

By observing chickens, Christiaan Eijkman helped discover a cure for the vitamin deficiency disease beriberi, subsequently winning a Nobel Prize. Eijkman found that chickens fed cooked white rice quickly became ill with beriberi, whereas those fed brown rice never developed the disease. Subsequent research demonstrated that the milling and polishing of brown rice to make white rice also stripped the rice of thiamin, a B-vitamin. Learn more at www.NobelPrize.org.

13 Micronutrients in Energy and Amino Acid Metabolism

Chapter Outline

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- 13.15 Other Compounds Linked with Energy and Amino Acid Metabolism

Student Learning Outcomes

After studying this chapter, you will be able to

1. Identify the micronutrients involved in energy and amino acid metabolism.
2. Identify important food sources for the micronutrients involved in energy and amino acid metabolism.
3. Describe how each micronutrient involved in energy and amino acid metabolism is absorbed, transported, stored, and excreted.
4. List the major functions of and deficiency symptoms for each micronutrient involved in energy and amino acid metabolism.
5. Describe the toxicity symptoms of the excess consumption of each micronutrient involved in energy and amino acid metabolism.
6. Explain why carnitine and taurine are referred to as vitamin-like compounds.

FOR CENTURIES, BERIBERI, PELLAGRA, GOITER, and other micronutrient deficiency diseases and conditions caused fatigue, enormous suffering, and death. It wasn't until early in the 20th century that scientists discovered that these illnesses are caused by the absence from the diet of certain vitamins and minerals involved in energy metabolism.¹ Researchers discovered that restoring micronutrients to the diet dramatically reverses deficiency diseases, if supplied before significant deterioration of the body took place.

As you know from Chapter 9, *metabolism* refers to the entire network of chemical processes involved in maintaining life. Micronutrients are required for energy metabolism—that is, the biochemical pathways that enable us to release and use energy from carbohydrate, fat, protein, and alcohol. The B-vitamins thiamin, riboflavin, niacin, pantothenic acid, biotin, and vitamin B-6 play critical roles in these pathways. Several minerals, including chromium and manganese, also are used in energy metabolism.

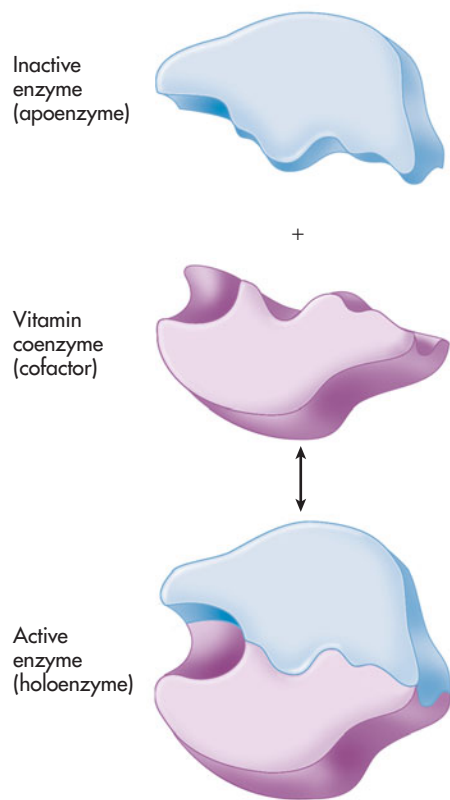


Figure 13-1 The enzyme-coenzyme interaction. The B-vitamins form coenzymes, which are one type of cofactor. Cofactors enable specific enzymes to function.

Protein, because of its amino group, has some special needs related to metabolism. Recall from Chapter 9 that amino acids undergo deamination and transamination reactions. Deamination reactions remove amino groups; this permits the carbon skeleton to be used for energy, gluconeogenesis, or the formation of other compounds. Transamination reactions allow the synthesis of nonessential amino acids. Both deamination and transamination reactions require vitamin B-6. Vitamin B-12, folate, manganese, and molybdenum also play important roles in amino acid metabolism.

Iron, copper, and magnesium also are vital to energy metabolism. Chapter 14 describes iron's role in the citric acid cycle and the role of both iron and copper in the electron transport chain. See Chapter 15 for more detail on magnesium's role in glycolysis, gluconeogenesis, and the citric acid cycle.

This chapter also briefly describes choline, a newcomer to the list of important nutrients, as well as some vitamin-like compounds that may be needed in the diet under atypical circumstances. These compounds are involved in metabolism but currently are not classified as true vitamins because a healthy person does not require a dietary source of them and because no specific deficiency disease results when they are absent from the diet.

13.1 Cofactors: A Common Role of B-Vitamins and Some Minerals

All B-vitamins form **coenzymes** (see Chapter 9), which are small, organic molecules that are a type of **cofactor**. **Cofactors** combine with inactive enzymes (called apoenzymes) to form active enzymes (called holoenzymes), which are able to catalyze specific reactions (Fig. 13-1). Table 13-1 lists examples of the coenzymes formed from B-vitamins. The B-vitamin coenzymes aid the work of enzymes in dozens of biochemical reactions. In many cases, the B-vitamin coenzymes act as electron donors or acceptors. Minerals, such as manganese and magnesium (see Chapter 15), are another type of cofactor. They bind to the enzyme, permitting it to catalyze the biochemical reaction.

Figure 13-2 shows where the B-vitamin coenzymes and some mineral coenzymes function in energy and amino acid metabolism. Because of the role of B-vitamins in energy metabolism, the need for many of them increases somewhat with higher amounts of physical activity. Still, this is not a major concern because the higher food intake that usually accompanies an increase in energy expenditure contributes more B-vitamins to the diet.

Table 13-1 B-Vitamins and Coenzyme Examples

B-Vitamin	Coenzyme Example*	Abbreviation	Function/Transfer
Thiamin	Thiamin pyrophosphate (thiamin diphosphate)	TPP (TDP)	Decarboxylation
Riboflavin	Flavin adenine dinucleotide	FAD	Electron (hydrogen) transfer
	Flavin mononucleotide	FMN	Electron (hydrogen) transfer
Niacin	Nicotinamide adenine dinucleotide	NAD	Electron (hydrogen) transfer
	Nicotinamide adenine dinucleotide phosphate	NADP	Electron (hydrogen) transfer
Pantothenic acid	Coenzyme A	CoA	Acyl (2-C groups) transfer
Biotin	N-carboxylbiotinyl lysine		Carboxylation; CO ₂ transfer
Vitamin B-6	Pyridoxal phosphate	PLP	Transamination: amino group transfer
Folic acid	Tetrahydrofolic acid	THFA	1-carbon unit transfer
Vitamin B-12	Methylcobalamin		1-carbon unit transfer

*Some B-vitamins form more than 1 coenzyme.

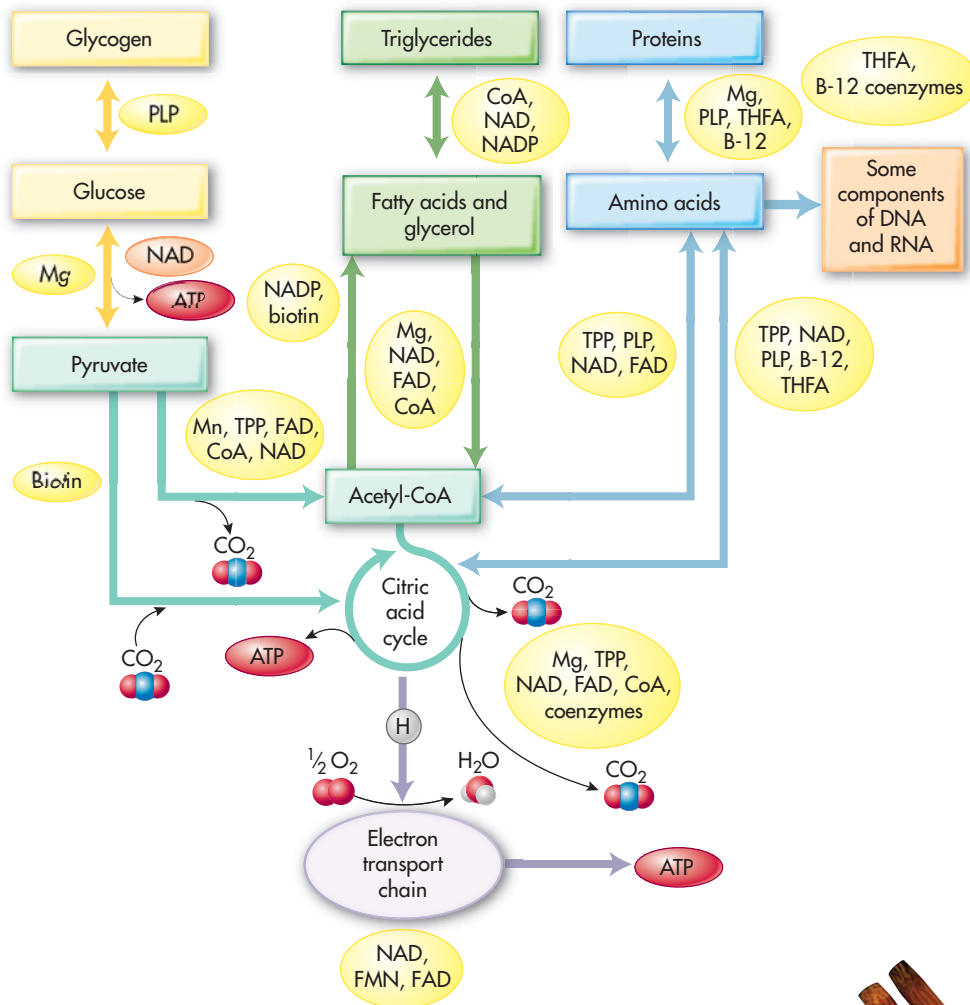


Figure 13-2 Many metabolic pathways, including those involved in energy metabolism, use coenzyme forms of the B-vitamins and mineral cofactors.

13.2 Thiamin

For centuries, the devastating effects of the disease beriberi were known in Asian countries where white rice, lacking the nutrient-rich germ, was the main (staple) food. In the late 1800s, beriberi became even more common and one of the leading causes of death. This occurred because the rice-milling technology introduced at that time completely removed the bran and the germ, resulting in highly polished white rice but also stripping the rice grains of their thiamin content. However, scientists did not link beriberi with a nutrient deficiency until early in the 1900s, when it was discovered that a vital factor in rice germ cures the disease. That factor is the B-vitamin thiamin, also known as vitamin B-1. The symptoms of beriberi include impaired nervous system function and weakness, which is a direct result of thiamin's role in energy metabolism.

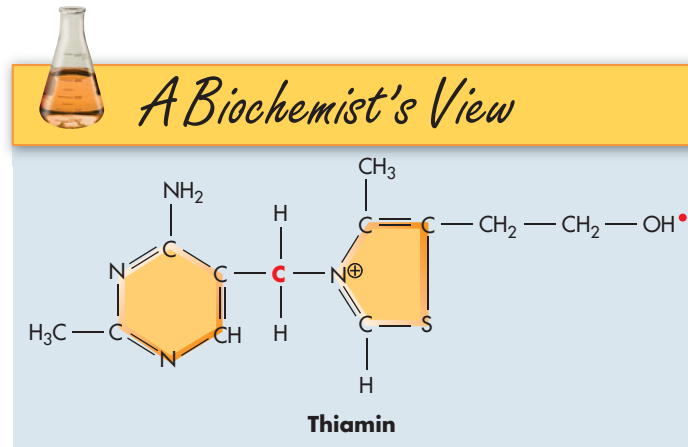
Thiamin consists of a central carbon attached to a 6-member, nitrogen-containing ring and a 5-member, sulfur-containing ring. Its name comes from *thio*, meaning “sulfur,” and *amine*, referring to the nitrogen groups in the molecule. Two phosphate groups are added (at the red dot in thiamin's structure), to form this vitamin's coenzyme, thiamin pyrophosphate (TPP).

The chemical bond between each ring and the central carbon in thiamin (shown in red in the structure) is easily broken by prolonged exposure to heat, as can occur in cooking. When this happens, the vitamin can no longer function in the body. This destruction also occurs if food is cooked in alkaline (basic)

In tropical areas of the world, white rice has been favored over brown rice because it stays fresh longer. That's because, in warm climates and without refrigeration, the fat in the germ of brown rice goes rancid quickly.

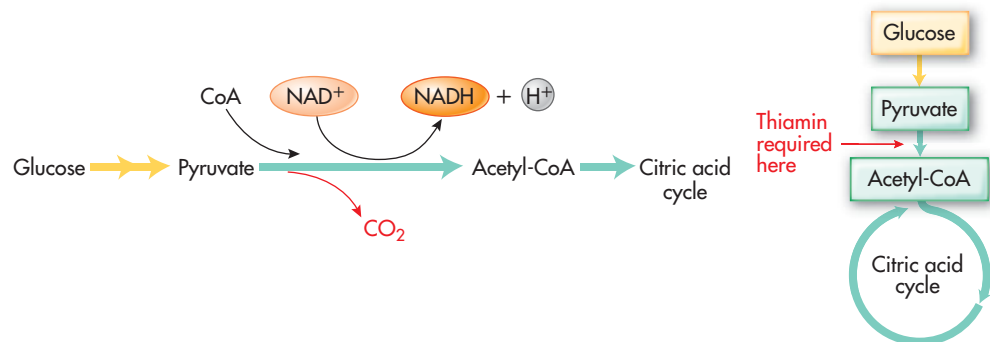


solutions (pH ≥ 8.0). Thus, the practice of adding baking soda (a base) to the cooking water of fresh green vegetables, to retain their color, is not recommended.

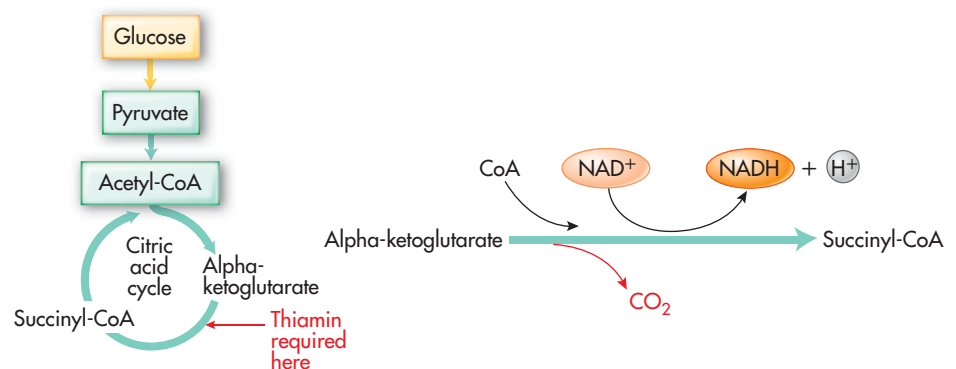


Functions of Thiamin

The coenzyme thiamin pyrophosphate (TPP), also referred to as thiamin diphosphate (TDP), is required for the metabolism of carbohydrates and branched-chain amino acids.^{2,3} TPP is necessary for 2 different types of reactions. First, it works with specific enzymes to remove carbon dioxide (known as **decarboxylation**) from certain compounds. The conversion of pyruvate to acetyl-CoA, a critical reaction in the aerobic respiration of glucose, is an example of the decarboxylation action of TPP.



A similar decarboxylation reaction occurs in the citric acid cycle. As shown in the following diagram, TPP aids in the conversion of the intermediate compound alpha-ketoglutarate to succinyl-CoA.



decarboxylation Removal of 1 molecule of carbon dioxide from a compound.

In addition to TPP, both of the previously mentioned reactions require 3 additional B-vitamin coenzymes: CoA (pantothenic acid), NAD (niacin), and FAD (riboflavin)

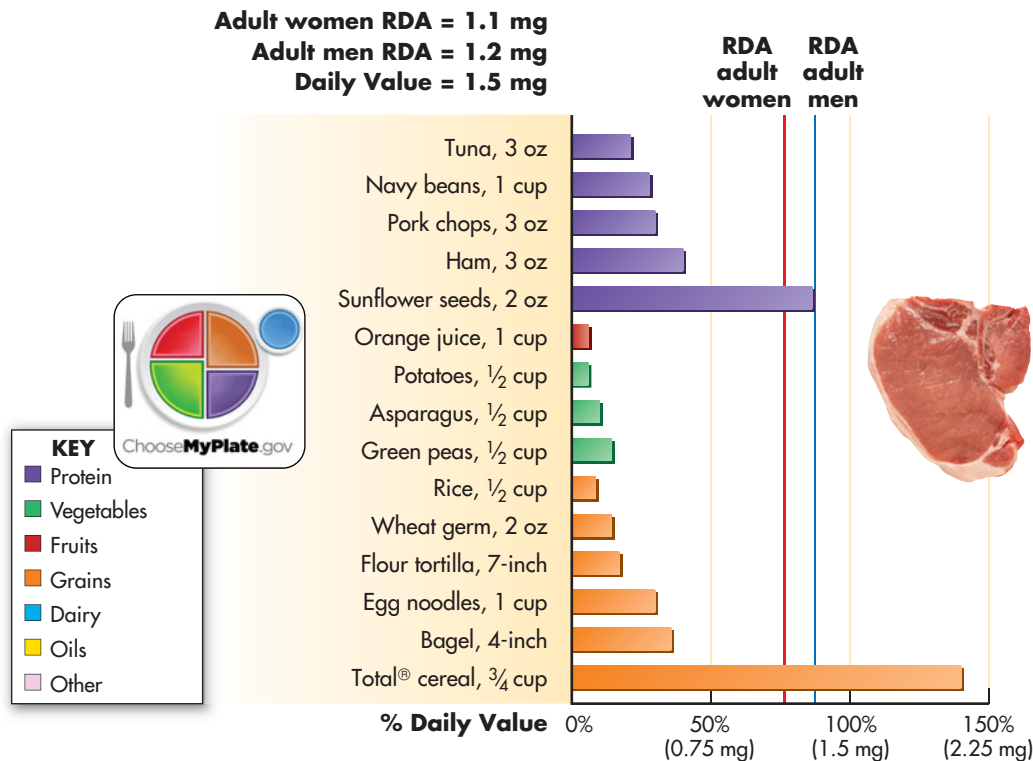


Figure 13-3 Food sources of thiamin. In the MyPlate graphic, in addition to the food groups, yellow is used for oils and pink is used for substances that do not fit easily into food groups (e.g., candy, salty snacks).

(see Fig. 13-2). TPP functions in a similar manner (as a decarboxylase) in the metabolism of the branched-chain amino acids valine, leucine, and isoleucine.

TPP also functions as a coenzyme for **transketolase**, an enzyme in the pentose phosphate pathway. In this pathway, the 6-carbon glucose is converted to the 5-carbon sugar used to form DNA and RNA.

transketolase Enzyme whose functional component is thiamin pyrophosphate (TPP). It converts glucose to other sugars.

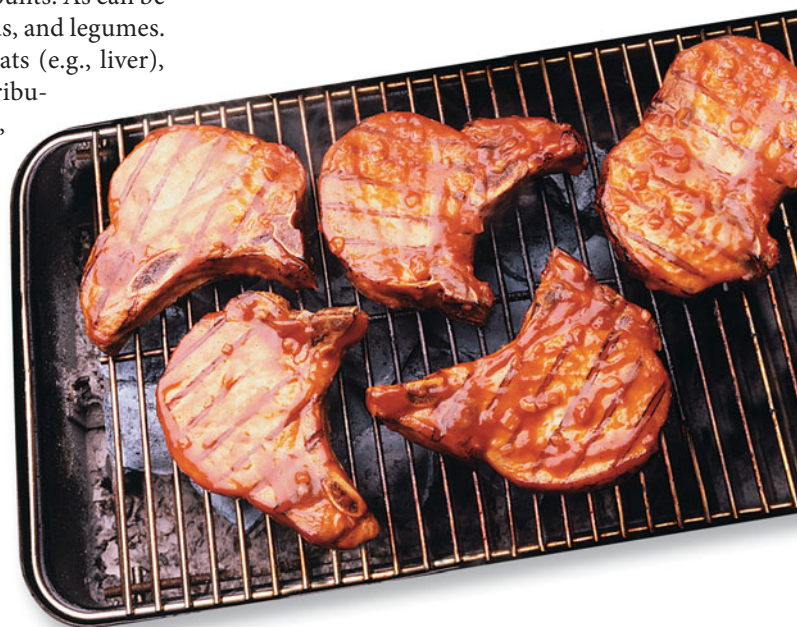
Thiamin in Foods

Thiamin is found in a wide variety of foods, although generally in small amounts. As can be seen in Figure 13-3, foods rich in thiamin are pork products, sunflower seeds, and legumes. Whole and enriched grains and cereals, green peas, asparagus, organ meats (e.g., liver), peanuts, and mushrooms also are good sources. In the U.S., the major contributors of thiamin are bread and rolls, ready-to-eat cereals, pasta, ham, milk, bakery products, potatoes, rice, orange juice, tomatoes, and beef.⁴ Eating a variety of foods in accord with MyPlate is a reliable way to obtain sufficient thiamin.

A few foods contain compounds, called thiamin antagonists, that lower the bioavailability of thiamin. Some species of fresh fish and shellfish contain thiaminase enzymes, which destroy thiamin; however, cooking inactivates these enzymes. Other foods, including coffee, tea, blueberries, red cabbage, brussels sprouts, and beets, contain compounds that oxidize thiamin and make it inactive.⁵ However, eating these foods has not been linked to thiamin deficiency.

Thiamin Needs and Upper Level

The RDAs for thiamin are 1.2 mg per day for men and 1.1 mg per day for women.⁶ The Daily Value on food and supplement labels is 1.5 mg. In the U.S., for men, the average daily intake for thiamin from food is 2.0 mg per day.



Pork is a rich source of thiamin.

For women, it is approximately 1.4 mg per day.⁷ There appear to be no adverse effects with excess intakes of thiamin from food or supplements because it is readily excreted in the urine. Thus, no Upper Level is established for this nutrient.⁶

Absorption, Transport, Storage, and Excretion of Thiamin

Thiamin is absorbed mainly in the small intestine by an active absorption process. It is transported mainly by red blood cells in its coenzyme form (thiamin pyrophosphate). Little thiamin is stored; only a small reserve (25–30 mg) is found in the muscles, brain, liver, and kidneys.⁵ Any excess intake is rapidly filtered out by the kidneys and excreted in the urine.⁶

Thiamin Deficiency

As described previously, the thiamin deficiency disease beriberi has been associated with diets consisting mainly of white rice. For example, in the 1800s, 25 to 40% of those in the Japanese navy experienced beriberi because ship rations included white rice but little else. When meat and legumes were added to the navy rations, beriberi was eliminated. Although much less common today, beriberi still occurs infrequently in persons living in refugee camps and detention centers.⁸ A form of beriberi, called Wernicke-Korsakoff syndrome, is found in developed countries in some individuals with alcoholism.

Beriberi

In Sinhalese, the language of Sri Lanka, the word *beriberi* means “I can’t, I can’t.” Those with beriberi are very weak because a deficiency of thiamin impairs the nervous, muscular, gastrointestinal, and cardiovascular systems and hinders energy metabolism. The symptoms of beriberi include **peripheral neuropathy** and weakness, muscle pain and tenderness, enlargement of the heart, difficulty breathing, edema, anorexia, weight loss, poor memory, and confusion.^{2,5} The nervous system is especially affected because of its reliance on glucose for energy. In thiamin deficiency, glucose metabolism is severely disrupted because pyruvate cannot be converted to acetyl-CoA, the entry compound into the citric acid cycle (see Fig. 13-2).

Beriberi often is described as either dry or wet beriberi. In dry beriberi, the main symptoms are related to the nervous and muscular systems. In wet beriberi, in addition to the neurological symptoms, the cardiovascular system is affected. The heart is enlarged, breathing may be difficult, and **congestive heart failure** may occur. Like most water-soluble vitamins, only small amounts of thiamin are stored in the body; thus, some signs of beriberi can develop after only 14 days on a thiamin-free diet.⁹

Wernicke-Korsakoff Syndrome

Wernicke-Korsakoff syndrome (also known as cerebral beriberi) is found mainly among heavy users of alcohol. These individuals have a 3-pronged problem related to thiamin: alcohol decreases thiamin absorption, alcohol increases thiamin excretion in the urine, and alcoholics may consume a poor-quality diet without enough thiamin. Because thiamin is not readily stored in the body, the syndrome can occur rapidly. The symptoms include changes in vision (double vision, crossed eyes, rapid eye movements), **ataxia**, and impaired mental functions. The symptoms, especially those of the eye, improve with high doses of thiamin.⁸

peripheral neuropathy Problem caused by damage to the nerves outside the spinal cord and brain. Symptoms include numbness, weakness, tingling, and burning pain, often in the hands, arms, legs, and feet.

congestive heart failure Condition resulting from severely weakened heart muscle, resulting in ineffective pumping of blood. This leads to fluid retention, especially in the lungs. The symptoms include fatigue, difficulty breathing, and leg and ankle swelling.

ataxia Inability to coordinate muscle activity during voluntary movement; incoordination.



Knowledge Check

1. How is the coenzyme TPP involved in energy metabolism? What is 1 critical reaction that requires TPP?
2. What are 3 foods that are rich sources of thiamin?
3. What dietary practices are likely to lead to beriberi?
4. Why do individuals with beriberi feel tired?

13.3 Riboflavin

Riboflavin, also known as vitamin B-2, was once called “yellow enzyme” because it has a distinctive yellow-green fluorescence. In fact, its name comes from its color (*flavin* means “yellow” in Latin). Riboflavin contains 3 linked, 6-membered rings, with a sugar alcohol attached to the middle ring.

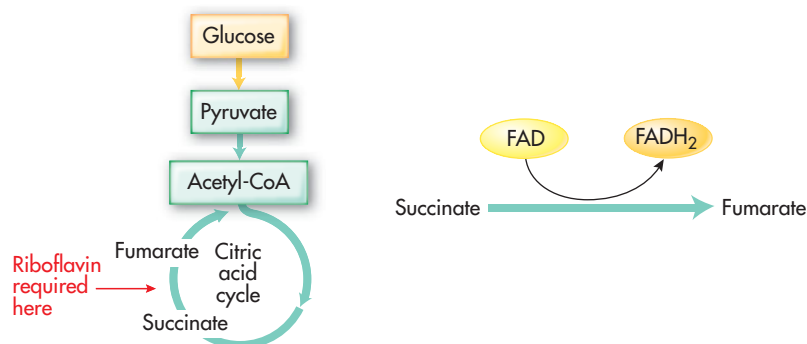
Functions of Riboflavin

Riboflavin is a component of 2 coenzymes that play key roles in energy metabolism: flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).¹⁰ These coenzymes, also referred to as flavins, have oxidation and reduction functions.¹⁰ (See Section 9.1 in Chapter 9.) FAD is the oxidized form of the coenzyme. When it is reduced (gains 2 hydrogens, equivalent to 2 hydrogen ions and 2 electrons), it is known as FADH₂.

The riboflavin coenzymes are involved in many reactions in various metabolic pathways.¹⁰ They are critical for energy metabolism and are involved in the formation of other compounds, including other B-vitamins and antioxidants.

Energy Metabolism

- In the citric acid cycle, the oxidation of succinate to fumarate requires the FAD-containing enzyme *succinate dehydrogenase*. The FADH₂ formed in this reaction donates hydrogen to the electron transport chain.



- In fatty acid breakdown (beta-oxidation) to acetyl-CoA, the enzyme *fatty acyl dehydrogenase* requires FAD (see Chapter 9).
- FMN shuttles hydrogen atoms into the electron transport chain.

Other B-Vitamin Functions

- The formation of niacin from the amino acid tryptophan requires FAD (see Section 13.4).
- The formation of the active vitamin B-6 coenzyme (pyridoxal phosphate) requires FMN.
- FAD is required for the synthesis of the folate metabolite 5-methyl-tetrahydrofolate; in this way, riboflavin participates indirectly in homocysteine metabolism (see Sections 13.9 and 13.10).

Antioxidant Function

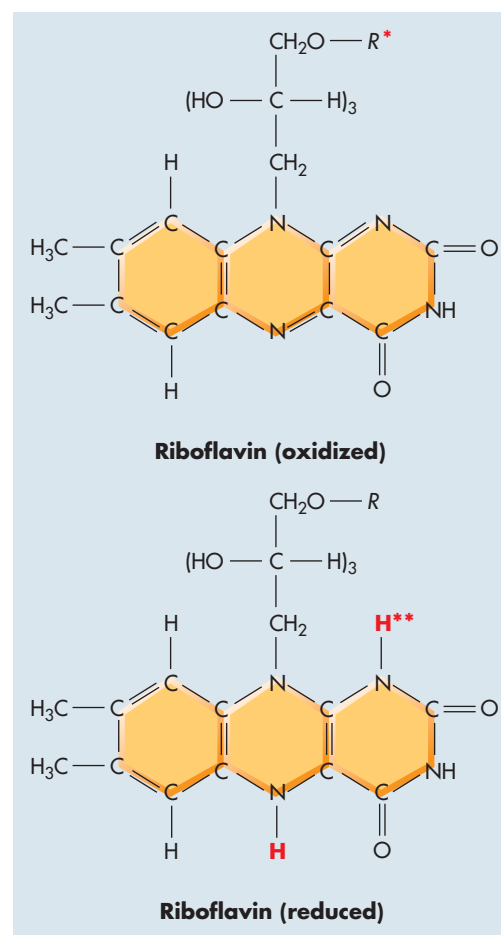
- The synthesis of the antioxidant compound glutathione depends on the FAD-containing enzyme *glutathione reductase*. As you'll see in Chapter 15, glutathione is an important part of the cell's antioxidant defense network.

Riboflavin in Foods

Almost one-quarter of the riboflavin in our diets comes from milk products. The rest typically is supplied by enriched white bread, rolls, and crackers, as well as eggs and meat.⁴ Foods rich

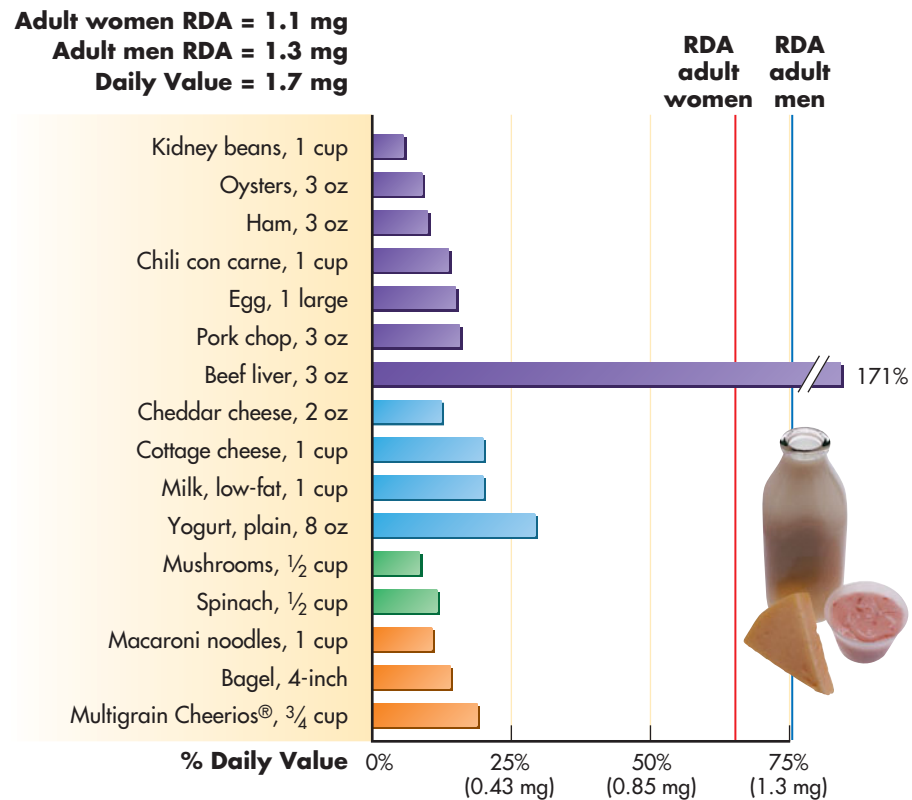


Milk products are good sources of riboflavin. Plastic and cardboard containers protect the riboflavin from UV radiation, which causes riboflavin to break down.



R* = H in free riboflavin; phosphate in the coenzyme FMN; adenine dinucleotide in the coenzyme FAD
 ** = Addition of 2 hydrogens (in red) in the reduced form.

Figure 13-4 Food sources of riboflavin.



in riboflavin are liver, mushrooms, spinach and other green, leafy vegetables, broccoli, asparagus, milk, and cottage cheese (Fig. 13-4). Exposure to light (ultraviolet radiation) causes riboflavin to break down rapidly. To prevent this light-induced breakdown, paper and plastic containers—not glass—should be used as packaging for riboflavin-rich foods, such as milk, milk products, and cereals.

Riboflavin Needs and Upper Level

The RDAs for riboflavin for adult men and women are 1.3 and 1.1 mg/day, respectively. The Daily Value on food and supplement labels is 1.7 mg. In the U.S., the average intake from food for riboflavin is approximately 2.7 mg/day for men and 2.0 mg/day for women.⁷ There appear to be no adverse effects from consuming large amounts of riboflavin because of its limited absorption and rapid excretion via the urine, so no Upper Level has been set.⁶

Absorption, Transport, Storage, and Excretion of Riboflavin

In the stomach, hydrochloric acid (HCl) releases riboflavin from its bound forms. About 60 to 65% of the free riboflavin is absorbed, primarily via active transport or facilitated diffusion in the small intestine.¹¹ In the blood, riboflavin is transported by protein carriers. Riboflavin is converted to its coenzyme forms in most tissues, but this occurs mainly in the small intestine, liver, heart, and kidneys. A small amount of riboflavin is stored in the liver, kidneys, and heart. Any excess intake is excreted in the urine.¹⁰ For people who take excessive amounts in supplement form, riboflavin imparts a bright yellow color to the urine, which glows under a black light.

► A few small clinical trials suggest that high doses of riboflavin supplements (400 mg/day) may reduce the frequency and duration of migraine headaches.^{70, 71} Researchers hypothesize that riboflavin may improve mitochondrial function in the brain. Check with your physician before initiating riboflavin supplements.

Riboflavin Deficiency

Riboflavin deficiency, called **ariboflavinosis**, primarily affects the mouth, skin, and red blood cells. The symptoms include inflammation of the throat, mouth (stomatitis), and tongue (glossitis); cracking of the tissue around the corners of the mouth (angular cheilitis); and

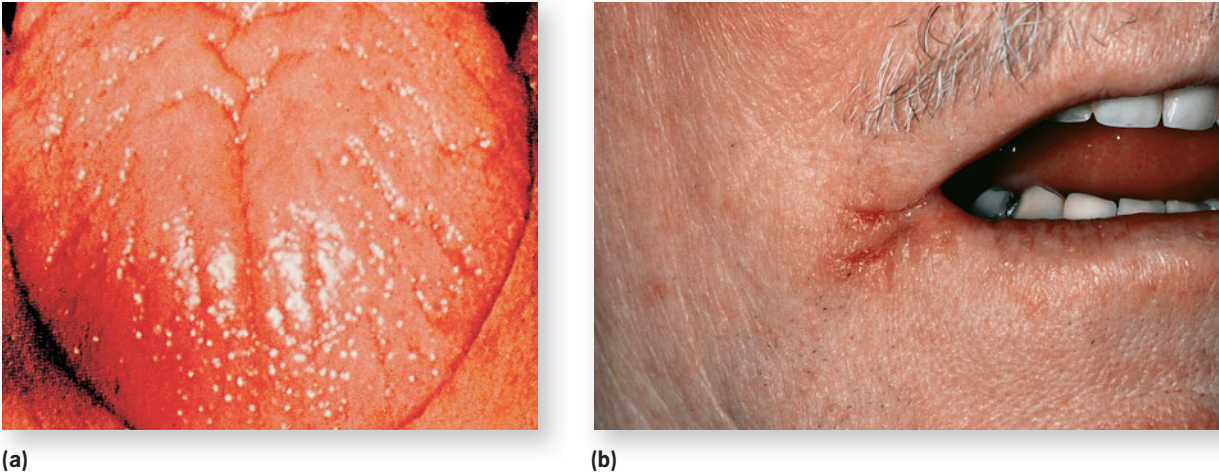


Figure 13-5 (a) Glossitis is a painful, inflamed tongue that can signal a deficiency of riboflavin, niacin, vitamin B-6, folate, or vitamin B-12. (b) Angular cheilitis, also called cheilosis or angular stomatitis, is another result of a riboflavin deficiency. It causes painful cracks at the corners of the mouth. Both glossitis and angular cheilitis can be caused by other medical conditions; thus, further evaluation is required before diagnosing a nutrient deficiency.

moist, red, scaly skin (seborrheic dermatitis) (Fig. 13-5). Anemia, fatigue, confusion, and headaches also may occur. Some of the symptoms of ariboflavinosis may result from deficiencies of other B-vitamins because they work in the same metabolic pathways as riboflavin and are often supplied by the same foods.

Ariboflavinosis develops after 2 months on a riboflavin-deficient diet and is rare in otherwise healthy people. Biochemical evidence of deficiency (low riboflavin levels in red blood cells or reduced activity of the enzyme glutathione reductase) is most often seen in adolescent girls and elderly people. Correcting moderate riboflavin deficiency with supplementation improves hematologic status.¹² Diseases such as cancer, certain forms of cardiovascular disease, and diabetes can lead to or worsen a riboflavin deficiency.⁶ People with alcoholism, malabsorption disorders, or very poor diets may be at risk of riboflavin deficiency. The long-term use of phenobarbital also may adversely affect riboflavin status because this drug increases the breakdown of riboflavin and other nutrients in the liver. Marginal riboflavin intake may occur in those who do not consume milk or milk products. Presently, little is known about the effects of a marginal riboflavin deficiency.

CRITICAL THINKING

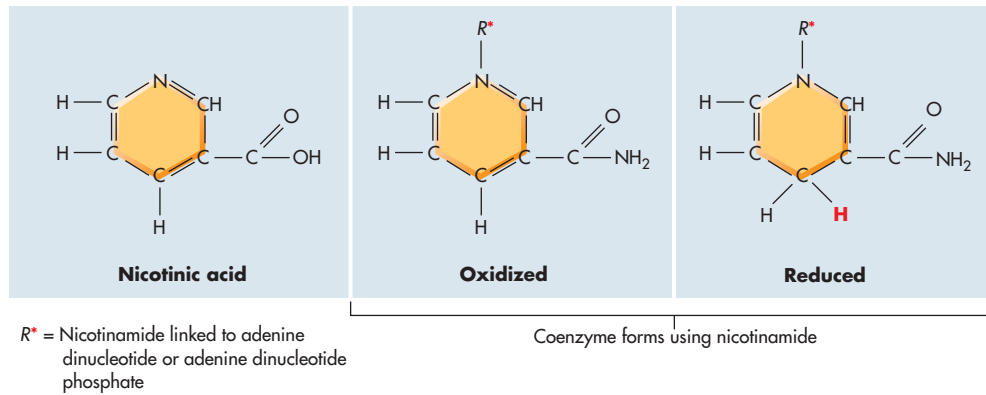
Gary suffers from alcoholism and pays no attention to his diet. In addition to the detrimental effects on the liver, excess alcohol consumption can cause deficiencies in certain B-vitamins. Explain why this problem can occur.

Knowledge Check

1. What foods are rich in riboflavin?
2. What are 3 general functions of riboflavin?
3. What are the 2 coenzymes formed from riboflavin?
4. Identify 2 symptoms of a riboflavin deficiency.

13.4 Niacin

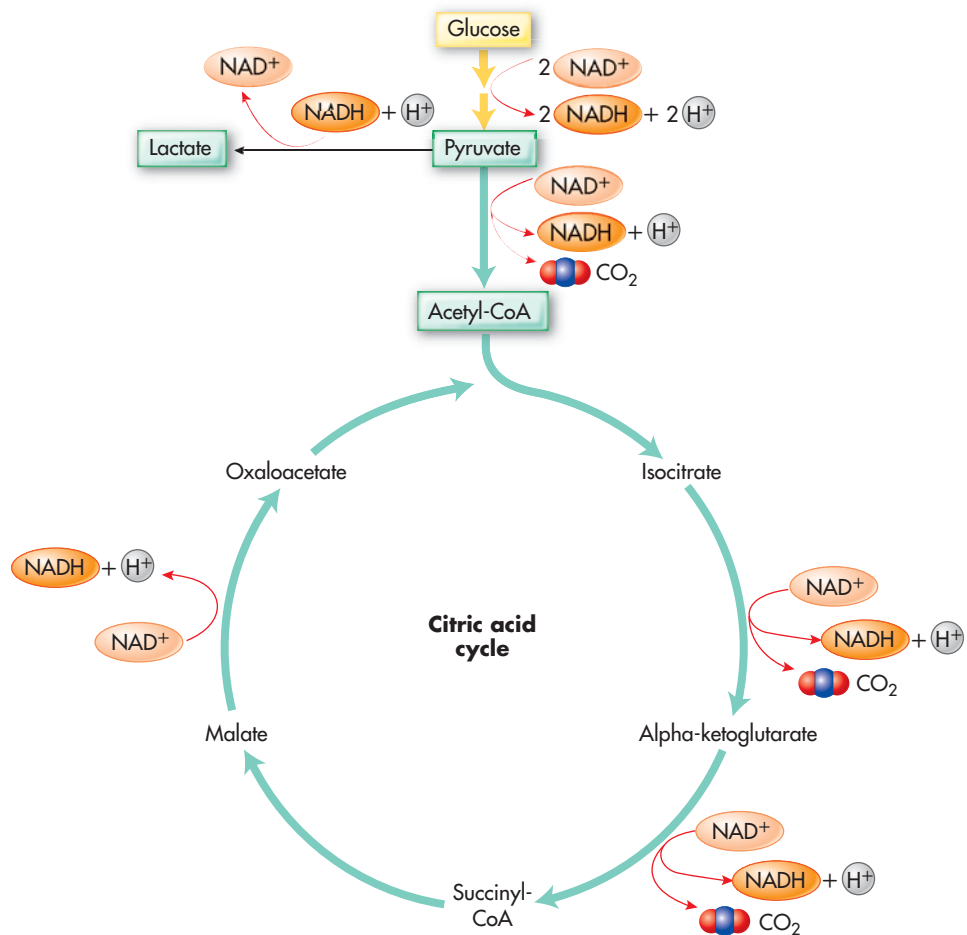
Pellagra—the deficiency disease of the B-vitamin niacin—is the only dietary deficiency disease ever to reach epidemic proportions in the U.S.¹³ In the early 1900s, pellagra affected thousands in the southeastern states before scientists discovered its link with niacin-poor diets. Niacin, or vitamin B-3, exists in 2 forms—nicotinic acid (niacin) and nicotinamide (niacinamide). Both forms are used to synthesize the niacin coenzymes: nicotinamide adenine dinucleotide (NAD⁺) and nicotinamide adenine dinucleotide phosphate (NADP⁺).



Functions of Niacin

Like the coenzyme forms of riboflavin, the coenzyme forms of niacin, NAD^+ and $NADP^+$, are active participants in oxidation-reduction reactions.¹⁴ The niacin coenzymes function in at least 200 reactions in cellular metabolic pathways, especially those that produce ATP. NAD^+ is required mainly for the catabolism of carbohydrates, proteins, and fats (Fig. 13-6). NAD^+ acts as an electron and hydrogen acceptor in glycolysis and the citric acid cycle. Under anaerobic conditions, NAD^+ is regenerated when pyruvate is converted to lactate. Under aerobic conditions, $NADH + H^+$ donates electrons and hydrogens to acceptor molecules in the electron transport chain, thereby contributing to ATP synthesis. Alcohol metabolism also requires niacin coenzymes (see Section 9.5 in Chapter 9).

Figure 13-6 The coenzyme form of niacin, NAD^+ , is required for glycolysis and the citric acid cycle. The NAD^+ is reduced to $NADH$. When pyruvate is reduced to form lactate, $NADH$ is converted to NAD^+ .



These reactions start with an oxidized form of a niacin coenzyme. However, synthetic pathways in the cell—those that make new compounds—use $\text{NADPH} + \text{H}^+$, the reduced form of the coenzyme. This coenzyme is important in the biochemical pathway for fatty acid synthesis. Cells that synthesize a lot of fatty acids (e.g., those in the liver and female mammary glands) have higher concentrations of $\text{NADPH} + \text{H}^+$ than do cells not involved in fatty acid synthesis (e.g., muscle cells).

Niacin in Foods

Niacin can be obtained from foods as the vitamin itself (preformed niacin) or synthesized in the body from the essential amino acid tryptophan.¹⁴ Poultry, meat, and fish provide about 25% of the preformed niacin in North American diets. Another 11% comes from enriched bread and bread products. Coffee and tea also contribute a little preformed niacin to the diet. Figure 13-7 shows some rich sources of preformed niacin—mushrooms, wheat bran, fish, poultry, and peanuts. Protein-rich foods also are good sources of niacin because they provide tryptophan. Unlike some other water-soluble vitamins, niacin is very heat stable, and little is lost in cooking.

In the synthesis of niacin from tryptophan, 60 mg of dietary tryptophan is needed to make about 1 mg of niacin.⁶ Riboflavin and vitamin B-6 coenzymes also are required. Protein is about 1% tryptophan, so 1 g of protein provides 10 mg of tryptophan. The overall contribution of dietary protein to niacin can be roughly estimated as shown in the following example of a diet containing 90 g of protein.

$$\begin{aligned}
 &1 \text{ g protein yields } 10 \text{ mg tryptophan} \\
 &60 \text{ mg tryptophan yields } 1 \text{ mg niacin} \\
 &90 \text{ g protein} \times 10 \text{ mg tryptophan/g protein} = 900 \text{ mg tryptophan} \\
 &\frac{900 \text{ mg tryptophan}}{60 \text{ mg tryptophan/mg niacin}} = 15 \text{ mg niacin}
 \end{aligned}$$

A “shortcut” for this calculation is to divide protein intake (in grams) by 6. In the previous example, $90 \text{ g protein}/6$ yields 15 mg niacin.

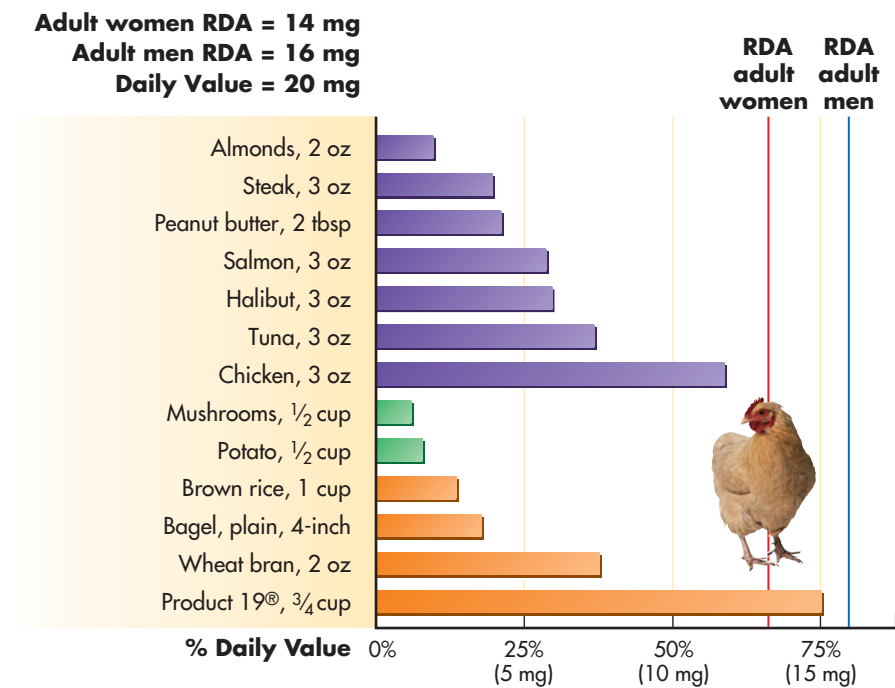


Figure 13-7 Food sources of niacin.

To account for the direct (preformed) and indirect (from tryptophan) sources of niacin, dietary requirements and the amounts in foods are expressed as niacin equivalents (NE).⁶ Thus, a diet that provides 13 mg preformed niacin and 90 g protein supplies approximately 28 NE (13 mg preformed + 15 mg from tryptophan). Individuals with an adequate protein intake meet much of their niacin requirement through tryptophan. Nutrient databases often underestimate niacin in the diet because the amount of tryptophan in many foods has not yet been determined.

Niacin Needs and Upper Level

The niacin RDA for adult men is 16 mg/day; for adult women, it is 14 mg/day. The RDA for niacin is expressed as niacin equivalents (NE) to account for preformed niacin in foods and niacin synthesized from tryptophan. Niacin intake is ample in the U.S., with intakes of preformed niacin from food averaging 32 mg/day for men and 21 mg/day for women.⁷ These figures underestimate intake, however, because they do not include niacin synthesized from tryptophan, which supplies about half the NE in the diet. The Daily Value for niacin on food and supplement labels is 20 mg. The Upper Level for niacin, 35 mg/day, applies only to niacin supplements and fortified foods.⁶

Absorption, Transport, Storage, and Excretion of Niacin

Nicotinic acid and nicotinamide are readily absorbed from the stomach and the small intestine by active transport and passive diffusion, so generally almost all the niacin that is consumed is absorbed. However, the bioavailability of niacin is low in some grains, especially corn. This is because the niacin is tightly bound to protein; thus, less than 30% can be absorbed. Niacin can be released from the protein and its bioavailability improved by soaking corn in a solution of calcium hydroxide dissolved in water (known as lime water). This practice, done to release the skin from the corn, so that the dough can be formed, is common among the indigenous peoples of Latin America who live where corn, often in the form of tortillas, is a staple food. This culinary practice brings the added benefit of protection against niacin deficiency. After being absorbed from the small intestine, niacin is transported via the portal vein to the liver, where it is stored or delivered to the body's cells. Niacin is converted to its coenzyme forms in all tissues. Any excess niacin is excreted in the urine.¹⁴

Niacin Deficiency

Because almost every metabolic pathway uses either NAD^+ or $\text{NADPH} + \text{H}^+$, it is not surprising that a niacin deficiency causes widespread damage in the body. The niacin deficiency disease pellagra, once a significant public health problem in the U.S., is now eradicated here, thanks to the enrichment of grains and protein-rich diets. The discovery of how pellagra develops from a poor diet, rather than a bacterial infection (as most believed until the early 1900s), is a fascinating story.

The first official record of pellagra, made in 1735 by Spanish physician Gaspar Casal, called this disease *mal de la rosa*, or “red sickness.” This name referred to the rough, red rash that appears on skin exposed to sunlight, such as the forearms, backs of the hands, face, and neck (called Casal’s necklace). The name *pellagra* comes from the Italian *pelle*, meaning “skin,” and *agra*, meaning “rough” (Fig. 13-8). Other symptoms of pellagra include diarrhea and dementia. Thus, pellagra is identified by the 3 Ds: dermatitis, diarrhea, and dementia. Death, a fourth D, can result if the disease is not treated.

Pellagra has long been associated with corn-based diets. Although there is no evidence of pellagra among the indigenous populations of North, Central, and South America, where corn (maize) has been the staple food in the diet for thousands of years, pellagra outbreaks



(a)



(b)

Figure 13-8 The dermatitis of pellagra. (a) Dermatitis on both sides (bilateral) of the body is a typical symptom of pellagra. Sun exposure worsens the condition. (b) The rough skin around the neck is referred to as Casal's necklace.

followed the introduction of corn into Europe and Africa. As mentioned previously, the main reason for this was that the indigenous peoples of Latin America treated corn with alkali (from lime water or wood ashes), which released the niacin that is tightly bound to protein. Unfortunately, this culinary practice was not adopted in Europe, Africa, or the U.S. When maize became a staple food, especially among poor people who could afford few other foods, the result was a very low niacin intake, often resulting in pellagra. Scientists have since discovered another reason that corn-based diets can lead to pellagra—corn contains little of the amino acid tryptophan.

During the early 1900s, pellagra was rampant in the southeastern U.S., where corn was the staple food of poor people. More than 10,000 Americans died of pellagra in 1915. From 1918 until the end of World War II in 1945, approximately 200,000 Americans suffered from this disease. Many people had such severe dementia that they were forced to live out their lives in mental institutions. One reason that pellagra remained a problem for so long was the false belief that pellagra was an infectious disease. In the 1910s and 1920s, Dr. Joseph Goldberger, a public health specialist, observed that institutionalized patients had pellagra but the better-fed staff did not—if pellagra was infectious, he reasoned, the staff should have “caught” it from their patients. He, his wife, and his colleagues proved that pellagra is not caused by an infectious pathogen by participating in experiments that exposed them to biological samples, such as skin, feces, and scabs, from pellagra patients. Goldberger also induced pellagra in volunteer prisoners by serving a cornmeal-only diet, then cured them by adding meat, milk, and vegetables to their diets. Finally, in 1937, researchers discovered that nicotinic acid dramatically cures a similar disease in dogs, called black tongue. Soon after, the enrichment of grain products with niacin in the U.S. virtually eliminated pellagra, although isolated cases still occur due to severe malabsorption, chronic alcoholism, or Hartnup disease (a genetic disorder in which the tryptophan to niacin pathway is blocked). Today, pellagra still can be found in Africa, particularly when famine occurs, or in refugee camps when rations are mostly maize.^{15, 16}

Pharmacological Use of Niacin

Niacin, as nicotinic acid, is sometimes prescribed by physicians to increase HDL-cholesterol and lower triglyceride levels in the blood.^{17, 18} When combined with diet, exercise, and other cholesterol-lowering medications, nicotinic acid may reduce the risk of heart attack, but it is still undergoing testing. The dose required, 1 to 2 g daily, is more than 60 times the RDA. Although niacin is readily available in dietary supplement form, it must not be used as a substitute for the prescription formulation of niacin, which is carefully prepared to an exact dosage and has controlled time-release.¹⁷ Recall that dietary supplements are not regulated by the FDA. The most common side effect is flushing of the skin, but GI tract upset and liver damage also can occur. The flushing seen with excess niacin intake was used to determine its Upper Level of 35 mg.⁶



Chicken is a good source of niacin. Also, the tryptophan that chicken contains can be used to synthesize niacin.

CRITICAL THINKING

Both the vitamin niacin and protein-rich foods can cure pellagra. Why are both effective?

Knowledge Check

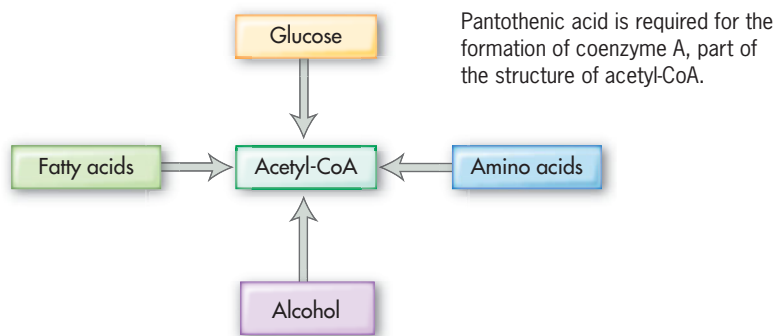
1. What are 2 metabolic pathways that require a niacin coenzyme?
2. In addition to preformed niacin in foods, what is another source of niacin in the diet?
3. Why are populations in Latin America not afflicted with pellagra, despite relying heavily on a corn-based diet?



Many breakfast cereals are fortified with pantothenic acid.

13.5 Pantothenic Acid

The name *pantothenic acid* was taken from the Greek word *pantothern*, meaning “from every side,” because it is present in all body cells and is supplied by a wide variety of foods. Pantothenic acid is part of coenzyme A (CoA), which is used throughout the body in energy metabolism. CoA forms when pantothenic acid combines with a derivative of adenosine diphosphate (ADP) and part of the amino acid cysteine. Cysteine provides the sulfur atom, which is the functional end of the coenzyme.¹⁹



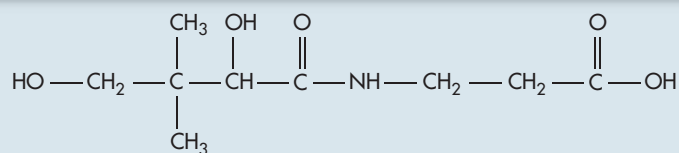
Functions of Pantothenic Acid

Coenzyme A is essential for the formation of acetyl-CoA from the breakdown of carbohydrate, protein, alcohol, and fat.³ Acetyl-CoA molecules most often enter the citric acid cycle (with eventual ATP production). However, acetyl-CoA also is an important biosynthetic building block used to build fatty acids, cholesterol, bile acids, and steroid hormones.

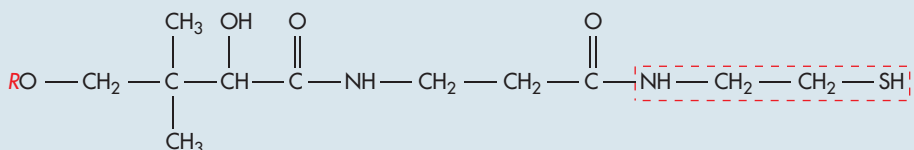
Pantothenic acid also forms part of a compound called the acyl carrier protein. This protein attaches to fatty acids and shuttles them through the metabolic pathway designed to increase their chain length. As coenzyme A, pantothenic acid also donates fatty acids to proteins in a process that can determine their location and function within a cell.



A Biochemist's View



Pantothenic acid



Coenzyme A (CoA)

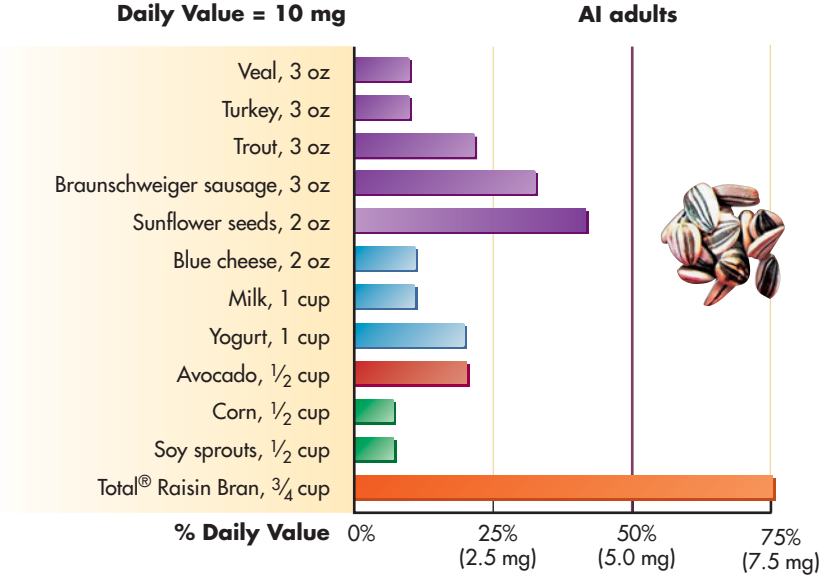
Pantothenic acid is part of the coenzyme A (CoA) molecule

R = Derivative of adenosine diphosphate (ADP)

Boxed area = Part of the amino acid cysteine

Adult women AI = 5 mg
 Adult men AI = 5 mg
 Daily Value = 10 mg

Figure 13-9 Food sources of pantothenic acid.



Pantothenic Acid in Foods

Our food supply provides ample amounts of pantothenic acid. Common sources include meat, milk, and many vegetables (Fig. 13-9). Other foods rich in pantothenic acid include mushrooms, peanuts, egg yolks, yeast, broccoli, and soy milk. In general, unprocessed foods are better sources than processed foods because milling, refining, freezing, heating, and canning can reduce pantothenic acid in foods.⁶

Pantothenic Acid Needs and Upper Level

For adults, the Adequate Intake for pantothenic acid is 5 mg/day.⁶ Adults generally consume the Adequate Intake or more. The Daily Value on food and supplement labels is 10 mg. There is no known toxicity for pantothenic acid, so no Upper Level has been set.¹⁹

Absorption, Transport, Storage, and Excretion of Pantothenic Acid

The pantothenic acid portion of any coenzyme A in the diet is released during digestion in the small intestine. It is then absorbed and transported throughout the body bound to red blood cells. Storage is minimal and is in the coenzyme form. The excretion of pantothenic acid is via the urine.¹⁹

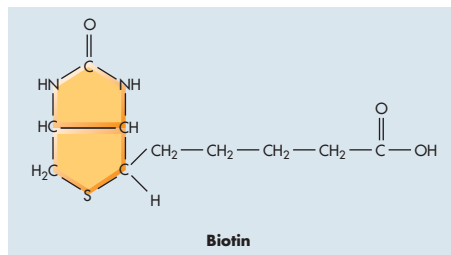
Pantothenic Acid Deficiency

Pantothenic acid deficiency is very rare and has been observed only when a deficiency was experimentally induced.⁶ Its symptoms include headache, fatigue, impaired muscle coordination, and GI tract disturbances.



Knowledge Check

1. What is the coenzyme formed from pantothenic acid?
2. How is pantothenic acid related to the formation of ATP?
3. What are 3 good sources of pantothenic acid?



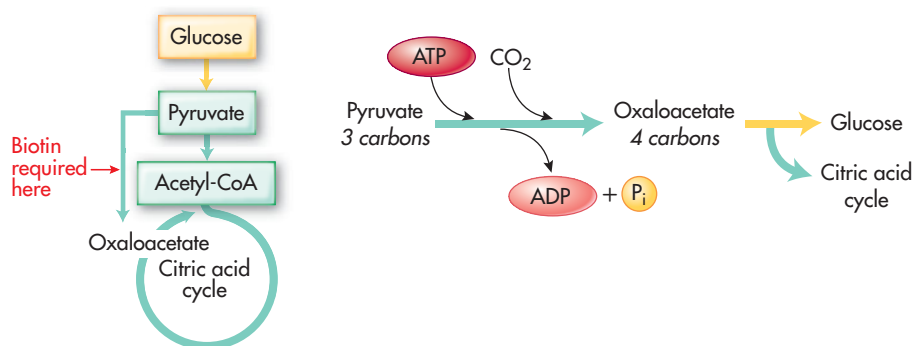
13.6 Biotin

Biotin's discovery was linked to what researchers in the 1920s called “egg-white injury.” Rats fed large amounts of raw egg whites developed severe rashes, lost their fur, and became paralyzed. These symptoms were reversed when the rats were fed yeast, liver, and other foods. These observations led to the discovery of this B-vitamin.

Functions of Biotin

Biotin functions as a coenzyme in reactions, known as carboxylations, that add carbon dioxide to compounds when carbohydrates, proteins, and fats are metabolized.^{20, 21} The following reactions are dependent on biotin:

- Carboxylation of pyruvate to form oxaloacetate, a citric acid cycle intermediate. Recall that, when the body's glucose supplies run low, oxaloacetate serves as a starting point for gluconeogenesis (see Chapter 9).



- Breakdown of the amino acids threonine, leucine, methionine, and isoleucine for use as energy
- Carboxylation of acetyl-CoA to form malonyl-CoA, so that fatty acids can be synthesized (see Section 13.5)

Biotin also binds to the proteins that help DNA fold in the cell nucleus. In this role, biotin is thought to help maintain gene stability.²¹

Sources of Biotin: Food and Microbial Synthesis

The adequate intake level for biotin can be met with 3 tablespoons of peanuts.



Biotin is widely distributed in foods and is found as the free vitamin and **biocytin**—biotin bound to the amino acid lysine in proteins. Good sources include whole grains, egg yolks, nuts, and legumes (Fig. 13-10). The biotin content of food has been determined for only a small number of foods, so nutrient databases are incomplete.

We excrete more biotin than we consume; thus, it appears that bacteria in the large intestine synthesize biotin. However, it is not yet known the extent to which the biotin synthesized by the flora in the large intestine is bioavailable because biotin is absorbed most efficiently from the small intestine.

Biotin Needs and Upper Level

For adults, the Adequate Intake for biotin is 30 µg/day.⁶ The diets of adults generally meet the Adequate Intake level. The Daily Value on food and supplement labels is 300 µg, 10 times the current estimate of needs. There is no Upper Level for biotin.⁶

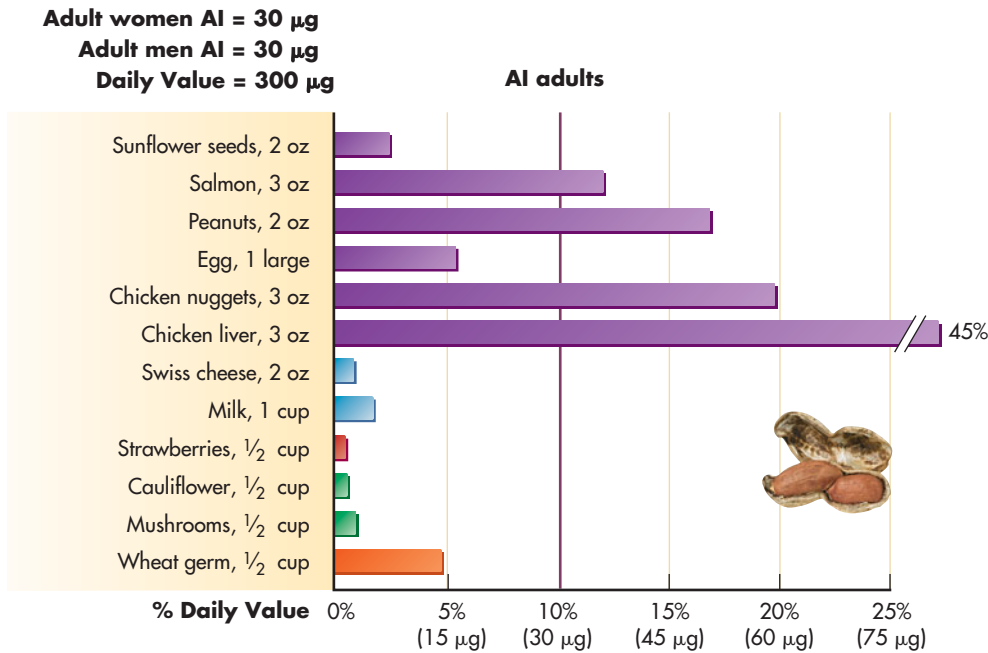


Figure 13-10 Food sources of biotin.

Absorption, Transport, Storage, and Excretion of Biotin

In the small intestine, the enzyme biotinidase releases biotin from protein and lysine. Free biotin is absorbed in the small intestine via a sodium-dependent carrier. Biotin is stored in small amounts in the muscles, liver, and brain, and its excretion is mostly via the urine, although some is excreted in bile.²⁰

Biotin Deficiency

Overall, biotin deficiencies are rare. About 1 in 112,000 infants is born with a genetic defect that results in very low amounts of the enzyme biotinidase.²² As a result, these infants cannot break down biocytin in foods for absorption. A biotin deficiency develops, and symptoms (skin rash, hair loss, convulsions, low muscle tone, and impaired growth) occur within a few weeks to months following birth. The affected individual is typically treated throughout life with regular doses of biotin supplements.

Biotin deficiency also has resulted from the use of anticonvulsant medications, malabsorption in those with severe intestinal diseases, and the regular ingestion of large amounts (>12) of raw eggs each day. Raw eggs contain a protein, **avidin**, that binds biotin, limiting its absorption.²⁰ Cooking eggs denatures avidin, which prevents it from binding to biotin.

carboxylation Addition of a carboxyl group, COOH, into a compound or molecule.

biocytin Biotin bound to the amino acid lysine in food proteins.

avidin Protein, found in raw egg whites, that can bind biotin and inhibit its absorption. Cooking destroys avidin.

Knowledge Check

1. Biotin is a coenzyme for several carboxylase enzymes. In general, what do these enzymes do?
2. How can a biotin deficiency occur?

13.7 Chromium (Cr)

The importance of chromium in the diet has been recognized only in recent years. Like many trace minerals, the functions of this nutrient are emerging with advances in research technology. Chromium may be involved in the regulation of blood glucose levels.

Functions of Chromium

The functions of chromium are not fully known. It may enhance insulin action, promote glucose uptake into cells, and normalize blood sugar levels.²³ However, chromium supplementation in patients with type 2 diabetes has not been shown to be effective in controlling blood glucose.^{23,24} Many athletes use chromium supplements to enhance muscle mass and strength, despite a lack of research evidence supporting its effectiveness.



Broccoli is a good source of chromium.

Chromium in Foods

Chromium is widely distributed in a variety of foods. However, information regarding the chromium content of foods is lacking. Thus, many nutrient databases do not yet include values for it. Meats, liver, fish, eggs, whole-grain products, broccoli, mushrooms, dried beans, nuts, and dark chocolate tend to be good sources of the mineral. Chromium is used to manufacture steel; thus, small amounts of chromium also can be transferred to food through food-processing equipment.

Dietary Needs for Chromium

The Adequate Intakes for chromium in adults age 19 to 50 years are 35 µg/day for men and 25 µg/day for women.²⁵ After age 50, the Adequate Intake decreases to 30 µg/day for men and 20 µg/day for women. The Adequate Intake is based on the amounts typically found in nutritious diets. The average intake in North America generally meets the Adequate Intake level. The Daily Value for chromium is 120 µg.

Absorption, Transport, Storage, and Excretion of Chromium

The body absorbs very little chromium from dietary sources. Absorption appears to increase when intakes are low and when chromium is consumed with vitamin C, although bioavailability of the mineral has been difficult to assess. It is likely that phytates in whole grains decrease absorption. Once absorbed, chromium is transported by transferrin via the bloodstream and accumulates in the bones, liver, kidneys, and spleen. Concentrations in human tissues are very low because most dietary chromium is excreted in the feces, with some excretion via urine.

Chromium Deficiency and Toxicity

Chromium deficiency has been difficult to assess due to the lack of sensitive measures of chromium status. Several cases of chromium deficiency have been reported in individuals receiving chromium-free parenteral solutions. The symptoms include weight loss, glucose intolerance, and nerve damage.

Few serious effects have been reported from excess dietary chromium intake. Thus, an Upper Level has not been set.²⁵ However, nutritionists have expressed concern about the safety of high doses of chromium supplements (especially chromium picolinate), used by many athletes, and have recommended continued monitoring for possible toxicities.



Knowledge Check

1. What are the proposed functions of chromium?
2. What are rich food sources of chromium?
3. What are the symptoms of chromium deficiency?

13.8 Vitamin B-6

Up to this point, the nutrients discussed in this chapter have been involved mainly in energy metabolism. Now, we turn our attention to those playing key roles in amino acid metabolism. Nearly all amino acids require a vitamin B-6 coenzyme in their metabolism. Vitamin B-6 is a family of 3 compounds: pyridoxal, pyridoxine, and pyridoxamine. All 3 forms can be phosphorylated (have a phosphate group added) to become active vitamin B-6 coenzymes. The primary vitamin B-6 coenzyme is pyridoxal phosphate (PLP). Vitamin B-6 is converted to PLP by adding a phosphate group (PO_4) to its hydroxyl group. The generic name for this vitamin is B-6, or pyridoxine.²⁶

Functions of Vitamin B-6

Vitamin B-6 coenzymes participate in numerous metabolic reactions. For example, PLP is a coenzyme in more than 100 enzymatic reactions, almost all of which involve nitrogen-containing compounds, such as amino groups (NH_2).

Metabolism

A major role of PLP is to participate in amino acid metabolism. A very important function of PLP is as a coenzyme for transamination reactions that transfer amino groups to allow the synthesis of nonessential amino acids (see Chapter 7). Without PLP, every amino acid would be essential because it would have to be supplied by the diet (Fig. 13-11).²⁶ PLP also helps convert homocysteine to the amino acid cysteine, which occurs during the metabolism of the amino acid methionine (see Appendix C for details on methionine and homocysteine metabolism).

PLP also is required for the release of glucose from glycogen. In this way, PLP helps maintain blood glucose concentration.²⁶

Synthesis of Compounds

In red blood cells, PLP catalyzes a step in the synthesis of heme, a nitrogen-containing ring that is inserted into certain proteins to hold iron in place. The best known of these proteins is hemoglobin, which uses iron to transport oxygen in the blood.²⁶

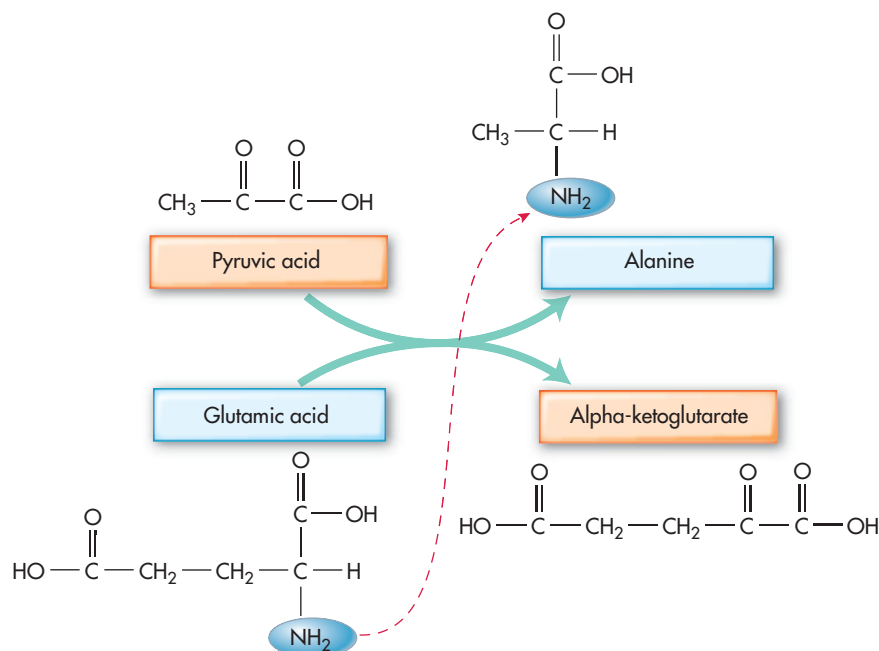
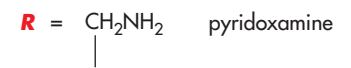
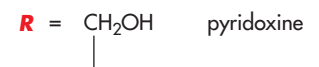
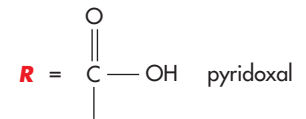
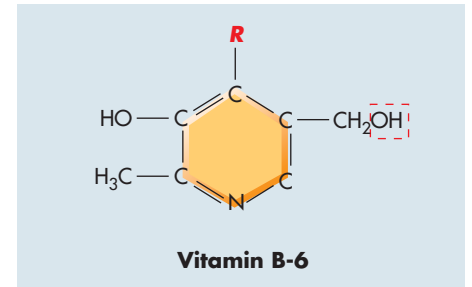


Figure 13-11 An example of a transaminase enzyme pathway that utilizes vitamin B-6. This pathway allows cells to synthesize nonessential amino acids. In this example, pyruvate gains an amino group from glutamic acid to form the nonessential amino acid alanine.



Boxed area = Hydroxyl group where phosphate is added

► Homocysteine is receiving a great deal of attention, especially regarding the development of brain disorders, bone disorders, and cardiovascular disease. Meeting B-vitamin (riboflavin, vitamin B-6, folate, and vitamin B-12) and choline needs allows for the metabolism of homocysteine to nutrients, such as the amino acids methionine and cysteine. This keeps homocysteine blood levels low and helps protect the body from homocysteine's potentially toxic consequences.



Bananas are a good plant source of vitamin B-6.

Amino acids are used not only to build proteins but also to make nonprotein nitrogen-containing compounds. Many of these compounds are neurotransmitters, which are important for brain function. PLP is required for the synthesis of several neurotransmitters: **serotonin** from tryptophan, **dopamine (DOPA)** and **norepinephrine** from tyrosine, and **gamma-aminobutyric acid (GABA)** from glutamic acid. The synthesis of **histamine** from the amino acid histidine also requires vitamin B-6.²⁶

PLP participates in vitamin formation, too. It plays an important role in the synthesis of the B-vitamin niacin from the amino acid tryptophan.²⁶

Other Functions

Vitamin B-6 helps support normal immune function and the regulation of gene expression.⁵ It also may help prevent colon cancer. A recent meta-analysis of vitamin B-6 intake and blood levels found that those who had the highest intake and blood levels had a lower risk of colorectal cancer.²⁷

Vitamin B-6 in Foods

Vitamin B-6 is stored in the muscle tissues of animals; thus, meat, fish, and poultry are some of the richest sources. Although vitamin B-6 in foods of animal origin is often more readily absorbed than that in foods of plant origin, whole grains also are good sources of vitamin B-6. However, vitamin B-6 is lost during the refining of grains, and it is not one of the vitamins added during enrichment. Most fruits and vegetables are not good vitamin B-6 sources, but there are some exceptions: carrots, potatoes, spinach, bananas, and avocados (Fig. 13-12). The leading sources of vitamin B-6 in the U.S. are fortified ready-to-eat cereals, poultry, beef, potatoes, and bananas.⁴ Like many other water-soluble vitamins, vitamin B-6 can be lost when foods are exposed to heat and other processing.

Vitamin B-6 Needs and Upper Level

The RDA for vitamin B-6 is 1.3 mg/day for adult men and women up to age 50. For older adults, the RDA increases to 1.7 mg/day for men and 1.5 mg/day for women. The Daily Value on food and supplement labels is 2 mg. In the U.S., the average daily intakes of vitamin B-6 from food are 2.5 mg for men and 1.7 mg for women.⁷

serotonin Neurotransmitter that affects mood (sense of calmness), behavior, and appetite and induces sleep.

dopamine (DOPA) Neurotransmitter that leads to feelings of euphoria, among other functions, and forms norepinephrine.

norepinephrine Neurotransmitter released from nerve endings; also a hormone produced by the adrenal gland during stress. It causes vasoconstriction and increases blood pressure, heart rate, and blood sugar.

gamma-aminobutyric acid (GABA) Chief inhibitory neurotransmitter.

histamine Bioactive amine that participates in immune response, stimulates stomach acid secretion, and triggers inflammatory response. It regulates sleep and promotes smooth muscle contraction, increased nasal secretions, blood vessel relaxation, and airway constriction.

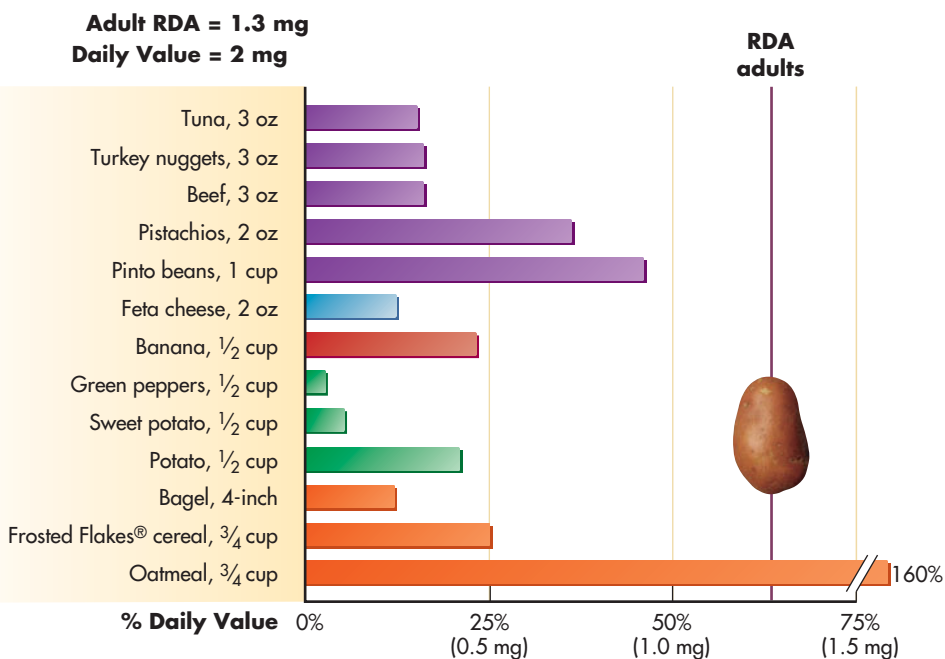


Figure 13-12 Food sources of vitamin B-6. Note that, after age 51, the RDA increases (men: 1.7 mg; women: 1.5 mg).

The Upper Level for adults is set at 100 mg/day.⁶ Intakes of 2 to 6 g of vitamin B-6 (attainable only with a dietary supplement) have caused nerve damage so severe that the individuals were unable to walk.²⁶ Less severe neurological symptoms, such as hand and foot numbness, may occur with lower amounts (200 to 500 mg) of vitamin B-6.

Absorption, Transport, Storage, and Excretion of Vitamin B-6

The absorption of vitamin B-6 is by passive diffusion. The coenzyme form is normally converted to the free vitamin form for absorption, but at high concentrations some of the coenzyme may be absorbed as such. Vitamin B-6 is transported via the portal vein to the liver, where most of it is phosphorylated. From the liver, the phosphorylated forms (mainly PLP) are released for transport in the blood bound to the transport protein albumin. Muscle tissue is the main storage site for vitamin B-6. Excess vitamin B-6 is generally excreted in the urine.²⁶

Vitamin B-6 Deficiency

Vitamin B-6 deficiency is rare in North America. When a deficiency does occur, the symptoms include seborrheic dermatitis, **microcytic hypochromic anemia** (from decreased hemoglobin synthesis), convulsions, depression, and confusion due to altered tryptophan metabolism or neurotransmitter synthesis.²² Low blood concentrations of PLP have been observed in the elderly, Blacks, smokers, users of oral contraceptive agents, alcoholics, and those who are underweight or consume poor diets.^{6,28} Acetaldehyde, produced during alcohol metabolism, decreases the formation of PLP by cells and may reduce its biological activity. A number of medications can decrease the amount of PLP in the blood: L-DOPA, used to treat Parkinson disease; isoniazid, an antituberculosis medication; and theophylline, used to treat asthma. Individuals taking these medications may need vitamin B-6 supplementation.

► In the early 1950s, some infants were accidentally fed a commercial formula in which vitamin B-6 had been destroyed by oversterilization. The infants developed abnormal electroencephalogram (EEG) readings and experienced convulsions. The reason was probably a lack of neurotransmitter synthesis in the brain. The situation was successfully treated.

Pharmacological Use of Vitamin B-6

Supplemental vitamin B-6 has a long history as a treatment for carpal tunnel syndrome, premenstrual syndrome, and nausea during pregnancy. Carpal tunnel syndrome, a common, painful nerve disorder of the wrist and hand, has been treated with large daily doses (typically, 50 to 300 mg/day) of vitamin B-6. How vitamin B-6 might be related to carpal tunnel syndrome is unclear; theories include that it repairs damaged nerves and that it reduces pain perceptions. A comprehensive review of research studies in this area concluded that, despite limitations in the quality of the research in this area, there is some support for using vitamin B-6 to treat carpal tunnel syndrome.²⁹ This therapy should be supervised by a physician, not self-administered, especially because vitamin B-6 toxicity can worsen nerve damage.

There is little evidence that vitamin B-6 supplementation improves premenstrual syndrome (PMS). PMS is a multisymptom disorder that occurs 1 to 2 weeks prior to menstruation. The symptoms include fluid retention, bloating and weight gain, breast tenderness, abdominal discomfort, headache, cravings for sugar and alcohol, mild depression, and anxiety. Most menstruating women experience one or more of these symptoms to some degree. Because studies of vitamin B-6 and PMS have not shown significant benefit, vitamin B-6 cannot be recommended as a treatment for this disorder.³⁰

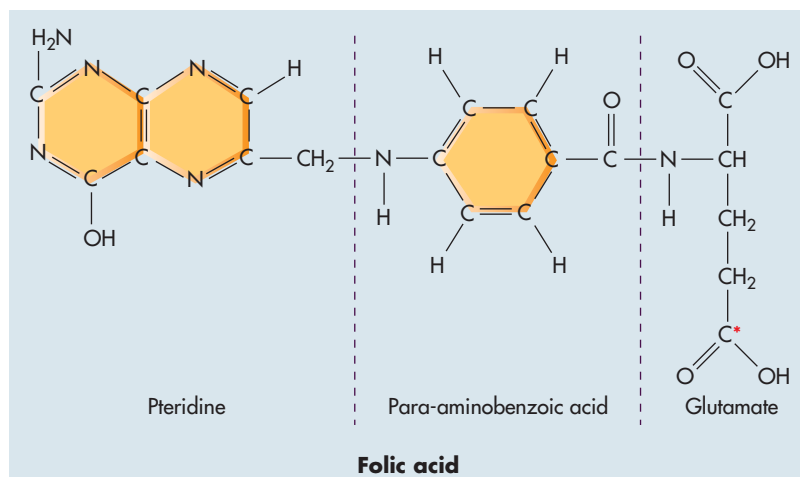
Nausea is experienced by 70 to 85% of women during the first trimester of pregnancy (see Chapter 16). Sometimes physicians recommend vitamin B-6 supplementation—typically, 30 to 75 mg/day—to reduce nausea. Although some research studies support this practice, many others do not.³¹ Even though vitamin B-6 supplements to treat nausea are available without a prescription, pregnant women should first discuss this option with their physician.



Knowledge Check

1. How is the PLP coenzyme used in amino acid metabolism?
2. What are 3 good food sources of vitamin B-6?
3. What are 2 signs of vitamin B-6 toxicity?

microcytic hypochromic anemia Anemia characterized by small, pale red blood cells that lack sufficient hemoglobin and thus have reduced oxygen-carrying ability. It also can be caused by an iron deficiency.



* = In foods, additional glutamate molecules are usually linked here to the carboxyl group

► THFA transfers these single-carbon groups:

Methyl ($-\text{CH}_3$)

Formyl ($-\text{CH}=\text{O}$)

Methylene ($-\text{CH}_2-$)

Methenyl ($-\text{CH}=\text{}$)

► PABA by itself is sometimes added to supplements, but there is no current scientific rationale for this.

have 3 or more glutamates attached to the carboxyl group (red asterisk in the structure) and are known as polyglutamates.³²

Functions of Folate

Folate coenzymes are required for the synthesis and maintenance of new cells. Folate coenzymes function in metabolic pathways in which single carbon groups (listed in the margin) are exchanged. The folate coenzymes are generated from a central coenzyme form called tetrahydrofolic acid (THFA). Folate coenzymes are critical for amino acid metabolism, DNA synthesis, and other functions.^{32, 33}

Amino Acid Metabolism

THFA is important in amino acid metabolism, especially the interconversions of amino acids.^{32, 33} It accepts 1-carbon groups from various amino acids and is responsible for converting the amino acid glycine to the amino acid serine (the main source of methyl groups for THFA) and converting the essential amino acid histidine to the amino acid glutamic acid. THFA, along with vitamin B-12, is involved in a pathway that converts the amino acid homocysteine to the amino acid methionine (described in Section 13.10).

DNA Synthesis

THFA is required for the synthesis of DNA, which contains 4 nitrogenous bases: cytosine and thymine (pyrimidines) and adenine and guanine (purines). The pyrimidine thymine is formed by the addition of a methylene group (CH_2) to the pyrimidine uracil. A folate coenzyme supplies the CH_2 . Folate and vitamin B-12 function are closely linked. A vitamin B-12 coenzyme is required to recycle the folate coenzyme needed for DNA synthesis (see Section 13.10). Thus, folate and vitamin B-12 deficiencies can produce identical signs and symptoms.



THFA also is needed for the synthesis of the purines (adenine and guanine) in DNA. Thus, DNA synthesis and repair may decline in a folate shortage.

The cancer drug methotrexate takes advantage of the key role of THFA in DNA synthesis. Methotrexate, referred to as a folate antagonist, interferes with THFA metabolism. This, in turn, reduces DNA synthesis throughout the body. This reduction in DNA synthesis can halt the growth of cancer cells, but it also affects other rapidly proliferating cells, such as intestinal and red blood cells. As a result, the typical side effects of methotrexate therapy are the same as those of a folate deficiency (e.g., diarrhea and anemia). Methotrexate also is used



13.9 Folate

The name of the B-vitamin folate comes from the Latin word *folium*, meaning “leaf.” It was given this name because leafy, green vegetables are excellent sources. *Folate* is the generic name, referring to the various forms of the vitamin found naturally in foods. The term **follic acid** refers to the synthetic form of the vitamin found in supplements and fortified foods. Folate is known for its role in DNA synthesis and amino acid metabolism. Thus, folate is needed to make new cells, including red blood cells.

Folate consists of 3 parts: pteridine, para-aminobenzoic acid (PABA), and 1 or more molecules of the amino acid glutamic acid (glutamate). If, as shown in its structure, only 1 glutamate molecule is present, it is designated folic acid (folate monoglutamate). In food, about 90% of the folate molecules



Lentils are a rich food source of folate.

to treat several immunological disorders, such as rheumatoid arthritis, psoriasis, asthma, and inflammatory bowel disease. Individuals treated with methotrexate are sometimes advised to take supplemental folic acid to reduce the drug's toxic side effects.³⁴ This supplementation probably does not influence the effectiveness of methotrexate.

Other Functions

Another key function of folate is the formation of the neurotransmitters serotonin, norepinephrine, and dopamine in the brain. A few studies suggest that supplementing antidepressant medications with folic acid can enhance the treatment of depression.^{35, 36} Folate also may help maintain normal blood pressure and reduce the risk of developing colon cancer.

Although folate deficiency can be induced to treat cancer, folate deficiency also may cause concern with regard to cancer. Because folate aids in the transfer of methyl groups for DNA synthesis, even mild folate deficiency may contribute to DNA damage, which in turn affects cancer risk. A daily intake of 400 µg (the RDA) may protect against cancers such as colorectal cancer.

Folate in Foods

The biological availability of folate in food from a mixed diet is generally thought to be about 50% of folic acid, but it may be closer to 80%.³⁷ Foods that have the largest amount and most bioavailable folate are liver, legumes, and leafy, green vegetables (Fig. 13-13). Other rich sources of folate include avocados and oranges. Bread and cereal products from milled grains are fortified with folic acid, making them good sources as well. Ready-to-eat cereals, bread, legumes, orange and grapefruit juice, lettuce, milk, and potatoes are leading sources of folate in the U.S. diet. Although milk and potatoes are not particularly rich sources, they are so commonly consumed that their contribution to folate intake is relatively high.

Food processing and preparation can destroy 50 to 90% of the folate in food. Folate is extremely susceptible to destruction by heat, oxidation, and

Adult women RDA = 400 µg
Adult men RDA = 400 µg
Daily Value = 400 µg

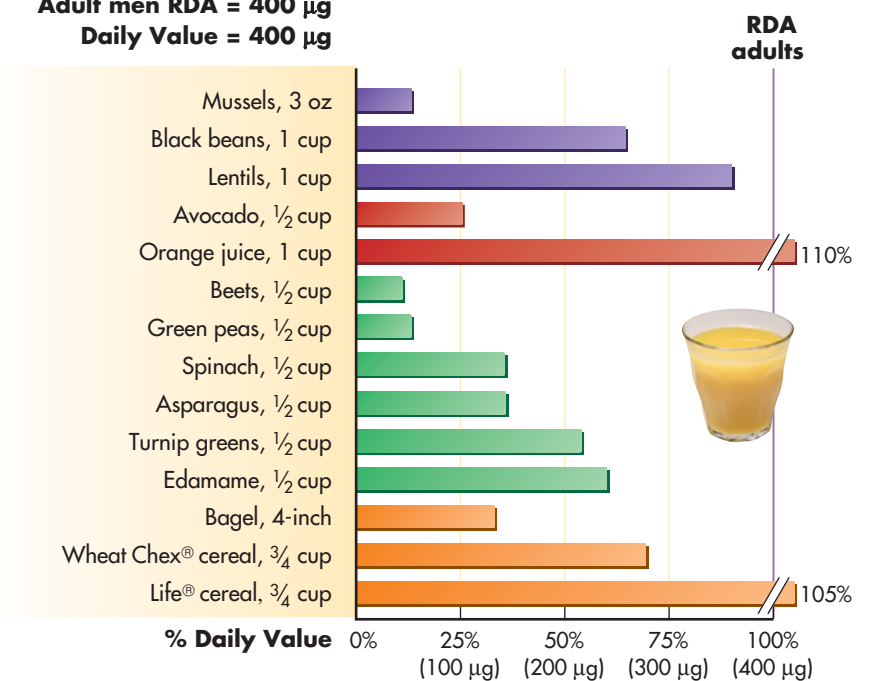


Figure 13-13 Food sources of folate.

ultraviolet light. (Vitamin C in foods helps protect folate from oxidative destruction.) The regular consumption of fresh or lightly cooked fruits and vegetables can help you gain the full benefits of their folate contents.

Dietary Folate Equivalents

The RDA for folate is expressed as dietary folate equivalents (DFE).⁶ DFE reflect the differences in the absorption of food folate and synthetic folic acid. The relationship between DFE, food folate, and folic acid is as follows.

$$1 \text{ DFE} = 1 \mu\text{g food folate} = 0.6 \mu\text{g folic acid} = 0.5 \mu\text{g folic acid taken} \\ \text{taken with food} \quad \text{on an empty stomach}$$

DFE are calculated using this equation:

$$\text{DFE} = \mu\text{g food folate} + (\mu\text{g folic acid} \times 1.7)$$

For example, the Daily Value for a serving of ready-to-eat breakfast cereal is listed on the label as 50%, so the amount of folic acid is 200 μg per serving (Daily Value of 400 μg \times 0.50). Because this folate is mainly synthetic folic acid, the 200 μg is multiplied by 1.7, yielding 340 μg DFE. If the diet also contains 300 μg of food folate, the total DFE intake is 640 μg DFE (300 μg + 340 μg), which exceeds the adult RDA. Nutrient databases typically report several values for folate, including μg food folate, μg folic acid, total folate (μg food folate + μg folic acid), and folate DFE (μg food folate + [μg folic acid \times 1.7]).

Folate Needs

► Some people have a genetic defect that results in reduced activity in an enzyme important in folate metabolism. This causes folate to be less biologically active and may predispose them to a higher risk of cancer or a pregnancy affected by a neural tube defect. This is currently an active area of research in folate nutrition. Testing for this defect is not yet routine, but it may be one day.

The folate RDA for adults is 400 $\mu\text{g}/\text{day}$, expressed as DFE. For women capable of becoming pregnant, the RDA specifies that this amount be consumed as folic acid—that is, from fortified foods and supplements—in addition to folate from the diet. This recommendation is in response to evidence that supplemental folic acid protects against the development of neural tube birth defects that occur early in pregnancy (see Medical Perspective).³⁸ In the U.S., the average folate intake from food exceeds the RDA. The average daily intake in adult men is 636 DFE; in adult women, it is 469 DFE.⁷ Despite this good intake, nearly 20% of women of childbearing age do not consume enough of this vitamin and are at risk of developing a folate deficiency.³⁹ The Daily Value on food and supplement labels is 400 $\mu\text{g}/\text{day}$.

Upper Level for Folate

The Upper Level for synthetic folic acid is set at 1000 μg (1 mg); intakes above this level may mask a vitamin B-12 deficiency (see Section 13.10).⁶ The Upper Level does not apply to folate in foods because absorption is limited. In response to the concern that high doses of folic acid might mask a vitamin B-12 deficiency, the FDA limits the amount of folic acid in nonprescription vitamin supplements. These levels are set at 400 μg for nonpregnant individuals when no statement of age is listed on the supplement label. When age-related doses are listed, there can be no more than 100 μg for infants, 300 μg for children, and 400 μg for adults. Over-the-counter prenatal supplements can contain 800 μg .

Absorption, Transport, Storage, and Excretion of Folate

To be absorbed, folate polyglutamates must be broken down (hydrolyzed) in the GI tract to the monoglutamate form. Enzymes known as folate conjugases, produced by the absorptive cells, remove the additional glutamates. The monoglutamate form is then actively transported across the intestinal wall. Very large doses of folic acid from supplements are absorbed by passive diffusion. When synthetic folic acid is consumed as a supplement and without food, it is nearly 100% bioavailable. Consumed with food, as in fortified cereal grains, absorption is slightly reduced.⁶

The portal vein delivers the monoglutamate form of folate from the small intestine to the liver. Then, folate is either stored in the liver or released into the blood for delivery to other tissues in the body. Once folate is transported into a cell, it is converted to a polyglutamate

form that “traps” the folate in the cell. Some liver folate is excreted in bile and reabsorbed by the enterohepatic circulation. Alcohol interferes with this process, which is one reason alcoholics often become folate deficient. Folate is excreted in both the urine and the feces.

Folate Deficiency

Folate deficiency was once fairly common in the U.S. However, folic acid fortification of the food supply has dramatically decreased the number of persons with folate deficiency. Prior to fortification, 30% of the U.S. population had low red blood cell folate, a measure of long-term body stores, but in 2006 this had dropped to 2.8% of the population.⁴⁰

Despite this improvement, folate deficiency still occurs.⁴¹ It can result from low intake, malabsorption, an increased requirement, compromised utilization, the use of certain medications, and excessive excretion. Persons at risk of developing a folate deficiency include those with very poor diets and chronic alcoholics who may malabsorb folate. In individuals with a vitamin B-12 deficiency, folate utilization and metabolism are abnormal (see Section 13.10), resulting in a “functional” folate deficiency. Certain medications (e.g., some anticonvulsants) also can cause a folate deficiency. In addition, pregnancy greatly increases the need for this vitamin (600 µg DFE/day) because of the increased rate of cell division, and thus of DNA synthesis, in the mother’s body and that of her developing offspring.⁶ Prenatal care often includes prenatal multivitamin and mineral supplements fortified with folate to compensate for the extra needs associated with pregnancy.

A deficiency of folate first affects cell types that are actively synthesizing DNA because these cells have a short life span and rapid turnover rate. For instance, red blood cells have a 120-day life span and are vulnerable to folate deficiency. Without folate, precursor cells in the bone marrow cannot form new DNA and therefore cannot divide normally to become mature red blood cells. The cells grow larger because there is continuous formation of RNA, leading to the increased synthesis of protein and other cell components. Hemoglobin synthesis also intensifies. However, when it is time for the cells to divide, they lack sufficient DNA for normal division.

Unlike normal mature red blood cells, these cells (called **megaloblasts**) retain their nuclei and remain in a large, immature form. Most megaloblasts do not make it out of the bone marrow. Any of these large cells that do enter the bloodstream are called **macrocytes**. Their presence results in a form of anemia called **megaloblastic**, or **macrocytic**, **anemia** (Fig. 13-14).

► Steps in Folate Deficiency

1. A decrease in blood folate concentration
2. A decrease in red cell folate
3. Defective DNA synthesis
4. A change in the structure of certain white blood cells
5. An increase in blood concentration of homocysteine (and methylmalonic acid)
6. Megaloblastic changes in bone marrow and other rapidly dividing cells
7. An increase in the size of circulating red blood cells
8. Megaloblastic (macrocytic) anemia

megaloblast Large, nucleated, immature red blood cell in the bone marrow, which results from the inability of a precursor cell to divide when it normally should.

macrocyte Literally, “large cell,” such as a large red blood cell.

megaloblastic (macrocytic) anemia

Anemia characterized by abnormally large, nucleated, immature red blood cells, which result from the inability of a precursor cell to divide normally.

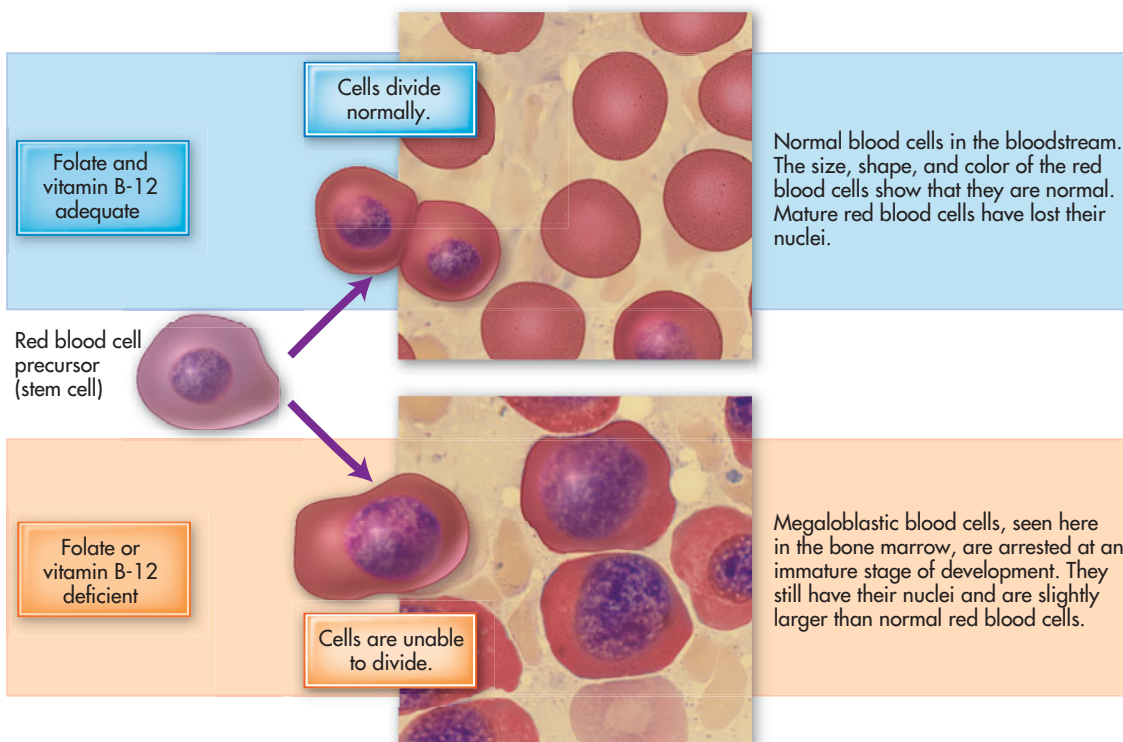


Figure 13-14 Megaloblastic anemia occurs when blood cells are unable to divide, leaving large, immature red blood cells. Either a folate or a vitamin B-12 deficiency may cause this condition. Measurements of blood concentrations of both vitamins are taken to help determine the cause of the anemia. The incidence of megaloblastic anemia due to folate deficiency has decreased substantially since folate fortification of grains began in 1998.

MEDICAL PERSPECTIVE

Neural Tube Defects

A maternal deficiency of folate and a genetic predisposition have been linked to the development of **neural tube defects** in the fetus (Fig. 13-15). These defects include spina bifida (a spinal cord or spinal fluid bulge through the back) and anencephaly (the absence of a brain). In both cases, there is a defect in the very early development of the neural tube, the structure that subsequently forms the brain, spinal cord, spinal nerves, and spinal column. Victims of spina bifida may exhibit paralysis, incontinence, hydrocephalus (the abnormal buildup of spinal fluid in the brain), and learning disabilities. Children born with anencephaly die shortly after birth.

Folate is critical to normal neural tube development. The neural tube forms and closes very early in pregnancy—the first 21 to 28 days after conception (see Chapter 16). During this time of critical development, many women are unaware that they are pregnant. Thus, ensuring good folate status for all women capable of becoming pregnant is critical.⁴² As discussed earlier in this chapter, the folic acid fortification of

refined cereals and grains was begun in the U.S. in 1998. Before fortification, about 4000 pregnancies per year were affected by a neural tube defect. Since fortification, the number of babies born with a neural tube defect has decreased by one-quarter, but the likelihood of a neural tube defect varies by race and ethnicity. The highest rates are in Hispanic women, followed by White women. The lowest rates are among Black and Asian women.⁴³ Some scientists are urging the government to double folic acid fortification levels to decrease further the incidence of neural tube defects, but others are concerned that higher levels may have unintended consequences, such as masking a vitamin B-12 deficiency (see Section 13.10). Currently, it is recommended that all women capable of becoming pregnant consume 400 µg of folic acid daily from supplements (about 40% of women take a supplement with folic acid⁴⁴) or fortified foods, in addition to getting folate from a varied diet. Food fortification supplies adults in the U.S. with about 200 µg/day of folic acid.



Fumonisin mycotoxins may pose another risk factor for neural tube defects. Fumonisin is produced in mold-contaminated corn and are thought to disrupt cell metabolism in the embryo. Populations that rely heavily on corn as a dietary staple are most likely to be affected.⁶⁹

► Women who have had a child with a neural tube defect are advised to consume 4 mg/day of folic acid beginning at least 1 month before any future pregnancy. This must be done under strict physician supervision. For further information about neural tube defects, see the website www.sbaa.org.

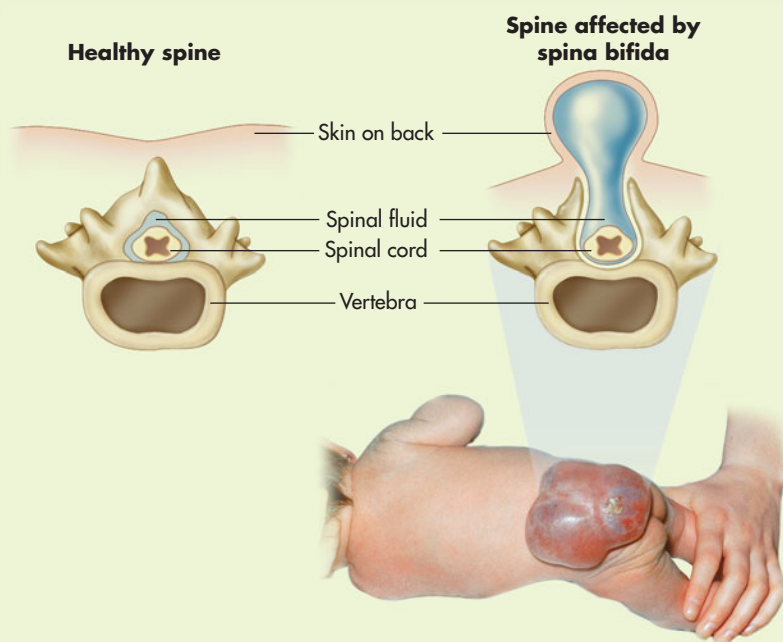


Figure 13-15 Neural tube defects result from a developmental failure affecting the spinal cord or brain in the embryo. Very early in fetal development, a ridge of neural-like tissue forms along the back of the embryo. As the fetus develops, this material differentiates into the spinal cord and body nerves at the lower end and into the brain at the upper end. At the same time, the bones that make up the vertebrae gradually surround the spinal cord on all sides. If any part of this sequence of events goes awry, many defects can appear. The worst is total lack of a brain (anencephaly). Much more common is spina bifida, in which the backbones do not form a complete ring to protect the spinal cord. Deficient folate status in the mother during the beginning of pregnancy increases the risk of neural tube defects, as does a genetic predisposition.

Large, immature cells also appear throughout the GI tract during chronic folate deficiency.³² This occurs because DNA synthesis is impaired, which hinders cell division in the GI tract. This change contributes to a decreased absorptive capacity of the GI tract and persistent diarrhea. White blood cell synthesis also is disrupted by a folate deficiency because these cells are made in rapid bursts during immune challenges (e.g., infections). Thus, immune function can be diminished during a folate deficiency.

Knowledge Check



1. How do folate in food and synthetic folic acid differ? Which form is better absorbed?
2. What are 3 foods that are good sources of folate?
3. How is folate involved in DNA synthesis and amino acid metabolism?
4. What type of anemia signifies a folate deficiency?

CASE STUDY



Suzanne and Ted are planning to start a family. They are especially concerned because Suzanne's sister gave birth

last year to a baby with spina bifida. In preparation for her pregnancy, Suzanne takes a multivitamin supplement and eats fortified breakfast cereal most days. She also tries to include oranges, orange juice, broccoli, and spinach salads in her diet. What is spina bifida? How do Suzanne's diet and multivitamin supplement help prevent this serious disorder?

13.10 Vitamin B-12

Vitamin B-12, also known as cobalamin, is unique among the vitamins on 2 accounts. First, foods of animal origin, such as meat, poultry, fish, and dairy products, are the only reliable sources of vitamin B-12. Second, it is the only vitamin that contains a mineral (cobalt) as part of its structure.⁴⁶ Vitamin B-12 has a complex, multi-ring structure. The cyanocobalamin form of vitamin B-12 forms 2 active coenzymes (methylcobalamin and 5-deoxyadenosylcobalamin) by replacing the cyano group (shown in red in the Biochemist's View in the margin) with another group, such as a methyl group or a hydroxyl group. The discovery of vitamin B-12 and how it prevents the vitamin B-12 deficiency disease pernicious anemia was so significant that vitamin B-12 researchers were awarded 6 Nobel Prizes in the time period 1934–1965. The abnormal red blood cells in pernicious anemia are linked to the role of vitamin B-12 in amino acid metabolism and the resulting relationships between vitamin B-12 and folate metabolism.

Functions of Vitamin B-12

Vitamin B-12 is required for 2 enzymatic reactions.⁴⁵ First, the formation of the amino acid methionine from the amino acid homocysteine is catalyzed by the enzyme methionine synthase, which requires the vitamin B-12 coenzyme methylcobalamin (Fig. 13-16). Homocysteine accepts a methyl group from methylcobalamin, which forms methionine. Methionine, in turn, is the source of S-adenosyl methionine (SAM). In many reactions, SAM serves as a methyl donor. Methylation reactions are important for DNA and RNA regulation, myelin regulation, and the synthesis of many biochemical compounds. The methionine synthesis reaction also explains the close link between vitamin B-12 and folate: methylcobalamin obtains its methyl group from the folate coenzyme 5-methyl-tetrahydrofolate (5-Me-THFA). When the methyl group is donated to vitamin B-12, the folate coenzyme THFA is re-formed. When vitamin B-12 is lacking, THFA declines and the symptoms of folate deficiency can ensue. When either folate or vitamin B-12 is lacking, methionine and SAM synthesis decline, and the amount of homocysteine in the body increases. Choline also can provide methyl groups to homocysteine.

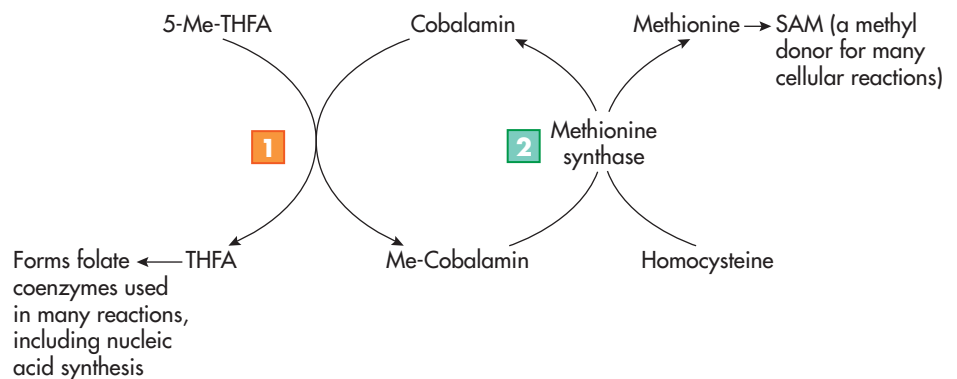
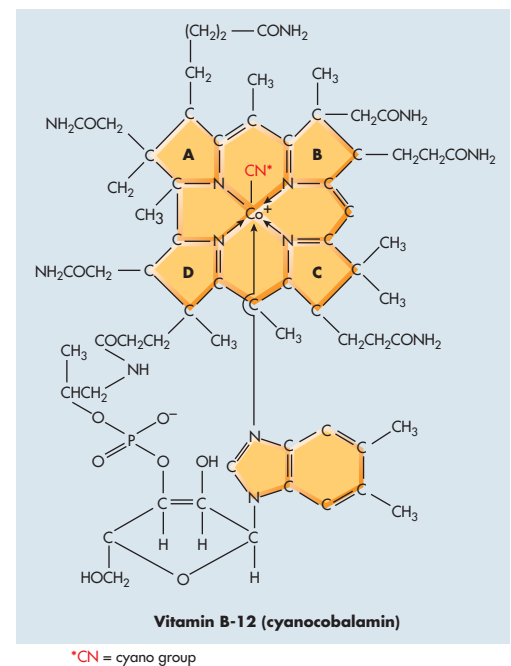


Figure 13-16 Interrelationships of vitamin B-12 and folate with the amino acids homocysteine and methionine. **1** One methyl group from 5-methyl tetrahydrofolate (5-Me-THFA) is donated to cobalamin (vitamin B-12). This reaction generates tetrahydrofolate (THFA) and methyl cobalamin (Me-Cobalamin). **2** Me-Cobalamin donates the methyl group to homocysteine. This reaction is catalyzed by the enzyme methionine synthase. This reaction generates cobalamin and methionine. When vitamin B-12 is lacking, 5-Me-THFA builds up and THFA decreases, which slows or stops nucleic acid synthesis. Homocysteine levels also rise.



Fish, seafood, and related products are good sources of vitamin B-12.

The enzyme methylmalonyl **mutase** requires the second vitamin B-12 coenzyme, 5-deoxyadenosylcobalamin. This enzyme is needed for the metabolism of fatty acids with an odd number of carbon molecules (most fatty acids have an even number of carbon molecules). It allows these fatty acids to be oxidized in the citric acid cycle and to provide energy.

Vitamin B-12 in Foods

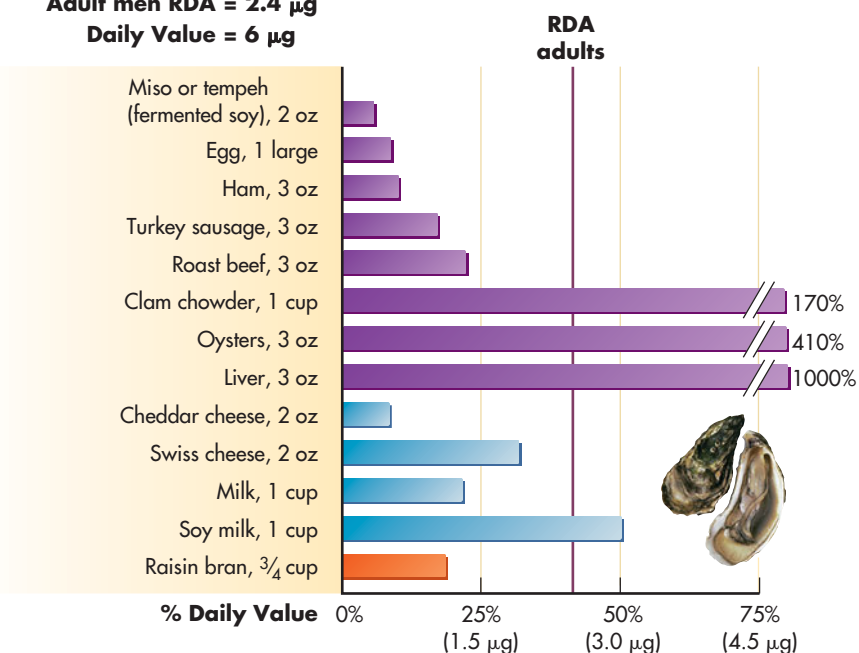
Plants do not synthesize vitamin B-12. In fact, all vitamin B-12 compounds are synthesized exclusively by microorganisms, mainly bacteria. Animals acquire vitamin B-12 from the soil they ingest while eating and grazing. Ruminant animals, such as cows and sheep, also synthesize vitamin B-12 from bacteria in the multiple compartments of their stomachs.

For humans, the sources of vitamin B-12 are foods of animal origin, such as meat, poultry, seafood, eggs, and dairy products. Especially rich sources of vitamin B-12 are organ meats, such as liver, kidneys, and heart, and fortified foods, such as ready-to-eat cereals (Fig. 13-17). Although algae and fermented soy products, such as tempeh and miso, are sometimes advertised as being good plant sources of vitamin B-12, vegans should not rely on them to meet their vitamin B-12 requirements. These foods often contain vitamin B-12 analogs (compounds similar to vitamin B-12) that do not function as vitamin B-12 in the body.

Vitamin B-12 Needs and Upper Level

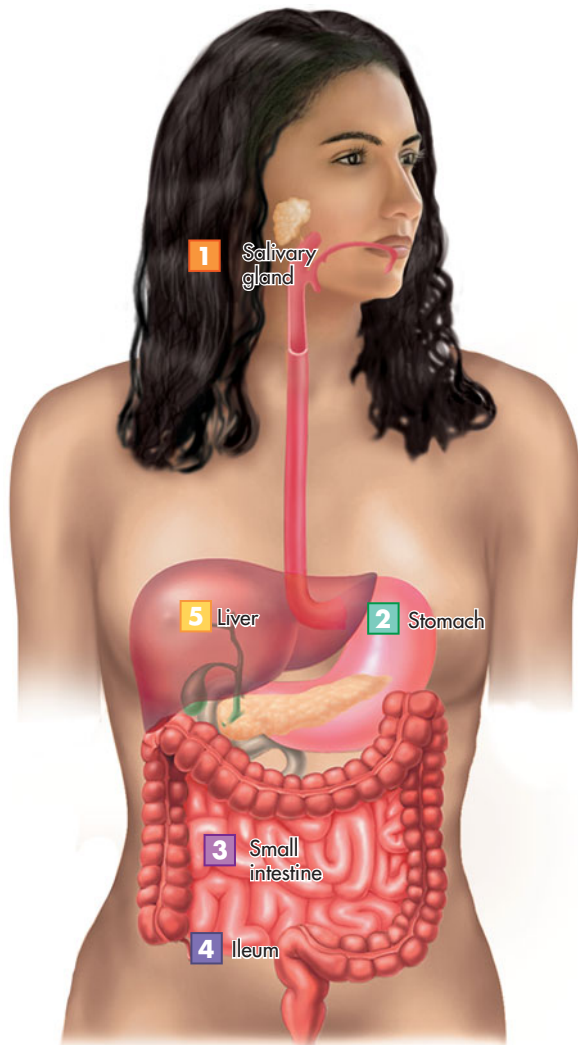
The RDA of vitamin B-12 for adults is 2.4 $\mu\text{g}/\text{day}$. The Daily Value on food and supplement labels is 6 μg . Intake of vitamin B-12 from food in the U.S. typically exceeds the RDA. Adult men average 6.9 $\mu\text{g}/\text{day}$, adult women 4.5 $\mu\text{g}/\text{day}$.⁷ This high intake provides the average meat-eating person with a 2 to 3 years' storage of vitamin B-12 in the liver. No adverse effects have been observed with excess vitamin B-12 intake from food or from supplements, so there is no Upper Level for this vitamin.⁶

Adult women RDA = 2.4 μg
 Adult men RDA = 2.4 μg
 Daily Value = 6 μg



mutase Enzyme that rearranges the functional groups on a molecule.

Figure 13-17 Food sources of vitamin B-12.



Vitamin B-12



- 1 Mouth:** Salivary glands produce R-protein.
- 2 Stomach**
 - a. HCl and pepsin release vitamin B-12 bound to protein in food.
 - b. Free vitamin B-12 binds with R-protein.
 - c. Parietal cells secrete intrinsic factor.
- 3 Small intestine**
 - a. Trypsin from the pancreas releases R-protein from vitamin B-12.
 - b. Vitamin B-12 links with intrinsic factor.
- 4 Ileum:** Vitamin B-12/intrinsic factor complex is absorbed into blood and binds to transport protein transcobalamin II.
- 5 Liver:** Vitamin B-12 is stored in the liver.

Figure 13-18 The absorption of vitamin B-12 requires several compounds produced in the mouth, stomach, and small intestine. Defects arising in the stomach or small intestine can interfere with vitamin B-12 absorption, in turn causing pernicious anemia.

Absorption, Transport, Storage, and Excretion of Vitamin B-12

As shown in Figure 13-18, the absorption of vitamin B-12 is quite complex. In food, vitamin B-12 is bound to protein. HCl and pepsin in gastric juice release vitamin B-12 from these proteins. In the stomach, the free vitamin B-12 binds to **R-protein**, which originates in the salivary glands. In the small intestine, pancreatic protease enzymes (e.g., trypsin) release vitamin B-12 from the R-protein/vitamin B-12 complex. The free vitamin B-12 then combines with **intrinsic factor**, a proteinlike compound produced by parietal cells in the stomach that enhances vitamin B-12 absorption. The vitamin B-12 intrinsic factor complex travels to the ileum, where vitamin B-12 is absorbed and transferred to the blood transport protein transcobalamin II. This vitamin B-12/transcobalamin II complex enters the portal vein and is delivered to the liver.⁴⁵ The liver can store enough vitamin B-12 to last several years, which is not the case with other water-soluble vitamins. Although vitamin B-12 is continually secreted into the bile, most of it is reabsorbed by enterohepatic circulation, thereby efficiently “recycling” this vitamin. Little vitamin B-12 is excreted in the urine.

Normally, healthy adults absorb about 50% of the vitamin B-12 in foods. However, the absorption of vitamin B-12 can be disrupted by numerous defects, including the following.^{6,41}

- The absence of or defective synthesis of R-protein, pancreatic proteases, or intrinsic factor
- Defective binding of the intrinsic factor/vitamin B-12 complex to receptor cells in the ileum
- The absence (or surgical removal) of much or all of the ileum and stomach
- Diseases in the ileum, such as Crohn’s disease

R-protein Protein, produced by the salivary glands, that enhances the absorption of vitamin B-12, possibly by protecting the vitamin during its passage through the stomach.

intrinsic factor Substance in gastric juice that enhances vitamin B-12 absorption.

- Atrophic gastritis, which decreases the production of HCl and digestive enzymes needed to cleave the R-protein/vitamin B-12 complex in foods; 10 to 30% of older adults have atrophic gastritis and, thus, are advised to eat foods fortified with vitamin B-12 and/or take a supplement because they contain free vitamin B-12 in crystalline form, which is readily absorbed
- Infections, such as *Helicobacter pylori*, tapeworm infestation, *Giardia lamblia* (parasite infection), bacterial overgrowth of the small intestine, or HIV/AIDS
- The use of certain anti-reflux medications that significantly reduce acid production by the parietal cells (e.g., omeprazole [Prilosec])
- The use of the medication metformin to lower blood sugar in type 2 diabetes⁴⁶
- Chronic malabsorption syndromes, as may occur with various gastrointestinal disorders, such as celiac disease

Vitamin B-12 Deficiency

Researchers in mid-19th-century England noted a form of anemia that causes death within 2 to 5 years of initial diagnosis. They called this disease **pernicious anemia** (*pernicious* means “leading to death”). It is now known that this disease can result from the inadequate production of the intrinsic factor required for vitamin B-12 absorption. Poor vitamin B-12 status is still fairly common today, and impaired absorption of the vitamin B-12 found in foods is most often to blame.

Macrocytic Anemia

When a vitamin B-12 deficiency is severe enough that body stores are gone or almost gone, a megaloblastic (macrocytic) anemia results. The anemia produced in vitamin B-12 deficiency is identical to that produced in a folate deficiency. Because a lack of vitamin B-12 impairs folate metabolism, normal DNA and red blood cell synthesis is disrupted, resulting in megaloblastic anemia (see Fig. 13-14).

Neurological Changes

A vitamin B-12 deficiency produces nerve degeneration in some individuals, which can be fatal. The neurological complications produce sensory disturbances in the legs, such as burning, tingling, prickling, and numbness (collectively referred to as paresthesia).⁴⁵ Walking is difficult and balance is seriously affected. Many mental problems exist as well, such as loss of concentration and memory, disorientation, and dementia. As the condition worsens, bowel and bladder control is lost. Visual disturbances are common, too. There also are numerous GI tract problems, ranging from a sore tongue to constipation. The neurological complications often precede the development of anemia.

Elevated Plasma Homocysteine Concentrations

Poor vitamin B-12, folate, and vitamin B-6 status can each result in high circulating levels of the amino acid homocysteine (see Fig. 13-16). Many studies have shown that high homocysteine levels in the blood are a risk factor for heart attacks and strokes. Some researchers have found that high levels of plasma homocysteine also are associated with cognitive dysfunction and osteoporotic fractures.⁴⁷

Researchers have long known that supplementing the diet with folate, vitamin B-12, and vitamin B-6 can reduce blood levels of homocysteine. However, the evidence that supplementing with these vitamins can reduce the diseases associated with high blood levels of homocysteine is not strong. Several large studies that compared vitamin supplements with placebo treatments found that the supplements did not prevent heart disease, even though homocysteine levels declined.⁴⁸⁻⁴⁹ In addition, it appears that supplements of vitamin B-12, vitamin B-6, and folate do not improve cognitive function.⁵⁰ Even though B-vitamin supplements have not been shown to decrease the risk of heart disease or improve cognition, ample B-vitamin intakes are vital for normal physiological function and good health.

► Because of their critical roles in DNA synthesis and methylation, folate, vitamin B-6, and vitamin B-12 are thought to play an important role in cancer prevention. However, there is also concern that high intakes of these nutrients may promote tumor growth. In several research studies, nutrition scientists have tested whether *supplements* of these B-vitamins prevent cancer. Most clinical trials with B-vitamin supplements show no effect, either positive (preventing cancer) or negative (promoting cancer), but the results are not entirely consistent.^{72, 73} At this point, supplementation with vitamin B-6, vitamin B-12, and folic acid cannot be recommended as a way to prevent cancer. Cancer and diet are discussed further in the Medical Perspective in Chapter 12.



Take Action

B-Vitamin Supplements

B-vitamins are sometimes marketed as a way to gain energy. Consider the following common scenario. Dan, age 20, is a junior in college with a full load of classes, a part-time job, and additional campus activities. He often feels tired and stressed and attributes this to his poor eating habits. Dan frequently misses meals and fills up on fast food and snacks. One of his friends suggests that he try a B-complex vitamin supplement to boost his energy. The supplement Dan chooses is called B-complex 100. According to the label, 1 pill provides the following:

Thiamin	100 mg
Riboflavin	100 mg
Niacin	100 mg
Vitamin B-6	100 mg
Folic acid	400 µg
Vitamin B-12	100 mg
Biotin	100 µg
Pantothenic acid	100 mg
Para-aminobenzoic acid	100 mg
Choline	100 mg
Carnitine	100 mg

Compare the amounts provided in the supplement with the DRIs, including the UL for Dan. Is B-complex 100 a good supplement for Dan? Do you think it will increase his energy? What are para-aminobenzoic acid and carnitine? What are other recommendations you might make to help Dan improve his energy and nutritional health?



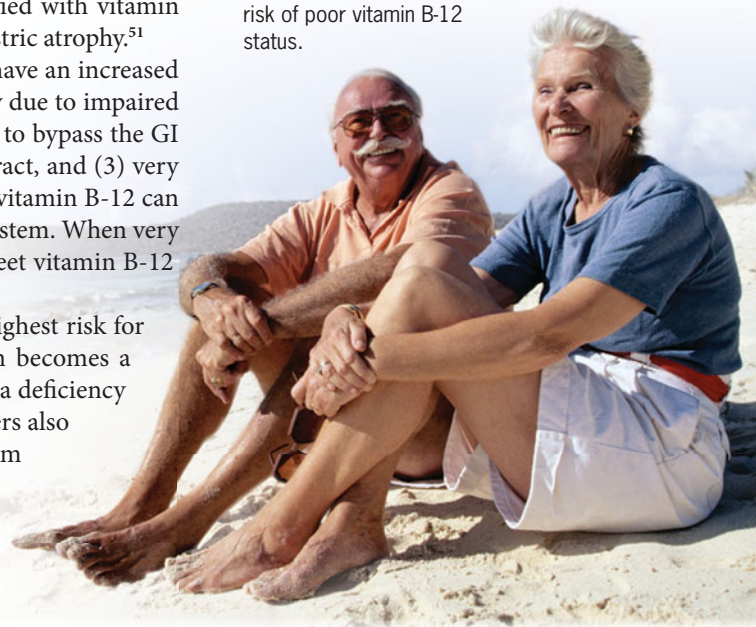
Persons at Risk of Vitamin B-12 Deficiency

Poor vitamin B-12 status affects about 20% of older Americans. In the elderly, most cases are due to impaired absorption of the vitamin B-12 in foods due to atrophic gastritis. This deficiency usually is not severe enough to produce anemia, but it can cause neurological problems and elevated blood homocysteine. The consumption of crystalline vitamin B-12, either as a dietary supplement or in fortified foods (many breakfast cereals are fortified with vitamin B-12), can improve vitamin B-12 status in older persons with or without gastric atrophy.⁵¹

As noted earlier, those with a malabsorption syndrome of any kind have an increased need for vitamin B-12. For those diagnosed with a vitamin B-12 deficiency due to impaired absorption, 3 options are available: (1) monthly injections of vitamin B-12 to bypass the GI tract, (2) the use of a vitamin B-12 nasal gel, which also bypasses the GI tract, and (3) very high oral doses (1 to 2 mg) daily of vitamin B-12. A very small amount of vitamin B-12 can be absorbed by passive diffusion and does not require the intrinsic factor system. When very large amounts of vitamin B-12 are ingested, enough can be absorbed to meet vitamin B-12 requirements and correct vitamin B-12 deficiency.^{52, 53}

Vegetarians also can become vitamin B-12 deficient; vegans are at highest risk for deficiency because they consume no animal foods. However, if a person becomes a vegetarian in adulthood, vitamin B-12 stores in the liver can delay signs of a deficiency for several years. Infants born to or breastfed by vegetarian or vegan mothers also can develop vitamin B-12 deficiency, accompanied by anemia and long-term neurological problems, such as diminished brain growth, degeneration of the spinal cord, and poor intellectual development. Vegetarians have several options for obtaining vitamin B-12. If they are not vegans, they can obtain vitamin B-12 from dairy products and eggs. In addition, vitamin B-12 supplements and food products fortified with vitamin B-12 are available.

Older adults have an increased risk of poor vitamin B-12 status.



Knowledge Check

1. What roles do HCl, intrinsic factor, the stomach, and the ileum play in vitamin B-12 absorption?
2. How are vitamin B-12 and folate metabolism related?
3. Which foods are good sources of vitamin B-12?

13.11 Manganese (Mn)

Manganese has been recognized as an essential trace mineral since the early 1930s. It is an important cofactor in metabolism. As scientists develop more sensitive measures of trace mineral status and function, they will have a clearer picture of the role of manganese in metabolism, health, and disease.

Functions of Manganese

Manganese shares some similarities with the B-vitamins because it serves as a cofactor for many enzymes in the body. Many manganese-dependent enzymes have important functions in nitrogen and carbohydrate metabolism, gluconeogenesis, collagen formation, and the antioxidant defense network (as Mn superoxide dismutase). In the body, manganese can alternate between different oxidation states (Mn^{2+} and Mn^{3+}), enabling it to participate in various metabolic reactions.

Manganese in Foods

Whole-grain cereals, nuts, legumes, leafy greens, and tea are the best sources of manganese (Fig. 13-19). Meat and dairy products contribute very little manganese to the diet. Based on dietary surveys, the North American diet provides between 2 and 6 mg/day.

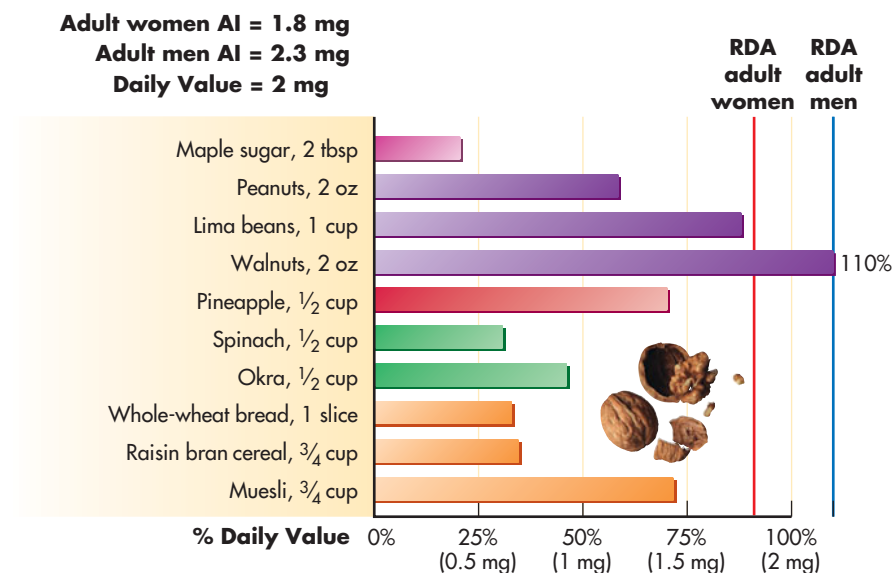
Dietary Needs for Manganese

Data are currently insufficient to determine the dietary requirement for manganese. Thus, an Adequate Intake for manganese was set at 2.3 mg/day for adult men and 1.8 mg/day for adult women.²⁵ The Daily Value for manganese on food and supplement labels is 2 mg.



Manganese is found in peanuts and other legumes.

Figure 13-19 Food sources of manganese.



Absorption, Transport, Storage, and Excretion of Manganese

Manganese is absorbed in the small intestine via simple diffusion and active transport. Following absorption, most manganese is bound to alpha-2-macroglobulin for transport to the liver and then transported via transferrin, alpha-2-macroglobulin, or albumin to other tissues, such as the pancreas, kidneys, and bone. Excretion occurs mainly via bile, which is the primary means of regulating manganese levels in the body.⁵⁴

Approximately 5 to 10% of the manganese in food is absorbed. Absorption is affected by the amount of manganese in the diet and by iron status. Absorption is increased by low manganese intake and iron deficiency (manganese and iron compete for transporters when iron intake is higher) and is decreased by high intakes of manganese and possibly copper, nonheme iron, fiber, phytates, and oxalates.

Manganese Deficiency and Toxicity

Manganese deficiency has not been well documented in humans. In fact, only a few cases have ever been reported. The symptoms associated with deficiency include impaired carbohydrate and lipid metabolism, nausea and vomiting, poor growth, skeletal abnormalities, and abnormal reproductive function.⁵⁴

Although manganese is considered to be less toxic than most trace minerals, toxicities have been reported in children receiving long-term parenteral nutrition and from the inhalation of airborne industrial and automobile emissions.⁵⁴ Toxicity causes severe neurological impairment and the development of symptoms similar to those seen in Parkinson disease (muscle stiffness, tremors). Thus, an Upper Level of 11 mg/day was set for manganese to prevent possible damage to the nervous system.²⁵



Knowledge Check

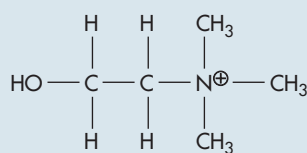
1. What are 3 rich sources of manganese?
2. How is manganese function similar to that of B-vitamins?
3. How is manganese status regulated in the body?

13.12 Molybdenum (Mo)

Molybdenum is an ultratrace mineral that functions as a cofactor; it is essential for the activity of several enzymes. Molybdenum is involved in the metabolism of the sulfur-containing amino acids, purines, and pyrimidines. Molybdenum content is greatest in plant-based foods, such as grains, legumes, and nuts. Like iodine, the molybdenum content of foods can vary, depending on the soil in which the plant was grown. The RDA for molybdenum is very small (45 µg/day) and is based on its role as a cofactor required for the activity of several oxidase enzymes.²⁵ The dietary intakes in North America typically meet or exceed the RDA. The Daily Value used on food and supplement labels is 75 µg. Deficiencies of molybdenum are very rare, as are toxicities. However, an Upper Level of 2000 µg/day for adults was set to prevent the development of the goutlike symptoms of joint inflammation noted in several studies.²⁵

13.13 Choline

Choline, recognized by the Institute of Medicine as an essential nutrient in 1998, is a relative newcomer to the list of essential nutrients.⁶ It cannot be considered a B-vitamin because it does not have a coenzyme function and the amount in the body is much greater than that of the B-vitamins. Choline can be obtained from the diet and can be synthesized in cells. However, synthesis alone is not sufficient to meet the body's choline requirements, and liver

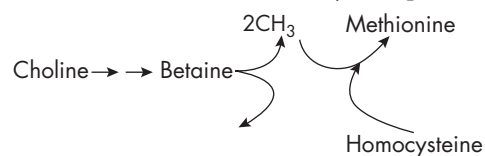


Choline

and muscle damage can occur in those with low dietary intakes.^{6,55} Choline is needed for normal nervous system function and lipid and homocysteine metabolism.

Functions of Choline

Choline has many functions in the body. It is an important source of methyl ($-\text{CH}_3$) groups required in many reactions in the body. In amino acid metabolism, choline forms betaine, which can be used to form methionine from homocysteine, and supplementation with choline in healthy men has shown to decrease homocysteine concentrations.⁵⁵ In its role as a methyl donor, choline also may help prevent neural tube defects.^{55,56} Choline also is a component of cell membranes and sphingomyelin, required for the synthesis of myelin (the substance that protects nerve fibers and facilitates the transmission of electrical impulses), and it is a component of phospholipids, such as phosphatidylcholine (lecithin). Because of the rapid growth of brain and nervous tissue during pregnancy and the first year of life, choline use and requirements are high during these periods.⁵⁷ Choline also functions as a precursor for acetylcholine, a neurotransmitter associated with attention, learning, memory, muscle control, and many other functions. Phosphatidylcholine also is needed for the formation of very-low-density lipoprotein (VLDL) and, thus, for the export of triglycerides from the liver. Choline appears to have a role in the transport of carnitine into tissues; carnitine helps move fatty acids into the mitochondria of cells for energy production (see Section 13.15). Preliminary research suggests that high choline intakes are associated with lower plasma concentrations of C-reactive protein, a compound that indicates inflammation.⁵⁸ Because inflammation increases the risk of cardiovascular disease, choline may offer protection against this disease.



Choline in Foods

Choline in foods is found either as free choline or as part of another compound, such as lecithin (see Chapter 6). Foods of animal origin (e.g., milk, eggs, chicken, beef, and pork) are large contributors of choline in the diet (Fig. 13-20). Grains, nuts, vegetables, and fruits also provide choline. Lecithins added to food during processing are yet another source. Data on the choline content of foods are still incomplete.⁵⁹

Choline Needs and Upper Level

The Adequate Intake for choline for adult men is 550 mg/day; for adult women, it is 425 mg/day. Although Adequate Intakes are set for choline, it may be that the choline requirement can be met by body synthesis at some or all stages of life. The *What We Eat in America* survey suggests that average choline intakes are less than recommended.⁷ The Upper Level for adults is 3.5 g/day. Very high doses of choline have been associated with a fishy body odor (arising from a breakdown product), low blood pressure, vomiting, salivation, sweating, and GI tract effects.⁶

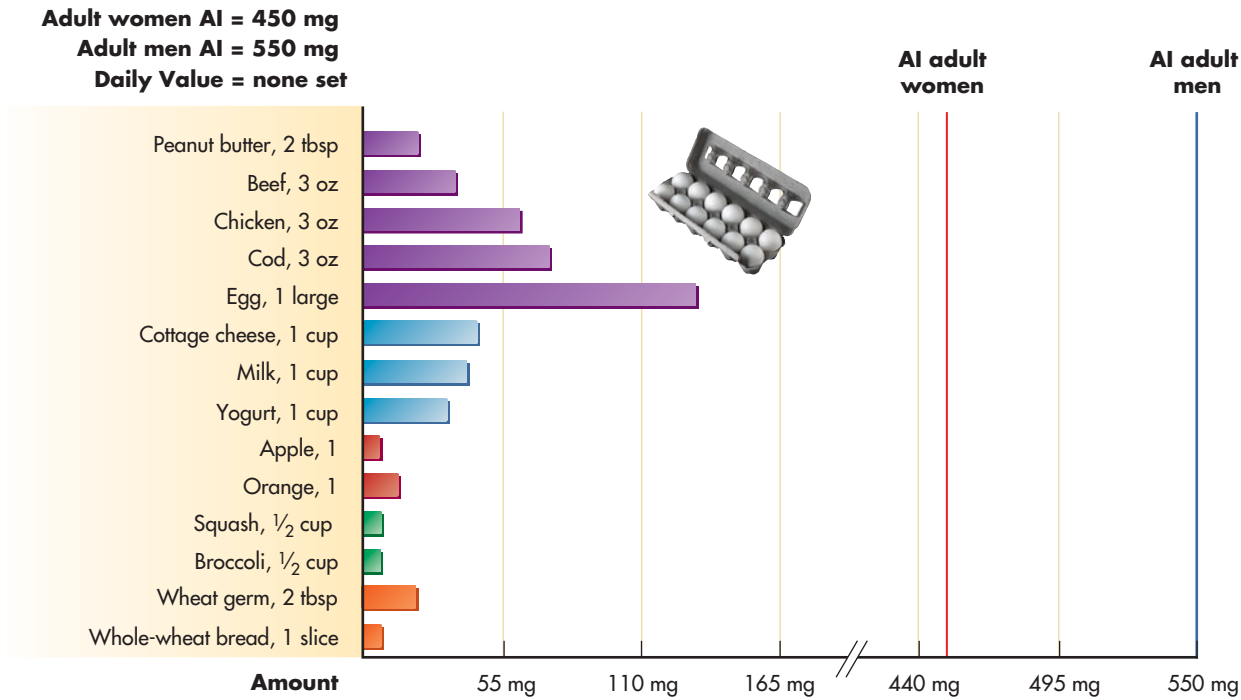
Absorption, Transport, Storage, and Excretion of Choline

Choline is absorbed from the small intestine by way of transport proteins. The liver takes up choline rapidly from the blood delivered by the portal vein from the small intestine. All tissues contain some stores of choline. Some choline is excreted in the urine, but most of the excess is converted to a related donor (betaine) of single-carbon groups (e.g., methyl groups).

Choline Deficiency

There is no deficiency disease associated with choline. However, liver and muscle damage has been observed in adults fed choline-deficient diets. Because of its critical roles in human metabolism, identifying and understanding the health effects of inadequate choline intake is an active area of research.

Figure 13-20 Food sources of choline.



Knowledge Check

1. Which foods are the best sources of choline?
2. Which organs are most affected by a choline-free diet?
3. Briefly describe 3 functions of choline.

13.14 Iodine (I₂)

Iodine (I₂), present in food as iodide (I⁻) and other nonelemental forms, is unique in many ways from other trace minerals. It is the heaviest element needed for human health and is responsible for only 1 function in the body, the synthesis of thyroid hormones, which are critical to the regulation of energy metabolism.⁶⁰

Functions of Iodine

Iodine is an essential component of the thyroid hormones thyroxine (T₄) and triiodothyronine (T₃). Most of the circulating thyroid hormone in the body is in the form of T₄. Within body cells, T₄ loses an iodine molecule and is converted to T₃, the active form of the hormone. The enzymes involved in this conversion (called deiodinase enzymes) require the trace mineral selenium. Thus, a selenium deficiency can limit the activity of deiodinase enzymes, resulting in decreased T₃ levels.

Although iodine has a singular function, this function has widespread consequences because of the vital role that thyroid hormones play in maintaining normal metabolism. As a component of T₃, iodine is involved in the regulation of many important metabolic and developmental functions. This includes the regulation of basal energy expenditure, macronutrient metabolism, brain and nervous system development, and overall growth.⁶⁰

Thyroxine (T₄). Triiodothyronine (T₃) has a similar structure but lacks 1 iodine (I), indicated in this figure with a red asterisk.

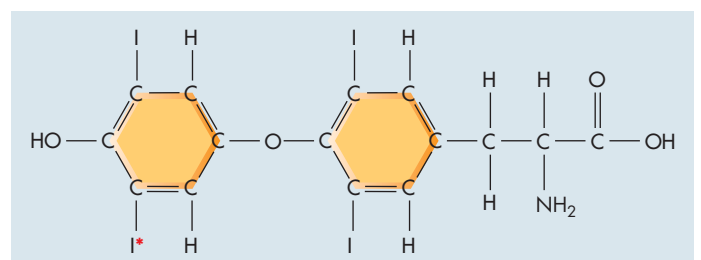
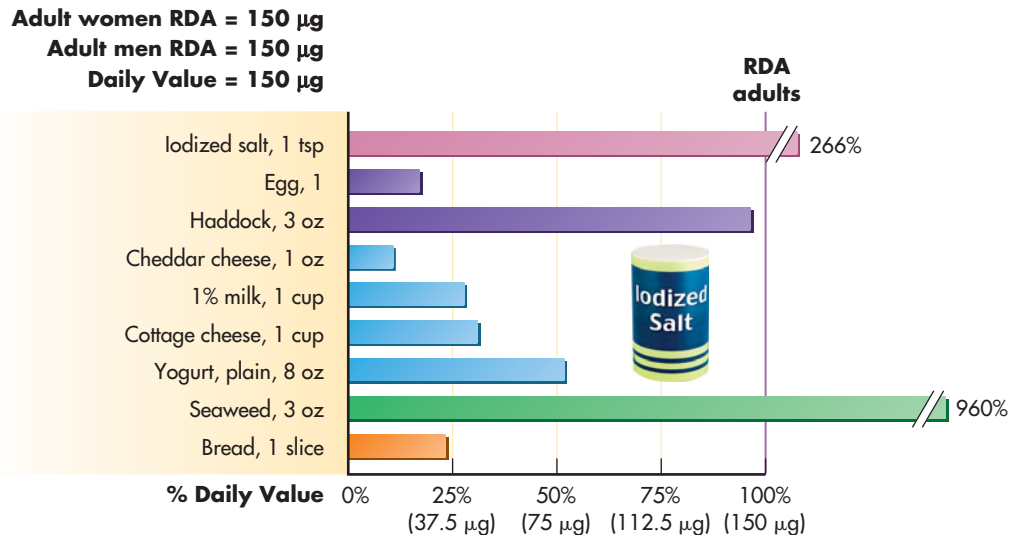


Figure 13-21 Food sources of iodine.



Iodine in Foods

The natural iodine content of most foods is relatively low. Saltwater seafood, seaweed, iodized salt, and dairy products are the best sources of iodine (Fig. 13-21). Dairy products are not naturally good sources, but they often provide significant amounts because iodine is added to cattle feeds and sanitizing solutions used in dairy processing. Breads and cereals also may contribute dietary iodine if they are prepared with iodized salt and/or dough conditioners (compounds that strengthen dough and improve bread volume and texture) because these contain iodates (IO_3^-).

Plant-based foods also may provide iodine if the soil in which they were grown was rich in this mineral. However, soil content can vary significantly from region to region, resulting in great differences in iodine content. Iodine-rich soil tends to be near oceans because seawater is naturally high in iodine. When seawater evaporates, the iodine in the air falls on nearby soil.

For many Americans, iodized salt used in cooking and at the table provides most of their iodine. Iodized salt contains 76 μg of iodine per gram of salt. In practical terms, this means that about a half teaspoon (about 2 g) of salt supplies the adult RDA for iodine. Although many Americans also have a significant salt intake from processed foods, non-iodized salt is typically used in processed foods. Many specialty salts, including sea salts, also are non-iodized, so it is important to read labels when purchasing different types of salt.

The bioavailability of iodine is decreased by compounds, called goitrogens, found in raw vegetables such as turnips, cabbage, Brussels sprouts, cauliflower, broccoli, rutabagas, potatoes, and cassava, as well as peanuts, soy, peaches, and strawberries. **Goitrogens** decrease iodine absorption in the intestinal tracts and inhibit iodine use by the thyroid gland. The risk of iodine deficiency is elevated in less developed parts of the world where raw vegetable intake is high and iodine intake is low.⁶¹ Goitrogens are of little concern in developed countries because these vegetables are typically cooked (which helps destroy goitrogen activity) and iodine-rich foods are widely available.

Dietary Needs for Iodine

The adult RDA for iodine is 150 $\mu\text{g}/\text{day}$.²⁵ This recommendation is based on the amount needed to maintain adequate uptake and turnover by the thyroid gland. In the U.S., usual dietary iodine intakes range between 190 and 300 $\mu\text{g}/\text{day}$. This does not account for amounts provided by iodized salt sprinkled on foods at the table. The Daily Value for iodine used on food and supplement labels is 150 μg .

A small amount of iodized salt in the diet meets the body's iodine needs.



Absorption, Transport, Storage, and Excretion of Iodine

Most of the iodine in foods is in the form of iodide and, to a lesser extent, iodates. These forms are very efficiently absorbed throughout the small intestine. After absorption, most of the iodine (the general term used for the mineral) is transported to the thyroid gland. Using a sodium-dependent active transport system, the thyroid gland actively accumulates iodine—in essence, “trapping” it to support thyroid hormone synthesis. Excess iodine is excreted primarily via the kidneys into the urine. Very little iodine is excreted in the feces.

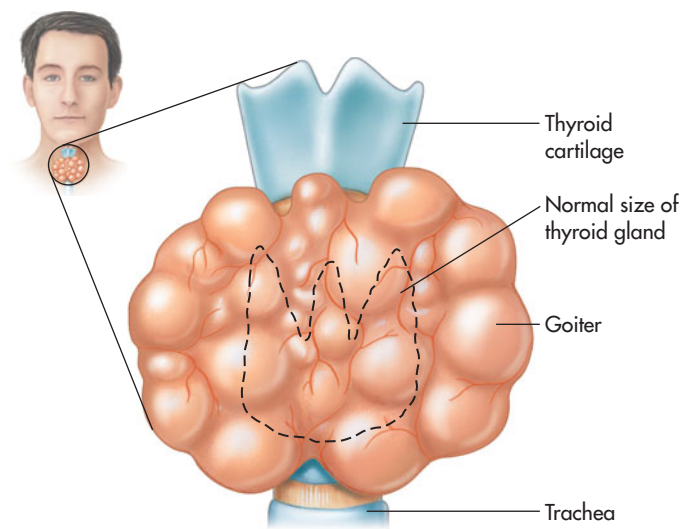
Iodine Deficiency Disorders (IDD)

Iodine deficiency disorders, the collective name for **endemic** goiter and endemic cretinism, occur when dietary iodine intake is insufficient. When iodine availability decreases and plasma levels of T_4 hormone drop, the pituitary gland secretes thyroid-stimulating hormone (TSH). In response to increased TSH levels, the thyroid gland enlarges in an attempt to increase its efficiency at trapping iodine. The characteristic enlargement of the thyroid gland that occurs is called a **goiter**. This early adaptive response allows the thyroid gland to temporarily maintain thyroid hormone synthesis. Although a goiter is a painless condition, it can cause pressure on the esophagus and trachea, impairing their function. If the underlying iodine deficiency is not corrected, decreased T_4 synthesis, slowed metabolism, and more serious complications can develop.⁶¹

Iodine deficiency is of particular concern during pregnancy because of the adverse effects it can have on the developing offspring.^{61,62} These include congenital abnormalities, low birth weight, neurological disorders, impaired mental function, poor physical development, and death. The resulting restriction of brain development and growth, called **cretinism** (Fig. 13-22), is characterized by severe mental retardation, loss of hearing and speech abilities, short stature, and muscle spasticity.

Descriptions of goiter have been documented for many centuries in China and other parts of the world. Prior to World War I, goiter was very common in the Great Lakes region of the U.S., where the soil and lake waters are very low in iodine. Cretinism also was common in parts of the U.S. Today, approximately one-third of the world’s population remains at risk of iodine deficiency.⁶¹⁻⁶³ Almost every country in the world still has iodine-deficient

endemic Habitual presence of a disease within a given geographic area.



(a)



(b)

Figure 13-22 (a) This Nigerian woman has a goiter caused by iodine deficiency. (b) This 35-year-old Peruvian woman is 43 inches (110 cm) tall due to cretinism, which is caused by an iodine deficiency.

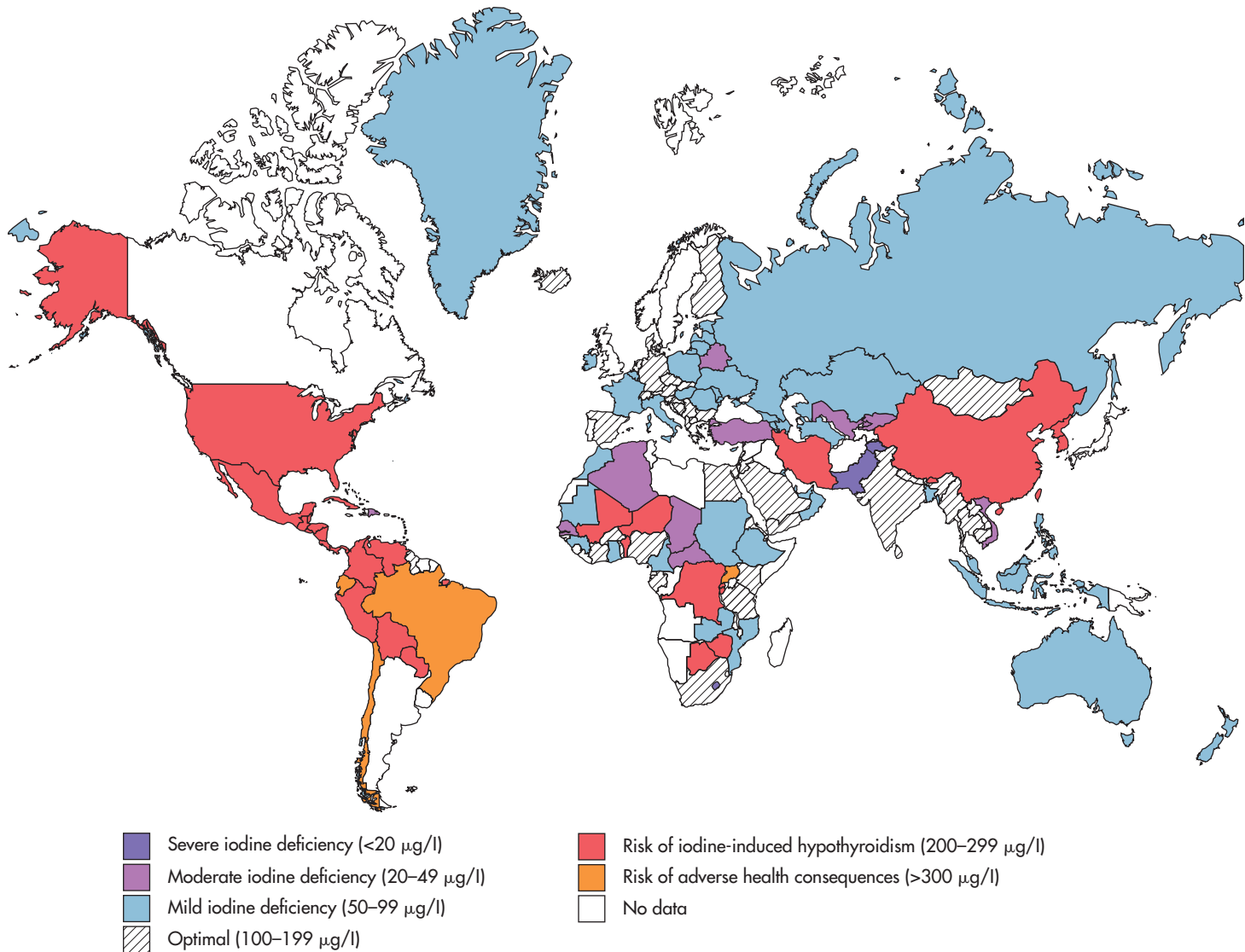


Figure 13-23 Iodine deficiency disorders are moderate to severe in many areas of the world. Adverse health consequences can occur from excessive dietary iodine as well.

Courtesy of the World Health Organization, *Iodine Status Worldwide*, WHO Global Database on Iodine Deficiency.

areas (Fig. 13-23). The highest incidence of iodine deficiency disorders occurs in South America, Asia, Africa, and the Middle East.⁶¹ The discovery in the early 1920s, by scientists in the U.S. and Switzerland, that iodine can prevent the development of goiter resulted in the fortification of table salt in the U.S. and many other countries. Using a small amount of iodized salt has eradicated endemic iodine deficiency in these areas. Unfortunately, many countries have yet to adopt iodine fortification programs. Consequently, iodine deficiency remains an international public health problem.⁶⁴ In fact, approximately 50% of the world's population live in countries where iodine deficiency is still a significant concern. The World Health Organization (WHO) believes that iodine deficiency is the “greatest single cause of preventable brain damage and mental retardation” and has set a goal of eliminating this deficiency within the next decade by increasing the use of iodine-fortified foods, including salt, oil, and milk.^{61, 62}

Iodine Toxicity

The Upper Level is set at 1100 µg/day for adult men and women to prevent health-related risks.²⁵ Like iodine deficiency, iodine toxicity can cause enlargement of the thyroid gland

GLOBAL PERSPECTIVE

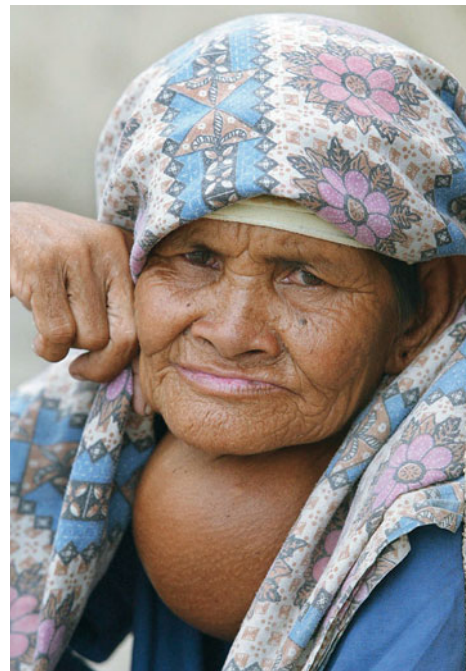
The Micronutrient Initiative

Over half of the young children in developing countries are at risk of poor physical and mental development due to deficiencies of iodine and iron.⁶³ Also, millions of children die needlessly every year from measles, diarrhea, and other illnesses because deficiencies of micronutrients, especially vitamin A and zinc, compromise their ability to fight infections.^{63,66} Dedicated to eliminating such worldwide vitamin and mineral deficiencies, the Micronutrient Initiative, an international organization, was formed in 1990. The Canadian-based network is comprised of nutritional scientists, practitioners, and policymakers who work together to use basic research knowledge to find solutions for ending micronutrient malnutrition. The focus of the Micronutrient Initiative has been to develop local food fortification programs and cultivate working partnerships with governments, food industries, international agencies, and the private sector to have a sustained impact on improving the health and well-being of our world's population.⁶³

The Micronutrient Initiative has been actively involved in nutritional programs in 75 countries. The following are some of the key achievements of the network.

- Expansion of universal salt iodization
- Folic acid and iron fortification of flour in the Middle East and North Africa
- Marketing of complementary foods in South Asia
- Partnerships with private foundations to develop global food fortification coalitions
- Establishment of the Global Vitamin A Initiative to provide vitamin A supplements to 1.5 billion children in 70 countries

To learn more about the Micronutrient Initiative, visit its website: www.micronutrient.org.



and decreased thyroid hormone synthesis.⁶⁵ Toxicities have been reported in Japan, due to high intakes of iodine-rich seaweed, and in Chile, due to high levels of environmental iodine, increased iodine use in water purification, and excessive fortification of salt. Although hypothyroidism is the most common result of iodine toxicity, excess iodine intakes also may increase the risk of hyperthyroidism, autoimmune thyroid disease, and thyroid cancer.

Knowledge Check

1. What are 3 rich sources of iodine?
2. What is the main function of iodine?
3. Why is iodine deficiency still prevalent in many areas of the world?
4. What are the symptoms of iodine deficiency?

13.15 Other Compounds Linked with Energy and Amino Acid Metabolism

Sulfur (S)

Sulfur, a bright yellow mineral, is provided primarily by the sulfur-containing amino acids methionine and cysteine. Sulfur is not required for amino acid metabolism, per se, but it is part of the structure of several compounds critical to metabolism. This mineral also is required for the synthesis of several sulfur-containing compounds, it helps stabilize the structure of proteins (e.g., collagen, hair, nails, skin), and it participates in regulating the acid-base



Protein-rich foods supply sulfur in the diet.

balance in the body. Inorganic sulfate also is found in water and food—for example, as a preservative that protects the color of dried fruits and white wines. There is no AI or RDA for sulfur, nor is an Upper Level established because we are able to obtain ample sulfur from protein-containing foods.⁶⁷ No deficiency or toxicity symptoms are associated with sulfur.

Vitamin-like Compounds

The vitamin-like compounds carnitine and taurine are necessary to maintain normal metabolism in the body. The body can synthesize them, but their biosynthesis often occurs at the expense of other nutrients, such as essential amino acids. The need for these compounds often increases during times of rapid tissue growth, as in preterm infants. Deficiencies of these vitamin-like compounds do not exist in the average healthy adult. Nevertheless, more research is needed to clarify if metabolism is impaired or altered during certain disease states and whether the compounds should be included in infant formulas and total parenteral nutrition solutions. Currently, many manufacturers add these vitamin-like compounds to infant formulas.

Carnitine

Within the cell, carnitine transports fatty acids from the cytosol into the mitochondria, where fatty acids are metabolized for energy. Carnitine also aids the mitochondria in removing excess organic acids produced by metabolic pathways. In addition, carnitine has displayed usefulness as a pharmacological agent in the removal of compounds that can build to toxic amounts in people with inborn errors of metabolism.⁶⁸ Dosages approximately 10 times typical dietary intakes also have been shown to improve the condition of persons with progressive muscle disease and heart muscle deterioration. Although carnitine supplements have been promoted as a weight-loss or exercise aid, the research on these uses is very limited.

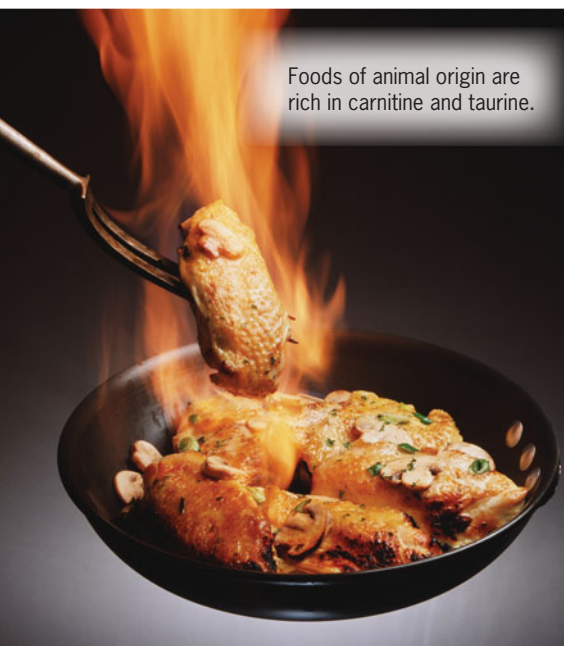
Human needs for carnitine are met by both animal foods and biosynthesis in the liver from the amino acids lysine and methionine.⁵ Meat and dairy products are the main sources of carnitine; little is found in foods of plant origin. We consume about 100 to 300 mg/day.

Adults and children who are severely malnourished or on total parenteral nutrition can have low concentrations of carnitine in their blood. Inadequate protein intake (e.g., a lack of the amino acids needed for making carnitine) leads to abnormal fatty acid metabolism. Even though vegetarian diets are very low in carnitine, vegetarians show normal blood concentrations of carnitine. Consequently, it is doubtful that carnitine is necessary in the diets of healthy people. Carnitine may be considered a conditionally essential nutrient in times of recovery from disease and malnutrition, serious trauma, cirrhosis, kidney dialysis, or preterm birth.

Taurine

Although its functions are not well understood, taurine is involved in many vital functions. It is associated with insulin action, cell differentiation and growth, photoreceptor activity in the eye, antioxidant defense activity in white blood cells and the lungs, normal nervous system function, platelet aggregation, and cardiac contraction. There is no scientific evidence that taurine controls nervous system conditions (e.g., epileptic seizures, motor tics, and facial twitches) or prevents cardiovascular disease or cataracts. No clear cases of taurine deficiencies have been diagnosed in vegans, even though it is not found in plants, suggesting that synthesis by the body meets needs. Thus, it appears that healthy people need not worry about consuming taurine.

Taurine is synthesized in the body from the sulfur-containing amino acids methionine and cysteine. It is abundant in muscle, platelets, and nerve tissue. It also is attached to bile acids. Dietary sources include only foods of animal origin. North Americans consume about 40 to 400 mg/day.



Foods of animal origin are rich in carnitine and taurine.

Taurine supplementation may be of benefit to children with cystic fibrosis. Some of these children experience improved growth when treated with taurine, perhaps because of increased fat absorption from the action of taurine as part of bile. Preterm infants supplemented with taurine also may exhibit improved fat absorption.



Knowledge Check

1. Name two minerals with a connection to sulfur-containing amino acids.
2. Describe carnitine's role in the metabolism of fatty acids for energy.
3. List 2 functions of taurine.

CASE STUDY FOLLOW-UP



Suzanne and Ted should remember that spina bifida is caused by a failure of the spinal cord to close during the first 28 days of pregnancy, a time when neither Ted nor Suzanne may realize that Suzanne is pregnant. The B-vitamin folate must be available

at the time of conception to prevent spina bifida and other birth defects. The fact that a close relative of Suzanne's has already produced a child with this birth defect should be a warning sign. Suzanne and Ted would be wise to seek the advice of a registered dietitian to ensure that Suzanne's prepregnancy diet provides enough synthetic folic acid.

Summary

- 13.1** The B-vitamins function as coenzymes; these organic coenzymes are one type of cofactor. Minerals, such as magnesium and manganese, also function as a type of cofactor. Through cofactor functions, B-vitamins and minerals have critical roles in energy and amino acid metabolic pathways.
- 13.2** Thiamin in its functional form as TPP serves as a coenzyme in energy release. Thiamin deficiency results in the disease beriberi. In North America, alcoholics are at risk of thiamin deficiency. Pork, pork products, and enriched grains are reliable sources of thiamin.
- 13.3** Riboflavin coenzymes, FAD and FMN, participate in a wide variety of oxidation-reduction reactions, including those in numerous metabolic pathways that produce energy. A specific riboflavin deficiency is unlikely but can accompany other B-vitamin deficiencies. Dairy products and enriched grains are good dietary sources.
- 13.4** Niacin as NAD^+ and NADP^+ are coenzymes. NAD^+ is important in oxidation-reduction reactions in energy-yielding pathways. A deficiency of the vitamin produces the disease pellagra, which is seen most often in corn-based diets. Alcoholism can lead to a deficiency. Food sources of niacin are enriched cereal grains and protein foods. The body is able to synthesize the vitamin from the amino acid tryptophan. The nicotinic form of niacin is used as a medication to improve blood lipids. The UL for niacin is based on the flushing seen with high doses.
- 13.5** Among its functions, pantothenic acid in coenzyme form (CoA) shuttles 2 carbon fragments from the metabolism of glucose, amino acids, fatty acids, and alcohol into the citric acid cycle during energy metabolism. A deficiency of pantothenic acid is unlikely because it is widely distributed in foods.
- 13.6** Biotin functions as a cofactor in enzymes that add carbon dioxide to a substance. These enzymes are required for the metabolism of macronutrients. Biotin is widely distributed in foods. Intestinal bacteria also synthesize biotin. No deficiency exists in healthy people.
- 13.7** The functions of chromium are not fully known. Chromium may be involved in carbohydrate metabolism. Chromium is widely distributed in a variety of foods. Chromium deficiency and toxicity have not been well documented in humans.
- 13.8** The vitamin B-6 coenzyme PLP participates in amino acid metabolism, especially the synthesis of nonessential amino acids, and in the breakdown of glycogen. It is essential in the synthesis of heme in hemoglobin, the formation of certain

- neurotransmitters, and the metabolism of homocysteine. Anemia, convulsions, and decreased immune response are symptoms of a deficiency, although deficiency is rare. Animal protein foods, a few fruits and vegetables, and whole-grain cereals are good sources of this vitamin. One of the toxic effects of excess consumption is nerve damage.
- 13.9** Folate in its many coenzyme forms (tetrahydrofolic acid; THFA) functions in metabolic pathways that require the exchange of single carbon groups. THFA is important in amino acid metabolism. The most notable function performed by folate is DNA synthesis. It also participates in homocysteine metabolism. A dietary lack of this vitamin produces megaloblastic anemia and increases the risk of spina bifida. Deficiency is common among alcoholics. Folate is found in green vegetables, legumes, liver, and fortified cereal grains.
- 13.10** Vitamin B-12 in its coenzyme form transfers 1-carbon groups needed for normal amino acid metabolism. Because of its interaction with folate, a deficiency of vitamin B-12 results in the same type of megaloblastic anemia, as well as excess homocysteine in the blood. Defective absorption of vitamin B-12 is the cause of the deficiency disease pernicious anemia. In such cases, injection of the vitamin or another pharmacological approach is necessary. Vitamin B-12 is found in animal foods, but not in plant foods. Vegans need to look for foods fortified with the vitamin or take it as part of a multivitamin and mineral supplement.
- 13.11** Manganese functions as a cofactor for enzymes in nitrogen, carbohydrate, and cholesterol metabolism and has a role in the antioxidant defense system. Manganese is found in whole grains, nuts, legumes, and tea. Manganese deficiency and toxicity rarely have been reported in humans.
- 13.12** Molybdenum is a cofactor required for the activity of several enzymes involved in amino acid and nitrogen reactions. The best dietary sources of molybdenum are legumes, grains, and nuts. Reports of molybdenum deficiency and toxicity are very rare.
- 13.13** Choline provides methyl groups required in many reactions in the body. It is needed for the formation of the neurotransmitter acetylcholine and is incorporated into phospholipids. Eggs, meat, milk, and fish are good sources of choline, but it also is found in other foods and is synthesized in the body. Individuals fed choline-deficient diets may develop liver and muscle damage; however, choline deficiency is rare.
- 13.14** Iodine is an essential part of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) and thus plays a role in many metabolic and developmental functions in the body. The iodine content of the soil in which a plant was grown determines the iodine content of the plant food. The iodine content of most foods is low; thus, many populations obtain iodine from iodized salt. Iodine fortification programs have eradicated endemic iodine deficiency in these areas. In countries where foods fortified with iodine are not available, iodine deficiency is a serious health concern. Iodine deficiency results in enlargement of the thyroid gland (goiter) and severe growth and mental impairment (cretinism).
- 13.15** Sulfur is incorporated into certain amino acids and vitamins; it is a component of the cozymes of thiamin, pantothenic acid, and biotin. Its ability to bond with other sulfur atoms enables it to stabilize protein structure. There is no AI, RDA, or UL established for sulfur. Carnitine assists with energy metabolism by transporting fatty acids into mitochondria for energy release. Taurine is involved with insulin activity. Although participating in many important biochemical reactions in the body, carnitine and taurine are not true vitamins because they can be synthesized in the body from readily available precursors. In some medical circumstances, dietary intake may be needed to augment cellular production.

Study Questions

- Thiamin pyrophosphate, TPP, is required for _____.
 - protein synthesis
 - fatty acid synthesis
 - carbohydrate metabolism
 - DNA synthesis
- Thiamin deficiency can be found among _____.
 - heavy users of alcohol
 - poor people in developing countries reliant on white rice as a staple food
 - poor people in developing countries reliant on corn as a staple food
 - both a and b
 - both a and c
- Which of the following water-soluble vitamins participate in oxidation-reduction reactions?
 - thiamin and riboflavin
 - thiamin and vitamin B-6
 - pantothenic acid and niacin
 - riboflavin and niacin
- An alcoholic who consumes no dairy products is most at risk of developing _____ deficiency.
 - choline
 - vitamin B-6
 - riboflavin
 - thiamin
- Niacin can be synthesized in cells from _____.
 - riboflavin
 - fatty acids
 - glucose
 - tryptophan



Take Action

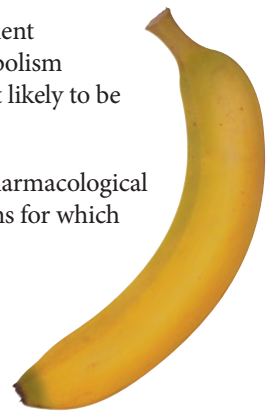
Spotting Fraudulent Claims for Vitamins and Vitamin-like Substances

Using your favorite search engine, search terms such as *energy boost*, *stress*, *mental acuity*, and *disease prevention*, along with *vitamin supplement*. Identify several claims for vitamin supplements that you consider fraudulent or misleading.

1. What is the cost of these supplements?
2. How do the amounts of vitamins they contain compare with the DRIs?
3. What compounds are included that are not considered essential nutrients?
4. What disclaimers or warnings are made about the products?
5. How likely is the supplement to improve a person's health?



6. Deficiencies of _____ and _____ are extremely rare.
 - a. biotin; pantothenic acid
 - b. biotin; niacin
 - c. riboflavin; niacin
 - d. thiamin; niacin
7. Transamination reactions allow the formation of nonessential amino acids. Which vitamin is required for these reactions?
 - a. thiamin
 - b. niacin
 - c. riboflavin
 - d. vitamin B-6
8. Good sources of folate include _____.
 - a. lentils, spinach, asparagus, and fortified foods
 - b. papayas, limes, oranges, and potatoes
 - c. dairy products, fortified foods, and nuts
 - d. tuna, chicken, beef, and dairy products
9. Folate functions in DNA synthesis and amino acid metabolism.
 - a. true
 - b. false
10. Macrocytic anemia, peripheral neuropathy, and impaired cognitive function are signs of _____ deficiency.
 - a. ascorbic acid
 - b. niacin
 - c. vitamin B-12
 - d. vitamin B-6
11. Sources of vitamin B-12 include _____.
 - a. whole grains, tuna, and eggs
 - b. dairy products, meat, and fish
 - c. citrus fruits, papayas, and bananas
 - d. dairy products, whole grains, and leafy, green vegetables
12. Manganese is a cofactor for metabolic enzymes.
 - a. true
 - b. false
13. Which of the following is a function of iodine?
 - a. acts as a component of superoxide dismutase enzyme
 - b. aids in thyroid hormone metabolism
 - c. functions in antioxidant defense
 - d. enhances insulin activity
14. Which of the following is associated with the development of cretinism?
 - a. iron deficiency
 - b. zinc deficiency
 - c. iodine deficiency
 - d. selenium deficiency
15. Protein-rich foods are the main source of the mineral sulfur in our diets.
 - a. true
 - b. false
16. Define and explain the term *coenzyme*.
17. Draw a map of the metabolic pathways and identify where micronutrients participate in energy metabolism.
18. What are the main functions of chromium?
19. Describe the role of vitamin B-6 in amino acid reactions.
20. Draw MyPlate and place each micronutrient involved in energy and amino acid metabolism into the food groups where they are most likely to be found.
21. Name vitamins that have been used as pharmacological agents and identify the medical conditions for which they have been used as therapy.
22. What are the functions of taurine and carnitine? Why are they not considered vitamins?



Answer Key: 1-c; 2-d; 3-d; 4-c; 5-d; 6-a; 7-d; 8-a; 9-a; 10-c; 11-b; 12-
to Sections 13.2 to 13.15; 21-refer to Sections 13.4 and 13.8; 22-refer
to Sections 13.2 to 13.15; 18-refer to Section 13.7; 19-refer to Section 13.8; 20-refer
a; 13-b; 14-c; 15-a; 16-refer to Section 13.1; 17-refer to Sections 13.2
to Section 13.15



Websites

To learn more about the topics covered in this chapter, visit these websites.

Energy and Amino Acid Metabolism Nutrients

www.hsph.harvard.edu/nutritionsource/vitamins.html

www.fda.gov/ForConsumers

lpi.oregonstate.edu/infocenter/

ods.od.nih.gov

www.nlm.nih.gov/medlineplus/medlineplus.html

Beriberi

emedicine.medscape.com/article/116930-overview

nobelprize.org/educational/medicine/vitamin_b1/eijkman.html

Pellagra

history.nih.gov/exhibits/Goldberger

Pernicious Anemia

www.nhlbi.nih.gov/health/dci/Diseases/prnanmia/prnanmia_what.html

emedicine.medscape.com/article/204930-overview

Neural Tube Defects

www.sbaa.org

www.marchofdimes.com

Iodine Deficiency Disorders

www.who.int/nutrition/topics/idd/en/index.html

Micronutrient Initiative

www.micronutrient.org

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