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# 20: Amino Acids: Degradation and Synthesis

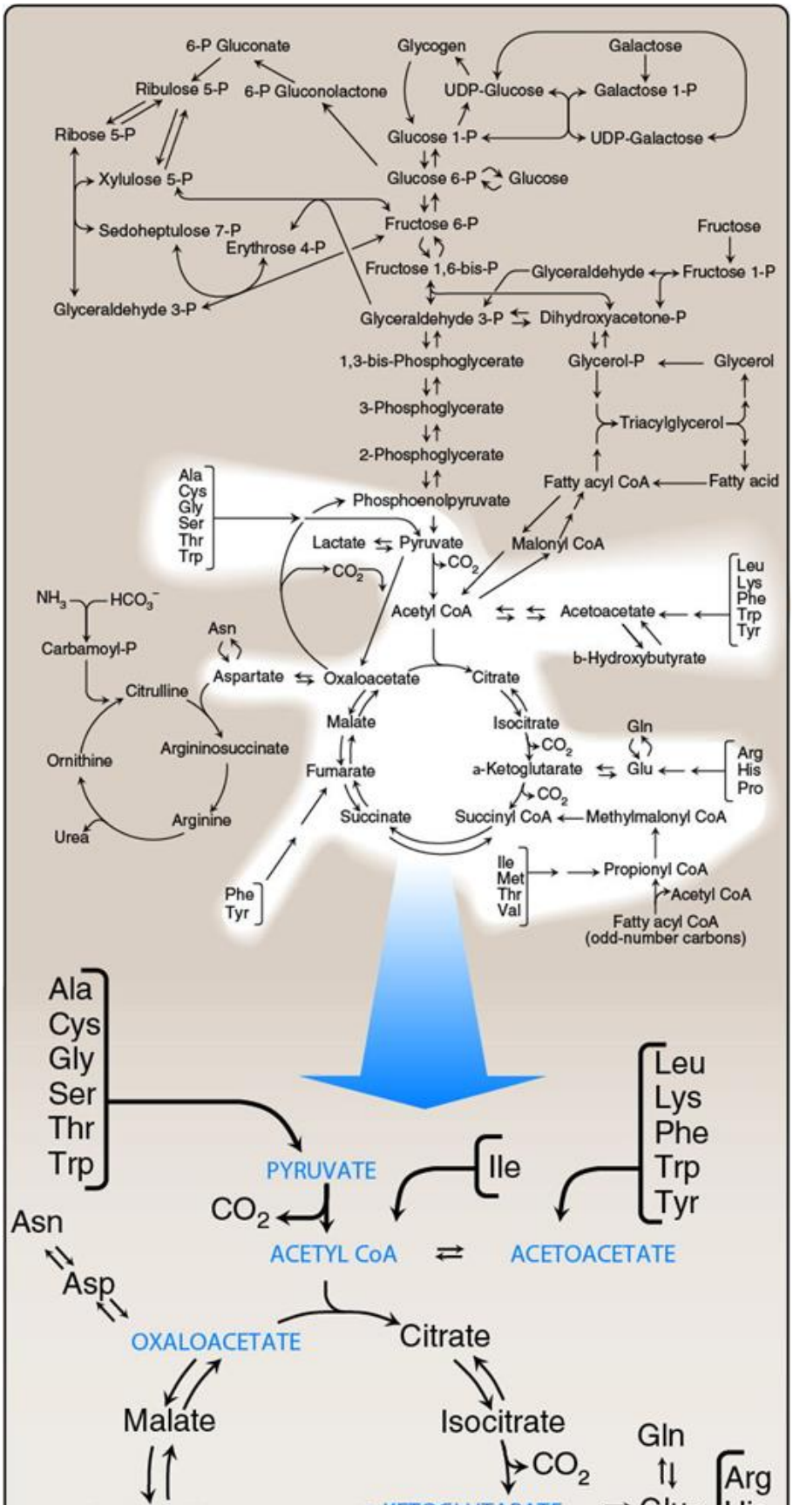
## Overview

Amino acid degradation involves removal of the α-amino group, followed by the catabolism of the resulting α-keto acids (carbon skeletons). The degradation pathways of the various amino acids converge to form seven intermediate products: oxaloacetate, pyruvate, α-ketoglutarate, fumarate, succinyl coenzyme A (CoA), acetyl CoA, and acetoacetate. The products directly enter the pathways of intermediary metabolism, resulting either in the synthesis of glucose, ketone bodies, or lipids or in the production of energy through their oxidation to carbon dioxide ($CO_2$) by the tricarboxylic acid (TCA) cycle. Figure 20.1 provides an overview of these pathways, with a more detailed summary presented in Figure 20.15 (see p. 299). Nonessential amino acids (Fig. 20.2) can be synthesized in sufficient amounts from the intermediates of metabolism or, as in the case of cysteine and tyrosine, from essential amino acids. In contrast, because the essential amino acids cannot be synthesized (or synthesized in sufficient amounts) by humans, they must be obtained from the diet in order for normal protein synthesis to occur. Genetic defects in the pathways of amino acid metabolism can cause serious disease.

**FIGURE 20.1**

## Amino acid metabolism shown as a part of the essential pathways of energy metabolism.

(see Fig. 8.2 for a more detailed map of metabolism.) CoA = coenzyme A; $CO_2$ = carbon dioxide.



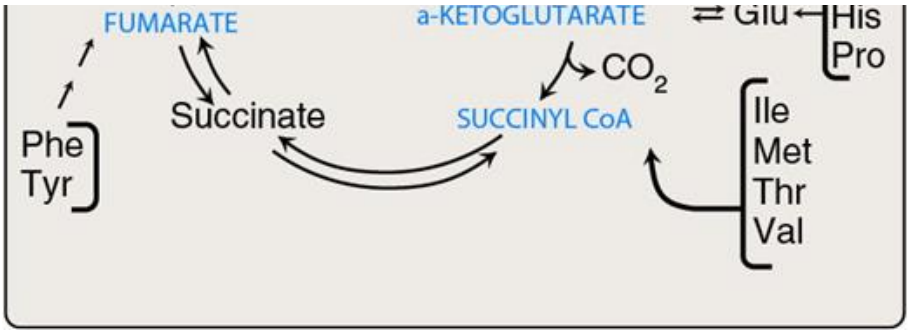



**FIGURE 20.2**

### 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<br>Arginine<br>Asparagine<br>Aspartate<br>Cysteine<br>Glutamate<br>Glutamine<br>Glycine<br>Proline<br>Serine | Tyrosine | |
| Essential | Histidine<br>Methionine<br>Threonine<br>Valine | Isoleucine<br>Phenyl-alanine<br>Tryptophan | Leucine<br>Lysine |

## Glucogenic and Ketogenic Amino Acids

Amino acids can be classified as glucogenic, ketogenic, or both, based on which of the seven intermediates are produced during their catabolism (see Fig. 20.2).

### Glucogenic amino acids

Amino acids whose catabolism yields pyruvate or one of the intermediates of the TCA cycle are termed glucogenic. Because these intermediates are substrates for gluconeogenesis (see p. 129), they can give rise to the net synthesis of glucose in the liver and kidney.

**Color-coding used in this chapter:**

- BLUE CAPS TEXT = names of seven products of amino acid metabolism
- Red text = names of glucogenic amino acids
- Brown text = names of glucogenic and ketogenic amino acids
- Green text = names of ketogenic amino acids
- Cyan text = one-carbon compounds

### Ketogenic amino acids

Amino acids whose catabolism yields either acetyl CoA (directly, without pyruvate serving as an intermediate) or acetoacetate (or its precursor acetoacetyl CoA) are termed ketogenic (see Fig. 20.2). Acetoacetate is one of the ketone bodies, which also include 3-hydroxybutyrate and acetone (see p. 216). Leucine and lysine are the only exclusively ketogenic amino acids found in proteins. Their carbon skeletons are not substrates for gluconeogenesis and, therefore, cannot give rise to the net synthesis of glucose.

## Amino Acid Carbon Skeleton Catabolism

The pathways by which amino acids are catabolized are conveniently organized according to which one (or more) of the seven intermediates listed above is produced from a particular amino acid.

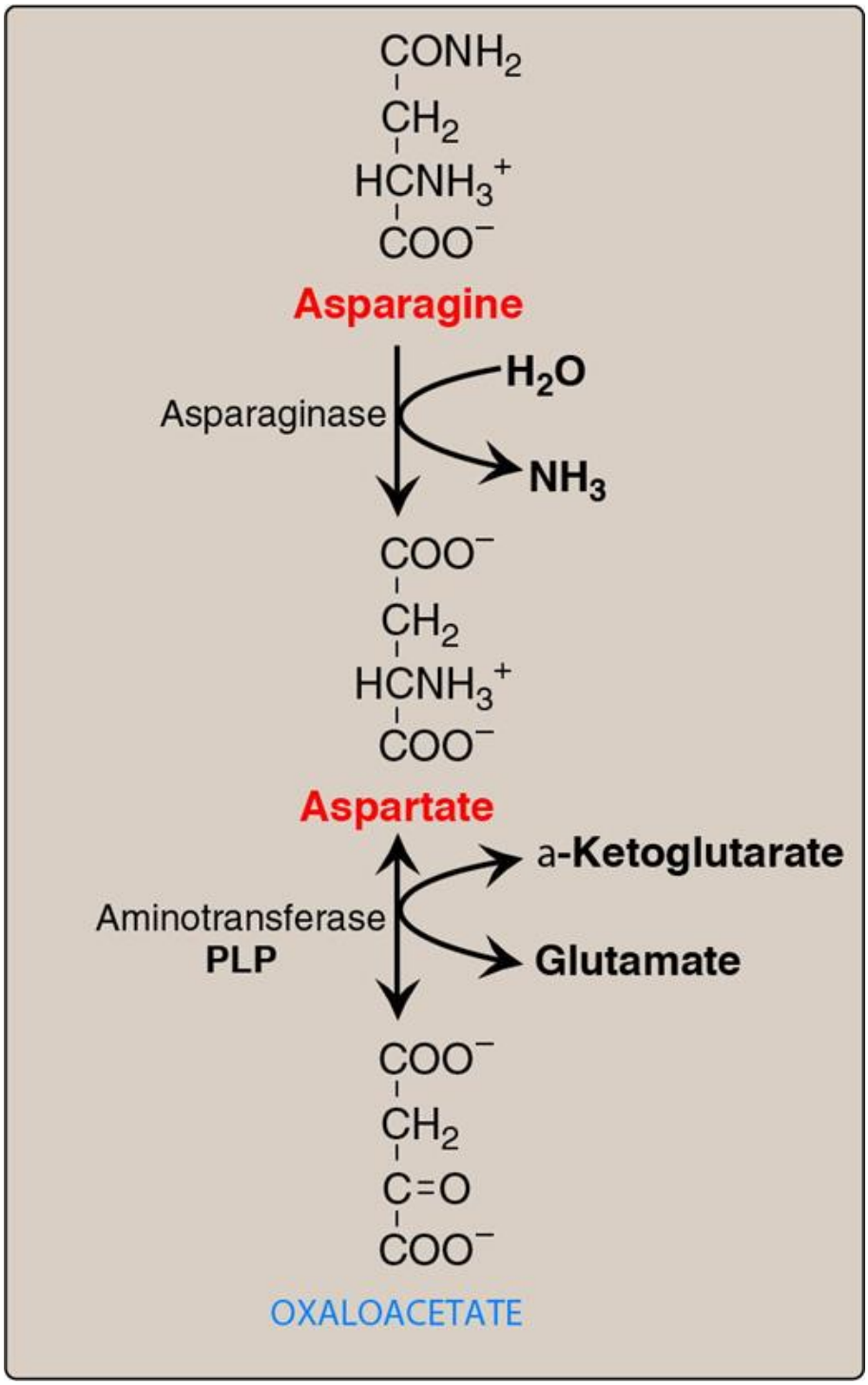
### Amino acids that form oxaloacetate

Asparagine is hydrolyzed by asparaginase, liberating ammonia and aspartate (Fig. 20.3). Aspartate is converted to its corresponding ketoacid by transamination to form oxaloacetate (see Fig. 20.3). (Note: Some rapidly dividing leukemic cells are unable to synthesize sufficient asparagine to support their growth. This makes asparagine an essential amino acid for these cells, which, therefore, require asparagine from the blood. Asparaginase, which hydrolyzes asparagine to aspartate, can be administered systemically to treat leukemia. Asparaginase lowers the level of asparagine in the plasma, thereby depriving cancer cells of a required nutrient.)

**FIGURE 20.3**

### Metabolism of asparagine and aspartate.

PLP = pyridoxal phosphate; $NH_3$ = ammonia.




## Amino acids that form α-ketoglutarate via glutamate

### Glutamine

This amino acid is hydrolyzed to glutamate and ammonia by the enzyme glutaminase (see p. 283). Glutamate is converted to α-ketoglutarate by transamination or through oxidative deamination by glutamate dehydrogenase (see p. 278).

### Proline

This amino acid is oxidized to glutamate. Glutamate is transaminated or oxidatively deaminated to form α-ketoglutarate.

### Arginine

This amino acid is hydrolyzed by arginase to produce ornithine (and urea). (Note: The reaction occurs primarily in the liver as part of the urea cycle [see p. 281].) Ornithine is subsequently converted to α-ketoglutarate, with glutamate semialdehyde as an intermediate.

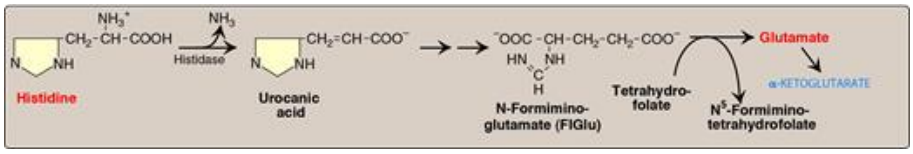
### Histidine

Histidine is oxidatively deaminated by histidase to urocanic acid, which subsequently forms N-formiminoglutamate ([FIGlu], Fig. 20.4). FIGlu donates its formimino group to tetrahydrofolate (THF), leaving glutamate, which is degraded as described above. A deficiency in histidase results in the relatively benign inborn error of metabolism histidinemia, characterized by elevated levels of histidine in blood and urine. (Note: Individuals deficient in folic acid excrete increased amounts of FIGlu in the urine, particularly after ingestion of a large dose of histidine. The FIGlu excretion test has been used in diagnosing a deficiency of folic acid. See p. 296 for a discussion of folic acid, THF, and one-carbon metabolism.)

**FIGURE 20.4**

### Degradation of histidine.

$NH_3$ = ammonia.




## Amino acids that form pyruvate

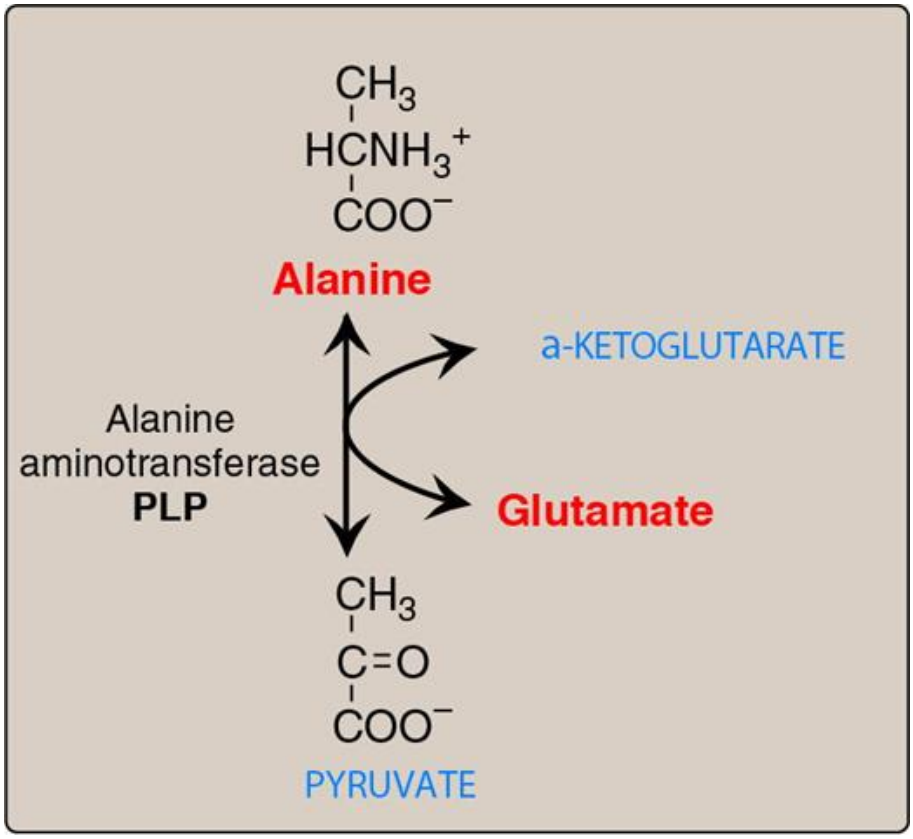
### Alanine

This amino acid loses its amino group by transamination to form pyruvate (Fig. 20.5). (Note: Tryptophan catabolism produces alanine and, therefore, pyruvate [see Fig. 20.10 on p. 294].)

**FIGURE 20.5**

### Transamination of alanine to pyruvate.

PLP = pyridoxal phosphate.

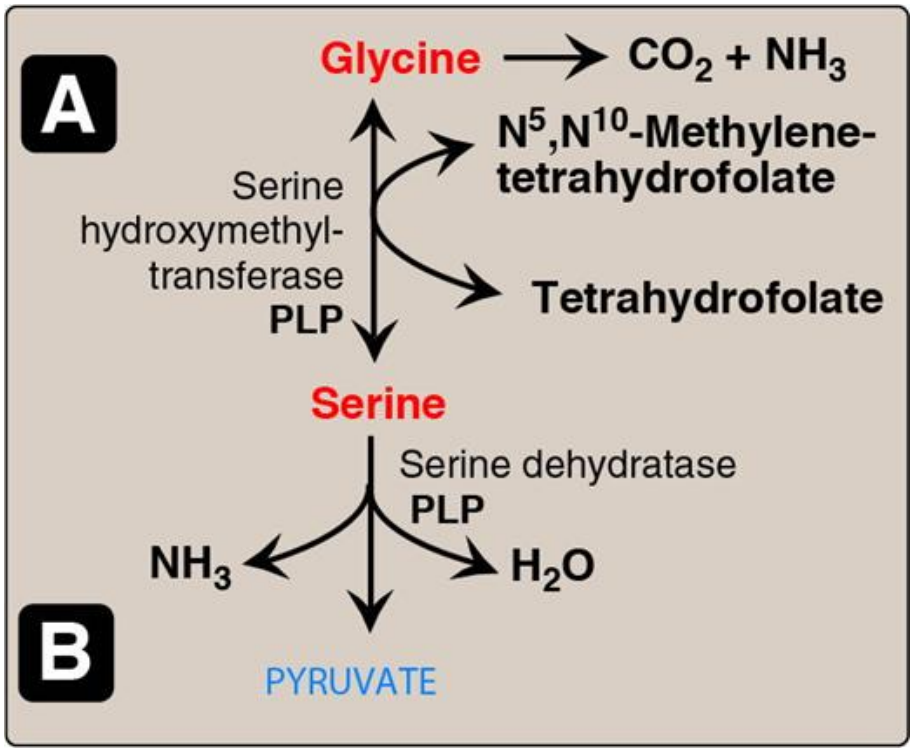



### Serine

This amino acid can be converted to glycine as THF becomes $N^5$,$N^{10}$-methylenetetrahydrofolate ($N^5$,$N^{10}$-MTHF), as shown in Figure 20.6A. Serine can also be converted to pyruvate (see Fig. 20.6B).

**FIGURE 20.6**

**A:** Interconversion of serine and glycine and oxidation of glycine. **B:** Dehydration of serine to pyruvate. PLP = pyridoxal phosphate; $NH_3$ = ammonia.




### Glycine

This amino acid can be converted to serine by the reversible addition of a methylene group from $N^5,N^{10}$-MTHF (see Fig. 20.6A) or oxidized to $CO_2$ and ammonia by the glycine cleavage system. Glycine can be deaminated to glyoxylate (by a d-amino acid oxidase; see p. 279), which can be oxidized to oxalate or transaminated to glycine. Deficiency of the transaminase in liver peroxisomes causes overproduction of oxalate, the formation of oxalate stones, and kidney damage (primary oxaluria type 1).

### Cysteine

This sulfur-containing amino acid undergoes desulfurization to yield pyruvate. (Note: The sulfate released can be used to synthesize 3′-phosphoadenosine-5′-phosphosulfate [PAPS], an activated sulfate donor to a variety of acceptors.) Cysteine can also be oxidized to its disulfide derivative, cystine.

### Threonine

This amino acid is converted to pyruvate in most organisms but is a minor pathway (at best) in humans.

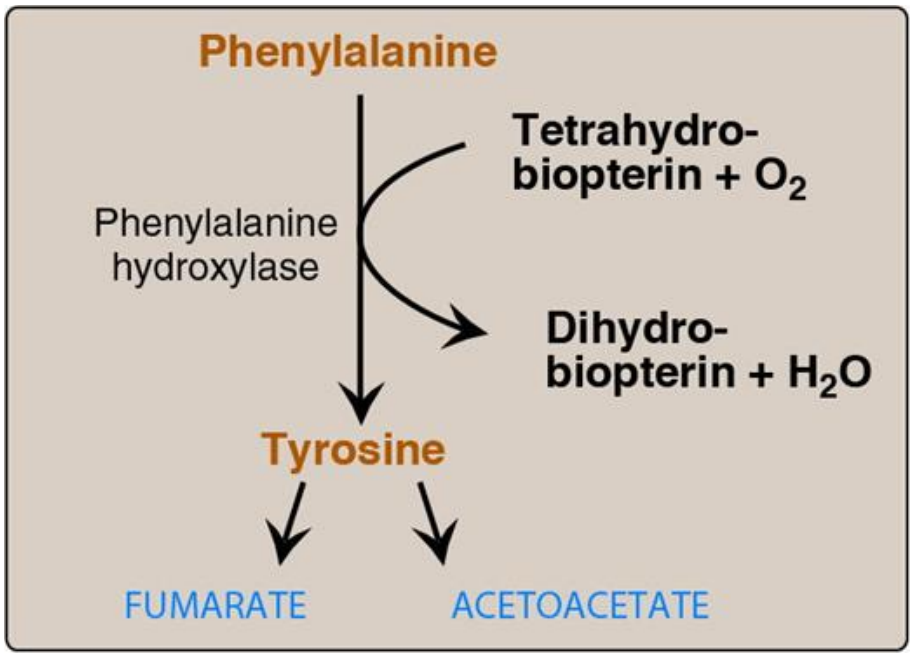
## Amino acids that form fumarate

### Phenylalanine and tyrosine

Hydroxylation of phenylalanine produces tyrosine (Fig. 20.7). This irreversible reaction, catalyzed by tetrahydrobiopterin ($BH_4$)-requiring phenylalanine hydroxylase (PAH), initiates the catabolism of phenylalanine. Thus, phenylalanine metabolism and tyrosine metabolism merge, leading ultimately to fumarate and acetoacetate formation. Therefore, phenylalanine and tyrosine are both glucogenic and ketogenic.

**FIGURE 20.7**

**Degradation of phenylalanine.**




### Inherited deficiencies

Inherited deficiencies in the enzymes of phenylalanine and tyrosine metabolism lead to the diseases phenylketonuria (PKU) (see p. 298), tyrosinemia (see p. 303), and alkaptonuria (see p. 303) as well as the condition of albinism (see p. 303).

## Amino acids that form succinyl CoA: methionine

Methionine is one of four amino acids that form succinyl CoA. This sulfur-containing amino acid deserves special attention because it is converted to *S*-adenosylmethionine (SAM), the major methyl group donor in one-carbon metabolism (Fig. 20.8). Methionine is also the source of homocysteine (Hcy), a metabolite associated with atherosclerotic vascular disease and thrombosis (see p. 294).

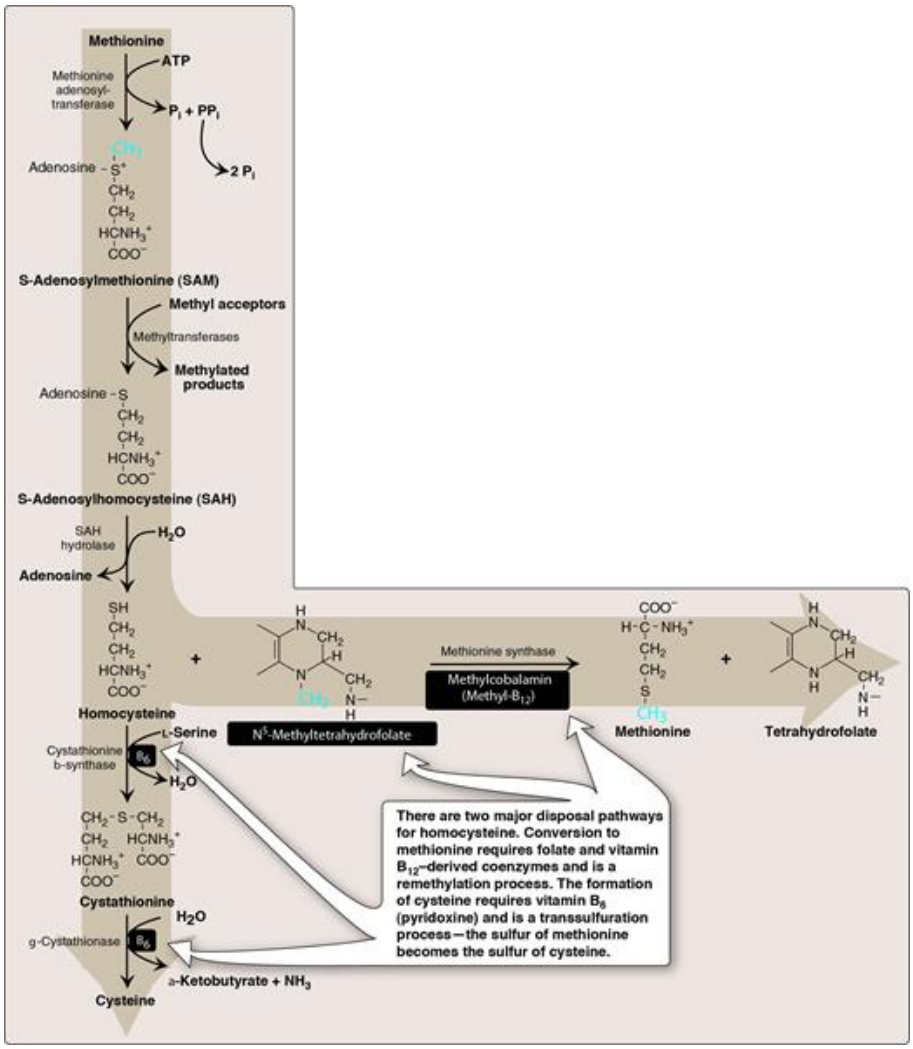
### S-Adenosylmethionine synthesis

Methionine condenses with ATP, forming SAM, a high-energy compound that is unusual in that it contains no phosphate. The formation of SAM is driven by hydrolysis of all three phosphate bonds in ATP (see Fig. 20.8).

**FIGURE 20.8**

## 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 [$-CH_3$] group. In all other reactions, SAM is the methyl group carrier and donor.) $PP_i$ = pyrophosphate; $P_i$ = inorganic phosphate; $NH_3$ = ammonia.




## Activated methyl group

The methyl group attached to the sulfur in SAM is activated and can be transferred by methyltransferases to a variety of acceptors such as norepinephrine in the synthesis of epinephrine. The methyl group is usually transferred to nitrogen or oxygen atoms (as with epinephrine synthesis and degradation, respectively; see p. 318) and sometimes to carbon atoms (as with cytosine). The reaction product, *S*-adenosylhomocysteine (SAH), is a simple thioether, analogous to methionine. The resulting loss of free energy makes methyl transfer essentially irreversible.

## S-Adenosylhomocysteine hydrolysis

After donation of the methyl group, SAH is hydrolyzed to Hcy and adenosine. Hcy has two fates. If there is a deficiency of methionine, Hcy may be remethylated to methionine (see Fig. 20.8). If methionine stores are adequate, Hcy may enter the transsulfuration pathway, where it is converted to cysteine.

#### Methionine resynthesis

Hcy accepts a methyl group from $N^5$-methyltetrahydrofolate ($N^5$-methyl-THF) in a reaction requiring methylcobalamin, a coenzyme derived from vitamin $B_{12}$ (see p. 425). (Note: The methyl group is transferred by methionine synthase from the $B_{12}$ derivative to Hcy, regenerating methionine. Cobalamin is remethylated from $N^5$-methyl-THF.)

#### Cysteine synthesis

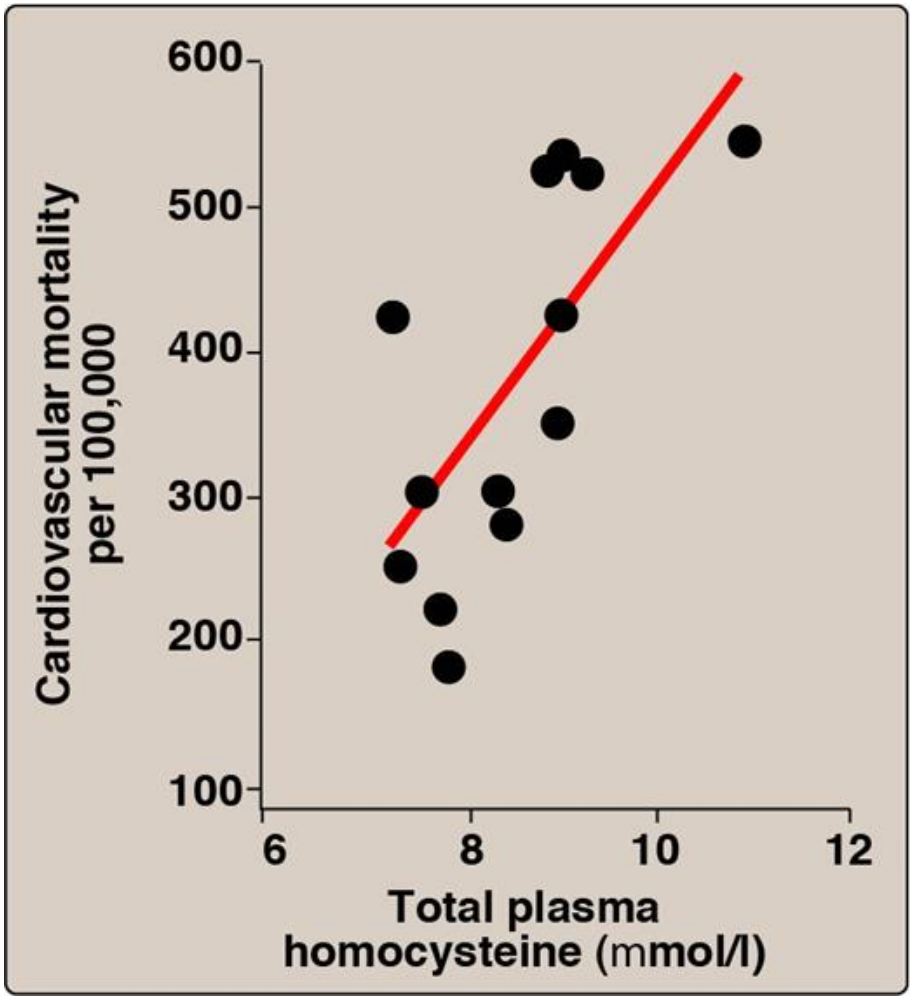
Catalyzed by cystathionine β-synthase, Hcy condenses with serine, forming cystathionine, which is hydrolyzed to α-ketobutyrate and cysteine (see Fig. 20.8). This vitamin $B_6$–requiring sequence has the net effect of converting serine to cysteine and Hcy to α-ketobutyrate, which is oxidatively decarboxylated to form propionyl CoA. Propionyl CoA is converted to succinyl CoA (see Fig. 16.20). Because Hcy is synthesized from the essential amino acid methionine, cysteine is not an essential amino acid as long as sufficient methionine is available.

### Relationship of homocysteine to vascular disease

Elevations in plasma Hcy levels promote oxidative damage, inflammation, and endothelial dysfunction and are an independent risk factor for occlusive vascular diseases such as cardiovascular disease (CVD) and stroke (Fig. 20.9). Mild elevations (hyperhomocysteinemia) are seen in ~7% of the population. Epidemiologic studies have shown that plasma Hcy levels are inversely related to plasma levels of folate, $B_{12}$, and $B_6$, the three vitamins involved in the conversion of Hcy to methionine and cysteine. Supplementation with these vitamins has been shown to reduce circulating levels of Hcy. However, in patients with established CVD, vitamin therapy does not decrease cardiovascular events or death. This raises the question as to whether Hcy is a cause of the vascular damage or merely a marker of such damage. (Note: Large elevations in plasma Hcy as a result of rare deficiencies in cystathionine β-synthase of the transsulfuration pathway are seen in patients with classic homocystinuria [resulting from severe hyperhomocysteinemia (>100 μmol/l), see p. 303].) Deficiencies in the remethylation reaction also result in a rise in Hcy.

**FIGURE 20.9**

**Association between cardiovascular disease mortality and total plasma homocysteine.**




In pregnant women, elevated Hcy levels usually indicate a deficiency in folic acid, which is associated with an increased incidence of neural tube defects (improper closure, as in spina bifida) in the fetus (see p. 425). Periconceptual supplementation with folate reduces the risk of such defects.

## Other amino acids that form succinyl CoA

Degradation of valine, isoleucine, and threonine also results in the production of succinyl CoA, a TCA cycle intermediate and gluconeogenic compound. (Note: It is metabolized to pyruvate.)

### Valine and isoleucine

These amino acids are branched-chain amino acids (BCAAs) that generate propionyl CoA, which is converted to methylmalonyl CoA and then succinyl CoA by biotin- and vitamin $B_{12}$–requiring reactions.

### Threonine

This amino acid is dehydrated to α-ketobutyrate, which is converted to propionyl CoA and then to succinyl CoA. Propionyl CoA, then, is generated by the catabolism of the amino acids methionine, valine, isoleucine, and threonine. (Note: Propionyl CoA also is generated by the oxidation of odd-numbered fatty acids [see p. 215].)

## Amino acids that form acetyl CoA or acetoacetyl CoA

Tryptophan, leucine, isoleucine, and lysine form acetyl CoA or acetoacetyl CoA directly, without pyruvate serving as an intermediate. As noted earlier, phenylalanine and tyrosine also give rise to acetoacetate during their catabolism (see Fig. 20.7). Therefore, there are a total of six partly or wholly ketogenic amino acids.

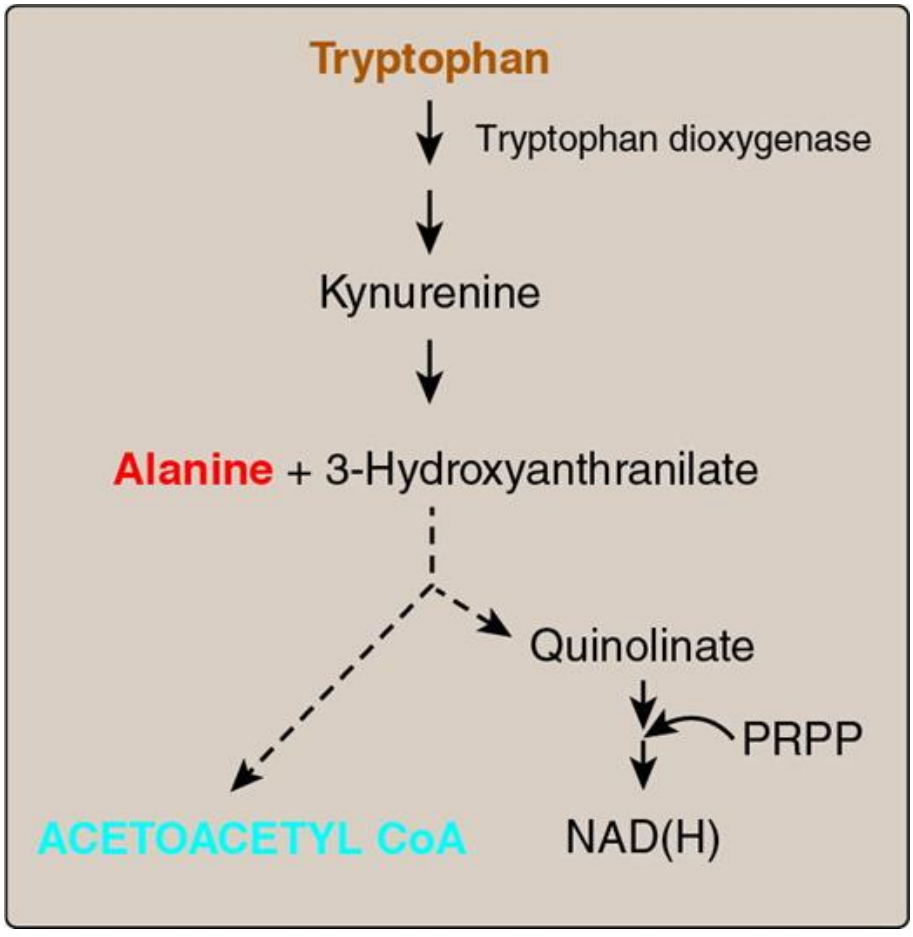
### Tryptophan

This amino acid is both glucogenic and ketogenic, because its catabolism yields alanine and acetoacetyl CoA (Fig. 20.10). (Note: Quinolinate from tryptophan catabolism is used in the synthesis of nicotinamide adenine dinucleotide [(NAD), see p. 430].)

**FIGURE 20.10**

**Metabolism of tryptophan by the kynurenine pathway (abbreviated).**

CoA = coenzyme A; PRPP = phosphoribosyl pyrophosphate; NAD(H) = nicotinamide adenine dinucleotide.



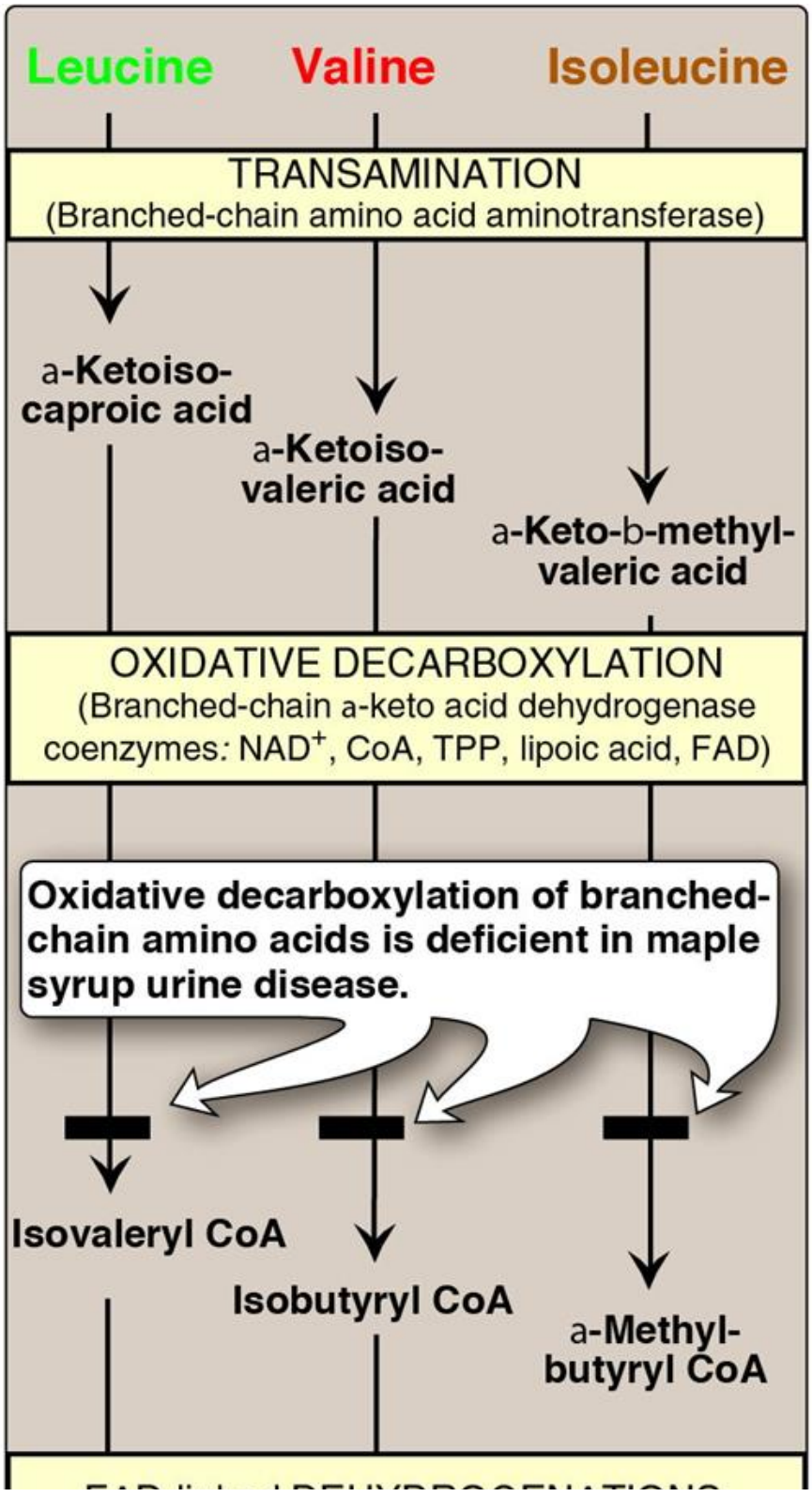

### Leucine

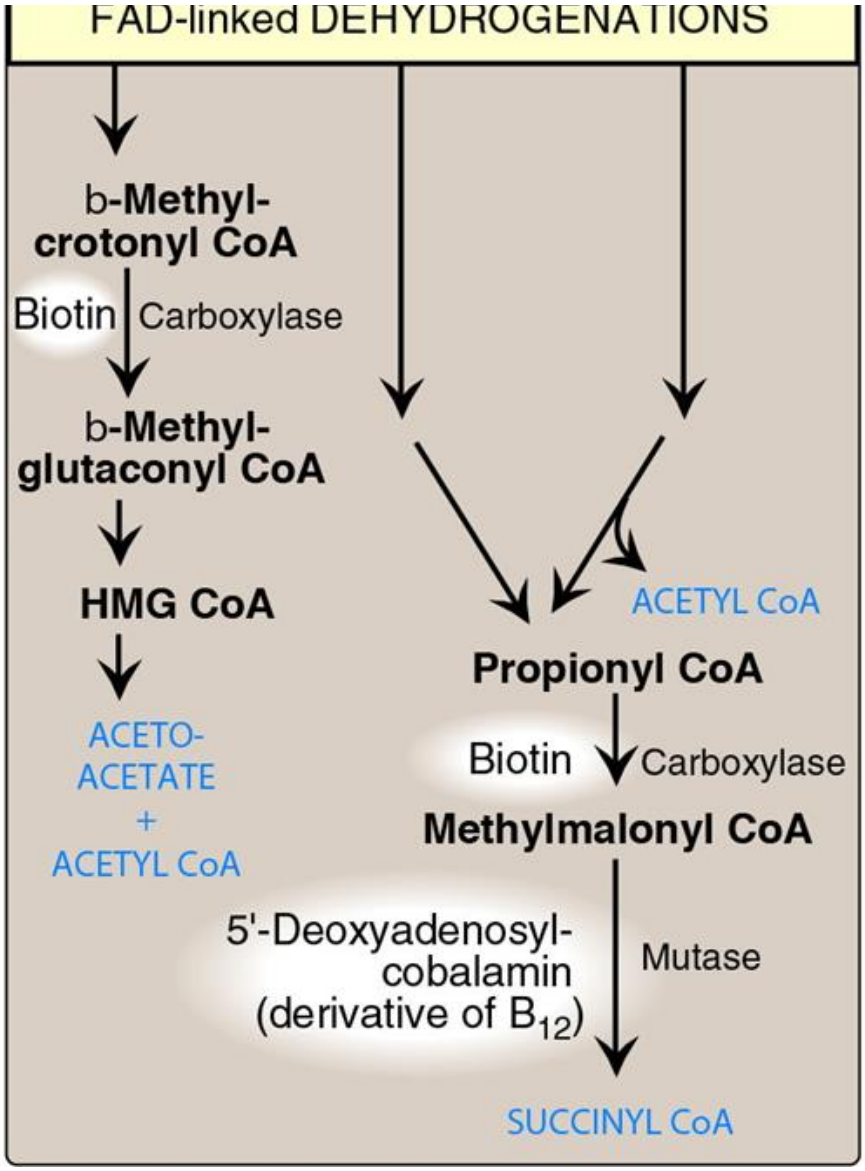
This amino acid is exclusively ketogenic, because its catabolism yields acetyl CoA and acetoacetate (Fig. 20.11). The first two reactions in the catabolism of leucine and the other BCAAs, isoleucine and valine, are catalyzed by enzymes that use all three BCAAs (or their derivatives) as substrates (see H. below).

**FIGURE 20.11**

### Degradation of leucine, valine, and isoleucine.

(Note: β-Methylcrotonyl CoA carboxylase is one of four biotin-requiring carboxylases discussed in this book. The other three are pyruvate carboxylase, acetyl CoA carboxylase, and propionyl CoA carboxylase.) TPP = thiamine pyrophosphate; FAD = flavin adenine dinucleotide; CoA = coenzyme A; NAD = nicotinamide adenine dinucleotide; HMG = hydroxymethylglutarate.






### Isoleucine

This amino acid is both ketogenic and glucogenic, because its metabolism yields acetyl CoA and propionyl CoA.

### Lysine

This amino acid is exclusively ketogenic and is unusual in that neither of its amino groups undergoes transamination as the first step in catabolism. Lysine is ultimately converted to acetoacetyl CoA.

## Branched-chain amino acid degradation

The BCAAs, isoleucine, leucine, and valine are essential amino acids. In contrast to other amino acids, they are catabolized primarily by the peripheral tissues (particularly muscle), rather than by the liver. Because these three amino acids have a similar route of degradation, it is convenient to describe them as a group (see Fig. 20.11).

### Transamination

Transfer of the amino groups of all three BCAAs to α-ketoglutarate is catalyzed by a single, vitamin $B_6$–requiring enzyme, branched-chain amino acid aminotransferase that is expressed primarily in skeletal muscle.

### Oxidative decarboxylation

Removal of the carboxyl group of the α-keto acids derived from leucine, valine, and isoleucine is catalyzed by a single multienzyme complex, branched-chain α-keto acid dehydrogenase (BCKD) complex. An enzymatic deficiency in this complex results in maple syrup urine disease (MSUD) (see Fig. 20.11, and p. 302). This complex uses thiamine pyrophosphate, lipoic acid, oxidized flavin adenine dinucleotide (FAD), $NAD^+$, and CoA as its coenzymes and produces NADH. (Note: This reaction is similar to the conversion of pyruvate to acetyl CoA by the pyruvate dehydrogenase [PDH] complex [see p. 120] and α-ketoglutarate to succinyl CoA by the α-ketoglutarate dehydrogenase complex [see p. 123]. The dihydrolipoyl dehydrogenase [Enzyme 3, or E3] component is identical in all three complexes.)

### Dehydrogenations

Oxidation of the products formed in the BCKD reaction produces α-β-unsaturated acyl CoA derivatives and $FADH_2$. These reactions are analogous to the FAD-linked dehydrogenation in the β-oxidation of fatty acids (see p. 212). (Note: Deficiency in the dehydrogenase specific for isovaleryl CoA causes neurologic problems and is associated with a “sweaty feet” odor in body fluids.)

### End products

The catabolism of isoleucine ultimately yields acetyl CoA and succinyl CoA, rendering it both ketogenic and glucogenic. Valine yields succinyl CoA and is glucogenic. Leucine is ketogenic, being metabolized to acetoacetate and acetyl CoA. In addition, NADH and $FADH_2$ are produced in the decarboxylation and dehydrogenation reactions, respectively. (Note: BCAA catabolism also results in glutamine and alanine being synthesized and sent out into the blood from muscle [see p. 279].)

## Folic Acid and Amino Acid Metabolism

Some synthetic pathways require the addition of single-carbon groups that exist in a variety of oxidation states, including formyl, methenyl, methylene, and methyl. These single-carbon groups can be transferred from carrier compounds such as THF and SAM to specific structures that are being synthesized or modified. The “one-carbon pool” refers to the single-carbon units attached to this group of carriers. (Note: $CO_2$, coming from bicarbonate [$HCO_3^-$], is carried by the vitamin biotin [see p. 431], which is a prosthetic group for most carboxylation reactions but is not considered a member of the one-carbon pool. Defects in the ability to add or remove biotin from carboxylases result in multiple carboxylase deficiency. Treatment is supplementation with biotin.)

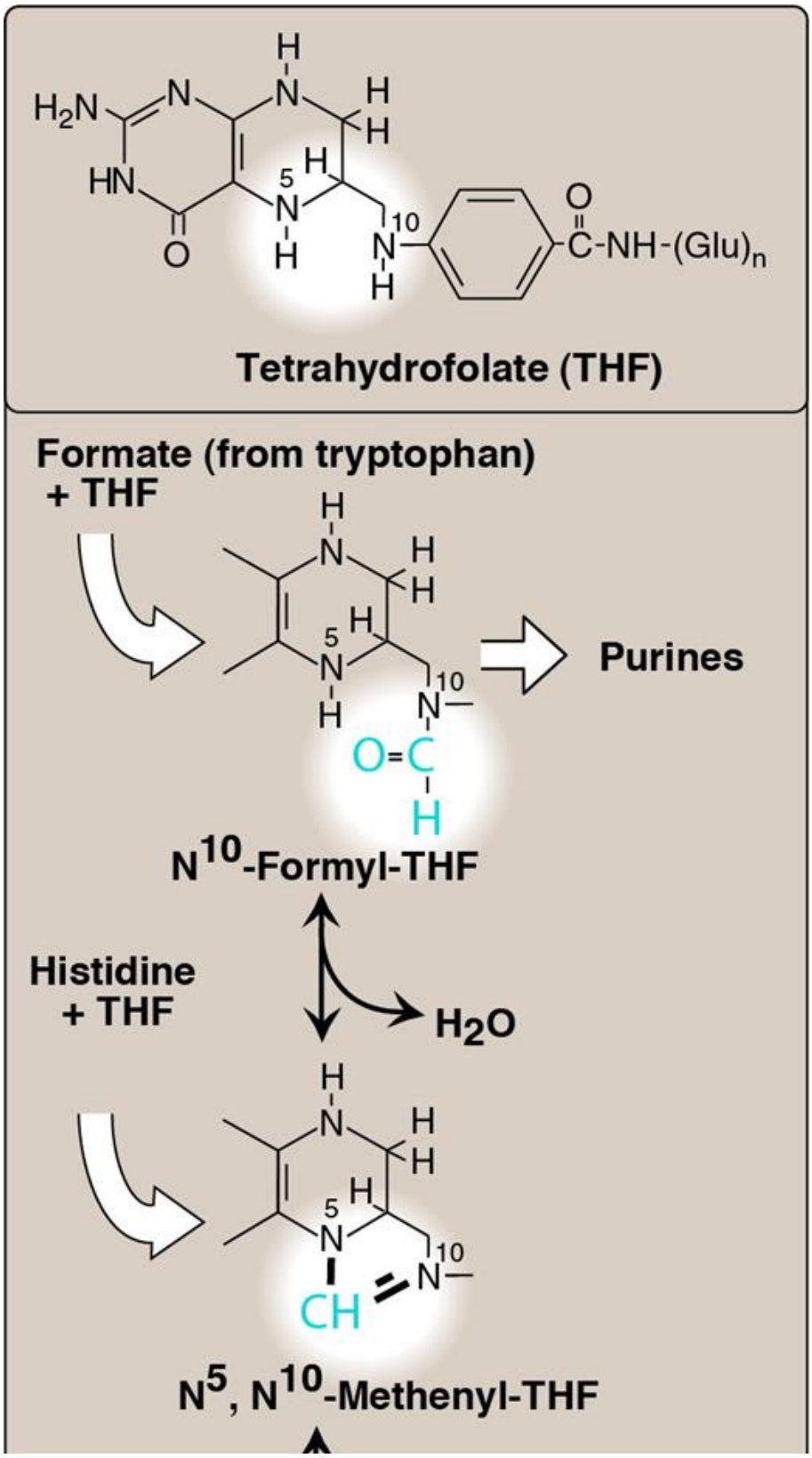
### Folic acid and one-carbon metabolism

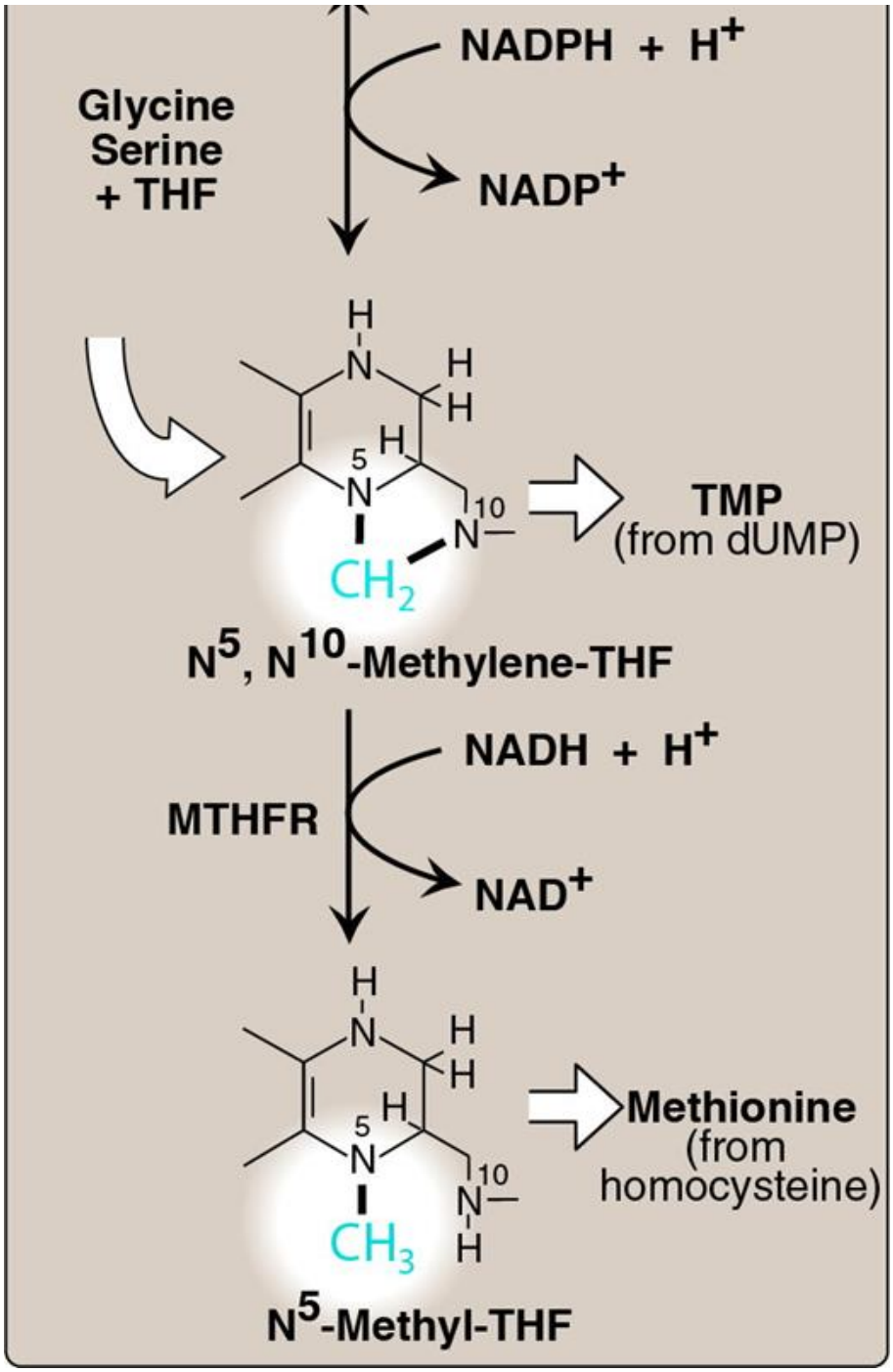
The active form of folic acid, THF, is produced from folate by dihydrofolate reductase in a two-step reaction requiring two nicotinamide adenine dinucleotide phosphate (NADPH). The one-carbon unit carried by THF is bound to $N^5$ or $N^{10}$ or to both $N^5$ and $N^{10}$. Figure 20.12 shows the structures of the various members of the THF family and their interconversions and indicates the sources of the one-carbon units and the synthetic reactions in which the specific members participate. (Note: Folate deficiency presents as a megaloblastic anemia because of decreased availability of the purines and of the thymidine monophosphate needed for DNA synthesis [see p. 336].)

**FIGURE 20.12**

## Summary of the interconversions and uses of THF.

(Note: $N^5$,$N^{10}$-Methenyl-THF also arises from $N^5$-formimino-THF [see Fig. 20.4].) NADP(H) = nicotinamide adenine dinucleotide phosphate; NAD(H) = nicotinamide adenine dinucleotide; TMP = thymidine monophosphate; dUMP = deoxyuridine monophosphate; MTHFR = $N^5$,$N^{10}$-methylene-THF reductase.






## Biosynthesis of Nonessential Amino Acids

Nonessential amino acids are synthesized from intermediates of metabolism or, as in the case of tyrosine and cysteine, from the essential amino acids phenylalanine and methionine, respectively. The synthetic reactions for the nonessential amino acids are described below and are summarized in Figure 20.15. (Note: Some amino acids found in proteins, such as hydroxyproline and hydroxylysine [see p. 47], are produced by posttranslational modification [after incorporation into a protein] of their precursor [parent] amino acids.)

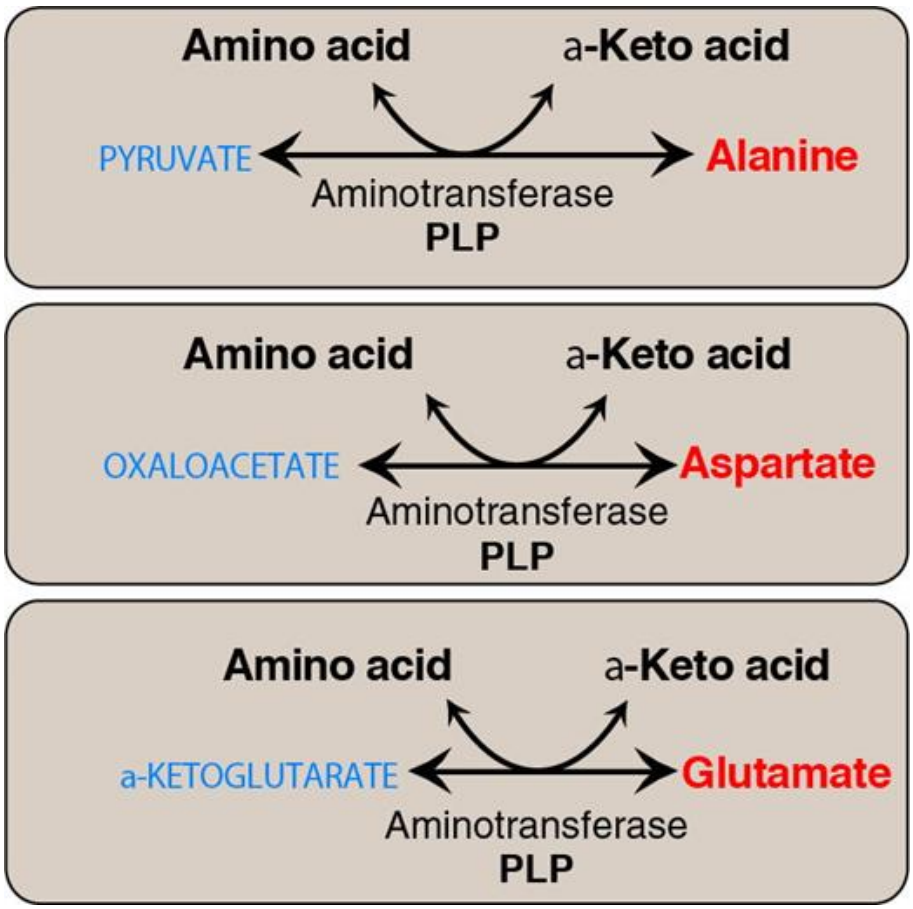
### Synthesis from α-keto acids

Alanine, aspartate, and glutamate are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and α-ketoglutarate, respectively. These transamination reactions (Fig. 20.13) are the most direct of the biosynthetic pathways. Glutamate is unusual in that it can also be synthesized by reversal of oxidative deamination, catalyzed by glutamate dehydrogenase, when ammonia levels are high (see Fig. 19.11).

**FIGURE 20.13**

**Formation of alanine, aspartate, and glutamate from the corresponding α-keto acids by transamination.**

PLP = pyridoxal phosphate.




## Synthesis by amidation

### Glutamine

This amino acid, which contains an amide linkage with ammonia at the γ-carboxyl, is formed from glutamate and ammonia by glutamine synthetase (see Fig. 19.18, p. 283). The reaction is driven by the hydrolysis of ATP. In addition to producing glutamine for protein synthesis, the reaction also serves as a major mechanism for the transport of ammonia in a nontoxic form. (See p. 283 for a discussion of ammonia metabolism.)

### Asparagine

This amino acid, which contains an amide linkage with ammonia at the β-carboxyl, is formed from aspartate by asparagine synthetase, using glutamine as the amide donor. Like the synthesis of glutamine, the reaction requires ATP and has an equilibrium far in the direction of amide synthesis.

### Proline

Glutamate via glutamate semialdehyde is converted to proline by cyclization and reduction reactions. (Note: The semialdehyde can also be transaminated to ornithine.)

### Serine, glycine, and cysteine

The pathways of synthesis for these amino acids are interconnected.

#### Serine

This amino acid arises from 3-phosphoglycerate, a glycolytic intermediate (see Fig. 8.18), which is first oxidized to 3-phosphopyruvate and then transaminated to 3-phosphoserine. Serine is formed by hydrolysis of the phosphate ester. Serine can also be formed from glycine through transfer of a hydroxymethyl group by serine hydroxymethyltransferase using $N^5$,$N^{10}$-MTHF as the one-carbon donor (see Fig. 20.6A). (Note: Selenocysteine [Sec], the 21st genetically encoded amino acid, is synthesized from serine and selenium [see p. 454], while serine is attached to transfer RNA. Sec is found in ~25 human proteins including glutathione peroxidase [see p. 163] and thioredoxin reductase [see p. 330].)

#### Glycine

This amino acid is synthesized from serine by removal of a hydroxymethyl group, also by serine hydroxymethyltransferase (see Fig. 20.6A). THF is the one-carbon acceptor.

#### Cysteine

This amino acid is synthesized by two consecutive reactions in which Hcy combines with serine, forming cystathionine, which, in turn, is hydrolyzed to α-ketobutyrate and cysteine (see Fig. 20.8). (Note: Hcy is derived from methionine, as described on p. 293. Because methionine is an essential amino acid, cysteine synthesis requires adequate dietary intake of methionine.)

### Tyrosine

Tyrosine is formed from phenylalanine by PAH (see p. 292). The reaction requires molecular oxygen and the coenzyme $BH_4$, which is synthesized from guanosine triphosphate. One atom of molecular oxygen becomes the hydroxyl group of tyrosine, and the other atom is reduced to water. During the reaction, $BH_4$ is oxidized to dihydrobiopterin ($BH_2$). $BH_4$ is regenerated from $BH_2$ by NADH-requiring dihydropteridine reductase. Tyrosine, like cysteine, is formed from an essential amino acid and is, therefore, nonessential only in the presence of adequate dietary phenylalanine.

## Amino Acid Metabolism Disorders

These single-gene disorders, a subset of the inborn errors of metabolism, are generally caused by loss-of-function mutations in enzymes involved in amino acid metabolism. The inherited defects may be expressed as a total loss of enzyme activity or, more frequently, as a partial deficiency in catalytic activity. Without treatment, the amino acid disorders almost invariably result in intellectual disability or other developmental abnormalities, as a consequence of harmful accumulation of metabolites. Although >50 of these disorders have been described, many are rare, occurring in <1 per 250,000 in most populations (Fig. 20.14). Collectively, however, they constitute a very significant portion of pediatric genetic diseases (Fig. 20.15).

**FIGURE 20.14**

**Incidence of inherited diseases of amino acid metabolism.**

(Note: Cystinuria is the most common inborn error of amino acid transport.)

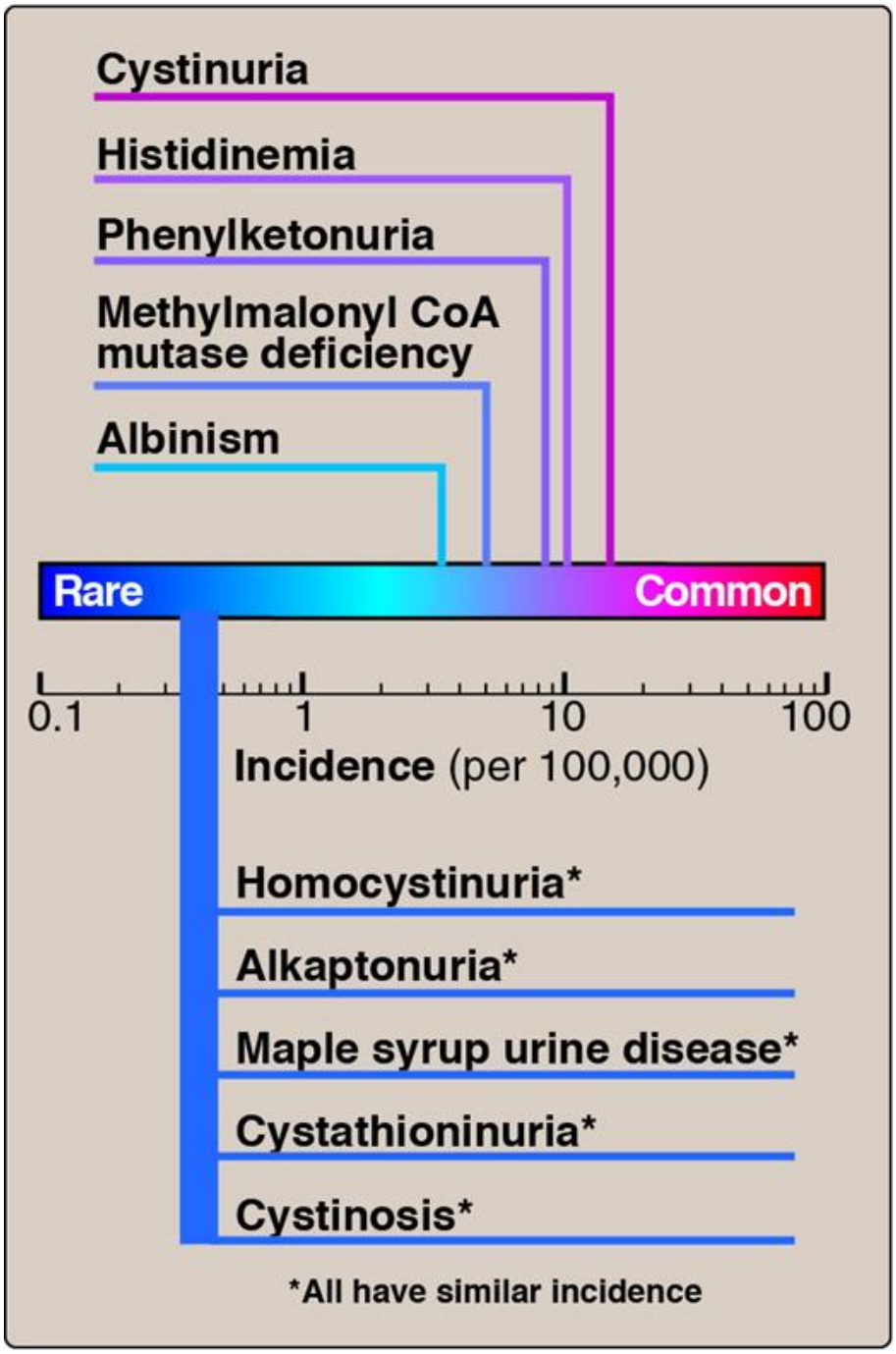
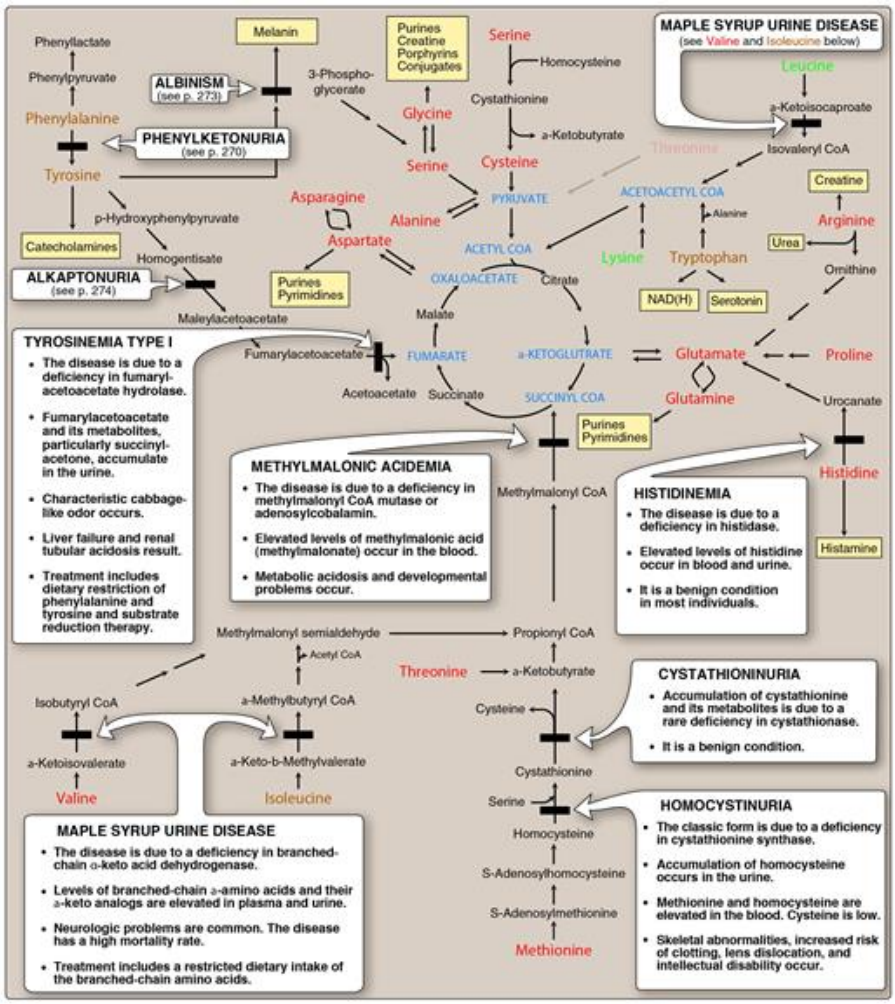


**FIGURE 20.15**

## Summary of the metabolism of amino acids in humans.

Genetically determined enzyme deficiencies are summarized in white boxes. Nitrogen-containing compounds derived from amino acids are shown in small, yellow boxes. Classification of amino acids is color coded: *Red* = glucogenic; *brown* = glucogenic and ketogenic; *green* = ketogenic. Compounds in *blue all caps* are the seven metabolites to which all amino acid metabolism converges. CoA = coenzyme A; NAD(H) = nicotinamide adenine dinucleotide.




## Phenylketonuria

PKU is the most common clinically encountered inborn error of amino acid metabolism (incidence 1:15,000). Classical PKU is an autosomal recessive disorder resulting from loss of function mutations in the gene coding for PAH (Fig. 20.16). Biochemically, PKU is characterized by hyperphenylalaninemia. Phenylalanine is present in high concentrations (10 times normal) not only in plasma but also in urine and body tissues. Tyrosine, which normally is formed from phenylalanine by PAH, is deficient. Treatment includes dietary restriction of phenylalanine and supplementation with tyrosine. (Note: Hyperphenylalaninemia may also be caused by rare deficiencies in any of the several enzymes required to synthesize $BH_4$ or in dihydropteridine reductase, which regenerates $BH_4$ from $BH_2$ [Fig. 20.17]. Such deficiencies indirectly raise phenylalanine concentrations, because PAH requires $BH_4$ as a coenzyme. $BH_4$ is also required for tyrosine hydroxylase and tryptophan hydroxylase, which catalyze reactions leading to the synthesis of neurotransmitters, such as serotonin and the catecholamines. Simply restricting dietary phenylalanine does not reverse the central nervous system effects due to deficiencies in neurotransmitters. Supplementation with $BH_4$ and replacement therapy with L-3,4-dihydroxyphenylalanine [L-DOPA, see p. 318] and 5-hydroxytryptophan [products of the affected tyrosine hydroxylase– and tryptophan hydroxylase–catalyzed reactions] improves the clinical outcome in these variant forms of hyperphenylalaninemia, although the response is unpredictable.)

## Additional characteristics

As the name suggests, PKU is also characterized by elevated levels of a phenylketone in the urine.

### Elevated phenylalanine metabolites

Phenylpyruvate (a phenylketone), phenylacetate, and phenyllactate, which are not normally produced in significant amounts in the presence of functional PAH, are also elevated in PKU, in addition to phenylalanine (Fig. 20.18). These metabolites give urine a characteristic musty (“mousy”) odor.

**FIGURE 20.16**

**A deficiency in phenylalanine hydroxylase results in the disease phenylketonuria (PKU).**

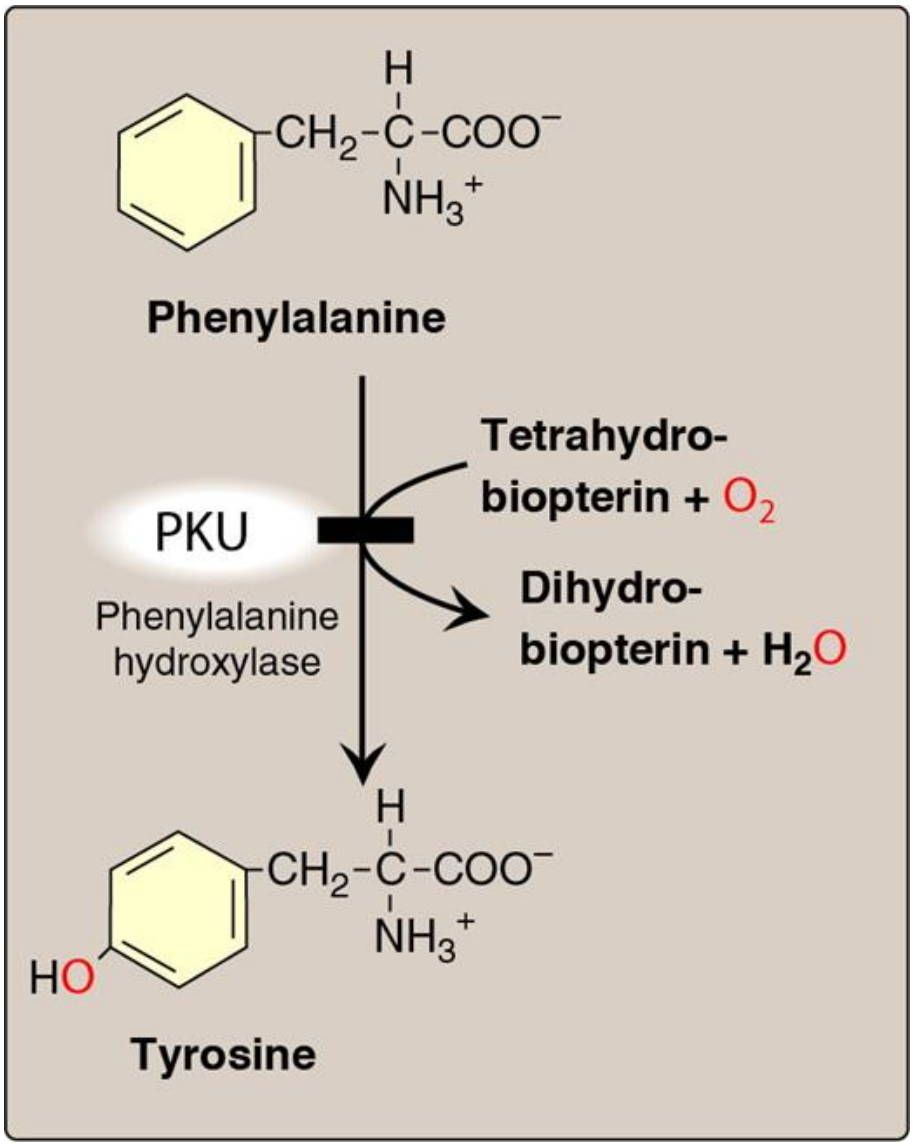
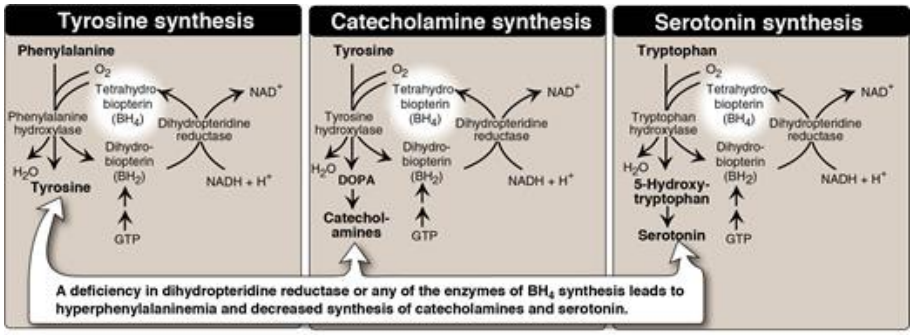


**FIGURE 20.17**

## Biosynthetic reactions involving amino acids and tetrahydrobiopterin.

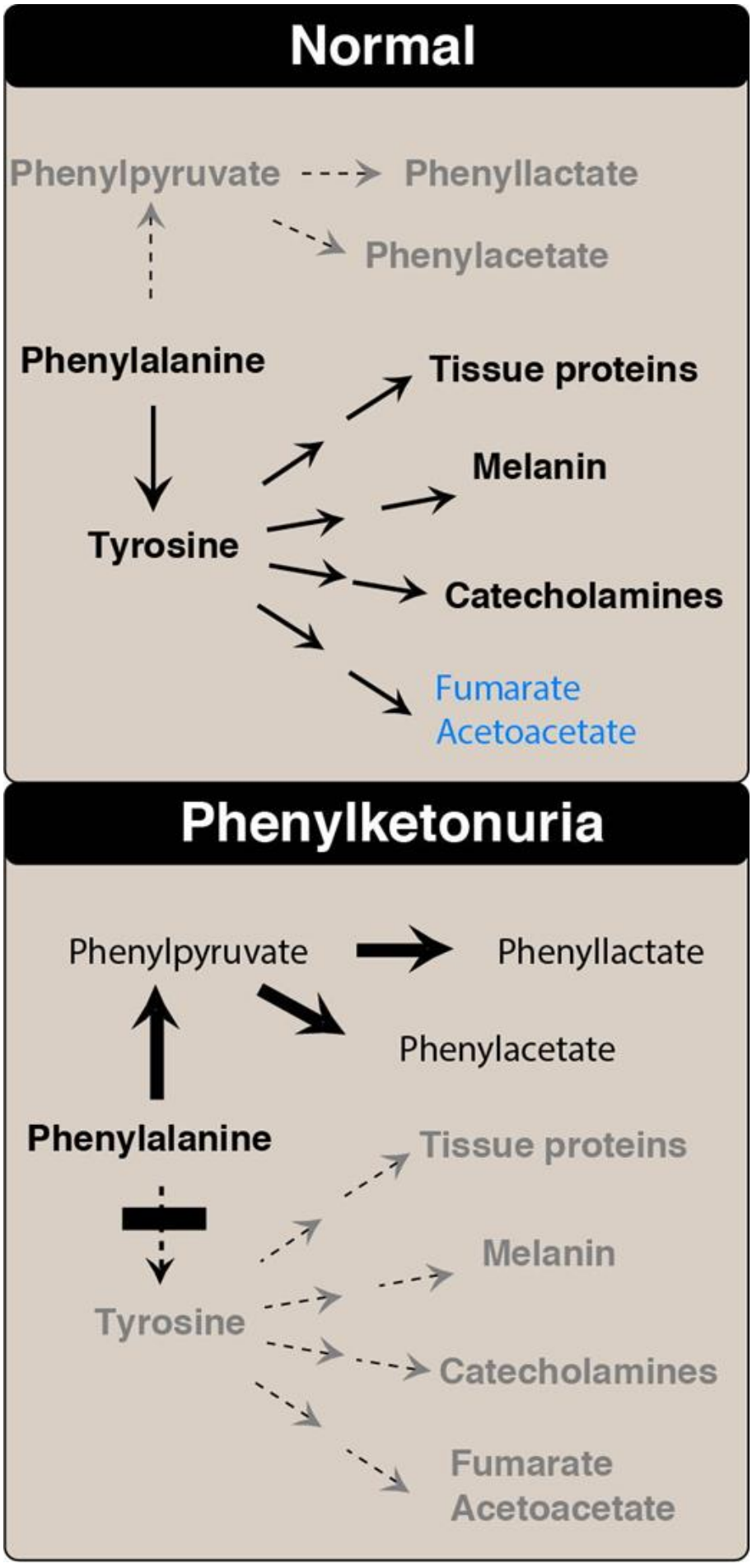
(Note: Aromatic amino acid hydroxylases use $BH_4$ and not PLP [pyridoxal phosphate].) NAD(H) = nicotinamide adenine dinucleotide; GTP = guanosine triphosphate; DOPA = L-3,4-dihydroxyphenylalanine.




Screening of newborns for a number of treatable disorders, including inborn errors of amino acid metabolism, is done by tandem mass spectrometry of blood obtained from a heel prick. By law, all states must screen for >20 disorders, with some screening for >50. All states screen for PKU.

**FIGURE 20.18**

**Pathways of phenylalanine metabolism in normal individuals and in patients with phenylketonuria.**


Normal
Phenylpyruvate
Phenyllactate
Phenylacetate
Phenylalanine
Tissue proteins
Melanin
Tyrosine
Catecholamines
Fumarate
Acetoacetate
Phenylketonuria
Phenylpyruvate
Phenyllactate
Phenylacetate
Phenylalanine
Tissue proteins
Melanin
Tyrosine
Catecholamines
Fumarate
Acetoacetate

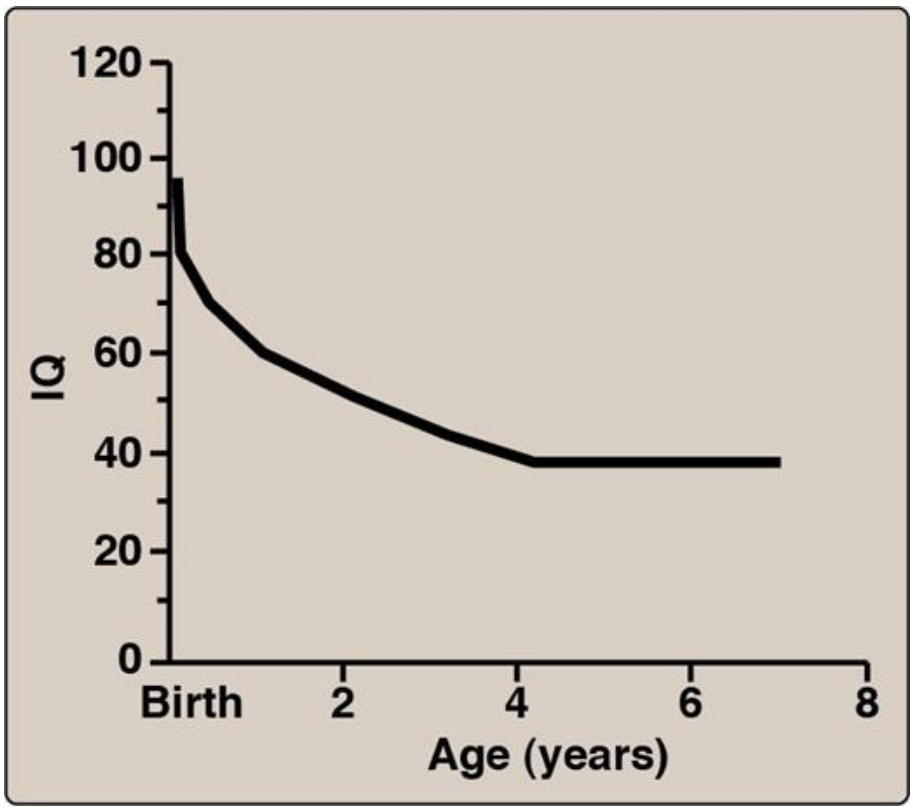
### Central nervous system effects

Severe intellectual disability, developmental delay, microcephaly, and seizures are characteristic findings in untreated PKU. The affected individual typically shows symptoms of intellectual disability by age 1 year and rarely achieves an intelligence quotient (IQ) >50 (Fig. 20.19). (Note: These clinical manifestations are now rarely seen as a result of newborn screening programs, which allow early diagnosis and treatment.)

**FIGURE 20.19**

**Typical intellectual ability in untreated patients of different ages with phenylketonuria.**

IQ = intelligence quotient.




### Hypopigmentation

Patients with untreated PKU may show a deficiency of pigmentation (fair hair, light skin color, and blue eyes). The hydroxylation of tyrosine by copper-requiring tyrosinase, which is the first step in the formation of the pigment melanin, is decreased in PKU because tyrosine is decreased.

## Newborn screening and diagnosis

Early diagnosis of PKU is important because the disease is treatable by dietary means. Because of the lack of neonatal symptoms, laboratory testing for elevated blood levels of phenylalanine is mandatory for detection. However, the infant with PKU frequently has normal blood levels of phenylalanine at birth because the mother clears increased blood phenylalanine in her affected fetus through the placenta. Normal levels of phenylalanine may persist until the newborn is exposed to 24 to 48 hours of protein feeding. Thus, screening tests are typically done after this time to avoid false negatives. For newborns with a positive screening test, diagnosis is confirmed through quantitative determination of phenylalanine levels.

### Prenatal diagnosis

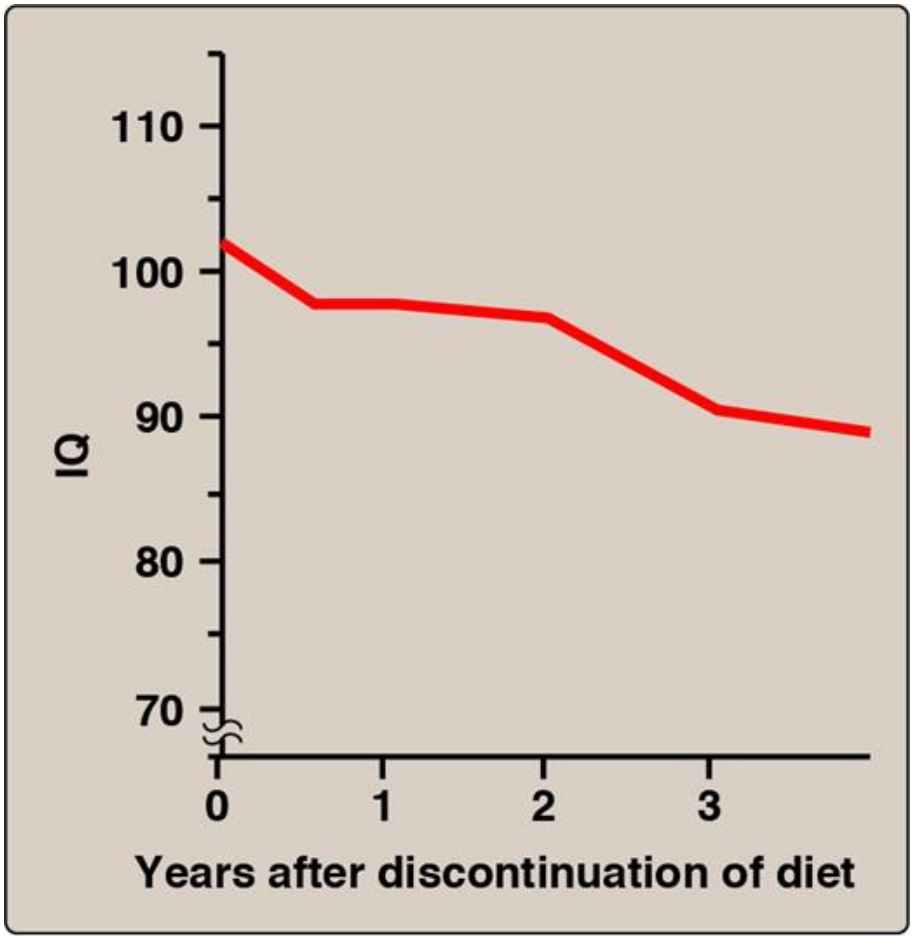
Classic PKU is caused by any of 100 or more different mutations in the gene that encodes PAH. The frequency of any given mutation varies among populations, and the disease is often doubly heterozygous (i.e., the *PAH* gene has a different mutation in each allele). Despite this complexity, prenatal diagnosis is possible (see p. 544).

### Treatment

Because most natural protein contains phenylalanine, an essential amino acid, it is impossible to satisfy the body's protein requirement without exceeding the phenylalanine limit when ingesting a normal diet. Therefore, in PKU, blood phenylalanine level is maintained close to the normal range by feeding synthetic amino acid preparations free of phenylalanine, supplemented with some natural foods (such as fruits, vegetables, and certain cereals) selected for their low phenylalanine content. The amount is adjusted according to the tolerance of the individual as measured by blood phenylalanine levels. The earlier treatment is started, the more completely neurologic damage can be prevented. Individuals who are appropriately treated can have normal intelligence. (Note: Treatment must begin during the first 7 to 10 days of life to prevent cognitive impairment.) Because phenylalanine is an essential amino acid, overzealous treatment that results in blood phenylalanine levels below normal is avoided. In patients with PKU, tyrosine cannot be synthesized from phenylalanine, and, therefore, it becomes an essential amino acid and must be supplied in the diet. Discontinuance of the phenylalanine-restricted diet in early childhood is associated with poor performance on IQ tests. Adult PKU patients show deterioration of IQ scores after discontinuation of the diet (Fig. 20.20). Therefore, lifelong restriction of dietary phenylalanine is recommended. (Note: Individuals with PKU are advised to avoid aspartame, an artificial sweetener that contains phenylalanine.)

**FIGURE 20.20**

**Changes in intelligence quotient (IQ) scores after discontinuation of low-phenylalanine diet in patients with phenylketonuria.**




### Maternal phenylketonuria

If women with PKU who are not on a low-phenylalanine diet become pregnant, the offspring can still be affected with maternal PKU syndrome. Even if the fetus has not inherited the disease (i.e., the fetus is heterozygous for the *PAH* mutation), high blood phenylalanine in the mother has a teratogenic effect, causing microcephaly and congenital heart abnormalities in the fetus. Because these developmental responses to high phenylalanine occur during the first months of pregnancy, dietary control of blood phenylalanine must begin prior to conception and be maintained throughout the pregnancy.

## Maple syrup urine disease

MSUD is a rare (1:185,000), autosomal-recessive disorder in which there is a partial or complete deficiency in BCKD, the mitochondrial enzyme complex that oxidatively decarboxylates leucine, isoleucine, and valine (see Fig. 20.11). These BCAAs 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, ketoacidosis, changes in muscle tone, neurologic problems that can result in coma (primarily because of the rise in leucine), and a characteristic maple syrup–like odor of the urine because of the rise in isoleucine. If untreated, the disease is fatal. If treatment is delayed, intellectual disability results.

### Classification

MSUD includes a classic type and several variant forms. The classic, neonatal-onset form is the most common type of MSUD. Leukocytes or cultured skin fibroblasts from these patients show little or no BCKD activity. Infants with classic MSUD show symptoms within the first several days of life. If not diagnosed and treated, classic MSUD is lethal in the first weeks of life. Patients with intermediate forms have a higher level of enzyme activity (up to 30% of normal). The symptoms are milder and show an onset from infancy to adolescence. Patients with the rare thiamine-dependent variant of MSUD respond to large doses of this vitamin.

### Screening and diagnosis

As with PKU, prenatal diagnosis and newborn screening are available, and most affected individuals are compound heterozygotes.

### Treatment

MSUD is treated with a synthetic formula that is free of BCAA, supplemented with limited amounts of leucine, isoleucine, and valine to allow for normal growth and development without producing toxic levels. (Note: Elevated leucine is the cause of the neurologic damage in MSUD, and its level is carefully monitored.) Early diagnosis and lifelong dietary treatment are essential if the child with MSUD is to develop normally. (Note: BCAAs are an important energy source in times of metabolic need, and individuals with MSUD are at risk of decompensation during periods of increased protein catabolism.)

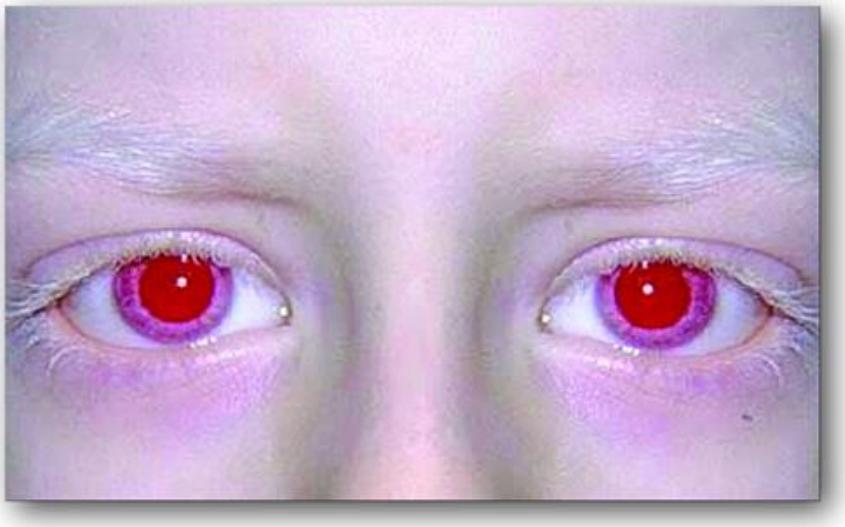
## Albinism

Albinism refers to a group of conditions in which a defect in tyrosine metabolism results in a deficiency in the production of melanin. These defects result in the partial or full absence of pigment from the skin, hair, and eyes. Albinism appears in different forms, and it may be inherited by one of several modes: autosomal recessive (primary mode), autosomal dominant, or X linked. Total absence of pigment from the hair, eyes, and skin (Fig. 20.21), tyrosinase-negative oculocutaneous albinism (type 1 albinism), results from an absent or defective copper-requiring tyrosinase, which catalyzes the first two steps in the synthesis of melanin from tyrosine. It is the most severe form of the condition. In addition to hypopigmentation, affected individuals have vision defects and photophobia (sunlight hurts their eyes). They also are at increased risk for skin cancer.

**FIGURE 20.21**

**Patient with oculocutaneous albinism, showing white eyebrows and lashes and eyes that appear red in color.**

Success in MRCO path. http://www.mrcophth.com/iriscases/albinism.html.



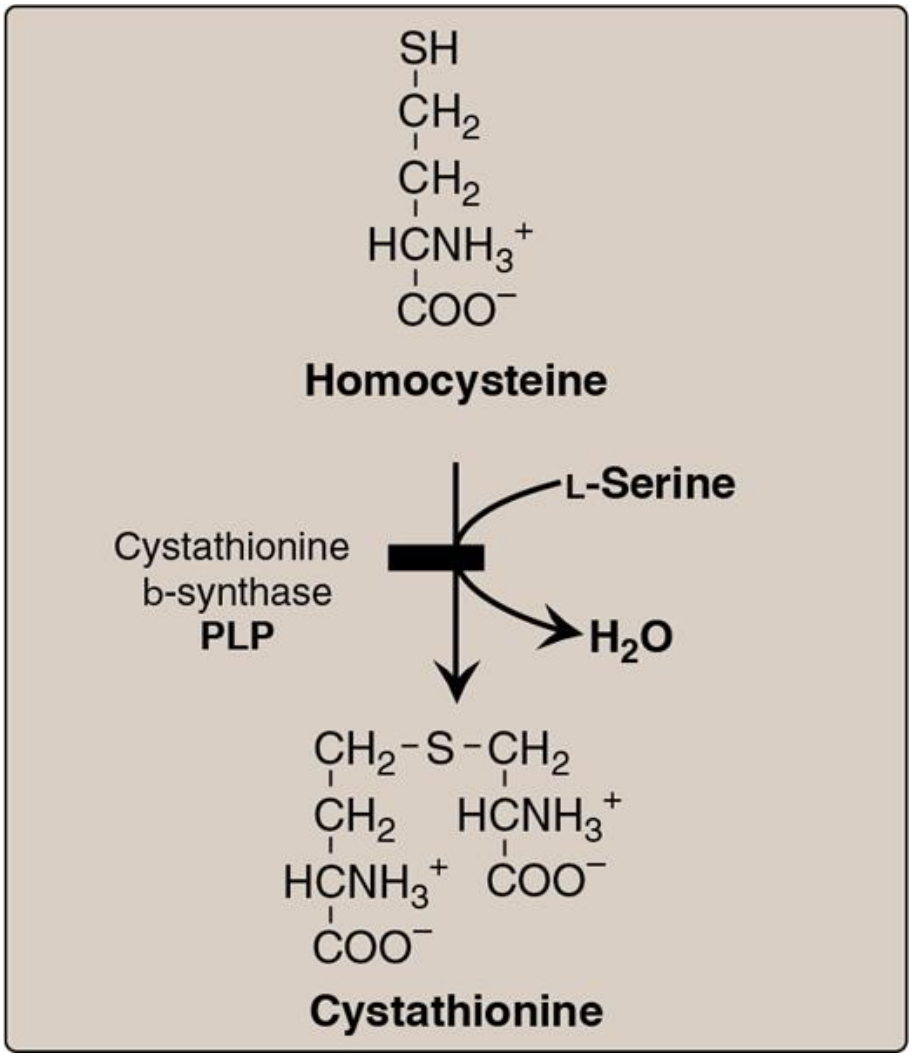
## Homocystinuria

The homocystinurias are a group of disorders involving defects in the metabolism of Hcy. These autosomal-recessive diseases are characterized by high urinary levels of Hcy, high plasma levels of Hcy and methionine, and low plasma levels of cysteine. The most common cause of homocystinuria is a defect in the enzyme cystathionine β-synthase, which converts Hcy to cystathionine (Fig. 20.22). Individuals homozygous for cystathionine β-synthase deficiency exhibit dislocation of the lens (ectopia lentis), skeletal anomalies (long limbs and fingers), intellectual disability, and an increased risk for developing thrombi (blood clots). Thrombosis is the major cause of early death in these individuals. Treatment includes restriction of methionine and supplementation with vitamin $B_{12}$ and folate. Cysteine becomes an essential amino acid, and must be supplemented. As glutathione is synthesized from cysteine (Fig. 13.6), adding cysteine to the diet is also helpful to reduce oxidative stress. Additionally, some patients are responsive to oral administration of pyridoxine (vitamin $B_6$), which is converted to pyridoxal phosphate, the coenzyme of cystathionine β-synthase. These patients usually have a milder and later onset of clinical symptoms compared with $B_6$-nonresponsive patients. (Note: Deficiencies in methylcobalamin [see Fig. 20.8] or $N^5$,$N^{10}$-MTHF reductase [(MTHFR), see Fig. 20.12] also result in elevated Hcy.)

**FIGURE 20.22**

### Enzyme deficiency in homocystinuria.

PLP = pyridoxal phosphate.




## Alkaptonuria

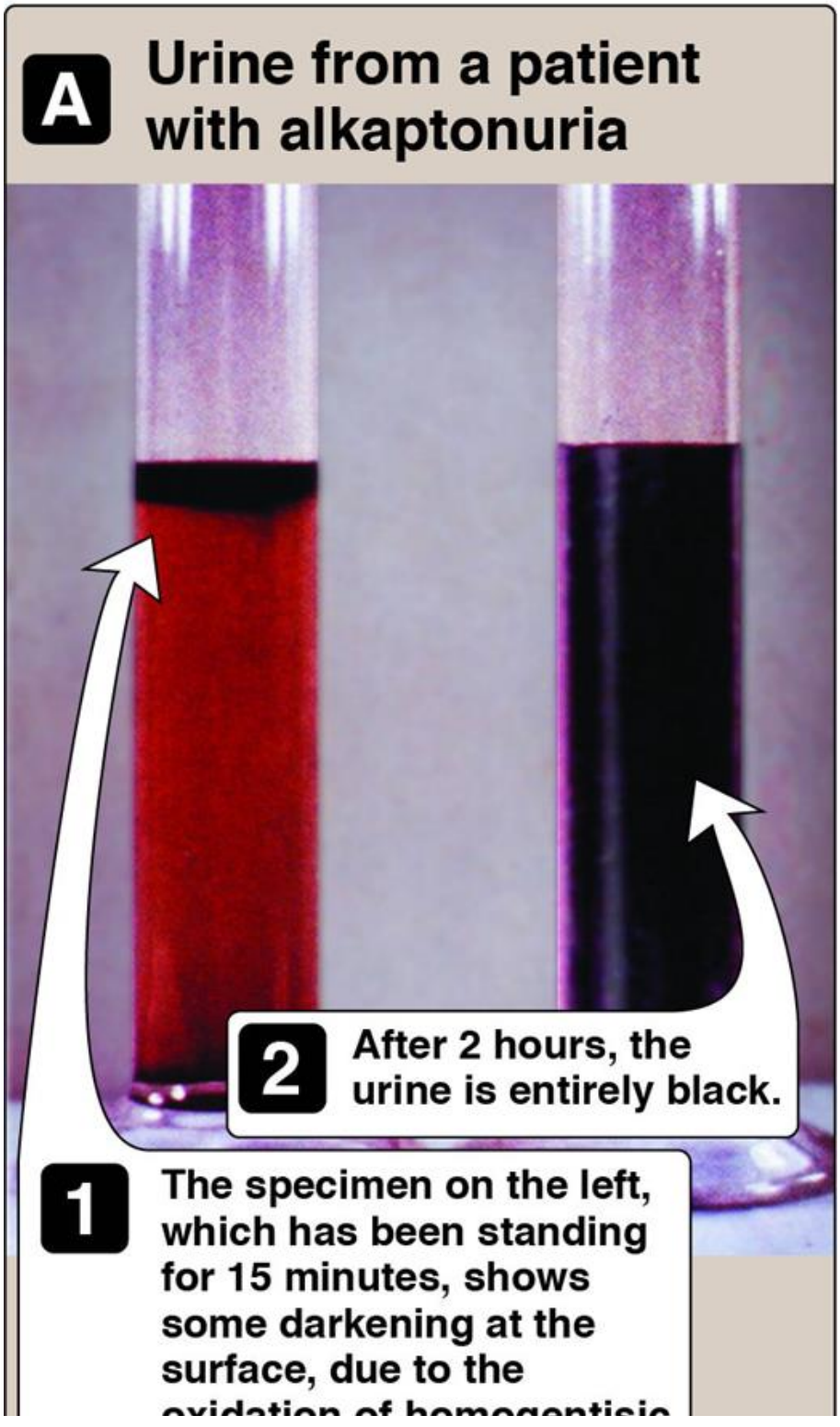
Alkaptonuria is a rare organic aciduria involving a deficiency in homogentisic acid oxidase, resulting in the accumulation of homogentisic acid (HA), an intermediate in the degradative pathway of tyrosine (see Fig. 20.15). The condition has three characteristic symptoms: homogentisic aciduria (the urine contains elevated levels of HA, which is oxidized to a dark pigment on standing, as shown in Fig. 20.23A), early onset of arthritis in the large joints, and deposition of black pigment (ochronosis) in cartilage and collagenous tissue (see Fig. 20.23B). Dark staining of diapers can indicate the disease in infants, but usually no symptoms are present until about age 40 years. Treatment includes dietary restriction of phenylalanine and tyrosine to reduce HA levels. Although alkaptonuria is not life threatening, the associated arthritis may be severely crippling. (Note: Deficiencies in fumarylacetoacetate hydrolase, the terminal enzyme of tyrosine metabolism, result in tyrosinemia type I [see Fig. 20.15] and a characteristic cabbage-like odor to urine.)

**FIGURE 20.23**

## Specimens from a patient with alkaptonuria.

**A:** Urine. **B:** Vertebrae.

**A:** Bullough PG. Orthopaedic Pathology. 5th ed. Mosby, Inc.; 2010, Figure 11–31. **B:** Modified from Vigorita VJ. Orthopaedic Pathology. 3rd ed. Wolters Kluwer; 2016, Figure 16–53B.



oxidation of homogentisic acid.


## Methylmalonic acidemia

Methylmalonic acidemia (MMA) is a rare (1:100,000) autosomal recessive disorder caused by a deficiency in methylmalonyl CoA mutase, which converts L-methylmalonyl CoA to succinyl CoA. Since the mutase requires vitamin $B_{12}$, the disease can also result from a severe $B_{12}$ deficiency. The breakdown of odd-chain length fatty acids, valine, isoleucine, methionine, and threonine can all result in MMA, due to this enzyme deficiency. Elevation of methylmalonate in the blood and urine can result in a metabolic acidosis. There may also be an increase in propionyl-CoA, exacerbating the aciduria with an accumulation of additional propionic acid. Symptoms appear in early infancy, varying due to the degree of the enzyme deficiency, including failure to thrive, vomiting, dehydration, hypotonia, developmental delay, seizures, hepatomegaly, hyperammonemia, and a progressive encephalopathy. If severe and left untreated, it can lead to intellectual disability, chronic renal or hepatic damage, pancreatitis, and coma or death. Treatment includes a low-protein, high-calorie diet, and vitamin $B_{12}$ supplementation. The diet limits the intake of isoleucine, threonine, methionine, and valine, as these amino acids can lead to the buildup of methylmalonic acid by the mutase deficiency.

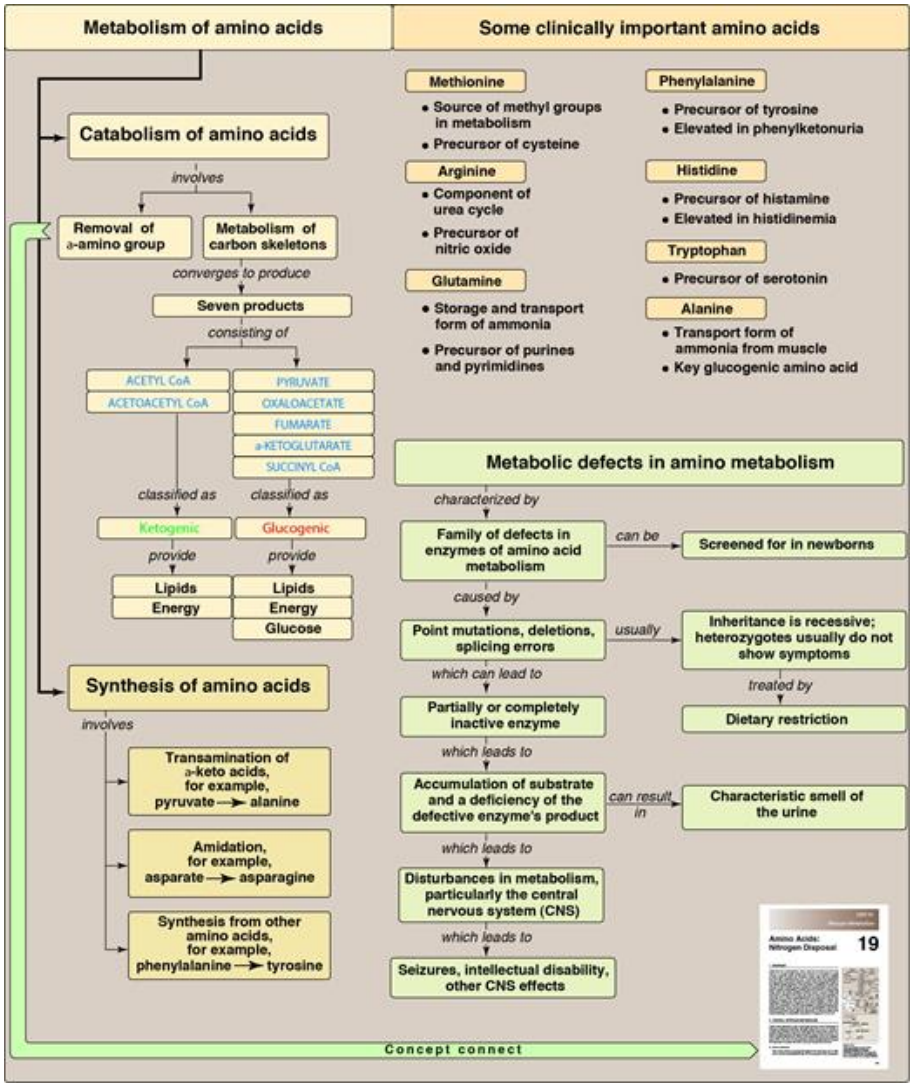
## Chapter Summary

- **Amino acids** whose catabolism yields **pyruvate** or an **intermediate** of the **TCA cycle** are termed **glucogenic** (Fig. 20.24). They can give rise to the net formation of **glucose** in the **liver** and **kidneys**. The solely glucogenic amino acids are glutamine, glutamate, proline, arginine, histidine, alanine, serine, glycine, cysteine, methionine, valine, threonine, aspartate, and asparagine.

**FIGURE 20.24**

### Key concept map for amino acid metabolism.

CoA = coenzyme A.




- Amino acids whose catabolism yields either acetyl CoA (directly, without pyruvate serving as an intermediate) or acetoacetate (or its precursor acetoacetyl CoA) are termed **ketogenic**. Leucine and lysine are solely ketogenic.
- Tyrosine, phenylalanine, tryptophan, and isoleucine are both ketogenic and glucogenic.
- **Nonessential amino acids** can be synthesized from metabolic intermediates or from the carbon skeletons of essential amino acids.

- **Essential amino acids** need to be obtained from the **diet**. They include histidine, methionine, threonine, valine, isoleucine, phenylalanine, tryptophan, leucine, and lysine.
- **PKU** is caused by a **deficiency** of **PAH**, which converts phenylalanine to tyrosine. **Hyperphenylalaninemia** may also be caused by deficiencies in the enzymes that synthesize or regenerate the coenzyme for PAH, **$BH_4$**. Untreated individuals with PKU suffer from severe intellectual disability, developmental delay, microcephaly, seizures, and a characteristic musty (mousy) smell of the urine. Treatment involves controlling dietary phenylalanine. **Tyrosine** becomes an essential dietary component for people with PKU.
- **MSUD** is caused by a partial or complete deficiency in **BKCD**, the enzyme that decarboxylates the **BCAAs, leucine**, **isoleucine**, and **valine**. Symptoms include feeding problems, vomiting, ketoacidosis, changes in muscle tone, and a characteristic sweet smell of the urine. If untreated, the disease leads to neurologic problems that result in death. Treatment involves controlling BCAA intake.
- Other important genetic diseases associated with amino acid metabolism include **albinism**, **homocystinuria**, **MMA**, **alkaptonuria**, **histidinemia**, **tyrosinemia**, and **cystathioninuria**.

## Study Questions

**Choose the ONE best answer.**

For Questions 20.1 to 20.3, match the deficient enzyme with the associated clinical sign or laboratory finding in urine.

A. Black pigmentation of cartilage

B. Sweaty feet–like odor of fluids

C. Cystine crystals in urine

D. White hair, red eye color

E. Increased branched-chain amino acids

F. Increased homocysteine

G. Increased methionine

H. Increased phenylalanine

**20.1. Cystathionine β-synthase**

**20.2. Homogentisic acid oxidase**

**20.3. Tyrosinase**

Correct answers = F, A, D, respectively. A deficiency in cystathionine β-synthase of methionine degradation results in a rise in homocysteine. A deficiency in homogentisic acid oxidase of tyrosine degradation results in a rise in homogentisic acid, which forms a black pigment that is deposited in connective tissue (ochronosis). A deficiency in tyrosinase results in decreased formation of melanin from tyrosine in the skin, hair, and eyes. A sweaty feet–like odor is characteristic of isovaleryl coenzyme A dehydrogenase deficiency. Cystine crystals in urine are seen with cystinuria, a defect in intestinal and renal cystine absorption. Increased branched-chain amino acids are seen in maple syrup urine disease, increased methionine is seen in defects in homocysteine metabolism, and increased phenylalanine is seen in phenylketonuria.

**20.4. A 1-week-old infant, who was born at home in a rural, medically underserved area, has undetected classic phenylketonuria. Which statement about this baby and/or her treatment is correct?**

A. A diet devoid of phenylalanine should be initiated immediately.

B. Dietary treatment will be discontinued in adulthood.

C. Supplementation with vitamin $B_6$ is required.

D. Tyrosine is an essential amino acid.

E. Folic acid supplementation may increase PAH activity.

Correct answer = D. In patients with phenylketonuria, tyrosine cannot be synthesized from phenylalanine and, hence, becomes essential and must be supplied in the diet. Phenylalanine in the diet must be controlled but cannot be eliminated entirely because it is an essential amino acid. Dietary treatment must begin during the first 7 to 10 days of life to prevent intellectual disability, and lifelong restriction of phenylalanine is recommended to prevent cognitive decline. Additionally, elevated levels of phenylalanine are teratogenic to a developing fetus. The cofactor for PAH is tetrahydrobiopterin ($BH_4$). $BH_4$ supplementation may help reduced phenyalanine levels if the enzyme defect is in $BH_4$ production or its reduction from dihydrobiopterin.

**20.5. Which one of the following statements concerning amino acids is correct?**

A. Alanine is ketogenic.

B. Amino acids that are catabolized directly to acetyl coenzyme A (CoA) (without forming pyruvate as an intermediate) are glucogenic.

C. Branched-chain amino acids are catabolized primarily in the liver.

D. Cysteine is essential for individuals consuming a diet severely limited in methionine.

E. Alanine is an essential amino acid.

Correct answer = D. Methionine is the precursor of cysteine, which becomes essential if methionine is severely restricted. Alanine is a key glucogenic amino acid. Acetyl CoA cannot be used for the net synthesis of glucose. Amino acids catabolized to acetyl CoA, acetoacetate, and acetoacetyl CoA are ketogenic. Branched-chain amino acids are catabolized primarily in skeletal muscle. Alanine is a nonessential amino acid, synthesized from pyruvate by a transaminase.

**20.6. In an individual with the dihydrolipoyl dehydrogenase (E3)-deficient form of maple syrup urine disease, why would lactic acidosis be an expected finding?**

The three α-ketoacid dehydrogenase complexes (pyruvate dehydrogenase [PDH], α-ketoglutarate dehydrogenase, and branched-chain α-keto acid dehydrogenase [BCKD]) have Enzyme 3, or E3 in common. In E3-deficient maple syrup urine disease, in addition to the branched-chain amino acids and their α-keto acid derivatives accumulating as a result of decreased activity of BCKD, lactate will also be increased because of decreased activity of PDH.

**20.7. In contrast to the vitamin $B_6$–derived pyridoxal phosphate required in most enzymic reactions involving amino acids, what coenzyme is required by the aromatic amino acid hydroxylases?**

Tetrahydrobiopterin, made from guanosine triphosphate, is the required coenzyme.