MEDICAL EDUCATION RESOURCE

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: BH?
Rate-limiting step

Step 2: DOPA ? Dopamine

Enzyme: DOPA decarboxylase
Cofactor: PLP (Vitamin B6)

Step 3: Dopamine ? Norepinephrine

Enzyme: Dopamine ?-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**
- BH? 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 **BH?-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 **BH? (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
- BH? supplementation (sapropterin) in BH?-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 BH? 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.

? Clinical Notes

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, Fe²?, ?-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 NH? 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

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

? PHENYLKETONURIA (PKU)

- Deficiency of phenylalanine hydroxylase or BH?.
- ? 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 ? **black urine**, ochronosis, early arthritis.

? TYROSINEMIAS (High-Yield Overview)

- **Type I**: Fumarylacetoacetate hydrolase defect ? 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 + palmoplantar 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 ?-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. Trytophan 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 (T?) and **epinephrine**.

---

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

Tyrosine ? DOPA via tyrosine hydroxylase.

---

6. Which enzyme converts dopamine ? norepinephrine?

Dopamine ?-hydroxylase.

---

7. Which cofactor does dopamine ?-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 B?).

---

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.