

Aromatic Amino Acids and Amino Acidurias (Phenylalanine, Tyrosine, Tryptophan, Proline)

? PHENYLALANINE

Overview

- **Essential aromatic amino acid**
- Converted to **tyrosine**, which then forms melanin, thyroid hormones, and catecholamines.

Major Reaction

Phenylalanine ? Tyrosine

Enzyme: Phenylalanine hydroxylase

Cofactor: Tetrahydrobiopterin (**BH?**)

Byproduct: BH? (regenerated by dihydropteridine reductase)

Importance

- First step in **enzymatic pathway to dopamine, adrenaline, noradrenaline, thyroid hormones, melanin**
 - Provides precursor for **fumarate** (glucogenic) and **acetoacetate** (ketogenic)
-

? TYROSINE

Properties

- **Non-essential**, but becomes **conditionally essential** in PKU
- Both **glucogenic & ketogenic**

Functions

- Precursor of:
 - **Melanin**
 - **Catecholamines**
 - **Thyroid hormones (T3, T4)**
 - **Fumarate + Acetoacetate**
 - **Dopa and dopamine**
 - **Norepinephrine & Epinephrine**

? MELANIN SYNTHESIS

Pathway

Tyrosine ? **DOPA** ? **Dopaquinone** ? **Melanin**

Key Enzyme:

Tyrosinase (copper-dependent)

Types of Melanin

- **Eumelanin:** Brown-black
- **Pheomelanin:** Yellow-red

Clinical Notes

1. Albinism:

- Defect in **tyrosinase** ? no melanin
- Pigment absent in skin, eyes, hair

2. Vitiligo:

- Autoimmune destruction of melanocytes (melanin absent *in patches*)

3. Melasma / post-inflammatory pigmentation:

- Excess melanin deposition

? CATECHOLAMINE SYNTHESIS

This is a crucial exam topic.

? Full Pathway

Tyrosine ? DOPA ? Dopamine ? Norepinephrine ? Epinephrine

Step 1: Tyrosine → DOPA

Enzyme: Tyrosine hydroxylase

Cofactor: BH₄

Rate-limiting step

Step 2: DOPA → Dopamine

Enzyme: DOPA decarboxylase

Cofactor: PLP (Vitamin B6)

Step 3: Dopamine → Norepinephrine

Enzyme: Dopamine β-hydroxylase

Cofactor: Vitamin C + Copper

Location: Inside vesicles

Step 4: Norepinephrine → Epinephrine

Enzyme: Phenylethanolamine N-methyltransferase (PNMT)

Methyl donor: SAM

Stimulated by: Cortisol

→ CATECHOLAMINE DEGRADATION

Major enzymes

- **MAO:** Monoamine oxidase
- **COMT:** Catechol-O-methyl transferase

End products

- **Vanillylmandelic acid (VMA):** NE/Epinephrine breakdown
- **Homovanillic acid (HVA):** Dopamine breakdown

Clinical Uses

- High **VMA** ? Pheochromocytoma
- High **HVA** ? Neuroblastoma

? IMPORTANT DISORDERS (from Tyrosine & Catecholamine Pathways)

1. Phenylketonuria (PKU)

Caused by:

- Phenylalanine hydroxylase deficiency **OR**
- BH₄ deficiency

Features

- High phenylalanine
- Intellectual disability
- Seizures

- Musty/mousy odor
 - Hypopigmentation (? tyrosine ? ? melanin)
-

2. Alkaptonuria

Defect: **Homogentisate oxidase**
? Homogentisic acid accumulation

Signs

- Black urine on standing
 - Ochronosis (bluish-black tissues)
 - Early osteoarthritis
-

3. Tyrosinemia Type I

Defect: **Fumarylacetoacetate hydrolase**

Features

- Liver failure
 - Renal tubular dysfunction
 - “Cabbage-like” odor
 - Can lead to hepatocellular carcinoma
-

? Ultra-Short Revision

- Phenylalanine ? tyrosine via **BH⁴-dependent hydroxylase**.
- Melanin requires **tyrosinase** (Cu-dependent).
- Catecholamines: Tyrosine ? DOPA ? Dopamine ? NE ? E.
- PNMT converts NE ? E (needs **SAM** & cortisol).
- PKU ? high phenylalanine, low tyrosine, musty odor.
- Alkaptonuria ? black urine, homogentisate oxidase defect.
- Tyrosinemia I ? liver failure, cabbage odor.

? PHENYLKETONURIA (PKU)

? Cause

Defect in **phenylalanine hydroxylase**

OR

Defect in **BH⁴ (tetrahydrobiopterin)** regeneration.

Phenylalanine ? **cannot convert to tyrosine** ? accumulates.

? Biochemical Results

- ? Phenylalanine

- ? Tyrosine (becomes essential)
- ? Phenylpyruvate, phenylacetate, phenyllactate (ketones)

? Clinical Features

- Severe intellectual disability (if untreated)
- Seizures
- Musty/mousy body odor
- Light hair & skin (? melanin)
- Eczema
- Developmental delay
- Microcephaly

? Investigations

- Newborn screening: **Guthrie test** / tandem mass spectrometry
- Elevated phenylalanine in blood

? Treatment

- **Low phenylalanine diet** (life-long)
- Tyrosine supplementation
- Avoid aspartame
- BH₄ supplementation (sapropterin) in BH₄-responsive cases

? Key Points

- Tyrosine becomes **essential**.
- Mental retardation is **preventable** with newborn screening.
- Musty odor due to **phenylacetate**.

? ALKAPTONURIA

? Cause

Deficiency of **homogentisate oxidase**, an enzyme in the **tyrosine degradation pathway**.

Tyrosine → homogentisate → ? cannot convert further.

? Accumulated Metabolite

Homogentisic acid

? Clinical Features

- **Black urine** on standing (air oxidation)
- **Ochronosis**
 - Bluish-black pigmentation of sclera, ear cartilage, nose
- **Early-onset osteoarthritis** (due to ochronotic pigment deposition in joints)
- Darkening of sweat or diapers

? Diagnosis

- Elevated homogentisic acid in urine
- Characteristic black color on exposure to air/alkali

? Treatment

- Mostly supportive
- High dose **Vitamin C** sometimes offered (questionable value)
- Low phenylalanine/tyrosine diet (milder benefit)
- Nitisinone (NTBC) used experimentally to reduce homogentisate production

? Key Points

- Autosomal recessive
- Pigment deposition = hallmark
- Urine darkens **only after standing**, not fresh.

? ALBINISM

? Definition

A group of disorders with **absent or reduced melanin** due to defects in melanin synthesis.

? Most Common Type

Oculocutaneous albinism Type I

? Cause

Deficiency of **tyrosinase** (Cu-dependent)

? Tyrosine ? cannot convert to **DOPA**

? No melanin

? Clinical Features

- Very light skin, white hair
- Photophobia

- Nystagmus
- Decreased visual acuity
- Increased risk of sunburn, skin cancers
- Normal number of melanocytes, but **lack melanin production**

? Diagnosis

- Clinical appearance
- Ophthalmic signs
- Molecular testing (if required)

? Treatment

- UV protection (sunscreen, clothing)
- Ophthalmologic follow-up
- No specific cure

? Key Points

- Melanocyte number = **normal**
- Enzyme defect ? impaired **melanin synthesis**

- Tyrosinase is key

? Ultra-Short Revision

- **PKU:**

- Phenylalanine hydroxylase or BH₄ defect
- Musty odor, ↑ tyrosine, intellectual disability
- Treat with low Phe diet + tyrosine

- **Alkaptonuria:**

- Homogentisate oxidase defect
- Black urine, ochronosis, early arthritis

- **Albinism:**

- Tyrosinase defect
- Normal melanocytes, ↓ melanin

? TRYPTOPHAN

? Overview

- Aromatic, essential amino acid
- Both **glucogenic (alanine)** and **ketogenic (acetyl-CoA)**
- Precursor of multiple biologically important molecules.

? Major Products of Tryptophan

- Niacin (NAD⁺/NADP⁺)
- Serotonin (5-HT)
- Melatonin
- Kynurenine ? NAD pathway
- Indole ? Indican (excretory product)
- Formylkynurenine ? formate (one-carbon pool)

? Key Requirements

- Niacin synthesis from tryptophan requires:
 - Vitamin B6 (PLP)
 - Riboflavin (FAD)

- **Iron**

- **Hartnup disease** reduces tryptophan absorption ? pellagra-like symptoms.

? NICOTINIC ACID (NIACIN) PATHWAY

? Pathway (Condensed)

Tryptophan ? **Kynurenine** ? **3-Hydroxykynurenine** ? **3-Hydroxyanthranilate** ? **Quinolinate**
? **NAD?** / **NADP?**

? Key Points

- 60 mg tryptophan = 1 mg niacin (approx.)
- Requires **Vitamin B6 (PLP)**
- Deficiency ? **pellagra** ("3 D's": dermatitis, diarrhea, dementia)

? Conditions with Low Niacin Synthesis

- **Hartnup disease** (defective neutral amino acid transport ? ? tryptophan)
- **Carcinoid syndrome** (majority of tryptophan shunted to serotonin pathway)
- **Isoniazid therapy** (B6 deficiency)

? SEROTONIN (5-Hydroxytryptamine, 5-HT)

? Synthesis

Tryptophan ? **5-Hydroxytryptophan** ? **Serotonin (5-HT)**

Enzymes

1. Tryptophan hydroxylase

- Requires **BH?**

2. Aromatic amino acid decarboxylase

- Requires **PLP (Vitamin B6)**

? Location

- **Enterochromaffin cells** of intestine (~90%)
- CNS neurons
- Platelets (uptake only)

? Functions

- Mood regulation
- Sleep and appetite
- Gut motility

- Vasoconstriction
- Precursor for melatonin

? Disorders

Carcinoid Syndrome

- Excess serotonin production by carcinoid tumor
- Features:
 - Diarrhea
 - Flushing
 - Wheezing
 - Right-sided heart lesions
- Investigation: **High urinary 5-HIAA**

? MELATONIN

? Source

- Pineal gland

? Synthesis

Serotonin ? **Melatonin**

Enzymes

- N-acetyltransferase
- Hydroxy-indole-O-methyltransferase (uses **SAM**)

? Functions

- Regulates **sleep–wake (circadian) rhythm**
- Antioxidant
- Modulates reproductive cycles
- Lower at daytime; highest at night

? INDICAN (Indoxyl sulfate)

? Formation

- From **bacterial degradation of tryptophan** in the intestine:
 - Tryptophan ? **Indole** ? absorbed ? liver ? **Indoxyl sulfate (Indican)**
 - Excreted in urine.

Increased Indican

- **Hartnup disease** (poor absorption ? more tryptophan reaches colon)
- Intestinal malabsorption
- Bacterial overgrowth

Diagnostic Significance

- Excess indican ? **blue diaper** (reaction with air/oxidation)
- Seen in tryptophan malabsorption disorders

? Ultra-Short Revision Capsule

- Tryptophan ? **serotonin ? melatonin**
- Tryptophan ? **niacin (needs B6, Fe, FAD)**
- Carcinoid ? serotonin ?, 5-HIAA ?, niacin ?
- Indican ? in tryptophan malabsorption
- Melatonin regulates **circadian rhythm**
- Niacin deficiency ? **pellagra**

? HARTNUP'S DISEASE

? Definition

A hereditary defect of **neutral amino acid transport** in:

- Intestine
- Kidney proximal tubules

Neutral amino acids include:

Tryptophan, Alanine, Serine, Threonine, Valine, Leucine, Isoleucine, Phenylalanine, Tyrosine.

Tryptophan is the most clinically important.

? Biochemical Problem

- ? Absorption and reabsorption of **neutral amino acids**
 - ? Tryptophan availability ? ? Niacin synthesis
 - Results in **secondary pellagra-like syndrome**
-

? Clinical Features

- Dermatitis (sun-exposed areas)
- Diarrhea

- Cerebellar ataxia
 - Mood changes
 - Intermittent episodes triggered by stress/infection
 - Aminoaciduria (neutral amino acids)
-

? Investigations

- Elevated **neutral amino acids** in urine
 - Low niacin deficiency markers
 - Increased **indican** due to colonic bacterial conversion of unabsorbed tryptophan to indole
-

? Treatment

- **High-protein diet**
 - **Niacin/Nicotinamide supplementation**
 - Sun protection
 - Avoid prolonged fasting and stress triggers
-

? PROLINE METABOLISM

? Overview

Proline is a **cyclic imino acid** derived from **glutamate**.

? Synthesis of Proline

Glutamate ? Glutamate semialdehyde ? **Pyrroline-5-carboxylate** ? **Proline**

? Functions

- Essential for **collagen** (gives tensile strength)
- Hydroxyproline helps stabilize collagen triple helix
- Important in wound healing

? HYDROXYPROLINE

? Formation

Proline ? **Hydroxyproline**

Enzyme: Prolyl hydroxylase

Cofactors: Vitamin C, Fe^{2+} , α -ketoglutarate

? Clinical Significance

- **Vitamin C deficiency ? scurvy**
 - Poor collagen hydroxylation

- Bleeding gums, poor wound healing
- Fragile capillaries
- Hydroxyproline is a major urinary marker of **bone turnover**.

? INTER-RELATION OF AMINO ACIDS

Amino acids interconvert through:

? Transamination

- Most amino acids ? glutamate
- ALT and AST use **PLP (Vitamin B6)**

? Deamination

- Removal of NH₂ for urea cycle (mainly via glutamate dehydrogenase)

? Amidation

- Glutamate ? glutamine
- Aspartate ? asparagine

? One-carbon transfers

- Serine ? glycine (THF + B6)
- Methionine ? homocysteine ? cysteine

- Tryptophan ? formate ? one-carbon pool

? Common metabolic intermediates

Many amino acids share key intermediates:

- **Pyruvate:** alanine, serine, cysteine, glycine
- **Oxaloacetate:** aspartate, asparagine
- **?-Ketoglutarate:** glutamate, glutamine, proline
- **Fumarate:** tyrosine, phenylalanine
- **Succinyl-CoA:** valine, isoleucine, methionine, threonine

This forms the metabolic basis for amino acids being:

- Glucogenic
- Ketogenic
- Or both

? AMINO ACIDURIAS (HIGH-YIELD OVERVIEW)

Disorders with abnormal urinary excretion of specific amino acids.

? 1. Phenylketonuria (PKU)

- Phenylalanine hydroxylase defect

- Musty odor, intellectual disability
 - ? Phenylalanine, phenylpyruvate
 - Treat: Low Phe diet, tyrosine supplementation
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? 2. Alkaptonuria

- Homogentisate oxidase defect
 - Black urine, ochronosis, early arthritis
-

? 3. Albinism

- Tyrosinase defect ? melanin absent
 - Normal melanocyte number
-

? 4. Maple Syrup Urine Disease (MSUD)

- Branched-chain ?-ketoacid dehydrogenase defect
 - Maple-syrup odor, lethargy, seizures
 - ? Leucine, isoleucine, valine
-

? 5. Cystinuria

- Renal transport defect of **COLA** amino acids
 - Cystine stones (hexagonal crystals)
-

? 6. Homocystinuria

- CBS deficiency
 - Downward lens dislocation, thrombosis, marfanoid habitus
-

? 7. Cystathioninuria

- Cystathionine γ -lyase defect
 - Usually benign, B6 responsive
-

? 8. Hartnup's Disease

- Neutral aminoaciduria, pellagra-like features
-

? 9. Tyrosinemias (Types I, II, III)

- Defects in downstream tyrosine metabolism
-

- Type I ? severe liver failure

? 10. Indicanuria

- Excess indican excretion
- Seen in Hartnup disease, malabsorption

? Ultra-Short Revision

- Hartnup: neutral amino acids, pellagra-like, ? indican.
- Proline derived from glutamate; hydroxyproline needs vitamin C.
- Amino acids interconvert via transamination and one-carbon transfers.
- Amino acidurias = inherited defects in amino acid metabolism/transport (PKU, MSUD, cystinuria).

? IMPORTANT POINTS TO REMEMBER (WHOLE CHAPTER)

? PHENYLALANINE & TYROSINE PATHWAYS

- **Phenylalanine** is essential; converted to **tyrosine** by *phenylalanine hydroxylase* (needs BH?).

- **Tyrosine** becomes **conditionally essential** in PKU.
- Tyrosine is precursor for:
 - **Melanin**
 - **Catecholamines** (DOPA ? dopamine ? NE ? epinephrine)
 - **Thyroid hormones (T?, T?)**
 - **Fumarate + acetoacetate**
- **BH? deficiency** can mimic classic PKU.
- **Tyrosine degradation defects** ? alkaptonuria, tyrosinemias.

? MELANIN & ALBINISM

- Melanin formed from **tyrosine ? DOPA ? dopaquinone**.
- **Tyrosinase** (Cu-dependent) is key enzyme.
- **Oculocutaneous albinism:** Tyrosinase defect ? absent melanin.
- Melanocyte number is **normal**, melanin formation is defective.

? CATECHOLAMINES

Pathway:

Tyrosine ? **DOPA** ? **Dopamine** ? **Norepinephrine** ? **Epinephrine**

- Rate-limiting enzyme: **Tyrosine hydroxylase**.

- Dopamine β -hydroxylase requires **Vitamin C + Copper**.
- PNMT converts NE $\rightarrow$ E; requires **SAM** and induced by **cortisol**.
- Breakdown products:
 - NE/Epi $\rightarrow$ **VMA**
 - Dopamine $\rightarrow$ **HVA**

? PHENYLKETONURIA (PKU)

- Deficiency of phenylalanine hydroxylase or BH $_4$.
- ? Phenylalanine, ? tyrosine (becomes essential).
- Clinical: Musty odor, seizures, intellectual disability, pale skin.
- Treatment: **Low Phe diet + tyrosine supplementation**.

? ALKAPTONURIA

- Defect of **homogentisate oxidase**.
- Accumulation of homogentisic acid $\rightarrow$ **black urine**, ochronosis, early arthritis.

? TYROSINEMIAS (High-Yield Overview)

- **Type I**: Fumarylacetoacetate hydrolase defect $\rightarrow$ severe liver failure; cabbage-like odor.

- **Type II:** Tyrosine aminotransferase defect ? keratitis, skin lesions.
- **Type III:** Hydroxyphenylpyruvate dioxygenase defect; neurological symptoms.

? TRYPTOPHAN METABOLISM

- Tryptophan is precursor of:
 - **Serotonin**
 - **Melatonin**
 - **Niacin (requires B6, iron, riboflavin)**
 - **Kynurenine pathway intermediates**
 - **Indole ? Indican**
- 60 mg tryptophan ? 1 mg niacin.

? SEROTONIN & MELATONIN

- Serotonin synthesized mainly in **enterochromaffin cells**.
- Carcinoid tumor diverts tryptophan ? serotonin ? **5-HIAA ?**.
- Serotonin ? melatonin in pineal gland.
- Melatonin regulates **sleep–wake cycle**.

? NICOTINIC ACID (NIACIN) PATHWAY

- Derived from tryptophan via **kynurenine** pathway.
- Deficiency (pellagra) seen in:
 - Hartnup disease
 - Carcinoid syndrome
 - Isoniazid therapy (B6 deficiency)

? INDICAN

- Gut bacteria convert tryptophan → indole → liver converts to **indoxyl sulfate (Indican)**.
- Excess indican seen in:
 - **Hartnup disease**
 - Malabsorption
 - Bacterial overgrowth.

? HARTNUP'S DISEASE

- Defective transport of **neutral amino acids** (especially tryptophan).
 - Features: Pellagra-like dermatitis, ataxia, aminoaciduria.
 - ? Indican due to bacterial metabolism of unabsorbed tryptophan.
 - Treat: **High-protein diet + niacin**.
-

? PROLINE & HYDROXYPROLINE

- Proline synthesized from **glutamate**.
- Hydroxyproline formed by **prolyl hydroxylase** (needs **Vitamin C**).
- Hydroxyproline stabilizes **collagen triple helix**.
- Vitamin C deficiency ? **scurvy** (poor collagen stability).

? AMINO ACIDURIAS (HIGH-YIELD LIST)

- **PKU** (phenylalanine hydroxylase defect)
- **Alkaptonuria** (homogentisate oxidase)
- **Cystinuria** (COLA transport defect)
- **Hartnup disease** (neutral AA transport defect)
- **Homocystinuria** (CBS defect)
- **Tyrosinemias (I, II, III)**
- **MSUD** (BCKD defect)

? Ultra-Short Revision for Exams

- Phenylalanine ? Tyrosine (BH? required).
- Tyrosine makes melanin, catecholamines, thyroid hormones.

- PKU = high phenylalanine + low tyrosine + musty odor.
- Alkaptonuria = black urine + ochronosis.
- Albinism = tyrosinase defect.
- Tryptophan makes serotonin, melatonin, niacin.
- Carcinoid = serotonin ?, niacin ?, 5-HIAA ?.
- Hartnup = neutral aminoaciduria + pellagra-like.
- Proline/hydroxyproline essential for collagen (needs vitamin C).

? CLINICAL CASE-BASED QUESTIONS

? 1. Infant with Musty Odor + Seizures + Fair Skin

A 3-month-old infant presents with developmental delay, seizures, and pale skin and hair. Parents report a “musty/mousy” odor.

Blood analysis shows very high **phenylalanine** and low **tyrosine**.

Diagnosis:

Phenylketonuria (PKU)

Clue Summary:

- Musty odor ? phenylacetate
- ? tyrosine ? hypopigmentation

- Progressive intellectual disability if untreated

? 2. Teenager with Black Urine on Standing

A 17-year-old boy notices that his urine turns **black** when left standing. He has chronic back pain and pigmentation of ear cartilage.

Diagnosis:

Alkaptonuria

Key Findings:

- Homogentisate oxidase defect
- Ochronosis
- Early osteoarthritis

? 3. Child with White Hair, Photophobia, and Normal Melanocyte Count

A 4-year-old child has very light skin, white hair, nystagmus, and severe visual impairment. Melanocyte count in skin biopsy is **normal**, but melanin is absent.

Diagnosis:

Oculocutaneous Albinism (Tyrosinase deficiency)

Important:

- Melanocyte number normal
- Tyrosine → melanin conversion blocked

? 4. Infant with Liver Failure + Cabbage-Like Odor

A 6-month-old child presents with failure to thrive, jaundice, renal tubular acidosis, and a characteristic **cabbage-like odor**.

Plasma tyrosine is very high.

Diagnosis:

Tyrosinemia Type I

Reason:

- Fumarylacetoacetate hydrolase defect
- Severe liver/kidney involvement

? 5. Child with Skin Lesions + Corneal Ulcers + High Tyrosine

A 2-year-old has painful corneal erosions, thickened skin on palms/soles, and high serum tyrosine.

Diagnosis:

Tyrosinemia Type II

“Richner–Hanhart syndrome.”

? 6. Young Adult with Episodic Ataxia + Pellagra-Like Rash

A 20-year-old presents with intermittent **ataxia**, psychiatric symptoms, and photosensitive **dermatitis**.

Urine analysis: Elevated **neutral amino acids**.

Increased **indican**.

Diagnosis:

Hartnup Disease

Explanation:

- ? Tryptophan absorption ? ? Niacin ? Pellagra-like symptoms

? 7. Patient with Severe Flushing + Diarrhea + Wheezing

A 35-year-old patient presents with episodic flushing, diarrhea, and wheezing.
Urinary **5-HIAA is massively elevated**.

Diagnosis:

Carcinoid Syndrome

Key Biochemistry:

- Excess serotonin formation
- Tryptophan diverted ? ? niacin ? pellagra risk

? 8. Night-Shift Worker with Sleep Disturbance

A software engineer who works night shifts complains of poor sleep regulation.
Melatonin level is low.

Diagnosis:

Melatonin deficiency due to circadian disruption

Biochemical Link:

- Serotonin ? melatonin (pineal gland)
- Pathway dependent on darkness and suprachiasmatic nucleus signaling

? 9. Child with Blue Diaper Syndrome

A baby's diaper turns **blue** after exposure to air.

Urinary indican is very high.

Diagnosis:

Indicanuria (seen in Hartnup disease/malabsorption)

Reason:

- Tryptophan ? indole (gut bacteria) ? oxidized to blue pigments

? 10. Osteoarthritis in a 35-Year-Old with "Black Ear"

A man in his mid-30s has progressive joint pain.

Ear cartilage appears bluish-black.

Diagnosis:

Alkaptonuria

? 11. Neonate with Persistent Vomiting + Musty Odor After Breastfeeding

Newborn becomes irritable and vomits after feeds.

Musty smell noted.

Phenylalanine is very high.

Diagnosis:

Classic PKU

Importance:

Newborn screening prevents neurological damage.

? 12. Patient with Anxiety + Sweating + High VMA

A 40-year-old woman has episodes of palpitations, sweating, and tremors.
Urine VMA is high.

Diagnosis:

Pheochromocytoma

? 13. Toddler with Brittle Hair + Poor Growth + Low Niacin

A 3-year-old child has alopecia, dermatitis, and diarrhea.
Niacin levels are low.
Carcinoid syndrome is ruled out.

Diagnosis:

Hartnup Disease (tryptophan malabsorption ? niacin deficiency)

? 14. Man with Depression + Low Serotonin + High Kynurenine

A 28-year-old man has chronic depression.
Biochemical testing reveals low serotonin, but normal tryptophan.

Diagnosis:

Increased diversion of tryptophan into kynurenine pathway
(seen in chronic inflammation or vitamin B6 deficiency)

? 15. Infant with Severe Photosensitivity + High Tyrosine

Non-healing corneal ulcers + painful keratoconjunctivitis + palmo-plantar hyperkeratosis.

Diagnosis:

Tyrosinemia Type II

? 16. Man with Low Melatonin + High Cortisol

A stressed executive shows insomnia and altered sleep-wake cycle.

Biochemical Insight:

Cortisol suppresses melatonin synthesis in the pineal gland.

? 17. Elderly Woman with Progressive Joint Degeneration + Urine Turns Brown

She complains of dark urine on standing and chronic arthritis.

Diagnosis:

Alkaptonuria

? 18. Infant on Soy Milk Diet Developing Dermatologic Symptoms

Soy diet ? low tryptophan ? niacin deficiency symptoms.

Diagnosis:

Secondary **pellagra** due to tryptophan deficiency.

? 19. Schizophrenia Patient with High Kynurenic Acid

Kynurenine pathway imbalance contributes to neurotoxicity/neuropsychiatric symptoms.

? 20. Teenager with Normal Phenylalanine Levels but PKU-like Symptoms

Likely **BH?** deficiency, not enzyme defect.

? MCQs — Whole Chapter

1. Phenylalanine ? Tyrosine requires which cofactor?

- A. FAD
- B. NADPH
- C. PLP
- D. **BH?**

Answer: D

2. Tyrosine becomes essential in which disorder?

- A. Alkaptonuria
- B. Homocystinuria
- C. **PKU**
- D. Hartnup disease

Answer: C

3. The enzyme deficient in alkaptonuria is:

- A. Fumarylacetoacetate hydrolase
- B. Homogentisate oxidase
- C. Tyrosine aminotransferase
- D. Tyrosinase

Answer: B

4. A patient's urine turns black after standing. Most likely diagnosis:

- A. MSUD
- B. PKU
- C. **Alkaptonuria**

D. Hartnup disease

Answer: C

5. Tyrosinase is required for synthesis of:

- A. Dopamine
- B. Melatonin
- C. **Melanin**
- D. Indican

Answer: C

6. Which amino acid is precursor of catecholamines?

- A. Tryptophan
- B. Glycine
- C. **Tyrosine**
- D. Serine

Answer: C

7. The rate-limiting enzyme in catecholamine synthesis is:

- A. DOPA decarboxylase
- B. PNMT
- C. Dopamine β -hydroxylase
- D. **Tyrosine hydroxylase**

Answer: D

8. Norepinephrine ? Epinephrine conversion requires:

- A. Vitamin C
- B. Biotin
- C. **SAM**
- D. B12

Answer: C

9. Elevated VMA in urine indicates overproduction of:

- A. Serotonin
- B. **Norepinephrine/Epinephrine**
- C. Dopamine
- D. Melanin

Answer: B

10. Melatonin is synthesized in which organ?

- A. Hypothalamus
- B. Liver
- C. Thyroid
- D. **Pineal gland**

Answer: D

11. Tryptophan ? Serotonin requires which cofactor?

- A. Biotin
- B. B12
- C. **BH?**

D. Vitamin C

Answer: C

12. Carcinoid tumor causes deficiency of:

A. Vitamin C

B. **Niacin**

C. B12

D. Biotin

Answer: B

13. Niacin synthesis from tryptophan requires:

A. Folic acid

B. Vitamin K

C. **Vitamin B6**

D. Vitamin D

Answer: C

14. Pellagra-like symptoms + neutral aminoaciduria suggests:

A. MSUD

B. PKU

C. **Hartnup disease**

D. Cystinuria

Answer: C

15. Excess indican in urine is seen in:

- A. PKU
- B. **Hartnup disease**
- C. Alkaptonuria
- D. MSUD

Answer: B

16. Which metabolite causes black urine in alkaptonuria?

- A. Dopamine
- B. Serotonin
- C. **Homogentisic acid**
- D. Indole

Answer: C

17. Melatonin is synthesized from:

- A. Tyrosine
- B. Alanine
- C. **Serotonin**
- D. Tryptophan only

Answer: C

18. A patient with “musty odor” most likely has defect in:

- A. Homogentisate oxidase
- B. Tyrosinase
- C. **Phenylalanine hydroxylase**

D. MAO

Answer: C

19. High 5-HIAA in urine indicates:

- A. PKU
- B. Tyrosinemia
- C. **Carcinoid syndrome**
- D. Alkaptonuria

Answer: C

20. Vitamin C is cofactor for which catecholamine step?

- A. Tyrosine ? DOPA
- B. DOPA ? Dopamine
- C. **Dopamine ? Norepinephrine**
- D. Norepinephrine ? Epinephrine

Answer: C

21. Tryptophan is BOTH glucogenic and ketogenic. Which products form these pathways?

- A. Succinate & Fumarate
- B. **Alanine & Acetyl-CoA**
- C. Pyruvate & Propionate
- D. Acetoacetate & Citrate

Answer: B

22. Which disorder shows ochronosis?

- A. PKU
- B. Hartnup disease
- C. MSUD
- D. **Alkaptonuria**

Answer: D

23. Which hormone induces PNMT enzyme?

- A. TSH
- B. Insulin
- C. GH
- D. **Cortisol**

Answer: D

24. Requirements for proline hydroxylation are:

- A. B12 + Mg^{2+}
- B. **Vitamin C + Fe^{2+}**
- C. Biotin + ATP
- D. FAD + NADH

Answer: B

25. Blue diaper syndrome is due to excess:

- A. VMA
- B. Phenylacetate
- C. **Indican**

D. HVA

Answer: C

26. A baby with cataracts + skin lesions + high tyrosine likely has:

- A. Hartnup disease
- B. PKU
- C. **Tyrosinemia Type II**
- D. MSUD

Answer: C

27. Which of the following becomes essential in PKU?

- A. Valine
- B. Leucine
- C. **Tyrosine**
- D. Serine

Answer: C

28. A lab report shows high HVA in urine. This indicates excess breakdown of:

- A. Serotonin
- B. **Dopamine**
- C. Tyrosine
- D. Tryptophan

Answer: B

29. The first step in melanin synthesis is:

- A. Tyrosine ? Dopamine
- B. Tyrosine ? Indole
- C. **Tyrosine ? DOPA**
- D. DOPA ? Epinephrine

Answer: C

30. A patient with insomnia + low melatonin likely has decreased activity of:

- A. Tyrosine hydroxylase
- B. **Hydroxy-indole-O-methyltransferase**
- C. MAO
- D. COMT

Answer: B

? VIVA VOCE – AROMATIC AMINO ACIDS & AMINO ACIDURIAS

1. What is the precursor of tyrosine?

Phenylalanine.

2. Which cofactor is required for conversion of phenylalanine ? tyrosine?

BH? (Tetrahydrobiopterin).

3. What happens to tyrosine in PKU?

It becomes **essential**, because its synthesis from phenylalanine is blocked.

4. Name two hormones formed from tyrosine.

Thyroxine (T₄) and epinephrine.

5. What is the rate-limiting step of catecholamine synthesis?

Tyrosine → DOPA via tyrosine hydroxylase.

6. Which enzyme converts dopamine → norepinephrine?

Dopamine β-hydroxylase.

7. Which cofactor does dopamine β-hydroxylase require?

Vitamin C (and copper).

8. What converts norepinephrine → epinephrine?

PNMT (Phenylethanolamine N-methyltransferase).

9. Which hormone induces PNMT?

Cortisol.

10. What is the breakdown product of dopamine?

HVA (Homovanillic acid).

11. What is the breakdown product of norepinephrine/epinephrine?

VMA (Vanillylmandelic acid).

12. Tyrosinase deficiency leads to which condition?

Albinism.

13. Is melanocyte number normal in albinism?

Yes. The defect is in **melanin synthesis**, not melanocyte count.

14. What gives the musty odor in PKU?

Phenylacetate.

15. Which enzyme is defective in alkaptonuria?

Homogentisate oxidase.

16. What is ochronosis?

Bluish-black pigmentation of cartilage seen in **alkaptonuria**.

17. Which amino acid produces serotonin?

Tryptophan.

18. Which cofactor is required for serotonin synthesis?

BH? for tryptophan hydroxylase, and **PLP** for decarboxylation.

19. Where is most serotonin produced?

Enterochromaffin cells of intestine.

20. What is the urinary marker for serotonin excess?

5-HIAA.

21. What disorder produces high 5-HIAA levels?

Carcinoid syndrome.

22. Melatonin is synthesized from which compound?

Serotonin.

23. Where is melatonin produced?

Pineal gland.

24. Tryptophan forms which vitamin?

Niacin (Vitamin B₃).

25. Niacin synthesis from tryptophan requires which vitamin?

Vitamin B₆.

26. What is the classic triad of pellagra?

Dermatitis, diarrhea, dementia.

27. Which disorder mimics pellagra due to tryptophan deficiency?

Hartnup disease.

28. What is the defect in Hartnup disease?

Defective transport of **neutral amino acids** (including tryptophan).

29. Why is indican increased in Hartnup disease?

Unabsorbed tryptophan ? converted to **indole** ? **indican**.

30. What causes blue diaper syndrome?

Excess **indican** oxidizing in the diaper.

31. Name the enzyme involved in hydroxylation of proline.

Prolyl hydroxylase.

32. Which vitamin is required for proline and lysine hydroxylation?

Vitamin C.

33. What happens to collagen when vitamin C is deficient?

Poor hydroxylation ? **scurvy** (bleeding, poor wound healing).

34. Which tyrosinemia presents with cabbage-like odor?

Tyrosinemia Type I.

35. Which tyrosinemia presents with corneal ulcers?

Tyrosinemia Type II.

36. What is the major product of catecholamine breakdown in neuroblastoma?

HVA.

37. What disorder shows black urine on standing?

Alkaptonuria.

38. Why does alkaptonuric urine turn black only after standing?

Homogentisic acid **oxidizes in air.**

39. What is the amino acid precursor for thyroid hormones?

Tyrosine.

40. What causes neurological damage in PKU?

Accumulated **phenylalanine** interferes with brain myelination.