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AMINO ACID METABOLISM

IMPORTANT COENZYMES

- ✗ **Pyridoxal phosphate** (PLP, B₆), transamination and certain carbon skeleton catabolism
- ✗ **Tetrahydrofolate** (FH₄), folic acid, one-carbon transfer regardless of the oxidation state, degradation and synthesis pathways
- ✗ **Tetrahydrobiopterin** (BH₄), required for ring hydroxylation reactions (e.g., phenylalanine to tyrosine), utilize molecular O₂

SYNTHESIS OF AMINO ACIDS

- ✗ 11 non-essential, 9 essential
- ✗ 9/11 can be produced from glucose plus a source of nitrogen
- ✗ 2/11 (tyrosine and cysteine [S only]), require essential for synthesis

Essential	Conditionally Non-Essential	Non-Essential
Histidine	Arginine	Alanine
Isoleucine	Asparagine	Asparatate
Leucine	Glutamine	Cysteine
Methionine	Glycine	Glutamate
Phenylalanine	Proline	
Threonine	Serine	
Tryptophan	Tyrosine	
Valine		
Lysine		

- ✗ 10/11 (glucose derived); 4/10 (serine, glycine, cysteine, and alanine) are produced from intermediates of glycolysis; 6/10 are produced from TCA cycle intermediates
- ✗ 4/6 (glutamate, glutamine, proline, and arginine) have α -Ketoglutarate as the precursor; 2/6 (aspartate and asparagine) have oxaloacetate as the precursor

DEGRADATION OF AMINO ACIDS

- ✗ Generally, pathways are **distinct** from biosynthesis (regulation)
- ✗ Almost every amino acid will have a degradative pathway that can generate **NADH**
- ✗ The fate of the carbons depends on the physiologic state of the individual (fed vs. fasting)

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

- ✗ The liver is the only tissue that has all of the pathways of amino acid synthesis and degradation
- ✗ Degradation classify amino acids to glucogenic, ketogenic, or both
- ✗ Carbons are degraded and converted to (a) CO_2 , (b) glucose (pyruvate and TCA intermediates $-\alpha\text{-SCoA-F-O}$) and (c) ketone bodies precursors (acetoacetate and acetyl CoA)

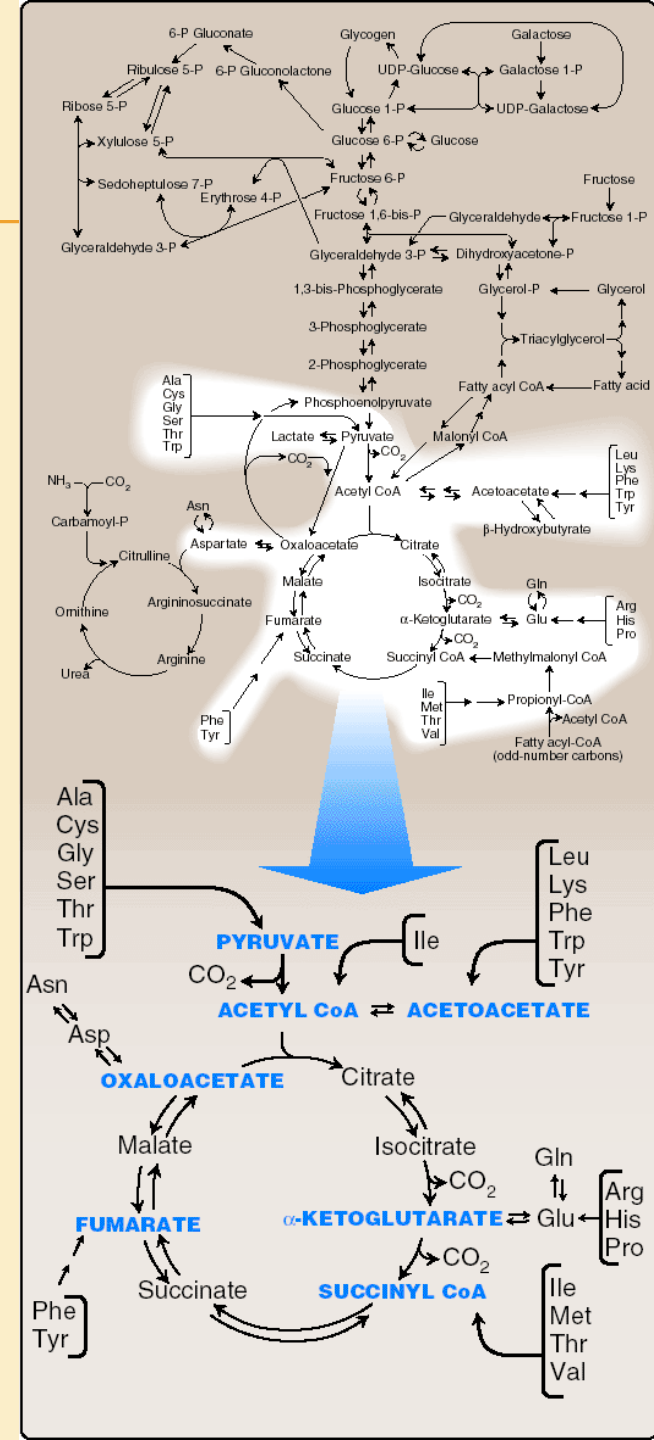
DEGRADATION OF AMINO ACIDS

✖ Breakdown of the carbon skeletons converge to form seven intermediate products:

- + Oxaloacetate
- + α -ketoglutarate
- + Pyruvate
- + Fumarate
- + succinyl coenzyme A (CoA)
- + Acetyl CoA
- + Acetoacetate

✖ These products result either in:

- ✖ Synthesis of glucose
- ✖ Synthesis of lipid
- ✖ Production of energy (CO_2 & H_2O) by TCA cycle



A. AMINO ACIDS THAT FORM OXALOACETATE

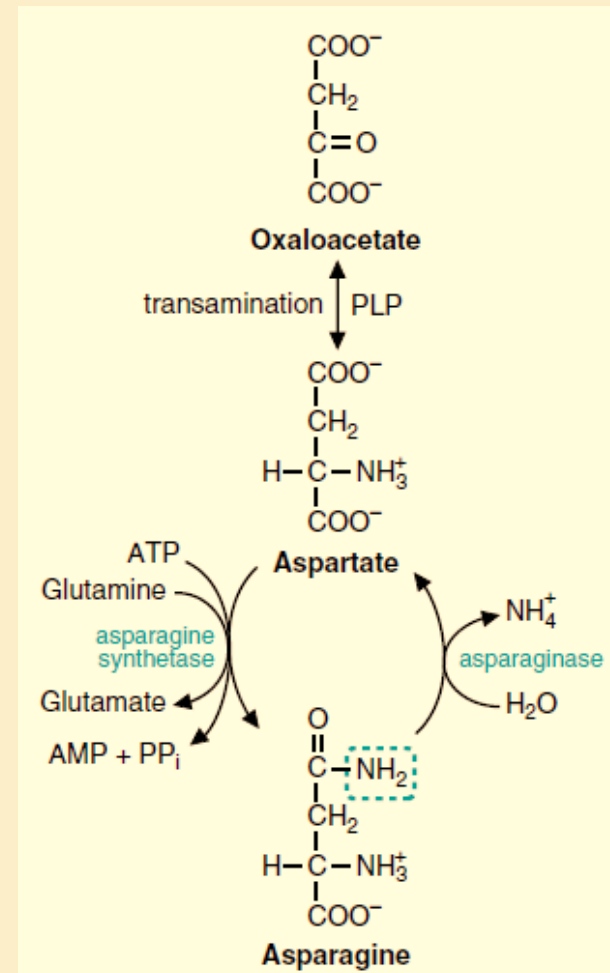
✗ Aspartate

- + Is produced by transamination of oxaloacetate (reversible)

✗ Asparagine

- + Is formed from aspartate (glutamine provides the nitrogen); different from glutamine
- + Degraded by asparaginase to give NH_4^+ and aspartate; similar to glutaminase

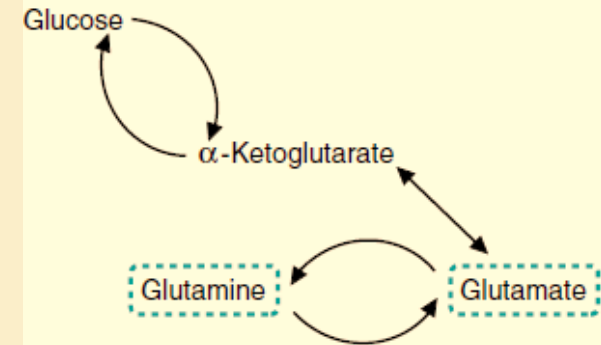
- ✗ Asparagine is essential amino acid for some rapidly dividing leukemic cells (Asparaginase can be administered systemically to treat leukemic patients)



B. α -KETOGLUTARATE RELATED

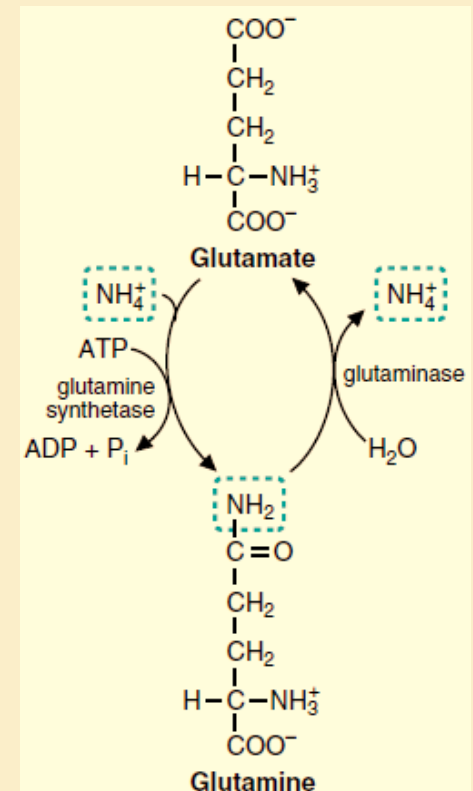
✖ 1. GLUTAMATE

- + Transamination or by the glutamate dehydrogenase (reversible)
- + Used for the synthesis of other amino acids (glutamine, proline, ornithine, and arginine)
- + Used for the synthesis of Glutathione; an important antioxidant



✖ 2. GLUTAMINE

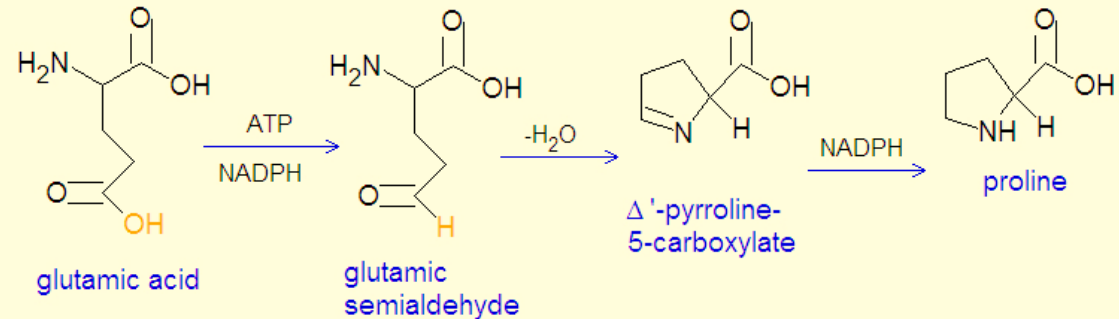
- + Glutamine synthetase
- + 3 human enzymes fix free ammonia (glutamate DH & CPSI)
- + Reconverted to glutamate by a different enzyme, glutaminase



B. α -KETOGLUTARATE RELATED

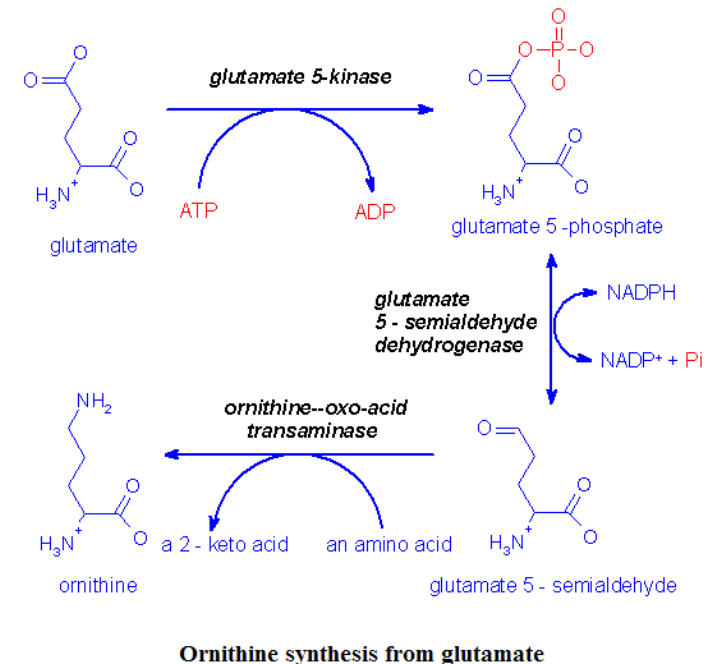
✖ 3. PROLINE

- + Glutamate converted to an aldehyde, spontaneously cyclizes followed by reduction to proline
- + Proline can be converted back to glutamate



✖ 4. ARGININE

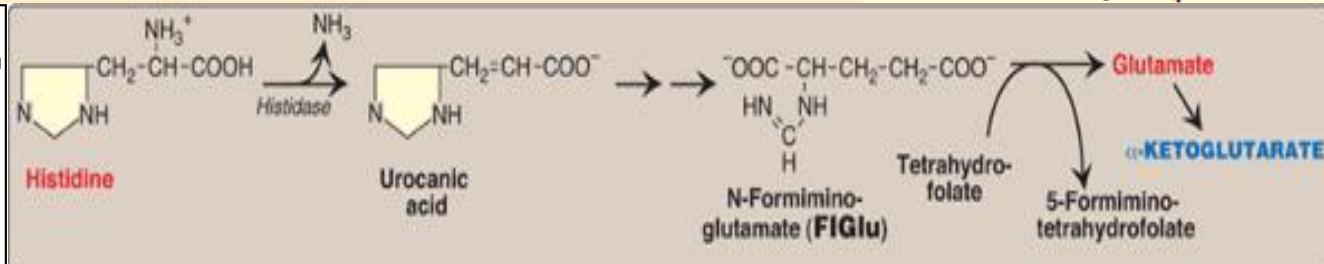
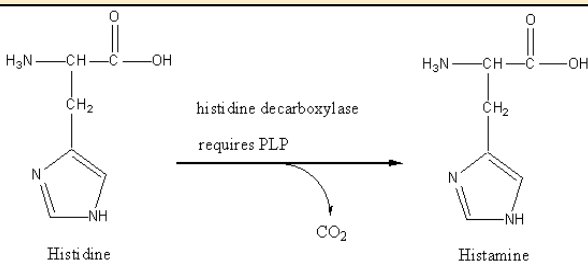
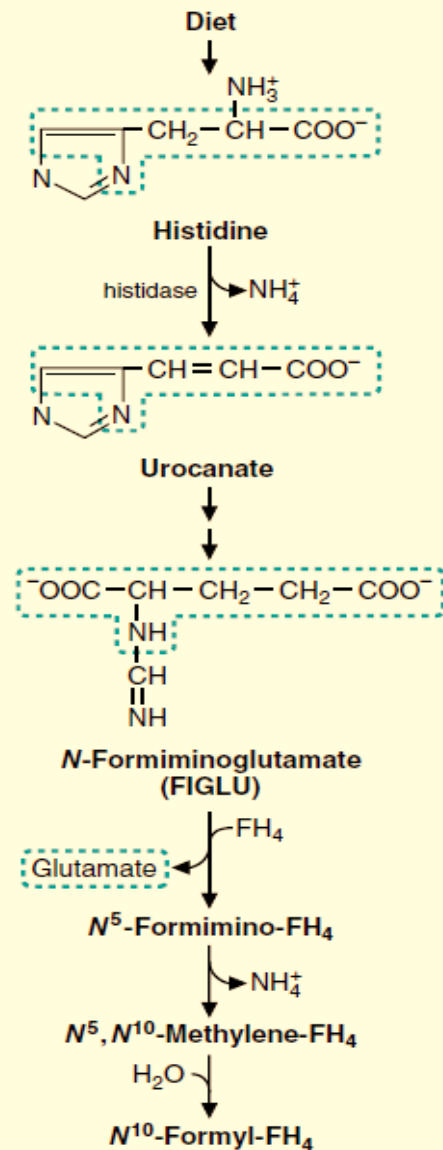
- + Cleaved by arginase to form urea & ornithine
- + If ornithine is in excess, transaminated to α -ketoglutarate followed by another transamination to glutamate



B. α -KETOGLUTARATE RELATED

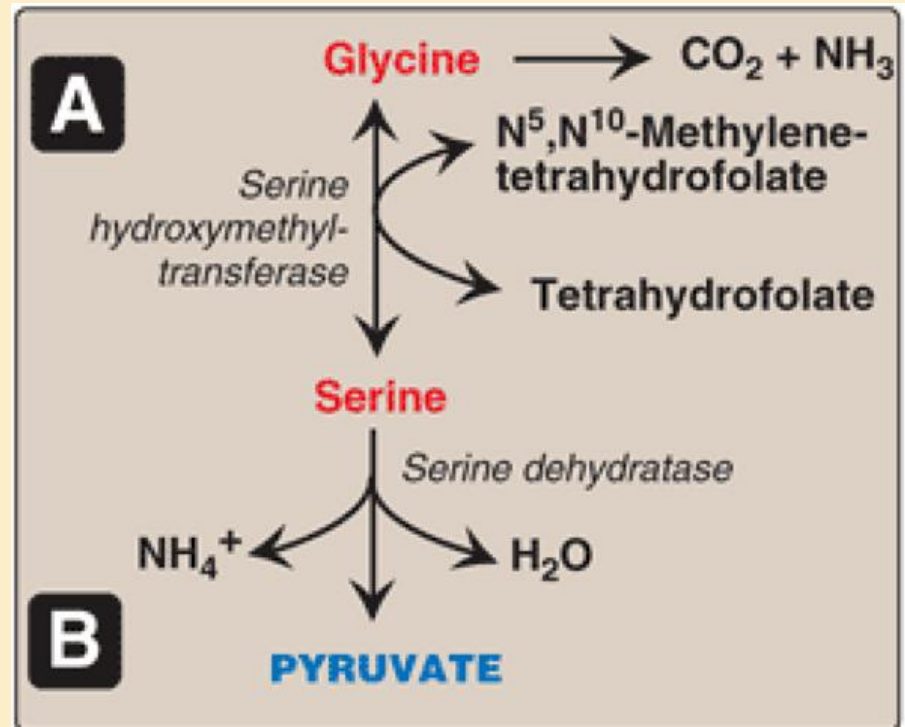
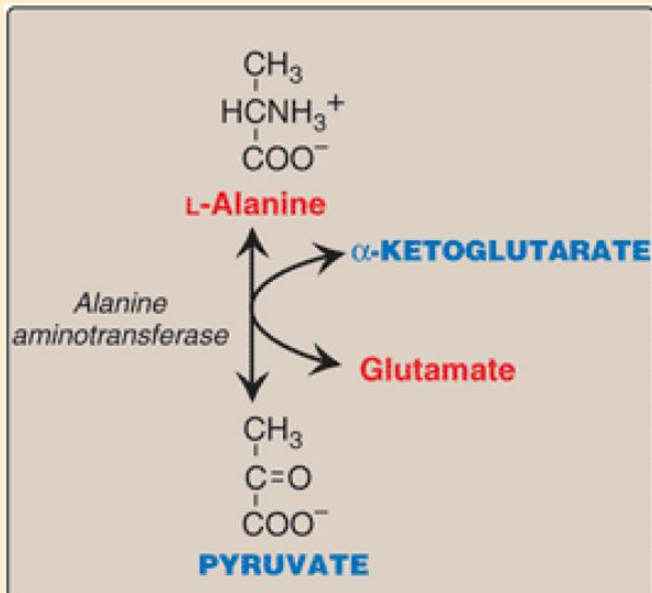
✗ 5. HISTIDINE

- + Essential, however, 5 carbons come from glutamate
- + In a series of steps, histidine is converted to N-Formiminoglutamate (FIGLU). The subsequent reactions transfer one carbon of FIGLU to the FH_4 pool and release NH_4^+ and glutamate
- + The FIGlu excretion test has been used in diagnosing a deficiency of folic acid



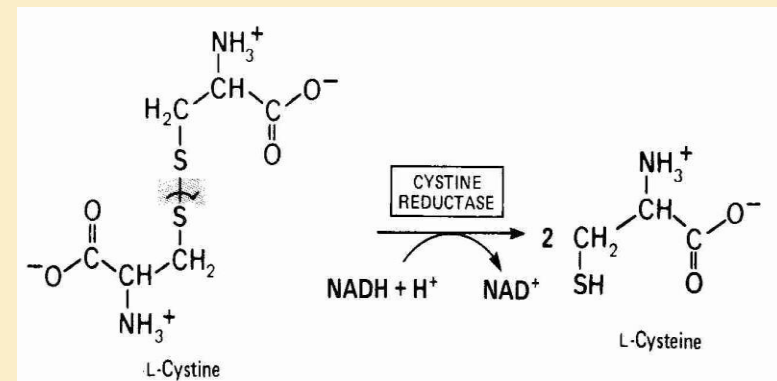
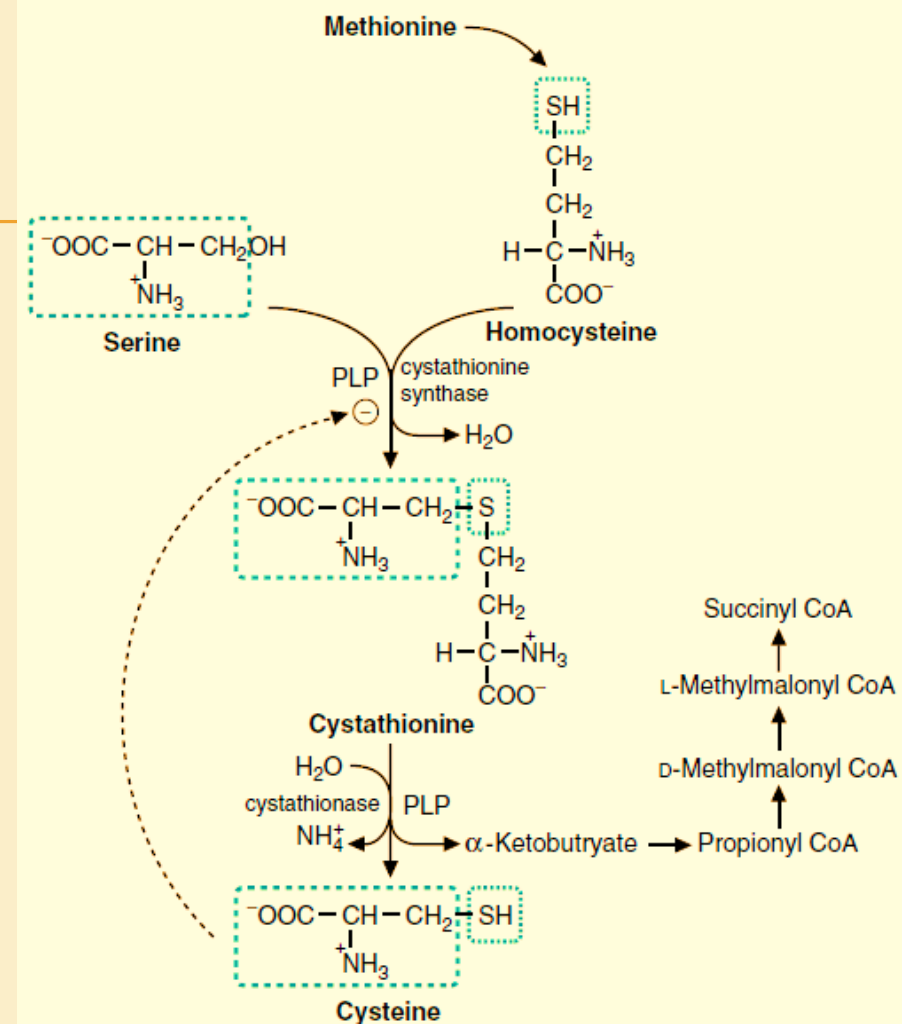
C. PYRUVATE RELATED

- ✗ 1. **Alanine:** transamination (ALT)
- ✗ 2. **Serine:**
 - + To glycine & N⁵,N¹⁰-methylenetetrahydrofolate
 - + To pyruvate by serine dehydratase
- ✗ 3. **Glycine:**
 - + To serine
 - + Oxidized to CO₂ and NH₃



C. PYRUVATE RELATED

- ✖ 4. Cystine & Cysteine:
- ✖ Cystine reduced to cysteine (NADH)
- ✖ C&N from serine, S from methionine
- ✖ Feedback inhibition through cysteine
- ✖ Cysteine essentiality is governed by methionine
- ✖ Excess cysteine in diet spares methionine
- ✖ This is the only degradative route for homocysteine
- ✖ Requires PLP
- ✖ liver desulfurase produces hydrogen sulfide (H_2S) & pyruvate

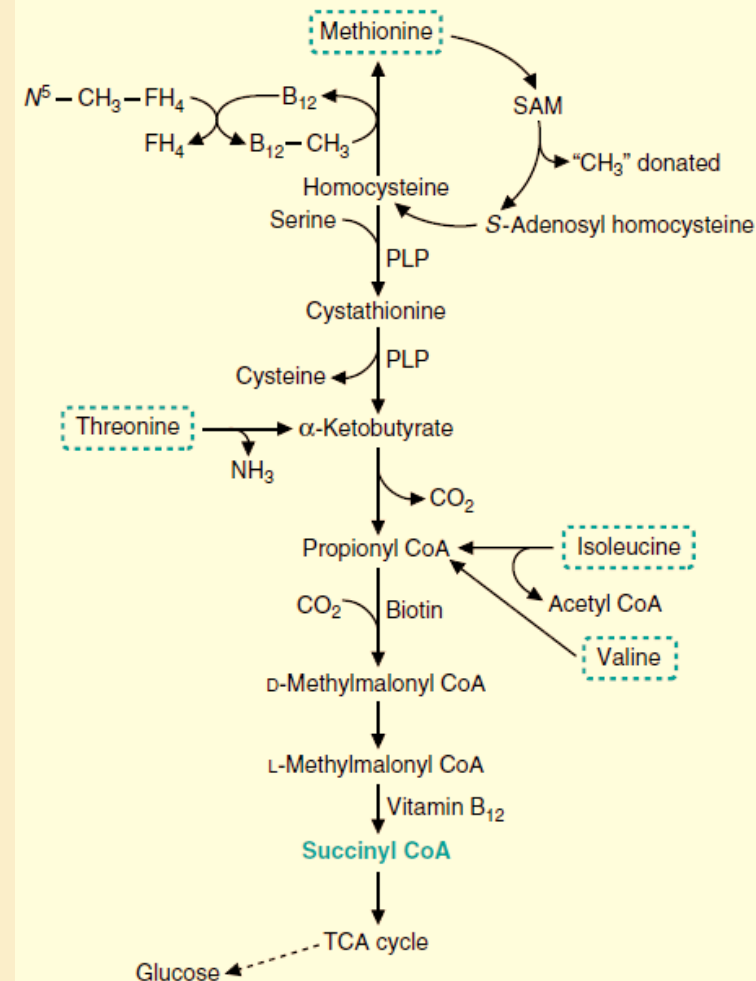


C. PYRUVATE RELATED

✖ 5. THREONINE

- + Converted to pyruvate or to α -ketobutyrate
- + Degraded by threonine dehydratase (PLP) to ammonia and α -ketobutyrate, which subsequently undergoes oxidative decarboxylation to form propionyl CoA (succinyl CoA)

threonine \rightarrow α ketobutyrate + NH_4^+



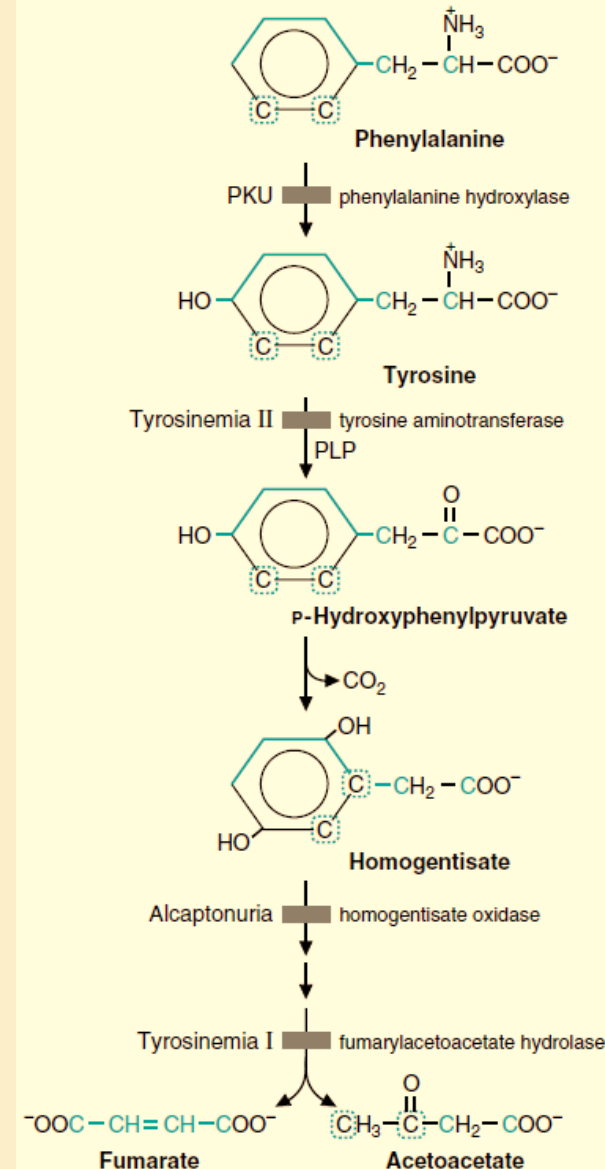
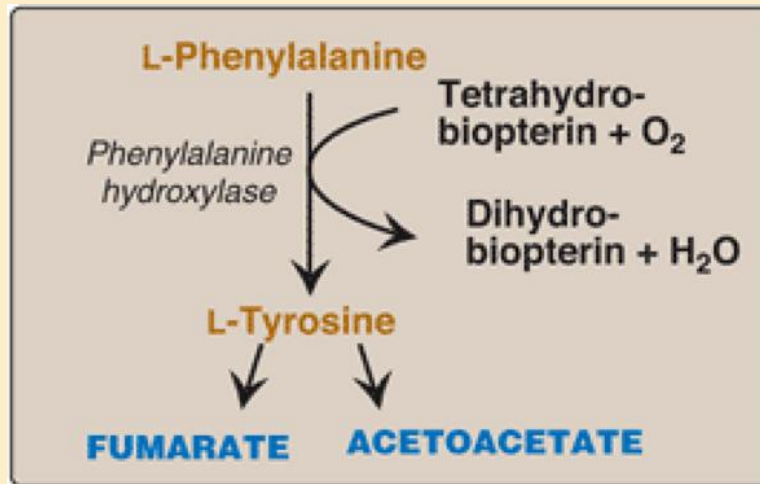
D. AMINO ACIDS THAT FORM FUMARATE

✖ 1. ASPARTATE

- + Urea cycle
- + Fumarate to malate; anaplerotic or oxidative purposes

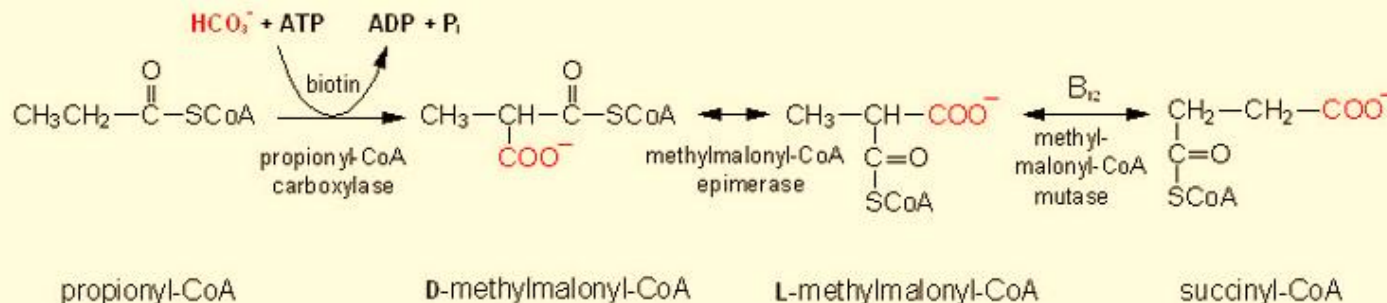
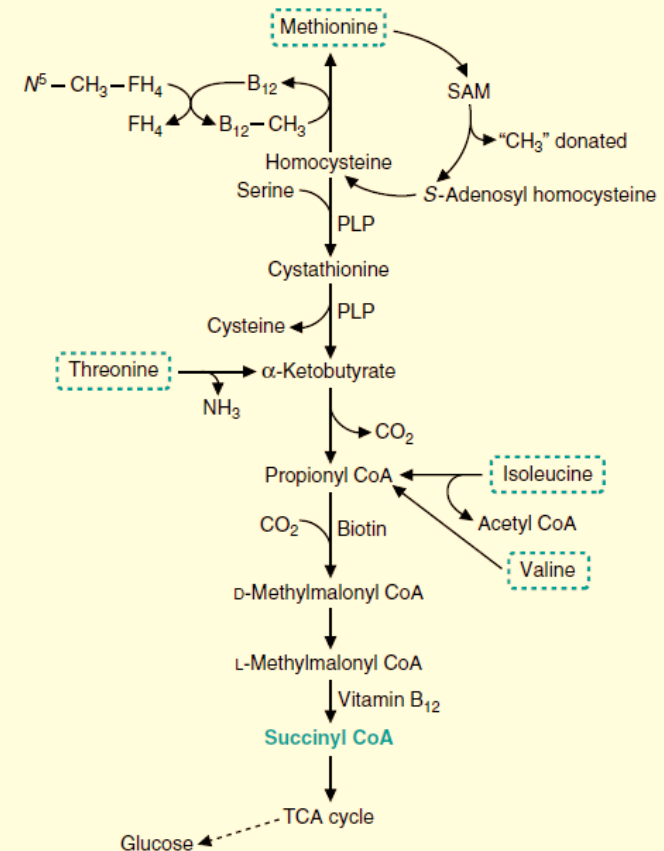
✖ 2. PHENYLALANINE & TYROSINE

- + Tyrosine, hydroxylated or diet, is oxidized to form acetoacetate and fumarate
- + Diseases



E. AMINO ACIDS THAT FORM SUCCINYL- COA

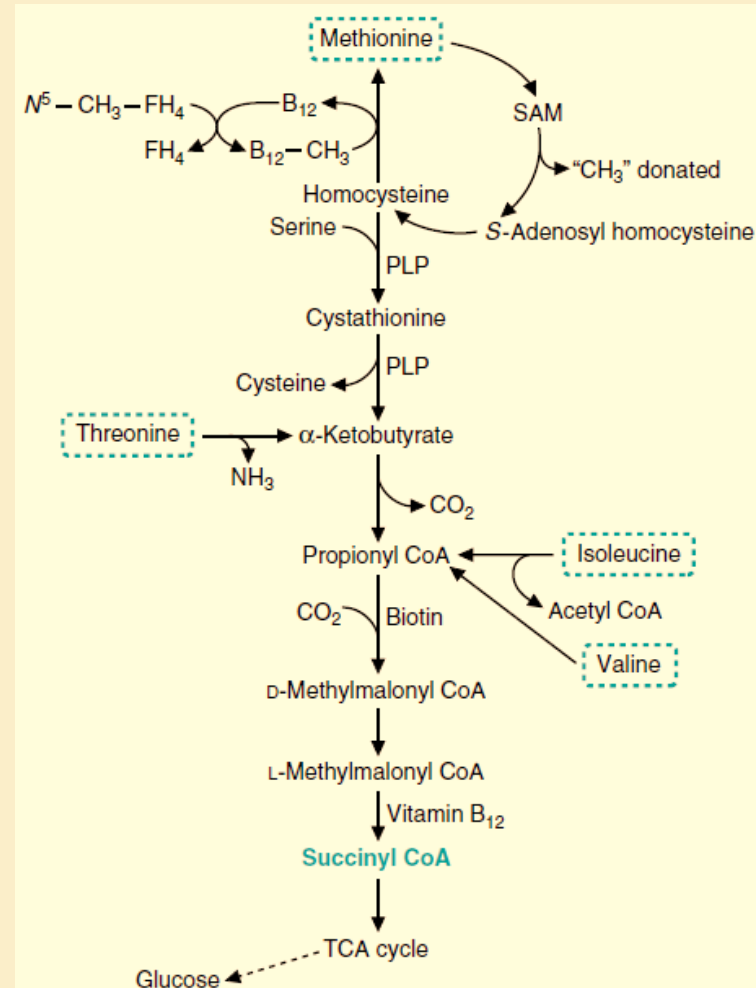
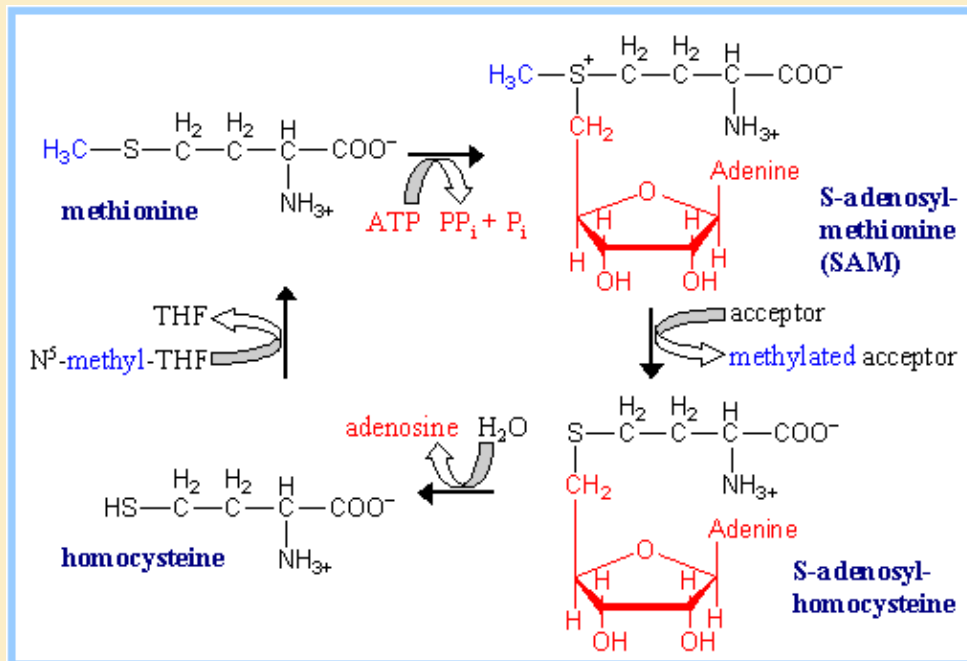
- ✗ The essential amino acids **methionine, valine, isoleucine, & threonine** are degraded to form **propionyl-CoA**
- ✗ The conversion of propionyl CoA to succinyl CoA is common to their degradative pathways
- ✗ Propionyl CoA is carboxylated (requires biotin) then converted to succinyl CoA (requires vitamin B₁₂)



E. AMINO ACIDS THAT FORM SUCCINYL- COA

✖ 1. METHIONINE

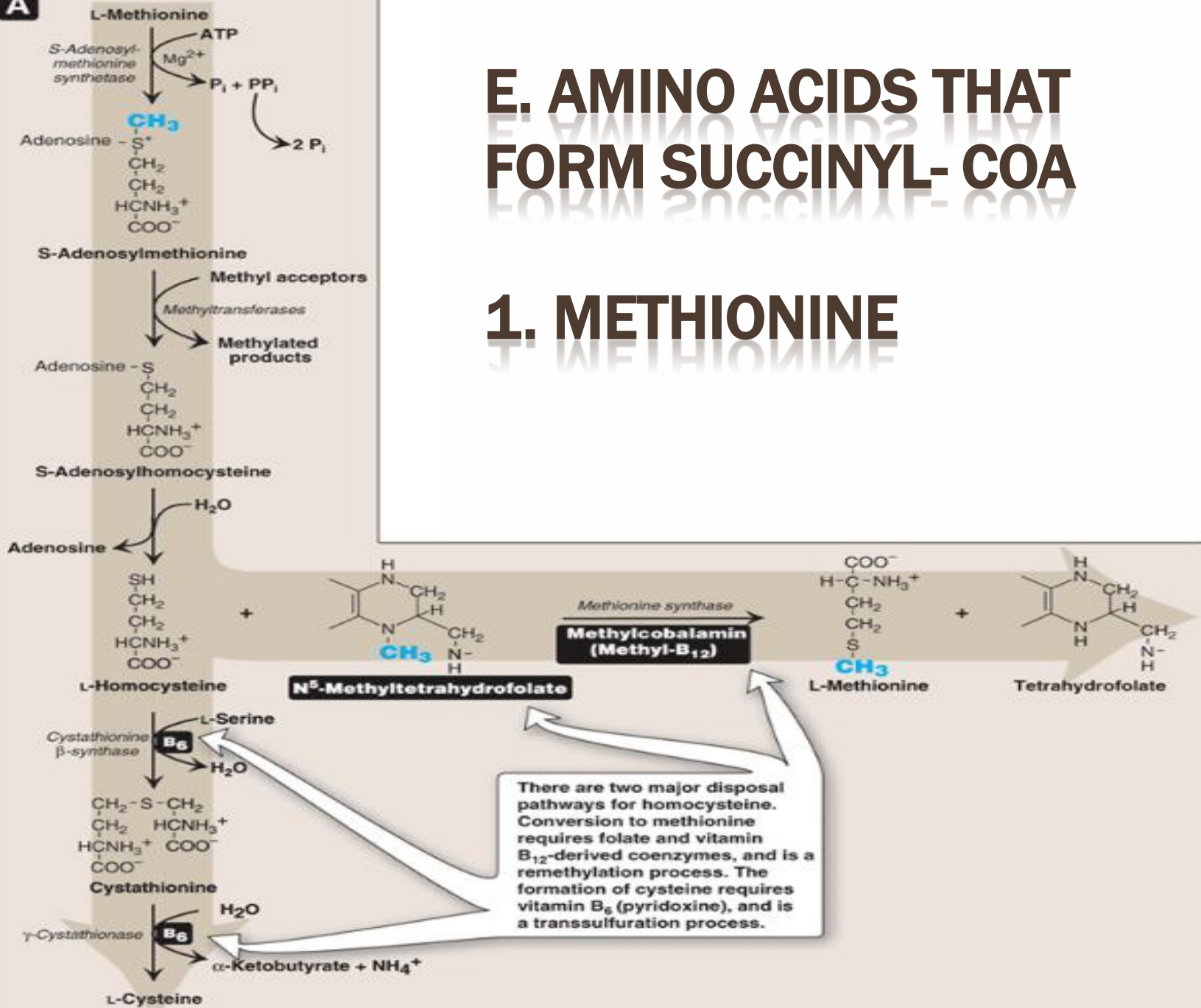
- + Methionine \rightarrow SAM \rightarrow S-adenosylhomocysteine (SAH).
- + SAH \rightarrow homocysteine \rightarrow cysteine (PLP)
- + Methionine can be regenerated from homocysteine (FH4 & vitamin B₁₂)



A

E. AMINO ACIDS THAT FORM SUCCINYL- COA

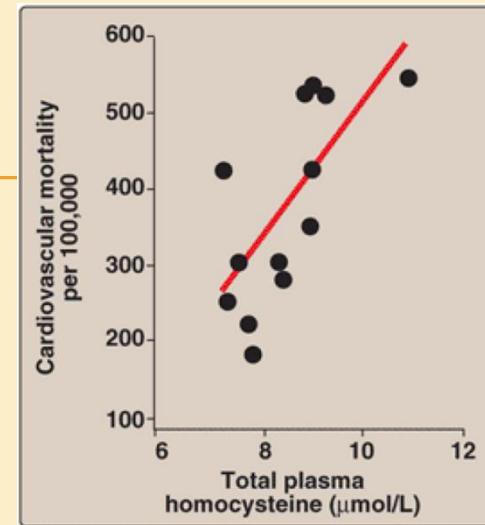
1. METHIONINE



RELATIONSHIP OF HOMOCYSTEINE TO VASCULAR DISEASE

✗ Elevations in plasma homocysteine levels promote:

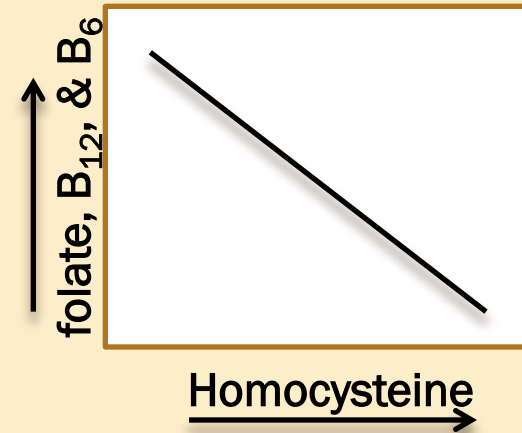
- + Oxidative damage
- + Inflammation
- + Endothelial dysfunction



✗ Independent risk factor for occlusive vascular disease

✗ Mild elevations are seen in $\approx 7\%$ of the population

✗ Plasma homocysteine levels are inversely related to (folate, B₁₂, & B₆)



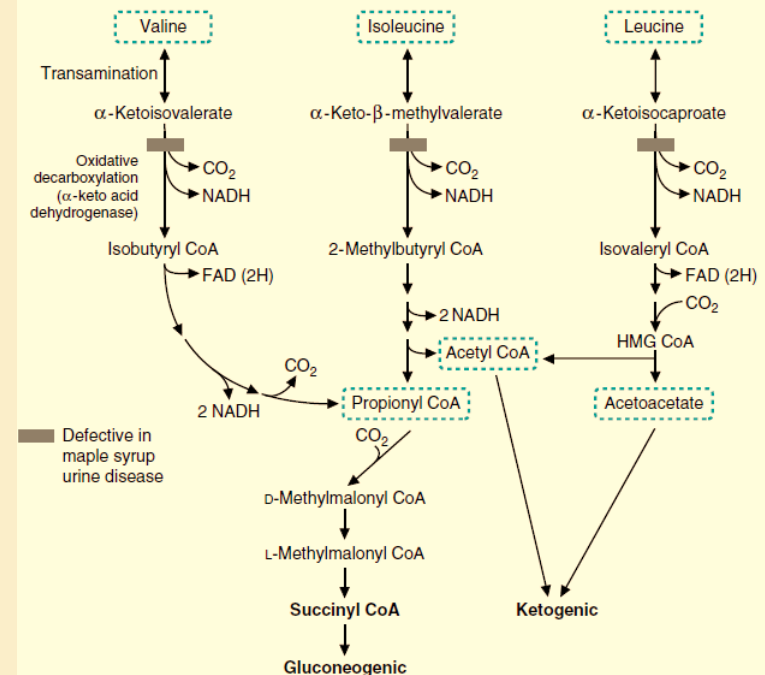
✗ Vitamins are involved in conversion of homocysteine to methionine or cysteine

✗ Supplementation reduce circulating levels of homocysteine; however, no proof to result in reduced cardiovascular morbidity and mortality (a cause or a marker)

E. AMINO ACIDS THAT FORM SUCCINYL- COA

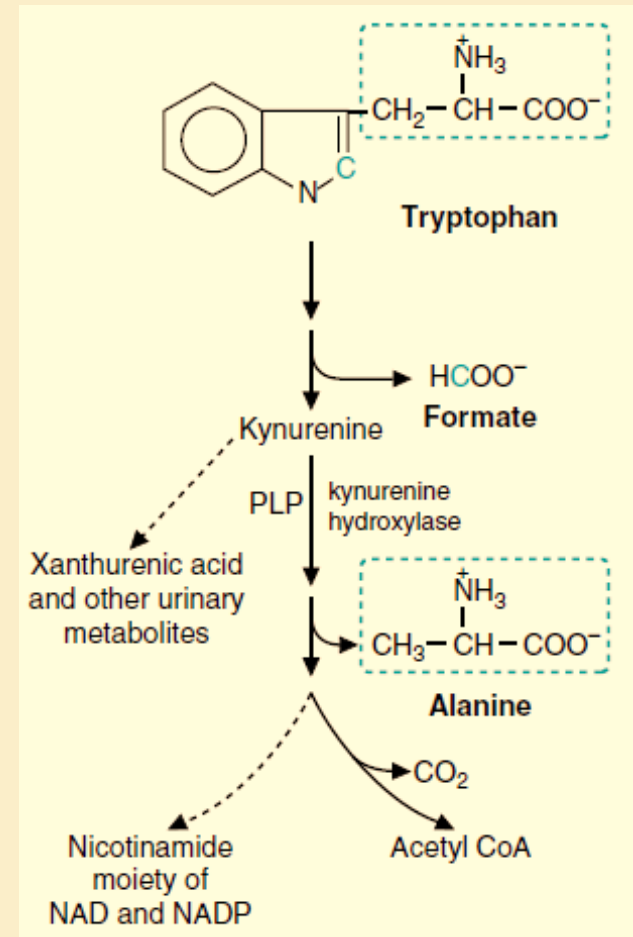
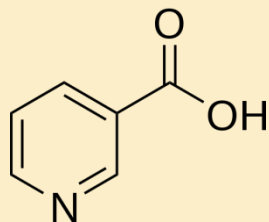
✗ 2. VALINE & ISOLEUCINE

- + Branched-chain amino acids (V, I, L)
- + Almost 25% of the content of the average protein (energy)
- + Highest degradation activity is in muscle (energy)
- + Degradative pathway functions: energy generation & anaplerotic
- + Starts with branched-chain α -amino acid aminotransferase (PLP), followed by oxidative decarboxylation (α -keto acid dehydrogenase) (TPP, Lipoate, FAD)
- + NADH & FADH₂ are generated (energy)
- + Isoleucine also forms, in addition, acetyl CoA
- + Leucine, does not produce succinyl CoA (acetoacetate and acetyl CoA), strictly ketogenic



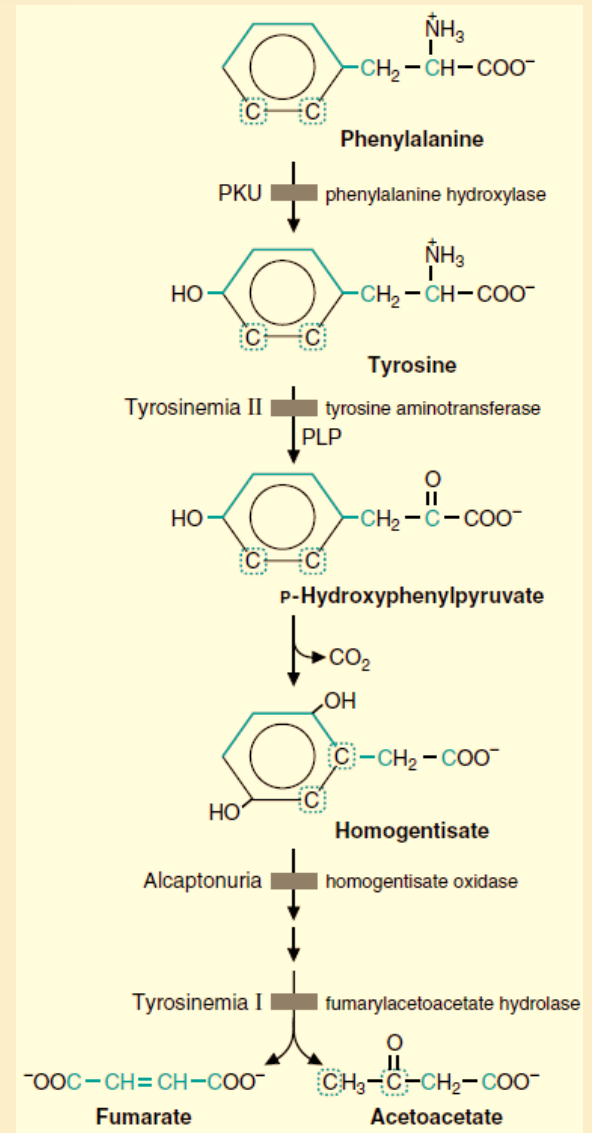
F. AMINO ACIDS THAT FORM ACETYL COA & ACETOACETATE (KETOGENIC)

- ✗ Leucine and lysine produce acetyl CoA and acetoacetate, therefore strictly ketogenic
- ✗ Others are ketogenic and glucogenic
- ✗ **A. Tryptophan**
 - + Non-ring carbons oxidized to form alanine
 - + Ring carbon oxidized to acetyl CoA
 - + NAD^+ & NADP^+ can be produced from the ring structure of tryptophan (niacin requirements)



F. AMINO ACIDS THAT FORM ACETYL COA & ACETOACETATE

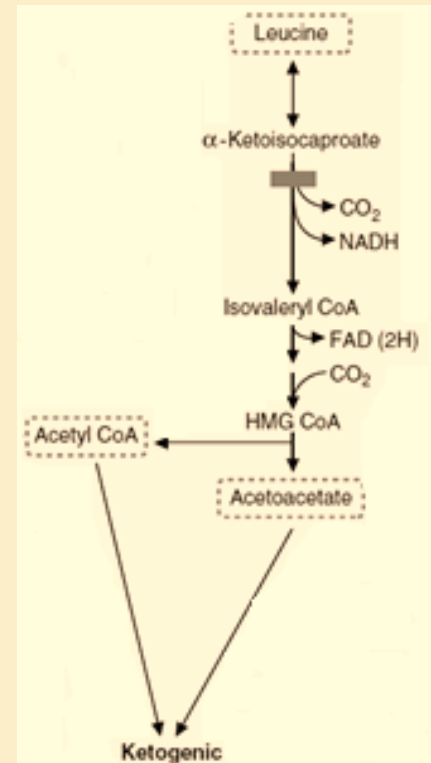
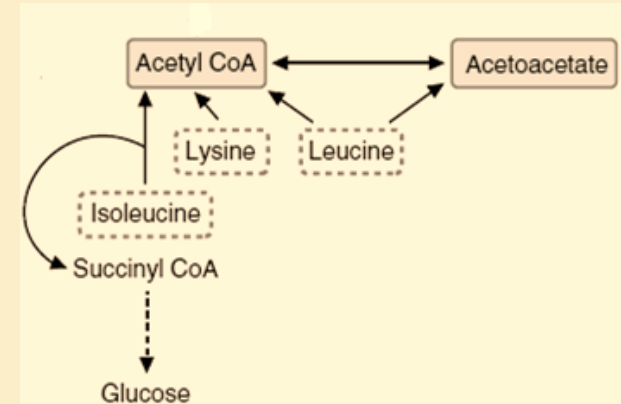
- ✗ B. Phenylalanine and Tyrosine
 - + Phenylalanine hydroxylase (PAH)
 - + Requires molecular O_2 and BH_4
 - + Tyrosine undergoes oxidative degradation
 - + Eventually forms fumarate & acetoacetate
 - + Deficiencies of different enzymes result in phenylketonuria, tyrosinemia, and alcaptonuria



F. AMINO ACIDS THAT FORM ACETYL COA & ACETOACETATE

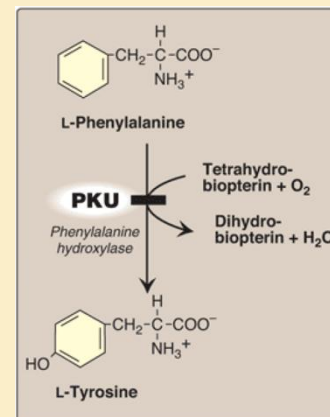
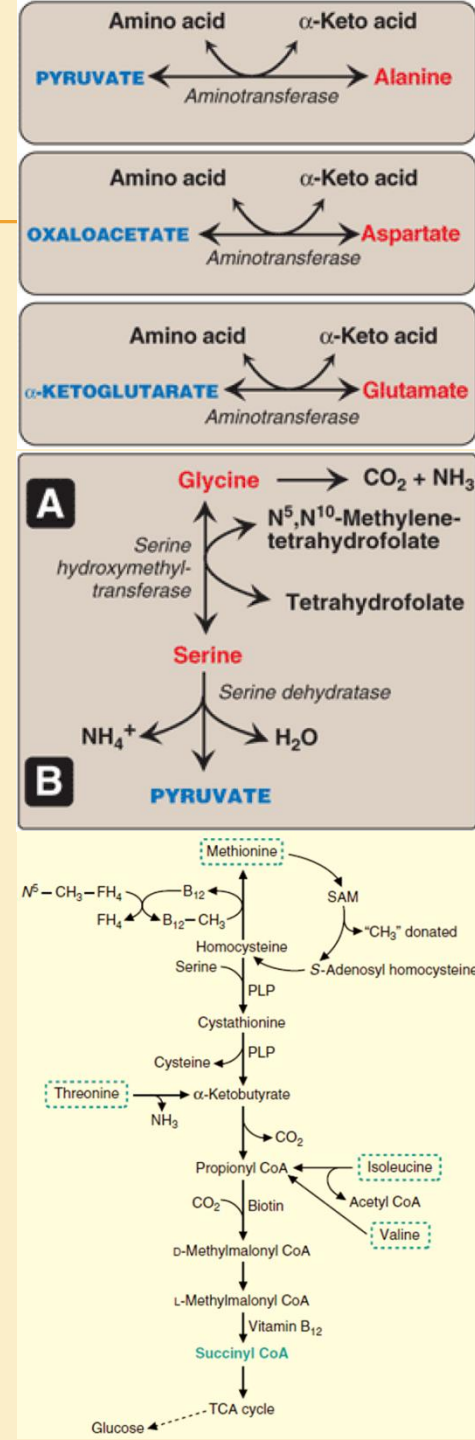
✖ C. Isoleucine, Leucine, & Lysine

- + Leucine and Isoleucine, as previously
- + Leucine produces hydroxymethylglutaryl CoA (HMGCoA), which is cleaved to form acetyl CoA and acetoacetate
- + Lysine is purely ketogenic (acetyl CoA)
- + During the degradation pathway NADH & FADH₂ are generated for energy



BIOSYNTHESIS OF NONESSENTIAL AMINO ACIDS

- ✗ Synthesized from intermediates of metabolism or, as in the case of tyrosine & cysteine
- ✗ A. Synthesis from α -keto acids: Alanine, aspartate, and glutamate
- ✗ B. Synthesis by amidation: Glutamine & Asparagine
- ✗ C. Proline: Glutamate converted to proline by cyclization & reduction rxns
- ✗ D. Serine, glycine, & cysteine:
 - + Serine: from glycine (serine hydroxymethyl transferase)
 - + Glycine: from serine (serine hydroxymethyl transferase)
 - + Cysteine: from homocysteine & serine
- ✗ E. Tyrosine: from phenylalanine

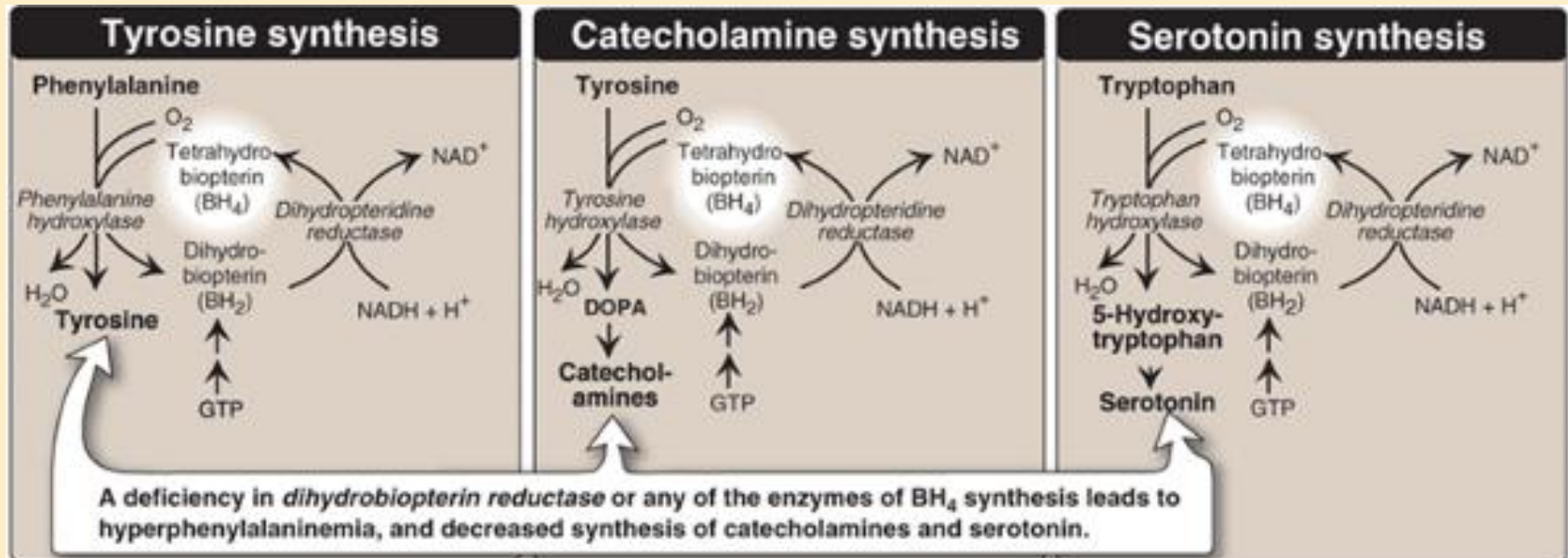


METABOLIC DEFECTS IN AMINO ACID METABOLISM

- ✗ Commonly caused by mutant genes
- ✗ The inherited defects may be total or, mostly, partial deficiency in catalytic activity
- ✗ Without treatment, result in mental retardation or other developmental abnormalities
- ✗ More than 50 have been described, many are rare
- ✗ Phenylketonuria is relatively common

PHENYLKETONURIA (PKU)

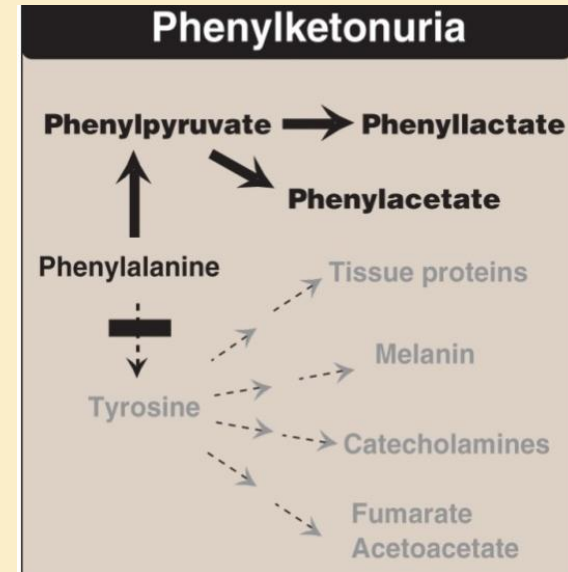
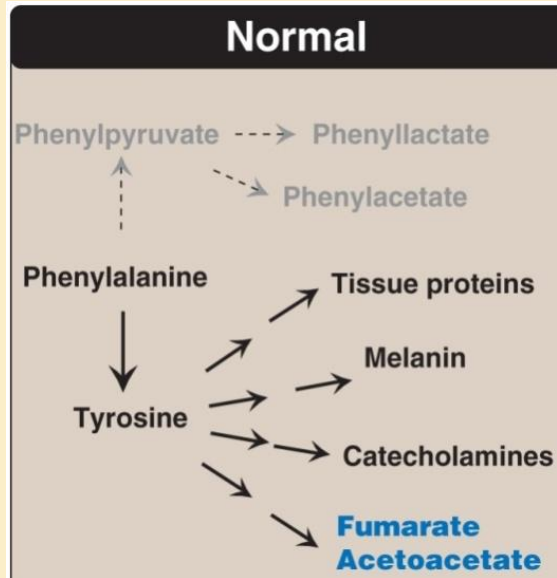
- ✗ Deficiency of phenylalanine hydroxylase, most common clinically encountered inborn error of amino acid metabolism
- ✗ Characterized by accumulation of phenylalanine & a deficiency of tyrosine
- ✗ Restricting dietary phenylalanine does not reverse the CNS effects (deficiencies in neurotransmitters)
- ✗ Replacement therapy improves the clinical outcome



PHENYLKETONURIA (PKU)

✖ Characteristics of PKU:

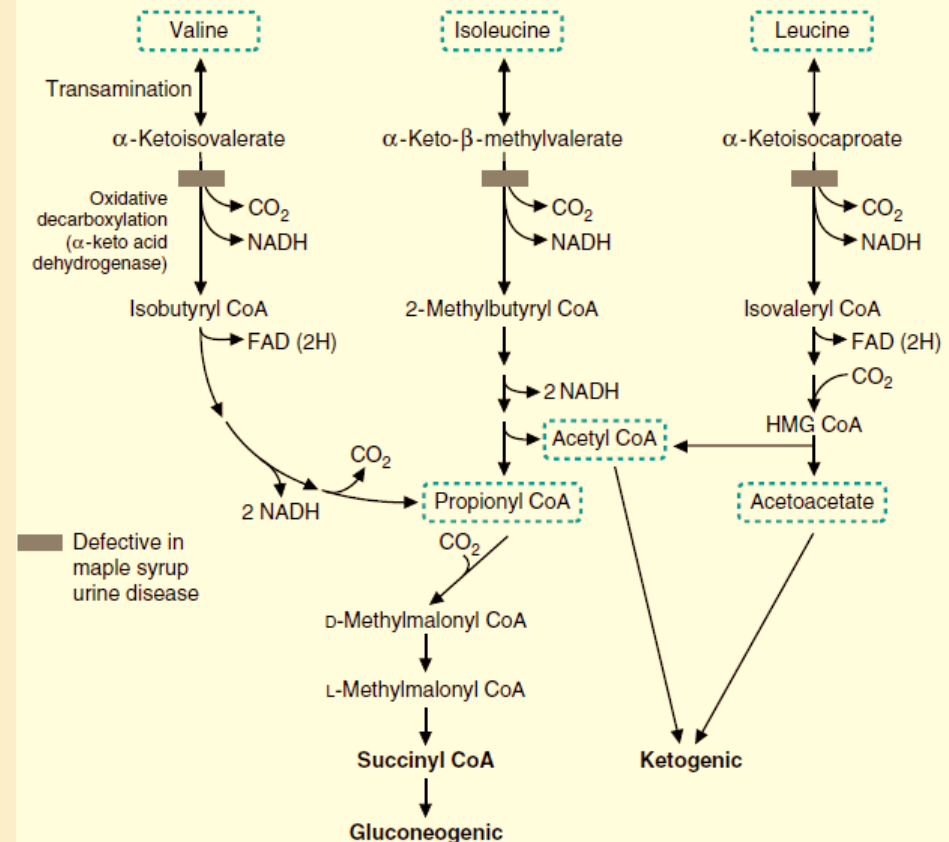
- + Elevated metabolites: musty (“mousey”) odor
- + CNS symptoms: Mental retardation, failure to walk or talk, seizures,, and failure to grow



- + Untreated PKU typically shows symptoms of mental retardation by year 1 (neonatal screening, 24 to 48 hours of protein feeding)
- + Hypopigmentation: fair hair, light skin color, and blue eyes. The hydroxylation of tyrosine by tyrosinase, is the first step in the formation of the pigment melanin. It is competitively inhibited by the high levels of phenylalanine

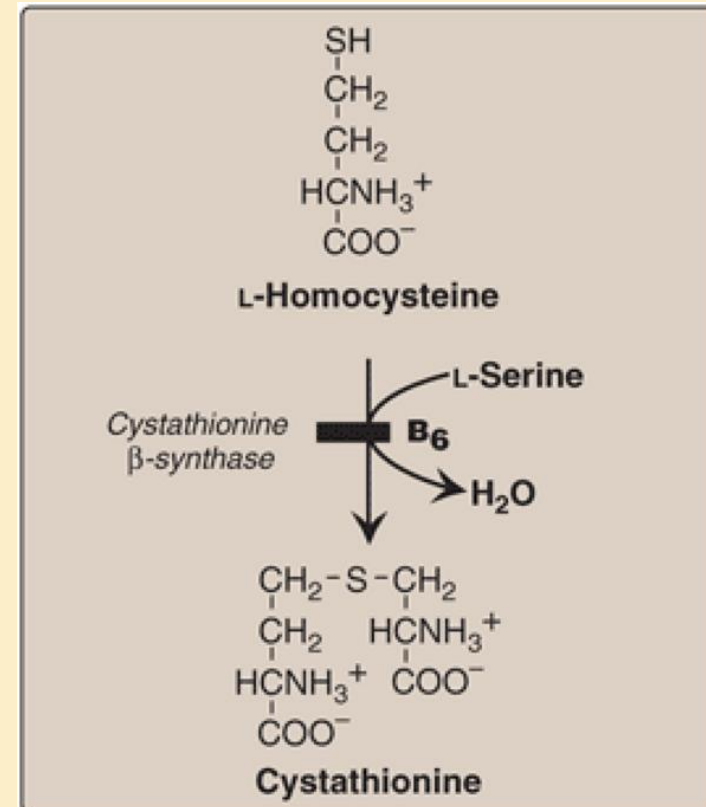
MAPLE SYRUP URINE DISEASE

- ✖ Rare (1:185,000), autosomal recessive disorder
- ✖ Partial/complete deficiency (branched-chain α -keto acid dehydrogenase)
- ✖ These amino acids and their corresponding α -keto acids accumulate in the blood, causing a toxic effect that interferes with brain functions
- ✖ The disease is characterized by feeding problems, vomiting, dehydration, severe metabolic acidosis, & a characteristic maple syrup odor to the urine
- ✖ If untreated, leads to mental retardation, physical disabilities, & even death
- ✖ Screening/diagnosis are available
- ✖ Treatment: synthetic formula - limited amounts of leucine, isoleucine, and valine — sufficient



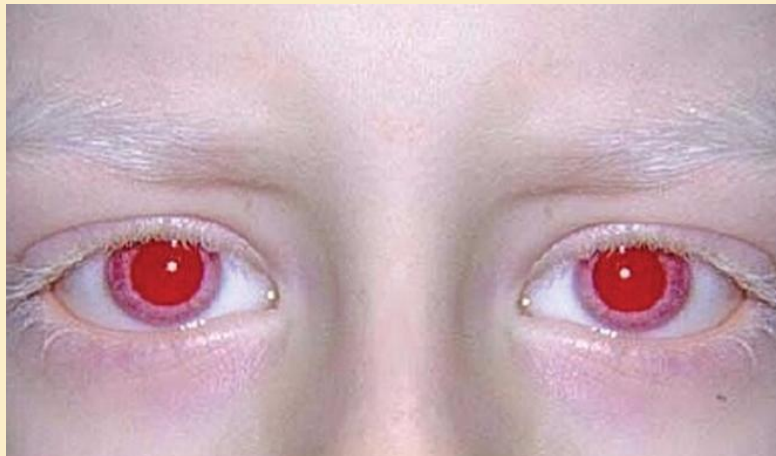
HOMOCYSTINURIA

- ✗ A group of disorders involving defects in the metabolism of homocysteine
- ✗ Inherited as autosomal recessive illnesses
- ✗ Characterized by high plasma and urinary levels of homocysteine & methionine & low levels of cysteine
- ✗ The most common cause of homocystinuria is a defect in the enzyme cystathionine β -synthase, which converts homocysteine to cystathionine
- ✗ Patients can be responsive or nonresponsive to oral pyridoxine (B_6)—a coenzyme of cystathionine β -synthase
- ✗ Responsive patients usually have a milder and later onset of clinical symptoms
- ✗ Treatment: restriction of methionine intake & supplementation with vitamins B_6 , B_{12} , & folate



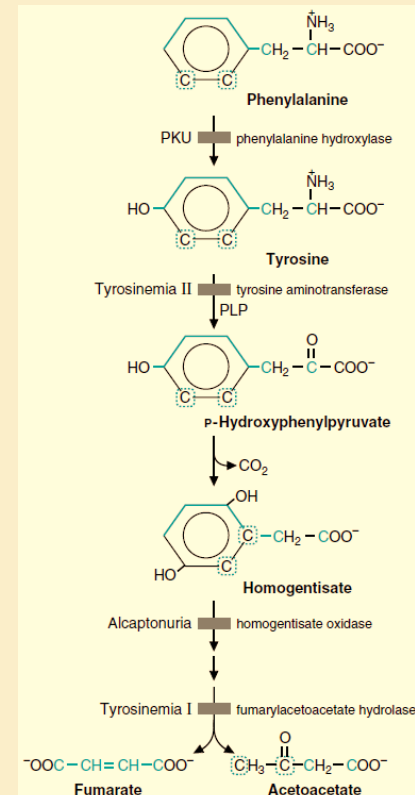
ALBINISM

- ✗ Refers to a group of conditions in which a defect in tyrosine metabolism results in a partial or full deficiency in the production of melanin
- ✗ Inherited by several modes: autosomal recessive, autosomal dominant, or X-linked
- ✗ Complete albinism - rare (the most severe form of the condition) results from a complete deficiency of tyrosinase activity, causing a total absence of pigment from the hair, eyes, and skin
- ✗ In addition: vision defects and photophobia and higher risk for skin cancer

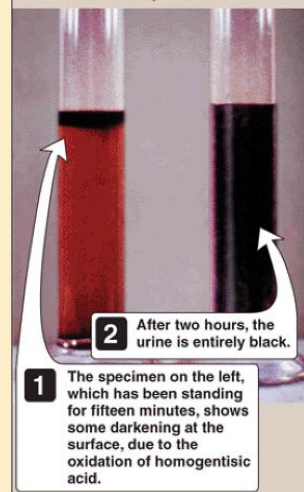


ALKAPTONURIA

- ✗ A rare metabolic disease
- ✗ A deficiency in homogentisic acid oxidase → accumulation of homogentisic acid (degradative pathway of tyrosine)
- ✗ Three characteristic symptoms:
 - + Homogentisic aciduria (elevated levels of homogentisic acid, which is oxidized to a dark pigment)
 - + Large joint arthritis
 - + Black ochronotic pigmentation of cartilage & collagenous tissue
- ✗ Patients asymptomatic until about age 40
- ✗ Diets low in protein— especially Phe & Tyr
- ✗ Although alkaptonuria is not life-threatening, the associated arthritis may be severely crippling



A Urine from a patient with alkaptonuria



B Vertebrae from a patient with alkaptonuria

