CLINICAL BIOCHEMISTRY ESSENTIALS

MBBS Curriculum

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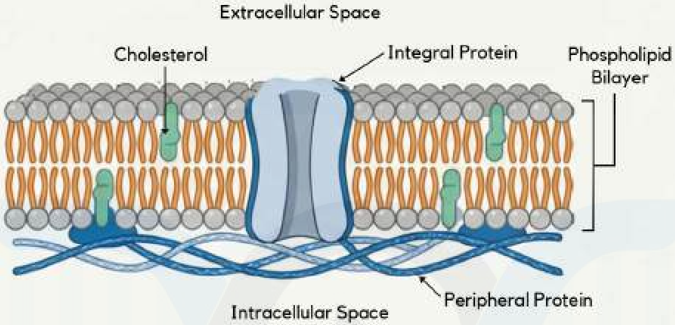
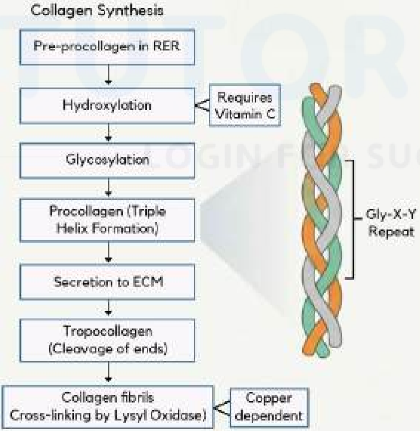
The Cellular Blueprint: **Membrane & Matrix**



- **Fluid Mosaic Model:** A dynamic lipid bilayer with proteins described as "icebergs in a sea of lipids.“
- **Asymmetric Lipid Composition:** Outer leaflet (Phosphatidylcholine, Sphingomyelin) vs. Inner leaflet (Phosphatidylserine, Phosphatidylethanolamine).
- **Cholesterol's Role:** Regulates membrane fluidity.



Clinical Correlations

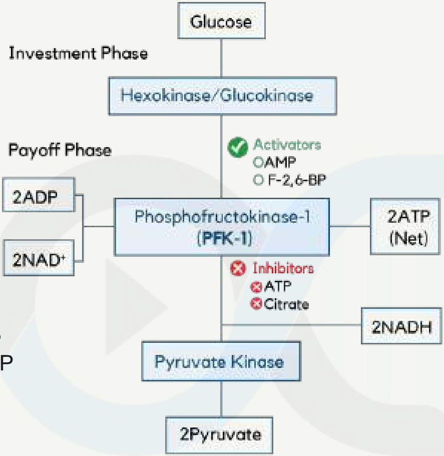
+ *Hereditary Spherocytosis:* Defective Spectrin/Ankyrin ➔ loss of biconcave shape, hemolysis.

+ *Scurvy:* Vitamin C deficiency impairs collagen hydroxylation ➔ bleeding gums.

+ *Menkes Disease:* Copper deficiency impairs Lysyl Oxidase ➔ "kinky hair," defective collagen.

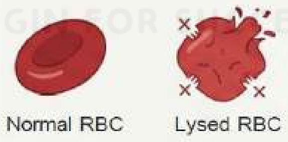
Glycolysis: Universal Fuel for the Cell

- **Location:** Cytosol of all cells
- **Core Function:** The sole source of ATP for erythrocytes (RBCs).
- **Rate-Limiting Enzyme (RLE):** Phosphofructokinase - 1 (PFK-1).
- **Net ATP Yield:** 2 ATP (Anaerobic); 5 or 7 ATP (Aerobic).



Clinical Correlate: Pyruvate Kinase Deficiency

- **The most common glycolytic enzyme defect.**
- **Causes chronic hemolytic anemia.**



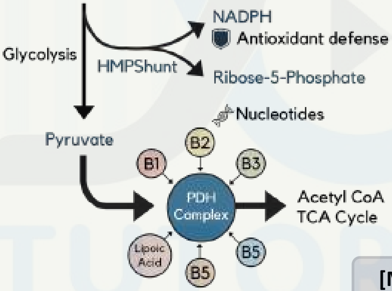
ATP depletion ➔ Na+/K+ pump failure ➔ Cell lysis.

Metabolic Crossroads:
The Fate of Pyruvate & Glucose-6-Phosphate

HMP Shunt (Pentose Phosphate Pathway)

- **Site:** Cytosol. No ATP produced or consumed.
- **Dual Functions:**
  1. **NADPH Production:**
     For fatty acid synthesis & antioxidant defense.
  2. **Ribose-5-Phosphate:** For nucleotide synthesis.

Glucose-6-Phosphate



Pyruvate Dehydrogenase (PDH) Complex

- Irreversibly links glycolysis to the TCA cycle.
- Requires 5 cofactors: Thiamine (B1), Lipoic acid, CoA (B5), FAD (B2), NAO (B3).

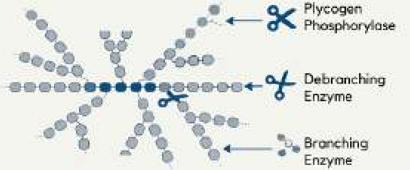
[Mnemonic: 'TLC For Nancy]

Clinical correlate:- : G6PD Deficiency

- Defect in the HMP shunt's rate-limiting enzyme ➔ J.. NADPH.
- RBCs become vulnerable to oxidative damage from triggers (fava beans, sulfa drugs).

Glycogen Storage Disorders:
When Fuel Reserves Fail

- Caused by inherited defects in enzymes of glycogen metabolism.
- Presentation depends on affected tissue (liver vs. muscle).



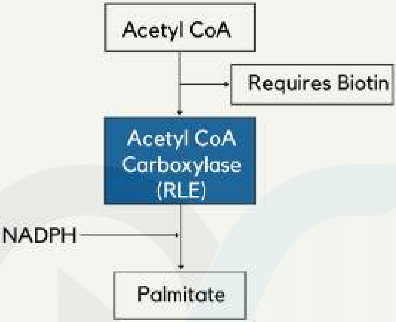
Type	Name	Enzyme defect	Organ(s) involved	Characteristic features
I	Von Glerke's disease (type I glycogenosis)	Glucose 6-phosphatase	Liver, kidney and intestine	Glycogen accumulates in hepatocytes and renal cells. enlarged liver and kidney, fasting hypoglycemia, lactic acidemia, hyperlipidemia; kelosis; gouty arthritis.
II	Pompe's disease	Lysosomal a-1,4 gluco-sidase (acid mallase)	All organs	Glycogen accumulates in lysosomes in almost all the tissues; heart is mostly involved; enlarged liver and heart, nervous system is also affected; death occurs at an early age due to heart failure.
III	Cori's disease (limit dextrinosis, Forbe's disease)	Amylo cr-1.6-glucosidase (debranching enzyme)	Liver, muscle, heart, leucocyles	Branched chain glycogen accumulates; liver enlarged; clinical manilestations are similar but milder compared to von Glerke's disease.
IV	Anderson's disease (amylopectin osis)	Glucosyl 4-6 transterase (branching enzyme)	Most lissues	A rare disease, glycogen with only few branches accumulate; cirrhosis of liver, impairment in liver tunction.
V	MoArdle's disease (type V glycogenosis)	Muscle glycogen phosphorylase	Skeletal muscle	Muscle glycogen stores very high, not available during exercise; subjects cannot perform strenous exercise; suffer from muscle cramps; blood lactate and pyruvate do not increase atter exercise; muscles may get damaged due to inadequate energy supply.
VI	Her's disease	Liver glycogen phosphorylase	Liver	Liver enlarged; liver glycogen cannot form glucose; mild hypoglycemia and ketosis seen.
VII	Tarui's disease	Phosphofructo kinase	Skeletal muscle, erythrocyles	Muscle cramps due to exercise; blood lactate not elevated; hemolysis occurs.

Rare glycogen disorders VIII, IX, X and XI have been identified. They are due to defects in the enzymes concerned with activating and deactivating liver phosphorylase.

Lipid Metabolism:
Building Fats and Alternative Fuels

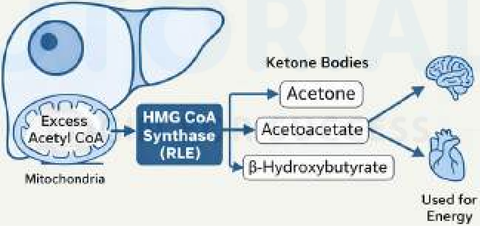
Fatty Acid Synthesis

- **Site:** Cytosol of the liver.
- **Substrate:** Acetyl CoA.
- **Product:** Palmitate (16:0).



Ketone Body Metabolism

- **Synthesis:** Liver mitochondria.
- **Utilization:** Extrahepatic tissues (brain, heart).
- **Critical Concept:** Liver produces ketone bodies but lacks Thiophorase to use them.

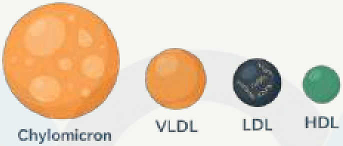


Clinical correlate:- Diabetic Ketoacidosis (DKA)

- Insulin deficiency ➔ massive lipolysis ➔ excess Acetyl CoA shunted into ketogenesis.
- Results in metabolic acidosis and a 'fruity' breath (acetone).

Lipoprotein Transport and the Dyslipidemias

- **Chylomicrons:** Transport dietary triglycerides (Apo 8-48).
- **VLDL:** Transports endogenous triglycerides (Apo 8-100).
- **LDL:** Delivers cholesterol to tissues ("Bad Cholesterol"; Apo 8-100).
- **HDL:** Reverse cholesterol transport ("Good Cholesterol"; Apo A-1).



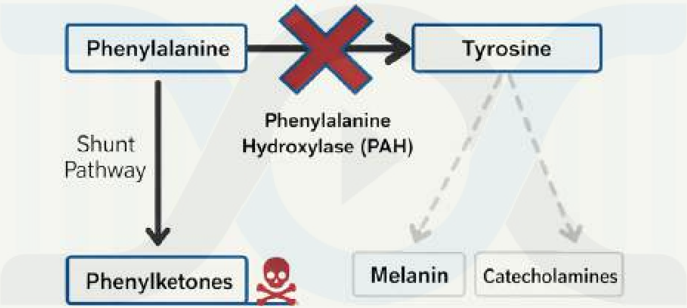
Familial Dyslipidemias

Type	Hyperlipo-proteinemia Type	Increased plasma lipoprotein(s)	Increased plasma lipid (most)	Risk of athero-sclerosis	Suggested treatment
I	Chylomicrons	Triacylglycerols	Deficiency of lipoprotein lipase	May increase	Low fat diet
IIa	LDL	Cholesterol	Deficiency of LDL receptors	Very high (mostly in coronary artery)	Low cholesterol fat diet; cholestyramine
IIb	LDL and VLDL	Triacylglycerols and cholesterol	Overproduction of apo-B	- do -	- do -
III	IDL	Triacylglycerols and cholesterol	Abnormality in apo-E	Very high (mostly in peripheral vessels)	Low fat and low caloric diet; clofibrate
IV	VLDL	Triacylglycerols	Overproduction of TG	May or may not increase	Low fat and low caloric diet; niacin
V	Chylomicrons and VLDL	Triacylglycerols	-	- do -	- do -

Phenylketonuria:
A Classic Inborn Error of Metabolism

The Defect & The Block

- Deficiency of Phenylalanine Hydroxylase (PAH) or its cofactor, BH4.
- Phenylalanine cannot be converted to Tyrosine.
- Tyrosine becomes an essential amino acid.



Clinical Presentation

- **Neurological:** Severe intellectual disability, seizures.
- **Odor:** Musty or mousy body and urine odor.
- **Pigmentation:** Hypopigmentation
  (fair skin, blonde hair, blue eyes).
- **Skin:** Eczema.

Management

- New born screening followed by a lifelong low-phenylalanine diet and tyrosine supplementation. Aspartame must be avoided.

Disorders of Sulfur-Containing Amino Acids

Homocystinuria (Classical)

- **Defect:** Cystathionine [3-Synthase deficiency (Vitamin 86-dependent).
- **Features:** Marfanoid habitus, intellectual disability, **downward** lens dislocation, high risk of **thromboembolism.**

Cystinuria

- **Defect:** Faulty kidney transporter for Cystine, Ornithine, Lysine, Arginine (COLA).
- **Feature:** Recurrent hexagonal cystine kidney stones.

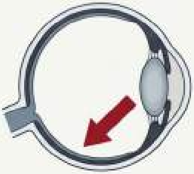
Homocysteine $\xrightarrow{\times}$ Cystathionine

Cystathionine β-Synthase

Homocystinuria vs. Marfan Syndrome: Key Differentiators

Feature	Homocystinuria	Marfan Syndrome
Inheritance	Autosomal Recessive	Autosomal Dominant
Defect	Cystathionine [3-Synthase]	Fibrillin-1
lens Dislocation	**Downward** & Inward	**Upward** & Outward
Intellect	Often impaired	Normal
Major Complication	Thromboembolism	Aortic Root Dilatation

Homocystinuria



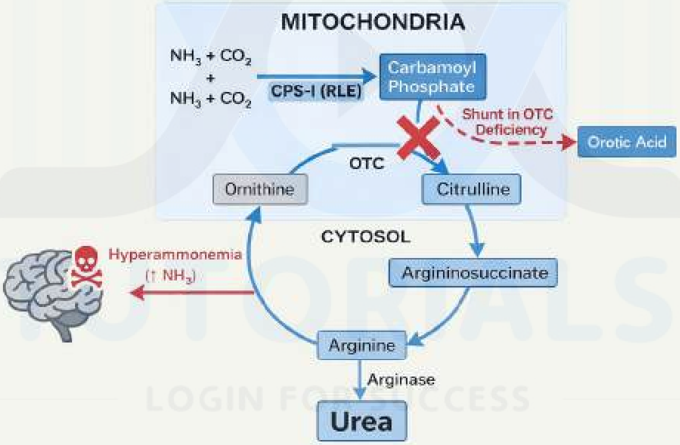
Homocystinuria

Marfan Syndrome

Marfan Syndrome

The Urea Cycle:
Detoxifying Ammonia

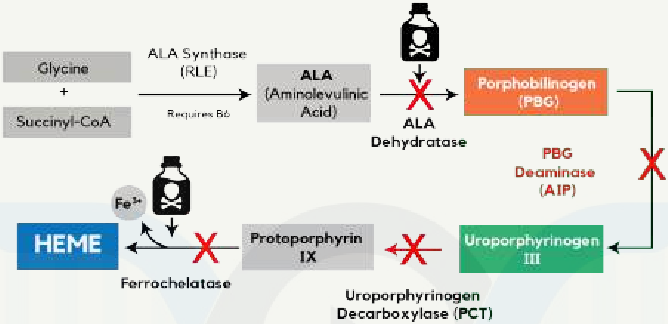
- **Purpose:** To convert toxic ammonia (NH_3) into non-toxic urea for excretion.
- **Site:** Liver only (mitochondria + cytosol).
- **RLE:** Carbamoyl Phosphate Synthetase I (CPS-I).
- **Nitrogen Sources:** Free NH_3 and Aspartate



Clinical correlate: Ornithine Transcarbamylase (OTC) Deficiency

- Most common urea cycle disorder (X-linked).
- Presents with severe, neurotoxic hyperammonemia.
- Key Finding: **Increased urinary orotic acid.**

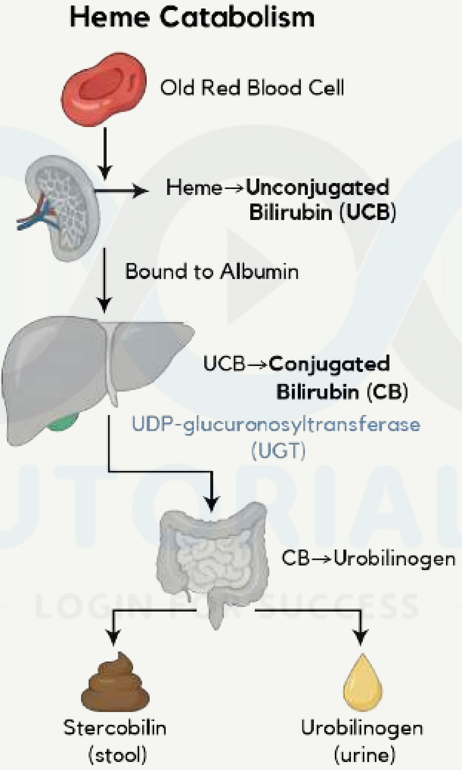
Heme Synthesis and the Porphyrias



Key Porphyrias & Their Features

Type	Porphyria	Enzyme Defect	Key Features
Acute Neuro - psychiatric	Acute Intermittent Porphyria (AIP)	PBG Deaminase	**5P's**  Painful abdomen, Port-wine urine, Polyneuropathy, Psychological disturbance Precipitated by drugs. No photosensitivity
Cutaneous Photosensitive	Porphyria Cutanea Tarda (PCT)	Uroporphyrinogen Decarboxylase	Blistering photosensitivity, hyperpigmentation. Most common porphyria.
Toxic Acquired	Lead Poisoning	Inhibits ALA Dehydratase & Ferro chelatase	Microcytic anemia with basophilic stippling, wrist/foot drop, abdominal pain.

Heme Catabolism and the Clinical Patterns of Jaundice



Differentiating Jaundice by Lab Profile

Type	Cause	UCB	CB	Urine Bilirubin	Urine Urobilinogen	Clinical Signs
Pre-hepatic	Hemolysis	↑↑	Normal	Absent	↑↑	Normal stool/urine color
Hepatic	Liver Damage	↑	↑	Present	Variable	Jaundice
Post-hepatic	Obstruction	Normal /↑	↑↑	Present	Absent/↓	 Dark urine  Pale stools

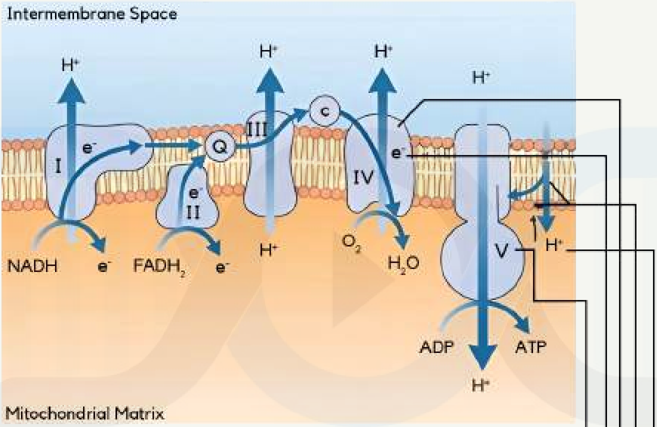
Genetic UGT Defects

- ****Gilbert Syndrome:*** Mildly decreased UGT activity.

X ***Crigler-Najjar Syndrome:*** Complete or partial absence of UGT.

CLINICAL EDITORIAL

The Electron Transport Chain: Inhibitors & Uncouplers



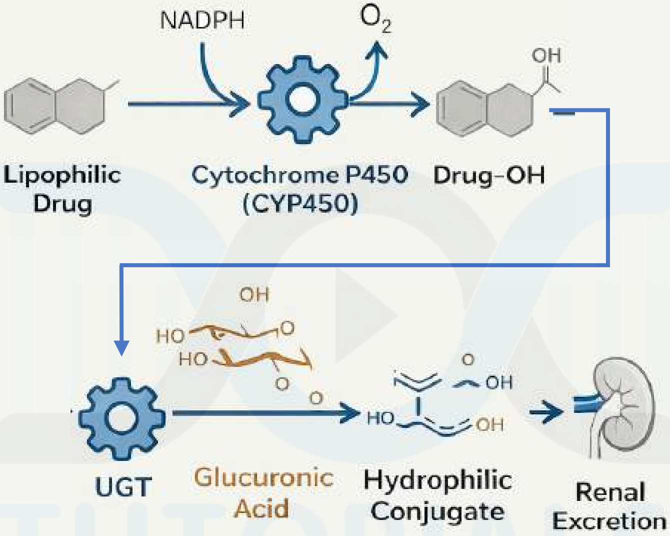
Sites of Action for ETC Inhibitors and Uncouplers

Function	Inhibitor(s)	Complex
Accepts e from NADH	**Rotenone**	I
Transfers e- to Cytochrome c	**Antimycin A**	III
Transfers e to O_2	**Cyanide, CO**	IV
ATP Synthase	**Oligomycin**	V
Dissipates Proton Gradient	**2,4-Dinitrophenol (DNP)**	Uncoupler

Inhibitors: Block electron flow, stopping O_2 consumption and ATP synthesis.

Uncouplers: Dissipate the proton gradient, producing heat. O_2 consumption increases, but ATP synthesis ceases.

Xenobiotics:
The Body's Detoxification System



Clinical Relevance

CYP450 Inducers

- Speed up drug metabolism ➔ therapeutic failure.

Mnemonic: CRAP GPS (Carbamazepine, Rifampicin, Alcohol (chronic), Phenytoin ...)

CYP450 Inhibitors

- Slow down drug metabolism ➔ potential toxicity.

Mnemonic: SICK FACES.COM (Sodium valproate, Isoniazid, Cimetidine, Ketoconazole ...)

The Fat-Soluble Vitamins:
A, D, E, K

Vitamin A (Retinal)

Function

Crucial for **vision,** epithelial differentiation, and immunity

Deficiency

Night blindness, Bitot's spots, Keratomalaci

Vitamin D (Calcitriol)

Function

Primary regulator of **calcium** & phosphate homeostasis for bone health

Deficiency

Rickets in children (bow legs), Osteomalacia in adults (bone pain)

Vitamin E (Tocopherol)

Function

Major lipid-soluble **antioxidant** that protects cell membranes

Deficiency

Hemolytic anemia, spinocerebellar ataxia

Vitamin K

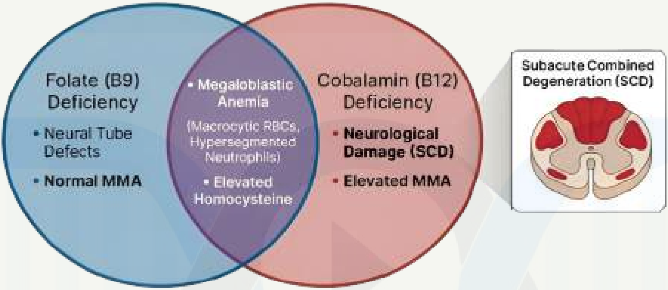
Function

Required cofactor for y-carboxylation of **clouting factors** II, VII, IX, X

Deficiency

Hemorrhagic disease of the newborn; elevated PT and aPTT in adults

Folate & B12:
The Megaloblastic Anemias and the Neurologic Divide



The Clinical Trap

Supplementing with folate alone in a B12-deficient patient will correct the anemia but mask the deficiency, allowing irreversible neurological damage to progress.

NOTES

NOTES

TUTORIALS

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