF ANALYTES

00:58:33

Analyte	Method
Glucose	• Glucose oxidase / Peroxidase
Urea	• Glutamate dehydrogenase

Creatinine	• Widely used
	  ○ Kinetic Jaffe
	• Specific
	  ○ Enzymatic assay

Bilirubin	• Van den Bergh reaction / Diazo method
Total protein	• Biuret method • Copper sulphate reacts with multiple peptide linkages to give a purple-colored complex
Albumin	• BCG method
Electrolyte	• ISE (Ion selective electrodes) / potentiometry

HbA1c	• Widely used
	  ○ Ion exchange chromatography
	• IFCC
	  ○ Electrophoresis

ESTIMATION OF SPECIAL ANALYTE

01.02.23

Glycated Hemoglobin

FMGE 2023, 2025

- Proportion of hemoglobin that is irreversibly, non-enzymatically glycated with carbohydrate residue to the N-terminal valine of -globin chain of normal adult hemoglobin
- Gives an estimation of glycemic control over 3 months
- Limitation
  - Iron deficiency anemia
    → Falsely high value - Due to the increased life span of RBC
    → Following which dose of medication increased leads to hypoglycemia, especially in elderly women
  - Hemolytic anemia
    → Falsely low value

Fructosamine

- Glycated albumin
- Used in patients with Iron deficiency anemia and Hemolytic anemia
- Limitation
  - Gives an estimation of glycemic control over 3-4 weeks because of the life span of albumin

NEET PG 2020

Urine Colour Reaction

01.08.35

Abnormal constituent	Colour reaction	Observation

Reducing substance	Benedict's test	• Colour of urine changes from Blue to
		  ○ Green
		  ○ Yellow
		  ○ Orange
		  ○ Red
		• Depending on the amount of reducing sugar

Ketone body	Rothera's test	• A purple-coloured ring is formed
Protein	Sulfosalicylic acid test	• White precipitate
Blood	Benzidine test	• Dark green/Black precipitate

Bile salt	Hay's test/Sulphur test	• In the presence of bile salts in urine, surface tension is reduced, and sulphur sinks to the bottom
Bile pigment	Fouchet's test	• Green precipitate in filter paper

AMINO ACIDS, GROUPS & COLOR REACTIONS

01:14:40

Amino acid	Group	Color reaction	Color
Phenylalanine	Benzene	Xanthoproteic acid test	• Addition of dilute NO produce → yellow color • Addition of alkyl intensifies → and forms Orange
Tyrosine	Phenol	Xanthoproteic test	Yellow → Orange
		Millon's test	Red
Tryptophan	Indole	Aldehyde test	Purple
Histidine	Imidazole	Pauly's test	Cherry red
Arginine	Guanidine	Sakaguchi test	Red
Proline	Pyrrolidine	Ninhydrin test	Yellow

MNEMONIC

HIP - Histidine, Imidazole group, Pauly's test
TIA - Tryptophan, Indole group, Aldehyde test
AGS - Arginine, Guanidine group, Sakaguchi test
MPS - Millon's test, Pauly's test, Sakaguchi test → Red

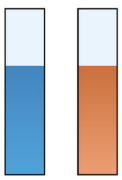
PYQ

01.18.43

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

A. 

C. 

B. 

D. 

Answer: C

Q. The additive that is used in the given blood collection tube is?
A. Sodium fluoride
B. K2EDTA
C. Heparin
D. Silica

Answer: D

Q. Which of the following pathways only takes place in a cell's cytoplasm? FMGE JAN 2023
A. Glycolysis
B. Beta oxidation
C. TCA
D. Urea cycle

Answer: A

Q. The marker enzyme of microsomes is
A. Galactosyl transferase
B. Cathepsin
C. Lactate dehydrogenase
D. Glucose 6-phosphatase

Answer: D

Q. Mitochondrial matrix enzyme is? FMGE JAN 2024
A.Citrate synthase
B.Monoamino oxidase
C.ATP synthase
D.Catalase

Answer: A

Q. Zellweger syndrome is due to which of the following?
A. Peroxisomes
B. Nucleosomes
C. Lysosomes
D. Ribosomes

Answer: A

Q. Which of the following substances is used for sample collection in a tube for blood alcohol concentration measurement?
A. Heparin+EDTA
B. Sodium fluoride + Potassium dichromate
C. Heparin

D. Sodium citrate

Answer: B

Q. Which color-coded collection tube is used for coagulation studies?
A. Blue
B. Green
C. Lavender
D. Red

Answer: A

Q. The most widely used technique for HbA1C estimation?
A. Ion exchange chromatography
B. Affinity chromatography
C. Immunoassay
D. Electrophoresis

Answer: A

Q. Long-term glycemic control in a person with hemolysis is assessed by estimating fructosamine. Fructosamine is a/an?
A. Glycosaminoglycan
B. Urea
C. Fructose
D. Protein

Answer: D

INICET May 2023

Q. A young boy with Type 1 diabetes presents with unconsciousness. His urine is subjected to a test, and the result is provided below. What test is done?

A. Benedict's test
B. Rothera's test
C. Biuret test
D. Fouchet test

Answer: B

Q. The group present in Tryptophan is?
A. Benzene
B. Phenol
C. Indole
D. Imidazole

Answer: C

Q. Which is the right order of blood draw?

A. Yellow , Blue , Grey , Green , Red , Gold

B. Yellow , Blue , Red , Gold , Green , Grey

C. Grey , Green , Gold , Red , Blue , Yellow

D. Gold , Red , Green , Grey , Blue , Yellow

Answer: B

SUMMARY

01.25.31

- Metabolism occurring in the cytoplasm
  - Glycolysis
  - Glycogen metabolism
  - HMP shunt
  - Fatty acid synthesis
- Metabolism occurring in mitochondria
  - PDH complex
  - TCA cycle
  - Fatty acid oxidation
  - Ketone body synthesis
- Metabolism occurs partly in the cytoplasm and mitochondria
  - Urea cycle
  - Heme synthesis
- Metabolism occurring in SER
  - Cholesterol synthesis
  - Bile acid synthesis
- Microsomal enzyme marker → Glucose 6-phosphatase
- Lavender-topped tube used for the estimation of
  - HbA1C
  - Ammonia
  - PTH
  - ACTH
- Detection of ketone bodies in urine
  - Rothera's test

ERROR FILES

01.27.12

- Metabolism occurring in the peroxisome
  - Very long-chain fatty acid oxidation
- Enzyme marker
  - Outer mitochondrial membrane → MAO
  - Inner mitochondrial membrane → ATP synthase
  - Mitochondrial matrix → Citrate synthase
- Serum electrolytes → Red / Yellow
- Plasma electrolytes → Green
- Blood alcohol estimation → grey, which contains sodium fluoride and potassium dichromate

- Blood analyte estimation
  - Creatinine estimation
    → Most commonly used → Kinetic Jaffe's method
    → Ideal method → Enzymatic method
- Hemolytic anemia causes falsely low HbA1C values
- IDA causes falsely high HbA1c values
- Bile pigments → blue or green in the filter paper
- Histidine has an imidazole group
- Tryptophan has an indole ring

2. RAPID REVISION PART 2

INTRODUCTION TO METABOLISM

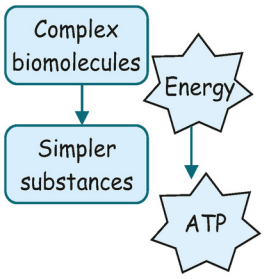
00:01:36

- Process by which we assimilate the food we intake
- It includes
  - Catabolism
  - Anabolism

Catabolism

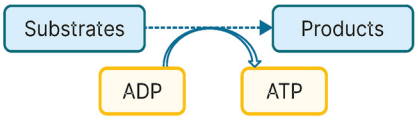
00:01:45

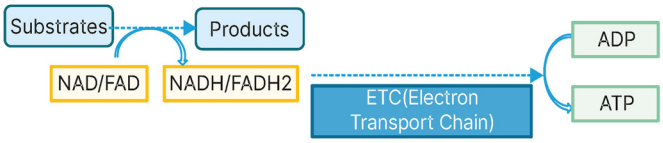
- Process by which complex biomolecules are broken down into simpler substances by breaking the covalent linkage
- Energy is released and trapped as ATP
- Importance of energy being trapped as ATP
  - If energy is not being trapped as ATP, it will be liberated as heat
  - ATP being energy fuel and is required for other anabolic pathway
- 2 types
  - Basis: Depending on how energy is being trapped as ATP
    → Substrate-level phosphorylation
    → Oxidative phosphorylation



Substrate-level phosphorylation	Oxidative phosphorylation

• Process in which substrates are converted to products and energy released is trapped as ATP
• Enzyme of this pathway ends with a kinase
E.g.
• Glycolysis
  ○ Phosphoglycerate kinase
  ○ Pyruvate kinase
• TCA cycle
  ○ Succinyl thiokinase
• Creatine kinase of muscle
	• Process in which substrates are converted to products and energy released is trapped as NADH/FADH2
	• NADH/FADH2 enters ETC, where ATP is formed
	• Enzyme of this pathway ends with Dehydrogenase
	E.g.
	• All other catabolic pathways

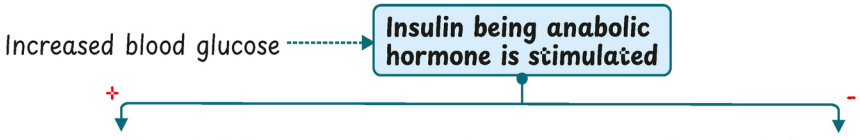




EFFECT OF HORMONES

00.08.09

WELL-FED STATE



Pathways Activated (Anabolic)
- Glycolysis
- Glycogen synthesis
- FA/Cholesterol/TAG/Cholesterol ester/Protein synthesis

Pathways inhibited (Catabolic)
- Glycogenolysis
- Gluconeogenesis
- Peripheral lipolysis/Fatty acid and amino acid oxidation/ Protein breakdown

STARTVATION

Decreased blood glucose ⟶
- Insulin inhibited
- Counter regulatory hormones are released
  - Glucagon
  - GH
  - Norepinephrine
  - Cortisol

Pathways activated (Catabolic)
- Glycogenolysis
- Gluconeogenesis
- Peripheral lipolysis/Fatty acid and amino acid oxidation/ Protein breakdown

- Insulin inhibited
- Counter regulatory hormones are released
  - Glucagon
  - GH
  - Norepinephrine
  - Cortisol

FATE OF GLUCOSE

00.14.08

Low Energy state

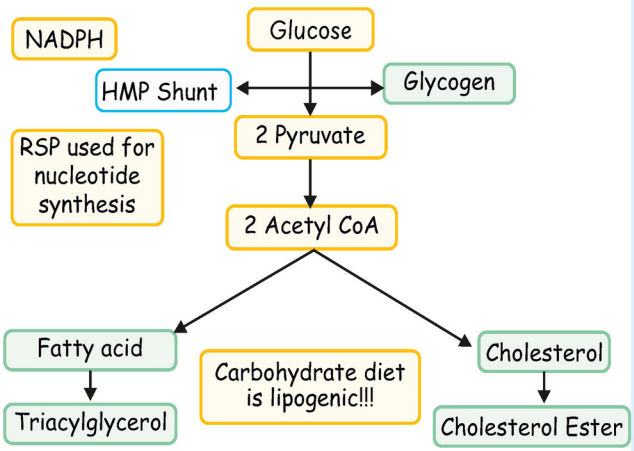
- Glucose entering through the cell is used through Glycolysis

In the absence of oxygen	In the presence of oxygen

• Pyruvate → 2 molecules of lactate
  ○ 2 ATP is generated
	• Glucose → 2 molecules of pyruvate
	  ○ 7 ATP is generated
	• 2 molecules of pyruvate → 2 molecules of Acetyl CoA by Pyruvate dehydrogenase
	  ○ 2 NADH is generated from NAD
	  ○ 5 ATP is formed from 2 NADH
	• 2 molecules of acetyl-CoA are completely oxidized by entering the citric acid cycle, and the CO_2 generated is exhaled
	  ○ 20 ATP is formed

High Energy state

- Glucose → 2 Pyruvate → 2 Acetyl CoA
- Glucose → Glucose 6 phosphate → Glycogen
- Glucose → Glucose 6 phosphate → HMP shunt
  - HMP Shunt pathway is a source for
    → NADPH
    → Source of Ribose phosphate pathway required for nucleotide synthesis
- Acetyl-CoA (does not enter the TCA cycle) is a source for
  - Fatty acid synthesis is stored as TAG
  - Cholesterol synthesis is stored as cholesterol ester



DIFFERENCE BETWEEN NADH & NADPH

NEET PG 2019

Property	NADH	NADPH

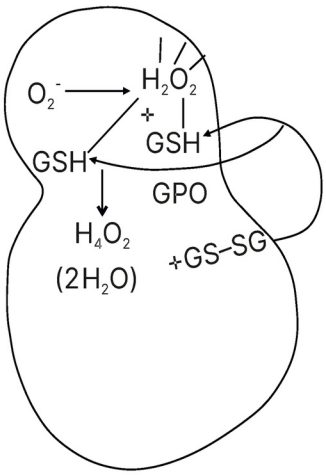
Uses	• Enters ETC and generates 2.5 ATP	• Act as a coenzyme for the reductive biosynthesis of Lipid
		  ○ FA/Cholesterol/Bile acid/Steroid synthesis
		• Regenerate Glutathione
		  ○ Acts as an antioxidant in RBC
		• Required for the ribonucleotide reductase enzyme
		  ○ RNA → DNA
		• Cytochrome P_{450} needs NADPH as a coenzyme

Source	• Glycolysis
	• PDH complex
	• TCA cycle
	• Amino acid / FA oxidation
		• HMP Shunt
		• Cytoplasmic isocitrate dehydrogenase
		  ○ Mitochondrial isocitrate dehydrogenase → generates NADH
		  ○ Cytoplasmic isocitrate dehydrogenase → generates NADPH
		• Malic enzyme
		  ○ Malate → Pyruvate

Significance of NADPH in RBC

- RBC carries maximum oxidative stress
- $O_2 \rightarrow O_2^- \rightarrow H_2O_2$
- H_2O_2 can cause damage to the RBC membrane and lead to hemolysis
- 2 Glutathione + 1 H_2O_2 → 2 H_2O + GS-SG
  - Enzyme- glutathione peroxidase
- Regeneration of glutathione
  - Enzyme- Glutathione reductase
  - Requires NADPH
- G6PD deficiency
  - X-linked recessive
  - The HMP shunt pathway does not occur
  - As a result, NADPH is not formed
  - Glutathione is not regenerated
  - Clinical features- Hemolytic anemia on exposure to oxidative stress
  - Caused by the intake of Primaquine and Flava beans

G6PD deficiency
↓
Hmp shut
↓
↓NADPH
↓
↓GR
↓
↓GSH ⟶ ↑H_2O_2



PREFERRED FUEL FOR A CELL

00.37.28

- Cells utilize energy depending on whether the cell is aerobic or anaerobic.
- Anaerobic cell- Glucose
  - RBC, Retinal and Corneal cell utilizes energy from glucose because they lack mitochondria
  - White muscle fibre because they lack myoglobin, which is the storage form of RBC

Important Information

Isometric Exercise

- Length remains the same, but Tension in the muscle increases
- Contraction of muscle fibre → vasoconstriction of blood vessels

- Decreased oxygen to muscle
  - Red muscle fibre having myoglobin utilizes oxygen → Aerobic cell
  - White muscle fibre lacks myoglobin not utilize oxygen → Anaerobic cell

  - Renal medulla
    → Blood supply is mainly by end arteries
    → Have decreased oxygen
- Aerobic cell
  - Utilizes fatty acid or glucose
  - Cells utilizing fatty acids are
    → Cardiac muscle fibres → have more mitochondria
    → Red muscle fibres → presence of myoglobin
    → 106 ATP produced on the oxidation of Palmitic acid
    → 120 ATP is produced on the oxidation of Stearic acid
  - Cells utilizing glucose
    → Neuron → surrounded by BBB. FA bound to albumin cannot cross the BBB. So utilizes glucose
    → 32 ATP are produced on oxidation

Cell	Fed state	Starvation
RBC	Glucose	Glucose
Neuron	Glucose	Glucose, Ketone bodies
Cardiac muscle fibre	Fatty acid	Fatty acid, Ketone bodies
Skeletal muscle	White muscle fibers- Glucose Red muscle fibers- Fatty acid	Fatty acid, Ketone bodies
Adipose tissue	Glucose	Fatty acid
Liver	Amino acid • Glucose kinase has a low affinity for glucose • Fatty acids absorbed as chylomicrons enters systemic circulation • Not absorbed through portal circulation, and the liver is not utilized	Fatty acid

GLYCOLYTIC ENZYME DEFECT

00.52.39

- Deficiency of glycolytic enzymes affects only those cells that are indispensably dependent on glucose
- It includes RBC and white muscle fibre FMGE 2020, 2021 & 2023, INICET 2021, 2023
- Clinical features
  - RBC

Absence of glycolysis
↓
No ATP synthesized
↓
Failure of Na^+K^+ ATPase (responsible for pumping out 3 Na^+ and pump in K^+)

↓

Na^+ accumulates in RBC

↓

Sodium, being osmotically active, draws water

↓

Cell swelling and hemolysis

↓

Hemolytic anemia

- White muscle fibre
  → Exercise intolerance mainly to anaerobic exercise

Important Information

Metabolic causes of Hemolytic anemia

- G6PD deficiency
- Glycolytic enzyme defect
  - PFK-1 defect
    → Glycogen storage disorder type VII- Tarui's disease
  - Pyruvate kinase defect

MCQ 00.58.40

Q. Cells dependent on glycolysis are all except

A. RBC
B. Neuron
C. White muscle fibres
D. Cardiac muscle fibres

Answer: **D**

Q. The preferred fuel for hepatocytes in the fed state is

A.Glucose
B.Fatty acid
C.Ketone Bodies
D.Amino acid

Answer: **D**

PYQ 00.59.35

Q. Primaquine can precipitate hemolytic anemia in individuals with an enzyme deficiency. The enzyme is related to which pathway? NEET 2022

A. Gluconeogenesis
B. Glycolysis
C. HMP Shunt
D. Glycogen metabolism

Answer: **C**

Q. What is the metabolic fuel for RBC during starvation? INICET NOV 2021

A. Amino acids
B. Ketone bodies
C. Glucose
D. Fatty acids

Answer: **C**

Q. During starvation, which of the following hormones is primarily produced to maintain blood glucose levels?
A.Glucagon
B.Insulin
C.Amylase
D.Somatostatin

Answer: **A**

SUMMARY

01.00.43

- Substrate-level phosphorylation
  - Glycolysis
    → Phosphoglycerate kinase
    → Pyruvate kinase
  - TCA cycle
    → Succinyl thiokinase
  - Creatine kinase of muscle
- Well-fed state → Insulin released → Anabolic hormone
- Fasting state → Glucagon released → Catabolic hormone
- Anabolic pathways
  - Glycolysis
    → Because it forms Acetyl CoA, which is used for FA and cholesterol synthesis
  - Gluconeogenesis
    → 11 high energy phosphate are used for the synthesis of glucose
    → Happening in a catabolic background
- Source of NADPH
  - HMP Shunt
  - Cytoplasmic isocitrate dehydrogenase
  - Malic enzymes
- Metabolic causes of Hemolytic anemia
  - G6PD deficiency → after exposure to oxidative stress
  - Glycolytic enzyme defect → accompanied by exercise intolerance
- Preferred fuel in a well-fed state
  - RBC, Neuron → Glucose
  - Red muscle fibres, cardiac muscle fibres → fatty acid
  - Liver → Amino acid
- Preferred fuel in the fasting state

- RBC → Glucose
- Neuron → Ketone bodies
- Red muscle fibres, cardiac muscle fibres → fatty acid, ketone bodies
- Liver → fatty acid

ERROR FILES

01.05.20

- Substrate-level phosphorylation
  - Kinase
- Oxidative phosphorylation
  - Dehydrogenase
- Insulin → Anabolic
- Glucagon → Catabolic
- Insulin
  - Hates → Hormone-sensitive lipase
  - Loves → Lipoprotein lipase
- Glucose
  - On anaerobic glycolysis → 2 ATP
  - On aerobic glycolysis → 7 ATP
  - Complete oxidation → 32 ATP
- Preferred fuel for Red muscle fibres is Fatty acid
- Preferred fuel for white muscle fibres is Glucose
- Hemolytic anemia accompanied by exercise intolerance → Glycolytic enzyme defect
- Hemolytic anemia on exposure to oxidative stress → G6PD deficiency

3. RAPID REVISION PART 3 - CARBOHYDRATE METABOLISM

CHANGES IN STARVATION

00.02.10

- Starvation is a state of fuel deficiency → Deficiency of Glucose, Fatty acid & Aminoacids
- Plasma glucose is maintained by:
  - Dietary glucose → Maintains the blood glucose for 2-2.5 hours of previous meal
  - Liver glycogenolysis → Starts maintaining blood glucose after 2.5 hours of the previous meal and maintains till 12-18 hours of starvation
  - Gluconeogenesis → Starts maintaining blood glucose after 6 hours of the previous meal

GLUCONEOGENESIS

NEET PG 2020, 2022, 2023, 2024
FMGE 2019, 2020, 2021, 2022, 2023, 2025
INICET 2021, 2022, 2023, 2024, 2025

- Reversal of Glycolysis
- Synthesis of glucose from non-carbohydrate precursors
- Requirement
  - Substrate → Glycerol, Lactate, Alanine
  - Energy → 11 ATP
- Gluconeogenesis is dependent on peripheral lipolysis to meet the requirement

Peripheral Lipolysis

In Adipose Tissue

- TAG → FA + Glycerol
- Mediated by Hormone-Sensitive Lipase
  - Inhibited by → Insulin
  - Stimulated by → Glucagon, GH, Nor-epinephrine, Cortisol

In Liver

- FA and Glycerol reach the liver
- Glycerol acts as a substrate for gluconeogenesis and is converted to glucose
- FA is oxidized to provide energy to gluconeogenesis

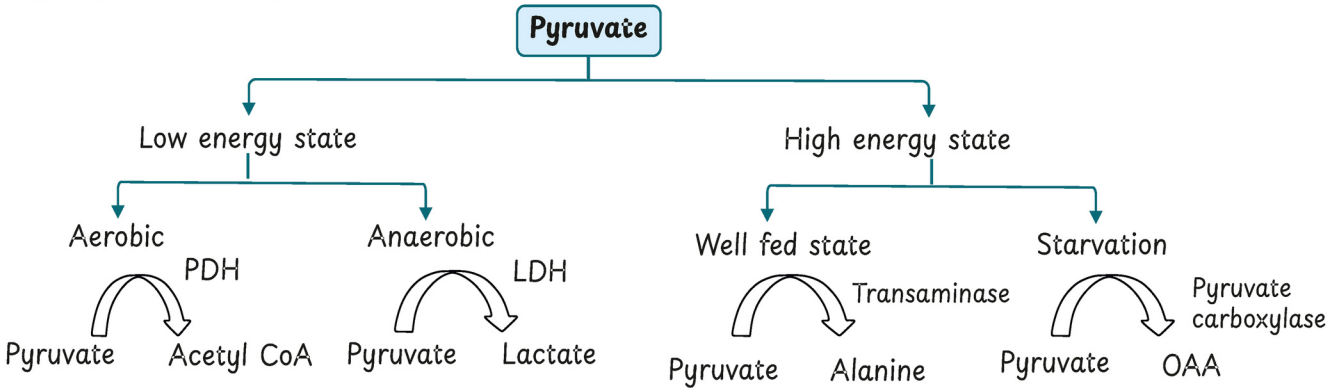
Important Information

- Pyruvate →Oxaloacetate by an enzyme, Pyruvate Carboxylase
  - In starvation, oxaloacetate is used for gluconeogenesis
- During oxidation of Fatty acid → n/2 Acetyl CoA is formed
  - In starvation, Acetyl CoA cannot enter the TCA cycle due to depletion of oxaloacetate, and acetyl CoA is converted to ketone bodies
  - Ketone bodies act as a fuel for the brain after 2 days of starvation

- Other substrates are:
  - Lactate from anaerobic cell
  - Alanine from protein breakdown → Emaciation and reduction in muscle mass

FATES OF PYRUVATE

00.15.13



Functions of Transaminases

- Helps in amino acid breakdown
- Requires Vitamin B6 / Pyridoxal phosphate as a cofactor
- E.g
  - Aspartate + Alpha Ketoglutarate → Glutamate + OAA
    → Enzyme - Aspartate Transaminase (AST)/ Serum Glutamate-Oxaloacetic Transaminase (SGOT)
  - Alanine + Alpha Ketoglutarate → Glutamate + pyruvate
    → Enzyme - Alanine Transaminase (ALT)/Serum Glutamate-Pyruvic Transaminase (SGPT)

PYRUVATE DEHYDROGENASE COMPLEX

00.24.49

- Pyruvate → Acetyl CoA
  - Formation of Acetyl CoA from Pyruvate is catalyzed by the enzyme Pyruvate Dehydrogenase
- PDH complex is present in mitochondria
- Irreversible step
  - Acetyl CoA and Even chain Fatty acid is never Gluconeogenic - only ketogenic
- Catalyzes Oxidative Decarboxylation
  - Oxidation: Removes hydrogen from pyruvate and gives it to coenzyme NAD
    → As a result, NADH is formed
  - Decarboxylation: Releases Co2
- Substrate → Pyruvate, NAD, CoA
- Products → Acetyl CoA, NADH, Co2
- 3 Subunits and 5 Coenzymes

PDH	
Subunits	**Coenzymes**
E1 - Pyruvate Dehydrogenase / Pyruvate Decarboxylase	Vitamin B1 / Thiamine Pyrophosphate
E2 - Dihydrolipoyl Transacetylase	Lipoamide CoA
E3 - Dihydrolipoyl dehydrogenase	NAD- Niacin FAD- Riboflavin

- PDH complex is inhibited by Arsenite

Important Information

- Arsenate inhibits Phosphoglycerate kinase

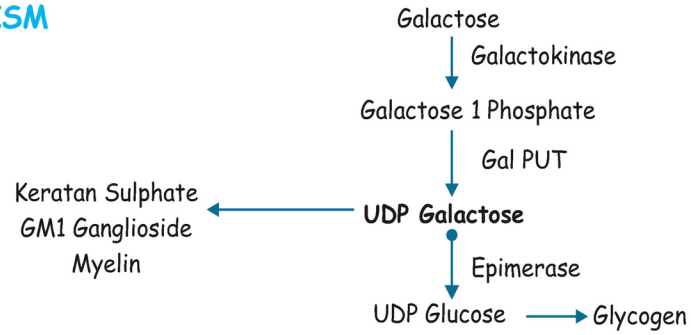
RATE LIMITING ENZYMES

00.32.28

Pathways	Rate-limiting enzymes
Glycolysis	Phosphofructokinase 1
TCA cycle	Isocitrate Dehydrogenase
Glycogen synthesis	Glycogen synthase
Glycogenolysis	Glycogen phosphorylase
Gluconeogenesis	Fructose 1,6 Bisphosphatase
HMP shunt	Glucose 6-Phosphate Dehydrogenase

GALACTOSE METABOLISM

00.34.06

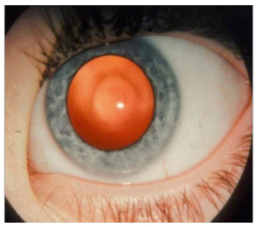


- GALPUT → Galactose 1-phosphate uridyl transferase

GALACTOSEMIA

Enzyme deficient	• Galactokinase

Clinical presentation	• Excess galactose in the blood
	• Galactose present in urine → Benedict's test positive
	• Galactose accumulates in the lens
	  ○ Galactose → Galactitol by an enzyme Aldose Reductase
	  ○ Galactitol attracts water leads to swelling of lens fibres and cataractous changes → Oil drop cataract



CLASSICAL GALACTOSEMIA

Enzyme deficient	• Galactose 1-phosphate uridyl transferase
Clinical presentation	• Excess galactose 1-phosphate • Feedback inhibition on Glucokinase → Excess Galactose • Galactose present in urine → Benedict's test positive • Galactose accumulates in the lens

- Galactose → Galactitol by an enzyme Aldose Reductase
- Oil drop cataract

- Phosphate is trapped → Hypophosphatemia → ATP deficiency →Liver and PCT affected
  - Liver
    → Jaundice and Hepatomegaly
    → Glycogen phosphorylase inactivated due to low phosphate → Glycogenolysis is impaired → Hypoglycemia
  - PCT
    → Solutes are not reabsorbed →Fanconi syndrome
    → Glucose , Phosphate ,$HCO3^-$, amino acid in urine , polyuria and polydipsia
- Neonate presents with sepsis due to E.coli
- Premature ovarian failure

MUCOPOLYSACCHARIDES

00.44.28

Structure

- Long straight unbranched chains containing repetitive units of Uronic acid and Amino sugar
  - Except: Keratan sulphate → Galactose instead of Uronic acid
- Uronic acid, present in all mucopolysaccharide is Glucuronic acid
  - Except: Heparin, Heparan sulphate, and Dermatan sulphate have Iduronic acid
- Amino sugar present in all mucopolysaccharides is Glucosamine
  - Except: Chondroitin sulphate and Dermatan sulphate have Galactosamine
- All mucopolysaccharide is either sulphated or acetylated
  - Except: Hyaluronic acid is neither sulphated nor acetylated

Important Information

- Hyaluronic acid = Glucuronic acid + Glucosamine
  - Follows all rules
- Dermatan sulphate = Iduronic acid + Galactosamine
  - Does not follow any rules

LOCATION

Mucopolysaccharide	Location
Hyaluronic acid	Synovium and Vitreous
Keratan sulphate I	Cornea
Keratan sulphate II	Loose connective tissue
Heparin	Natural anticoagulant secreted by mast cells
Heparan sulphate	Glomerular basement membrane, Aortic wall
Chondroitin sulphate	Cartilages and Bone
Dermatan sulphate	Widely distributed- Universal

MUCOPOLYSACCHARIDOSIS

Type	Name	Enzyme defect	MPS accumulated
I	Hurler's disease	L-Iduronidase	Heparan sulphate Dermatan sulphate
II	Hunter's disease	Iduronate sulphatase	Heparan sulphate Dermatan sulphate
III	San Filippo A to D		Heparan sulphate
IV	Morquio A Morquio B	Galactose sulphatase Beta galactosidase	Keratan sulphate
VI	Morteaux-Lamy disease	Aryl sulphatase	Dermatan sulphate
VII	Sly syndrome	Beta glucuronidase	Heparan sulphate Chondroitin sulphate Dermatan sulphate
IX	Natowicz disease	Hyaluronidase	Hyaluronic acid

GLUT TRANSPORTERS

01.00.31

- Belong to facilitated passive diffusion

GLUT Transporter	Location
GLUT 1	• Neurons, RBC, Placenta, Neoplastic cells • Have a high affinity to glucose
GLUT 2	• Enterocytes, Hepatocytes, Beta cells, Renal Tubular cells
GLUT 3	• Neurons, RBC, Placenta • Have a high affinity to glucose
GLUT 4	• Insulin-dependent glucose transporters • Skeletal muscle, Cardiac muscle, Adipose tissue
GLUT 5	• Fructose transporters • Enterocytes, Seminal vesicle

Important Information

- Warburg effect:
  - In neoplastic cells Glucose is converted to 2 molecules of Lactate even in the presence of oxygen
    → Due to the faster rate of ATP production
    → The intermediate of glycolysis is used for anabolism.
    → E.g: pyruvate formed is used for the synthesis of Alanine, which is used for protein synthesis
- α Glucosidase defect → Pompe's disease
- β Glucosidase defect → Gaucher's disease

GLYCOGEN STORAGE DISORDER

01.07.59

Type	Name	Enzyme defect
0	Glycogen synthase deficiency	
I	Von Gierke's disease	Glucose 6 phosphatase
II	Pompe's disease	Acid maltase / Glucosidase
III	Cori's disease	Debranching enzyme
IV	Anderson's disease	Branching enzyme
V	Mc Ardle's disease	Muscle phosphorylase
VI	Her's disease	Hepatic Phosphorylase
VII	Tarui's disease	Phosphofructokinase 1

POMPE'S DISEASE

- Both Glycogen and Lysosomal storage disorder
- 2% of glycogen is metabolized by Acid maltase / Glucosidase in skeletal muscle and cardiac muscle
  - Glycogen accumulates in cardiac muscle → Cardiomegaly, Cardiomyopathy, and Heart failure
  - Glycogen accumulates in skeletal muscle → Respiratory difficulty and Infantile floppy baby
- Infantile floppy baby
- Rapidly progressive disease death occurs within 2 years
- Treatment → Enzyme Replacement therapy

Important Information

- Liver Glycogenolysis and Gluconeogenesis maintains blood glucose
- Glucose 6-phosphatase is the common enzyme of both pathways
- Glycogen is stored in the liver and muscles
- Liver glycogen maintains blood glucose in the fasting state
  - Absence of Glucose 6 phosphatase → Fasting Hypoglycemia
- Muscle glycogen is used as a fuel for exercise
  - Absence of Glucose 6 phosphatase → Exercise Intolerance

CLASSIFICATION OF GLYCOGEN STORAGE DISORDER

- Disorder presents with fasting hypoglycemia
  - Type 0
  - Type I
  - Type III
  - Type VI
- Disorder presents with exercise intolerance
  - Type 0
  - Type III
  - Type V
  - Type VII

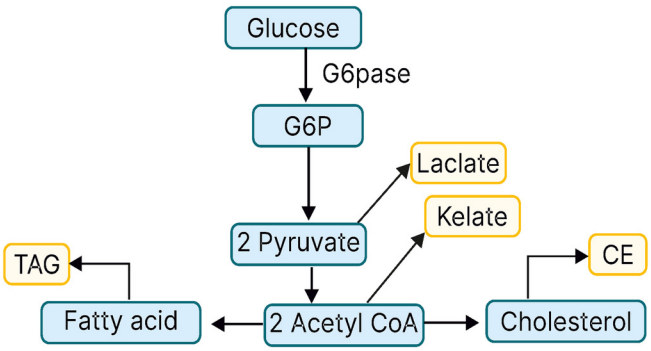
- Disorder presents with both Hypoglycemia and exercise intolerance
  - Type 0
  - Type III
- Disorder presents with neither hypoglycemia nor exercise intolerance
  - Type II
  - Type IV

Glycogen Storage Disorders With Hypoglycemia

Type	Name	Features
0	Glycogen synthase deficiency	• Fasting hypoglycemia • Exercise intolerance (Anaerobic exercise) • No hepatomegaly • Liver biopsy → no glycogen stored in liver
I	Von Gierke's disease	• Fasting hypoglycemia that does not respond to counter-regulatory hormone administration
III	Cori's disease / Limit dextrinosis	• Fasting hypoglycemia • Exercise intolerance • Presence of hepatomegaly • Liver biopsy → abnormal glycogen with branch point accumulates → Limit dextrin
VI	Her's disease	• Fasting hypoglycemia (mild- moderate) that responds to counter-regulatory hormone administration

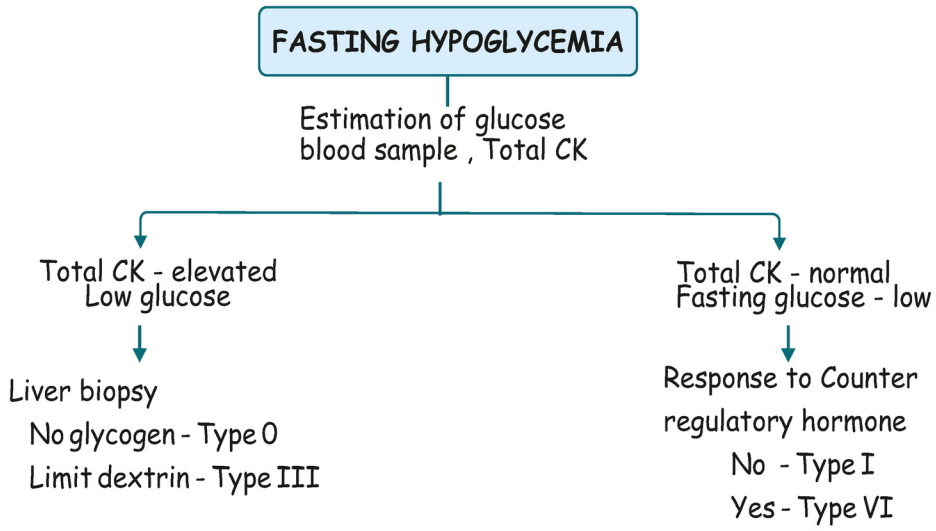
VON GIERKE'S DISEASE

- Deficiency of Glucose 6 Phosphatase
- Glucose 6-phosphate is directed to other pathways
- Glucose 6 phosphate → 2 Pyruvate
  - 2 Pyruvate → 2 Acetyl CoA
    → Acetyl CoA → Fatty acid → TAG
    → Acetyl CoA → Cholesterol → Cholesterol ester
    → Acetyl CoA →Ketone bodies → Ketosis
  - 2 Pyruvate → Lactate → Lactic acidosis
- Glucose 6 phosphate → HMP shunt → purine and pyrimidines → Uric acid



- Clinical presentation:
  - Severe hypoglycemia not responding to counter-regulatory hormone administration
  - Lactic acidosis
  - Ketosis
  - Hypertriglyceridemia → Doll-like facies, hepatomegaly, and renomegaly
  - Hypercholesterolemia → Multiple xanthoma

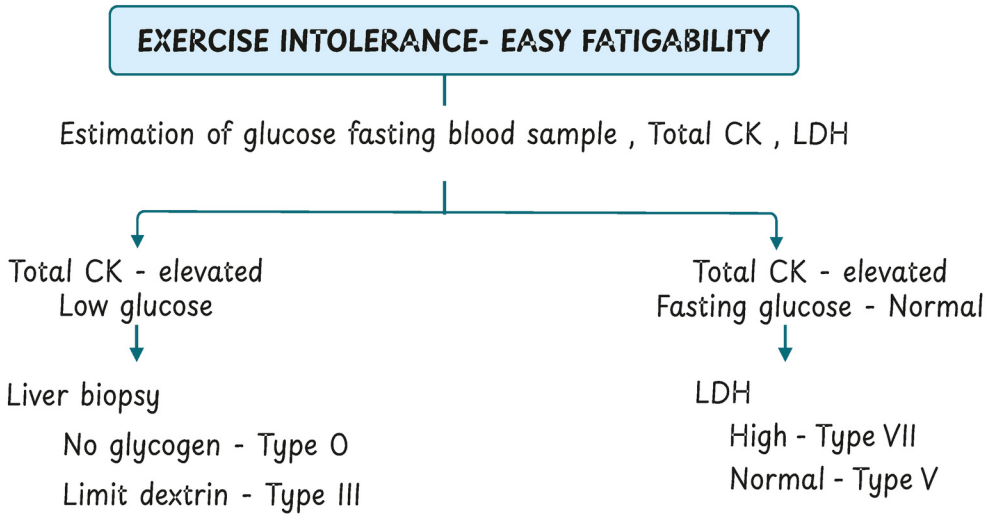
ALOGORITHM



GLYCOGEN STORAGE DISORDERS WITH EXERCISE INTOLERANCE

Type	Name	Feature
0	Glycogen synthase deficiency	• Fasting hypoglycemia • Exercise intolerance • No hepatomegaly • Liver biopsy → no glycogen stored in liver
III	Cori's disease / Limit dextrinosis	• Fasting hypoglycemia • Exercise intolerance • Presence of hepatomegaly • Liver biopsy → Limit dextrin
V	Mc Ardle's disease	• Exercise intolerance (Anaerobic exercise) • Muscle cramps due to sudden ATP depletion • Post exercise → Glucose and lactate level is low
VII	Tarui's disease	• Hemolytic anemia → Elevated LDH • Exercise intolerance to anaerobic exercise

ALOGORITHM



Glycogen Storage Disorders With Neither Hypoglycemia NOR Exercise Intolerance

Type	Name	Features
II	Pompe's disease	• Cardiomegaly, Cardiomyopathy, and Heart Failure • Respiratory difficulty and Infantile floppy baby
IV	Anderson's disease	Hepatomegaly → Liver cirrhosis

MCQs

01.44.04

Q. All of the following are fates of pyruvate except?
A. Acetyl CoA
B. Lactate
C. Alanine
D. Valine

Answer: D

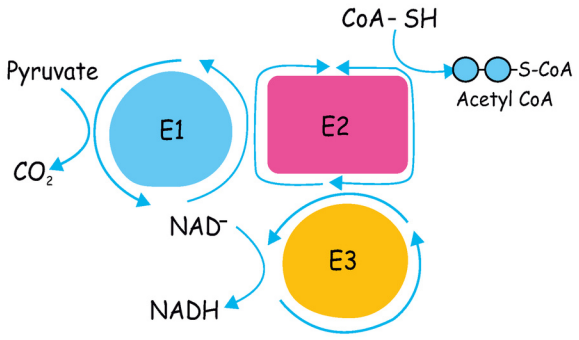
- Pyruvate → PDH → Acetyl CoA
- Pyruvate → LDH → Lactate
- Pyruvate → Transminase → Alanine

Q.All of the following are coenzymes of pyruvate dehydrogenase complex except?
A.Thiamine
B. Riboflavine
C. Niacin
D. Biotin

Answer: D

- Biotin is required for Carboxylase

Q.Identify E1 and E2
A. Pyruvate decarboxylase, Dehydrogenase
B. Pyruvate decarboxylase, Transacetylase
C.Transacetylase, Dehydrogenase
D. Dehydrogenase, Decarboxylase



Answer: B

Q.Which of the following is not a glucogenic substrate?
A. Acetyl CoA
B. Glycerol
C. Lactate
D. Alanine

Answer: A

Q.A breast fed infant begins to vomit frequently and lose weight. Several days later, she is jaundiced, her liver is enlarged, and cataracts are noticed in her lenses. She is diagnosed with classical galactosemia. The enzyme responsible for cataract in this condition is?
A. Galactose 1 Phosphate uridyl transferase
B. Lactose
C. Aldose reductase
D. Aldolase B

Answer: **C**

Q.All the following are components of Mucopolysaccharides except?
A. Uronic acid
B. Amino sugar
C. Sulphate
D. NANA

Answer: **D**

- NANA is a component of Glycolipids

Q.The mucopolysaccharide present in the glomerular basement membrane is? INICET NOV 2021
A. Hyaluronic acid
B. Heparan sulphate
C. Dermatan sulphate
D. Keratan sulphate

Answer: **B**

Q.A child was fatigued after exercise, and the blood sample collected soon after exercise showed low glucose and lactate levels. The probable diagnosis is?
A. Mc Ardle's disease
B. Von Gierke's disease
C. Tarui's disease
D. Anderson's disease

Answer: **A**

Q.A 4 year old child has easy fatiguability. The mother also complained that the child was hungrier between meals, and the child recovered after eating. Liver examination revealed no glycogen. What is the deficiency?
A. Branching enzyme NEET PG 2023
B. Debranching enzyme
C. Glucose 6 phosphatase
D. Glycogen synthase

Answer: **D**

Q.A man is trapped in a tunnel for 5 consecutive days without access to food, but survives. What is the primary source of energy for his brain during this period?
A. Gluconeogenesis
B. Glycogenolysis
C. Ketosis
D. Lipolysis

Answer: **C**

Q.Which of the following is excreted in the urine of patients with pentosuria?
A. L xylulose
B. D ribose
C. D ribulose
D. D lactose

Answer: **A**

- Essential pentosuria is caused by deficiency of Xylitol dehydrogenase and Xylulose reductase

Q.A breastfed infant presents with lethargy, hepatomegaly, and cataracts. Which of the following enzyme deficiencies is most likely responsible for this presentation? FMGE JULY 2025
A. Galactokinase
B. Galactose-1-phosphate uridyltransferase (GALPUT)
C. Aldolase B
D. Fructokinase

Answer: **B**

- Classical galactosemia
  - Mother fed infant
  - Breast milk has Lactose → Galactose + Glucose
  - Galactose-1-phosphate uridyltransferase (GALPUT) deficiency
  - Oil drop cataract
- Hereditary fructose intolerance
  - Infant started on complementary feeding
  - Sucrose → Fructose + glucose
  - Aldolase B deficiency
  - No cataractous changes

Q.Which vitamin deficiency can lead to lactic acidosis?
A.Thiamine
B. Riboflavin
C. Niacin
D. Biotin

Answer: **A**

- Pyruvate dehydrogenase requires Thiamine for its metabolism
- In thiamine deficiency, pyruvate is not converted to acetyl-CoA
- As a result, pyruvate is converted to lactate, causing Lactic acidosis

Q.A child presents with abdominal distention and liver enlarged by 8cm below the costal margin. The liver is smooth on palpation. Which of the following is the most likely diagnosis?
A. Glycogen storage disease
B. Lysosomal storage disease
C. Hepatocellular carcinoma
D. Autoimmune hepatitis

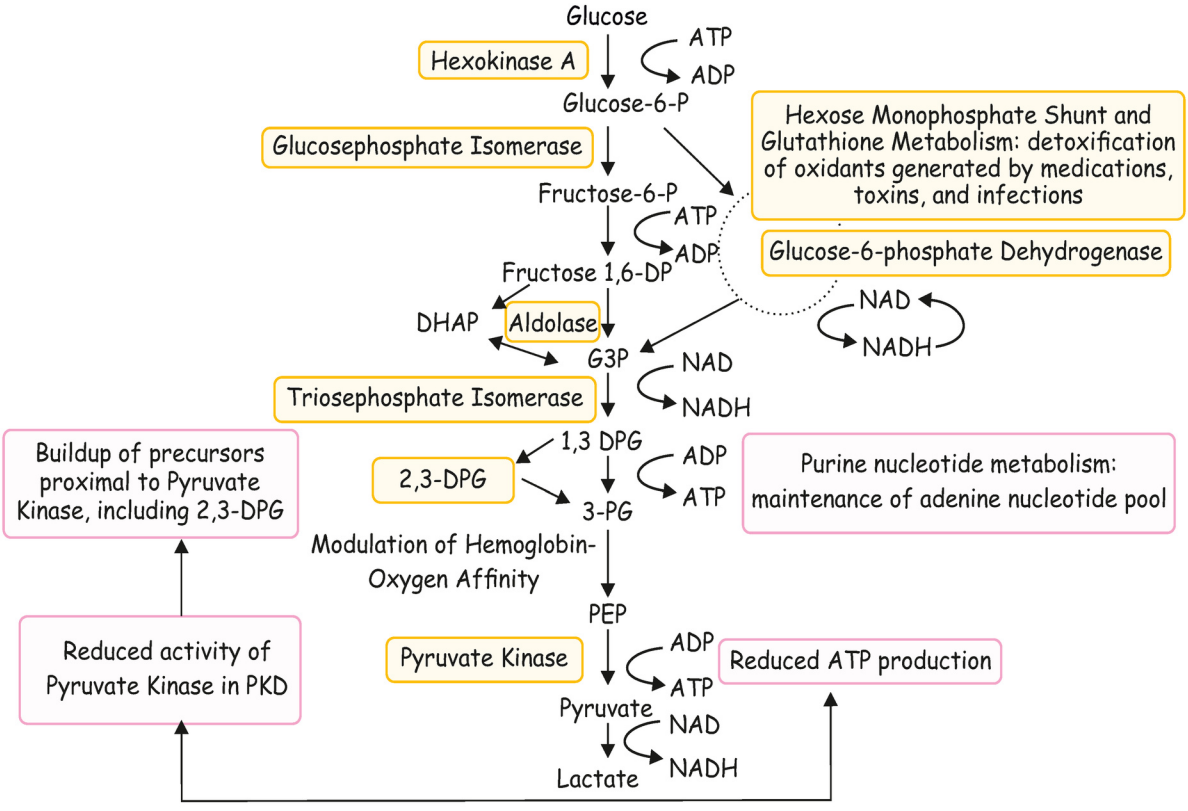
Answer: **A**

- Lysosomal storage disease → Hepatosplenomegaly
- Hepatocellular carcinoma → Nodular liver

Q.Deficiency of which enzyme leads to increased 2,3-BPG levels and low glucose values in vitro?
A. Pyruvate kinase INICET NOV 2022
B. Phosphoglycerate kinase
C. G6PD
D. Hexokinase

Answer: **B**

- Deficiency of Phosphoglycerate kinase: Both glycolysis and gluconeogenesis are affected
- As a result, 2,3-BPG levels are elevated, and blood glucose is lowered



Q. A Child presents with fatigue and hepatomegaly; liver enzymes (ALT, AST) are elevated. Ketosis was significant. Liver biopsy shows excess glycogen accumulation. After feeding blood glucose level rises, but there is no rise in glucose after overnight fasting. Which of the following enzyme deficiencies is most likely responsible for this presentation?
A.Glucose 6-phosphatase
B.Liver phosphorylase
C. Muscle phosphorylase
D.Debranching enzyme

Answer: **A**

Q.Cancer cell take up excess glucose because?
A. Lactate is produced even in the presence of oxygen
B. High NADH/NAD ratio
C. High GLUT 2
D. Formation of acetyl-CoA from pyruvate

Answer: **A**

Q.A person gives blood sample for fasting plasma glucose estimation at 7 am. His last meal was dinner at 8 pm the previous night. The major source of plasma glucose is?
A.Gluconeogenesis
B.Liver Glycogenolysis
C.Dietary glucose
D.Ketone bodies

Answer: **B**

Q.During starvation, which of the following hormones is primarily produced to maintain the blood glucose level?
A. Glucagon FMGE JAN 2025
B. Insulin
C. Amylase
D. Somatostatin
Answer: A

- Other counter-regulatory hormones are GH, norepinephrine, and cortisol

Q.The rate limiting enzyme of the HMP shunt is?
A. Glucose 6-phosphatase
B. Glucose 6-phosphate dehydrogenase
C. Phosphofructokinase 1
D. Glycogen Phosphorylase

Answer: **B**

Q. A 8 month old infant presents with hypoglycemia. On examination, hepatomegaly was observed. Blood investigation revealed lactic acidosis, ketosis, and xanthomas on the buttocks. What is the probable enzyme deficiency? FMGE JUNE 2021

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

Answer: **A**

- Myophosphorylase defect → Presents only with exercise intolerance
- Debranching enzyme defect:
  - Liver Debranching Enzyme Defect: fasting hypoglycemia
    → Due to defect in liver glycogenolysis
    → Gluconeogenesis is stimulated → Lactate ↓
  - Muscle Debranching Enzyme Defect: exercise intolerance

Q.A child was fatigued after exercise, and blood sample collected soon after exercise showed low glucose and lactate levels. The probable diagnosis is?
A. Mc Ardle's disease
B. Von Gierke's disease
C. Tarui's disease
D. Anderson's disease

Answer: **A**

Q.Which receptor plays a crucial role in glucose uptake by skeletal muscle?
A. GLUT 1
B. GLUT 2
C. GLUT 3
D. GLUT 4

Answer: **D**

ERROR FILES

02.07.39

- Pyruvate on transamination forms Alanine, OAA on transamination forms Aspartate
- PDH is inhibited by Arsenite, Phosphoglycerate kinase is inhibited by Arsenate
- Exercise intolerance + Post exercise low glucose is McArdle's disease
- Exercise intolerance + Fasting hypoglycemia is Type 0 and Type III
- The enzyme responsible for classical galactosemia is Galactose-1-phosphate uridyl transferase
- The enzyme responsible for cataract formation in classical galactosemia is Aldose reductase
- Energy fuel of brain
  - Till day 2 of starvation → Glucose
  - From Day 3 to Day 5 → Glucose and Ketone bodies (60%)
  - > 5 Days → Glucose and Ketone bodies (70-80%)

4. RAPID REVISION PART IV

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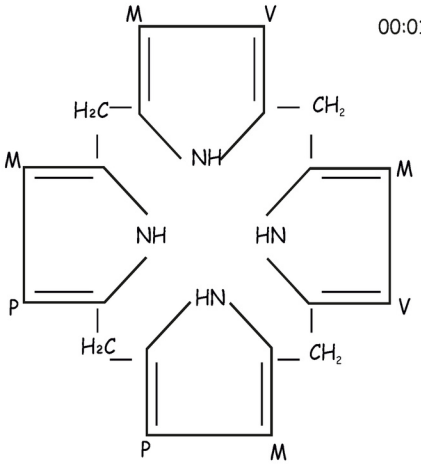
HEME STRUCTURE

Porphyrinogen

- 4 Pyrrole rings are connected by a single bond

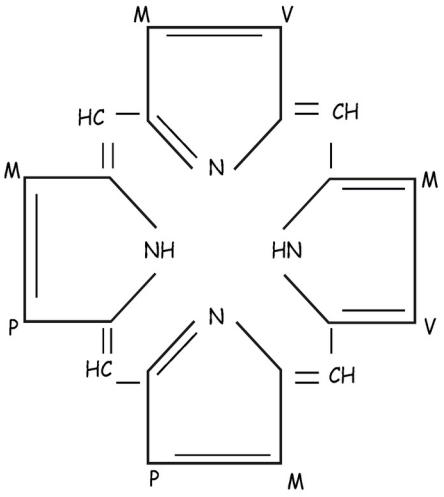


Protoporphyrinogen IX

Porphyrin

- 4 Pyrrole rings are connected by double bond
- Significance of double bond
  - Absorb light at 400nm → Soret Band → Used as bedside test to detect porphyria

Patient with H/O photosensitivity
↓
On exposure to sunlight
↓
Itching, Burning sensation, Blister, Atrophic scar
Hypertrichosis, Onycholysis
↓
Urine sample of the patient is collected
↓
Placed in front of white light
↓
Observation through spectroscope
↓
At 400 nm
↓
Dark band is visible
Soret Band
↓
Interpretation - sample contains Porphyrins



Protoporphyrin IX

  - Emit light at 600 nm →corresponds to Red colour

Congenital Erythropoietic Porphyria

- A/K/A Vampire disease

- On exposure to sunlight → Formation of blister and atrophic scarring seen → peripherally distributed beard
- Porphyrin accumulates in teeth → red colour is being emitted→ Red fluorescence of teeth → Erythrodontia
- Urine of the patient contains porphyrin → red colour is being emitted → Portwin appearance

Photosensitivity

- Porphyrins absorb shorter wavelengths photon and emit longer wavelength photons

$$\text{Energy} \propto \frac{1}{\text{wavelength}}$$

- Porphyrins absorb higher energy and emits lower energy
- Energy difference is liberated as heat → free energy → Excites Oxygen in medium → formation of superoxide radical → photooxidation

HEME SYNTHESIS DISORDERS

00.07.06

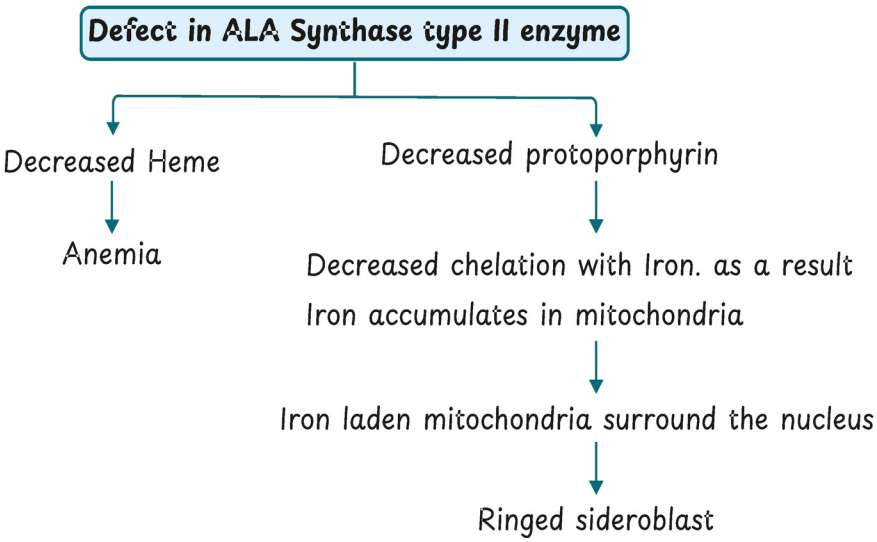
Important Information

- All enzymes of the Heme synthesis are partially defective except ALA Synthase type II, which is completely defective
- ALA synthase II enzyme → present in RBC precursor and helps in heme synthesis

Complete enzyme defect

ALA Synthase II

- A/K/A X-linked sideroblastic anemia
- Pathology



Partial enzyme defect

- Pathology

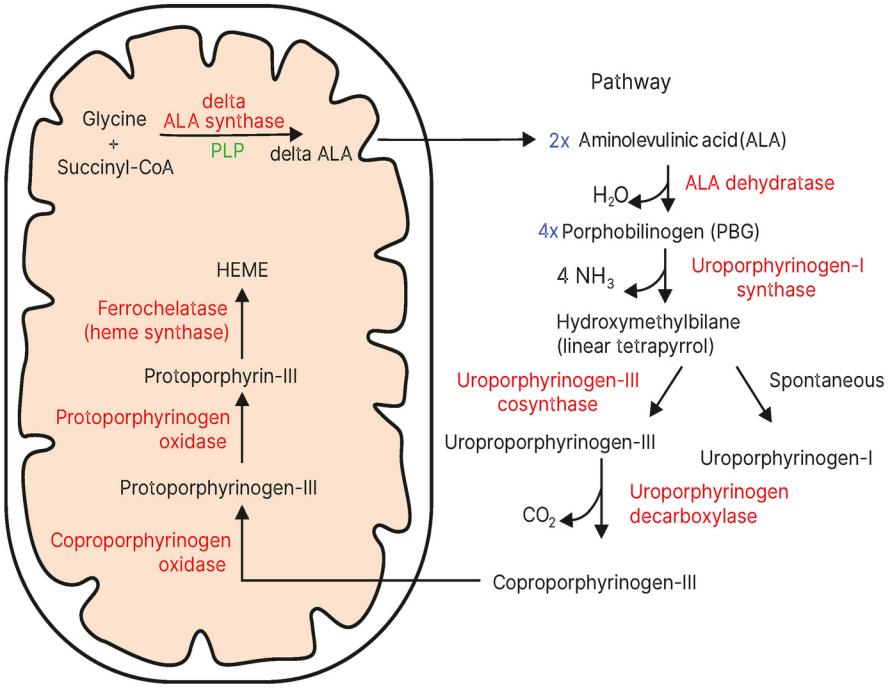
Partial enzyme defect
↓
Due to Feedback mechanism
↓
Heme synthesis is occurs
↓
No manifestation of anemia

  - Clinical manifestations seen → depending on type of precursor accumulation

- ALA/PBG/Both accumulate →Neuropsychiatric Behaviour
  - Neurological features
    → Peripheral sensory nerves gets affected →Paraesthesia→Acute Abdomen
    → Sensory nerve →Motor nerve→Autonomic nerve
  - Psychiatric features
- Porphyrin accumulation → Photosensitivity
- Classifications
  - Type I → ALA/PBG accumulation →Neuropsychiatric Behaviour
  - Type II → Porphyrin accumulation → Photosensitivity
  - Type III → ALA/PBG/Porphyrin accumulation →Neuropsychiatric Behaviour + photosensitivity

Types of porphyria and enzyme defect

AIIMS 2019



Classification of Porphyriyas

Types of porphyria	Enzymes defective	Precursors accumulated	Clinical features
ALA Synthase II defect	ALA Synthase II- Complete enzyme defect		X-linked sideroblastic anemia
ALA Dehydratase Defective Porphyria	ALA Dehydratase	ALA	Neuropsychiatric features
Acute Intermittent Porphyria	Uroporphyrinogen-I synthase/Porphobilinogen deaminase/ Hydroxymethylbilane synthase	ALA & Porphobilinogen	Neuropsychiatric features
Congenital Erythropoietic Porphyria	Uroporphyrinogen-III synthase	Hydroxymethylbilane → spontaneous oxidation to Uroporphyrinogen-I	Photosensitivity - Severe

Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	Uroporphyrinogen- I and III	Photosensitivity
Hereditary Coproporphyria	Coproporphyrinogen oxidase	Coproporphyrinogen • Inhibits ALA Dehydratase through feedback mechanism → ALA accumulation	Neuropsychiatric features + Photosensitivity
Variegate porphyria	Protoporphyrinogen oxidase	Protoporphyrinogen • Inhibits ALA Dehydratase through feedback mechanism → ALA accumulation	Neuropsychiatric features + Photosensitivity
Erythropoietic protoporphyria	Ferrochelatase	Protoporphyrin	Photosensitivity

LEAD POISONING

00.28.28

FMGE 2023, 2025

- Lead inhibits 3 enzymes
  - Ferrochelatase
    → Iron cannot chelate with protoporphyrin; instead, zinc chelates with protoporphyrin
  - Coproporphyrinogen oxidase
  - ALA dehydratase
- Lab findings
  - Zinc protoporphyrin elevated
  - Coproporphyrinogen elevated
  - ALA elevated

Q.A paint shopkeeper presents with anemia. Which of the following enzyme inhibitors causes anemia?

NEET PG 2022

A. ALA Synthase
B. Uroporphyrinogen III Synthase
C. Uroporphyrinogen I Synthase
D. Ferrochelatase

Answer: **D**

Q.A patient's relative sent a message on social media to the consulting doctor. He is unaware about the other investigations. But he mentioned that urinary Coproporphyrin is positive. What is the probable cause?

NEET PG 2024

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

Answer: **A**

LIPID CHEMISTRY

00:31:20

Phosphatidyl Choline

- A/K/A Lecithin

- Produced by Type II Pneumocytes
- Surfactants→ Reduces surface tension of lung
- Infant respiratory distress syndrome
  - In premature baby → Surfactants production is reduced → Surface tension of lung increased → Work of breathing of the lung is increased

Diphosphatidyl glycerol

- A/K/A cardiolipin

Mutation of Tafazzeni gene
↓
Codes for Acyl transferase
↓
Synthesize Cardiolipin → present in mitochondrial membrane

- Barth syndrome
  - Mutation of Tafazzeni gene →Defective cardiolipin
  - Dilated cardiomyopathy, Heart failure
  - Neutropenia

FMGE 2019

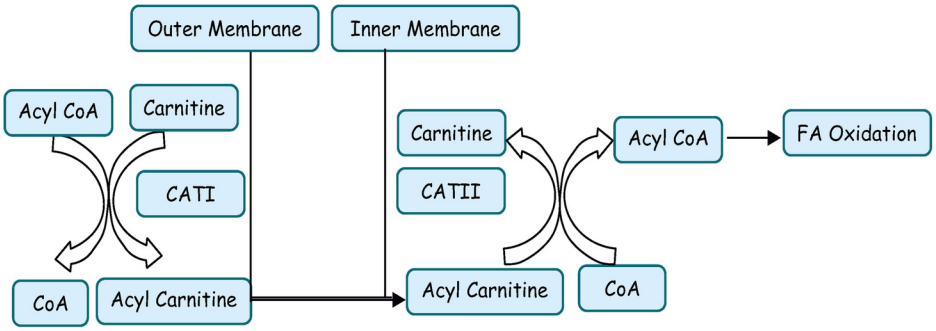
FATTY ACID OXIDATION

00:34:13

- Site → Mitochondria

Important Information

- Phosphatidyl choline → Lecithin
- Phosphatidyl ethanolamine → Cephalin
- Diphosphatidyl glycerol → Cardiolipin
- All fatty acids are oxidized in Mitochondria except VLCFA and BCFA, which is oxidized in Peroxisomes



In cytoplasm

- FA → Acyl CoA
  - 2 high energy phosphate are used
- Acyl CoA + Carnitine →Acyl Carnitine + CoA
  - Enzyme → Carnitine Acyl Transferase 1 (CAT 1) → Rate-limiting enzyme
  - Not dependent on ATP
- Acyl Carnitine can cross the mitochondrial membrane

In mitochondria

- Acyl Carnitine + CoA → Acyl CoA + Carnitine

- Enzyme → Carnitine Acyl Transferase 2 (CAT 2)
- Acyl CoA → FA oxidation (occurs in 2 Phases)
- Phase 1
  - nCFA → {(n/2) -1 cycle} → n/2 Acetyl CoA → 4 ATP are produced
- Phase 2
  - n/2 Acetyl CoA → TCA Cycle → 10 ATP and 2 molecules of CO2 are produced

Important Information

- Palmitic acid → 16C
  - 7 cycles of FA Oxidation → 8 molecules of Acetyl CoA
  - Number of ATP produced = {n/2-1}x4 + {n/2}x10 - 2
    = {16/2-1}x4 + {16/2}x10 -2
    = 106 ATP
- Stearic acid → 18C
  - 8 cycles of FA Oxidation → 9 molecules of Acetyl CoA
  - Number of ATP produced = {n/2-1}x4 + {n/2}x10 - 2
    = {18/2-1}x4 + {18/2}x10 -2
    = 120 ATP

- FA Oxidation pathway is the source of energy for Gluconeogenesis
  - FA oxidation defects → Fasting hypoglycemia

Clinical Features

- Fasting Hypoglycemia → No source of energy for Gluconeogenesis
  - Hypoglycemia due to FA oxidation defect → Non Ketotic Hypoglycemia
- Cardiomegaly → Cardiac muscle fibres depend on FA
- Easy fatigability → Red muscle fibres depend on FA
- Hyperammonemia → Due to increased Amino acid Oxidation
- Dicarboxylic aciduria

Defective FA oxidation in mitochondria
↓
As a result enters Peroxisomes
↓
Oxidised to Very short chain FA (E.g Butyric acid)
↓
Enters Omega oxidation
↓
Dicarboxylic acid is formed

- Hypertriglyceridemia → because FA undergoes conjugation with glycerol → TAG

Investigations

- Hypoglycemia
- Hyperammonemia
- Dicarboxylic aciduria

- Hypertriglyceridemia
- Biopsy →Fat globules

Rate Limiting Enzyme Of Lipid Metabolism

00.50.16

NEET PG 2025

Pathways	Rate Limiting Enzyme
Fatty acid synthesis	Acetyl CoA Carboxylase
Fatty acid oxidation	Carnitine Acyl Transferase I
Cholesterol synthesis	HMG CoA reductase Statins inhibit HMG CoA reductase
Ketone body synthesis	HMG CoA lyase/synthase
Bile acid synthesis	7 Alpha hydroxylase

HYPERLIPOPROTEINEMIAS

00:52:34

NEET PG 2021

- Friedrickson's classification → 6 types
  - Type I
  - Type Iia
  - Type Iib
  - Type III
  - Type IV
  - Type V
- Hyperlipoproteinemias present with:
  - Hypercholesterolemia
  - Hypertriglyceridemia
  - Hypercholesterolemia + Hypertriglyceridemia

Types of Hyperlipoproteinemias	Clinical manifestations	Friedrickson's classification
Hypercholesterolemia	• Tendon xanthomas ○ Small eruptive lesions along the line of attachment of tendon • Accelerated atherosclerosis	Type IIa / Familial Hypercholesterolemia
Hypertriglyceridemia	• Eruptive xanthomas ○ Eruptive lesions along the extensor surface • Recurrent pancreatitis • Lipemia retinalis	Type I, IV, and V
Hypercholesterolemia + Hypertriglyceridemia	• Tendon xanthomas • Eruptive xanthomas • Accelerated atherosclerosis • Lipemia retinalis	Type IIb and III

Type I Hyperlipoproteinemia

NEET PG 2019

- A/K/A Familial Hyperchylomicronemia syndrome

Pathology

Dietary TAG

↓

Chylomicrons

(Apo CII , Apo B48 , Apo E)

↓

Apo CII activates LPL → Chylomicron remnants

↓

Triacylglycerol/ TAG

↓

FA + Glycerol

FA is stored in extrahepatic tissue as TAG

- Defect in Apo CII or Lipoprotein lipase(LPL) causes hyperchylomicronemia → hypertriglyceridemia
- Chylomicrons carry dietary/ exogenous TAG from intestine to the extrahepatic tissue

Clinical features

- Eruptive xanthomas
- Recurrent pancreatitis
- Lipemia retinalis

Eruptive Xanthomas

Investigations

- Triglyceride levels are elevated >1500 mg/dL (normal - 150 mg/dL)
- LPL activity is low → Demonstrated by post heparinized blood sample

Important Information

- Heparin sulphate a mucopolysaccharide attaches LPL in the vessel wall

Type-IIA Hyperlipoproteinemia

- A/K/A Familial Hypercholesterolemia
- Isolated elevation of cholesterol

Pathology

LDL receptors presents in the target tissue and the liver

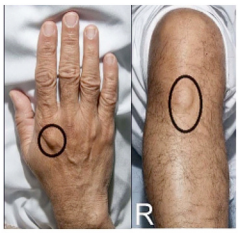
↓

Accepts Lipoprotein(LDL), which are having apo B100 receptors

- Defect in LDL receptor →Hypercholesterolemia
- Autosomal Dominant

Clinical features

- Tendon xanthoma
- Accelerated atherosclerosis

Tendon Xanthomas

Type III Hyperlipoproteinemia

- A/K/A Remnant disease / Broad Beta disease / Familial Dysbetalipoproteinemia

Pathology

- Normal - E3/E3
- Type III Hyperlipoproteinemia - E2/E2

Homozygos E2/E2
↓
Defect in Apo E
↓
Leads to defective clearance of remnants
↓
Elevated Triglyceridemia and Hypercholesterolemia

Clinical features

- Elevation of cholesterol and triglycerides
- Palmar eruptive xanthoma
- Xanthoma Palmaris Striae → Yellowish discoloration of the palmar crease

Palmar eruptive xanthomas

Xanthoma palmaris striae

INVESTIGATIONS

- On electrophoresis → Broad Beta band is observed

Type IV Hyperlipoproteinemia

- A/K/A Familial Hypertriglyceridemia

Pathology

- Autosomal Dominant

Increased VLDL synthesis and decreased VLDL catabolism
↓
Increased VLDL catabolism
↓
Increased Endogenous Triglycerides

Type V Hyperlipoproteinemia

- A/K/A Familial Hypertriglyceridemia with Chylomicronemia

Pathology

- Autosomal Dominant
- Increased VLDL →Increased endogenous Triglycerides
- Increased Chylomicrons →Apo CII defect and LPL Defect

Important Information

Autosomal Dominant mode of Inheritance

- Type IIa hyperlipoproteinemia
- Type IV hyperlipoproteinemia
- Type V hyperlipoproteinemia

GLYCOSPHINGOLIPIDOSIS

01.14.01

INICET 2021, 2023
NEET 2024, 2025
FMGE 2025

Enzyme defect	Name of the Disorder
Beta Galactosidase	• GMI →GM1 Gangliosidosis • Keratin Sulphate → Morquio B disease • Myelin → Krabbe's disease
Alpha Galactosidase	• Fabry's Disease
Beta Glucosidase / Beta Glucosylcerebrosidase	• Gaucher's Disease
Alpha Glucosidase	• Pompe's Disease / Type II GSD

Disorder	Lipid Accumulation
GM1 Gangliosidosis	• GM1 Ganglioside
GM2 Gangliosidosis:	• **Tay Sachs Disease:** GM2 Ganglioside • **Sandhoff Disease:** GM2 Ganglioside, Globoside
Sialidosis / GM3 Gangliosidosis	• GM3 Ganglioside
Fabry's Disease	• Globoside
Gaucher's Disease	• Cerebroside

Gaucher Disease

01.18.54

- Enzyme defect → Beta Glucosidase / Beta Glucosylcerebrosidase
- Lipid accumulated → Glucosylcerebroside

Glucosylcerebroside accumulates in the membrane of RBC and Platelets

↓

RBCs and Platelets are being engulfed by macrophages (fibrils)

↓

Refractory anemia and Thrombocytopenia

↓

Compensatory Erythropoiesis

↓

BM expansion and erosion → Bone pain

Hepatosplenomegaly

- Clinical features
  - Refractory anemia and Thrombocytopenia
  - Bone pain
  - Hepatosplenomegaly
- Investigations
  - BM Biopsy → HPE → fibrils appearance on the RBC and Platelets membrane → Crumpled tissue paper appearance
  - X-ray of knee → Erlnermayer flask deformity

Fabry's Disease

01.22.41

- Enzyme defect → Alpha Galactosidase
- Lipid accumulated → Galactosyl ceramide (Globoside)
- X Linked Recessive inheritance
- Clinical features
  - Reddish purple spot →Angiokeratoma
  - Massive proteinuria → CKD
  - Early MI

Farber's Disease

01.24.34

- Defective ceramidase
- It is a granulomatous disorder
- Present as painful subcutaneous nodules and CKD

Important Information

- No cherry Red spots in → KGF-M
  - Krabbe's Disease
  - Gaucher's Disease
  - Fabry's Disease
  - Metachromatic Leukodystrophy → Deficiency of arylsulphatase
- No mental retardation in → GF
  - Gaucher's Disease
  - Fabry's Disease
- No organomegaly in
  - Tay Sachs Disease
  - Krabbe's Disease
- Tay Sachs Disease
  - Neurological manifestations
  - Exaggerated startle reflex
  - With or without organomegaly
  - With cherry red spot
- Niemann Pick disease
  - Neurological manifestations
  - Massive hepatosplenomegaly

PYQ 01.31.01

Q. Barth syndrome presents with heart failure. Deficiency of which of the following structures in the mitochondrial membrane is the cause of this syndrome?
INICET MAY 2023
A.Lysolecithin
B.Plasmalogen
C.Lecithin
D.Cardiolipin

Answer:**D**

Q.Respiratory Distress Syndrome is caused by a deficiency of?
A. Cephalin
B. Sphingomyelin
C. Lecithin
D. Cardiolipin

Answer: **C**

Q. Which of the following helps in transporting fatty acids across the inner mitochondrial membrane, for them to be utilized in mitochondria?
INICET MAY 2024
A.Acyl carrier protein
B. LCAT
C. Malate
D. Carnitine

Answer: **D**

Q.Patients with high TAG esterified with LCFA present with fatigue, and biopsy of muscle shows fat vacuoles. Which of the following is the diagnosis?
A. Carnitine deficiency
B. FA synthase defect
C. LPL defect
D. LDL defect

Answer: **A**

Q. A 6 month old infant is brought to the emergency department with lethargy, vomiting, and poor feeding. The episode occurred after prolonged fasting. Laboratory results reveal hypoglycemia, low ketone levels (hypoketosis), and mild hepatomegaly. These findings suggest a defect in fat metabolism. Which of the following is the most likely underlying disorder?
FMGE JULY 2025
A. Her's disease
B. Medium chain acyl -CoA dehydrogenase (MCAD) deficiency
C. Hereditary fructose intolerance
D. Glycogen storage disease type I (Von Gierke disease)

Answer: **B**

Q.Which of the following is not true about the beta oxidation of fatty acids?
A. Both CAT I and CAT II are involved in the transport of fatty acids across mitochondrial membrane
B. ATP is utilized in the transport of fatty acids across mitochondrial membrane
C. CoA is released in the cytosol while formation of acyl carnitine
D. Carnitine is released in the mitochondrial side

Answer:**B**

Q. Patient with xanthomas on the Achilles tendon. Which of the following is the diagnosis? NEET PG 2024
A. Familial Hypercholesterolemia
B. Tangier's disease
C. Familial hyperchylomicronemia
D. Familial dysbetalipoproteinemia

Answer: **A**

Q. A patient came to the emergency room with severe pain in the abdomen. Serum triglyceride level was 1500 mg/dl. Identify the defect? NEET PG 2024
A. Apo B 48
B. Apo B 100
C. Apo CII
D. LDL receptor

Answer: **C**

Q. A patient has multiple tendon xanthomas. Serum cholesterol 398 mg/dL and LDL 220 mg/dL were found to be raised. What is the defect?
A. Lipoprotein Lipase deficiency
B. LDL receptors defect
C. Apo E defect
D. LCAT deficiency

Answer: **B**

Q. A man presents with high VLDL and chylomicrons, with eruptive xanthomas. What is the most likely diagnosis?
A. Familial hyperlipidemia FMGE JULY 2025
B. Familial dysbetalipoproteinemia
C. Familial hypertriglyceridemia
D. Familial hypercholesterolemia

Answer: **C**

Q. A 25 year old male presents with hypercholesterolemia. His elder brother has also died of heart disease a few years back. LDL receptor defect was observed. What is the most probable cause?
A. Abetalipoproteinemia
B. Familial Hypercholesterolemia

C. Familial Combined Hyperlipidemia
D. Apo E deficiency

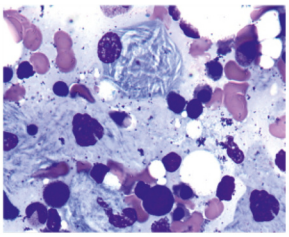
Answer: **B**

Q.Which gene defect causes familial hypercholesterolemia? INICET MAY 2024
A. Apo E
B. Apo CII
C. LDL receptor
D. Apo B48

Answer: C

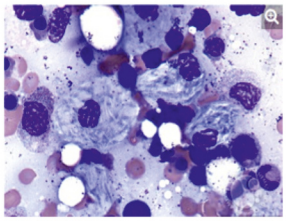
NEET PG 2024

Q.Crumpled tissue paper appearance and pancytopenia are seen in which of the following enzyme defects?
A. Alpha-glucosidase
B. Gluco-cerebrosidase
C. Beta galactosidase
D. Alpha galactosidase



Answer: **B**

Q. A child presented with refractory anemia. Below is provided the smear of the bone marrow biopsy of the child. What is the probable enzyme deficiency? INICET MAY 2024
A. Beta Glucocerebrosidase
B. 1,4 Alpha-glucosidase
C. Hexosaminidase A
D. Hexosaminidase B



Answer: **A**

Q. A child presented with difficulty in vision on examination, cherry red spots were seen on the macula. There was no organomegaly. Identify the disease
A. Gaucher disease
B. Hunter disease
C. Tay-Sachs disease
D. Niemann Pick disease

Answer: **C**

Q.When there is low Insulin: Glucagon ratio, which of the following enzymes is stimulated?
A.Lipoprotein Lipase
B. Hormone-sensitive Lipase
C.Phosphofructokinase I
D.Glycogen synthase

Answer: **B**

- Low insulin → Lipoprotein Lipase is suppressed
- Low insulin → Hormone-sensitive lipase is stimulated

Q. A young boy is having difficulty in breathing while running and is unable to rise from a squatting position. His fundus examination image is provided below. The probable condition is? NEET PG 2022

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

Answer: **A**

Q.A child presents with anemia and thrombocytopenia. On examination, hepatosplenomegaly is observed. The child also complains of bony pain. Light microscopy reveals crumpled tissue paper appearance. The enzyme defect is?
A. Alpha-glucosidase
B. Beta-glucosidase
C. Alpha-galactosidase
D. Beta-galactosidase

Answer: **B**

Q.What is the diagnosis? INICET NOV 2022

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

Answer: **C**

- Tangier's disease
  - Greyish orange tonsil
  - ABCA I defect → Defective HDL metabolism
  - Hepatosplenomegaly, Mononeuritis multiplex

- Wolman's disease
  - Acid lipase defect
  - Adrenal gland calcification

- Gaucher's disease
  - Beta-glucosidase defect
  - Erlenmeyer flask deformity

Q.A child presents with hepatomegaly and a cherry red spot on the macula. Neurological regression is also noted. Startling reflex is exaggerated. These findings are suggestive of a lysosomal storage disorder. Which of the following enzyme deficiencies is most likely responsible?

A. Aryl sulfatase A

B. Hexosaminidase A

C. Sphingomyelinase

D. Galactocerebrosidase

Answer: **B**

Q.After a high-carbohydrate meal, weight gain is explained by all except?

A. Malonyl CoA

B. Tricarboxylate transporter

C. Acetyl CoA carboxylase

D. Mitochondrial carnitine

Answer: **D**

- Following a high-carbohydrate meal, insulin is secreted
- Insulin stimulates
  - Phosphofructokinase
    → Glucose → Pyruvate
  - Pyruvate dehydrogenase complex
    → Pyruvate → Acetyl CoA → formed in Mitochondria
  - Tricarboxylate transporter
    → Acetyl-CoA enters the cytoplasm
  - Acetyl CoA carboxylase
    → Acetyl CoA → Malonyl CoA

Important Information

- Insulin stimulates LPL and inhibits HSL
- Autosomal Dominant Hyperlipoproteinemia Type IIa, IV, and V
- CAT I utilizes carnitine, and CAT II releases carnitine
- Globosides accumulate in Fabry's disease
- Cerebrosides accumulate in Gaucher's disease
- GM2 gangliosides accumulate in Tay-Sachs disease, and GM2 ganglioside
- Globosides accumulate in Sandhoff disease

5. ETC AND PROTEIN

ELECTRON TRANSPORT CHAIN

00:01:10

NEET PG 2022, INICET NOV 2024, NEET PG AUGUST 2024, FMGE JAN 2023

Complexes Of Etc

- 5 stationary complexes
  - Numbered in roman letters 1-5
- 2 mobile complexes

Stationary Complexes

Complex i	• NADH linked dehydrogenase • Electrons from NADH enter the electron chain
Complex ii	• Succinate dehydrogenase • Citric acid cycle linked
Complex iii	• Cytochrome b and c 1
Complex iv	• Cytochrome a and a3
Complex v	• ATP synthase complex

Mobile Complexes

- Ubiquinone/ complex Q between 1 and 3
- Cytochrome c between 3 and 4
- Transports electrons from one complex to another

Direction Of Transport Of Electron

- I/c/o NADH linked electrons
  - Electrons start from complex 1 → Complex Q → Complex 3 → Cyt C → Complex 4 → Final acceptor is molecular oxygen
- I/c/o succinate dehydrogenase
  - FADH2 electrons enter the complex 2 directly → Complex Q → Complex 3 → Cyt C → Complex 4 → Final acceptor is molecular oxygen

Inhibitors Of Etc

- The electron transport between complex I and complex Q is inhibited by:
  - Amobarbital
  - Piericidin A
  - Rotenone
- Complex II or Succinate dehydrogenase is inhibited: Malonate
- The electron transport between complex II and complex Q is inhibited by:
  - TTFA
  - Carboxin

- The electron transport between complex III and complex C is inhibited by:
  - BAL
  - Antimycin
- The electron transport between complex IV and oxygen is inhibited by:
  - Hydrogen sulfide
  - Cyanide
  - Carbon monoxide

Important Information

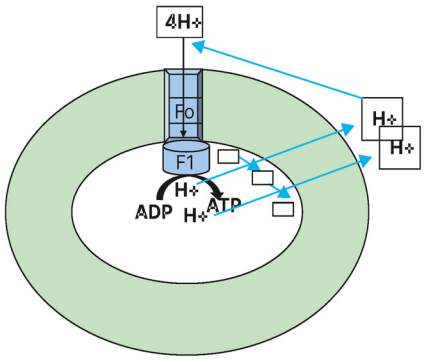
- All ETC inhibitors cause histotoxic hypoxia except Carbon monoxide
- Carbon monoxide causes anemic hypoxia
  - CO has high affinity for Fe^{2+} in hemoglobin → Forms carboxyhemoglobin → ↓ O_2 delivery

Uncouplers

- ETC couples fuel oxidation with phosphorylation of ADP →ATP giving out NADH and FADH2 (oxidative phosphorylation)
- The uncoupler uncouples oxidation from phosphorylation
- Effects of uncouplers
  - ↓ ATP: As phosphorylation is inhibited, ATP is not produced.
  - ↑ Heat: Oxidation happens continuously and hence energy is produced. As energy is not used for phosphorylation, energy is liberated as heat. Hence high heat production.
  - ↑ Rate of Oxidation of all fuels: For want of ATP, more fuels get oxidised, increasing the rate of oxidation of all fuels

Mechanism Of Action Of Uncouplers

- Uncouplers act as ionophores (H^+ carriers/channels)
- Insert into inner mitochondrial membrane
- Allow H^+ to bypass ATP synthase (Complex V)
- H^+ move down their gradient (high → low concentration)
  - No ATP formation
  - Energy released as heat



Examples Of Uncoupler

Physiological Uncouplers

- Thyroxine
  - Increases basal metabolic rate by upregulating the uncouplers in inner mitochondrial membrane
- Brown adipose tissue
  - Brown adipose tissue is brown in color due to abundant mitochondria housing uncoupler proteins.
  - These proteins bypass ATP production, leading to heat generation instead
  - This mechanism, known as non-shivering thermogenesis, aids neonates and hibernating animals in heat production

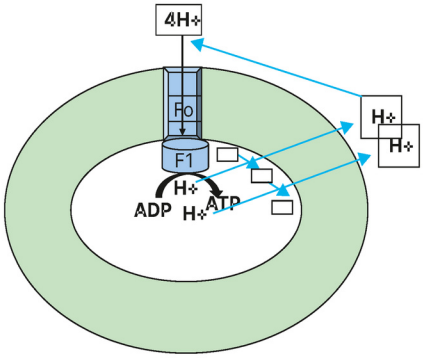
Artificial Uncouplers

- Includes
  - 2,4,DNP

- Valinomycin
- Nalinomycin
- Nigaricin

- These were once tried as anti-obesity drugs.
  - In the presence of these uncouplers, all the fuels will be oxidized, and energy will be liberated as heat,
  - No ATP production and no anabolism.
- Withdraw form market because of Intolerable heat production
- Fuel oxidation is not inhibited

Oligomycin



- Inhibiting Fo component of ATP synthase complex
- Not an uncoupler

Atractyloside

- Inhibits ATP/ADP translocator of inner mitochondrial membrane

PYQS

00:17:31

Q. Which of the following substances inhibits cytochrome complex IV, a component of the electron transport chain responsible for ATP synthesis?

a. Cyanide
b. Carbon dioxide
c. Oligomycin
d. Ouabain

Ans: a.cyanide

Q. A 5 year old girl was washing her doll with shampoo containing rotenone. Her mother noticed her in an unconscious state. Which is inhibited by the above chemical?

a. NADH dehydrogenase
b. Succinate dehydrogenase
c. Cytochrome C
d. Cytochrome oxidase

Ans: a.NADH dehydrogenase

Q. A patient is being treated with phenobarbitone. Which of the following is inhibited?
a. I-Q
b. II-Q
c. III-C
d. IV

Ans: a. 1-Q

PROTEIN CHEMISTRY AND METABOLISM

00:19:10

Amino Acid Must Know Facts

FMGE JUNE 2024, INICET NOV 2025

- General Structure
  - Central carbon (CH) atom.
  - Attached to an amino group and a carboxyl group on either side.
  - Contains a variable side chain (R group).
- Glycine
  - Simplest amino acid
  - R group consists of just a hydrogen (H) atom
  - Two valencies are satisfied by the same hydrogen atom → no asymmetric carbon atom.
  - Does not exhibit stereoisomerism
  - Optically inactive
- Aromatic Amino Acids
  - Include Phenylalanine, Tyrosine, and Tryptophan
  - Absorb UV light at 280 nm.
- Purines and Pyrimidines
  - Absorb UV light at 260 nm.
- Proline (Imino Acid)
  - Contains an NH group instead of an NH_2 group
  - Has one less hydrogen atom
  - Cannot effectively take part in hydrogen bonding.
  - Alpha-Helix stabilized by intra-chain hydrogen bonding.
    → Proline insertion disrupts the alpha-helix → due to one less hydrogen
    → Glycine insertion also disrupts the alpha-helix
- Histidine
  - pKa is 6 → close to the physiological pH of 7.4
  - Acts as an effective physiological buffer

Aminoacid Mnemonics

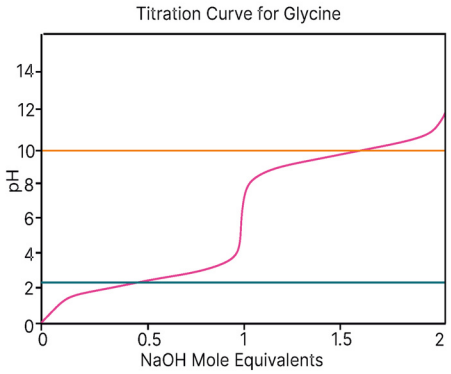
- HIP
  - Histidine has an Imidazole group → answers Pauly's test.
- TIA
  - Tryptophan has an Indole ring → answers Aldehyde test.
- AGS
  - Arginine has a Guanidinium group → answers Sakaguchi test.
- MPS
  - Color reactions yielding a red color.
  - Millon's test, Pauly's test, Sakaguchi test

Titration Curve Products

- pKa of a functional group
  - pH of the medium at which 50% of functional groups are ionized and 50% are unionized
  - Substances act as effective buffers around their pKa → no change in pH despite adding strong acid or base
- Isoelectric pH (pI)
  - pH at which the net charge carried by the particle is zero.
  - Electrophoretic mobility is zero → particles cannot move in an electrical field.
  - Solubility is the least → substances are soluble only when charged
  - Buffering capacity is the least → relies on an equal mix of ionized and unionized forms
  - Calculated as the average of the pKa of the two functional groups

Titration Curve Graph Interpretation

INICET MAY 2025



- X axis =number of equivalents of alkali added
- Y axis =changes in pH
- Initial addition of alkali → minimal change in pH → substance is acting as an effective buffer (corresponds to pKa 1, around pH 2)
- Further addition of alkali → steep rise in pH → buffering activity is lost.
- Continued addition of alkali → pH stabilization → acts as an effective buffer again (corresponds to pKa 2, around pH 10)
- Isoelectric pH (pI) = Average of pKa 1 and pKa 2 → (2 + 10) / 2 = 6

AMINOACID METABOLISM

00:33:09

Aa Breakdown

FMGE JUNE 2021, DEC 2021, DEC 2021, JAN 2023
INI CET NOV 2021, JULY 2021, NOV 2022,
MAY 2022, NOV 2023, MAY 2025, NOV 2022

- During AA breakdown, the amino group is given off first
  - Mechanisms → Transamination or Deamination.
  - Exceptions (neither transaminate nor deaminate directly) → Lysine, Threonine, Proline, Hydroxyproline
- Deamination releases the amino group as ammonia.
- Ammonia is highly toxic to neurons → require detoxification
- Detoxification occurs in the liver via the Urea Cycle → converts ammonia to urea
- Ammonia must be transported from peripheral tissues to the liver in a non-toxic form
- Most common non-toxic transport form → Glutamate
- Exceptions for transport:
  - Neurons form Glutamine instead of Glutamate
  - Muscles form Alanine instead of Glutamate

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Urea Cycle

00:36:22

INICET NOV 2024, NEETPG 2023

- Location
  - Takes place in the liver.
  - Partly in mitochondria, partly in cytoplasm.
  - Two enzymes are mitochondrial → remaining are cytoplasmic
- Mitochondrial Enzymes
  - Carbamoyl Phosphate Synthetase 1 (CPS-1).
  - Ornithine Transcarbamylase.

Step 1: Formation Of Carbamoyl Phosphate

- Catalyzed by CPS-1
- Carbon donor → Carbon dioxide
- Amino group donor → Ammonia
- Phosphate donor → ATP
- Consumes 2 ATP molecules

Step 2: Formation Of Citrulline

- Catalyzed by Ornithine Transcarbamylase
- Ornithine + Carbamoyl Phosphate → Citrulline
- Citrulline exits the mitochondria into the cytoplasm and Ornithine enters the mitochondria via Ornithine-Citrulline transporter
- Urea Structure & Nitrogen Sources
  - Central C=O attached to two NH_2 groups (N1 and N2).
  - N1 donor → Ammonia
  - N2 donor → Aspartate

Step 3: Formation Of Argininosuccinic Acid

- Catalyzed by Argininosuccinate Synthetase.
- Aspartate reacts with Citrulline → Argininosuccinic Acid
- Consumes 1 ATP → converted to AMP + PPi.
  - Equivalent to the utilization of 2 high-energy phosphates
  - Total high-energy phosphates invested so far = 4

Step 4: Formation Of Arginine & Fumarate

- Catalyzed by Argininosuccinate Lyase
- Argininosuccinic Acid → Arginine + Fumarate
- Fumarate Pathway:
  - Fumarate enters the Citric Acid (TCA) Cycle → converted to Malate → converted to Oxaloacetate.
  - Malate Dehydrogenase step yields NADH → equivalent to 2.5 ATPs
  - Net ATP utilized in Urea Cycle = 4 ATPs invested - 2.5 ATPs recovered = 1.5 ATPs
- Oxaloacetate undergoes transamination with Glutamate → regenerates Aspartate
- Direct link between Urea Cycle & Citric Acid Cycle → Fumarate
- Amino acid link between Urea Cycle & Citric Acid Cycle → Aspartate

Step 5: Formation Of Urea

- Catalyzed by Arginase.
- Arginine → Urea + Ornithine.
- Ornithine acts as a catalyst → gets regenerated to continue the cycle.

Difference Between Cps 1 And Cps Ii

Property	Cps i	Cps ii
Pathway	Urea Cycle	Pyradine synthesis
Location	Mitochondria	Cytoplasm
Amino Group Donor	NH3	Glutamine
Regulate	Allosterically stimulated by N-acetylglutamate.	Inhibited via feedback mechanism by its end products (Pyrimidine nucleotides: Cytidine, Uridine, Thymidine)

Urea Cycle Disorders

FMGE 2018, 2024, 2025, NEET PG 2019, 2024

- General Features
  - Any defect in the urea cycle (e.g., CPS-1, OTC, Arginase) leads to Hyperammonemia
  - Presents with a combination of Central Nervous System (CNS) stimulation and depression
- CNS Stimulation Manifestations
  - Seizures.
  - Vomiting
  - Hyperventilation → Respiratory alkalosis
  - Mechanism: Ammonia is converted to Glutamate (an excitatory neurotransmitter) → excess causes seizures and convulsions.
- CNS Depression Manifestations
  - Depression, apathy, comatose state.
  - EEG shows characteristic slowing of waves.
  - Mechanism: Ammonia sequesters hydrogen ions to form ammonium ions → without hydrogen ions, the electron transport chain cannot function → ATP cannot be generated → leads to CNS depression.

Management & Diagnostic Steps For Hyperammonemia

- Step 1: Dietary Management
  - Stop mixed balanced diet immediately → amino acid metabolism aggravates ammonia levels.
  - Start the patient on a glucose-only diet → alleviates features and reinforces the suspicion of hyperammonemia.
- Step 2: Ammonia Estimation
  - Collect a blood sample to estimate plasma ammonia levels in the local laboratory
  - Expected result: High ammonia levels.
- Step 3: Specialized Testing
  - Collect blood and urine samples
  - Send to a specialized Inborn Errors of Metabolism (IEM) screening lab
  - Purpose: Rule out specific urea cycle disorders
  - The lab provides seven key values for interpretation

Urea Cycle Disorders

- Type 1 Hyperammonemia
  - Defect: Carbamoyl Phosphate Synthetase 1 (CPS-1).
  - Biochemical Findings: High Ammonia, High Glutamate
  - Other values (Uracil, Orotic acid, Citrulline, etc.) are normal or low.
- Type 2 Hyperammonemia
  - Defect: Ornithine Transcarbamylase (OTC).
  - Biochemical Findings: High Ammonia, High Glutamate, High Uracil, High Orotic acid
  - Mechanism: Accumulated carbamoyl phosphate leaves mitochondria → enters cytoplasm → acts as an intermediate for pyrimidine synthesis → increases Uracil and Orotic acid
- Citrullinemia
  - Defect: Argininosuccinate Synthetase
  - Biochemical Findings: High Ammonia, High Glutamate, High Uracil, High Orotic acid, High Citrulline
- Argininosuccinic Aciduria
  - Defect: Argininosuccinate Lyase
  - Biochemical Findings: High Ammonia, High Glutamate, High Uracil, High Orotic acid, High Citrulline, High Argininosuccinic acid
  - Clinical presentation: Trichorrhexis nodosa (tufted, knotted, brittle hair)
- Argininemia
  - Defect: Arginase
  - Presentation is distinct from other disorders: presents around 2 months postnatally.
  - Does not typically present with CNS stimulation or depression
  - Presents with neurological deficits like spastic diplegia or spastic quadriplegia
  - Biochemical Findings: All values are high, including Arginine

Important Information

- Urea cycle disorder
  - Key Values Monitored: Ammonia, Glutamate, Uracil, Orotic acid, Citrulline, Argininosuccinic acid, Arginine
  - Interpretation should start from last value
  - If only Ammonia and glutamate are elevated → it can be either Type 1 Hyperammonemia or Decompensated liver disease
- Decompensated Liver Disease vs Type 1 Hyperammonemia
  - Both present with high Ammonia and high Glutamate.
  - Differentiated by liver function tests.
  - Decompensated liver disease: Elevated bilirubin, transaminases, alkaline phosphatase, GGT, prolonged prothrombin time, low albumin.
  - Type 1 Hyperammonemia: Normal liver function tests (apart from ammonia/glutamate)

- Triple H Syndrome
  - Defect: Ornithine-Citrulline Transporter.
  - Stands for: Hyperammonemia, Hyperornithinemia, Homocitrullinemia.
  - Mechanism:
    → Transporter defect prevents ornithine from entering mitochondria (Hyperornithinemia) and stops the urea cycle (Hyperammonemia)
    → Carbamoyl phosphate reacts with lysine instead of ornithine to form Homocitrulline (Homocitrullinemia)

SPECIALISED PRODUCTS FROM AMINO ACIDS

01:06:55

Amino acids	Specialised products
• Phenyalanine	• Tyrosine
• Tyrosine	• Dopamine, NE, epinephrine, thyroid hormone and melanin
• Tryptophan	• Niacin, serotonin, melatonin
• Arginine	• NO
• Glycine	• Glutathione, collagen, heme synthesis, creatine synthesis • Purine ring formation • Tetrahydrofolate derivatives

Glycine Clinical Significance

- Glycine Cleavage System
  - Cleaves Glycine into: Carbon dioxide, Ammonia, and a CH2 (methylene) group
  - The CH2 group is accepted by tetrahydrofolate to form N5 N10-methylene tetrahydrofolate
  - Reversible reaction: Glycine can be formed from these components

Ammonia Scavenging Agents

- Sodium Benzoate
  - If a child presents with seizures due to hyperammonemia, IV Sodium Benzoate can be administered.
  - Sodium Benzoate is conjugated in the liver with Glycine to form Hippuric Acid → excreted in urine
  - This process uses up Glycine → body shifts equilibrium to synthesize more Glycine using available Ammonia
  - One mole of Sodium Benzoate uses one mole of Glycine → scavenges one mole of Ammonia
- Phenylacetate:
  - Conjugates with Glutamine
  - Forms Phenylacetylglutamine → excreted in urine
  - Body synthesizes more Glutamine using Alpha-ketoglutarate and two moles of Ammonia
  - One mole of Phenylacetate scavenges two moles of Ammonia (more effective).
  - Note: Scavenging agents are only used when the liver is functioning normally (not in decompensated liver disease)

AROMATIC AMINOACID METABOLISM

01:17:00

Phenyalanine Metabolism

- Major Fate
  - Phenylalanine is converted to Tyrosine.
  - Enzyme: Phenylalanine Hydroxylase.
  - Mechanism:
    → One oxygen atom from an oxygen molecule is incorporated into Phenylalanine, forming Tyrosine
    → The other oxygen atom becomes water
  - Coenzyme required: Tetrahydrobiopterin (converts to Dihydrobiopterin during the reaction).
  - Regeneration step: Dihydrobiopterin is converted back to Tetrahydrobiopterin by Dihydrobiopterin Reductase.
- Minor Fate

- Phenylalanine undergoes transamination to form Phenylpyruvate (a phenyl ketone).
  → Enzyme: Transaminase
- Phenylpyruvate on reduction form Phenyllactate
- Phenylpyruvate on oxidative decarboxylation form Phenylacetate (which can then conjugate with glutamine to form Phenylacetylglutamine, excreted in urine)

Specialized Products From Tyrosine

NEET PG 2018, FMGE 2018, 2023
FMGE JUNE 2024, INICET NOV 2024

- Neurotransmitters
  - Tyrosine → Dopa (via Tyrosine Hydroxylase)
  - Dopa → Dopamine (via Dopa Decarboxylase, requires Vitamin B6 / Pyridoxal Phosphate)
  - Dopamine → Norepinephrine (via Dopamine Beta-Hydroxylase, requires Vitamin C).
  - Norepinephrine on methylation → Epinephrine
- Thyroid Hormones
  - Occurs in the thyroid gland follicles
  - Follicular cells release Thyroglobulin (a glycoprotein containing ~123 Tyrosine residues) into the colloid
  - Tyrosine residues undergo iodination → Monoiodotyrosine (MIT) and Diiodotyrosine (DIT)
  - Coupling reactions:
    → MIT + DIT = T3 (Triiodothyronine)
    → DIT + DIT = T4 (Thyroxine - maximum concentration)
    → DIT + MIT = Reverse T3 (least concentration)
- Melanin
  - Tyrosine → Dopa (via Tyrosinase).
    → Tyrosinase is a copper-dependent enzyme
  - Dopa undergoes a series of non-enzyme-catalyzed reactions to form Melanin
  - Copper deficiency or Tyrosinase defect leads to depigmented hair

Phenylketonuria

01:26:13

- Occurs when Phenylalanine cannot be converted to Tyrosine, leading to accumulation of phenyl ketones (Phenylpyruvate)

NEET PG 2021, AUGUST 2024, 2025

Causes

- Classical PKU: Defect in Phenylalanine Hydroxylase
- Toxic PKU: Defect in Dihydrobiopterin Reductase
  - Leads to deficient Tetrahydrobiopterin.
  - Inactivates Phenylalanine Hydroxylase, Tyrosine Hydroxylase, and Tryptophan Hydroxylase
  - Results in no synthesis of dopamine, norepinephrine, epinephrine, serotonin, or melatonin
  - Presents with aggressive behavior and seizures

Clinical Features

- Mental Retardation
  - D/t lack of neurotransmitters, thyroid hormones,
  - Accumulation of phenyl ketones which cross the blood-brain barrier
- Mousy Odor: D/t accumulation of Phenylacetate
- Hypopigmentation (no Tyrosine → no Melanin)

Screening Tests

- Ferric Chloride Test:
  - Done on urine
  - Ferric chloride added to urine forms a blue/green adsorption complex with phenyl ketones
  - Disadvantage: Not specific, as other ketones can give a positive result
- Guthrie's Test:
  - Done on blood
  - Based on the growth of Bacillus subtilis on a colony plate when patient blood (containing high Phenylalanine) is added
  - Obsolete/crude test
- Ideal Screening Test: HPLC with Tandem Mass Spectrometry (for any inborn error of metabolism)

NEET PG AUGUST 2024

01:34:28

Tyrosine Metabolism

Normal pathway	• Tyrosine → p-Hydroxyphenylpyruvate (via Tyrosine Transaminase). • p-Hydroxyphenylpyruvate → Homogentisic Acid (via p-Hydroxyphenylpyruvate Dioxygenase) • Homogentisic Acid → Maleylacetoacetate (via Homogentisate Oxidase) • Maleylacetoacetate → Fumarylacetoacetate (via cis-trans Isomerase) • Fumarylacetoacetate → Fumarate + Acetoacetate (via Fumarylacetoacetate Hydrolase)

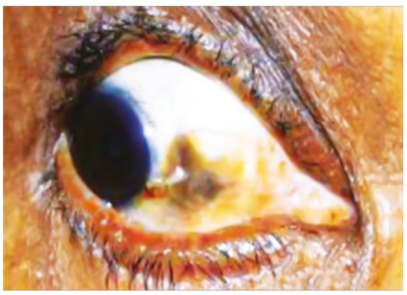
Type 1 tyrosinemia (hepatorenal syndrome)	• Defect: Fumarylacetoacetate Hydrolase
	• Mechanism: Fumarylacetoacetate accumulates and converts to Succinylacetone
	• Succinylacetone is toxic to live and Kidney → hepatorenal syndrome
	  ○ Toxic to liver → Jaundice, hepatomegaly, hypoglycemia (fasting state), cirrhosis, hepatocellular carcinoma
	  ○ Toxic to kidney → Fanconi syndrome, chronic kidney disease
	• Succinyl acetone Inhibits ALA Dehydratase → Accumulation of ALA (toxic to neurons) → Neuropsychiatric behavior mimicking Porphyria

Type 2 tyrosinemia (richner-hanhart syndrome)	• Defect: Tyrosine Transaminase • Features: Oculocutaneous syndrome → Presents with painful corneal erosions and palmar hyperkeratosis.
Type 3 tyrosinemia	• Defect: Loss of function mutation in p-Hydroxyphenylpyruvate Dioxygenase. • Presents with Intermittent seizures and ataxia.
Hawkinsinuria	• Defect: Gain of function mutation in p-Hydroxyphenylpyruvate Dioxygenase • Features: "Swimming pool" odor of urine.
Alkaptonuria	• Inborn error of tyrosine metabolism • Defect: Homogentisate Oxidase. • Mechanism: Homogentisic acid accumulates → oxidizes to Benzoquinone acetate → polymerizes into melanin-like fibrils. • Features:

Alkaptonuria

FMGE JAN 2025, NEET PG 2023

- Ochronosis: Pigment accumulates in cartilage → cartilage destruction. Patients present in mid-age with intervertebral disc prolapse/bulges and joint pain (elbow, knee, ankle)
- Pigmentation of the tip of the nose, thenar/hypothenar eminences.
- Osler's Sign:



→ Brownish/blackish pigmentation of the sclera (first sign of Alkaptonuria).

- Black Urine Disease: Urine turns dark on standing due to oxidation of homogentisic acid.

Management:

- High doses of Vitamin C (antioxidant) or Nitisinone
- Nitisinone
  - Mechanism of Action: Inhibits p-Hydroxyphenylpyruvate Dioxygenase
  - Indications:
    → Type 1 Tyrosinemia (Major indication)
    → Alkaptonuria
    → Hawkinsinuria

PYQS

01:47:30

Q. Which of the following amino acids primarily acts as a buffer in blood due to its ability to accept and donate protons at physiological pH?

a. Histidine
b. Arginine
c. Tryptophan
d. Tyrosine

Ans: **a. HISTIDINE**

Q. Defect of Tyrosine Transaminase causes?

FMGE JAN 2024

a. Type I Tyrosinemia
b. Type II Tyrosinemia
c. Alkaptonuria
d. Type III Tyrosinemia

Ans: **b. Type II tyrosinemia**

Q. Which of the following is deficient in a patient with phenylketonuria with normal phenyl alanine hydroxylase levels?

NEET PG 2024

a. Tyrosine transaminase
b. Dopa decarboxylase
c. Tyrosine hydroxylase
d. Dihydrobiopterine reductase

Ans: d. Dihydrobiopterine reductase

Q. A patient presents with arthritis, and arthroscopy reveals blackening of the joints. Which enzyme deficiency is most likely responsible for this condition?

FMGE JAN 2025

a. Homogentisate oxidase
b. Branched-chain alpha-ketoacid dehydrogenase
C. Tyrosinase
d. Fumarase

Ans: a. Homogentisate oxidase

Q. A 2-month-old infant presents with poor feeding, vomiting, and lethargy. Laboratory studies show hyperammonemia and elevated levels of orotic acid in the urine. Which of the following is the most likely enzyme deficiency?

FMGE JULY 2025

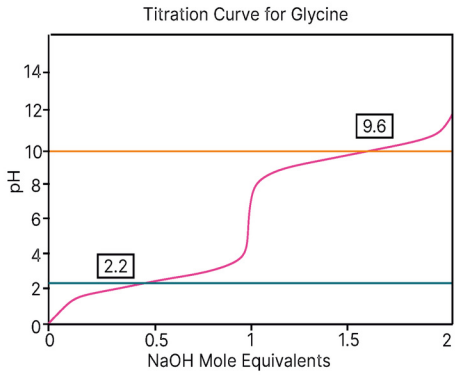
a. Carbamoyl phosphate synthetase I deficiency
b. Ornithine transcarbamylase (OTC) deficiency
c. Orotidine 5'-phosphate decarboxylase deficiency
d. Argininosuccinate lyase deficiency

Ans: b. Ornithine transcarbamylase (OTC) deficiency

INICET MAY 2025

Q. In the given glycine titration curve, calculate or identify the pH at which molecules exist in a zwitter ion form?

a. 4.4
b. 6
c. 9
d. 2.2



Ans: b. 6

Q. Melanin is synthesized from which of the following amino acid?

FMGE JAN 2023

a. Tyrosine
b. Tryptophan
c. Leucine
d. Phenylalanine

Ans: a. Tyrosine

Yourwish

Q. Nitric oxide is formed from which amino acid? FMGE JAN 2023

a. Arginine
b. Tryptophan
c. Leucine
d. Lysine

Ans: a. Arginine

Q. Which of the following is a precursor of niacin? FMGE JAN 2024

a. Riboflavin
b. Tryptophan
c. Thiamine
d. Pyridoxine

Ans: b. Tryptophan

Q. Heme is derived from which of the following aminoacids? FMGE JAN 2024

a. Glutamine
b. Glycine
c. Glutamate
d. Valine

Ans: b. Glycine

Q. Ammonia is transported from brain to liver in the form of which of the following aminoacids? FMGE JAN 2024

a. Glutamate
b. Alanine
c. Glycine
d. Glutamine

Ans: d. Glutamine

Q. Match the following amino acids with their derivatives:

A. tyrosine	i. Melatonin
B. tryptophan	ii. Taurine
C. glycine	iii. Thyroid hormones
D. cysteine	IV. Creatinine

a. A-i, B-ii, C-iii, D-iv
b. A-iii, B-i, C-iv, D-ii
c. A-iv, B-ii, C-i, D-iii
d. A-ii, B-i, C-iv, D-iii

Ans: b. A-iii, B-i, C-iv, D-ii

Q. Which amino acid donates nitrogen to sodium benzoate when given for urea cycle disorders?

a. Glutamine.

b. Glutamate

c. Glycine

d. Arginine

Ans: c. Glycine

ERROR FILES

01:53:46

- Amobarbital inhibits complex I→ Q, whereas Antimycin from Complex III → C
- Valinomycin is an uncoupler, Oligamycin inhibits ATP synthase complex
- Histidine has Imidazole group, Tryptophan has an Indole ring
- Aromatic amino acids absorb UV at 280nm, nitrogenous bases at 260nm
- Glutamine in neurons and Alanine in muscle
- CPSI is involved in Urea cycle, CPSII is pyrimidine synthesis
- Type I Tyrosinemia is hepatorenal syndrome, Type il is oculocutaneous syndrome

6. VITAMINS

ONE-LINERS

- Sulfur-containing vitamins: Thiamine and biotin
- The earliest manifestation of Vitamin A deficiency: Night blindness
- Active form of vitamin D: 1,25-dihydroxyvitamin D
- Rate-limiting enzyme of vitamin D synthesis: 1 alpha-hydroxylase, stimulated by PTH
- Vitamin E is a chain-breaking antioxidant of the lipid phase type
- Vitamin C is an aqueous-phase chain-breaking antioxidant
- Vitamin K is necessary for gamma-carboxylase as a coenzyme
- Vitamin K-dependent proteins are clotting factors 2, 7, 9, 10, protein C & S, and Osteocalcin
- Vitamin C is necessary as a coenzyme for the post-translational modification of collagen synthesis
- Copper is an essential nutrient for collagen maturation, as it helps with lysyl oxidase
- Neurological manifestations are caused by vitamin B1, B3, B6, and B12 deficiencies, as well as vitamin B6 toxicity.
- Biotin is necessary for carboxylases
- Biotin is bound by avidin
- Vitamin B6 is necessary for transaminases, decarboxylases, cystathionine beta-synthase, and kynureninase
- The 2 coenzyme forms of vitamin B12 are adenosyl B12 and methyl B12
- Coenzyme A is made up of adenosine 3'5' diphosphate, beta-mercaptoethylamine, and pantothenic acid
- Burning food syndrome is caused by a deficiency of pantothenic acid

THIAMINE

00:08:48

NEET PG 2023

Thiamine Dependent Enzymes

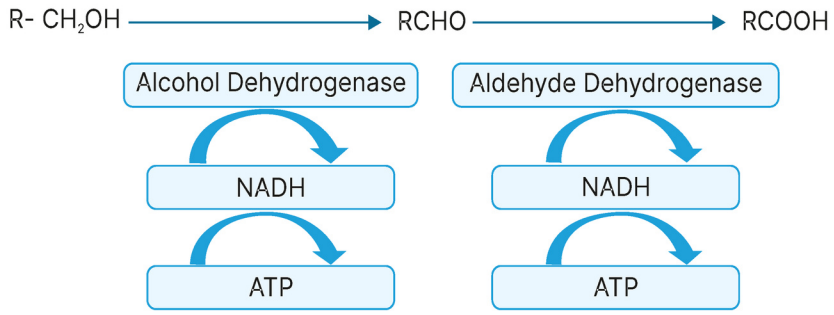
- PDH (pyruvate dehydrogenase complex) converts pyruvate to acetyl-CoA
- Alpha-ketoglutarate dehydrogenase
- Branched-chain keto acid dehydrogenase
- Transketolase

Thiamine Deficiency

- Inactive PDH: Pyruvate is converted to lactate rather than acetyl-CoA, causing lactic acidosis, leading to Wet beriberi
  - Lactic acid is an arterial dilator and a venoconstrictor, causing hypotension and tachycardia
  - High-output cardiac failure
  - Peripheral edema (increased hydrostatic pressure in capillaries, causing oozing of plasma into the interstitium)
  - Thiamine is present in the aleurone layer of whole grain, but it is deficient in polished rice
- BCKADH deficiency causes maple syrup urine disease; thus, they are started on thiamine supplementation
- RBC transketolase activity to be assessed in suspected thiamine deficiency

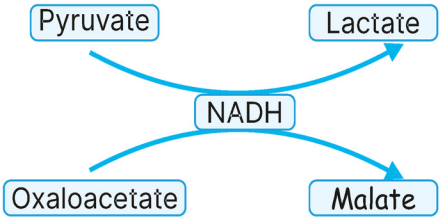
ALCOHOL METABOLISM

00:13:29



Effect of High Nadh

- Pyruvate gets converted to lactate, causing lactic acidosis: Low pyruvate
- Oxaloacetate gets converted to malate: Low oxaloacetate
- Low pyruvate and low oxaloacetate impair gluconeogenesis, causing hypoglycemia



Effects of High Energy

- A chronic alcoholic is prone to deficiency of essential nutrients d/t skipping meals
- A very common micronutrient deficiency in alcoholics is thiamine deficiency because,
  - Empty calorie
  - Alcohol interferes with thiamine absorption
  - Alcohol interferes with magnesium absorption:
    → The active form of thiamine is thiamine pyrophosphate, and its synthesis requires thiamine kinase, which requires magnesium

Thiamine Deficiency And Nerves

- Neurons are most affected
- Normally, glucose is utilized aerobically
- In alcoholics, the PDH complex is inactive, and aerobic utilization of glucose does not occur, affecting the neuronal metabolism

Thiamine Deficiency Forms:

- Acute: Wernicke's encephalopathy
  - Caused by treating hypoglycemia with dextrose in chronic alcoholics without thiamine supplementation
  - Features: GOA
    → **G**lobal confusion
    → **O**phthalmoplegia
    → **A**taxia
  - It is reversible
  - T/t: Thiamine + Dextrose
- Chronic: Korsakoff syndrome
  - Presents with retrograde and anterograde amnesia, confabulation (honest lying), and sensory agnosia
  - It is irreversible
  - On imaging: Mamillary and cerebellar body atrophy

Yourwish

PELLAGRA

00:27:10

FMGE 2021

- 3 D's of Pellagra
  - Diarrhea
  - Dermatitis: Hyperpigmented lesions in sun-exposed areas known as Casal's necklace
  - Dementia
- Caused by Vitamin B3 (niacin) deficiency

Synthesis

- Tryptophan is converted to niacin, serotonin, and melatonin
- Kynureninase, an enzyme dependent on vitamin B6, converts tryptophan to quinolinate, and with QPRTase (inhibited by leucine), it is converted to niacin

Causes

- Dietary deficiency of niacin
- Dietary deficiency of tryptophan: Maize-based diet
- Tryptophan malabsorption syndrome: Hartnup's disease
- Carcinoid syndrome: Increased production of serotonin and melatonin from tryptophan
- Vitamin B6 deficiency: Kynureninase is inactive; thus, kynurenine is converted to xanthurenic acid (test for this in urine after tryptophan load)
- Leucine pellagra: Sorghum-based diet

NEET PG 2024
INICET 2023

VITAMIN B6

00:34:45

- Transaminase
  - OAT converts ornithine to γ-glutamate semialdehyde, which enters the TCA cycle and comes out as Co_2
  - The source of ornithine is arginase
  - Thus, OAT deficiency leads to increased ornithine, which is toxic to the retinal pigment epithelium, resulting in gyrate atrophy of the retina
  - Treatment:
    → Ornithine-restricted diet
    → Arginine-restricted diet
    → Vitamin B6 supplementation

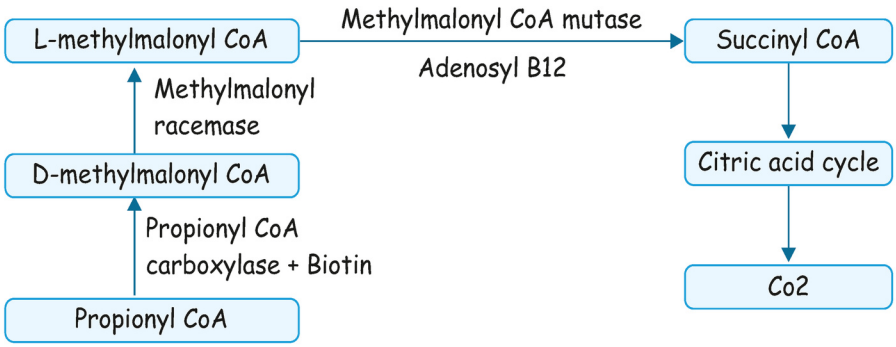
- Decarboxylase
  - Glutamate decarboxylase (GAD) converts glutamate to GABA
  - In deficiency, glutamate accumulates, and GABA is not synthesized, leading to increased excitatory and decreased inhibitory NT, resulting in seizures
  - ALA synthase: The first step of heme synthesis, thus anemia gets corrected when supplemented with vitamin B6.
- Kynureninase: Pellagra
- Cytathionine beta synthase
  - Used in homocysteine metabolism
  - The majority converted into cysteine, and the minority converted into methionine
  - Homocysteine + serine with cystathionine beta-synthase forms cystathionine, and with cystathioninase, it forms cysteine

- Homocysteine gets converted into methionine in the presence of methionine synthase, dependent on methyl B12 from methyl THFA
- Type 1 homocystinuria: A defect in the major pathway
  → Cystathionine beta-synthase deficiency
  → Low cysteine and high methionine
  → Causes accelerated atherosclerosis, thrombosis, and skeletal deformities: Flat foot, charlie chaplin foot, ectopia lentis
  → Treatment: Vitamin B6 supplementation
- Type 2 homocystinuria: A defect in the minor pathway
  → Methionine synthase defect
  → Low methionine and high cysteine
  → Treatment: Vitamin B12 and folate administration

VITAMIN B12

00:48:12

- 2 coenzyme forms,
  - Adenosyl B12,
    → Coenzyme for methylmalonyl-CoA mutase



    → In adenosyl B12 deficiency, methylmalonyl-CoA mutase is inactive, causing increased alpha-methylmalonyl-CoA
    → Methylmalonic aciduria: This is to be tested after an overnight fast
    → Neurological manifestations: This aciduria interferes with fatty acid synthesis, which interferes with myelin synthesis

Important Information

Vitamin deficiencies causing neurological manifestations are,

- Thiamine deficiency (Dry beriberi)
- Niacin deficiency
- Vitamin B6 deficiency and also hypervitaminosis of B6
- Vitamin B12 deficiency: starts as peripheral sensory neuropathy, then involves the spinothalamic tract and posterior column (subacute combined degeneration)

  - Methyl B12
    → Coenzyme for methionine synthase
    → Converts homocysteine to methionine
    → Methyl folate trap:
- In B12 deficiency, all THFA is trapped as methyl-THFA because the methyl group cannot be donated
- Low THFA

Folate Deficiency

- Causes macrocytic anemia
- Due to decreased THFA causing
  - Low N5, N10 methylene THFA: Helps in thymidine formation from uridine, therefore low thymidine
  - Low N10 formyl THFA: C2 of the purine ring cannot be synthesized
  - Thus, without replication, cell division cannot happen, which causes macrocytic anemia

Manifestations Of B12 Deficiency:

00:58:18

- Methylmalonic aciduria
- Neurological manifestations
- Homocystinuria
- Methyl folate trap (THFA deficiency)
- Macrocytic anemia

Foalte And B12 Deficiency

FEATURES	FOALTE	VITAMIN B12
Dietary history	Non-vegetarian	Vegan
Neurological manifestations	Absent	Present
Biochemical investigations	Increased FIGLU in urine after histidine load	Methymalonic aciduria after overnight fasting

VITAMIN A

01:02:20

NEET PG 2022, 2024
FMGE 2023, 2024

Vitamin A Forms

- Retinol: The form in which it is absorbed, transported, and stored in the liver
- Retinal: Seen in the eye as rhodopsin
- Retinoic acid:
  - All trans retinoic acid (ATRA): Helps in the growth and differentiation of cells
  - 13-cis retinoic acid: Suppresses keratinization of epithelium

Vitamin A Deficiency

- Xerophthalmia: Conjunctival xerosis
- Bitot's spot: Keratin debris accumulation (triangular foamy lesions)
- Corneal xerosis
- Keratomalacia
- Corneal ulcer
- Corneal scar
- Phrynoderma: Follicular hyperkeratosis along the extensor surfaces of the elbow

VITAMIN D

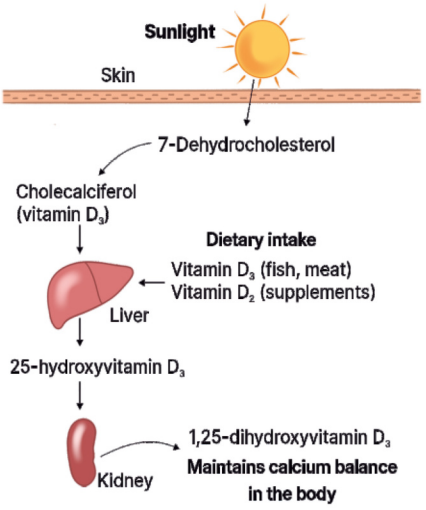
01:06:03

NEET PG 2024
FMGE 2021

Actions of Vitamin D

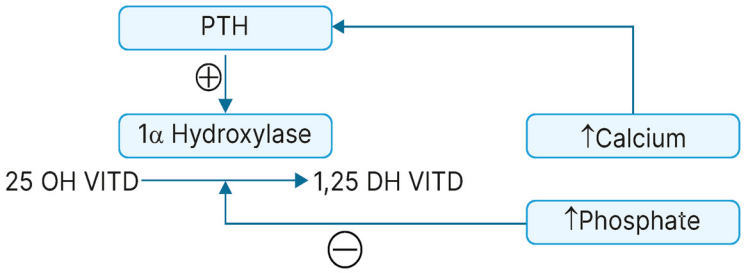
- Intestine: Upregulation of calbindins, thus increasing the absorption
- Bone: Stimulates osteoblasts directly and stimulates osteoclasts indirectly
- Kidney: Increases calcium and phosphate reabsorption

Bioactivation of Vitamin D



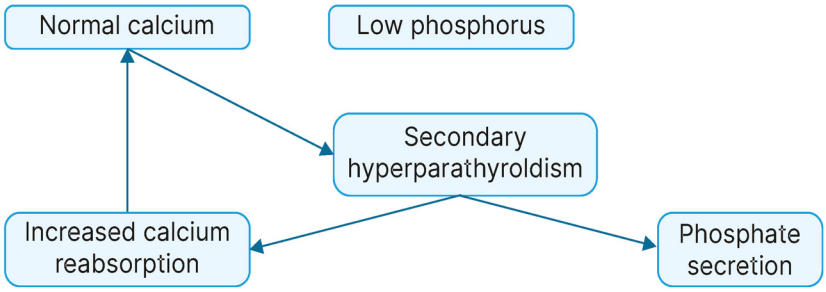
- In the skin, whenever UV light converts 7-DHC to cholecalciferol
- Cholecalciferol reaches the liver, where 25-alpha hydroxylase converts it into 25-hydroxy cholecalciferol
- 25-hydroxycholecalciferol reaches the kidney, where 1-alpha-hydroxylase (rate-limiting enzyme) converts it into 1,25-dihydroxycholecalciferol
- 1,25-dihydroxycholecalciferol is the active form of vitamin D
- 1-alpha-hydroxylase is a rate-limiting enzyme activated by PTH

Regulation of Vitamin D Synthesis



- 1-alpha-hydroxylase is a rate-limiting enzyme activated by PTH.
- 1,25-dihydroxycholecalciferol increases both blood calcium and phosphate levels
- Hyperphosphatemia directly inhibits 1-alpha-hydroxylase
- Hypercalcemia suppresses PTH secretion, thus indirectly inhibiting 1-alpha-hydroxylase

Vitamin D Deficiency



- Normal level: 30-80 ng/mL
  - The parameter estimated is the Total 25 OH vitamin D, as its half-life is longer
  - Total = 25 OH D2 + D3
  - D2: Ergocalciferol, manufactured and used for supplementation and fortification
  - D3: Cholecalciferol is endogenously synthesized by our bodies
- Hypocalcemia and hypophosphatemia
- Low calcium stimulates PTH secretion, causing secondary hyperparathyroidism
  - PTH increases calcium absorption and potassium secretion
  - Severe hypophosphatemia
- Normal/near-normal calcium
- Very low phosphate
- High PTH: Remodelling hormone of the bone, stimulates osteoblasts and osteoclasts, elevating ALP

Significance of 1,25 Dh Vitamin D

- Chronic kidney disease: Decreased 1-alpha hydroxylase, thus decreasing 1,25-DH vitamin D as well
- Hypoparathyroidism: 1,25-DH vitamin D cannot be synthesized, thus causing hypocalcemia
- Sarcoidosis: Elevation of 1,25-DH vitamin D causing hypercalcemia
- To differentiate
  - Vitamin D-dependent Rickets type 1: A defect in 1-alpha hydroxylase, thus decreasing 1,25-DH vitamin D as well
  - Vitamin D-dependent Rickets type 2: End-organ resistance (receptor failure), causing increased 1,25-DH vitamin D

Hypophosphatemic Rickets

- Mutation of the PHEX gene
- Function of the PHEX protein
  - Degrades FGF-23: Phosphaturic effects
  - Degrades Osteopontin: Inhibits bone mineralisation
- High FGF-23 causes an increased phosphaturic effect, thus causing hypophosphatemia
- High osteopontin causes hypomineralized bones, causing rickets
- Dx: Normal calcium and PTH

VITAMIN DEFICIENCY DIAGNOSIS

01:24:52

VITAMIN	INVESTIGATION	PREREQUISITE
Thiamine	RBC transketolase	-
Riboflavin (B_2)	RBC glutathione reductase	-
B6	Xanthurinic acid	After a tryptophan load
Folate	FIGLU	After the histidine load
B12	Methylmalonic acid	Overnight fasting

MCQs & PYQs

01:27:08

Q. A patient presents with gum bleeding, petechiae, poor wound healing, and other related symptoms. Which of the following vitamin deficiencies is most likely responsible for this presentation?

FMGE JAN 2025

a. Vitamin A
b. Vitamin B6
c. Vitamin B3
d. Vitamin C

Ans: d. Vitamin C

FMGE JAN 2025

Q. Which of the following enzymes is dependent on vitamin C for its activity?

a. Lysyl dehydrogenase
b. Lysyl oxidase
c. Prolyl hydroxylase
d. Hydroxyprolyl kinase

Ans. c. Prolyl hydroxylase

Important Information

Cu^{2+} is necessary for:

- Lysyl oxidase
- SOD (deficiency causes neutropenia)
- Tyrosinase (deficiency causes decreased melanin formation, causing depigmented hair)
- Ceruloplasmin (iron transport) (deficiency causing anemia)

Q. A patient presents with symptoms of dermatitis, dementia, and cognitive decline. Which micronutrient deficiency is most likely responsible?

NEET PG 2024

a. Niacin
b. Thiamine
c. Tryptophan
d. Retinol

Ans. a. Niacin

Q. A farmer is on a maize-based diet and develops skin rashes on the face, neck, and hands. Which of the following should be given?

NEET PG 2024

a. Niacin
b. Thiamine
c. Retinol
d. Vitamin B12

Ans. a. Niacin

Q. Which micronutrient deficiency causes anemia, bleeding gums, and a white line of Frenkel on an X-ray?

a. Copper
b. Iron
c. Zinc
d. Vitamin C

NEET PG 2024

Ans. d. Vitamin C

Q. Which of the following are methanol poisoning derivatives?

NEET PG 2024

a. Formic acid + oxalic acid
b. Formic acid + lactic acid
c. Glycolic acid + oxalic acid
d. Oxalic acid + lactic acid

Ans. b. Formic acid + lactic acid

NEET PG 2024

Q. What is the source of vitamin B1 (thiamine)?

a. A
b. B
c. C
d. D

Ans. b. A

Q. A patient with a history of binge alcohol intake presented to the emergency department with convulsions, altered sensorium, and a plasma glucose level of 45 mg/dL. Which of the following treatments is needed?

NEET PG 2024

a. Thiamine
b. 25% dextrose
c. Thiamine followed by dextrose
d. Fomepizole

Ans. c. Thiamine followed by dextrose

Q. A 45-year-old patient presented with joint pain and weakness. Patient is k/c/o homocystinuria. Which vitamin is required in the treatment?

NEET PG 2024

a. Vitamin B6
b. Vitamin B12
c. Vitamin B1
d. Vitamin B7

Ans. a. Vitamin B6

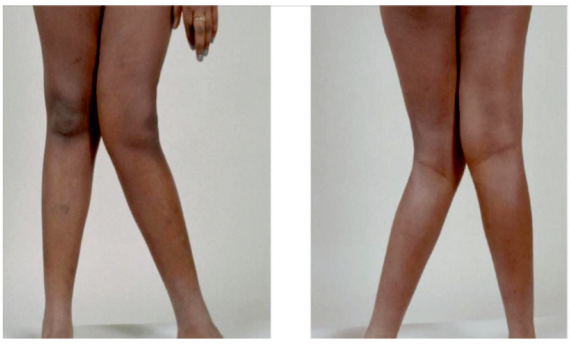
Q. Patient with anemia, neutropenia, and hypopigmentation of skin and hair. What is micronutrient deficiency?

NEET PG 2024

a. Zinc
b. Fe
c. Cu
d. Se

Ans. c. Cu

Q. A child presented with the following deformity: biochemical investigations are given below. Serum calcium is normal, PTH is normal, phosphate is low, and ALP is raised. What is the probable defect?



a. Hypophosphatemic rickets
b. VDDR type 1
c. VDDR type 2
d. Vitamin D deficiency

Ans. a. Hypophosphatemic rickets

Q. Deficiency causing a tingling sensation?

FMGE JUN 2022

a. Folic acid
b. Thiamine
c. Niacin
d. Riboflavin

Ans. b. Thiamine

Q. A person has a history of alcoholism for 20 years. He avoids alcohol for 2 days and presents with agitation, global confusion, disorientation, hallucinations, fever, high BP, diaphoresis, and autonomic hyperactivity. The most common cause is

FMGE DEC 2021

a. Delirium tremens
b. Wernicke's encephalopathy
c. Korsakoff syndrome
d. Pancreatitis

Ans. a. Delirium tremens

Q. A person presents with diarrhea, dementia, and dermatitis. What is the probable cause?
FMGE JUN 2021
a. Pellagra
b. Cystinuria
c. Alkaptonuria
d. Porphyria

Ans. a. Pellagra

Q. A patient presented to the OPD with complaints of diarrhea. The patient was later diagnosed with dementia and photosensitive dermatitis in sun-exposed areas. Which vitamin deficiency is responsible for this condition?
a. Vitamin B6
b. Niacin
FMGE JAN 2023
c. Ascorbic acid
d. Biotin

Ans. b. Niacin

Q. A known patient of TB, on INH for 6 months, presents with a tingling sensation and paresthesia. Deficiency of which of the following vitamins is the most probable cause?
NEET PG 2022
a. Vitamin B6
b. Vitamin B3
c. Vitamin B12
d. Vitamin B7

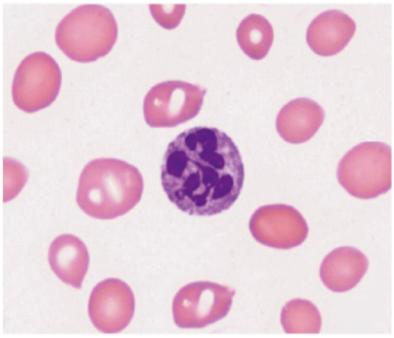
Ans. a. Vitamin B6

Q. A woman with complaints of pain, tingling sensation, and numbness of the foot has a history of taking vitamin supplements. Which of the following is responsible for this patient's condition?
a. Hypervitaminosis B6
FMGE JAN 2023
b. Beriberi
c. Increased vitamin B12
d. Vitamin A toxicity
Ans. a. Hypervitaminosis B6

Q. The micronutrient that is deficient following a post-ileal resection is?
FMGE JUN 2021
a. B12
b. Folate
c. Iron
d. Copper
Ans. a. B12

FMGE JUN 2021

Q. A vegetarian patient presents with anemia and hypersegmented neutrophils. What is the most probable cause?
a. Megaloblastic anemia
b. Iron deficiency anemia
c. Anemia of chronic disease
d. Sideroblastic anemia
Ans. a. Megaloblastic anemia



Q. Which of the following vitamin deficiencies causes the accumulation of methyl THFA and functional folate deficiency?

INICET NOV 2021

a. Folate
b. B12
c. Thiamine
d. Riboflavin

Ans. b. B12

Q. Which of the following enzyme activities can be established in RBCs to diagnose vitamin B12 deficiency?

a. Transketolase
b. Glutathione reductase

NEET PG 2022

c. Kynureninase
d. Pyruvate dehydrogenase

Ans. b. Glutathione reductase

Q. Which of the following activities are low in riboflavin deficiency?

FMGE JUN 2021

a. Transketolase
b. Glycogen phosphorylase
c. Propionyl CoA carboxylase
d. Glutathione reductase

Ans. d. Glutathione reductase

FMGE JUN 2021

Q. Which of the following plays a role in collagen maturation?

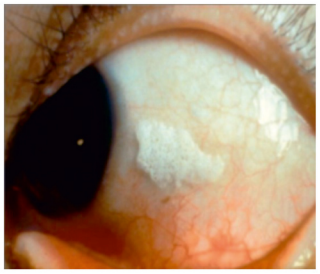
a. Copper and zinc
b. Copper and ascorbic acid
c. Proline
d. Phenylalanine

Ans. b. Copper and ascorbic acid

Q. Which of the following vitamin deficiencies causes the condition shown in the image?

NEET 2022

a. Vitamin A
b. Vitamin D
c. Vitamin E
d. Vitamin K



Ans. a. Vitamin A

Q. A woman on antidepressants presents with bleeding. She gives a history of bulky stools that stick to the pan. Which of the following vitamin deficiencies can cause bleeding in this condition?

NEET 2022

a. Vitamin A
b. Vitamin D
c. Vitamin E
d. Vitamin K

Ans. d. Vitamin K

Q. A family consumes only polished rice. Which of the following combinations of vitamin deficiency and enzymatic defect will be present in this family?

NEET PG 2023

a. Riboflavin-glutathione reductase
b. Thiamine-transketolase
c. Thiamine-transaminase
d. Riboflavin-transketolase

Ans. b. Thiamine-transketolase

Q. A child was brought with pedal edema and cheilosis. Cardiomegaly was present. What is the vitamin deficiency associated with the clinical presentation?

NEET PG 2023

a. Riboflavin
b. Thiamine
c. Pyridoxine
d. Niacin

Ans. b. Thiamine

Q. What could be the potential diagnosis for a 34-year-old male who has been consuming maize as his main diet for an extended period and is now experiencing symptoms such as abdominal pain, decreased appetite, and diarrhea? Additionally, upon examination, glossitis (inflammation of the tongue) and a pigmented rash in sun-exposed areas were observed, along with the lesion on his neck.

FMGE Dec 2021

a. Pellagra
b. Scurvy
c. Megaloblastic anemia
d. Beriberi

Ans. a. Pellagra

Q. Xanthurenic aciduria may be treated with high doses of which vitamin?

INICET Nov 2023

a. Vitamin B6
b. Vitamin B12
c. Vitamin B5
d. Vitamin B7

Ans. a. Vitamin B6

Q. An elderly patient who follows a vegetarian diet and exhibits symptoms of easy tiredness and paleness was examined. A peripheral blood smear revealed signs of macrocytic anemia. What could be the likely reason for anemia in this individual? Additional laboratory tests are as follows: Hb 9, MCV 110, serum homocysteine elevated, serum methylmalonic acid elevated

INICET May 2022

a. Vitamin B6 deficiency
b. Alcohol-induced macrocytosis
c. Vitamin B12 deficiency
d. Thiamine deficiency

Ans. c. Vitamin B12 deficiency

Q. A chronic alcoholic patient presents with agitation, confusion, and gait abnormalities. What vitamin deficiency is most likely responsible for these symptoms?

FMGE Jan 2024

a. Thiamine deficiency
b. Folate (Vitamin B9) deficiency
c. Methylcobalamin (Vitamin B12) deficiency
d. Tyrosinase

Ans. a. Thiamine deficiency

Q. A patient presents with anemia, a positive Romberg sign, and other neurological findings suggestive of vitamin B12 deficiency. Laboratory findings show elevated homocysteine levels. Which amino acid is likely to be deficient in this patient?

NEET PG 2025

a. Cysteine
b. Methionine
c. Tyrosine
d. Glutamate

Ans. b. Methionine

Q. A patient presents with follicular hyperkeratosis on the extensor aspect of the forearm and has a dietary history of vitamin A and C deficiency. What is the diagnosis?

NEET PG August 2024

a. Phrynoderma
b. Scurvy
c. Pellagra
d. Keratosis pilaris

Ans. a. Phrynoderma

Q. Which of the subsequent stages in vitamin D metabolism necessitates exposure to sunlight?

FMGE Dec 2021

a. 1,25-dihydroxycholecalciferol to 7-dehydrocholesterol
b. Cholecalciferol to 25-hydroxycholecalciferol
c. 7-dehydrocholesterol to cholecalciferol
d. 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol

Ans. c. 7-dehydrocholesterol to cholecalciferol

ERROR FILES

- Carboxylases need biotin; decarboxylases need pyridoxal phosphate
- Chronic alcoholism causes hypoglycemia because of high NADH and causes thiamine deficiency because of high energy status
- Global confusion, ophthalmoplegia, and ataxia are features of Wernicke's encephalopathy; global confusion, hallucinations, nightmares, and tremors are features of delirium tremens
- Adenosyl B12 is a coenzyme for methylmalonyl CoA mutase; methyl B12 is a coenzyme for methionine synthase

- Folate deficiency causes macrocytic anemia; B12 deficiency causes macrocytic anemia and neurological manifestations
- Type 1 homocysteinuria is dependent on vitamin B6; type II homocysteinuria is dependent on vitamin B12 and folate
- Retinol is the transport form; retinal is in the eye; retinoic acid suppresses keratinization of epithelium
- Vitamin A toxicity causes pseudotumor cerebri, vitamin E toxicity causes bleeding, vitamin K toxicity causes hemolytic anemia, and vitamin D toxicity causes hypercalcemia.

7. CLINICAL BIOCHEMISTRY

ABG INTERPRETATION

00:01:25

NEET PG 2022
INICET 2024
FMGE 2025

Normal Values

- pH: 7.36–7.44
- PCO_2: 36–44 mmHg
- HCO_3^-: 21–27 mEq/L

Steps

Step 1: Check Ph	• pH < 7.36 → Acidosis
	• pH > 7.44 → Alkalosis
	• Normal pH does NOT exclude acid-base disorder
	  ○ Seen in mixed disorders
	  ○ Example:
	  → Diabetic patient → DKA (metabolic acidosis)
	  → Vomiting → metabolic alkalosis
	  → When DKA patient presents with vomiting → pH may be normal
	• Always evaluate:
	  ○ HCO_3^-
	  ○ PCO_2
	  ○ Anion gap

Step 2: Determine Primary Disorder (metabolic Vs. Respiratory)	• **Acidosis**
	  ○ ↓ HCO_3^- → Metabolic acidosis
	  ○ ↑ PCO_2 → Respiratory acidosis
	• **Alkalosis**
	  ○ ↑ HCO_3^- → Metabolic alkalosis
	  ○ ↓ PCO_2 → Respiratory alkalosis

Step 3: Evaluate Compensation	**Basics of Compensation**
	• **Rule 1: Compensation is parallel**
	  ○ Primary defect is ↓ HCO_3^- → Compesation is ↓ PCO_2
	  ○ Primary defect is ↑ HCO_3^- → Compesation is ↑ PCO_2
	  ○ Primary defect is ↓ PCO_2 → Compesation is ↓ HCO_3^-
	  ○ Primary defect is ↑ PCO_2 → Compesat→ Kidneys compensate
	• **Metabolic acidosis compensation**
	  ○ ↓ HCO_3^- → ↓ pH
	  ○ Compensation → ↓ PCO_2 (hyperventilation)
	  ○ Mechanism: Kussmaul breathing
	  → ↑ H^+ in CSF → stimulates central chemoreceptors → Hyperventilation → CO_2 washout

- **Respiratory disorders compensation**
  - Respiratory acidosis: ↓ pH caused by an ↑ in PCO_2
  - Compensation will be an Increase in Bicarbonate
  - This compensation first happens quickly d/t Chemical equilibrium shift
    → ↑$CO_2 + H_2O \rightarrow H_2CO_3$
    → H_2CO_3 dissociates to form → $H^+ + HCO_3^-$
    → For every mole ↑ in CO_2 → equimolar rise in HCO_3^-
  - After sometime → renal compensation (slow)
    → Kidneys ↑ HCO_3^- reabsorption & generation
  - Chemical equilibrium shift is responsible for acute compensation
  - Kidneys are responsible for chronic compensation

Calculate compensation

- Metabolic acidosis: Winter's formula
  - Expected $PCO_2 = (1.5 \times HCO_3^-) + 8$
- Metabolic alkalosis
  - Expected $PCO_2 = (0.9 \times HCO_3^-) + 16$
- Example – Interpretation of compensation (Metabolic acidosis)
  - pH = 7.34 → Acidosis
  - HCO_3^- = 18 → Metabolic acidosis
  - Expected compensation: ↓ PCO_2
  - Expected $PCO_2 = 1.5 \times 18 + 8 = 35$ mmHg
  - **Case 1:** Actual PCO_2 = 40
    → No decrease from normal (40 → expected 35)
    → No compensation → Uncompensated metabolic acidosis
  - **Case 2:** Actual PCO_2 = 35
    → Expected = Actual → Compensated metabolic acidosis
  - **Case 3:** Actual PCO_2 = 30
    → More decrease than expected
    → Body never overcompensates → Hidden disorder present (Respiratory alkalosis)
    → Mixed disorder: metabolic acidosis + respiratory alkalosis

Compensation In Respiratory Disorders

Disorder	Acute	Chronic
Resp acidosis	1	3.5
Resp alkalosis	2	5

Respiratory Acidosis	• ↑ PCO_2 → ↑ HCO_3^-
	• Acute:
	  ○ For every 10 mmHg ↑ in PCO_2 → HCO_3^- ↑ by **1 mEq/L**
	• Chronic:
	  ○ For every 10 mmHg ↑ in PCO_2 → HCO_3^- ↑ by **3.5 mEq/L**

Respiratory Alkalosis	• ↓ PCO_2 →↓ HCO_3^-
	• Acute:
	  ○ For every 10 mmHg ↓ in PCO_2 → HCO_3^- ↓ by **2 mEq/L**
	• Chronic:
	  ○ For every 10 mmHg ↓ in PCO_2 → HCO_3^- ↓ by **5 mEq/L**

Examples

- A patient of COPD patient Presents with
  - pH = 7.34 → Acidosis
  - PCO_2 = 60 mmHg → Respiratory acidosis (chronic)
  - For every 10 mmHg ↑ in PCO_2 → HCO_3^- ↑ by 3.5 mEq/L
  - Here PCO_2 = 60 mmHg → 20mmHg increase
  - So HCO_3^- should ↑ by 7 mEq/L = 24 +7 =31 mEq/L
  - Expected HCO_3^- = 31 mEq/L
- Case 1: ABG report shows an actual HCO_3^- = 24
  - No compensation → Uncompensated chronic respiratory acidosis
- Case 2: ABG report shows an actual HCO_3^- = 31
  - Compensated chronic respiratory acidosis
- Case 3: ABG report shows an actual HCO_3^- = 35
  - More than expected → overcompensated → Hidden disorder (Metabolic alkalosis)
    → Mixed disorder: respiratory acidosis + metabolic alkalosis

Step 4: Anion Gap

- Only in metabolic acidosis
- To find cause of metabolic acidosis

Anion Gap – Basics

- Principle
  - In any solution sum of cations = sum of anions
- Cations of plasma:
  - Na^+ (major)
  - Unmeasured cations
- Cations of Anions:
  - Cl^-
  - HCO_3^-
  - Unmeasured anions
- Definition
  - Anion gap = Unmeasured anions – Unmeasured cations
- Formula
  - $AG = Na^+ - (Cl^- + HCO_3^-)$

Causes Of Metabolic Acidosis

00:26:54

Increased Utilization Of Hco_3^-	• Due to production of abnormal acids (HA) • Reaction: ○ $HA + HCO_3^- \rightarrow H_2CO_3 + A^-$

Increased Utilization Of Hco_3^-	• Effects: ○ ↓ HCO_3^- ○ ↑ Unmeasured anion (A^-) ○ High anion gap metabolic acidosis (HAGMA) • Inference ○ Presence of abnormal acid production **HIGH ANION GAP METABOLIC ACIDOSIS (HAGMA)** • D/t Production of abnormal acids • Important causes ○ Diabetic ketoacidosis (DKA) ○ Starvation ketosis ○ Lactic acidosis → Lactate accumulation → lactate anion →↑ anion gap ○ Hyperuricemia → Uric acid → urate anion ○ Chronic kidney disease (CKD) → Retention of metabolic acids ○ Toxic alcohols → Ethanol → acetic acid → acetate anion → Methanol → formic acid → formate anion → Ethylene glycol → oxalic acid → oxalate anion
Loss Of Hco_3^-	• Bicarbonate can be lost via GIT or Kidney • GI Loss: Diarrhea ○ Intestinal mucus is rich in HCO_3^- ○ Diarrhea → loss of mucus → loss of HCO_3^- → metabolic acidosis ○ Mechanism in diarrhea: HCO_3^- secretion via HCO_3^-/Cl^- exchanger → Cl^- reabsorbed → hyperchloremia • Renal Loss: Proximal Renal Tubular Acidosis (RTA) ○ Proximal Convoluted Tubule (PCT) fails to reclaim HCO_3^- ○ HCO_3^- is lost in urine → metabolic acidosis ○ Mechanism in RTA → Proximal Convoluted Tubule (PCT) fails to reabsorb HCO_3^- →↓ Na^+ reabsorption → Na^+ reabsorbed later with Cl^- (NKCC transporter) → ↑ Cl^- • In Both cases body reclaims chloride hence these 2 conditions are called as Hyperchloremic metabolic acidosis • Effect on anion gap ○ ↓ HCO_3^- compensated by ↑ Cl^- → Anion gap remains normal • Inference: Normal AG metabolic acidosis ○ Patient is suffering from Diarrhea or Renal tubular acidosis

DIABETES MELLITUS

00:37:00

FMGE 2025

- Definition: Absolute or relative insulin deficiency.
- Insulin-Dependent Tissues (Glucose Uptake via GLUT4):
  - Skeletal muscle.

- Cardiac muscle.
- Adipose tissue.

- Liver: Indirectly insulin-dependent; insulin stimulates Glucokinase for glucose uptake.
- Pathophysiology of Hyperglycemia:
  - Insulin deficiency → dependent tissues cannot take up glucose → glucose remains in circulation → Hyperglycemia.
- Glucose Toxicity (Insulin-Independent Tissues):
  - Excess glucose enters tissues that do not require insulin for uptake.
  - Affected tissues: Lens, Endothelium, Neurons, Kidney, Retina

Chronic Complications

- Diabetic Cataract
  - Mechanism: Lens takes up excess glucose.
  - Polyol Pathway:
    → Aldose Reductase (enzyme in lens) acts on glucose → converts it to Sorbitol (an alcohol).
    → Sorbitol is trapped within the lens
    → Sorbitol is osmotically active → attracts water
    → Lens fibers swell → cataractous changes.
  - Takeaway: Aldose Reductase is the enzyme responsible, and Sorbitol is the alcohol responsible for diabetic cataracts
- Other Tissues
  - Endothelium: Glucose toxicity → microvascular and macrovascular complications
  - Neurons: Excess glucose entry → Neuropathy
  - Kidney: Excess glucose entry → Nephropathy
  - Retina: Excess glucose entry → Retinopathy

Acute Complication- Diabetic Ketoacidosis (Dka)

- Biochemical Basis:
  - Insulin deficiency → Activation of Hormone-Sensitive Lipase (HSL) in adipose tissue.
  - HSL (inhibited by insulin) cleaves Triacylglycerol (TAG) → Glycerol + Free Fatty Acids (FA).
  - FA and Glycerol enter circulation.
- Adipose Tissue Impact: Peripheral lipolysis → weight loss.
- Liver Processing:
  - Gluconeogenesis: Stimulated by high Glucagon (counter-regulatory hormone).
  - Glycerol is used as a substrate for gluconeogenesis
  - Beta-Oxidation: FA are oxidized in the liver to provide energy for gluconeogenesis.
  - FA oxidation → production of n/2 Acetyl-CoA
- Ketogenesis:
  - Acetyl-CoA cannot enter the Citric Acid Cycle (TCA) due to lack of Oxaloacetate (OAA)
  - OAA is depleted because it is redirected for gluconeogenesis
  - Acetyl-CoA condenses → production of Ketone Bodies → Ketosis

HBA1C (Glycosylated Hemoglobin)

- Definition: Irreversible, non-enzymatic addition of carbohydrate residues to the N-terminal Valine of the Beta-globin chain of adult hemoglobin (HbA)

- Reflects glycemic control over the last 6–8 weeks.
- Limitation:
  - Dependent on Red Blood Cell (RBC) lifespan (Normal: 120 days).
- Interference with HbA1c Values:
  - Iron Deficiency Anemia: Body conserves RBCs → RBC lifespan ↑ (>120 days) → prolonged exposure to carbohydrates → False ↑ HbA1c
  - Hemolytic Anemia: RBC lifespan ↓ (<120 days) → reduced exposure to carbohydrates → False ↓ HbA1c
- Fructosamine (Glycated Albumin)
  - Used when RBC lifespan is altered (e.g., Iron Deficiency or Hemolytic Anemia).
  - Reflects glycemic control over the last 3–4 weeks (based on Albumin's shorter lifespan)

CONGENITAL ADRENAL HYPERPLASIA (CAH)

00:50:00

INICET 2024

FMGE 2021

- Definition: A group of disorders caused by defects in adrenal cortical hormone synthesis.
- 21-Beta Hydroxylase Deficiency:
  - Most common cause of CAH.
  - Features:
    → Salt wasting (↓ Na^+, hypotension)
    → Female pseudohermaphroditism
- 17-Alpha Hydroxylase Deficiency:
  - Enzyme required to convert cholesterol to male sex hormones.
  - 17α-hydroxylase deficiency → Male pseudohermaphroditism.
- Hypertensive CAH
  - 11β-hydroxylase deficiency
  - 17α-hydroxylase deficiency

CONN'S SYNDROME (PRIMARY HYPERALDOSTERONISM)

FMGE 2025

- Hormone involved → Aldosterone
- Excess aldosterone causes
  - ↑ Na^+ + water reabsorption → Hypertension
  - ↑ K^+ excretion → Hypokalemia
  - ↑ H^+ excretion → Metabolic alkalosis
- Clinical features
  - Hypertension
  - Hypokalemia
  - Metabolic alkalosis
  - No edema
  - Minimal hypernatremia
- Escape phenomenon
  - Aldosterone → sodium and water reabsorption → ↑ intravascular Volume → Atrial stretch → Release of ANP → ↑ Na^+ + water excretion → Prevents edema

WILSON'S & MENKE'S DISEASE

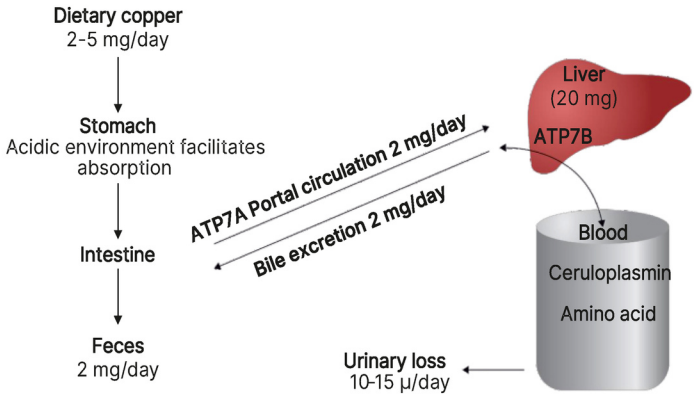
00:55:59

INICET 2024

Copper Metabolism

- Absorption and Transport
  - Absorbed in the intestine via ATP7A

- Enters portal circulation → Reaches the liver
- Liver Processing (ATP7B function)
  - Secretion of copper into bile (maintains copper balance)
  - Incorporation of copper into apoceruloplasmin → Ceruloplasmin
  - Ceruloplasmin stabilizes copper and carries it to tissues
- Copper-Dependent Enzymes
  - Lysyl oxidase: Necessary for collagen maturation
  - Tyrosinase
  - Superoxide dismutase



INICET 2024

Menkes Disease

- Etiology: Defect in ATP7A
- Pathophysiology: Copper is not absorbed from the intestine → Copper deficiency
- Impact: Lysyl oxidase becomes inactive → No collagen maturation
- Clinical Features: Kinky hair, fractures, and hypotonia

Wilson Disease (Copper Toxicity)

FMGE JULY 2025

- Etiology: Defect in ATP7B
- Pathophysiology
  - Copper is not secreted into bile → Copper toxicity
  - Copper is not incorporated into ceruloplasmin → Low ceruloplasmin levels
- Clinical Manifestations
  - Liver damage and damage to the lenticular nucleus → Also known as Hepatolenticular Degeneration.
  - Kayser-Fleischer (KF) ring: Copper accumulation in the Descemet's membrane of the cornea
  - Sunflower cataract: Copper accumulation in the lens
- Laboratory Paradox
  - Copper toxicity disorder but presents with low serum copper (as copper is excreted in urine)
  - ↑ Urinary copper levels
- Diagnostic Investigations
  - Serum ceruloplasmin < 0.2 g/L.
  - Urinary copper > 100 µg/24 hours.
  - Gold standard: Liver biopsy showing copper > 250 µg/g of tissue

FLUOROSIS

01:03:56

FMGE 2025

- Fluoride Levels in Drinking Water
  - Optimal: 0.5 to 1 mg/L
  - Safe upper limit: 1.5 mg/L
- Dental Fluorosis
  - Seen when levels are between 2 and 3 mg/L
  - Features: Mottled enamel, brownish discoloration, and pitting
- Skeletal Fluorosis

- Seen when levels are > 3 mg/L
- Mechanism: Fluoride incorporates hydroxyapatite crystals → Fluoroapatite crystals.
- Fluoroapatite stimulates osteoblasts → Excessive mineralization

- Clinical Features of Skeletal Fluorosis
  - Genu valgum (knock knees)
  - Compressive myelopathy
    → Distinction from Rickets: Rickets also has genu valgum but lacks compressive myelopathy.
  - Osteosclerosis: Thickened bones due to mineralization
  - Calcification of tendons, ligaments, and intermembranous spaces

Clinical manifestations of skeletal fluorosis vs. Lathyrism

- Skeletal fluorosis
  - Genu valgum
  - Restricted joints
  - History → High fluoride water (e.g. Nalgonda)
- Osteolathyrism
  - Genu varum
  - Hypermobile joints
  - History → Lathyrus consumption

LATHYRISM

01:09:00

Feature	Osteolathyrism	Neurolathyrism
Plant species	Lathyrus odoratus	Lathyrus sativus
Toxin	β-aminopropionitrile	BOAA
Mechanism	Inhibits lysyl oxidase → Defective collagen	Glutamate analog
Features	Genu varum, hypermobile joints	Spastic paralysis (UMN type)
Treatment	Vitamin C + Copper	

LIVER FUNCTION TEST

01:11:25

- Bilirubin Analysis
  - Conjugated hyperbilirubinemia → Obstructive jaundice
  - Unconjugated hyperbilirubinemia → Hemolytic jaundice
- Transaminases (ALT & AST)
  - ALT is more specific for the liver (located in the cytoplasm)
  - AST is less specific (also elevated in myocardial injury)
  - AST is located in mitochondria.
  - AST > ALT (Ratio > 2): Indicates alcohol-induced liver injury (due to mitochondrial toxicity)
  - Massive Elevation (> 1000 U/L): Seen in viral hepatitis, ischemic liver damage, and drug-induced liver damage (e.g., paracetamol poisoning).
- Alkaline Phosphatase (ALP)
  - Elevated in cholestasis (obstruction)
  - Can also be elevated in bone diseases

- Differentiating liver vs. bone origin: Check GGT
- Gamma-Glutamyl Transferase (GGT)
  - Elevated GGT + Elevated ALP → Liver origin (cholestasis)
  - GGT is the most sensitive marker for alcohol consumption
- Hypoalbuminemia & Prothrombin Time (PT)
  - Hypoalbuminemia: Indicates chronic liver dysfunction (due to impaired synthesis)
  - Elevated PT / INR: The most sensitive indicator of acute liver dysfunction
- Urobilinogen
  - Formed in the intestine when bile pigments reach the colon.
  - Diagnostic Value:
    → Elevated in urine → Hemolytic jaundice
    → Absent in urine → Obstructive jaundice (bile pigments cannot reach the intestine to form urobilinogen)

Congenital hyperbilirubinemia

FMGE 2025

Unconjugated hyperbilirubinemias (gcc)

- Causes: Gilbert Syndrome, Crigler-Najjar Syndrome Type 1, Crigler-Najjar Syndrome Type 2.
- Defect: UDP-glucuronosyltransferase (UDP-GT) deficiency
- Gilbert Syndrome:
  - Mild ↓ in UDP-GT activity
  - Usually asymptomatic but can present with mild jaundice during stress or infection

Crigler-Najjar Syndrome

Feature	Type I	Type II (Arias syndrome)
Enzyme activity	Complete absence of UDP-glucuronyl transferase	Partial deficiency
Severity	Severe	Milder
Serum bilirubin	Very high (20–50 mg/dL)	Moderate (<20 mg/dL)
Risk of kernicterus	Very high	Rare
Age of presentation	Neonatal period	Childhood / adolescence
Response to phenobarbital	No response	Responds (↓bilirubin by 25–50%)
Prognosis	Often fatal without transplant	Usually good
Treatment	Phototherapy, liver transplant	Phenobarbital

Conjugated Hyperbilirubinemias

- Causes: Dubin-Johnson Syndrome, Rotor Syndrome

Feature	Dubin-Johnson Syndrome	Rotor Syndrome
Defect	MRP2 defect	OATP1B1 & OATP1B3 defect
Liver color	Black liver	No pigmentation

Pigment	Melanin-like pigment deposition	No pigment
Urinary coproporphyrin	Total CP: normal Coproporphyrin I >80%	Total ↑ Coproporphyrin III >80%

CARDIAC FUNCTION TEST

01:25:00

- Myoglobin
  - Earliest marker to rise (within 1-2 hours) after myocardial infarction
  - Rapidly normalizes (within 24 hours)
  - Not specific for cardiac tissue
- CK-MB (Creatine Kinase-MB)
  - Rises within 3-6 hours
  - Normalizes within 2-3 days
  - Useful for assessing re-infarction
- Troponin
  - Gold standard and most specific marker for myocardial infarction.
  - Rises within 3-4 hours.
  - Remains elevated for 7-10 days.
- LDH (Lactate Dehydrogenase)
  - Normally, LDH2 > LDH1
  - In myocardial infarction, a "flipped pattern" occurs: LDH1 > LDH2

PANCREATIC FUNCTION TEST

01:28:25

INICET 2024

- Amylase
  - Not specific to the pancreas (also synthesized by salivary glands).
  - Rises early but normalizes within 5 days
  - Useful for assessing recurrent pancreatitis
- Lipase
  - More specific and more sensitive for pancreatic injury
  - Rises within 4 -8 hours but remain high till 8-14 days
- Key concept
  - The magnitude of elevation for both amylase and lipase does not correlate with disease severity

NEET PG 2024

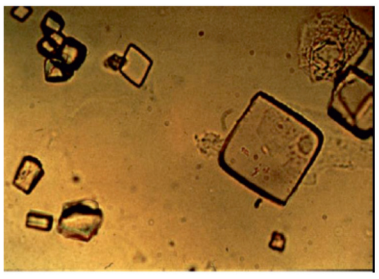
RENAL STONES

01:30:00

Hexagonal Crystals

- Cystine stones → Cystinuria

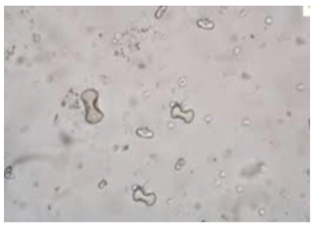
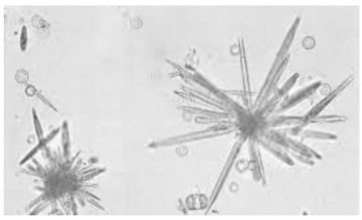
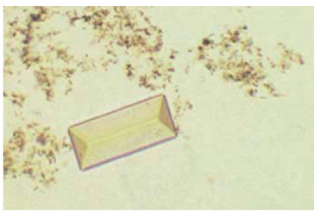
Rhomboid



- Uric acid stones

Envelope shape

- Calcium oxalate dihydrate

Dumbbell shape	Needle-shaped	Coffin lid → Staghorn calculus
		
• Calcium oxalate monohydrate	• Calcium phosphate	• Struvite (Magnesium ammonium phosphate) stone

PYQ

01:33:12

NEET PG 2024

Q. Identify the acid base disorder in a patient with the following values:

- pH = 7.2
- PO_2 = 90 mmHg
- pCO_2 = 80 mmHg
- Bicarbonate = 35 mEq/L

A. Metabolic alkalosis
B. Metabolic acidosis
C. Respiratory alkalosis
D. Respiratory acidosis

Answer: D

Q. Interpret the ABG report

- Blood pH: 7.30
- pCO_2: 29 mmHg
- Plasma HCO_3^-: 14 mEq/L

A. Compensated metabolic acidosis
B. Uncompensated metabolic acidosis
C. Compensated respiratory acidosis
D. Uncompensated respiratory acidosis

Answer: A

Q. Interpret the ABG report

- Blood pH: 7.30
- pCO_2: 29 mmHg
- Plasma HCO_3^-: 14 mEq/L
- Na^+: 130 mEq/L
- Cl^-: 90 mEq/L

A. Compensated increased anion gap metabolic acidosis
B. Uncompensated increased anion gap metabolic acidosis
C. Compensated normal anion gap metabolic acidosis
D. Uncompensated normal anion gap metabolic acidosis

Answer: A

Q. Severe vomiting leads to? INICET MAY 2023

A. Hypokalemia
B. Hypochloremia
C. Metabolic alkalosis
D. Respiratory alkalosis

Answer: A, B, C

Q. 60-year-old diabetic patient presented with repeated vomiting following a recent dine out. Her blood pressure was 90/60. pH was 7.3, HCO_3^-: 18 mEq/L, PCO_2: 35 mmHg. Identify the acid base disorder.

NEET PG 2022

A. Metabolic acidosis
B. Metabolic alkalosis
C. Respiratory alkalosis
D. Respiratory acidosis

Answer: A

Q. A 7-week-old baby was brought by the mother with complaints of repeated projectile vomiting and pellet stools. The probable metabolic disturbance is:

NEET PG 2022

A. Normal anion gap metabolic acidosis
B. Hypochloremic hypokalemic metabolic alkalosis
C. Hyperchloremic hypokalemic metabolic alkalosis
D. Respiratory acidosis

Answer: B

Q. The interpretation of the following ABG values is? INICET MAY 2024

- pH = 7.34
- Na = 135 mEq/L
- Cl = 93 mEq/L
- HCO_3^- = 20 mEq/L

A. Normal anion gap metabolic acidosis
B. High anion gap respiratory acidosis
C. High anion gap metabolic acidosis
D. Normal anion gap respiratory acidosis

Answer: C

Q. The interpretation of the following ABG values is? INICET MAY 2024

- pH = 7.5
- pCO_2 = 50 mmHg
- Bicarbonate = 30 mEq/L

A. Metabolic alkalosis
B. Metabolic acidosis
C. Respiratory acidosis

D. Respiratory alkalosis

Answer: B

Q. A hyperventilating hysterical woman presents with carpopedal spasm. The cause is: NEET PG 2022

A. High total calcium
B. Low total calcium
C. Alkalosis
D. Acidosis

Answer: C

Q. 26 year old male with colicky pain and the crystals in urine picture. Which of the following is the diagnosis? NEET PG 2024

A. Cystinuria
B. Glomerulonephritis
C. Calcium oxalate stones
D. ADPKD

Answer: A

Q. In a village of Assam, a man is observed walking with the help of a stick and has genu valgum. Many people in the same village present with similar symptoms. What is the most probable cause of this condition? FMGE JULY 2025

A. Calcium deficiency
B. Vitamin C deficiency
C. Skeletal fluorosis
D. Vitamin D deficiency (Osteomalacia)

Answer: C

Q. 15-year-old boy presents with tremors, difficulty in speech, and behavioral changes. On examination, he has hepatomegaly and a golden-brown ring at the limbus of the cornea (Kayser-Fleischer ring). Wilson's disease is suspected. Which of the following is the best investigation to support the diagnosis? FMGE JULY 2025

A. Serum ceruloplasmin
B. Liver biopsy for copper estimation
C. Serum copper
D. Copper excretion in urine

Answer: B

Q. A 4 day old neonate presents with a bilirubin of 15 mg/dL. The most probable cause is? FMGE JAN 2025

A. Physiological jaundice
B. Gilbert syndrome
C. Hemolysis

D. Crigler Najjar syndrome Type II

Answer: A

Q. The development of cataracts in patients with Diabetes Mellitus is primarily due to the accumulation of which of the following substances in the lens?

FMGE JAN 2025

A. Sorbitol
B. Dulcitol
C. Mannitol
D. Galactitol

Answer: A

Q. What is the primary mechanism behind tissue damage in long standing diabetes?
A. Insulin resistance
B. Sorbitol accumulation
C. Hyperglycemia
D. Decreased insulin secretion

Answer: C

Q. A diabetic patient presents with high VLDL is due to combination of which of the following?

INICET NOV 2024

A. High HSL, low LPL
B. High LPL, low HSL
C. High HSL, high LPL
D. Low LPL, low HSL

Answer: A

Q. True regarding pancreatitis:
A. Lipase indicates severity
B. Amylase remains high for 30 days
C. Lipase is more specific than amylase
D. Amylase is more specific than lipase

Answer: C

Q. Which of the following is true regarding serum calcium estimation?
A. Clenching the fist is advised
B. Tight tourniquet is to be applied
C. Prolonged immobilization causes increased free and total calcium
D. Citrate and oxalate tubes are to be used

Answer: C

Q. Deficiency of copper which is necessary of lysyl oxidase is seen in?
A. Scurvy
B. Scoliosis
C. Ehlers-Danlos syndrome
D. Menkes disease

INICET NOV 2024

Answer: D

Q. Which of the following is not a high anion gap metabolic acidosis?
A. Diabetic ketoacidosis
B. Renal failure
C. Diarrhea
D. Inborn errors of metabolism

Answer: C

Q. A hypertensive patient presents with hypernatremia, hypokalemia and metabolic alkalosis. What is the most likely diagnosis?
A. Conn's syndrome
B. Addison's syndrome
C. Bartter's syndrome
D. Gitelman's syndrome

Answer: A

Q. A male with hyperpigmentation, Tanner stage 5, presents with hypertension and precocious puberty. The causative defect is:
A. 21 β hydroxylase deficiency
B. 11 β hydroxylase deficiency
C. 17 β hydroxylase deficiency
D. 17 α hydroxylase deficiency

Answer: B

Q. A 2-month-old boy presented with ambiguous genitalia. His blood pressure was normal. The DHT value was low. The probable diagnosis is:
A. 21 beta hydroxylase deficiency
B. 11 beta hydroxylase deficiency
C. 17 alpha hydroxylase deficiency
D. 3 beta hydroxy steroid dehydrogenase deficiency

Answer: D

ERROR FILES

01:57:10

- Low pH and Low Bicarbonate is metabolic acidosis. Low pH and high PCO2 is respiratory acidosis

- High pH and High HCO3 is Metabolic alkalosis
- High pH and Low PCO2 is Respiratory alkalosis
- High anion gap metabolic acidosis is caused by DKA, starvation, Lactic acidosis, Hyperuricemia, Alcohol poisoning
- Diarrhea and RTA cause normal anion gap metabolic acidosis
- Diarrhea causes metabolic acidosis, vomiting causes metabolic alkalosis
- Conn's syndrome presents with hypernatremia, hypokalemia and metabolic alkalosis; Bartters and Gitelman's present with hyponatremia
- Hypertensive form with male pseudohermaphroditism is 17 alpha hydroxylase defect; Hypertensive form with male precocious pseudo puberty is 11 beta hydroxylase defect
- Menke's ATP7A defect; Wilson's is ATP7B defect
- Skeletal fluorosis presents with genu valgum and compressive myelopathy; rickets with genu valgum
- Skeletal fluorosis presents with genu valgum; Osteolathyrism presents with genu varum
- CKMG is used for reinfaction
- Amylase for recurrent pancreatitis

Yourwish

8. GENETICS

CHROMOSOME & GENE ORGANISATION

Levels Of Organization

00:01:30

Nitrogenous base
↓
Nucleoside
↓
Nucleotide
↓
Polynucleotide chain
↓
Double-stranded DNA (dsDNA)
↓
Chromosome

- 46 chromosomes = 46 long dsDNA molecules condensed with proteins
- Genes:
  - Located within chromosomes as specific segments
  - Every chromosome has multiple genes
- Gene → Transcription → mRNA → Translation →Protein

Nitrogenous Base

- Two types:
  - Purines
  - Pyrimidines

Purines

- Smaller name, bigger structure
- Two rings and nine atoms
- Includes: Adenine & Guanine

Sources Of Atoms

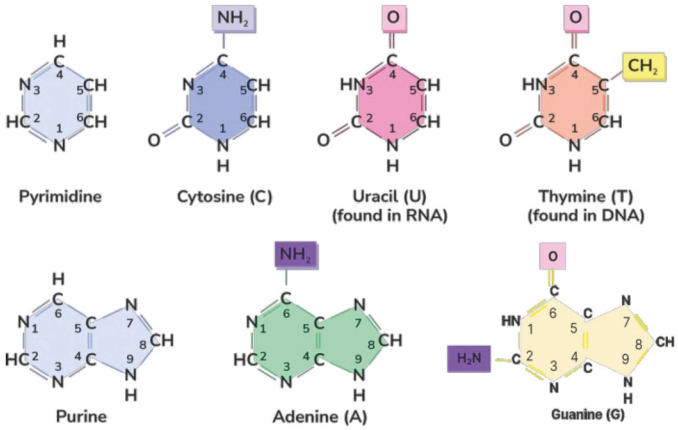
- N1: Derived from Aspartate
- C2 and C8 → Derived from Tetrahydrofolate (THF) derivatives
- N3 and N9 → Derived from Glutamine
- C4, C5, and N7→ Derived from Glycine
- C6 → Derived from Co_2

Pyrimidines

- Longer name, smaller structure
- Single ring and six atoms
- **Mnemonic: CUT**
  - Cytosine
  - Uracil
  - Thymine

SOURCES OF ATOMS

- N1: Derived from Aspartate
- C2: Derived from Co_2
- N3: Derived from Glutamine
- C4, C5, and C6: Derived from Aspartate



Important Information

- N1 (Aspartate) and N3 (Glutamine) are consistent sources for both purines and pyrimidines

Nucleosides And Sugars

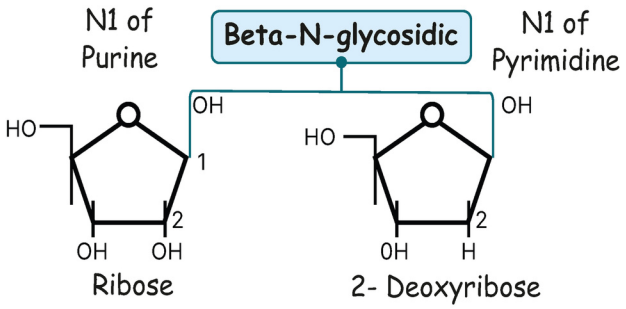
- Base + Ribose or Deoxyribose sugar → Nucleoside

Sugar Structure

- Ribose: A pentose (5-carbon) carbohydrate
- OH group at C1 (above ring), C2, C3, and C5 (outside ring)
- Deoxyribose (2-deoxyribose): Lacks oxygen at the C2 position

Linkage

- Formed between the sugar and base via a Beta-N-glycosidic linkage
  - Linkage point: C1 of sugar to N9 of Purine or N1 of Pyrimidine
  - "Beta" indicates the OH group is above the plane of the ring



Nucleotide

- Nucleoside + Phosphate group (PO_4) → NMP
  - The phosphate group attaches to the 5th hydroxyl (OH) group of the ribose sugar
  - Phosphoester linkage (formed between phosphate acid and sugar alcohol)

Forms

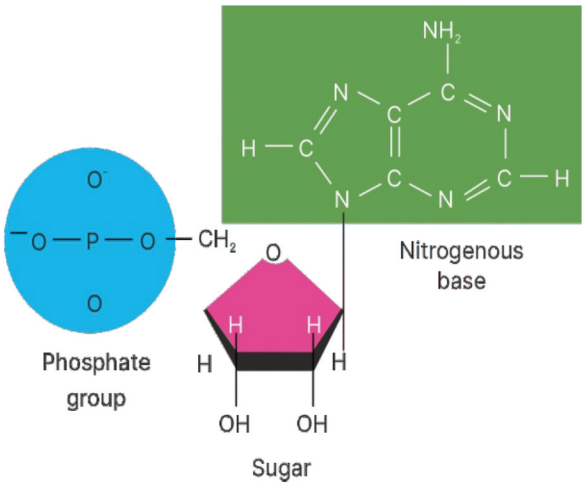
- Nucleotide monophosphate (NMP)
- NMP + PO_4= NDP(Nucleotide diphosphate)
- NTP+PO_4= NTP(Nucleotide triphosphate)

Important Information

- In Polynucleotide Chains: Only the monophosphate form (NMP) exists in DNA or RNA chains (e.g., AMP, TMP, GMP, CMP)

Structure Of Nucleotide Monophosphate

- Nitrogenous base (purine base) attaches to sugar (ribose sugar) with a beta-N-glycosidic linkage
- The phosphate group attaches to the 5th OH group with a phosphoester linkage



Polynucleotide Chain Formation

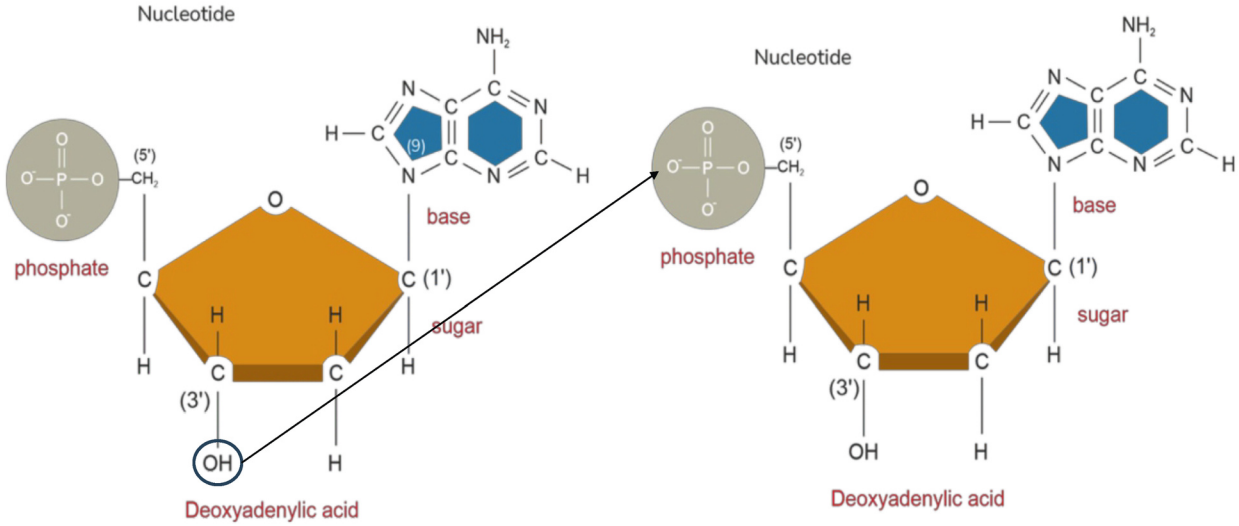
- Polymerization requires a free hydroxyl (OH) group
- In a monophosphate nucleotide:
  - C1, C2 (in deoxyribose), and C5 are unavailable for new links
  - Only the 3' Hydroxyl group remains free.

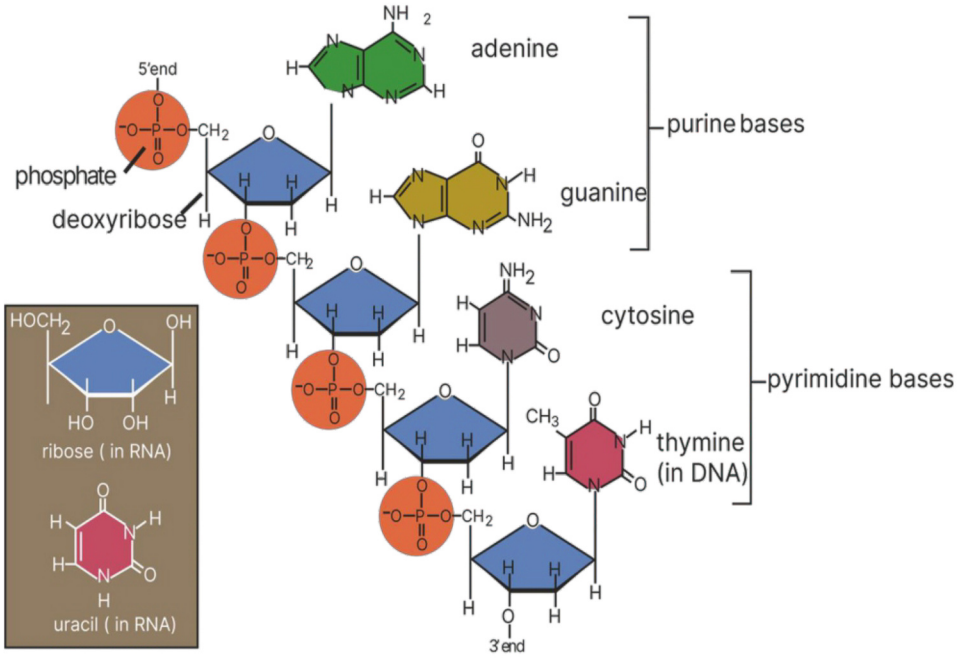
Chain Linkage

- 3' OH of one nucleotide links to the 5' Phosphate of the next nucleotide
- Resulting linkage: 3'-5' Phosphodiester linkage

Chain Directionality

- Chains are synthesized from the 5' end to the 3' end
- 5' end: Has a free 5' phosphate group
- 3' end: Has a free 3' hydroxyl group



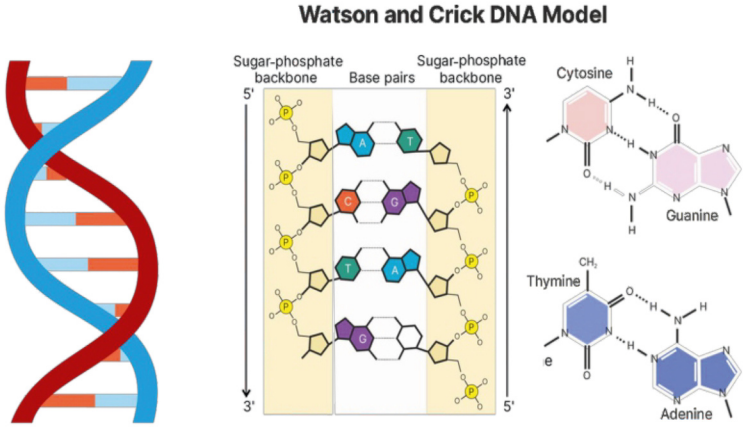


Rules Of Polymerization

- Only linkage possible in polynucleotide chain is 3' → 5' phosphodiester linkage
- New strands are always synthesized in the 5' → 3' direction. All polymerases (DNA and RNA) exhibit 5' → 3' activity
- The Template strand must be anti-parallel, read in the 3' → 5' direction

DNA STRUCTURE: WATSON AND CRICK

00:25:25



Strand Characteristics

- Two strands are exactly complementary and anti-parallel
- Complementarity
  - Adenine (A) on one strand pairs with Thymine (T) on the other; Guanine (G) pairs with Cytosine ©.
- Anti-parallel: One strand runs in 3'-5' direction; the other runs in 5'-3' direction

Physical Orientation

- Strands are oriented in a ladder-like fashion
- Backbone of the ladder:
  - Made of 3'-5' phosphodiester linkages with ribose or deoxyribose sugars

Yourwish

Steps Of The Ladder

- Made of nitrogenous bases linked by hydrogen bonds
  - Two hydrogen bonds link A and T
  - Three hydrogen bonds link G and C

Dna Bond Disruptions

- Hydrogen Bond Breakage → Unwinding or Denaturation
  - Results in the formation of two single strands from a double-stranded DNA
- β-N Glycosidic Linkage Breakage → Base Excision Error
  - Occurs between the base and the sugar
  - The backbone remains intact, but the base is lost
- 3'-5' Phosphodiester Linkage Breakage → Double-Stranded DNA Break
  - Involves the breakage of the backbone on both strands

Dna Packaging And Chromosome

Chromosome Structure

- A chromosome is a condensed, long, double-stranded DNA
- Consists of a centromere, a short arm, and a long arm

Histones

- Packaging is required because DNA (meters long) must fit into a nucleus (microns in diameter)
- Histones are basic, positively charged proteins
- DNA is negatively charged due to phosphate groups
- Electrostatic attraction → Negatively charged DNA winds around positively charged histones
- Five types of histones: H1, H2A, H2B, H3, and H4
- Histone Octamer: Formed by dimers of H2A, H2B, H3, and H4 (all except H1)

Nucleosome

- String-on-bead appearance
  - Bead: The histone octamer
  - String: A segment of double-stranded DNA
- Takeaway: H1 histone is NOT part of the nucleosome
- Linker Fragment: Connects nucleosomes; contains the H1 histone

Levels of Compactness

- 10 nm fiber: The chain of nucleosomes
- 30 nm fiber: Created by folding the 10 nm fiber on itself (second level of compactness)

Chromosome Scaffold

- Scaffold is a central tubular protein
- 46 scaffolds exist per nucleus (one per chromosome).
- 30 nm fiber forms loops 360 degrees around the scaffold and spirals around it
- Outcome → Formation of a highly condensed chromosome

Gene Expression

- Gene is a segment of a chromosome coding for a protein or RNA
- Contains
  - Coding sequences
  - Non-coding intervening sequences (Introns)

Transcription

- Immediate product: Primary transcript or Heteronuclear RNA (HnRNA)
  - Occurs within the nucleus
- HnRNA enters the nucleolus for post-transcriptional modification

Post Transcriptional Modifications

- 5' Capping: 7-methylguanosine cap added to the 5' end
- 3' Tailing: Poly-A tail added to the 3' end
- Splicing: Removal of introns and joining of exons
- Modifications protect mRNA terminals → Formation of functional mRNA

Translation

- mRNA enters the cytoplasm
- Ribosomes read mRNA from 5' to 3'
  - Every codon, one by one, is read
- Ribosomes recruit tRNA containing complementary anticodons
  - tRNA brings specific amino acids
  - Nucleotide sequence of mRNA → Amino acid sequence of a polypeptide chain
  - Polypeptide Growth: Occurs from the Amino (N) terminal to the Carboxy © terminal
  - 1st Amino Acid: Amino-terminal end
  - Last Amino Acid: Carboxy-terminal end

DNA ERRORS AND REPAIR MECHANISMS

00:44:52

Base Excision Error

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- Backbone is maintained normally, but the base is lost
- Caused by breaking the beta-N glycosidic linkage
- MC DNA error is because the linkage is very labile

Mismatch Error

- Incorrect base pairing (e.g., A pairing with G or C)
- Occurs during replication due to DNA polymerase mistakes

Pyrimidine- Pyrimidine Dimerization

- Caused by UV light exposure.
- Two adjacent pyrimidines dimerize → Creates an abnormal kink

Double-stranded Dna Break

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- Caused by ionizing radiation (e.g., Gamma rays)
- Breaks the 3'-5' phosphodiester backbone of both strands

Repair Mechanisms

- Base Excision Repair
- Mismatch Repair
- Nucleotide Excision Repair (NER)
  - UV-specific endonuclease makes two nicks
  - Excises the damaged nucleotide segment to remove the kink
- Double-Stranded Break Repair

Disorders Linked To Repair Mechanisms

- Mismatch Repair Defect
  - HNPCC (Hereditary Non-Polyposis Colon Cancer) / Lynch Syndrome
- Nucleotide Excision Repair (NER) Defect
  - Xeroderma Pigmentosa (Sunlight exposure → freckles → lesions)
  - Cockayne Syndrome
- Double-stranded DNA break repair mechanism happens in response to ionising radiation
  - NHEJ (non-homologous end joining):
    → MC repair method
    → Sub-optimal method because helicase causes loss of nucleotide sequences
    → Tolerated because 98.5% of DNA is non-coding; only 1.5% is coding
  - HDR (Homologous DNA Repair):
    → Optimal repair method
    → Uses the other chromosome copy (maternal or paternal) as a template
    → DNA polymerases use the normal sequence to fill the gap accurately.
  - Three disorders caused by defects in the double-strand DNA break repair mechanism (Mnemonic: ABF)
    → A: Ataxia Telangiectasia
    → B: Bloom Syndrome
    → F: Fanconi's Anemia

Non-homologous End Joining Defect

- Causes Ataxia Telangiectasia
- Causes Severe Combined Immunodeficiency (SCID)

Homologous Dna Repair Defect

- Causes Bloom Syndrome
- Causes Fanconi's Anemia
- Causes Human Breast and Ovarian Cancer (specifically involving BRCA1 mutation).
  - BRCA1 is involved in homologous DNA repair; a mutation makes a person prone to breast, ovarian, and colon cancers.

TYPES OF CHROMATIN

00:55:47

Euchromatin

- Transcriptionally active region of a chromosome
- Uncondensed structure
  - Uncondensing is required for replication and transcription functions
- Stains less densely

Heterochromatin

- Transcriptionally inactive region of a chromosome
- Highly condensed to enable packaging when inactive
- Stains more densely

Types

Constitutive Heterochromatin

- Always inactive
- Found in the centromeric region and telomeric ends
  - Centromeres are represented as dark dots due to being highly condensed and always inactive

Facultative Heterochromatin

- Sometimes active, sometimes inactive
- Example: Female X chromosomes
  - Somatic cells in females have two X chromosomes, but only one is transcriptionally active.
  - The inactive X chromosome is highly condensed and stains densely as a Barr body
  - Barr body is used for sex determination; its presence indicates more than one X chromosome
  - It is "facultative" because in one somatic cell, the paternal X may be inactive, while in another cell of the same female, the maternal X may be inactive

Karyotyping

- Imaging technique for chromosomes
- Obtained by staining chromosomes with Giemsa stain
- Displays alternating dark and light bands
  - Dark bands → Inactive regions
  - Light bands → Active regions

Condensation And Uncondensation Of The Chromosome

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- Condensation is required when the chromosome is idle
- Uncondensation is required for replication or transcription
  - Silence is achieved by condensing the chromosome again

Epigenetics And Gene Splicing

- Alteration in gene expression not caused by DNA sequence changes
- Gene silencing is caused by
  - Methylation of cytidine residues of CG islands
  - Deacetylation of histone

DNA POLYMERASES

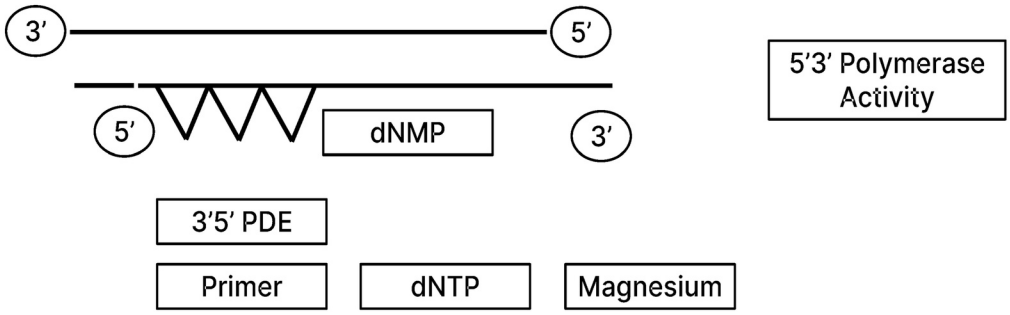
01:05:18

Requirements For Dna Polymerase

- Template Strand
  - Must be in the 3' to 5' direction so the new strand can be synthesized in the 5' to 3' direction
- Primer: Necessary to initiate the elongation of the DNA strand
- Deoxyribonucleotide Triphosphates (dNTPs):

- The polymerase recruits complementary nucleotides
- While the final chain contains monophosphates, triphosphates are required during synthesis
- Polymerase breaks the last two phosphate linkages → Releases energy → Used to form 3'-5' phosphodiester linkages

- Catalyst: Requires Magnesium (Mg^{2+}) or Manganese (Mn^{2+})
- Buffer: To maintain optimal pH



- Synthesis occurs via 5' to 3' polymerase activity.
- Proofreading occurs via 3' to 5' exonuclease activity (removes defective strands from the opposite end)
  - Exception: DNA Polymerase 1 possesses both 3' to 5' AND 5' to 3' exonuclease activity

Klenow Fragment

- A fragment of Taq DNA Polymerase (Type 1) used in Polymerase Chain Reaction (PCR)
- Taq DNA Polymerase 1 naturally has:
  - 5' to 3' polymerase activity
  - 3' to 5' exonuclease activity
  - 5' to 3' exonuclease activity
- The 5' to 3' exonuclease activity is detrimental to PCR because it would remove the newly synthesized strand as it is being made

Synthesis of Klenow Fragment

- Taq DNA polymerase is treated with the enzyme subtilisin
- Subtilisin removes the subunit responsible for 5' to 3' exonuclease activity
- The remaining part is called the Klenow fragment

POLYMERASE CHAIN REACTION

01:12:40

- An in-vitro amplification of a desired fragment of DNA
- Possible by choosing specific primers complementary only to the flanking sequences of the desired fragment

Steps Of Pcr

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Denaturation/unwinding

- Double-stranded DNA is separated into two single strands
  - Carried out at high temperatures: 94-95°C
  - Heat breaks the hydrogen bonds between strands

Annealing

- Two primers are added
- Primers hybridize to the flanking sequences of the target fragment
- Carried out at an optimal temperature: 5°C below the melting temperature (Tm) of the primers.
  - If the temperature is too high → Primers melt and do not anneal
  - If the temperature is too low → Violation of Watson-Crick base pairing (A-T, G-C) → Primers anneal non-specifically → Non-specific amplification

Elongation

- DNA polymerase elongates the new strands
  - Requires a thermostable enzyme: Taq DNA Polymerase (extracted from Thermus aquaticus, an organism living in hot springs)
  - Taq survives the cyclic heat of 95°C
  - Optimal elongation temperature: 72°C
- Thermocyclers are used to maintain the optimum temperature

Amplification Calculation

- The number of DNA copies doubles every cycle
  - After n cycles, the total number of copies = 2^n
  - Commonly set for 30–35 cycles

Loop Mediated Amplification Assay/lamp Assay

- Isolated temperature amplification technique
- Bacillus stearothermophilus is used
  - Bioindicator for autoclave
  - Extract Bst DNA polymerase
- I/C/O Bacillus Smithi is used
  - Bsm DNA polymerase is extracted
  - Have more strand invasion ability even at 60° instead of 90°
- All steps were carried out at a constant temperature of 60°
- Incubator used over the thermocycler
- Technical expertise not required to operate this machine

MCQS AND PYQS

01:27:30

Q. Pyrimidine ring is derived from all except:
a. Carbon dioxide
b. Glutamine
c. Aspartate
d. Glycine

Ans. d. Glycine

Q. A 39-year-old person presents with colon cancer. A tissue biopsy was sent to detect the presence of a mismatch repair defect and microsatellite stability index, which was high. The geneticist, however, detects multiple base excisions in the DNA. The linkage that is broken to cause a base excision is:
a. Phosphoester
b. Beta N glycosidic linkage
c. 3'5' phosphodiester linkage
d. 5'3' phosphodiester linkage

Ans. b. Beta N glycosidic linkage

Q. DNA is extracted from a blood sample and is subjected to dehydration. The form of DNA that is expected is:
a. B DNA
b. A DNA
c. Z DNA
d. C DNA

Ans. b. A DNA

B TYPE (MC physiologic form)	10 Bp/turn	Right-handed helix
A TYPE	11 bp/turn	Right-handed helix
Z TYPE	12 bp/turn	Left-handed helix

Q. The process of gene regulation involves condensation and uncondensation of chromosomes. This occurs by the binding of a variety of proteins to DNA by charge interactions. At physiological pH, the charge on DNA is:
a. Positive charge
b. Negative charge
c. Both
d. No charge
Ans. b. Negative charge

Q. Barr body is an example of:
a. Euchromatin
b. Constitutive heterochromatin
c. Facultative heterochromatin
d. Hypersensitive heterochromatin

Ans. c. Facultative heterochromatin

Q. In a rheumatoid arthritis patient, synovial tissue shows increased expression of TNF-alpha and IL-6, contributing to inflammation. Which epigenetic change most likely explains this?

a. Activation of DNA methylation
b. Inhibition of DNA methylation
c. Activation of histone deacetylation
d. Inhibition of histone acetylation

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Ans. b. Inhibition of DNA methylation

Q. Cancer cells show increased length of a specific RNA transcript/fragment when compared to normal cells. The most likely reason for this is:

a. Polyadenylation
b. Alternative RNA splicing
c. Gene amplification
d. Gene silencing

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Ans: b. Alternative RNA splicing

- Polyadenylation- Adding a Poly-A tail
- Alternative RNA splicing- Within a cell, an intron is considered an exon, which is not spliced out, leading to neoplasia
  - E.g., BCL-XL acts as an anti-apoptotic protein when the length increases

Q. All the following are true about Klenow fragment except

a. It is a product of DNA polymerase I
b. It has 5'3' polymerase activity
c. It has 5'3' exonuclease activity
d. It has 3'5' exonuclease activity

Ans. c. It has 5'3' exonuclease activity

Q. A person is working on finding out the polymorphisms of the Albumin gene. He wants a fragment of the albumin gene, which includes the 5^{th} to 9^{th} exons of the gene. He knows that human chromosomes can be unwound at 95 degrees. He constructed two primers - the melting temperature of the forward primer is 64 degrees, and that of the reverse primer is 60 degrees. He uses Bacillus smithii DNA polymerase enzyme. The elongation step temperature that he would use for this setup is:

a. 62 degrees
b. 72 degrees
c. 57 degrees
d. 60 degrees

Ans: d. 60 degrees

Q. Steps of PCR are:

a. Denaturation → Annealing →Extension
b. Denaturation → Annealing → Extension → Hybridization
c. Annealing → Extension → Denaturation
d. Extension → Denaturation → Annealing

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Ans: a. Denaturation → Annealing → Extension

Yourwish

Q. After how many cycles of PCR, are we expected to have half the number of copies as found after 26 cycles?

a. 27
b. 13
c. 25
d. 35

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Ans: c. 25

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

a. Mismatch repair
b. Nucleotide excision repair
c. Base excision repair
d. Point mutation

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Ans: a. Mismatch repair

Q. A woman with a strong family history of breast and ovarian cancer is being evaluated for BRCA1/BRCA2 mutations. Which of the following is the most appropriate test to detect multiple mutations at different codons in these genes?

a. qPCR - Measures BRCA1/2 expression levels
b. RT-PCR-Detects RNA-level mutations
c. Northern blot - Analyzes RNA expression
d. Exome sequencing

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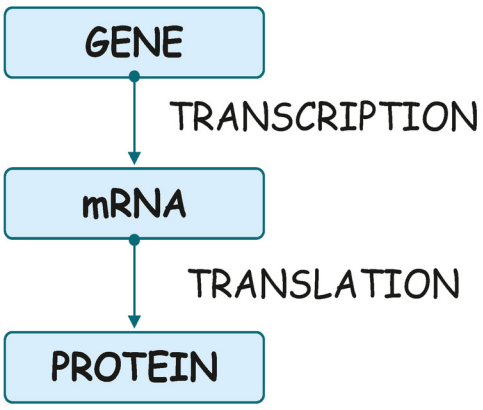
Ans: d. Exome sequencing

GENE EXPRESSION

01:46:50



Levels Of Disease Pathogenesis

- First level: Gene sequence alteration
- Second level: mRNA sequence alteration or difference in mRNA expression level
- Third level: Difference in protein sequence or protein expression

Detection Methods

Gene Level

- Exome sequencing or gene sequencing to detect sequence alterations.

mRNA LEVEL

- Sequence alterations: Northern Blot (uses specific probes that fail to bind if the sequence is altered).
- Expression changes: Reverse Transcriptase PCR (RT-PCR) followed by Real-Time PCR

	RT PCR	qPCR/REALTIME PCR
Abbreviation	• Reverse transcriptase PCR	• Quantifying PCR
Use	• RNA	• Quantify nucleic acids
Application	• The organism is an RNA virus • mRNA expression changes/sequence changes	• Pathogen load detection • RNA expression changes

- **Protein Level:** Sequence alterations- Western Blot

Blotting Techniques

- **Southern Blot:** DNA identification
- **Northern Blot:** RNA detection
- **Western Blot:** Protein identification
- **Eastern Blot:** Detection of protein modifications
  - Co-translational
  - Post-translational
- **South-Western Blot:** DNA-Protein interactions
- **North-Western Blot:** RNA-Protein interactions
- **Far-Western Blot:** Protein-Protein interactions

Q. Which of the following techniques are correctly matched with their uses? INICET May 2025

a. Southern blot - RNA identification, Northern blot - DNA identification, Western blot - Protein identification
b. Southern blot - DNA identification, Northern blot - Protein identification, Western blot - RNA identification
c. Southern blot - Protein identification, Northern blot - RNA identification, Western blot - DNA identification
d. Southern blot - DNA identification, Northern blot - RNA identification, Western blot Protein identification

Ans. d. Southern blot - DNA identification, Northern blot - RNA identification, Western blot Protein identification

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

a. CTAGATG
b. GTAGATC
C. GAUCUAC
d. GUAGAUC

Ans. d. GUAGAUC

Replication V/s Transcription

Replication

- Parent double-stranded DNA undergoes unwinding
- Both strands act as templates
- Result → Two new double-stranded DNA molecules

Transcription

- Goal → Synthesize single-stranded RNA from a double-stranded gene
- Gene undergoes unwinding
- Only the strand in the **3' to 5' direction** acts as a template
- Result → New RNA synthesized in the **5' to 3' direction**
- **Template Strand:** The 3' to 5' strand used for synthesis
- **Coding Strand:** The other 5' to 3' strand that does not participate in transcription
  - Has the same polarity and sequence as the new mRNA
  - Difference: Thymine (T) in the coding strand is replaced by Uracil (U) in RNA

Predicting Rna Sequence From Dna Template

Sequence Analysis Steps

- Step 1: Check the polarity of the provided template strand
- Step 2: Always write the template strand in the 3' to 5' direction
- Step 3: Write the complementary bases
- Step 4: Mark the product as 5' to 3'
- Note: If no polarity is mentioned, it is implied to be 5' to 3' (standard rule)

Coding Strand/gene Sequence

  - If the coding strand or gene sequence is given:
  - Maintain the polarity.
  - Maintain the sequence.
  - Simply replace T with U

Q. miRNA is used for?

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a. Gene Knockdown

b. Gene knock out

c. Gene knock-in. RNA editing

Ans. a. **Gene Knockdown**

Sirna/gene Interference Rna

- miRNA is a precursor to siRNA (small interference RNA)
- siRNA interferes with gene expression at the **translation level**

Mechanism

- siRNA finds complementary sequences on functional mRNA
- siRNA hybridizes with the **3' Untranslated Region (UTR)**

- 5' UTR: Sequences before the start codon (AUG)
- Translated Region: From AUG to stop codon
- 3' UTR: Sequences beyond the stop codon

- The ribosome reaches the 3' end, finds the complex super secondary structure, and takes it as a signal to fragment the mRNA
- Fragmented mRNA cannot be translated →↓ protein product
  - **Result:** Gene Knockdown (downregulation of gene expression)

Gene Knockout V/s Knockin

- Both are gene editing mechanisms
- **Gene Knockout:** Removal of a defective gene
- **Gene Knock-in:** Replacing a defective gene with a normal gene (better)
- Both are achieved via CRISPR-mediated gene editing

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Repair Mechanism

- Cas enzyme creates a double-stranded DNA break
  - **Non-homologous end joining:** Results in loss of nucleotide sequences → Gene Knockout
  - **Homologous DNA repair:** Uses a normal sequence to guide repair → Gene Knock-in
- Nobel Prize was awarded to Emmanuelle Charpentier for demonstrating this

Q. miRNA binds to?
a. 5'UTR
b. 3'UTR
c. Gene promotor
d. Gene exons

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Ans. b. 3'UTR

Q. Following CRISPR-mediated gene nicks, which of the following can result in gene knock-in?
a. Non-Homologous End Joining
b. Homologous DNA repair
c. Interference
d. Ku helicase-mediated repair

Ans. b. Homologous DNA repair

Q. A paternal dispute case was filed by the mother. The forensic centre checked 5 VNTR systems.

INDIVIDUAL	VNTR1	VNTR2	VNTR3	VNTR4	VNTR5
CHILD	9/10	8/11	10/12	9/8	6/7
MOTHER	7/9	8/9	11/10	9/11	6/9

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

a. 7/8, 9/11, 11/12, 8/10,6/8
b. 7/8,9/11,10/12, 8/10, 6/8
c. 10/11, 11/10, 12/11, 8/7, 7/9
d. 10/11,11/10,11/10, 11/9, 9/10

Ans. c. 10/11, 11/10, 12/11, 8/7, 7/9

Satellite Dna Characteristics

- AKA Highly repetitive sequences
- Distributed at various loci
  - The number of repeats is unique to every individual
  - Used for person identification and forensic applications
  - Clear paternal dispute cases

Paternity Dispute Case Interpretation

- Analyze the child's number of repeats at specific loci
- One repeat must come from the mother; the other must match the biological father
- Example: If the child has 9/10 repeats and the mother has 9, the biological father must possess the 10 repeat at that locus

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

1. RT-PCR
2. Sample collection
3. FISH
4. RFLP5. Cytogenetics
6. Conventional PCR
7. DNA extraction

a. 2, 7, 1, 3
b. 2, 7, 6, 4
c. 7, 2, 1, 3
d. 2, 6, 7, 3

Ans. b. 2, 7, 6, 4

MOLECULAR DIAGNOSIS OF KNOWN MUTATION SITES (SICKLE CELL ANEMIA)

- Sickle cell anemia is caused by a point mutation in the 6th codon of the beta-globin gene
- Step 1: Blood sample collected
- Step 2: DNA extraction; Extraction of all 46 chromosomes
- Step 3: Conventional PCR (Using specific primers to amplify the beta-globin fragment containing the 6th codon)

Analysis

- Sequencing: Direct identification of the mutation
- RFLP (Restriction Fragment Length Polymorphism): Most common cost-effective method

RFLP

- Uses the restriction enzyme
- Specific sites
- Cuts the 6th codon only if it is normal
  - MST II is the enzyme
  - Sickle Cell Disease (Mutant): MST II cannot cut
  - Normal 6th codon → Cut by MST II → Two fragments produced (0.2 kb and 1.2 kb)
  - Mutated 6th codon → Not cut by MST2 → Single fragment remains (1.4 kb).
- PCR fragments are incubated with MST II and run through electrophoresis
- Longer fragments move slower; shorter fragments move faster
  - Length of base pair is 1.2 kb- Normal
  - Length of 1.4 kb (band does not move)- Mutated
  - 2 bands- One is 1.2 kb, and the other is 1.4 kb- Heterozygous

Summary Of Steps

- Blood sample collection → DNA extraction → Conventional PCR → RFLP or Sequencing

CYTOGENETICS

02:28:00

- Used to detect defects at the chromosomal level
- Identifies chromosomal aberrations, including:
  - Copy number variations (Trisomy 21, Trisomy 18)
  - Translocations (BCR-ABL)
  - Microdeletions or amplifications (Prader-Willi/Angelman Syndrome)

Karyotyping

- Blood sample collection → Centrifugation → Removal of buffy coat (contains WBCs)
- WBC culture is maintained
- Induction of Metaphase Arrest
  - Metaphase arrest is required because chromosomes are highly condensed and visible
  - Chromosomes are stained using Giemsa (G-banding)
- Chromosomes show alternating dark and light bands
- Arranged based on centromere location, arm size, and banding patterns
- Copy number variations seen

Fish

- Fluorescent In-Situ Hybridization
- Copy Number Variation (Trisomy 21):
  - Fluorescent labelled probe complementary to Chromosome 21 is added to metaphase-arrested cells.
  - Normal: 2 fluorescent signals
  - Trisomy 21: 3 fluorescent signals
- Translocation (BCR-ABL in Leukemia):
  - Two different probes were used: BCR (Green dye) and ABL (Red dye)
  - Normal: 2 separate green signals and 2 separate red signals from different chromosomes
  - Translocation: Green and red signals appear together on one chromosome → Structural alteration

- Microdeletion (Prader-Willi/Angelman):
  - Fluorescent labelled probe complementary to the specific region of Chromosome 15
  - Normal: 2 signals (one per chromosome)
  - Microdeletion: Only 1 signal present

Q. For mycobacterium species differentiation, the technique used is/are
a. Line probe assay
b. MIRU(mycobacterium interspersed repetitive units)
c. Spoligotyping
d. RFLP

Ans. ALL 4 CHOICES

- RFLP: Based on spacer and repeat sequences
- Spoligotyping: Repeat sequence identification (lower resolution)
- MIRU (Mycobacterium Interspersed Repetitive Unit): PCR-based detection of repeats
- Line Probe Assay (LPA): Detects species and drug susceptibility patterns

Q. The M13 bacteriophage vector has been used in molecular biology to identify specific gene sequences, such as those related to the SARS-CoV-2 (COVID-19) spike protein, through expression of the inserted gene fragment. Which of the following terms best describes this type of expression system?
a. Phage expression
b. Bacterial expression
c. Yeast expression
d. Mammalian expression

Ans: a. Phage expression

Q. A patient presents with skin cancer and hyperpigmentation that worsens with sunlight exposure. Which of the following DNA repair mechanisms is most likely defective in this condition?
a. Nucleotide excision repair
b. Base excision repair
c. Non-homologous end joining (NHEJ)
d. Mismatch repair

Ans. a. Nucleotide excision repair

Q. What is the repair mechanism associated with CRISPR-Cas9
a. Non-homologous end joining **INICET May 2022**
b. Base excision repair
c. Nucleotide excision repair
d. Mismatch repair

Ans. a. Non-homologous end joining

Q. A scientist treats experimental cells with a histone acetylase inhibitor. Which of the following is the most immediate epigenetic change of this treatment?

a. Increased expression of H3K9me2/3
b. Increased acetylation of H3K9ac
c. Chromatin condensation
d. DNA methylation

Ans. c. Chromatin condensation

Q. Which of the following is used in diagnosing aneuploidy

1. FISH
2. Cytogenetics
3. Sangers
4. PCR

a. 1, 2
b. 1, 2, 3
c. 2, 3
d. 1, 2, 3, 4

Ans. a. 1, 2

Q. Which of the following is the best test for quantitative analysis of an RNA sample?

- PCR: polymerase chain reaction
- RTPCR: Reverse transcriptase polymerase chain reaction

a. Real-time PCR
b. Reverse transcriptase PCR
c. PCR-restriction fragment length polymorphism
d. RTPCR followed by real-time PCR

Ans. d. RTPCR followed by real-time PCR

ERROR FILES

02:42:30

- RTPCR is used for detecting RNA, and qPCR is used for quantifying nucleic acids
- Gene knockdown is caused by the interference phenomenon
- Gene Knock Out is caused by NHEJ
- Gene Knock-In is caused by HDR
- Defect of Mismatch repair causes HNPCC
- Defect of nucleotide excision repair causes Xeroderma Pigmentosa & Cockayne Syndrome
- Defect of ds DNA break repair causes Ataxia Telangiectasia, Bloom Syndrome, and Fanconi's anemia