Chapter 15

Amino Acid Metabolism and the Urea Cycle

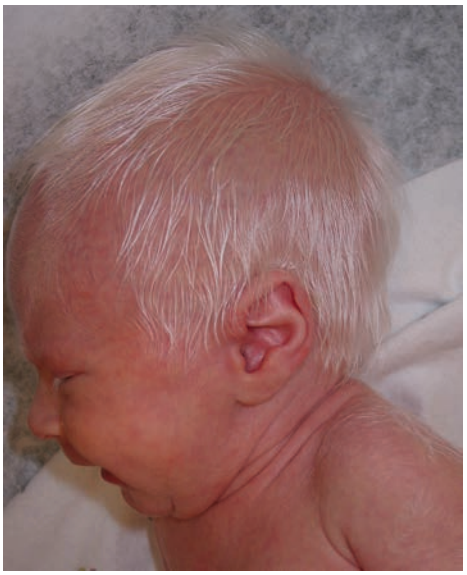
This chapter quizzes the student on amino acid metabolism and products derived from amino acids.

QUESTIONS

Select the single best answer.

1 Routine newborn screening identified a child with elevated levels of phenylpyruvate and phenyllactate in the blood. Despite treating the child with a restricted diet, evidence of developmental delay became apparent. Supplementation with which of the following would be beneficial to the child?
(A) Tyrosine
(B) 5-hydroxytryptophan
(C) Melanin
(D) Phenylalanine
(E) Alanine

2 A newborn has milky white skin, white hair, and red-appearing eye color (see the figure below). This disorder most often results from a defect in which of the following enzymes?



(A) Phenylalanine hydroxylase
(B) NADPH oxidase
(C) Dihydrofolate reductase
(D) Tyrosinase
(E) Homogentisic acid oxidase

3 A newborn becomes lethargic and drowsy 24 h after birth. Blood analysis shows hyperammonemia, coupled with orotic aciduria. This individual has an enzyme deficiency that leads to an inability to directly produce which of the following?
(A) Carbamoyl phosphate
(B) Ornithine
(C) Citrulline
(D) Argininosuccinate
(E) Arginine

4 Considering the patient in question 3, orotic acid levels are high in this patient due to which of the following?
(A) Elevated ammonia
(B) Elevated glutamine
(C) Bypassing carbamoyl phosphate synthetase II (CPS-II)
(D) Bypassing aspartate transcarbamoylase
(E) Inhibition of carbamoyl phosphate synthetase I (CPS-I)

5 Considering the patient discussed in the last two questions, a potential treatment for the patient is supplementation with which of the following?
(A) Arginine and glutamine
(B) Lysine and glutamine
(C) Arginine and benzoate
(D) Lysine and benzoate
(E) Glutamine and phenylbutyrate

6 Parents bring their 6-year-old son to the pediatrician due to the parents being concerned about "mental retardation." Blood work demonstrated a microcytic anemia and basophilic stippling. During the patient history, it became apparent that the boy often stayed with his grandparents, who owned a 150-year-old apartment. The boy admitted to eating paint chips from the radiators in the apartment. The boy's anemia is most likely the result of which one of the following?
(A) Inhibition of iron transport
(B) Reduction of heme synthesis
(C) Inhibition of the phosphatidyl inositol cycle
(D) Blockage of reticulocyte DNA synthesis
(E) Inhibition of β-globin gene expression

7 Routine newborn screening identified a child with elevated levels of α-ketoacids of the branched-chain amino acids. A certain subset of such children will respond well to which of the following vitamin supplementation?
(A) Niacin
(B) Riboflavin
(C) B_{12}
(D) B_6
(E) Thiamine

8 Another routine newborn screening identified a child with elevated levels of the branched-chain amino acids and their α-ketoacid derivatives. In addition, the child also exhibited lactic acidosis. Which enzyme listed below would you expect to be negatively affected (reduced activity) by this disorder?
(A) α-ketoglutarate dehydrogenase
(B) Isocitrate dehydrogenase
(C) Malate dehydrogenase
(D) Succinate dehydrogenase
(E) Acetyl-CoA carboxylase

9 A Russian child, 5 years old, was brought to the pediatrician for developmental delay. Blood analysis showed elevated levels of phenylalanine, phenyllactate, and phenylpyruvate. The developmental delay, in this condition, has been hypothesized to occur due to which of the following?
(A) Acidosis due to elevated phenyllactate
(B) Lack of tyrosine, now an essential amino acid
(C) Inhibition of hydroxylating enzymes due to accumulation of phenylalanine
(D) Lack of large, neutral amino acids in the brain
(E) Inhibition of neuronal glycolysis by phenylpyruvate

10 A 12-year-old boy is brought to the pediatrician because of behavioral problems noted by the parents. Upon examination, the physician notices brittle and coarse hair, red patches on the skin, long, thin arms and legs (reminiscent of Marfan syndrome patients), scoliosis, pectus excavatum, displaced lens, and muscular hypotonia. Blood work is likely to show an elevation of which of the following metabolites?
(A) Methionine
(B) Phenylpyruvate
(C) Cysteine
(D) Fibrillin fragments
(E) Homocystine

11 Considering the patient described in the previous questions, treatment with which of the following vitamins may be successful in controlling this disorder?
(A) B_1
(B) B_2
(C) B_3
(D) B_6
(E) B_{12}

12 A 13-year-old boy is admitted to the hospital due to flank and urinary pain. Analysis demonstrates the presence of kidney stones. The stones were composed of calcium oxalate. Family history revealed that the boy's father and mother had had similar problems. Oxalate accumulation arises in this patient due to difficulty in metabolizing which of the following?
(A) Alanine
(B) Leucine
(C) Lysine
(D) Glyoxylate
(E) Glycine

13 An 18-year-old boy was brought to the hospital by his mother due to a sudden onset of flank pain in his left side, radiating toward his pubic area. His urine was reddish-brown in color, and a urinalysis showed the presence of many red blood cells. When his urine was acidified with acetic acid, clusters of flat, hexagonal transparent crystals were noted. A radiograph of the abdomen showed radio-opaque stones in both kidneys. The boy eventually passed a stone whose major component was identified as cystine. A suggestion for treatment is which of the following?
(A) Increased ethanol consumption
(B) Restriction of dietary methionine
(C) Utilize drugs that acidify the urine
(D) Restrict dietary glycine
(E) Prescribe diuretics

14 You have an elderly patient with a history of heart attacks (MIs) and strokes (CVAs). Blood work indicates an elevated homocysteine level, which is reduced by the patient taking pharmacological doses of pyridoxamine. An enzyme that would benefit from such

treatment in lowering homocysteine levels is which of the following?
(A) Methionine synthase
(B) N5, N10 methylene tetrahydrofolate reductase
(C) Cystathionine β-synthase
(D) Cystathionase
(E) S-adenosyl homocysteine hydrolase

15 A 3-month-old boy of French–Canadian ancestry is seen by the pediatrician for failure to thrive and poor appetite. Physical exam denotes hepatomegaly and a yellowing of the eyes. The boy had been vomiting and had diarrhea, and a distinct cabbagelike odor was apparent. This disorder is due to a defect in the metabolism of which of the following amino acids?
(A) Alanine
(B) Tryptophan
(C) Tyrosine
(D) Histidine
(E) Lysine

16 Mr Smith had been prescribed a drug to treat his depression. One of the effects of the drug is to maintain elevated levels of a particular neurotransmitter that has been derived from which of the following amino acids?
(A) Tryptophan
(B) Tyrosine
(C) Glutamate
(D) Histidine
(E) Glycine

17 A patient has a "pill rolling" tremor, "cogwheel" rigidity, bradykinesis, speech difficulties, and a shuffling gait. The chemical that is lacking in this syndrome is a derivative of which of the following amino acids?
(A) Alanine
(B) Serine
(C) Tyrosine
(D) Tryptophan
(E) Phenylalanine

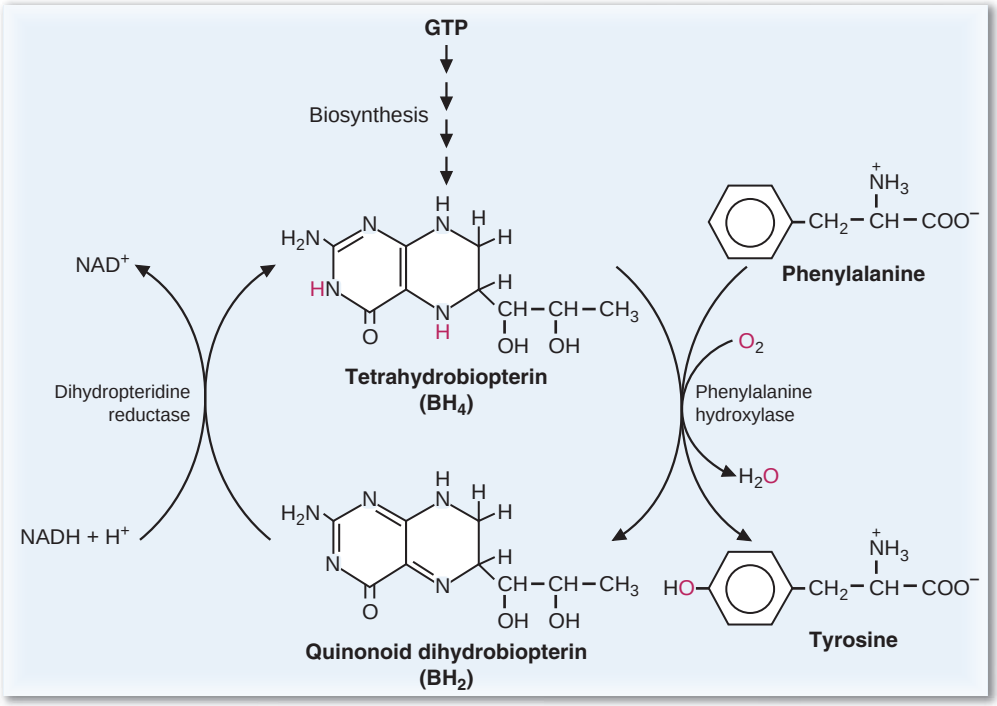
18 A patient presents with episodes of flushing, diarrhea, abdominal cramping, and wheezing. His blood pressure and pulse rate are normal during these episodes. Physical exam is normal except for scattered telangiectasias. In order to diagnose this problem, a 24-h urine collection for which of the following would be most appropriate?
(A) Vanillylmandelic acid (VMAs)
(B) Catechols
(C) Dopamine
(D) 5-hydroxyindoleacetic acid (5-HIAA)
(E) Cortisol

19 A patient taking a drug for depression experienced a greatly increased heart rate and sweating after eating red wine and gourmet, aged cheese. These symptoms appeared due to an inability to degrade which of the following?
(A) Tyrosine
(B) Tyramine
(C) Serotonin
(D) Glycine
(E) Glutamate

20 A 6-year-old boy is slightly anemic and is very sensitive to the sun, to the point where his skin blisters instead of healing normally from sunburn. His condition worsened when he was taking rifampin for a Methicillin Resistant Staph Aureus. The boy most likely has a defect in which of the following biochemical pathways?
(A) Glycogen synthesis
(B) Fatty acid oxidation
(C) DNA repair
(D) Transcription-coupled DNA repair
(E) Heme synthesis

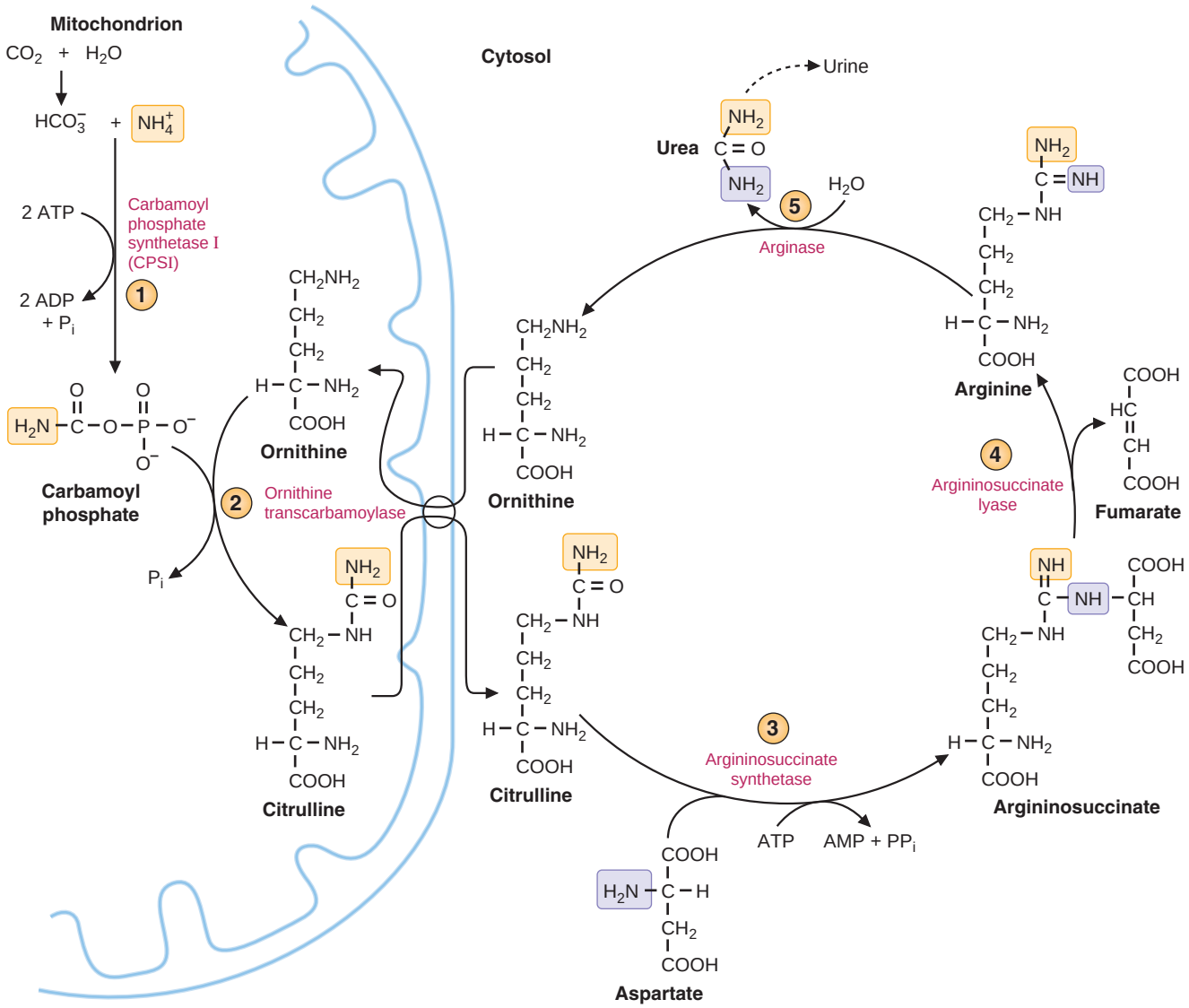
ANSWERS

1 **The answer is B: 5-hydroxytryptophan.** The child has nonclassical phenylketonuria (PKU). Classical PKU is due to a defect in phenylalanine hydroxylase, leading to accumulation of phenylalanine derivatives. These interfere with amino acid transport into the brain and can lead to cognitive disorders if not treated, usually, by a low-phenylalanine diet. However, in nonclassical PKU, the required cofactor for the phenylalanine hydroxylase reaction, tetrahydrobiopterin, is deficient. This will lead to similar biochemical symptoms (elevation of phenylalanine derivatives), but, in addition, the catecholamines (dopamine, epinephrine, and norepinephrine) and serotonin cannot be synthesized as those pathways require tetrahydrobiopterin. Giving 5-hydroxytryptophan bypasses the block in serotonin biosynthesis, and would have to be a supplement for these children along with dihydroxyphenylalanine (DOPA), which is the hydroxylated precursor for catecholamine biosynthesis. Providing tyrosine will not overcome the block in neurotransmitter biosynthesis. Providing phenylalanine just makes the problem worse. Neither melanin nor alanine will bypass the metabolic block of this disease. The role of tetrahydrobiopterin, indicating its oxidation and subsequent reduction, in the phenylalanine hydroxylase reaction is shown below.



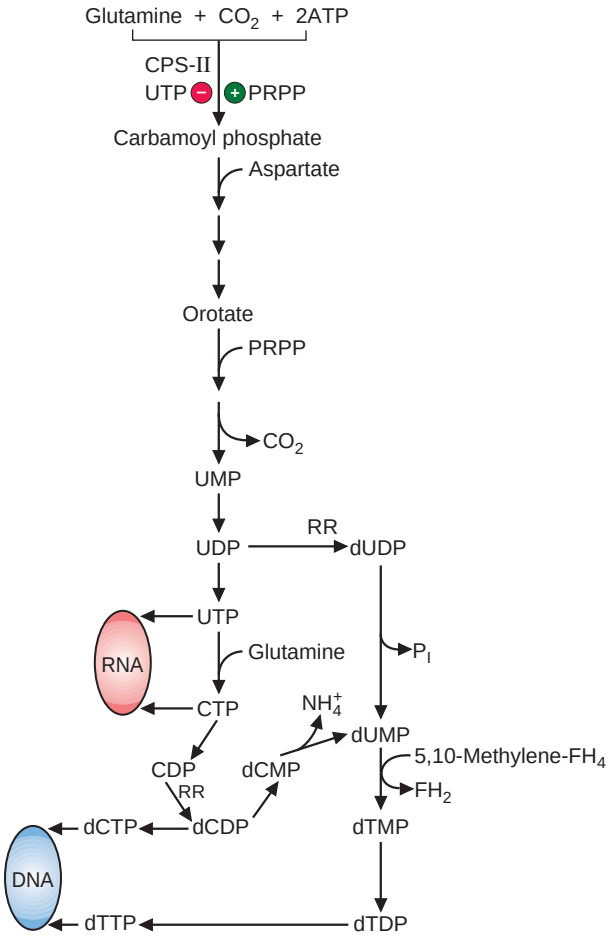
2 **The answer is D: Tyrosinase.** The child has albinism, a lack of pigment in the skin cells, which is produced by melanocytes. Melanocyte tyrosinase (a different isozyme than the neuronal tyrosinase that produces DOPA for catecholamine biosynthesis) is defective in albinism. The DOPA produced is then used for pigment production. A lack of phenylalanine hydroxylase leads to PKU. A lack of dihydrofolate reductase is most likely a lethal event as there are no reported cases of a lack of this enzyme. Tetrahydrofolate is not required for the conversion of tyrosine to DOPA in melanocytes. NADPH oxidase generates superoxide, which is not part of this pathway. Homogentisic acid is part of the phenylalanine and tyrosine degradation pathways, and is not involved in albinism.

3 **The answer is C: Citrulline.** The child has ornithine transcarbamoylase (OTC) deficiency, and cannot condense carbamoyl phosphate with ornithine to produce citrulline (see the figure on page 131). The excess carbamoyl phosphate produced leaks into the cytoplasm where it bypasses the regulated enzyme of de novo pyrimidine production, leading to excess orotic acid. Thus, in an OTC defect, carbamoyl phosphate can be produced, but citrulline cannot. Since citrulline cannot be produced, the later products of the urea cycle (argininosuccinate and arginine) are also produced at lower levels than normal, which is an indirect effect due to the inability to produce citrulline.



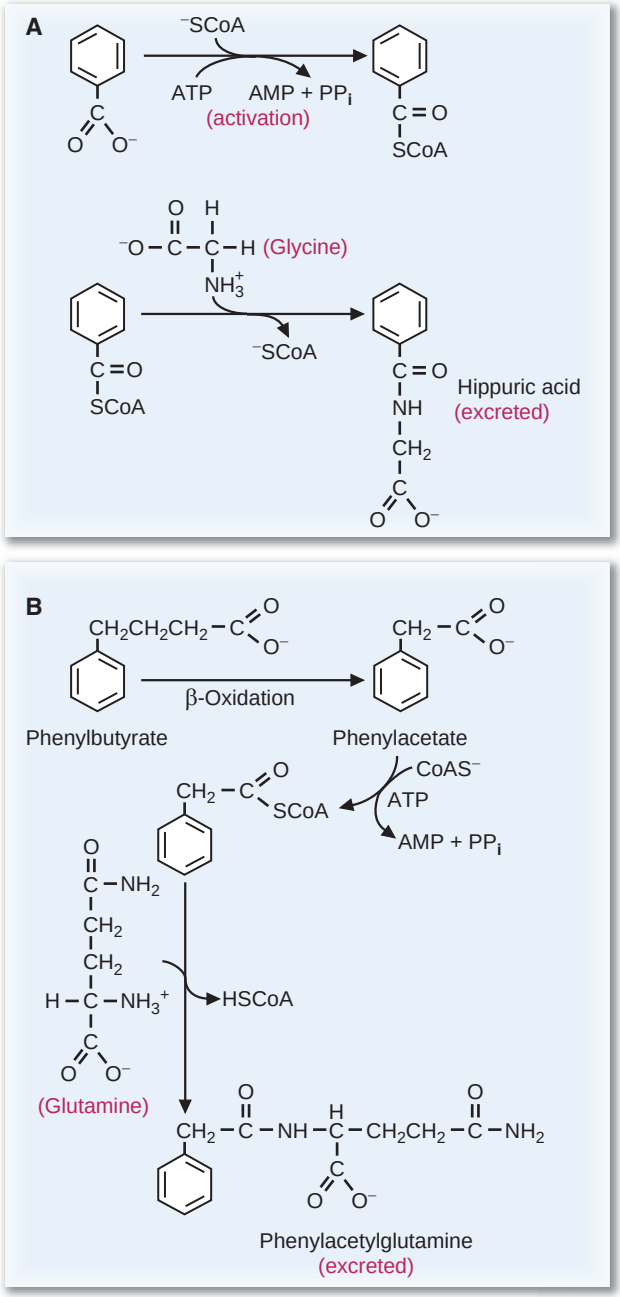
Answer 3: The urea cycle. Reaction 2 is defective in the disease described in this case.

4 **The answer is C: Bypassing carbamoyl phosphate synthetase II (CPS-II).** The rate-limiting step for de novo pyrimidine synthesis is carbamoyl phosphate synthetase II (CPS-II), which produces carbamoyl phosphate in the cytoplasm (see the figure on page 132). In an OTC deficiency, the carbamoyl phosphate produced in the mitochondria leaks into the cytoplasm, leading to orotic acid synthesis as the regulated step of the pathway is being bypassed. The elevated ammonia is not a substrate of CPS-II, and while glutamine is also elevated, and is a substrate of CPS-II, higher glutamine concentrations will not overcome enzyme inhibition by its allosteric inhibitor, UTP. Aspartate transcarbamoylase is the regulated step of pyrimidine biosynthesis in many prokaryotic cells, but not in humans. This step is necessary for pyrimidines to be synthesized starting with carbamoyl phosphate. CPS-I is a mitochondrial enzyme not involved in pyrimidine production.



An overview of pyrimidine synthesis, indicating the regulation that occurs at the carbamoyl phosphate synthetase II step. If carbamoyl phosphate can be generated outside of this pathway (as in an ornithine transcarbamoylase deficiency), then pyrimidine synthesis will bypass its regulated step, and an overproduction of pyrimidines would result.

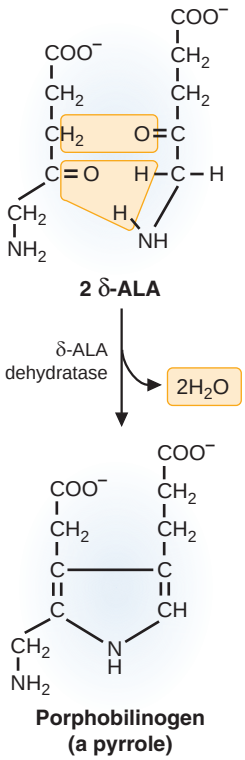
5 **The answer is C: Arginine and benzoate.** Whenever there is a urea cycle defect, arginine becomes an essential amino acid (as its route of synthesis is the urea cycle). Benzoate, along with phenylbutyrate, is given to patients with urea cycle defects to conjugate with a nitrogen carrying molecule (benzoate conjugates with glycine while phenylbutyrate, after activation to phenylacetate, conjugates with glutamine), which is then excreted. The reactions of benzoate and phenylbutyrate with nitrogen containing amino acids are shown above. The excretion of glycyl-benzoate reduces the glycine levels of the body, forcing more glycine to be produced and providing an alternative pathway for nitrogen disposal in the absence of a functional urea cycle. Giving lysine or glutamine will not help to reduce ammonia levels in the patient.



Removal of nitrogen using benzoic acid (**panel A**) and phenylbutyrate (**panel B**).

6 **The answer is B: Reduction of heme synthesis.** The boy is suffering from lead poisoning, which he obtained from eating the flaking paint chips. Lead inhibits the δ-aminolevulinic acid dehydratase step of heme synthesis, leading to reduced heme levels (see the figure on page 133). In addition, the ferrochelatase step (in which iron is inserted into the newly synthesized heme ring) is also inhibited by lead. The reduced heme levels reduce the amount of functional hemoglobin synthesized, leading

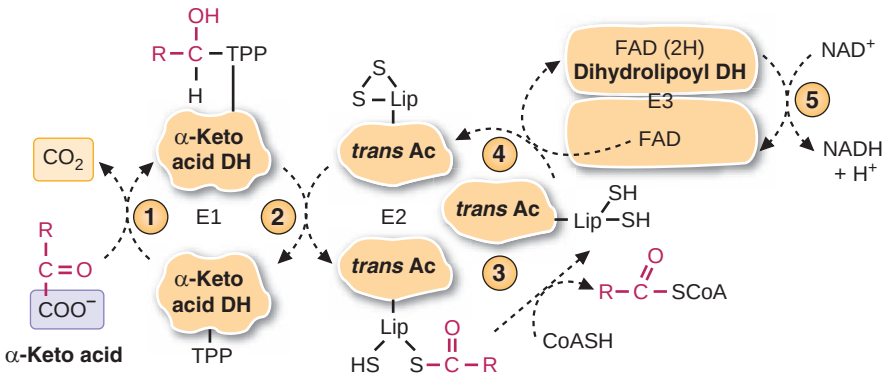
to the microcytic anemia observed in the child. Lead does not interfere with iron transport or inhibit part of the phosphatidyl inositol cycle (lithium is the metal that does that). DNA synthesis is not impaired by lead, nor does lead inhibit gene expression of the globin chains. Cytochrome synthesis is also decreased and may contribute to the lethargy observed in the child.



One of the two steps in heme biosynthesis that is sensitive to lead.

7 **The answer is E: Thiamine.** The child has maple syrup urine disease, a defect in the branched-chain α-keto acid dehydrogenase step that utilizes all three branched-chain α-keto acids as substrates. The reaction catalyzed by this enzyme is an oxidative decarboxylation reaction, which requires the same five cofactors as do pyruvate and α-ketoglutarate dehydrogenase; thiamine, NAD^+, FAD, lipoic acid, and coenzyme A. A subset of patients with this disorder has a mutation in the E1 subunit of the enzyme, which has reduced the affinity of the enzyme for vitamin B_1. Increasing the concentration of B1 can therefore overcome the effects of the mutation and allow the enzyme to exhibit sufficient activity to reduce the buildup of the toxic metabolites. While niacin and riboflavin are required for the enzyme, the mutation in the enzyme is such that the affinity of these cofactors for the enzyme has not been altered. B_{12} and B_6 are not required for this reaction.

8 **The answer is A: α-ketoglutarate dehydrogenase.** The child has a mutation in the shared E3 subunit of pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and the branched-chain α-ketoacid dehydrogenase. All three reactions are oxidative decarboxylation reactions and utilize a three-component enzyme complex, designated as E1, E2, and E3 (see the figure below). The E1 subunit binds thiamine pyrophosphate and catalyzes the decarboxylation reaction. The E2 subunit is a transacylase and is involved in the oxidation–reduction part of the reaction. The E3 component (dihydrolipoyl dehydrogenase) is shared among all three enzymes, and a mutation in this subunit will affect the activity of all three enzymes. This subunit reduces NAD^+, using electrons obtained from reduced lipoic acid. The key to solving the problem is the recognition that lactic acidosis occurs, which would happen when pyruvate dehydrogenase was defective. None of the other dehydrogenases listed (isocitrate dehydrogenase, malate dehydrogenase, and succinate dehydrogenase) require the E3 subunit for their activity, nor do they catalyze oxidative decarboxylation reactions. Acetyl-CoA carboxylase catalyzes a carboxylation reaction, and does not share subunits with the enzymes that catalyze oxidative decarboxylations.



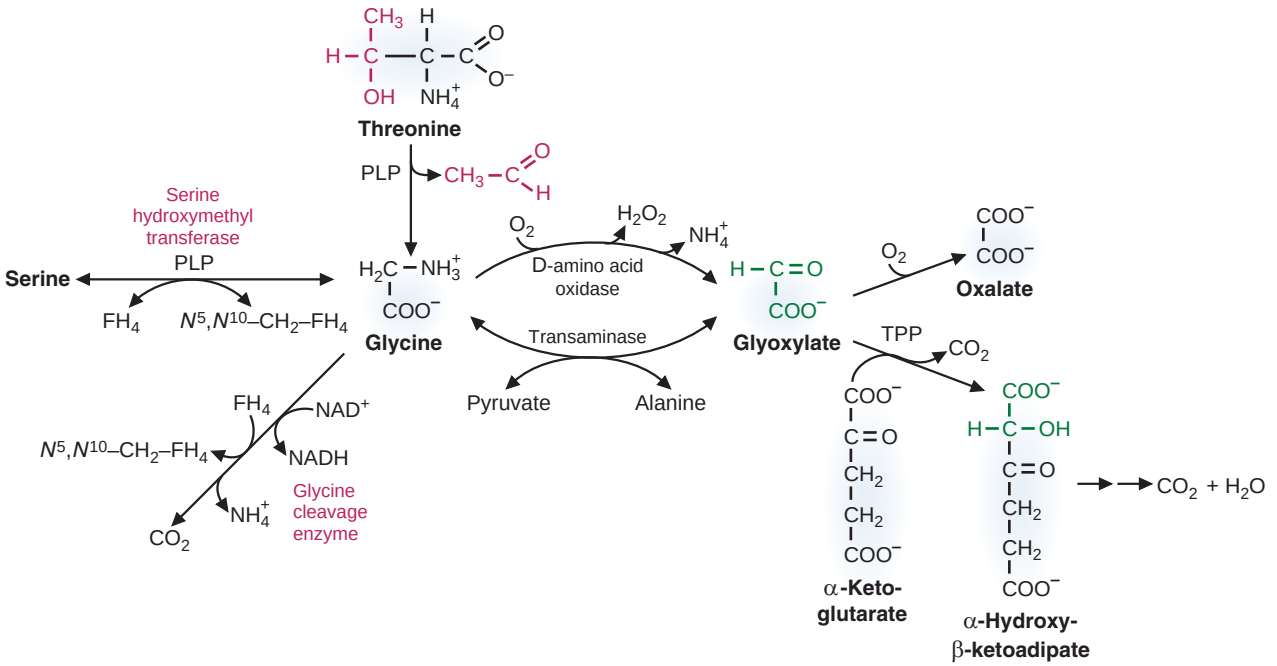
Answer 8: Mechanism of α-keto acid dehydrogenase complexes. R represents the portion of the α-keto acid that begins with the β carbon. Three different subunits are required for the reaction: E1 (α-ketoacid decarboxylase), E2 (transacylase), and E3 (dihydrolipoyl dehydrogenase). TPP refers to the cofactor thiamine pyrophosphate. Lip refers to the cofactor lipoic acid.

9 **The answer is D: Lack of large, neutral amino acids in the brain.** The child has PKU. The elevated phenylalanine levels in the blood are saturating the large, neutral amino acid transport protein in the nervous system (L-system), preventing other substrates from entering the brain (such as tryptophan, tyrosine, lysine, and leucine). This alters the ability of the brain to synthesize proteins, and leads to neurological problems. Providing large amounts of these large, neutral amino acids prevents saturation of the system by phenylalanine, and can be used as a treatment, along with restricted phenylalanine diet, for children with this disorder. (See J Inherit Metab Dis. 2006 Dec;29(6):732–738.) The developmental delay does not appear to be due to acidosis, lack of tyrosine, an inhibition of hydroxylating enzymes, or inhibition of neuronal glycolysis.

10 **The answer is E: Homocystine.** The boy is exhibiting the symptoms of homocystinuria, usually caused by a defect in cystathionine β-synthase. Cystathionine β-synthase will condense homocysteine with serine to form cystathionine. An inability to catalyze this reaction will lead to an accumulation of homocysteine, which will oxidize to form homocystine. The elevated serine can be metabolized back into the glycolytic pathway. Methionine will not increase in blood as the homocysteine produced is converted into homocystine. Phenylpyruvate is a diagnostic marker for PKU, but it is not relevant for homocysteine production or degradation. Fibrillin is mutated in Marfan syndrome, but this disorder is not Marfan syndrome.

11 **The answer is D: B_6.** Cystathionine β-synthase is a B_6 requiring enzyme (the reaction is a β-elimination of the serine hydroxyl group, followed by a β-addition of homocysteine to serine; both types of reactions require the participation of B_6). In some mutations, the affinity of the cofactor for the enzyme has been reduced, so significantly increasing the concentration of the cofactor will allow the reaction to proceed. The enzyme does not require the assistance of B_1, B_2, B_3 (niacin), or B_{12} to catalyze the reaction.

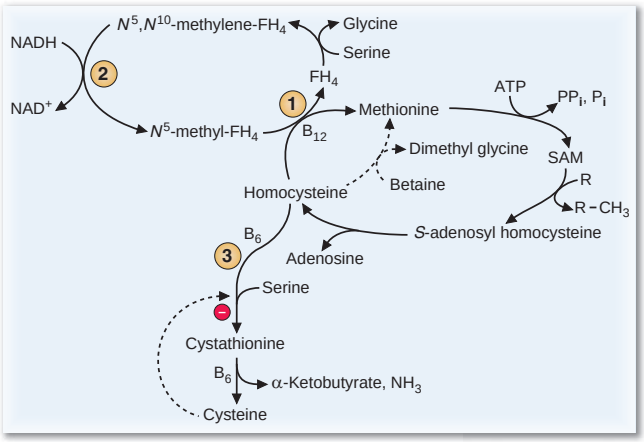
12 **The answer is D: Glyoxylate.** The boy has primary oxaluria type I, an autosomal recessive trait, which is a defect in a transaminase that converts glyoxylate to glycine. If this transaminase is defective, glyoxylate will accumulate. The glyoxylate will then be oxidized to oxalate, which, in the presence of calcium, will precipitate and form stones in the kidney. The metabolic pathway for glycine being converted to glyoxylate is shown below, and the enzyme that catalyzes this reaction is the D-amino acid oxidase. Alanine, leucine, and lysine metabolism do not give rise to oxalate.



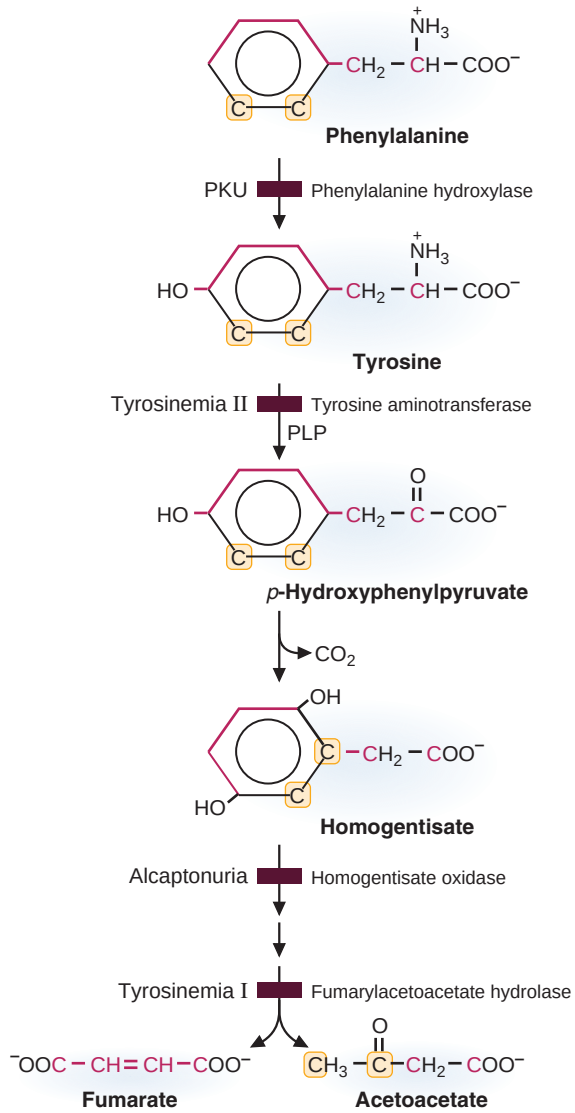
Answer 12

13 **The answer is B: Restriction of dietary methionine.** The boy has cystinuria, elevated levels of cystine in the urine, due to a defect in a kidney transporter that removes cystine from the urine and sends it back into the blood. Due to this, the concentration of cystine in the urine is higher than normal and reaches levels close to its solubility limit. Cysteine is derived from methionine, so a reduction in methionine levels will reduce cysteine levels, which then leads to a reduction in cystine levels. Increasing ethanol content will lead to dehydration, which will increase the concentration of cystine in the urine, leading to increased precipitation. This would also be the case if the urine were acidified (acidification also reduces the solubility of the cystine stones). Restricting glycine is not effective, as glycine is not a precursor of cysteine biosynthesis. Prescribing diuretics would force the boy to urinate more frequently, and would raise a risk for dehydration, which would lead to possible elevation of cystine concentrations.

14 **The answer is C: Cystathionine β-synthase.** Cystathionine β-synthase has a requirement of pyridoxal phosphate, and in about 50% of the cases of defective synthase enzymes, increasing the concentration of B_6 can overcome the effects of the mutation on the enzyme. While a defect in methionine synthase will lead to elevated homocysteine (see the figure below; cystathionine β-synthase is enzyme 3 and methionine synthase is enzyme 1), this enzyme requires B_{12}, not B_6. A defect in N5, N10 methylene tetrahydrofolate reductase will also lead to elevated homocysteine, but that enzyme has a requirement for NADH, not vitamin B_6. A defect in cystathionase (another B_6 requiring enzyme) will block the degradation of cystathionine, which will accumulate, but will not lead to significantly elevated homocysteine. S-adenosyl homocysteine hydrolase is the enzyme that converts S-adenosyl homocysteine to homocysteine and adenosine; lack of its activity will lead to a reduction, not an increase, in homocysteine levels.

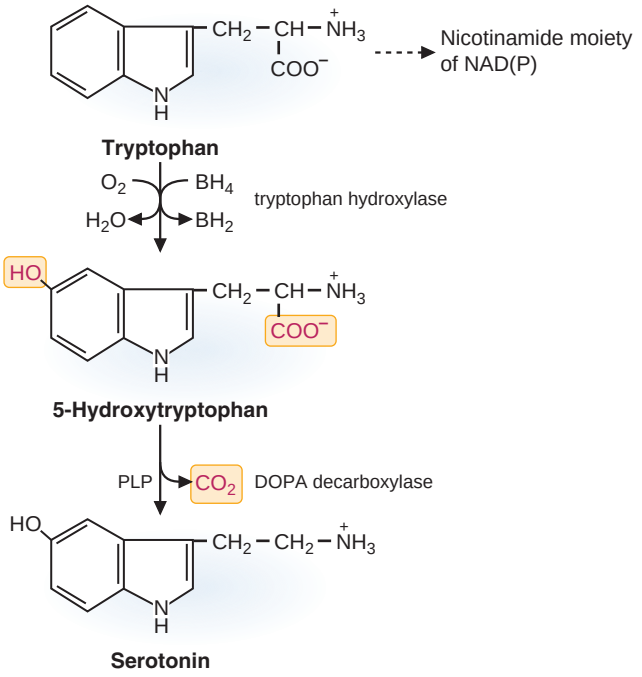


15 **The answer is C: Tyrosine.** The boy has the inherited disorder tyrosinemia type I, which is a defect in fumarylacetoacetate hydrolase, the last step in the degradation pathway for tyrosine (see the figure below). In its acute form, this disorder will lead to liver failure and death within 1 year of life. The accumulation of intermediates in the tyrosine degradation pathway triggers apoptosis

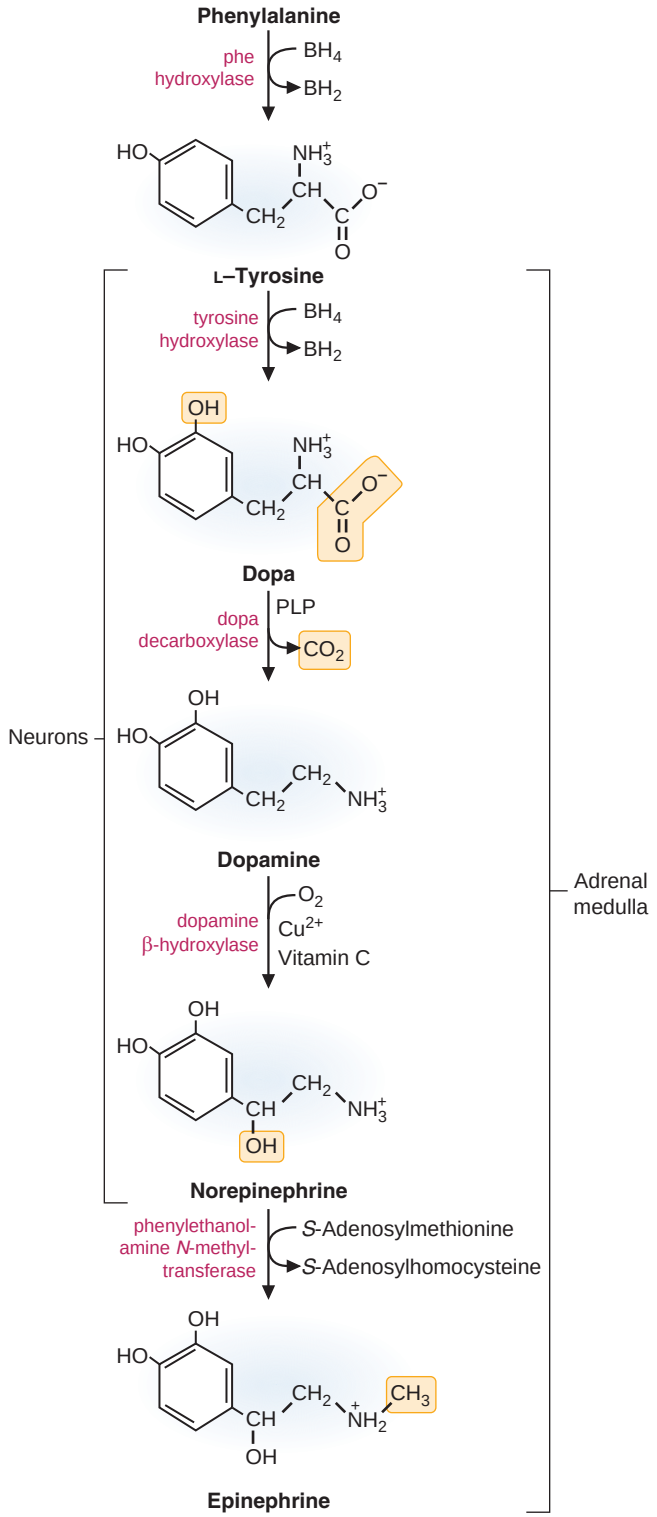


of the hepatocytes, leading to complete liver failure. The yellowing of the eyes (jaundice, due to accumulated bilirubin) is a result of liver failure. None of the other amino acids listed (alanine, tryptophan, histidine, and lysine) contribute to the formation of intermediates of the phenylalanine and tyrosine degradative pathways.

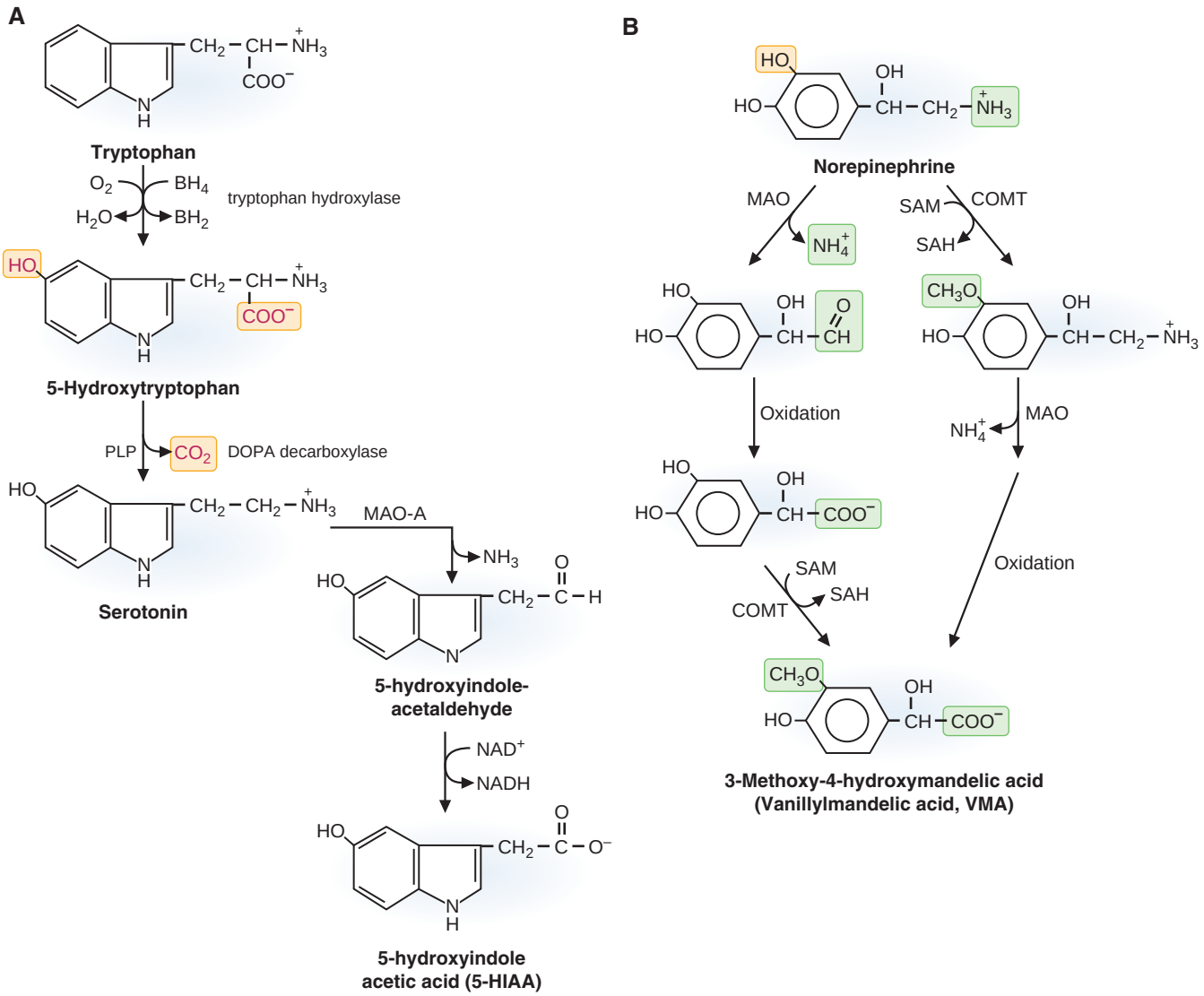
16 **The answer is A: Tryptophan.** Most drugs used to treat depression do so by elevating serotonin levels, and serotonin is derived from tryptophan (see the figure below). Tyrosine is the precursor for catecholamines, while glutamate is the precursor of GABA. Histidine is the precursor for histamine, while glycine itself acts as a neurotransmitter in the brain.



17 **The answer is C: Tyrosine.** This patient has Parkinson disease, which is a problem with dopamine synthesis in the substantia nigra. Dopamine is derived from tyrosine. Treatment with DOPA in the initial stages of the disease provides relief from the symptoms. DOPA cannot be synthesized from alanine, serine, tryptophan, or phenylalanine. The figure below indicates the biosynthetic pathway of DOPA and the catecholamines.



18 **The answer is D: 5-hydroxyindoleacetic acid (5-HIAA).** This patient has the classic presentation of a carcinoid tumor. This type of tumor secretes serotonin that causes these classic symptoms. The breakdown product of serotonin is 5-hydroxyindoleacetic acid (5-HIAA, see the figure below). Elevated levels of 5-HIAA in the urine confirms a high level of serotonin and the diagnosis of a carcinoid. VMA and/or catechols would be elevated if the patient had a pheochromocytoma producing epinephrine or norepinephrine (the VMAs are degradation products of these neurotransmitters, also seen in the figure below). The symptoms do not match a pheochromocytoma, particularly due to the lack of increase in heart rate or blood pressure. Dopamine is depleted in Parkinson disease, not in this condition. Cortisol levels would be high in Cushing syndrome, but not under these conditions.



Panel A shows the generation of 5-HIAA from serotonin degradation, while **panel B** indicates the generation of VMA from catecholamine degradation.

19 **The answer is B: Tyramine.** Tyramine is a degradation product of tyrosine (decarboxylated tyrosine), which, when elevated, will lead to norepinephrine release. Tyramine is found in red wine and aged foods such as certain cheeses. When ingested, tyramine is degraded by monoamine oxidase to a harmless compound, and excessive norepinephrine release does not occur. However, if a patient is taking a monoamine oxidase inhibitor (MAOI), it is possible that tyramine does not get degraded appropriately. MAOIs which covalently modify (as opposed to being competitive inhibitors) the enzyme are very useful medications for atypical

depression that is unresponsive to other modalities. Unfortunately, MAOIs have multiple interactions with many other medications and foods. A high tyramine level leads to a greatly elevated blood pressure due to the release of norepinephrine. Patients on MAOIs need to avoid foods high in tyramine, such as cheeses (aged and processed), red wine, caviar, brewer's yeast, miso soup, dried herring, and aged meats. MAOIs have no effect on glycoproteins or cholesterol.

20 The answer is E: Heme synthesis. The boy has porphyria, a reduced ability to synthesize heme. The supersensitivity to the sun is due to the presence of heme precursors in skin cells that are easily converted to radical form by the energy in sunlight, and which severely damage the cell. The drug the boy is taking is metabolized via a cytochrome P450 system, which is induced when the drug first enters the circulation. Induction of P450 systems induces the synthesis of heme, leading to increased concentrations of the heme intermediates and an increased sensitivity to the effects of these intermediates as induced by sunlight. The anemia is due to reduced heme levels in the red blood cells. This disorder is not due to defects in DNA repair, glycogen metabolism, or fatty acid metabolism.