"Amino Acids: Degradation and Synthesis"

I. Overview

A. General Process of Amino Acid Degradation

- Involves removal of the α-amino group.
- Followed by catabolism of the resulting α-keto acids (carbon skeletons).

B. Convergence of Degradation Pathways

- The degradation pathways of various amino acids converge to form seven intermediate products:
    - Oxaloacetate
    - Pyruvate
    - α-Ketoglutarate
    - Fumarate
    - Succinyl coenzyme A (CoA)
    - Acetyl CoA
    - Acetoacetate

C. Fate of Intermediate Products

- These products directly enter the pathways of intermediary metabolism, resulting in:
    - Synthesis of glucose
    - Synthesis of ketone bodies
    - Synthesis of lipids
    - Production of energy through their oxidation to carbon dioxide (CO_2) via the tricarboxylic acid (TCA) cycle

Nonessential vs Essential Amino Acids

A. Nonessential Amino Acids

- Can be synthesized in sufficient amounts from:
    - Intermediates of metabolism
    - Or, in specific cases:
        - Cysteine and Tyrosine are synthesized from essential amino acids

B. Essential Amino Acids

- Cannot be synthesized (or synthesized in sufficient amounts) by humans.

- Therefore, must be obtained from the diet.

- Required for normal protein synthesis to occur.

Clinical Correlation

A. Genetic Defects

- Genetic defects in the pathways of amino acid metabolism can cause serious disease.

II. Glucogenic and Ketogenic Amino Acids

- Amino acids can be classified as glucogenic, ketogenic, or both.

- Classification is based on which of the seven intermediates are produced during their catabolism

A. Glucogenic Amino Acids

- Defined as: Amino acids whose catabolism yields pyruvate or one of the intermediates of the TCA cycle

- These intermediates are:
    - Substrates for gluconeogenesis (see p. 129)
    - Capable of giving rise to the net synthesis of glucose in the liver and kidney

Gluconeogenic Potential

- Intermediates such as pyruvate and TCA cycle compounds support gluconeogenesis.
- Therefore, glucogenic amino acids → glucose synthesis.

B. Ketogenic Amino Acids

- Defined as: Amino acids whose catabolism yields either acetyl CoA (directly, without pyruvate as intermediate) or acetoacetate (or its precursor acetoacetyl CoA)

Ketone Body Production

- Acetoacetate is one of the ketone bodies, which include:
    - Acetoacetate
    - 3-hydroxybutyrate
    - Acetone

Exclusively Ketogenic Amino Acids

- Leucine and Lysine are the only exclusively ketogenic amino acids found in proteins
- Their carbon skeletons are not substrates for gluconeogenesis
- Therefore, they cannot give rise to the net synthesis of glucose

Classification of Amino Acids

(Note: Some amino acids can become conditionally essential; e.g., supplementation with glutamine and arginine has been shown to improve outcomes in patients with trauma, postoperative infections, and immunosuppression.)

	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

III. Amino Acid Carbon Skeleton Catabolism

- Catabolic pathways of amino acids are organized based on which of the seven intermediates is produced from a particular amino acid.

A. Amino Acids That Form Oxaloacetate

1. Asparagine

- Hydrolyzed by: Asparaginase
- Reaction yields:
  - Ammonia (NH_3)
  - Aspartate

2. Aspartate

- Converted to its corresponding ketoacid by transamination
- Product formed: Oxaloacetate

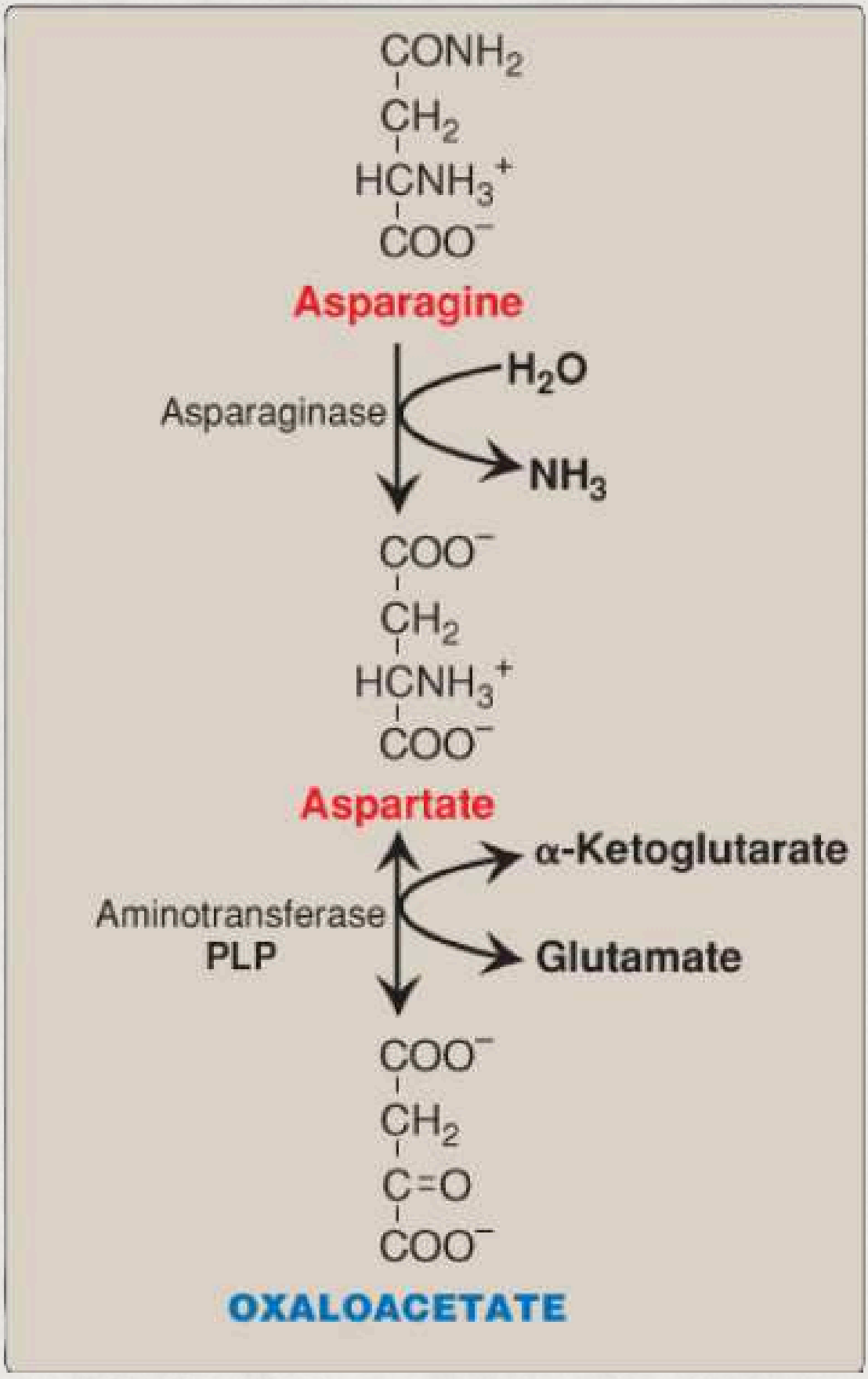
Clinical Note: Leukemia and Asparaginase Therapy

- Some rapidly dividing leukemic cells are unable to synthesize sufficient asparagine to support their growth.
- Therefore, asparagine becomes an essential amino acid for these cells.
- These cells require asparagine from the blood.

Therapeutic Strategy

- Asparaginase (which hydrolyzes asparagine to aspartate) can be administered systemically.
- Effect: Lowers the level of asparagine in plasma
- Outcome: Deprives leukemic cancer cells of a required nutrient, inhibiting their growth.

Metabolism of Asparagine and Aspartate



B. Amino Acids That Form α-Ketoglutarate via Glutamate

These amino acids are catabolized to glutamate, which is then converted to α-ketoglutarate either by transamination or oxidative deamination.

1. Glutamine

- Enzyme: Glutaminase
- Reaction:
  - Glutamine → Glutamate + Ammonia (NH_3)
- Glutamate → α-Ketoglutarate:
  - By transamination
  - Or oxidative deamination via glutamate dehydrogenase

2. Proline

- Proline → Glutamate:
  - Via oxidation

- Glutamate → α-Ketoglutarate:
    - By transamination
    - Or oxidative deamination

3. Arginine

- Enzyme: Arginase
- Reaction:
    - Arginine → Ornithine + Urea
    - (Note: Occurs primarily in the liver as part of the urea cycle)
- Ornithine → α-Ketoglutarate:
    - Through a pathway with glutamate semialdehyde as an intermediate

4. Histidine

- Step 1: Oxidatively deaminated by histidase
- → Produces urocanic acid

- Step 2:
    - Urocanic acid → N-formiminoglutamate (FIGLU)
- Step 3:
    - FIGLU donates formimino group to tetrahydrofolate (THF)
    - Leaves glutamate, which is degraded as described above

Clinical Notes

a. Histidinemia

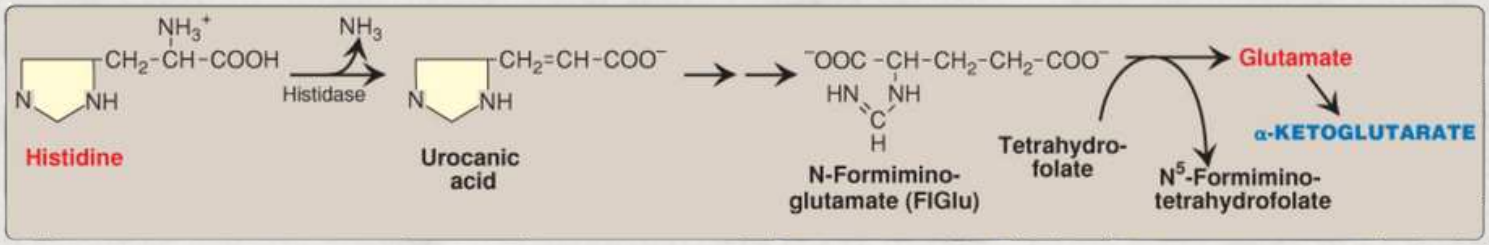
- Cause: Deficiency of histidase
- Result: Elevated levels of histidine in blood and urine
- Type: Relatively benign inborn error of metabolism

b. FIGLU Excretion Test for Folic Acid Deficiency

- In folic acid deficiency, increased urinary excretion of FIGLU

- Especially after ingestion of a large dose of histidine
- Use: Diagnosing folic acid deficiency

Degradation of Histidine

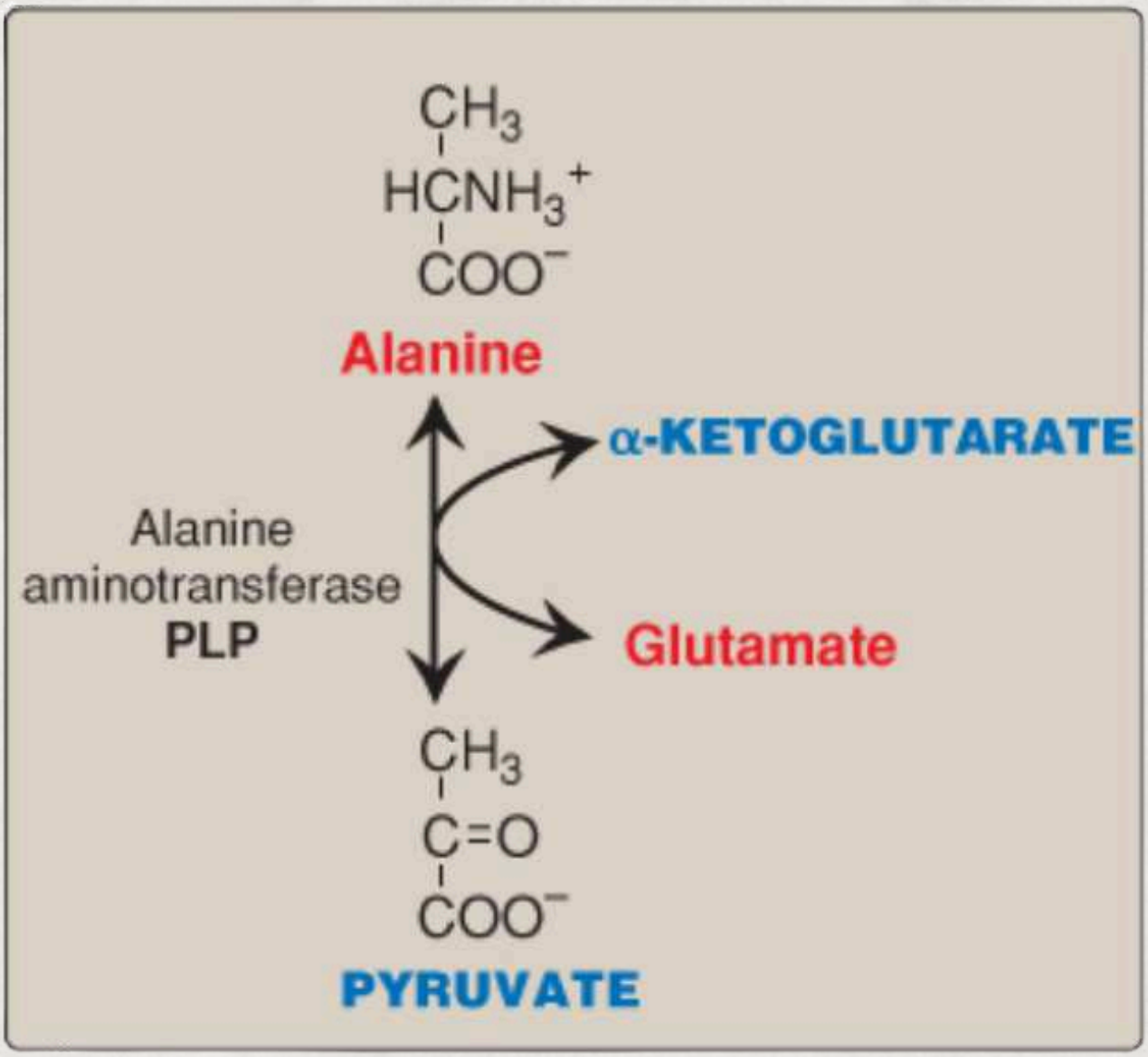


C. Amino Acids That Form Pyruvate

1. Alanine

- Reaction:
  - Alanine loses its amino group by transamination
  - → Forms pyruvate
- Note:
  - Tryptophan catabolism produces alanine, and therefore, pyruvate

Transamination of Alanine to Pyruvate.



2. Serine

- Conversion to Glycine:
    - Serine → Glycine
    - As THF becomes N^5,N^{10}-methylenetetrahydrofolate (N^5,N^{10}-MTHF)

- Conversion to Pyruvate:
    - Serine → Pyruvate

3. Glycine

- Conversion to Serine:
    - Glycine → Serine
    - Via reversible addition of a methylene group from N^5,N^{10}-MTHF
- Oxidation:
    - Glycine → CO_2 and ammonia (NH_3)
    - By the glycine cleavage system
- Deamination to Glyoxylate:
    - Enzyme: D-amino acid oxidase
    - Glycine → Glyoxylate
- Fate of Glyoxylate:
    - Can be oxidized to oxalate
    - Or transaminated back to glycine

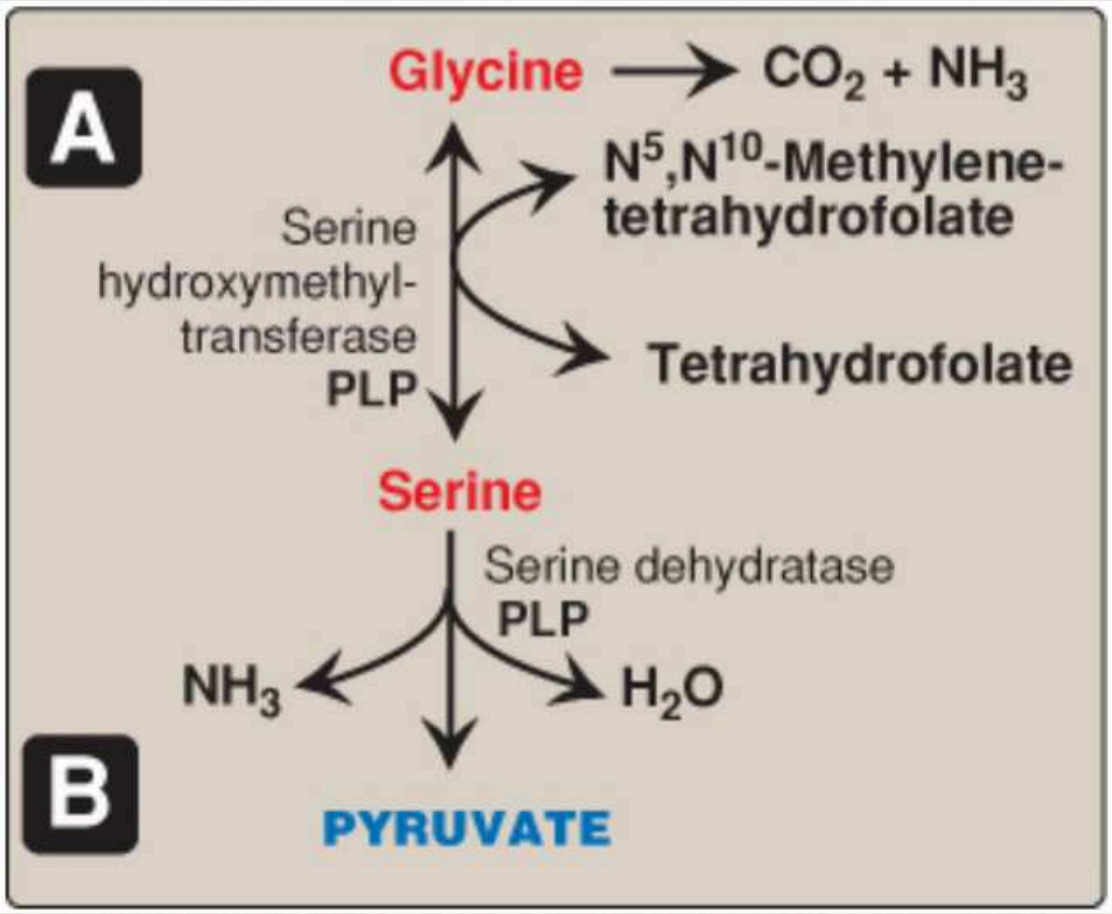
Clinical Note: Primary Oxaluria Type I

- Cause: Deficiency of glyoxylate transaminase in liver peroxisomes

- Consequence:

    - Overproduction of oxalate
    - Formation of oxalate stones
    - Leads to kidney damage

A: Interconversion of Serine and Glycine and Oxidation of Glycine. B: Dehydration of Serine to Pyruvate



4. Cysteine

- Desulfurization reaction:
    - Cysteine → Pyruvate
- Note:
    - Sulfate released during the reaction can be used to synthesize:
        - 3′-Phosphoadenosine-5′-phosphosulfate (PAPS)
        - PAPS is an activated sulfate donor to a variety of acceptors
- Oxidation product:
    - Cysteine can also be oxidized to its disulfide derivative, cystine

5. Threonine

- Conversion to Pyruvate:
    - Threonine → Pyruvate
    - Occurs in most organisms

- Note:
    - This is a minor pathway (at best) in humans

D. Amino Acids That Form Fumarate

1. Phenylalanine and Tyrosine

- Initial step:
    - Hydroxylation of phenylalanine → Tyrosine
    - Enzyme: Phenylalanine hydroxylase (PAH)
    - Cofactor required: Tetrahydrobiopterin (BH_4)
    - Reaction is irreversible

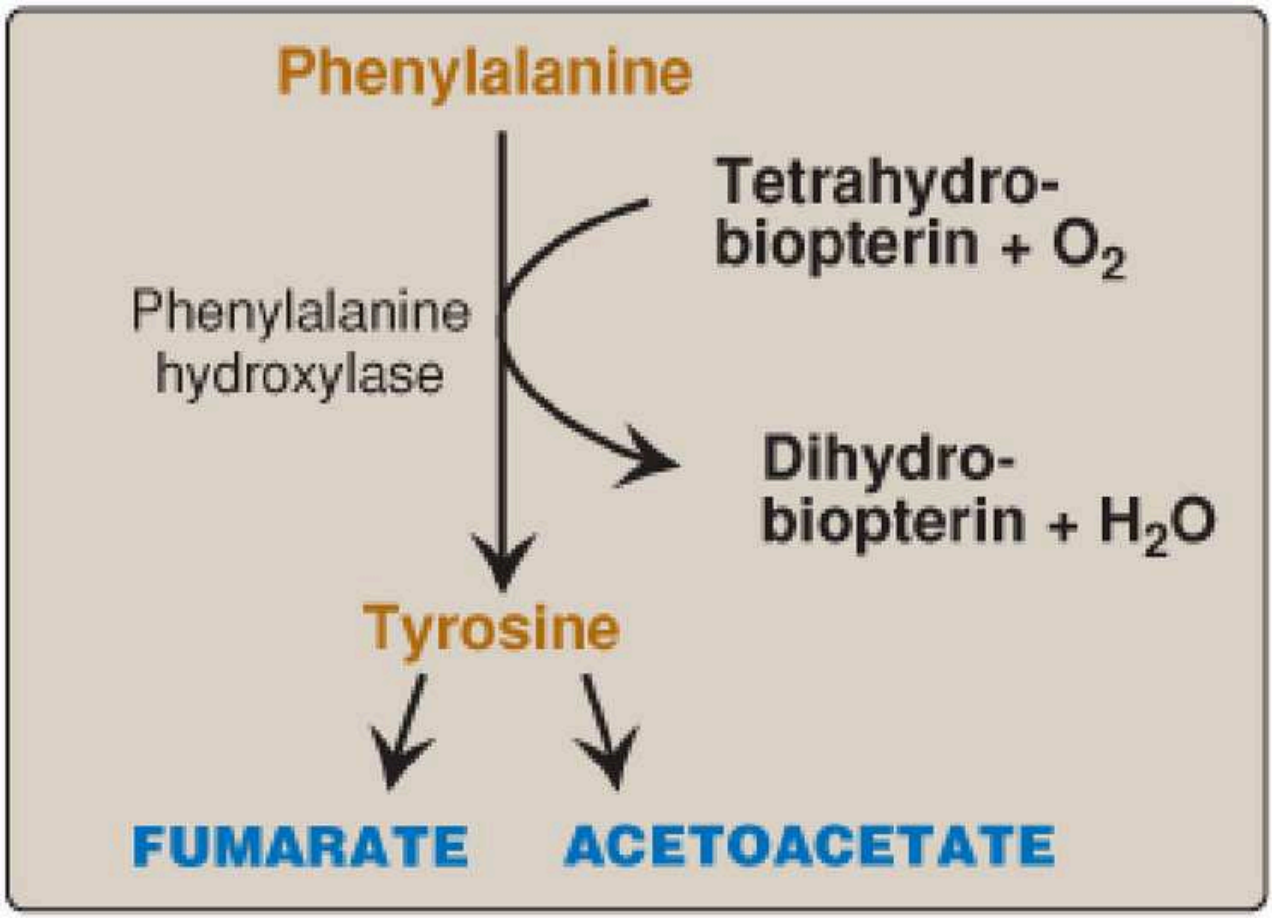
- Metabolic convergence:
    - This reaction initiates phenylalanine catabolism
    - Phenylalanine and tyrosine metabolism merge
    - Ultimately leads to formation of:
        - Fumarate
        - Acetoacetate

- Conclusion:
    - Phenylalanine and tyrosine are both glucogenic and ketogenic

2. Inherited Deficiencies in Phenylalanine and Tyrosine Metabolism

Deficiency	Enzyme Involved	Resulting Condition
Enzyme in phenylalanine metabolism	Phenylalanine hydroxylase (PAH)	Phenylketonuria (PKU)
Enzyme in tyrosine metabolism	Fumarylacetoacetate hydrolase (Type I)	Tyrosinemia
Enzyme in homogentisate pathway	Homogentisate oxidase	Alkaptonuria
Melanin synthesis enzymes	Tyrosinase	Albinism

Degradation of Phenylalanine



E. Amino Acids That Form Succinyl CoA: Methionine

- Methionine is one of four amino acids that form succinyl CoA.

- It is a sulfur-containing amino acid and deserves special attention because:

    - It is converted to S-adenosylmethionine (SAM)
    - → The major methyl group donor in one-carbon metabolism
    - It is the source of homocysteine (Hcy)

- → A metabolite associated with atherosclerotic vascular disease and thrombosis

1. S-Adenosylmethionine (SAM) Synthesis

- Reaction:
  - Methionine condenses with ATP
  - → Forms S-adenosylmethionine (SAM)
- Compound Characteristics:
  - High-energy compound
  - Unusual because it contains no phosphate
- Energy Source:
  - Formation of SAM is driven by hydrolysis of all three phosphate bonds in ATP

2. Activated Methyl Group

- SAM Structure:
  - The methyl group attached to sulfur is activated

- Methyl Transfer:
    - Transferred by methyltransferases to a variety of acceptors such as:
        - Norepinephrine in the synthesis of epinephrine
- Typical Transfer Targets:
    - Nitrogen atoms (e.g., epinephrine synthesis)
    - Oxygen atoms (e.g., epinephrine degradation)
    - Carbon atoms (e.g., methylation of cytosine)
- Reaction Product:
    - S-adenosylhomocysteine (SAH)
    - A simple thioether, analogous to methionine
- Energetics:
    - The loss of free energy makes methyl transfer essentially irreversible

3. S-Adenosylhomocysteine (SAH) Hydrolysis

- After methyl group donation:
    - SAH is hydrolyzed to:
        - Homocysteine (Hcy)
        - Adenosine

Fates of Homocysteine (Hcy):

- If methionine is deficient:
    - Hcy is remethylated to methionine
- If methionine stores are adequate:
    - Hcy enters the transsulfuration pathway
    - Converted to cysteine

a. Methionine Resynthesis

- Reaction:
    - Homocysteine (Hcy) accepts a methyl group from N^5-methyltetrahydrofolate (N^5-methyl-THF)

- Cofactor required: Methylcobalamin, a coenzyme derived from vitamin B_{12}

- Mechanism:

    - Methionine synthase transfers the methyl group from the B_{12} derivative to Hcy
    - This regenerates methionine
    - Cobalamin is remethylated from N^5-methyl-THF

b. Cysteine Synthesis

- Enzyme: Cystathionine β-synthase

- Reaction sequence:

    a. Hcy condenses with serine → cystathionine
    b. Cystathionine is hydrolyzed → α-ketobutyrate + cysteine

- Cofactor required: Vitamin B_6

- Net effect:

    - Serine → Cysteine
    - Hcy → α-ketobutyrate

- Further conversion:
    - α-Ketobutyrate is oxidatively decarboxylated → Propionyl CoA
    - Propionyl CoA → Succinyl CoA
- Nutritional classification:
    - Because Hcy is synthesized from methionine, an essential amino acid,
    - → Cysteine is not essential if sufficient methionine is available

4. Relationship of Homocysteine to Vascular Disease

- Elevated plasma Hcy levels:
    - Promote oxidative damage
    - Cause inflammation
    - Lead to endothelial dysfunction
    - Act as an independent risk factor for:
        - Occlusive vascular diseases
        - Cardiovascular disease (CVD)
        - Stroke

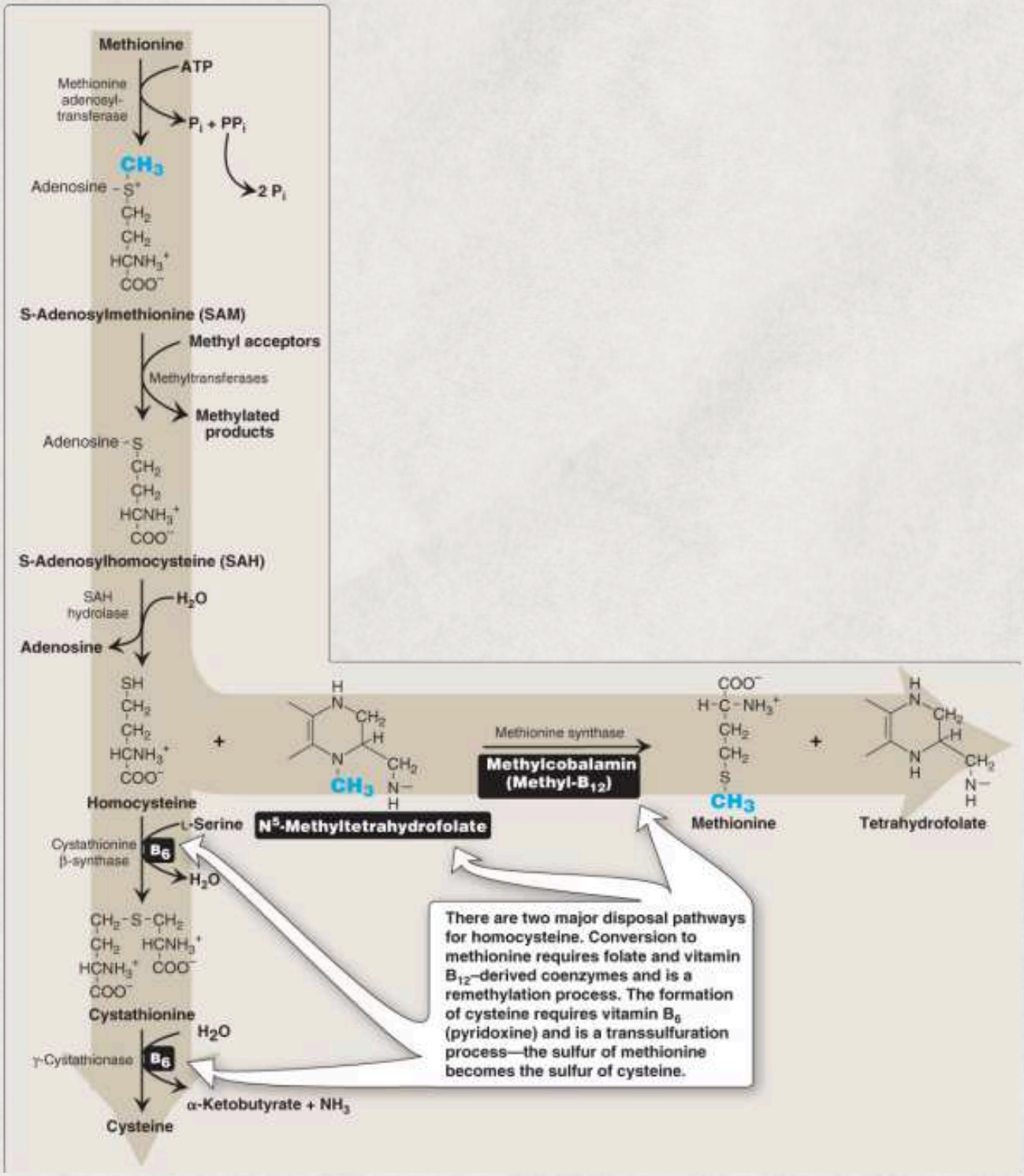
- Prevalence:
    - Mild elevations (hyperhomocysteinemia) seen in ~7% of the population
- Epidemiologic findings:
    - Plasma Hcy levels are inversely related to:
        - Folate
        - Vitamin B_{12}
        - Vitamin B_6
    - These three vitamins are involved in the conversion of Hcy to:
        - Methionine
        - Cysteine
- Supplementation findings:
    - Supplementation with these vitamins reduces circulating Hcy levels
    - However, in patients with established CVD, vitamin therapy does not decrease cardiovascular events or death

Clinical Note: Classic Homocystinuria

- Large elevations in plasma Hcy can occur due to:
    - Rare deficiencies in cystathionine β-synthase
    - Enzyme of the transsulfuration pathway
- Condition: Classic homocystinuria
    - Characterized by severe hyperhomocysteinemia (>100 μmol/L)
- Also caused by:
    - Deficiencies in the remethylation reaction
    - → Also result in a rise in Hcy

Degradation and Resynthesis of Methionine

(Note: The resynthesis of methionine from homocysteine is the only reaction in which tetrahydrofolate both carries and donates a methyl [-CH3] group. In all other reactions, SAM is the methyl group carrier and donor.)



Homocysteine and Pregnancy

- In pregnant women:
    - Elevated Hcy levels usually indicate a deficiency in folic acid
    - This is associated with an increased incidence of neural tube defects in the fetus
        - Example: Improper closure, as in spina bifida
- Prevention:
    - Periconceptual supplementation with folate reduces the risk of neural tube defects

F. Other Amino Acids That Form Succinyl CoA

- Amino acids:
    - Valine, isoleucine, and threonine
- End product:
    - Succinyl CoA
        - A TCA cycle intermediate
        - A gluconeogenic compound

- Note:
    - Succinyl CoA is metabolized to pyruvate

1. Valine and Isoleucine

- Branched-chain amino acids (BCAAs)
- Catabolic sequence:
    - → Propionyl CoA
    - → Methylmalonyl CoA
    - → Succinyl CoA
- Cofactors required:
    - Biotin
    - Vitamin B_{12}

2. Threonine

- Conversion pathway:
    - Dehydrated to α-ketobutyrate
    - → Converted to propionyl CoA
    - → Converted to succinyl CoA

- Summary:
    - Propionyl CoA is generated by the catabolism of:
        - Methionine
        - Valine
        - Isoleucine
        - Threonine
- Additional Note:
    - Propionyl CoA is also generated by the oxidation of odd-numbered fatty acids

G. Amino Acids That Form Acetyl CoA or Acetoacetyl CoA

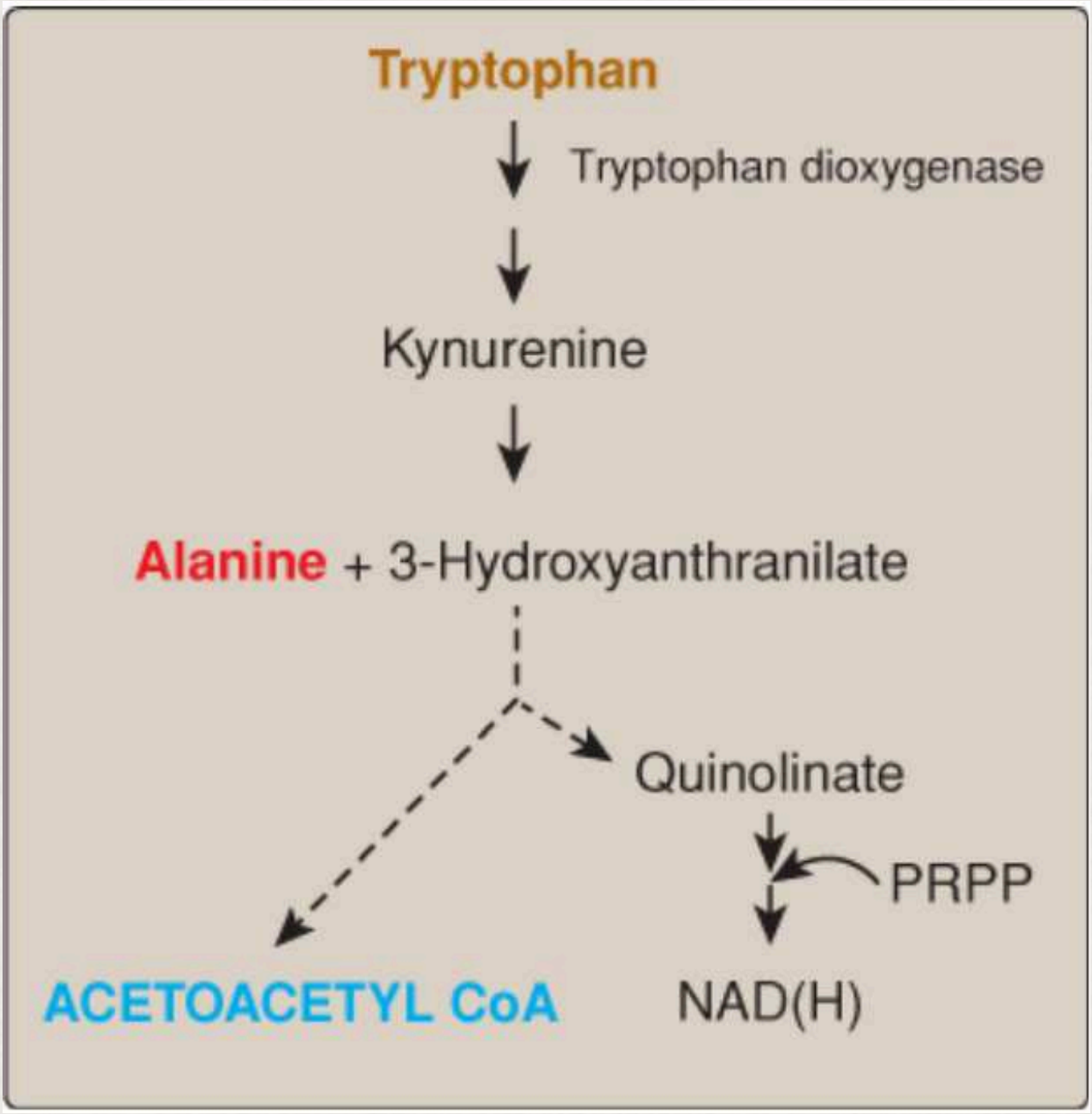
- Direct formation without pyruvate as intermediate
- Amino acids:
    - Tryptophan
    - Leucine
    - Isoleucine
    - Lysine
    - (Also: Phenylalanine and Tyrosine → Acetoacetate)

- Total:
    - Six amino acids are partly or wholly ketogenic

1. Tryptophan

- Dual classification:
    - Glucogenic and ketogenic
- Catabolic products:
    - Alanine
    - Acetoacetyl CoA
- Additional Note:
    - Quinolinate from tryptophan catabolism is used in the synthesis of:
        - Nicotinamide adenine dinucleotide (NAD)

Metabolism of Tryptophan by the Kynurenine Pathway



2. Leucine

- Classification:
    - Exclusively ketogenic
- Catabolic products:
    - Acetyl CoA
    - Acetoacetate
- Initial catabolic reactions:
    - The first two reactions in the catabolism of:
        - Leucine
        - Isoleucine
        - Valine
    - Are catalyzed by enzymes that use all three BCAAs (or their derivatives) as substrates

3. Isoleucine

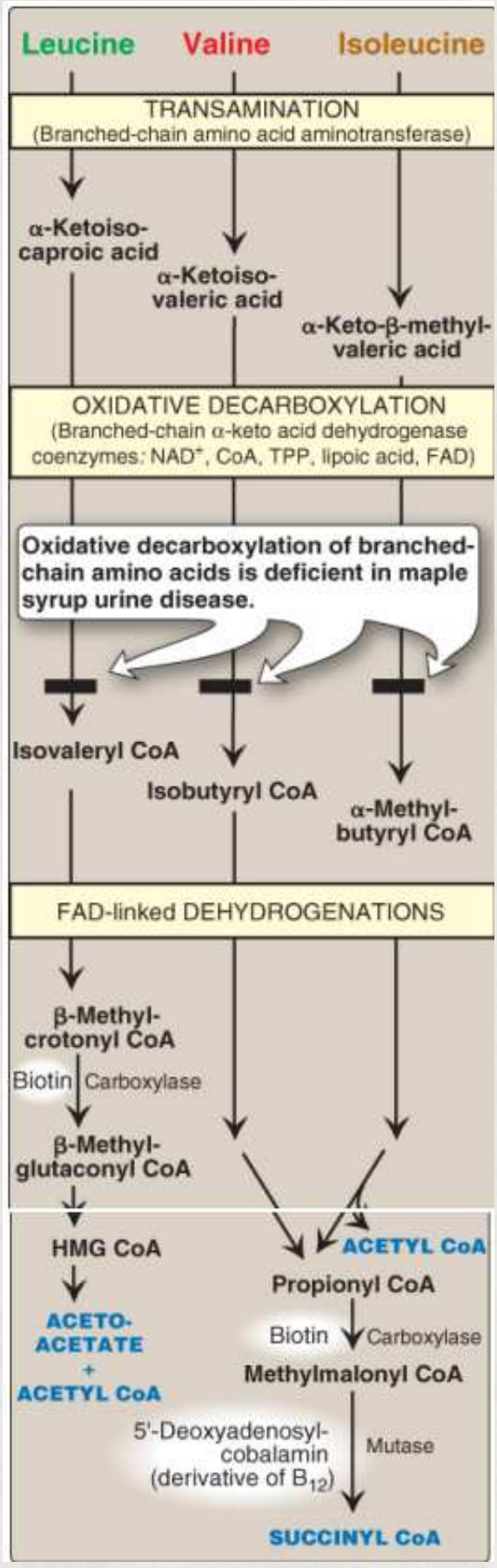
- Classification:
    - Both ketogenic and glucogenic

- Catabolic products:
    - Acetyl CoA
    - Propionyl CoA

Note:

- β-Methylcrotonyl CoA carboxylase is one of four biotin-requiring carboxylases.
- The other three are pyruvate carboxylase, acetyl CoA carboxylase, and propionyl CoA carboxylase.

Degradation of Leucine, Valine, and Isoleucine



4. Lysine

- Classification:
    - Exclusively ketogenic
- Unique feature:
    - Neither of lysine's amino groups undergoes transamination as the first step in catabolism
- End product:
    - Acetoacetyl CoA

H. Branched-Chain Amino Acid (BCAA) Degradation

- Amino acids:
    - Isoleucine, leucine, and valine
    - All are essential amino acids
- Tissue specificity:
    - Unlike other amino acids, BCAAs are catabolized primarily in peripheral tissues, especially muscle
    - Not primarily in the liver

- Shared degradation pathway:
    - BCAAs have a similar route of degradation

1. Transamination

- Reaction:
    - Amino groups of all three BCAAs are transferred to α-ketoglutarate
- Enzyme:
    - Branched-chain amino acid aminotransferase
- Requirements and location:
    - Vitamin B_6-requiring
    - Expressed primarily in skeletal muscle

2. Oxidative Decarboxylation

- Reaction:
    - Carboxyl groups of the α-keto acids (from leucine, valine, isoleucine) are removed

- Enzyme complex:
    - Branched-chain α-keto acid dehydrogenase (BCKD) complex
- Deficiency consequence:
    - Enzymatic deficiency → Maple syrup urine disease (MSUD)
- Coenzymes required:
    - Thiamine pyrophosphate (TPP)
    - Lipoic acid
    - Oxidized flavin adenine dinucleotide (FAD)
    - NAD^+
    - Coenzyme A (CoA)
- Products:
    - NADH is produced

- Note:
    - Reaction is similar to:
        - Pyruvate → Acetyl CoA (by PDH complex, see p. 120)
        - α-Ketoglutarate → Succinyl CoA (by α-ketoglutarate dehydrogenase complex)
    - Dihydrolipoyl dehydrogenase (Enzyme 3 / E3) is identical in all three complexes

3. Dehydrogenations

- Reaction:
    - Oxidation of BCKD products forms:
        - α-β-unsaturated acyl CoA derivatives
        - $FADH_2$
- Comparison:
    - Analogous to FAD-linked dehydrogenation in β-oxidation of fatty acids

- Clinical Note:
    - Deficiency in dehydrogenase specific for isovaleryl CoA:
        - Leads to neurologic problems
        - Associated with "sweaty feet" odor in body fluids

4. End Products of BCAA Catabolism

Amino Acid	End Products	Classification
Isoleucine	Acetyl CoA + Succinyl CoA	Ketogenic and glucogenic
Valine	Succinyl CoA	Glucogenic
Leucine	Acetoacetate + Acetyl CoA	Ketogenic

Ketogenic

- Additional Products:
    - NADH (from decarboxylation)
    - $FADH_2$ (from dehydrogenation)

- Additional Note:
    - BCAA catabolism in muscle also results in:
        - Synthesis and export of glutamine and alanine into the blood

IV. Folic Acid and Amino Acid Metabolism

Overview of One-Carbon Metabolism

- Some synthetic pathways require the addition of single-carbon groups
- → Exist in various oxidation states:
    - Formyl
    - Methenyl
    - Methylene
    - Methyl
- These single-carbon units can be transferred from carrier compounds to target molecules that are:
    - Being synthesized
    - Being modified

- Primary carrier compounds:
    - Tetrahydrofolate (THF)
    - S-adenosylmethionine (SAM)
- "One-carbon pool"
    - Refers to the single-carbon units attached to THF and SAM

Important Clarification:

- Carbon dioxide (CO_2) from bicarbonate (HCO_3^-):
    - Is carried by vitamin biotin
    - Biotin is a prosthetic group for most carboxylation reactions
    - Biotin is not considered part of the one-carbon pool
- Clinical Note:
    - Defects in the ability to add/remove biotin from carboxylases
    - → Result in multiple carboxylase deficiency
    - Treatment: Biotin supplementation

A. Folic Acid and One-Carbon Metabolism

- Active form of folic acid:
    - Tetrahydrofolate (THF)
- THF formation:
    - Produced from folate by the enzyme dihydrofolate reductase
    - Two-step reaction
    - Requires 2 molecules of NADPH (nicotinamide adenine dinucleotide phosphate)
- Binding sites of one-carbon unit on THF:
    - Attached to:
        - N^5
        - N^{10}
        - Or both N^5 and N^{10}

Clinical Note: Folate Deficiency

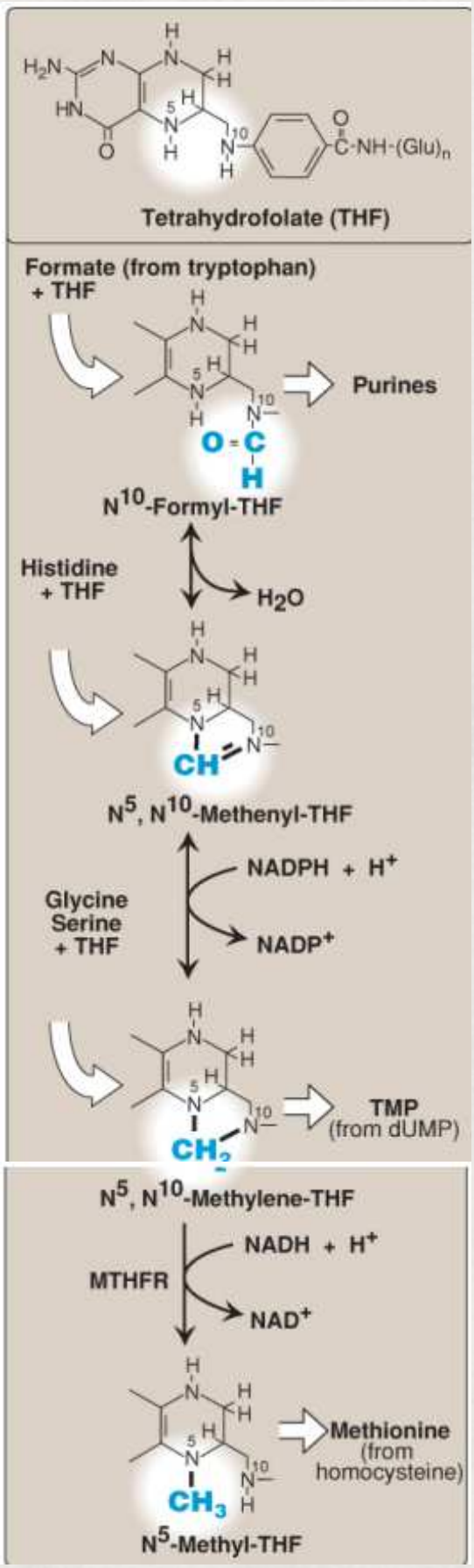
- Presents as:
    - Megaloblastic anemia

- Cause:
    - Decreased availability of:
        - Purines
        - Thymidine monophosphate (dTMP)
- Impact:
    - Impaired DNA synthesis

Note:

- N5 ,N10 -MethenylTHF also arises from N5 -formimino-THF

Summary of the Interconversions and Uses of THF



V. Biosynthesis of Nonessential Amino Acids

Overview

- Nonessential amino acids are synthesized from:
    - Intermediates of metabolism
    - Or, in special cases:
        - Tyrosine from phenylalanine
        - Cysteine from methionine
- Note:
    - Some amino acids found in proteins, such as:
        - Hydroxyproline
        - Hydroxylysine
    - Are produced by posttranslational modification (i.e., after incorporation into a protein) of their precursor (parent) amino acids

A. Synthesis from α-Keto Acids

Amino acids synthesized via transamination:

Amino Acid	α-Keto Acid Precursor
Alanine	Pyruvate
Aspartate	Oxaloacetate
Glutamate	α-Ketoglutarate

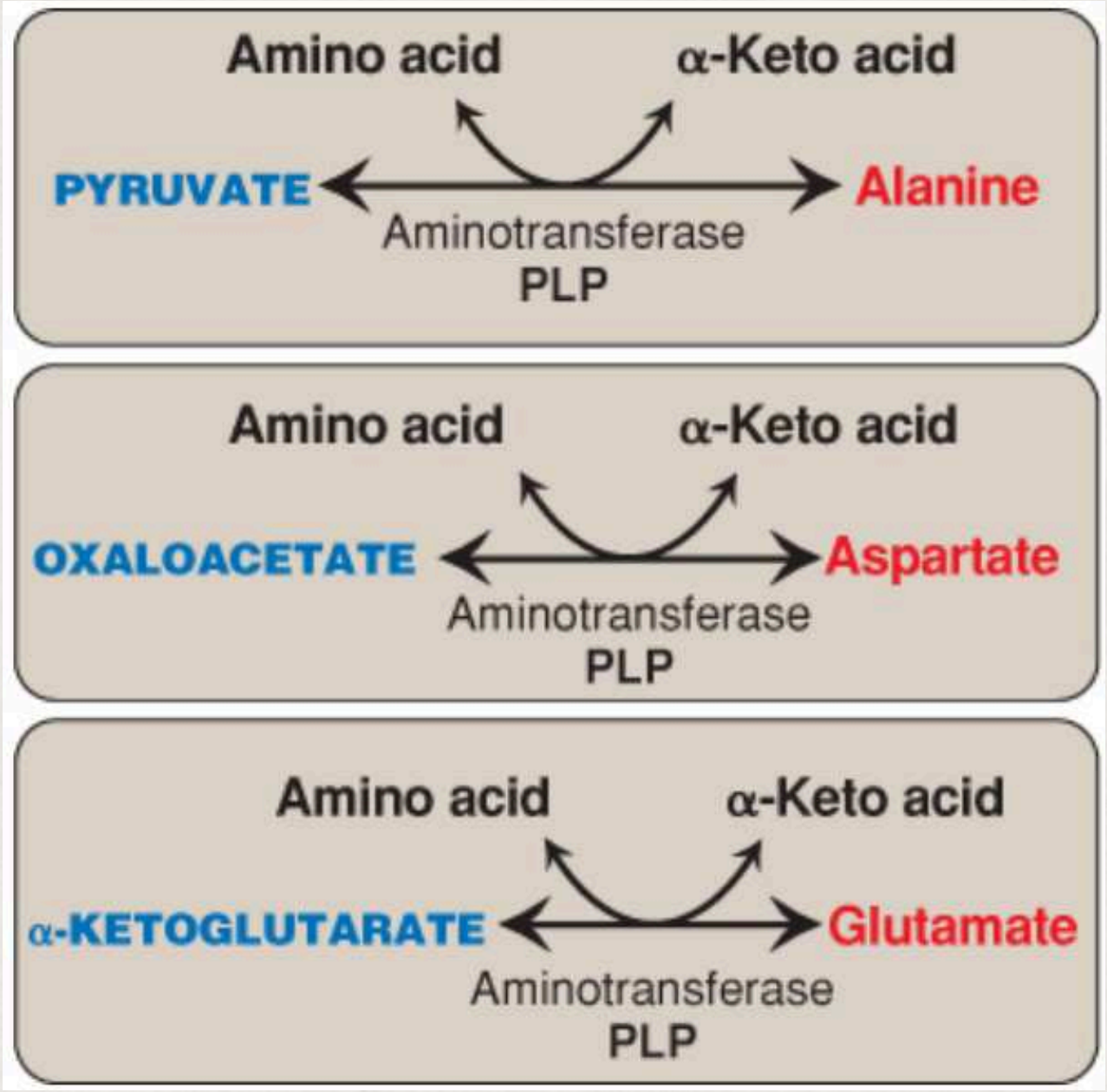
Reaction type:

- Transamination reactions
- These are the most direct biosynthetic pathways

Additional note on Glutamate:

- Can also be synthesized by:
    - Reversal of oxidative deamination
    - Catalyzed by glutamate dehydrogenase
    - Occurs when ammonia levels are high

Formation of Alanine, Aspartate, and Glutamate from the Corresponding α-Keto Acids by Transamination



B. Synthesis by Amidation

1. Glutamine

- Structure detail:
    - Contains an amide linkage with ammonia at the γ-carboxyl
- Synthesis reaction:
    - Formed from glutamate and ammonia
    - Enzyme: Glutamine synthetase
- Reaction characteristics:
    - Driven by hydrolysis of ATP
- Functions of this reaction:
    - Produces glutamine for protein synthesis
    - Serves as a major mechanism for ammonia transport in a nontoxic form

2. Asparagine

- Structure detail:
    - Contains an amide linkage with ammonia at the β-carboxyl
- Synthesis reaction:
    - Formed from aspartate
    - Enzyme: Asparagine synthetase
    - Amide donor: Glutamine
- Reaction requirements:
    - Requires ATP
    - Reaction has an equilibrium far in favor of amide synthesis

C. Proline

- Precursor:
    - Synthesized from glutamate via glutamate semialdehyde

- Reactions involved:
    - Cyclization
    - Reduction
- Note:
    - Glutamate semialdehyde can also be transaminated to ornithine

D. Serine, Glycine, and Cysteine

- The biosynthetic pathways of these three amino acids are interconnected

1. Serine

- Primary source:
    - Arises from 3-phosphoglycerate, a glycolytic intermediate

- Synthesis steps:
    - 3-phosphoglycerate is:
        - Oxidized to 3-phosphopyruvate
        - Transaminated to 3-phosphoserine
        - Hydrolyzed (phosphate ester removed) to form serine
- Alternative synthesis route:
    - Can also be formed from glycine via:
        - Hydroxymethyl group transfer
        - Enzyme: Serine hydroxymethyltransferase
        - One-carbon donor: N^5,N^{10}-methylenetetrahydrofolate (N^5,N^{10}-MTHF)
- Special Note - Selenocysteine (Sec):
    - Synthesized from serine and selenium
    - Occurs while serine is attached to tRNA
    - Sec = 21st genetically encoded amino acid
    - Found in ~25 human proteins, including:
        - Glutathione peroxidase
        - Thioredoxin reductase

2. Glycine

- Synthesis from serine:
    - Involves removal of hydroxymethyl group
    - Enzyme: Serine hydroxymethyltransferase
    - One-carbon acceptor: Tetrahydrofolate (THF)

3. Cysteine

- Synthesis steps:
    a. Homocysteine (Hcy) combines with serine to form cystathionine
    b. Cystathionine is hydrolyzed to:
        - α-Ketobutyrate
        - Cysteine

- Source of homocysteine:
    - Derived from methionine

- Nutritional dependency:
    - Since methionine is essential,
    - cysteine synthesis requires adequate dietary methionine

E. Tyrosine

- Synthesis from:
  - Phenylalanine
- Enzyme:
  - Phenylalanine hydroxylase (PAH)
- Reaction requirements:
  - Molecular oxygen (O_2)
  - Coenzyme: Tetrahydrobiopterin (BH_4)
    - Synthesized from guanosine triphosphate (GTP)
- Reaction mechanism:
  - One atom of O_2 → hydroxyl group of tyrosine
  - Other atom → reduced to water
  - During the reaction:
    - BH_4 is oxidized to dihydrobiopterin (BH_2)
    - BH_2 is regenerated to BH_4 by:
      - Enzyme: Dihydropteridine reductase
      - Cofactor: NADH

- Nutritional note:
    - Like cysteine, tyrosine is nonessential only if sufficient phenylalanine is available in the diet

VI. Amino Acid Metabolism Disorders

Overview

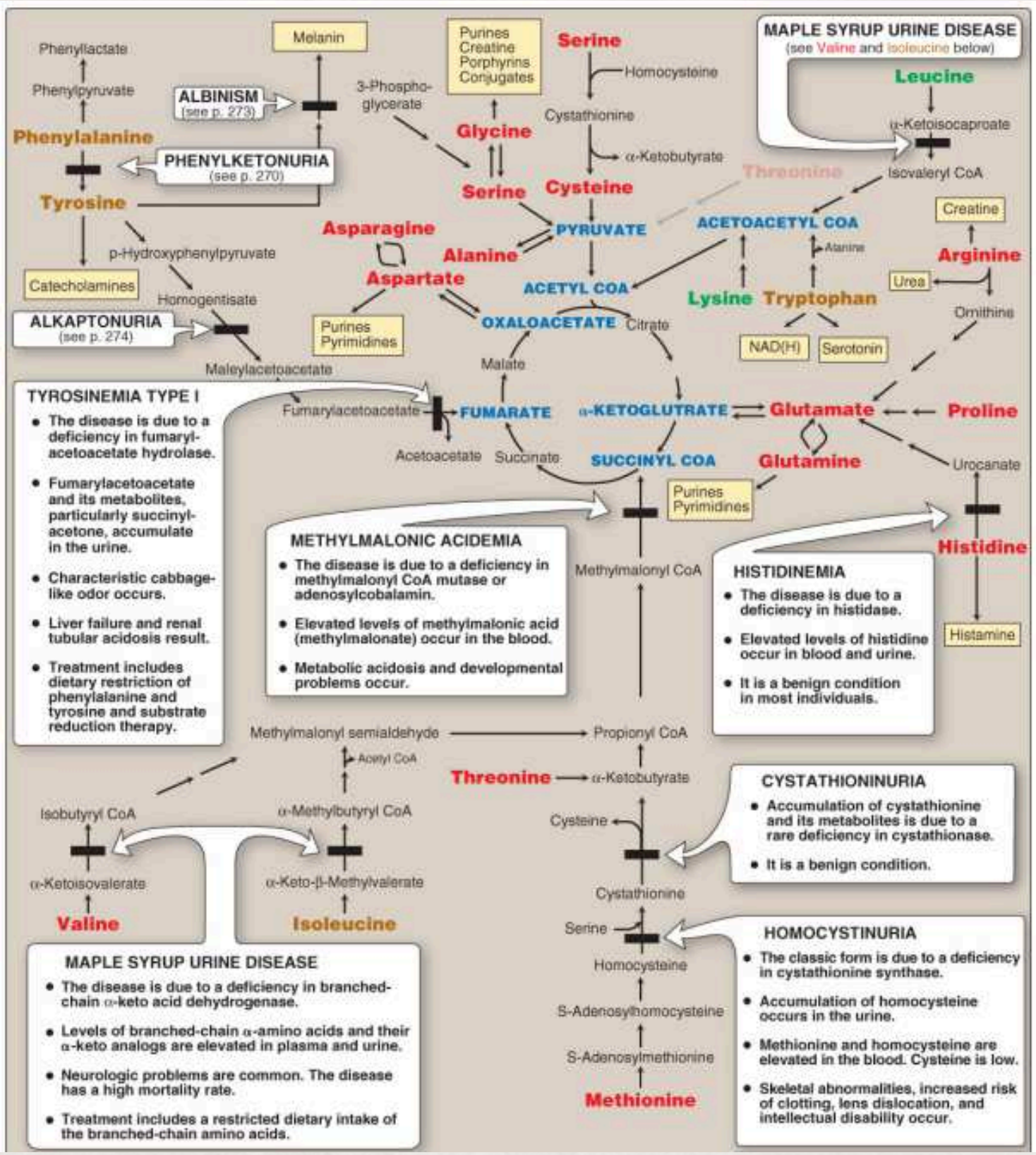
- These are single-gene disorders, part of the inborn errors of metabolism
- Cause:
    - Generally caused by loss-of-function mutations in enzymes involved in amino acid metabolism
- Enzyme activity effects:
    - May be expressed as:
        - Total loss of enzyme activity
        - More frequently: Partial deficiency in catalytic activity

- Consequences (if untreated):
    - Nearly always result in:
        - Intellectual disability
        - Or other developmental abnormalities
    - Due to harmful accumulation of metabolites

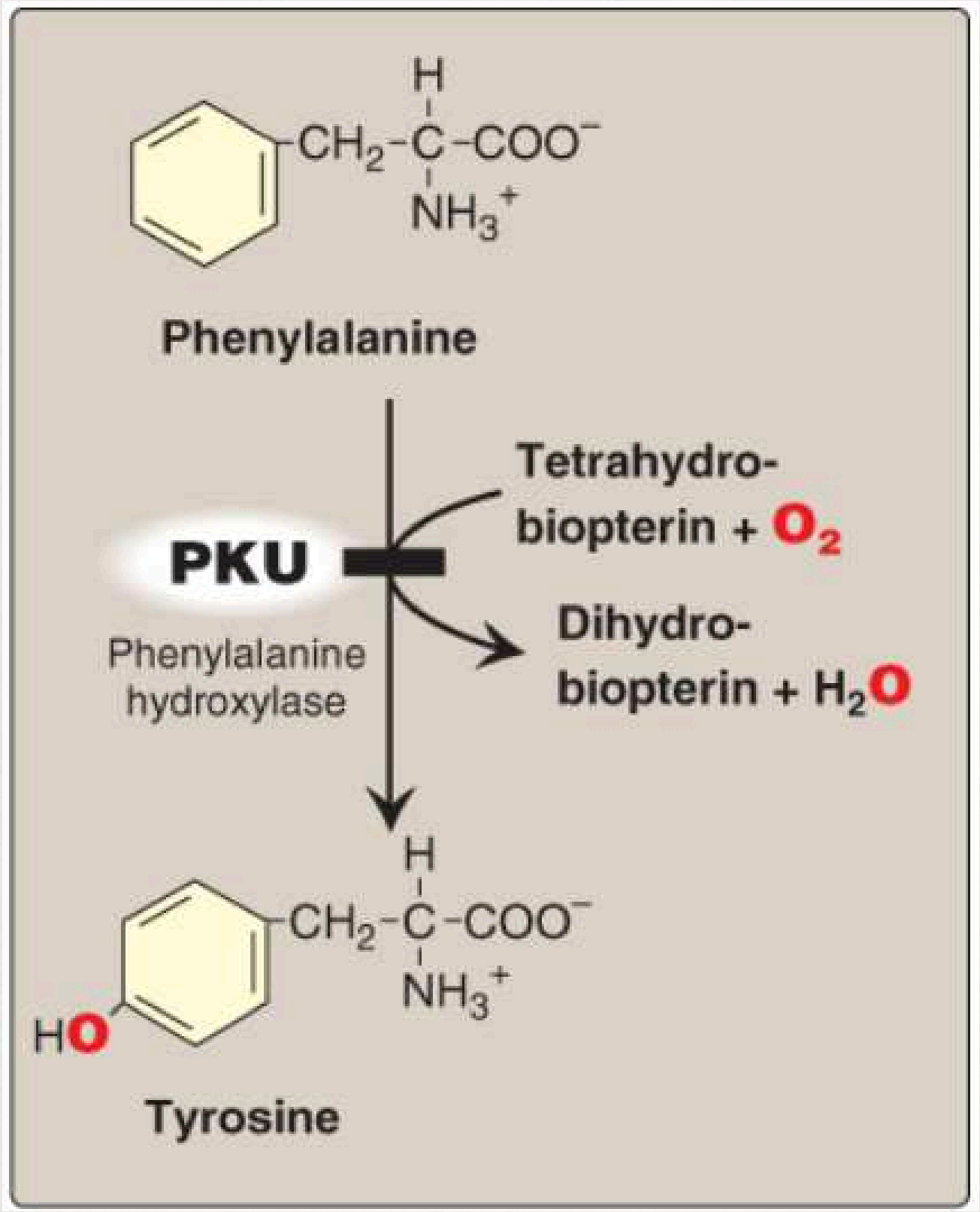
Prevalence

- >50 disorders of amino acid metabolism have been described
- Individual frequency:
    - Many are rare, occurring in <1 per 250,000 in most populations
- Collective impact:
    - Despite rarity, they represent a significant portion of pediatric genetic diseases

Summary of the Metabolism of Amino Acids in Humans



A deficiency in Phenylalanine Hydroxylase results in the disease Phenylketonuria (PKU)



A. Phenylketonuria (PKU)

Overview

- Most common clinically encountered inborn error of amino acid metabolism
- Incidence: 1 in 15,000
- Inheritance pattern: Autosomal recessive
- Cause:
    - Loss-of-function mutations in the gene coding for phenylalanine hydroxylase (PAH)

Biochemical Features

- Primary characteristic: Hyperphenylalaninemia
    - Phenylalanine present in 10× normal concentration in:
        - Plasma
        - Urine
        - Body tissues

- Secondary deficiency:
    - Tyrosine, which is normally formed from phenylalanine by PAH, is deficient

Treatment (Classical PKU)

- Dietary restriction of phenylalanine
- Supplementation with tyrosine

Variant Forms of Hyperphenylalaninemia

- May also be caused by rare deficiencies in:
    - Enzymes required to synthesize tetrahydrobiopterin (BH_4)
    - Dihydropteridine reductase, which regenerates BH_4 from BH_2
- Mechanism:
    - Deficiencies in BH_4 or its regeneration → indirectly raise phenylalanine levels
    - Because PAH requires BH_4 as a coenzyme

Additional Pathway Involvement

- BH_4 is also required for:
    - Tyrosine hydroxylase
    - Tryptophan hydroxylase
- These enzymes catalyze reactions leading to the synthesis of:
    - Neurotransmitters, such as:
        - Serotonin
        - Catecholamines

CNS Effects and Management in Variant PKU

- Phenylalanine restriction alone does not reverse CNS effects due to neurotransmitter deficiencies
- Supplementation required:
    - BH_4
    - L-3,4-dihydroxyphenylalanine (L-DOPA)
    - (Product of tyrosine hydroxylase–catalyzed reaction; see p. 318)
    - 5-Hydroxytryptophan

    - (Product of tryptophan hydroxylase-catalyzed reaction)

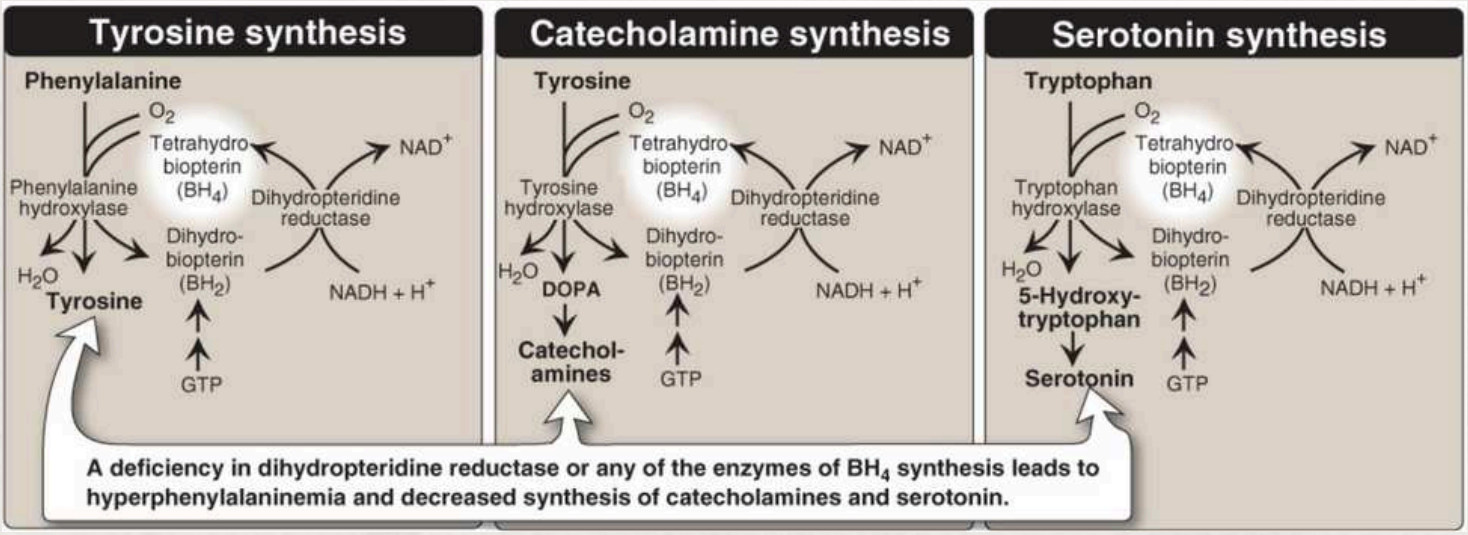
- Outcome:

    - Supplementation improves clinical outcome
    - However, response is unpredictable

Note:

- Aromatic amino acid hydroxylases use BH4 and not PLP [pyridoxal phosphate]

Biosynthetic Reactions involving Amino Acids and Tetrahydrobiopterin



Newborn Screening for Inborn Errors of Amino Acid Metabolism

Screening Method

- Technique: Tandem mass spectrometry
- Sample source: Blood obtained via heel prick

Legal Requirement in the U.S.

- All states:
  - Must screen for >20 disorders
  - Some screen for >50 disorders

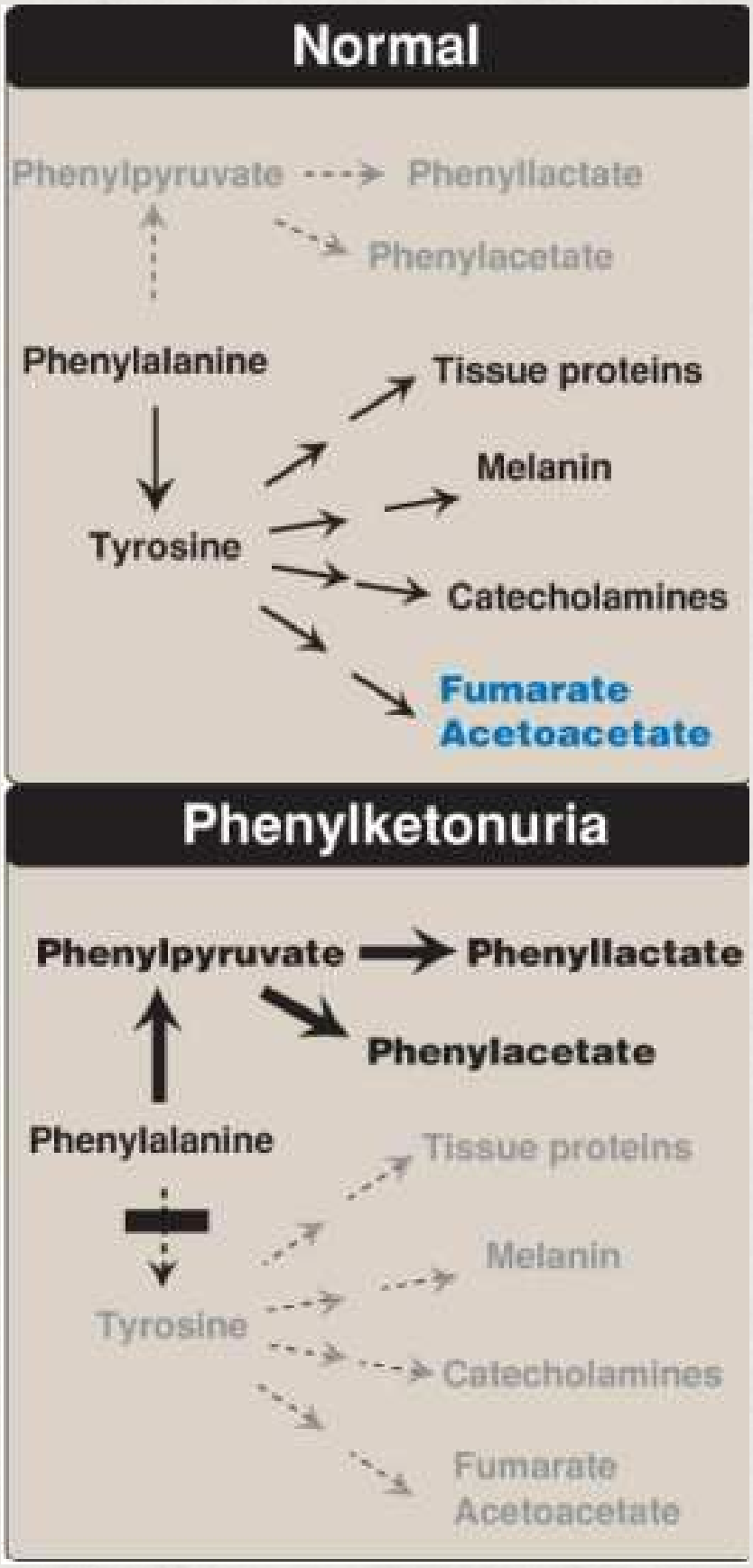
- All states specifically screen for PKU

I. Additional Characteristics of PKU

a. Elevated Phenylalanine Metabolites

- Phenylketonuria is named for the presence of a phenylketone in the urine
- Elevated metabolites include:
- (Not normally produced in significant amounts with functional PAH)
    - Phenylpyruvate → a phenylketone
    - Phenylacetate
    - Phenyllactate
- Additional finding:
    - Elevated phenylalanine also persists
- Clinical feature:
    - These metabolites give urine a characteristic musty ("mousy") odor

Pathways of Phenylalanine Metabolism in Normal Individuals and in Patients with Phenylketonuria.



b. Central Nervous System Effects in PKU

- Untreated PKU is characterized by severe neurological impairments, including:
    - Severe intellectual disability
    - Developmental delay
    - Microcephaly
    - Seizures
- Onset:
    - Symptoms of intellectual disability typically appear by age 1 year
    - Affected individuals rarely achieve an IQ >50
- Note:
    - These manifestations are now rarely seen due to:
        - Newborn screening programs
        - Early diagnosis and treatment

c. Hypopigmentation in PKU

- Untreated PKU patients may show deficiency of pigmentation, including:
    - Fair hair
    - Light skin color
    - Blue eyes
- Mechanism:
    - Hydroxylation of tyrosine by copper-requiring tyrosinase (first step in melanin synthesis) is decreased
    - Due to decreased tyrosine levels in PKU

2. Newborn Screening and Diagnosis

Importance

- Early diagnosis is critical because PKU is treatable through dietary restriction

Screening Requirement

- Laboratory testing for elevated blood phenylalanine is mandatory
    - Because PKU lacks neonatal symptoms

Maternal Influence and Timing

- Newborns with PKU often have normal phenylalanine levels at birth due to:
    - Maternal clearance of phenylalanine via the placenta
- Normal levels may persist until:
    - 24 to 48 hours after birth, once protein feeding begins
- Therefore:
    - Screening tests are typically done after 24–48 hours to avoid false negatives

Confirmation

- Positive screening test → followed by:
    - Quantitative determination of phenylalanine levels for diagnosis

3. Prenatal Diagnosis

- Cause: Classic PKU is caused by >100 different mutations in the gene encoding PAH
- Genetic pattern:
    - Disease is often doubly heterozygous
        - Each allele has a different mutation
- Despite genetic complexity:
    - Prenatal diagnosis is possible

4. Treatment of PKU

Dietary Challenge

- Phenylalanine is essential, present in most natural proteins
- Normal diet cannot meet protein needs without exceeding safe phenylalanine levels

Dietary Management

- Blood phenylalanine is maintained near the normal range by:
    - Synthetic amino acid preparations free of phenylalanine
    - Supplementation with natural foods low in phenylalanine:
        - Fruits
        - Vegetables
        - Certain cereals
    - Phenylalanine intake is adjusted based on individual blood phenylalanine levels

Timing of Treatment

- Earlier treatment = more complete prevention of neurologic damage
- Treatment must begin during the first 7–10 days of life to prevent cognitive impairment

Outcomes

- Appropriately treated individuals can achieve normal intelligence
- Discontinuation in early childhood → poor IQ performance
- Adult PKU patients show IQ deterioration after diet discontinuation

Tyrosine Supplementation

- In PKU, tyrosine cannot be synthesized from phenylalanine
- Tyrosine becomes essential and must be supplied in the diet

Over-Treatment Risk

- Avoid overzealous treatment causing blood phenylalanine levels below normal

Aspartame Warning

- Individuals with PKU should avoid aspartame
    - Aspartame is an artificial sweetener containing phenylalanine

5. Maternal Phenylketonuria

Maternal PKU Syndrome

- Women with PKU who are not on a low-phenylalanine diet and become pregnant:
    - May give birth to offspring with maternal PKU syndrome
        - Even if fetus is heterozygous (does not have PKU)

Teratogenic Effects of Maternal Hyperphenylalaninemia

- High maternal phenylalanine is teratogenic, leading to:
    - Microcephaly
    - Congenital heart abnormalities in the fetus

Prevention Strategy

- Dietary control must begin before conception and be maintained throughout pregnancy

B. Maple Syrup Urine Disease (MSUD)

Overview

- MSUD is a rare (1:185,000), autosomal-recessive disorder

- Caused by partial or complete deficiency of:
    - Branched-chain α-keto acid dehydrogenase (BCKD)
    - A mitochondrial enzyme complex that oxidatively decarboxylates:
        - Leucine
        - Isoleucine
        - Valine

Pathophysiology

- BCAAs and their corresponding α-keto acids accumulate in the blood
- These exert a toxic effect on brain function

Clinical Features

- Feeding problems
- Vomiting
- Ketoacidosis
- Changes in muscle tone
- Neurologic problems, potentially leading to coma
    - (Primarily due to rise in leucine)
- Maple syrup–like odor of urine
    - Caused by rise in isoleucine
- If untreated, the disease is fatal

- Delayed treatment → intellectual disability

I. Classification

Forms of MSUD

Type	Description	Onset
Classic MSUD	Most common type; neonatal-onset Leukocytes or fibroblasts show little or no BCKD activity Lethal in first weeks of life if untreated	First several days of life
Intermediate forms	Partial enzyme activity (up to 30% of normal) Milder symptoms	From infancy to adolescence
Thiamine-dependent type	Responds to large doses of thiamine	Rare

2. Screening and Diagnosis

- Prenatal diagnosis and newborn screening available
- Most affected individuals are compound heterozygotes

3. Treatment

Diet Management

- Use of synthetic formula free of BCAAs
- Supplemented with limited amounts of:
    - Leucine
    - Isoleucine
    - Valine
- Goal: support normal growth and development without reaching toxic levels

Note: Elevated leucine is the primary cause of neurologic damage

→ Leucine levels are carefully monitored

Prognosis

- Early diagnosis and lifelong dietary treatment are essential

- Properly managed children can develop normally

Note:

- BCAAs serve as an important energy source in times of metabolic stress

- Individuals with MSUD are at risk of decompensation during:

-> Infection
-> Fasting
-> Trauma
-> Periods of increased protein catabolism

C. Albinism

Definition

- A group of genetic disorders caused by defects in tyrosine metabolism

- Leads to deficiency of melanin production

Key Consequence

- Partial or complete absence of pigment from:
    - Skin
    - Hair
    - Eyes

Inheritance Patterns

- Autosomal recessive (most common)
- Autosomal dominant
- X-linked (less common)

Type 1 Oculocutaneous Albinism

(Tyrosinase-negative albinism)

- Most severe form

- Characterized by total absence of pigment in:
    - Hair
    - Eyes
    - Skin

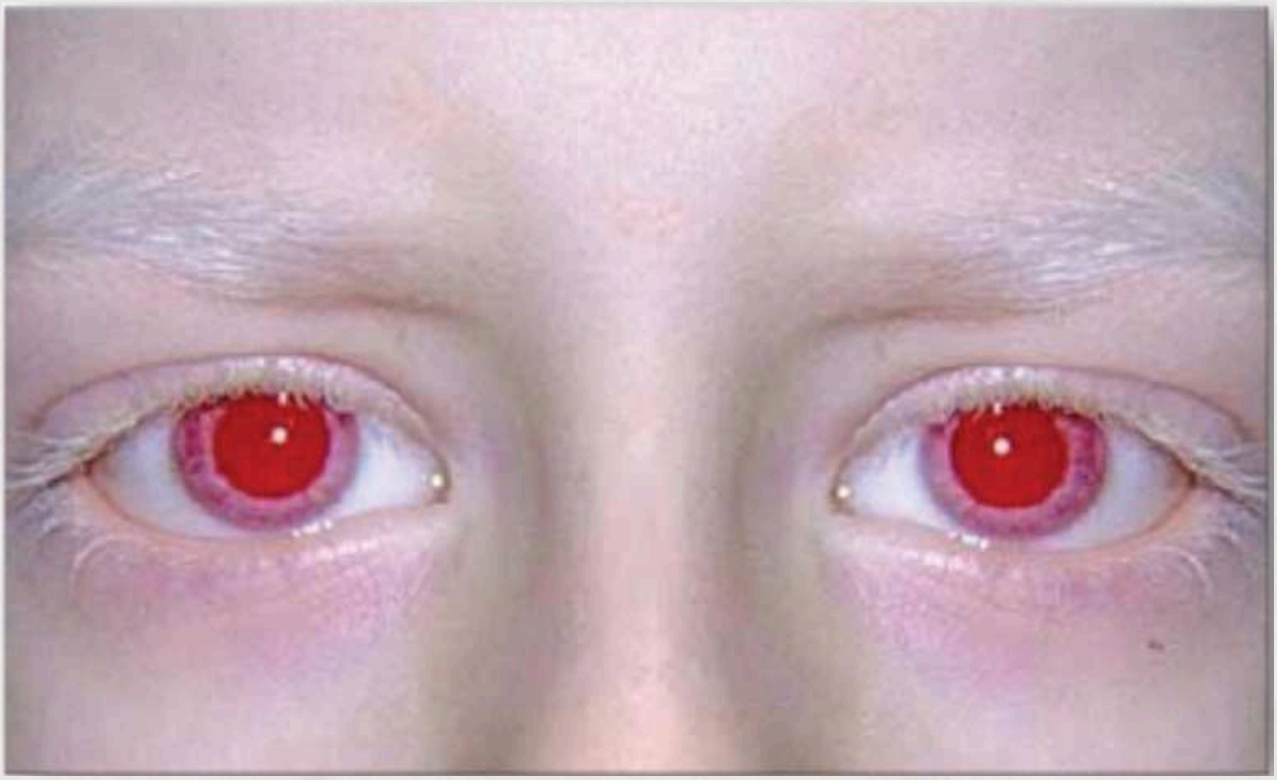
Biochemical Defect

- Caused by absent or defective tyrosinase
    - A copper-requiring enzyme
    - Catalyzes the first two steps in melanin synthesis from tyrosine

Clinical Features

- Hypopigmentation
- Vision defects
- Photophobia
- (Sunlight causes eye discomfort)
- Increased risk of skin cancer
- (Due to lack of melanin protection from UV rays)

Patient with Oculocutaneous Albinism, showing White Eyebrows and Lashes and Eyes that Appear Red in Color



D. Homocystinuria

Definition

- Group of autosomal recessive disorders involving defects in homocysteine (Hcy) metabolism

Biochemical Features

- ↑ Urinary homocysteine (Hcy)
- ↑ Plasma homocysteine (Hcy) and methionine
- ↓ Plasma cysteine

Most Common Cause

- Cystathionine β-synthase deficiency
    - Enzyme that converts Hcy → cystathionine

Clinical Features (Especially in homozygotes)

- Ectopia lentis
- (Lens dislocation)
- Skeletal abnormalities
- (Long limbs and fingers = Marfanoid habitus)
- Intellectual disability
- ↑ Risk of thromboembolism
    - Thrombosis = major cause of early death

Treatment Strategy

- Methionine restriction

- Supplement:

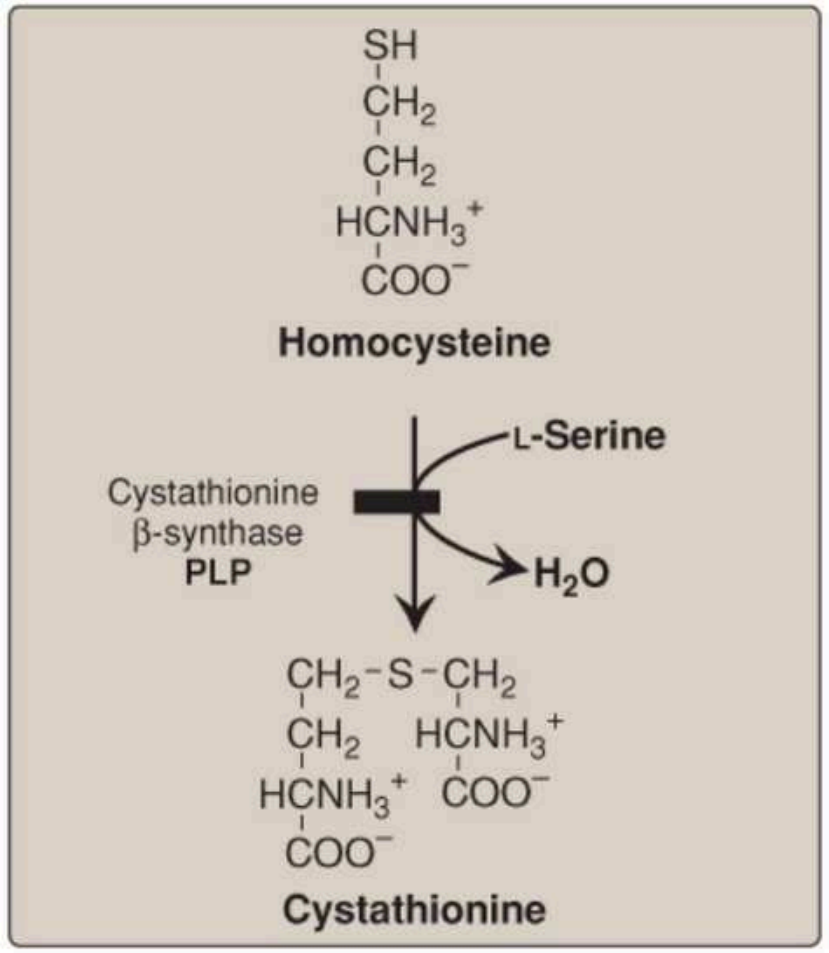
    - Vitamin B12
    - Folate
    - Cysteine (now becomes essential)
        - Also helps replenish glutathione (↓ oxidative stress)

- Vitamin B6 (pyridoxine) trial:
    - Converted to pyridoxal phosphate (coenzyme of cystathionine β-synthase)
    - Some patients respond (milder, later-onset cases)

Other Causes of Hyperhomocysteinemia

- Methylcobalamin deficiency
- MTHFR (N^5,N^{10}-methylenetetrahydrofolate reductase) deficiency

Enzyme Deficiency in Homocystinuria



E. Alkaptonuria

Definition

- Rare organic aciduria
- Caused by deficiency of homogentisic acid oxidase
- Leads to accumulation of homogentisic acid (HA)
    - Intermediate in tyrosine degradation

Pathophysiology

- Homogentisic acid (HA) builds up in:
    - Urine
    - Cartilage
    - Collagen-containing tissues

Classic Triad of Symptoms

1. Homogentisic aciduria

- Urine contains high levels of HA
- Darkens on standing (oxidized pigment)
- (Diagnostic clue in infants: dark-staining diapers)

2. Early-onset arthritis

    - Especially in large joints
    - Due to HA deposition in connective tissues

3. Ochronosis
    - Black-blue pigmentation in cartilage and collagen
    - (E.g., ear cartilage, sclera, intervertebral discs)

Age of Onset

- Often asymptomatic until ~40 years

- Early sign in infants: black discoloration of diapers (urine pigment)

Treatment

- Dietary restriction of:

    - Phenylalanine
    - Tyrosine
    - ↓ HA production

Prognosis

- Not life-threatening

- But arthritis may become severely crippling

Related Condition (Differential)

- Tyrosinemia Type I
    - Caused by deficiency of fumarylacetoacetate hydrolase
    - Urine smells like cabbage
    - Also part of tyrosine degradation pathway

Specimens from a Patient with Alkaptonuria

F. Methylmalonic Acidemia (MMA)

Definition

- Rare autosomal recessive disorder
    - Incidence: 1 in 100,000
- Caused by deficiency of methylmalonyl CoA mutase
    - Enzyme that converts L-methylmalonyl CoA → succinyl CoA
- Can also occur due to severe vitamin B12 deficiency
    - B12 is a required coenzyme for the mutase

Amino Acids & Substrates Involved

- MMA results from the catabolism of:
    - Odd-chain fatty acids
    - Valine
    - Isoleucine
    - Methionine
    - Threonine

Pathophysiology

- Enzyme deficiency → accumulation of:
    - Methylmalonic acid in blood & urine
    - Propionyl CoA → contributes to propionic acidemia
- Leads to metabolic acidosis and systemic toxicity

Clinical Presentation

- Onset: Early infancy
- Symptoms vary with enzyme activity level:
    - Failure to thrive
    - Vomiting, dehydration
    - Hypotonia
    - Developmental delay
    - Seizures
    - Hepatomegaly
    - Hyperammonemia
    - Progressive encephalopathy

Complications (if untreated)

- Intellectual disability
- Chronic kidney or liver damage
- Pancreatitis
- Coma or death

Diagnostic Findings

- Elevated methylmalonic acid in:
    - Blood
    - Urine
- Metabolic acidosis
- Possibly elevated ammonia and propionic acid

Treatment

- Low-protein, high-calorie diet
    - Restrict amino acids that feed into the pathway:
        - Valine, Isoleucine, Threonine, Methionine

- Vitamin B12 supplementation
    - Particularly effective if the MMA is B12-responsive

Disorders: Quick Review

1. Phenylketonuria (PKU)

Feature	Description
Enzyme Deficiency	Phenylalanine hydroxylase (PAH)
Cofactor Required	Tetrahydrobiopterin (BH_4)
Pathophysiology	Phenylalanine cannot be converted to tyrosine → buildup of phenylalanine and phenylketones
Clinical Features	Intellectual disability, seizures, microcephaly, musty odor, hypopigmentation
Diagnosis	Elevated phenylalanine & phenylketones in blood/urine; newborn screening
Treatment	Phenylalanine-restricted diet, tyrosine supplementation, avoid aspartame, possible BH_4 or neurotransmitter therapy
Special Note	Maternal PKU → microcephaly & congenital defects in fetus

2. Maple Syrup Urine Disease (MSUD)

Feature	Description
Enzyme Deficiency	Branched-chain α-keto acid dehydrogenase (BCKD)
Affected Amino Acids	Leucine, isoleucine, valine (BCAAs)
Pathophysiology	Inability to decarboxylate BCAA ketoacids → accumulation leads to neurotoxicity
Clinical Features	Vomiting, hypotonia, seizures, maple syrup odor of urine, coma
Diagnosis	Elevated BCAAs and ketoacids in blood, urine organic acid analysis
Treatment	BCAA-restricted diet, careful leucine monitoring, thiamine supplementation (in responsive cases)
Special Note	Risk of decompensation during illness due to protein breakdown

3. Albinism (Type 1)

Feature	Description
Enzyme Deficiency	Tyrosinase
Pathophysiology	No conversion of tyrosine → melanin
Clinical Features	Hypopigmentation of skin, hair, eyes; photophobia; vision defects
Diagnosis	Clinical presentation; family history
Treatment	Sun protection, low-vision support
Special Note	Autosomal recessive is most common inheritance mode

4. Homocystinuria

Feature	Description
Most Common Enzyme Deficiency	Cystathionine β-synthase
Other Possible Causes	Deficiency of methylcobalamin or MTHFR
Pathophysiology	Homocysteine cannot be metabolized → ↑ Hcy, ↓ cysteine
Clinical Features	Lens dislocation, long limbs, thrombi, intellectual disability
Diagnosis	↑ Hcy and methionine in blood, ↑ Hcy in urine
Treatment	Methionine restriction, cysteine supplementation, B6, B12, folate
Special Note	B6-responsive patients have milder symptoms

S. Alkaptonuria

Feature	Description
Enzyme Deficiency	Homogentisic acid oxidase
Pathophysiology	Accumulation of homogentisic acid (HA), an intermediate of tyrosine metabolism
Clinical Features	Dark urine on standing, ochronosis (pigment in cartilage), early arthritis
Diagnosis	Darkened urine, elevated HA, dark stains in diapers
Treatment	Low phenylalanine and tyrosine diet
Special Note	Arthritis can be severely debilitating; appears later in life

6. Methylmalonic Acidemia (MMA)

Feature	Description
Enzyme Deficiency	Methylmalonyl CoA mutase
Cofactor Deficiency	Vitamin B12 (may cause secondary MMA)
Pathophysiology	Buildup of methylmalonic acid and propionic acid → metabolic acidosis
Clinical Features	Failure to thrive, vomiting, encephalopathy, hepatomegaly, seizures
Diagnosis	Elevated methylmalonate in blood/urine, metabolic acidosis, hyperammonemia
Treatment	B12 supplementation, restrict methionine, valine, isoleucine, threonine
Special Note	Untreated severe forms → intellectual disability, coma, or death