Chapter 27— Principles of Nutrition I: Macronutrients

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27.1— Overview

Nutrition is best defined as the utilization of foods by living organisms. Since the process of food utilization is biochemical, the major thrust of the next two chapters is a discussion of basic nutritional concepts in biochemical terms. Simply understanding basic nutritional concepts is no longer sufficient. Nutrition attracts more than its share of controversy in our society, and a thorough understanding of nutrition almost demands an understanding of the issues behind these controversies. These chapters also explore the biochemical basis for some of the most important nutritional controversies.

Study of human nutrition can be divided into three areas: undernutrition, overnutrition, and ideal nutrition. **Undernutrition** is not a primary concern in this country because nutritional deficiency diseases are now quite rare. **Overnutrition** is a particularly serious problem in developed countries. Current estimates suggest that between 15% and 30% of the U.S. population is obese, and obesity is known to have a number of serious health consequences. Finally, there is increasing interest today in the concept of ideal or **optimal nutrition.** This is a concept that has meaning only in an affluent society. Only when food supply becomes abundant enough so that deficiency diseases are a rarity does it become possible to consider long-range effects of nutrients on health. This is probably the most exciting area of nutrition today.

27.2— Energy Metabolism

Energy Content of Food Is Measured in Kilocalories

You should be well acquainted with the energy requirements of the body. Much of the food we eat is converted to ATP and other high-energy compounds, which are utilized to drive biosynthetic pathways, generate nerve impulses, and power muscle contraction. We generally describe the energy content of foods in terms of **calories.** Technically speaking, we are actually referring to **kilocalories** of heat energy released by combustion of that food in the body. Some nutritionists prefer the term kilojoule (a measure of mechanical energy), but since the American public is likely to be counting calories rather than joules in the foreseeable future, we will restrict ourselves to that term. Caloric values of protein, fat, carbohydrate, and alcohol are roughly 4, 9, 4, and 7 kcal g^{-1}, respectively. Given these data and the composition of the food, it is simple to calculate the caloric content (input) of the foods we eat. Calculating caloric content of foods does not appear to be a major problem in this country. Millions of Americans are able to do it with ease. The problem lies in balancing caloric input with caloric output. Where do these calories go?

Energy Expenditure Is Influenced by Four Factors

There are four principal factors that affect individual energy expenditure: surface area (which is related to height and weight), age, sex, and activity level. (1) The effects of surface area are thought to be simply related to the rate of heat loss by the body—the greater the surface area, the greater the rate of heat loss. While it may seem surprising, a lean individual actually has a greater surface area, and thus a greater energy requirement, than an obese individual of the same weight. (2) Age may reflect two factors: growth and lean muscle mass. In infants and children more energy expenditure is required for rapid growth, and this is reflected in a higher **basal metabolic rate** (rate of energy utilization in resting state). In adults (even lean adults), muscle tissue is gradually replaced with fat and water during the aging process, resulting in a 2% decrease

in basal metabolic rate (BMR) per decade of adult life. (3) As for sex, women tend to have a lower BMR than men due to a smaller percentage of lean muscle mass and the effects of female hormones on metabolism. (4) The effect of activity levels on energy requirements is obvious. However, most of us overemphasize the immediate, as opposed to the long-term, effects of exercise. For example, one would need to jog for over an hour to burn up the calories found in one piece of apple pie.

Yet, the effect of a regular **exercise** program on energy expenditure can be quite beneficial. Regular exercise increases lean muscle mass, which has a higher basal metabolic rate than adipose tissue, allowing one to burn up calories more rapidly 24 hours a day. A regular exercise program should be designed to increase lean muscle mass and should be repeated 3–5 days a week but need not be aerobic exercise to have an effect on basal metabolic rate. For an elderly or infirm individual, even daily walking may, with time, help to increase basal metabolic rate slightly.

Hormone levels are important also, since thyroxine, sex hormones, growth hormone, and, to a lesser extent, epinephrine and cortisol increase BMR. The effects of epinephrine and cortisol probably explain in part why severe stress and major trauma significantly increase energy requirements. Finally, energy intake itself has an inverse relationship to expenditure in that during periods of **starvation** or semistarvation BMR can decrease up to 50%. This is of great survival value in cases of genuine starvation, but not much help to the person who wishes to lose weight on a calorie-restricted diet.

27.3— Protein Metabolism

Dietary Protein Serves Many Roles Including Energy Production

Protein carries a certain mystique as a "body-building" food. While it is true that protein is an essential structural component of all cells, protein is equally important for maintaining the output of essential secretions such as digestive enzymes and peptide or protein hormones. Protein is also needed to synthesize plasma proteins, which are essential for maintaining osmotic balance, transporting substances through the blood, and maintaining immunity. However, the average adult in this country consumes far more protein than needed to carry out these essential functions. Excess protein is treated as a source of energy, with the glucogenic amino acids being converted to glucose and the ketogenic amino acids converted to fatty acids and keto acids. Both kinds of **amino acids** will eventually be converted to triacylglycerol in adipose tissue if fat and carbohydrate supplies are already adequate to meet energy requirements. Thus for most of us the only body-building obtained from high-protein diets is in adipose tissue.

It has always been popular to say that the body has no storage depot for protein, and thus adequate dietary protein must be supplied with every meal. However, in actuality, this is not quite accurate. While there is no separate class of "storage" protein, there is a certain percentage of body protein that undergoes a constant process of breakdown and resynthesis. In the fasting state the breakdown of this store of body protein is enhanced, and the resulting amino acids are utilized for glucose production, synthesis of nonprotein nitrogenous compounds, and synthesis of the essential secretory and plasma proteins described above (see also Chapter 14). Even in the fed state, some of these amino acids are utilized for energy production and as biosynthetic precursors. Thus the turnover of body protein is a normal process—and an essential feature of what is called nitrogen balance.

Nitrogen Balance Relates Intake of Nitrogen to Its Excretion

Nitrogen balance (Figure 27.1) is a comparison between intake of nitrogen (chiefly in the form of protein) and excretion of nitrogen (chiefly in the form of undigested protein in the feces and urea and ammonia in urine). A normal adult is in nitrogen equilibrium, with losses just balanced by intake. Negative nitrogen balance results from inadequate dietary intake of protein, since amino acids utilized for energy and biosynthetic reactions are not replaced. It also occurs in injury when there is net destruction of tissue and in major trauma or illness when the body's adaptive response causes increased catabolism of body protein stores. Positive nitrogen balance is observed whenever there is a net increase in the body protein stores, such as in growing children, pregnant women, or convalescing adults.

Essential Amino Acids Must Be Present in the Diet

In addition to the amount of protein in the diet, several other factors must be considered. One is the complement of essential amino acids present in the diet. **Essential amino acids** are those amino acids that cannot be synthesized by the body (Chapter 11). If just one of these essential amino acids is missing from the diet, the body cannot synthesize new protein to replace the protein lost due to normal turnover, and a negative nitrogen balance results (Figure 27.1).

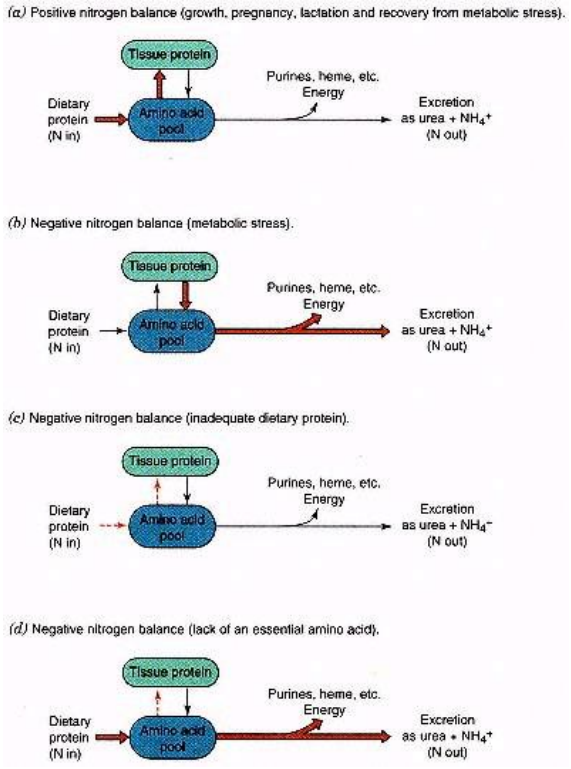

Figure 27.1
Factors affecting nitrogen balance.
Schematic representations of the metabolic interrelationship involved in determining nitrogen balance. Each figure represents the nitrogen balance resulting from a particular set of metabolic conditions. The dominant pathways in each situation are indicated by heavy red arrows.

Obviously then, the complement of essential amino acids in any dietary protein will determine how well it can be used by the body.

Generally, most animal proteins contain all essential amino acids in about the quantities needed by the human body. Vegetable proteins, on the other hand, often lack one or more essential amino acids and may, in some cases, be more difficult to digest. Even so, **vegetarian diets** can provide adequate protein provided enough extra protein is consumed to provide sufficient quantities of the essential amino acids and/or two or more different proteins are consumed together, which complement each other in amino acid content. For example, if corn (which is deficient in lysine) is combined with legumes (deficient in methionine but rich in lysine), the efficiency of utilization for the combination of the two vegetable proteins approaches that of animal protein. The adequacy of vegetarian diets with respect to protein and calories is discussed more fully in Clin. Corr. 27.1, and the need for high-quality protein in low-protein diets in renal disease is discussed in Clin. Corr. 27.2.

Protein Sparing Is Related to Dietary Content of Carbohydrate and Fat

Another factor that must be considered in determining protein requirements is dietary intake of fat and carbohydrate. If these components are present in insufficient quantities, some dietary protein must be used for energy generation and is unavailable for building and replacing tissue. Thus as energy (calorie) content of the diet from carbohydrate and fat increases, the need for protein decreases. This is referred to as **protein sparing.** Carbohydrate is somewhat more efficient at protein sparing than fat—presumably because carbohydrate can be used as an energy source by almost all tissues, whereas fat cannot.

Normal Adult Protein Requirements Depend on Diet

Assuming adequate calorie intake and 75% efficiency of utilization, which is typical of mixed protein in the average American diet, the **recommended**

CLINICAL CORRELATION 27.1

Vegetarian Diets and Protein–Energy Requirements

One of the most important problems of a purely vegetarian diet (as opposed to a lacto-ovo vegetarian diet) is the difficulty in obtaining sufficient calories and protein. Potential caloric deficit results from the fact that the caloric densities of fruits and vegetables are much less than the meats they replace (30–50 cal per 100 g versus 150–300 cal per 100 g). The protein problem is generally threefold: (1) most plant products contain much less protein (1–2 g of protein per 100 g versus 15–20 g per 100 g); (2) most plant protein is of low biological value; and (3) some plant proteins are incompletely digested. Actually, well-designed vegetarian diets usually provide enough calories and protein for the average adult. In fact, the reduced caloric intake may well be of benefit because strict vegetarians do tend to be lighter than their nonvegetarian counterparts.

However, whereas an adult male may require about 0.8 g of protein and 40 cal kg^{-1} of body weight, a young child may require 2–3 times that amount. Similarly, a pregnant woman needs an additional 10 g of protein and 300 cal day^{-1} and a lactating woman an extra 15 g of protein and 500 cal. Thus both young children and pregnant and lactating women run a risk of protein–energy malnutrition. Children of vegetarian mothers generally have a lower birth weight than children of mothers consuming a mixed diet. Similarly, vegetarian children generally have a slower rate of growth through the first 5 years, but generally catch up by age 10.

It is possible to provide sufficient calories and protein even for these high-risk groups provided the diet is adequately planned. Three principles should be followed to design a calorie–protein-sufficient vegetarian diet for young children: (1) whenever possible, include eggs and milk in the diet; they are both excellent sources of calories and high-quality protein; (2) include liberal amounts of those vegetable foods with high-caloric density in the diet, including nuts, grains, dried beans, and dried fruits; and (3) include liberal amounts of high-protein vegetable foods that have complementary amino acid patterns. It used to be thought that these complementary proteins must be present in the same meal. Recent animal studies, however, suggest that a meal low in (but not devoid of) an essential amino acid may be supplemented by adding the limiting amino acid at a subsequent meal.

First International Congress on Vegetarian Nutrition. *Proc. Am. J. Clin. Nutr.* 48(Suppl. 1):707, 1988; and Saunders, T. A. B. Vegetarian diets and children. *Pediatr. Nutr.,* 42:955, 1995.

CLINICAL CORRELATION 27.2

Low-Protein Diets and Renal Disease

Chronic renal failure is characterized by the buildup of the end products of protein catabolism, mainly urea. Some degree of dietary protein restriction is usually necessary because these toxic end products are responsible for many of the symptoms associated with renal failure. The amount of protein restriction is dependent on the severity of the disease. It is easy to maintain patients in nitrogen balance for prolonged periods on diets containing as little as 40 g of protein/day if the diet is calorically sufficient. Diets containing less than 40 g/day pose problems. Protein turnover continues and a balance must be found between enough protein to avoid negative nitrogen balance and little enough to avoid buildup of waste products.

The strategy employed in such diets is twofold: (1) provide a minimum of protein, primarily protein of high BV, and (2) provide the rest of the daily calories as carbohydrates and fats. The goal is to provide just enough essential amino acids to maintain positive nitrogen balance. In turn, the body should be able to synthesize the nonessential amino acids from other nitrogen-containing metabolites. Enough carbohydrate and fat are provided so that essentially all dietary protein can be spared from energy metabolism. With this type of diet, it is possible to maintain a patient on 20 g of protein per day for considerable periods. Because of the difficulty in maintaining nitrogen equilibrium at such low-protein intakes, the patient's protein status should be monitored. This can be done by measuring parameters such as serum albumin and transferrin.

Moreover, such diets are extremely monotonous and difficult to follow. A typical 20-g protein diet is shown below:

1. One egg plus 3/4 cup milk or 1 additional egg or 1 oz of meat.

2. One-half pound of deglutenized (low-protein) wheat bread; all other breads and cereals must be avoided—this includes almost all baked goods.

3. A limited amount of low-protein, low-potassium fruits and vegetables.

4. Sugars and fats to make up the rest of the needed calories; however, cakes, pies, and cookies need to be avoided.

The palatability of these diets can be improved considerably by starting with a vegan diet and supplementing it with a mixture of essential amino acids and ketoacid analogs of the essential amino acids. Recent studies indicate that this technique will help preserve renal function and allow a somewhat greater variety of foods.

Goodship, T. H. J., and Mitch, W. E. Nutritional approaches to preserving renal function. *Adv. Intern. Med.* 33:377, 1988; Dwyer, J. Vegetarian diets for treating nephrotic syndrome. *Nutr. Rev.* 51:44, 1993; and Barsotti, G., Morrell, E., Cupisti, A., Bertoncini, P., and Giovannetti, S. A special supplemented "vegan" diet for nephrotic patients. *Am. J. Nephrol.* 11:380, 1991.

protein intake is 0.8 g/kg^{-1} (body weight) day^{-}. This amounts to about 58 g protein day^{-1} for a 72-kg (160-lb) man and about 44 g day^{-1} for a 55-kg (120-lb) woman. These recommendations would need to be increased on a vegetarian diet if overall efficiency of utilization were less than 75%.

Protein Requirement Increases during Growth and Recovery from Illness

Because dietary protein is essential for synthesis of new body tissue, as well as for maintenance and repair, the need for protein increases markedly during periods of rapid growth. Such growth occurs during pregnancy, infancy, childhood, and adolescence.

Once growth requirements have been considered, age does not seem to have much effect on protein requirements. If anything, the protein requirement may decrease slightly with age. However, older people need and generally consume less calories, so high-quality protein should provide a larger percentage of their total calories. Furthermore, some older people may have special protein requirements due to malabsorption problems.

Illness, major trauma, and surgery all cause a major **catabolic response.** Energy needs are very large, and the body responds by increasing production of glucagon, glucocorticoids, epinephrine, and certain cytokines. In these situations breakdown of body protein is greatly accelerated and a negative nitrogen balance results unless protein intake is increased (Figure 27.1). Although this increased protein requirement is of little significance in short-term illness, it can be vitally important in the recovery of hospitalized patients as discussed in the next section (see also Clin. Corr. 27.3).

CLINICAL CORRELATION 27.3

Providing Adequate Protein and Calories for the Hospitalized Patient

The normal metabolic response to infection, trauma, and surgery is a complex and carefully balanced catabolic state. As discussed in the text, epinephrine, glucagon, cortisol, and cytokines are released, greatly accelerating the rates of lipolysis, proteolysis, and gluconeogenesis. The net result is an increased supply of fatty acids, amino acids, and glucose to meet the increased energy demands of such major stress. The high serum, glucose results in elevation of circulating insulin levels, which is more than counter-balanced by increased levels of epinephrine and other hormones. Skeletal muscle, for example, uses very little of the serum glucose but continues to rely on free fatty acids and its own catabolized protein as a primary source of energy. It also continues to export amino acids, primarily alanine, for use elsewhere in the body, resulting in a very rapid depletion of body protein stores.

A highly catabolic hospitalized patient may require 35–45 kcal kg^{-1} day^{-1} and 2–3 g of protein kg^{-1} day^{-1}. A patient with severe burns may require even more. A physician has a number of options available to provide this postoperative patient with sufficient calories and protein to ensure optimal recovery. When the patient is simply unable to ingest enough food, it may be adequate to supplement the diet with high-calorie–high-protein preparations, which are usually mixtures of homogenized cornstarch, egg, milk protein, and flavorings. When the patient is unable to ingest solid food or unable to digest complex mixtures of foods adequately, elemental diets are usually administered via a nasogastric tube. Elemental diets consist of small peptides or purified amino acids, glucose and dextrins, some fat, vitamins, and electrolytes. These diets are sometimes sufficient to meet most of the short-term caloric and protein needs of a moderately catabolic patient. When a patient is severely catabolic or unable to digest and absorb foods normally, parenteral (intravenous) nutrition is necessary. The least invasive method is to use a peripheral, slow-flow vein in a manner similar to any other i.v. infusion. The main limitation of this method is hypertonicity. However, a solution of 5% glucose and 4.25% purified amino acids can be used safely. This solution will usually provide enough protein to maintain positive nitrogen balance but will rarely provide enough calories for long-term maintenance of a catabolic patient.

The most aggressive nutritional therapy is total parenteral nutrition. Usually an indwelling catheter is inserted into a large fast-flow vessel such as the superior vena cava, so that the very hypertonic infusion fluid can rapidly be diluted. This allows solutions of up to 60% glucose and 4.25% amino acids to be used, providing sufficient protein and most of the calories for long-term maintenance. Intravenous lipid infusion is often added to boost calories and provide essential fatty acids. All of these methods can prevent or minimize the negative nitrogen balance associated with surgery and trauma. The actual choice of method depends on the patient's condition. As a general rule it is preferable to use the least invasive technique.

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27.4— Protein–Energy Malnutrition

The most common form of malnutrition in the world is **protein–energy malnutrition (PEM).** In developing countries inadequate intake of protein and energy is all too common, and it is usually the infants and young children who suffer most. While the symptoms of protein–energy insufficiency vary widely from case to case, it is common to classify most cases as either marasmus or kwashiorkor. **Marasmus** is usually defined as inadequate intake of both protein and energy. **Kwashiorkor** is defined as inadequate intake of protein with adequate energy intake. Often the diets associated with marasmus and kwashiorkor may be similar, with the kwashiorkor being precipitated by conditions of increased protein demand such as infection. The marasmic infant will have a thin, wasted appearance and will be small for his/her age. If PEM continues long enough the child will be permanently stunted in both physical and mental development. In kwashiorkor the child will often have a deceptively plump appearance due to edema. Other telltale symptoms associated with kwashiorkor are dry, brittle hair, diarrhea, dermatitis of various forms, and retarded growth. Perhaps the most devastating result of both marasmus and kwashiorkor is reduced ability of the afflicted individuals to fight off infection. They have a reduced number of T lymphocytes (and thus diminished cell-mediated immune response) as well as defects in the generation of phagocytic cells and production of immuno-globulins, interferon, and other components of the immune system. Many of

these individuals die from secondary infections, rather than from the starvation itself.

The most common form of PEM seen in the United States occurs in the hospital setting. A typical course of events is as follows: The patient has not been eating well for several weeks or months prior to entering the hospital due to chronic or debilitating illness. He/she enters the hospital with major trauma, severe infection, or for major surgery, all of which cause a large negative nitrogen balance. This is often compounded by difficulties in feeding the patient or by the necessity of fasting in preparation for surgery or diagnostic tests. The net result is PEM as measured by low levels of serum albumin and other serum proteins or by decreased cellular immunity tests. Recent studies have shown that hospitalized patients with demonstrable PEM have delayed wound healing, decreased resistance to infection, increased mortality, and increased length of hospitalization. Most major hospitals have programs to monitor the nutritional status of their patients and to intervene where necessary to maintain a positive nitrogen and energy balance (see Clin. Corr. 27.3).

27.5— Excess Protein–Energy Intake

Much has been said in recent years about the large amount of protein that the average American consumes. Certainly most consume far more than needed to maintain positive nitrogen balance. An average American currently consumes 99 g of protein, 68% from animal sources. However, most studies show that a healthy adult can consume that amount of protein with no apparent harm. Concern has been raised about possible effects of high-protein intake on calcium requirements. Some studies suggest that high-protein intake increases urinary loss of calcium and may accelerate bone demineralization associated with aging. However, this issue is far from settled.

Obesity Has Dietary and Genetic Components

Perhaps the more serious nutritional problem is excessive energy consumption. In fact, **obesity** is the most frequent nutritional disorder in the United States. It would, however, be unfair to label obesity as simply a problem of excess consumption. Overeating plays an important role in many individuals, as does inadequate exercise, but there is also a strong genetic component as well. While the biochemical mechanisms for this genetic predisposition are unclear, investigators have recently identified an obesity gene in mice that appears to regulate obesity through effects on both appetite and deposition of fat. A similar gene exists in humans, but its metabolic function is still not known (see p. 378). Detailed characterization of this and other genes that predispose to obesity in animals may yield valuable clues to the causes and treatment of obesity in humans.

Metabolic Consequences of Obesity Have Significant Health Implications

A discussion of the treatment of obesity is clearly beyond the scope of this chapter, but it is worthwhile to consider some of the metabolic consequences of obesity. One striking clinical feature of overweight individuals is a marked elevation of serum free fatty acids, cholesterol, and triacylglycerols irrespective of the dietary intake of fat. Why is this? Obesity is obviously associated with an increased number and/or size of adipose cells. These cells contain fewer **Insulin receptors** and thus respond more poorly to insulin, resulting in increased activity of the **hormone-sensitive lipase.** The increased lipase activity

along with the increased mass of adipose tissue is probably sufficient to explain the increase in circulating **free fatty acids.** These excess fatty acids are carried to the liver and metabolized to acetyl CoA, a precursor for triacylglycerol and cholesterol synthesis. Excess triacylglycerol and cholesterol are released as **very low density lipoprotein particles,** leading to higher circulating levels of both triacylglycerol and cholesterol (see Chapters 9 and 10).

A second striking finding in obese individuals is higher fasting blood sugar levels and decreased glucose tolerance. Fully 80% of **adult-onset diabetics** are overweight. Again the culprit appears to be the decrease in insulin receptors, since many adult-onset diabetics have higher than normal insulin levels. This hyperinsulinemia appears to stimulate the sympathetic nervous system, leading to sodium and water retention and vasoconstriction, which tend to increase blood pressure. Because of these metabolic changes, obesity is a primary risk factor in coronary heart disease, hypertension, and diabetes. This is nutritionally significant because all of these metabolic changes are reversible. Quite often reduction to ideal weight is the single most important aim of nutritional therapy. Furthermore, when the individual is at ideal body weight, the composition of the diet becomes a less important consideration in maintaining normal serum lipid and glucose levels.

Any discussion of weight reduction regimens should include a mention of one other metabolic consequence of obesity. As discussed above, obesity can lead to increased retention of both sodium and water. As the fat stores are metabolized, they produce water (which is denser than the fat), and the water may largely be retained. In fact, some individuals may actually observe short-term weight gain on certain diets, even though the diet is working perfectly well in terms of breaking down their adipose tissue. This metabolic fact of life can be psychologically devastating to dieters, who expect quick results for all their sacrifice.

27.6— Carbohydrates

The chief metabolic role of carbohydrates in the diet is for energy production. Any carbohydrate in excess of that needed for energy is converted to glycogen and triacylglycerol for long-term storage. The body can adapt to a wide range of carbohydrate levels in the diet. Diets high in carbohydrate result in higher steady-state levels of glucokinase and some of the enzymes involved in the hexose monophosphate shunt and triacylglycerol synthesis. Diets low in carbohydrate result in higher steady-state levels of some of the enzymes involved in gluconeogenesis, fatty acid oxidation, and amino acid catabolism. **Glycogen stores** are also affected by the carbohydrate content of the diet (see Clin. Corr. 27.4).

The most common nutritional problems involving carbohydrates are seen in those individuals with various **carbohydrate intolerances.** The most common form of carbohydrate intolerance is **diabetes mellitus,** caused either by lack of insulin production or lack of insulin receptors. This causes an intolerance to glucose and sugars that can readily be converted to glucose. Dietary treatment of diabetes is discussed in Clinical Correlation 27.5. **Lactase insufficiency** is also a common disorder of carbohydrate metabolism affecting over 30 million people in the United States alone. It is most prevalent among blacks, Asians, and Hispanics. Without the enzyme lactase, the lactose is not significantly hydrolyzed or absorbed. It remains in the intestine where it acts osmotically to draw water into the gut and serves as a substrate for conversion to lactic acid, CO_2, and H_2S by intestinal bacteria. The end result is bloating, flatulence, and diarrhea—all of which can be avoided simply by eliminating milk and milk products from the diet (see p. 1075).

CLINICAL CORRELATION 27.4

Carbohydrate Loading and Athletic Endurance

The practice of carbohydrate loading dates back to observations made in the early 1960s that endurance during vigorous exercise was limited primarily by muscle glycogen stores. Of course, the glycogen stores are not the sole energy source for muscle. Free fatty acids are present in the blood during vigorous exercise and are utilized by muscle along with the glycogen stores. Once the glycogen stores have been exhausted, however, muscle cannot rely entirely on free fatty acids without tiring rapidly. This is probably related to the fact that muscle becomes partially anaerobic during vigorous exercise. While glycogen stores are utilized equally well aerobically or anaerobically, fatty acids can only be utilized aerobically. Under those conditions, fatty acids cannot provide ATP rapidly enough to serve as the sole energy source.

Thus the practice of carbohydrate loading to increase glycogen stores was devised for track and other endurance athletes. Originally, it was thought that it would be necessary to trick the body into increasing glycogen stores. The original carbohydrate loading regimen consisted of a 3–4-day period of heavy exercise while on a low-carbohydrate diet, followed by 1–2 days of light exercise while on a high-carbohydrate diet. The initial low-carbohydrate–high-energy demand period caused a depletion of muscle glycogen stores. Apparently, the subsequent change to a high-carbohydrate diet resulted in a slight rebound effect, with the production of higher than normal levels of insulin and growth hormone. Under these conditions glycogen storage was favored and glycogen stores reached almost twice the normal amounts. This practice did increase endurance significantly. In one study, test subjects on a high-fat and high-protein diet had less than 1.6 g of glycogen per 100 g of muscle and could perform a standardized workload for only 60 min. When the same subjects then consumed a high-carbohydrate diet for 3 days, their glycogen stores increased to 4 g per 100 g of muscle and the same workload could be performed for up to 4 h.

While the technique clearly worked, the athletes often felt lethargic and irritable during the low-carbohydrate phase of the regimen, and the high-fat diet ran counter to current health recommendations. Fortunately, recent studies show that regular consumption of a high complex-carbohydrate–low-fat diet during training increases glycogen stores without the need for tricking the body with sudden dietary changes. Current recommendations are for endurance athletes to consume a high-carbohydrate diet (with emphasis on complex carbohydrates) during training. Then carbohydrate intake is increased further (to 70% of calories) and exercise tapered off during the 2–3 days just prior to an athletic event. This procedure increases muscle glycogen stores to levels comparable to the original carbohydrate loading regimen.

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CLINICAL CORRELATION 27.5

High-Carbohydrate Versus High-Fat Diets for Diabetics

For years the American Diabetes Association has recommended diets that were low in fat and high in complex carbohydrates and fiber for diabetics. The logic of such a recommendation seemed to be inescapable. Diabetics are prone to hyperlipidemia with attendant risk of heart disease, and low-fat diets appeared likely to reduce risk of hyperlipidemia and heart disease. In addition, numerous clinical studies had suggested that the high-fiber content of these diets resulted in improved control of blood sugar. This recommendation has proved to be controversial. An understanding of the controversies involved illustrates the difficulties in making dietary recommendations for population groups rather than individuals. In the first place, it is very difficult to make any major changes in dietary composition without changing other components of the diet. In fact, most of the clinical trials of the high-carbohydrate–high-fiber diets have resulted in significant weight reduction, either by design or because of the lower caloric density of the diet. Since weight reduction improves diabetic control, it is not entirely clear whether the improvements seen in the treated group were due to the change in diet composition *per se* or because of the weight loss. Second, there is significant individual variation in how diabetics respond to these diets. Many diabetic patients appear to show poorer control (as evidenced by higher blood glucose levels, elevated VLDL and/or LDL levels, and reduced HDL levels) on the high-carbohydrate–high-fiber diets than they do on diets high in monounsaturated fatty acids. However, diets high in monounsaturated fatty acids tend to have higher caloric density and are inappropriate for overweight individuals with type 2 (non-insulin dependent) diabetes. Thus a single diet may not be equally appropriate for all diabetics. Even the "glycemic index" concept (Table 27.2) may also turn out to be difficult to apply to the diabetic population as a whole, because of individual variation. Thus in 1994 the American Diabetes Association abandoned the concept of a single diabetic diet. Instead, their recommendations focus on achievement of glucose, lipid, and blood pressure goals, with weight reduction and dietary recommendations based on individual preferences and what works best to achieve metabolic control in that individual.

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27.7— Fats

Triacylglycerols, or fats, are directly utilized by many tissues of the body as an energy source and, as phospholipids, are an important part of membrane structure. Excess fat in the diet can only be stored as triacylglycerol. As with carbohydrate, the body adapts to a wide range of fat intakes. However, problems develop at the extremes (either high or low) of fat consumption. At the low end, **essential fatty acid (EFA)** deficiencies may become a problem. The fatty acids linoleic, linolenic, and arachidonic acid cannot be made by the body and thus are essential components of the diet. These EFAs are needed for maintaining the function and integrity of membrane structure, for fat metabolism and transport, and for synthesis of **prostaglandins.** The most characteristic symptom of essential fatty acid deficiency is a scaly dermatitis. EFA deficiency is very rare in the United States, occurring primarily in low-birth-weight infants fed artificial formulas lacking EFA and in hospitalized patients maintained on total parenteral nutrition for long periods of time. At the high end of the scale, there is concern that excess dietary fat causes elevation of serum lipids and thus an increased risk of heart disease. Recent studies also suggest that high-fat intakes are associated with increased risk of colon, breast, and prostate cancer, but it is not yet certain whether the cancer risk is associated with fat intake *per se* or with the excess calories associated with a high-fat diet. To the extent that fat intake is associated with cancer risk, animal studies suggest that polyunsaturated fatty acids of the **ω**-6 series may be more tumorigenic than other unsaturated fatty acids. The reason for this is not known, but it has been suggested that prostaglandins derived from the **ω**-6 fatty acids may stimulate tumor progression.

27.8— Fiber

Dietary fiber is defined as those components of food that cannot be broken down by human digestive enzymes. It is incorrect, however, to assume that fiber is indigestible since some fibers are, in fact, at least partially broken down by intestinal bacteria. Knowledge of the role of fiber in human metabolism has expanded significantly in the past decade. Our current understanding of the metabolic roles of dietary fiber is based on three important observations: (1) there are several different types of dietary fiber, (2) they each have different chemical and physical properties, and (3) they each have different effects on human metabolism, which can be understood, in part, from their unique properties.

The major types of fiber and their properties are summarized in Table 27.1. **Cellulose** and most **hemicelluloses** increase stool bulk and decrease transit time. These are the types of fiber that should most properly be associated with the effects of fiber on regularity. They decrease intracolonic pressure and appear to play a beneficial role with respect to diverticular diseases. By diluting out potential carcinogens and speeding their transit through the colon, they may also play a role in reducing the risk of colon cancer. **Lignins** have a slightly different role. In addition to their bulk-enhancing properties, they adsorb organic substances such as cholesterol and appear to have a cholesterol-lowering effect. **Mucilaginous fibers,** such as pectin and gums, tend to form viscous gels in the stomach and intestine and slow the rate of gastric emptying, thus slowing the rate of absorption of many nutrients. The most important clinical role of these fibers is to slow the rate at which carbohydrates are digested and absorbed. Thus both the rise in blood sugar and the subsequent rise in insulin levels are significantly decreased if these fibers are ingested along with carbohydrate-containing foods. **Water-soluble fibers** (pectins, gums, some hemicelluloses, and storage polysaccharides) also help to lower serum cholesterol levels in most people. Whether this is due to their effect on insulin levels (insulin

TABLE 27.1 Major Types of Fiber and Their Properties

Type of Fiber	*Major Source in Diet*	*Chemical Properties*	*Physiological Effects*
Cellulose	Unrefined cereals	Nondigestible	Increases stool bulk
	Bran	Water insoluble	Decreases intestinal transit time
	Whole wheat	Absorbs water	Decreases intracolonic pressure
Hemicellulose	Unrefined cereals	Partially digestible	Increases stool bulk
	Some fruits and vegetables	Usually water insoluble	Decreases intestinal transit time
	Whole wheat	Absorbs water	Decreases intracolonic pressure
Lignin	Woody parts of vegetables	Nondigestible	Increases stool bulk
		Water insoluble	Bind cholesterol
		Absorbs organic substances	Bind carcinogens
Pectin	Fruits	Digestible	Decreases rate of gastric emptying
		Water soluble	Decreases rate of sugar uptake
		Mucilaginous	Decreases serum cholesterol
Gums	Dried beans	Digestible	Decreases rate of gastric emptying
	Oats	Water soluble	Decreases rate of sugar uptake
		Mucilaginous	Decreases serum cholesterol

stimulates cholesterol synthesis and export) or to other metabolic effects (perhaps caused by end products of partial bacterial digestion) is unknown. Vegetables, wheat, and most grain fibers are the best sources of the water-insoluble cellulose, hemicellulose, and lignin. Fruits, oats, and legumes are the best source of the water-soluble fibers. Obviously, a balanced diet should include food sources of both soluble and insoluble fiber.

27.9— Composition of Macronutrients in the Diet

From the foregoing discussion it is apparent that there are relatively few instances of macronutrient deficiencies in the American diet. Thus much of the interest in recent years has focused on whether there is an ideal diet composition consistent with good health. It would be easy to pass off such discussions as purely academic, yet our understanding of these issues could well be vital. Heart disease, stroke, and cancer kill many Americans each year, and if some experts are even partially correct, many of these deaths could be preventable with prudent diet.

Composition of the Diet Affects Serum Cholesterol

With respect to heart disease, the current discussion centers around two key issues: (1) Can serum cholesterol and triacylglycerol levels be controlled by diet? (2) Does lowering serum cholesterol and triacylglycerol levels protect against heart disease? The controversies centered around dietary control of cholesterol levels illustrate perfectly the trap one falls into by trying to look too closely at each individual component of the diet instead of the diet as a whole. For example, there are at least four dietary components that can be identified as having an effect on serum cholesterol: cholesterol itself, **polyunsaturated fatty acids (PUFAs), saturated fatty acids (SFAs),** and fiber. It would seem that the more cholesterol one eats, the higher the serum cholesterol should be. However, cholesterol synthesis is tightly regulated via a feedback control at the hydroxymethylglutaryl-CoA reductase step, so decreases in dietary cholesterol have relatively little effect on serum cholesterol levels (see p. 415). One can obtain a more significant reduction in cholesterol and triacylglycerol levels by

increasing the ratio of PUFA/SFA in the diet. Finally, some plant fibers, especially the water-soluble fibers, appear to decrease cholesterol levels significantly.

While the effects of various lipids in the diet can be dramatic, the biochemistry of their action is still uncertain. Saturated fats inhibit receptor-mediated uptake of LDL, but the mechanism is complex. Palmitic acid (saturated, C16) raises cholesterol levels while stearic acid (saturated, C18) is neutral. Polyunsaturated fatty acids lower both LDL and HDL cholesterol levels, while oleic acid (monounsaturated, C18) appears to lower LDL without affecting HDL levels. Furthermore, the **ω**-3 and **ω**-6 polyunsaturated fatty acids have slightly different effects on lipid profiles (see Clin. Corr. 27.6). However, these mechanistic complexities do not significantly affect dietary recommendations. Most foods high in saturated fats contain both palmitic and stearic acid and are atherogenic. The data showing oleic acid lowers LDL levels mean that olive oil, and possibly peanut oil, may be considered as beneficial as polyunsaturated oils.

There is very little disagreement with respect to these data. The question is, what can be done with the information? Much of the disagreement arises from the tendency to look at each dietary factor in isolation. For example, it is debatable whether it is worthwhile placing a patient on a highly restrictive 300-mg cholesterol diet (1 egg = 213 mg of cholesterol) if his serum cholesterol is lowered by only 5–10%. Likewise, changing the **PUFA/SFA ratio** from 0.3 (the current value) to 1.0 would either require a radical change in the diet by elimination of foods containing saturated fat (largely meats and fats) or an addition of large amounts of rather unpalatable polyunsaturated fats to the diet. For many Americans this would be unrealistic. Fiber is another good example. One could expect, at the most, a 5% decrease in serum cholesterol by adding any reasonable amount of fiber to the diet. (Very few people would eat the

CLINICAL CORRELATION 27.6

Polyunsaturated Fatty Acids and Risk Factors for Heart Disease

Recent studies confirming that reduction of elevated serum cholesterol levels can reduce risk of heart disease have rekindled interest in the effects of diet on serum cholesterol levels and other risk factors for heart disease. We have known for years that one of the most important dietary factors regulating serum cholesterol levels is the ratio of polyunsaturated fats (PUFAs) to saturated fats (SFAs) in the diet. One of the most interesting recent developments is the discovery that different types of polyunsaturated fatty acids have different effects on lipid metabolism and on other risk factors for heart disease. As discussed in Chapter 9, there are two families of polyunsaturated essential fatty acids—the **ω**-6, or linoleic family, and the **ω**-3, or linolenic family. Recent clinical studies have shown that the **ω**-6 PUFAs (chief dietary source is linoleic acid from plants and vegetable oils) primarily decrease serum cholesterol levels, with only modest effects on triacylglycerol levels. The **ω**-3 PUFAs (chief dietary source is eicosapentaenoic acid from certain ocean fish and fish oils) cause modest decreases in serum cholesterol levels and significantly lower triacylglycerol levels. The biochemical mechanism behind these different effects on serum lipid levels is unknown.

The **ω**-3 PUFAs have yet another unique physiological effect that may decrease the risk of heart disease—they decrease platelet aggregation. The mechanism of this effect is a little clearer. Arachidonic acid (**ω**-6 family) is known to be a precursor of thromboxane A_2 (TXA_2), which is a potent proaggregating agent, and prostaglandin I_2 (PGI_2), which is a weak antiaggregating agent (see p. 436). The **ω**-3 PUFAs are thought to act by one of two mechanisms: (1) Eicosapentaenoic acid (**ω**-3 family) may be converted to thromboxane A_3 (TXA_3), which is only weakly proaggregating, and prostaglandin I_3 (PGI_3), which is strongly antiaggregating. Thus the balance between proaggregation and antiaggregation would be shifted toward a more antiaggregating condition as the **ω**-3 PUFAs displace **ω**-6 PUFAs as a source of precursors to the thromboxanes and prostaglandins. (2) The **ω**-3 PUFAs may also act by simply inhibiting the conversion of arachidonic acid to TXA_2.

The unique potential of eicosapentaenoic acid and other **ω**-3 PUFAs in reducing the risk of heart disease is being tested in numerous clinical trials. Although the results may affect dietary recommendations in the future, it is well to keep in mind that no long-term clinical studies of the **ω**-3 PUFAs have been carried out. No major health organization has recommended that we replace **ω**-6 with **ω**-3 PUFAs in the American diet.

Holub, B. J. Dietary fish oils containing eicosapentaenoic acid and the prevention of atherosclerosis and thrombosis. *Can. Med. Assoc. J.* 139:377, 1988; Simopoulos, A. P. Omega-3 fatty acids in health and disease and in growth and development. *Am. J. Clin. Nutr.* 54:438, 1991; and Gapinski, J. P., Van Ruiswyk, J. V., Heudebert, G. R., and Schectman, G. S. Preventing restenosis with fish-oils following coronary angioplasty. A meta-analysis. *Arch. Intern. Med.* 153:1595, 1993.

ten apples per day needed to lower serum cholesterol by 15%.) Are we to conclude then that any dietary means of controlling cholesterol levels is useless? Only if each element of the diet is examined in isolation. For example, recent studies have shown that vegetarians, who have lower cholesterol intakes plus higher PUFA/SFA ratios and higher fiber intakes, may average 25–30% lower cholesterol levels than their nonvegetarian counterparts. Perhaps, more to the point, diet modifications of the type acceptable to the average American have been shown to cause a 10–15% decrease in cholesterol levels in long-term studies. A 7-year clinical trial sponsored by the National Institutes of Health has proved conclusively that lowering serum cholesterol levels reduces the risk of heart disease in men. It is important to keep in mind that serum cholesterol is just one of many risk factors.

Effects of Refined Carbohydrate in the Diet Are Not Straightforward

Much of the nutritional dispute in the area of carbohydrates centers around the amount of *refined carbohydrate* in the diet. In the past, simple sugars (primarily sucrose) have been blamed for almost every ill from tooth decay to heart disease and diabetes. In the case of tooth decay, these assertions were clearly correct. In the case of heart disease, however, the linkage is more obscure (see Clin. Corr. 27.7). The situation with respect to diabetes is probably even less direct. Whereas restriction of simple sugars is often desirable in patients who already have diabetes, recent studies show less than expected correlation between the type of carbohydrate ingested and the subsequent rise in serum glucose levels (Table 27.2). Ice cream, for example, causes a much smaller increase in serum glucose levels than either potatoes or whole wheat bread. It turns out that other components of food—such as protein, fat, and the soluble fibers—are much more important than the type of carbohydrate present in determining how rapidly glucose will enter the bloodstream.

CLINICAL CORRELATION 27.7

Metabolic Adaptation: The Relationship between Carbohydrate Intake and Serum Triacylglycerols

In evaluating the nutrition literature, it is important to be aware that most clinical trials are of rather short duration (2–6 weeks), while some metabolic adaptations may take considerably longer. Thus even apparently well-designed clinical studies may lead to erroneous conclusions that will be repeated in the popular literature for years to come. For example, several studies carried out in the 1960s and 1970s tried to assess the effects of carbohydrate intake on serum triacylglycerol levels. Typically, young collegeage males were given a diet in which up to 50% of their fat calories were replaced with sucrose or other simple sugars for a period of 2–3 weeks. In most cases serum triacylglycerol levels increased markedly (up to 50%). This led to the tentative conclusion that high intake of simple sugars, particularly sucrose, might increase the risk of heart disease, a notion that was popularized by nutritional best sellers such as "Sugar Blues" and "Sweet and Dangerous." Unfortunately, while the original conclusions were promoted in the lay press, the experiments themselves were questioned. Subsequent studies showed that if these trials were continued for longer periods of time (3–6 months), the triacylglycerol levels usually normalized. The nature of this slow metabolic adaptation is unknown.

It should be noted that while the interpretation of the original clinical trials may have been faulty, the ensuing dietary recommendations may not have been entirely incorrect. Many of the snack and convenience foods in the American diet that are high in sugar are also high in fat and in caloric density. Thus removing some of these foods from the diet can aid in weight control, and being overweight is known to contribute to hypertriacylglycerolemia. Also, some individuals exhibit carbohydrate-induced hypertriacylglycerolemia. Triacylglycerol levels in these individuals respond dramatically to diets that substitute foods containing complex carbohydrates and fiber for these foods containing primarily simple sugars as a carbohydrate source.

MacDonald, I. Effects of dietary carbohydrates on serum lipids. *Prog. Biochem. Pharmacol*. 8:216, 1973; and Vrana, A., and Fabry, P. Metabolic effects of high sucrose or fructose intake. *World Rev. Nutr. Diet* 42:56, 1983.

TABLE 27.2 Glycemic Index[a] of Some Selected Foods

Grain and cereal products		Root vegetables	
Bread (white)	69 ± 5	Beets	64 ± 16
Bread (whole wheat)	72 ± 6	Carrots	92 ± 20
Rice (white)	72 ± 9	Potato (white)	70 ± 8
Sponge cake	46 ± 6	Potato (sweet)	48 ± 6
Breakfast cereals		Dried legumes	
All bran	51 ± 5	Beans (kidney)	29 ± 8
Cornflakes	80 ± 6	Beans (soy)	15 ± 5
Oatmeal	49 ± 8	Peas (blackeye)	33 ± 4
Shredded wheat	67 ± 10		
Vegetables		Fruits	
Sweet corn	59 ± 11	Apple (Golden Delicious)	39 ± 3
Frozen peas	51 ± 6	Banana	62 ± 9
		Oranges	40 ± 3
Dairy products		Sugars	
Ice cream	36 ± 8	Fructose	20 ± 5
Milk (whole)	34 ± 6	Glucose	100
Yogurt	36 ± 4	Honey	87 ± 8
		Sucrose	59 ± 10

Source: Data from Jenkins, D. A., et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am. J. Clin. Nutr.* 34:362, 1981.

[a] Glycemic index is defined as the area under the blood glucose response curve for each food expressed as a percentage of the area after taking the same amount of carbohydrate as glucose (mean: 5–10 individuals).

Mixed Vegetable and Animal Proteins Meet Nutritional Protein Requirements

Concern has been voiced recently about the type of protein in the American diet. Epidemiologic data and animal studies suggest that consumption of animal protein is associated with increased incidence of heart disease and various forms of cancer. One could assume that it is probably not the animal protein itself that is involved, but the associated fat and cholesterol. What sort of protein should we consume? Although the present diet may not be optimal, a strictly vegetarian diet may not be acceptable to many Americans. Perhaps a middle road is best. Clearly, there are no known health dangers associated with a mixed diet that is lower in animal protein than the current American standard.

An Increase in Fiber from Varied Sources Is Desirable

Because of our current knowledge about effects of fiber on human metabolism, most suggestions for a prudent diet recommend an increase in dietary fiber. The main question is: "How much is enough?" The current fiber content of the American diet is about 14–15 g per day. Most experts feel that an increase to at least 25–30 g would be safe and beneficial. Since we know that different fibers have different metabolic roles, this increase in fiber intake should come from a wide variety of fiber sources—including fresh fruits, vegetables, and legumes as well as the more popular cereal sources of fiber (which are primarily cellulose and hemicellulose).

Current Recommendations Are for a "Prudent Diet"

Several private and governmental groups have made specific recommendations with respect to the ideal dietary composition for the American public in recent years. This movement was spearheaded by the Senate Select Committee on Human Nutrition, which first published its *Dietary Goals for the United States*

in 1977. The Senate Select Committee recommended that the American public reduce consumption of total calories, total fat, saturated fat, cholesterol, simple sugars, and salt to "ideal" goals more compatible with good health (Figure 27.2). In recent years the USDA, the American Heart Association, the American Diabetes Association, the National Research Council, and the Surgeon General all have published similar recommendations, and the USDA has used these recommendations to design revised recommendations for a balanced diet (Figure 27.3). These recommendations have become popularly known as the **prudent diet.** How valid is the scientific basis of the recommendations for a prudent diet? Is there evidence that a prudent diet will improve the health of the general public? These remain controversial questions.

An important argument against such recommendations is that we presently do not have enough information to set concrete goals. We might be creating some problems while solving others. For example, the goals of reducing total fat and saturated fat in the diet are best met by replacing animal protein with vegetable protein. This might reduce the amount of available iron and vitamin B_{12} in the diet. It is also quite clear that the same set of guidelines do not apply for every individual. For example, exercise is known to raise serum HDL cholesterol and obesity is known to elevate cholesterol and triacylglycerols and reduce glucose tolerance. Thus the very active individual who maintains ideal body weight can likely tolerate higher fat and sugar intakes than an obese individual.

On the "pro" side, however, it clearly can be argued that all of the dietary recommendations are in the right direction for reducing nutritional risk factors in the general population. Besides, similar diets have been consumed by our ancestors and by people in other countries with no apparent harm. Whatever

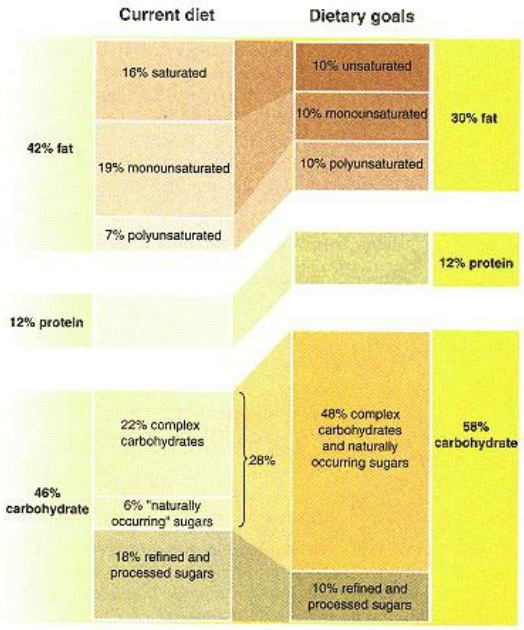

Figure 27.2
United States dietary goals.
Graphical comparison of the composition of the current U.S. diet and the dietary goals for the U.S. population suggested by the Senate Select Committee on Human Nutrition.
From *Dietary Goals for the United States*, 2nd ed.
Washington, DC: U.S. Government Printing Office, 1977.

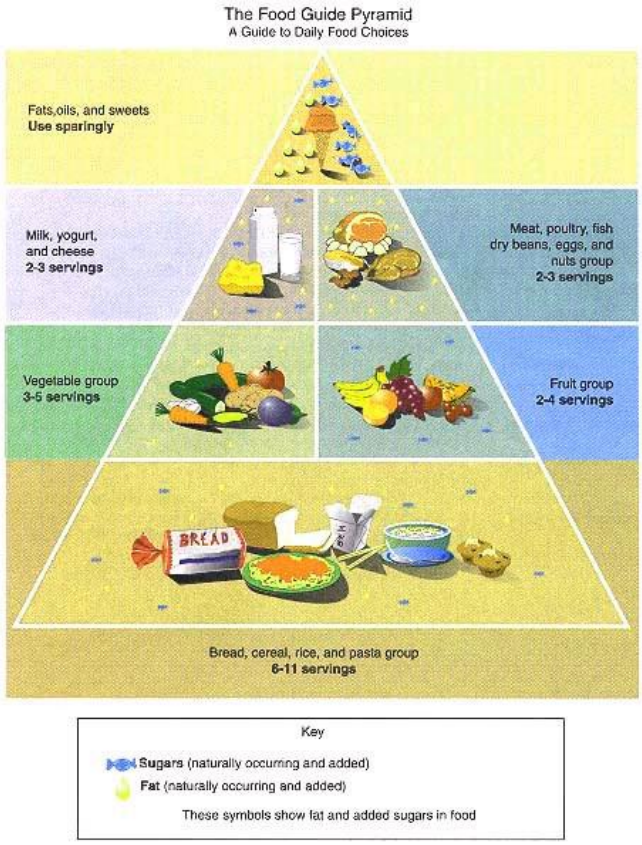

Figure 27.3
USDA food pyramid.
Graphical representation of USDA recommendations for a balanced diet.
HG Bulletin #252. Washington, DC: U.S. Government Printing Office, 1992.

the outcome of this debate, it will undoubtedly shape much of our ideas concerning the role of nutrition in medicine.

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Questions

C. N. Angstadt and J. Baggott

1. Of two people with approximately the same weight, the one with the higher basal energy requirement would most likely be:

   A. taller.

   B. female if the other were male.

   C. older.

   D. under less stress.

   E. all of the above.

2. Basal metabolic rate:

   A. is not influenced by energy intake.

   B. increases in response to starvation.

   C. may decrease up to 50% during periods of starvation.

   D. increases in direct proportion to energy expenditure.

   E. is not responsive to changes in hormone levels.

3. The primary effect of the consumption of excess protein beyond the body's immediate needs will be:

   A. excretion of the excess as protein in the urine.

   B. an increase in the "storage pool" of protein.

   C. an increased synthesis of muscle protein.

   D. an enhancement in the amount of circulating plasma proteins.

   E. an increase in the amount of adipose tissue.

4. Which of the following individuals would most likely be in nitrogen equilibrium?

   A. a normal, adult male

   B. a normal, pregnant female

   C. a growing child

   D. an adult male recovering from surgery

   E. a normal female on a very low protein diet

5. Vegetarian diets:

   A. cannot meet the body's requirements for all of the essential amino acids.

   B. contain only protein that is very readily digestible.

   C. are adequate as long as two different vegetables are consumed in the same meal.

   D. would require less total protein than meat proteins to meet the requirement for all of the essential amino acids.

   E. require that proteins consumed have essential amino acid contents that complement each other.

6. In which of the following circumstances would a protein intake of 0.8 g of protein kg^{-1} (body weight) day^{-1} probably be adequate?

   A. vegetarian diet

   B. infancy

   C. severe burn

   D. about 85–90% of total calories supplied by carbohydrate and fat

   E. pregnancy

7. Kwashiorkor is:

   A. the most common form of protein–calorie malnutrition in the United States.

   B. characterized by a thin, wasted appearance.

   C. an inadequate intake of food of any kind.

D. an adequate intake of total calories but a specific deficiency of protein.

E. an adequate intake of total protein but a deficiency of the essential amino acids.

8. An excessive intake of calories:

A. usually does not have adverse metabolic consequences.

B. leads to metabolic changes that are usually irreversible.

C. frequently leads to elevated serum levels of free fatty acids, cholesterol, and triglycerides.

D. is frequently associated with an increased number of insulin receptors.

E. is the only component of obesity.

9. A diet very low in carbohydrate:

A. would cause weight loss because there would be no way to replenish citric acid cycle intermediates.

B. would result in no significant metabolic changes.

C. could lead to a chronic ketosis.

D. would lead to water retention.

E. would be the diet of choice for a diabetic.

10. Lactase insufficiency:

A. is a more serious disease than diabetes mellitus.

B. has no clinical symptoms.

C. causes an intolerance to glucose.

D. causes an intolerance to milk and milk products.

E. affects utilization of milk by the liver.

11. Dietary fat:

A. is usually present, although there is no specific need for it.

B. if present in excess, can be stored as either glycogen or adipose tissue triacylglycerol.

C. should include linoleic and linolenic acids.

D. should increase on an endurance training program in order to increase the body's energy stores.

E. if present in excess, does not usually lead to health problems.

12. Which of the following statements about dietary fiber is/are correct?

A. Water-soluble fiber helps to lower serum cholesterol in most people.

B. Mucilaginous fiber slows the rate of digestion and absorption of carbohydrates.

C. Insoluble fiber increases stool bulk and decreases transit time.

D. All of the above are correct.

E. None of the above is correct.

13. Which one of the following dietary regimens would be *most* effective in lowering serum cholesterol?

A. restrict dietary cholesterol

B. increase the ratio of polyunsaturated to saturated fatty acids

C. increase fiber content

D. restrict cholesterol and increase fiber

E. restrict cholesterol, increase PUFA/SFA, increase fiber

14. Most nutrition experts currently agree that an excessive consumption of sugar causes:

A. tooth decay.

B. diabetes.

C. heart disease.

D. permanently elevated triacylglycerol levels.

E. all of the above.

Refer to the following for Questions 15 and 16:

A. 10% of total calories

B. 12% of total calories

C. 30% of total calories

D. 48% of total calories

E. 58% of total calories

15. The dietary goal recommended by the Senate Select Committee on Human Nutrition for Polyunsaturated fatty acids.

16. The dietary goal recommended by the Senate Select Committee on Human Nutrition for complex carbohydrates and naturally occurring sugars.

17. A complete replacement of animal protein in the diet by vegetable protein:

A. would be expected to have no effect at all on the overall diet.

B. would reduce the total amount of food consumed for the same number of calories.

C. might reduce the total amount of iron and vitamin B_{12} available.

D. would be satisfactory regardless of the nature of the vegetable protein used.

E. could not satisfy protein requirements.

Answers

1. A A taller person with the same weight would have a greater surface area. B: Males have higher energy requirements than females. C: Energy requirements decrease with age. D: Stress, probably because of the effects of epinephrine and cortisol, increase energy requirements (pp. 1088–1089).

2. C This is part of the survival mechanism in starvation. A and B: BMR decreases when energy intake decreases. D: BMR as defined (p. 1088) is independent of energy expenditure. Only when the exercise is repeated on a daily basis so that lean muscle mass is increased does BMR also increase. E: Many hormones increase BMR (p. 1089).

3. E Excess protein is treated like any other excess energy source and stored (minus the nitrogen) eventually as adipose tissue fat (p. 1089). A: Protein is not found in normal urine except in very small amounts. The excess nitrogen is excreted as NH_4^+ and urea, whereas the excess carbon skeletons of the amino acids are used as energy sources. B–D: There is no discrete storage form of protein, and although some muscle and structural protein is expendable, there is no evidence that increased intake leads to generalized increased protein synthesis.

4. A B, C, and D: Although normal, pregnancy is also a period of growth, requiring positive balance, as does a period of convalescence. E: Inadequate protein intake leads to negative balance (p. 1100).

5. E A–E: It is possible to have adequate protein intake on a vegetarian diet provided enough is consumed (protein content is generally low and may be more difficult to digest) and there is a mixture of proteins that supplies all of the essential amino acids since individual proteins are frequently deficient in one or more foods (Clin. Corr. 27.1, p. 1091).

6. D This level of calories from carbohydrate and fat is more than adequate for protein sparing. A: Essential amino acids are low in vegetable protein. B, C, and E: Periods of rapid growth require extra protein, as does major trauma (p. 1092).

7. D A: The most common protein–calorie malnutrition occurs in severely ill, hospitalized patients who would be more likely to have generalized malnutrition. B and C: These are the characteristics of marasmus. E: This would lead to negative nitrogen balance but does not have a specific name (p. 1093).

8. C Probably because an increased number and/or size of adipose cells will contain fewer insulin receptors. A: Excess caloric intake will lead to obesity if continued long enough. B: Fortunately, most of the changes accompanying obesity can be reversed if weight is lost. D: Many of the adverse effects of obesity are associated with an increased number of adipocytes that are deficient in insulin receptors. E: Inadequate exercise and genetic components also play roles in obesity (pp. 1094–1095).

9. C A: This is a popular myth but untrue because many amino acids are glucogenic. B and C: The liver adapts by increasing gluconeogenesis, fatty acid oxidation, and ketone body production. D: Low carbohydrate leads to a depletion of glycogen with its stored water, accounting for rapid initial weight loss on this kind of diet (p. 1095, Clin. Corr. 27.4). E: Diabetic diets need to be individualized. There is currently no generalized recommendation for the carbohydrate content of a diabetic diet (p. 1095 and Clinical Correlation 27.5).

10. D B, D, and E: Lactase insufficiency is an inability to digest the sugar in milk products, causing intestinal symptoms, but is easily treated by eliminating milk products from the diet. A and C: Diabetes, caused by inadequate insulin or insulin receptors, inhibits appropriate utilization of glucose (p. 1095).

11. C A and C: Linoleic and linolenic acids are essential fatty acids and so must be present in the diet. B and D: Excess carbohydrate can be stored as fat but the reverse is not true. D: Carbohydrate loading has been shown to increase endurance. E: High-fat diets are associated with many health risks (p. 1096, Clin. Corr. 27.5).

12. D These each illustrate the different properties and roles of the common kinds of fiber (p. 1097).

13. E Any of the measures alone would decrease serum cholesterol slightly, but to achieve a reduction of more than 15% requires all three (pp. 1098–1100).

14. A This is the only direct linkage shown. B and C: There may be an association with these conditions but not a direct cause–effect relationship. D: Transient elevations may occur on an isocaloric switch from a high-starch to a high-simple-sugar diet but not a permanent elevation (p. 1100).

15. A See Figure 27.2, p. 1102.

16. D See Figure 27.2, p. 1102.

17. C A and C: This would reduce the amount of fat, especially saturated fat, but could also reduce the amount of necessary nutrients that come primarily from animal sources. B: The protein content of vegetable0s is quite low, so much larger amounts of vegetables would have to be consumed. D and E: It is possible to satisfy requirements for all of the essential amino acids completely if vegetables with complementary amino acid patterns, in proper amounts, are consumed (p. 1101, Clin. Corr. 27.1).

Chapter 28— Principles of Nutrition II: Micronutrients

Stephen G. Chaney

28.1— Overview

Micronutrients play a vital role in human metabolism, being involved in almost every known biochemical reaction and pathway. However, the biochemistry of these nutrients is of little interest unless we also know if dietary deficiencies are likely. The American diet is undoubtedly the best it has ever been. Our current food supply provides us with an abundant variety of foods all year long and deficiency diseases have become medical curiosities. However, our diet is far from optimal. The old adage that we get everything we need from a balanced diet is true only if we eat a balanced diet. Unfortunately, most Americans do not consume a balanced diet. Foods of high caloric density and low nutrient density (often referred to as empty calories or junk food) are an abundant and popular part of the American diet, and our nutritional status suffers because of these food choices. Obviously then, neither alarm nor complacency is justified. We need to know how to evaluate the adequacy of our diet.

28.2— Assessment of Malnutrition

There are three increasingly stringent criteria for measuring **malnutrition.**

1. **Dietary intake studies,** which are usually based on a 24-hour recall, are the least stringent. The 24-hour recalls almost always tend to overestimate the number of people with deficient diets. Also, poor dietary intake alone is usually not a problem in this country unless the situation is compounded by increased need.

2. **Biochemical assays,** either direct or indirect, are a more useful indicator of the nutritional status of an individual. At their best, they indicate **subclinical nutritional deficiencies** that can be treated before actual deficiency diseases develop. However, all biochemical assays are not equally valid—an unfortunate fact that is not sufficiently recognized. Changes in biochemical parameters due to stress need to be interpreted with caution. The distribution of many nutrients in the body changes dramatically in a stress situation such as illness, injury, and pregnancy. A drop in level of a nutrient in one tissue compartment (usually blood) need not signal a deficiency or an increased requirement. It could simply reflect a normal metabolic adjustment to stress.

3. The most stringent criterion is the appearance of **clinical symptoms.** However, it is desirable to intervene long before symptoms became apparent.

The question remains: When should dietary surveys or biochemical assays be interpreted to indicate the necessity of nutritional intervention? The following general guidelines are useful. Dietary surveys are seldom a valid indication of general malnutrition unless the average intake for a population group falls significantly below the standard (usually two-thirds of the Recommended Dietary Allowance) for one or more nutrients. However, by looking at the percentage of people within a population group who have suboptimal intake, it is possible to identify high-risk population groups that should be monitored more closely. Biochemical assays can definitely identify subclinical cases of malnutrition where nutritional intervention is desirable provided (a) the assay has been shown to be reliable, (b) the deficiency can be verified by a second assay, and (c) there is no unusual stress situation that may alter micronutrient distribution. In assessing nutritional status, it is important for the clinician to be aware of those population groups at risk, the most reliable biochemical assays for monitoring nutritional status, and the symptoms of deficiencies if they should occur.

28.3— Recommended Dietary Allowances

Recommended Dietary Allowances are the levels of intake of essential nutrients considered by the Food and Nutrition Board of the National Research Council to be adequate to meet the nutritional needs of practically all healthy persons. Optimally, the RDAs are based on daily intake sufficient to prevent the appearance of nutritional deficiency in at least 95% of the population. This determination is relatively easy to make for those nutrients associated with dramatic deficiency diseases, for example, vitamin C and scurvy. In other instances more indirect measures must be used, such as tissue saturation or extrapolation from animal studies. In some cases, such as vitamin E, in which no deficiency symptoms are known to occur in the general population, the RDA is defined as the normal level of intake in the American diet. There is no set of criteria that can be used for all micronutrients, and there are always some uncertainty and debate as to the correct criteria. The criteria are constantly changed by new research. The Food and Nutrition Board normally meets every 6 years to consider currently available information and update its recommendations.

RDAs serve as a useful general guide in evaluating adequacy of diets. However, the RDAs have several limitations that should be kept in mind. Important limitations are as follows:

1. RDAs represent an ideal average intake for groups of people and are best used for evaluating nutritional status of population groups. RDAs are not meant to be standards or requirements for individuals. Some individuals would have no problem with intakes below the RDA, whereas a few may develop deficiencies on intakes above the RDA.

2. RDAs are designed to meet the needs of healthy people and do not take into account special needs arising from infections, metabolic disorders, or chronic diseases.

3. Since present knowledge of nutritional needs is incomplete, there may be unrecognized nutritional needs. To provide for these needs, the RDAs should be met from as varied a selection of foods as possible. No single food can be considered complete, even if it meets the RDA for all known nutrients. This is important, especially in light of the current practice of fortifying foods of otherwise low nutritional value.

4. As currently formulated, RDAs do not define the "optimal" level of any nutrient, since optimal levels are difficult to define. Because of information suggesting that optimal intake of certain micronutrients (e.g., vitamins A, C, and E) may reduce heart disease and cancer risk, some experts feel that the focus of the RDAs should shift from preventing nutritional deficiencies to defining optimal levels that may reduce the risk of other diseases.

28.4— Fat-Soluble Vitamins

Vitamin A Is Derived from Plant Carotenoids

The active forms of vitamin A are **retinol, retinal** (retinaldehyde), and **retinoic acid.** These substances are synthesized by plants as the more complex **carotenoids** (Figure 28.1), which are cleaved to retinol by most animals and stored in the liver as retinol palmitate. Liver, egg yolk, butter, and whole milk are good sources of the preformed retinol. Dark green and yellow vegetables are generally good sources of the carotenoids. Conversion of carotenoids to retinol is rarely 100%, so that the vitamin A potency of various foods is expressed in terms of retinol equivalents (1 RE is equal to 1 mg retinol, 6 mg β-carotene,

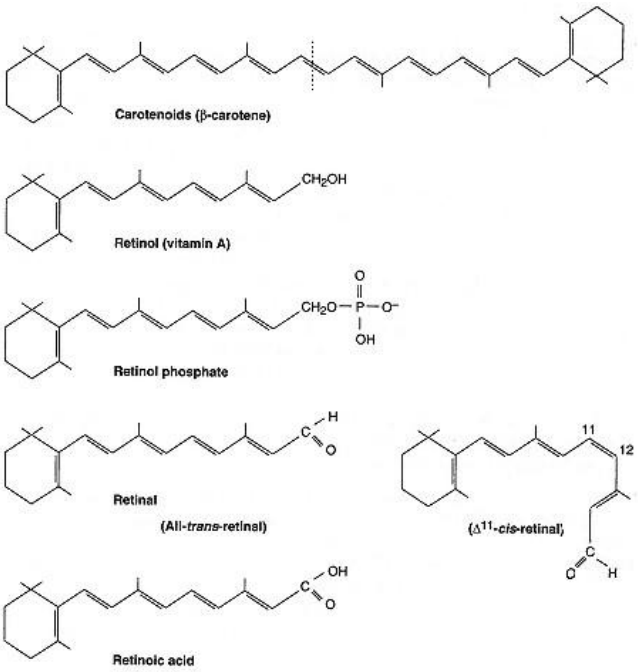

Figure 28.1
Structures of vitamin A and related compounds.

and 12 mg of other carotenoids). β-Carotene and other carotenoids are major sources of vitamin A in the American diet. These carotenoids are first cleaved to retinol and converted to other vitamin A metabolites in the body (Figure 28.1).

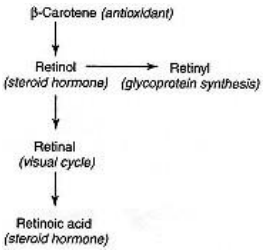

Figure 28.2
Vitamin A metabolism and function.

Vitamin A serves a number of functions in the body. Only in recent years has its biochemistry become well understood (Figure 28.2). ***β*-Carotene** and some other carotenoids have recently been shown to have an important role as **antioxidants.** At the low oxygen tensions prevalent in the body, β-carotene is a very effective antioxidant and may be expected to reduce the risk of those cancers initiated by free radicals and other strong oxidants. Several retrospective clinical studies have suggested that adequate dietary β-carotene may be important in reducing the risk of lung cancer, especially in people who smoke. However, supplemental β-carotene did not provide any detectable benefit and may have actually increased cancer risk in two recent multicenter prospective studies.

Retinol is converted to **retinyl phosphate** in the body. The retinyl phosphate appears to serve as a **glycosyl donor** in the synthesis of some glycoproteins and mucopolysaccharides in much the same manner as dolichol phosphate (see p. 738). Retinyl phosphate is essential for the synthesis of certain glycoproteins needed for normal growth regulation and for mucus secretion. Both retinol and retinoic acid bind to specific intracellular receptors, which then bind to chromatin and affect the synthesis of proteins involved in the regulation of cell growth and differentiation. Thus both retinol and retinoic acid can be considered to act like **steroid hormones** in regulating growth and differentiation.

Finally, in the Δ^{11}-*cis*-retinal form, vitamin A becomes reversibly associated with the **visual proteins.** When light strikes the retina, a number of complex

biochemical changes take place, resulting in the generation of a nerve impulse, conversion of the retinal to the all-trans form, and its dissociation from the visual protein (see p. 943). Regeneration of more visual pigments requires isomerization back to the ^{11}-*cis* form (Figure 28.3).

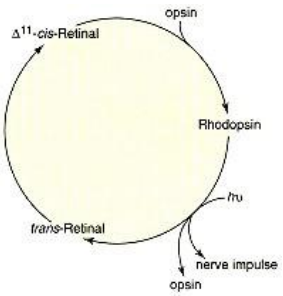

Figure 28.3
Role of vitamin A in vision.

Based on what is known about the biochemical mechanisms of vitamin A action, its biological effects are easier to understand. For example, vitamin A is required for the maintenance of healthy epithelial tissue. Retinol and/or retinoic acid are required to prevent the synthesis of high molecular weight forms of **keratin** and retinyl phosphate is required for the synthesis of glycoproteins (an important component of the mucus secreted by many epithelial tissues). The lack of mucus secretion leads to a drying of these cells, and the excess keratin synthesis leaves a horny keratinized surface in place of the normal moist and pliable epithelium. Vitamin A deficiency can lead to **anemia** caused by impaired mobilization of iron from the liver because retinol and/or retinoic acid are required for the synthesis of the iron transport protein transferrin.

Finally, vitamin A-deficient animals are more susceptible to both infections and cancer. Decreased resistance to infections is thought to be due to keratinization of mucosal cells lining the respiratory, gastrointestinal, and genitourinary tracts. Under these conditions fissures readily develop in the mucosal membranes, allowing microorganisms to enter. Vitamin A deficiency may impair the immune system as well. The protective effect of vitamin A against many forms of cancer probably results from the antioxidant potential of β-carotene and the effects of retinol and retinoic acid in regulating cell growth.

Since vitamin A is stored in the liver, deficiencies of this vitamin can develop only over prolonged periods of inadequate uptake. Mild **vitamin A deficiencies** are characterized by **follicular hyperkeratosis** (rough keratinized skin resembling "goosebumps"), anemia (biochemically equivalent to iron deficiency anemia, but in the presence of adequate iron intake), and increased susceptibility to infection and cancer. **Night blindness** is also an early symptom of vitamin A deficiency. Severe vitamin A deficiency leads to a progressive keratinization of the cornea of the eye known as xerophthalmia in its most advanced stages. In the final stages, infection usually sets in, with resulting hemorrhaging of the eye and permanent loss of vision.

For most people (unless they happen to eat liver) the dark green and yellow vegetables are the most important dietary source of vitamin A. Unfortunately, these are the foods most often missing from the American diet. Nationwide, dietary surveys indicate that between 40% and 60% of the population consumes less than two-thirds of the RDA for vitamin A. Clinical symptoms of vitamin A deficiency are rare in the general population, but vitamin A deficiency is a fairly common consequence of severe liver damage or diseases that cause fat malabsorption (see Clin. Corr. 28.1).

Vitamin A accumulates in the liver and over prolonged periods large amounts of this vitamin can be toxic. Doses of 25,000–50,000 RE per day over months or years will prove to be toxic for many children and adults. The usual symptoms include bone pain, scaly dermatitis, enlargement of liver and spleen, nausea, and diarrhea. It is, of course, virtually impossible to ingest toxic amounts of vitamin A from normal foods unless one eats polar bear liver (6000 RE/g) regularly. Most instances of **vitamin A toxicity** are due to the use of massive doses of vitamin A supplements. Fortunately, this practice is relatively rare because of increased public awareness of vitamin A toxicity.

Vitamin D Synthesis in the Body Requires Sunlight

Technically, vitamin D should be considered a hormone rather than a vitamin. **Cholecalciferol (D_3)** is produced in skin by UV irradiation of 7-dehydrocholesterol (Figure 28.4). Thus, as long as the body is exposed to adequate sunlight,

CLINICAL CORRELATION 28.1

Nutritional Considerations for Cystic Fibrosis

Patients with malabsorption diseases often develop malnutrition. As an example, let us examine the nutritional consequences of one disease with malabsorption components. Cystic fibrosis (CF) involves a generalized dysfunction of the exocrine glands that leads to formation of a viscid mucus, which progressively plugs the ducts. Obstruction of the bronchi and bronchioles leads to pulmonary infections, which are usually the direct cause of death. In many cases, however, the exocrine glands of the pancreas are also affected, leading to a deficiency of pancreatic enzymes and sometimes a partial obstruction of the common bile duct.

The deficiency (or partial deficiency) of pancreatic lipase and bile salts leads to severe malabsorption of fat and fat-soluble vitamins. Calcium tends to form insoluble salts with the long-chain fatty acids, which accumulate in the intestine. While these are the most severe problems, some starches and proteins are also trapped in the fatty bolus of partially digested foods. This physical entrapment, along with the deficiencies of pancreatic amylase and pancreatic proteases, can lead to severe protein–calorie malnutrition as well. Excessive mucus secretion on the luminal surfaces of the intestine may also interfere with the absorption of several nutrients, including iron.

Fortunately, microsphere preparations of pancreatic enzymes are now available that can greatly alleviate many of these malabsorption problems. With these preparations, protein and carbohydrate absorption rates are returned to near normal. Fat absorption is improved greatly but not normalized, since deficiencies of bile salts and excess mucus secretion persist. Because dietary fat is a major source of calories, these patients have difficulty obtaining sufficient calories from a normal diet. This is complicated by increased protein and energy needs resulting from the chronic infections often seen in these patients. Thus many experts recommend energy intakes ranging from 120–150% of the RDA.

Since inadequate energy intake results in poor growth and increased susceptibility to infection, inadequate caloric intake is of great concern for cystic fibrosis patients. Thus the current recommendations are for high-energy–high-protein diets without any restriction of dietary fat (50% carbohydrate, 15% protein, and 35% fat). If caloric intake from the normal diet is inadequate, dietary supplements or enteral feedings may be used. The dietary supplements most often contain easily digested carbohydrates and milk protein mixtures. Medium-chain triglycerides are sometimes used as a partial fat replacement since they can be absorbed directly through the intestinal mucosa in the absence of bile salts and pancreatic lipase.

Since some fat malabsorption is present, deficiencies of the fat-soluble vitamins often occur. Children aged 2–8 years need a standard adult multiple-vitamin preparation containing 400 IU of vitamin D and 5000 IU of vitamin A per day. Older children, adolescents, and adults need a standard multivitamin at a dose of 1–2 per day. If serum vitamin A levels become low, water-miscible vitamin A preparations should be used. For vitamin E the recommendations are: ages 0–6 mo, 25 IU day^{-1}; 6–12 mo, 50 IU day^{-1}; 1–4 years, 100 IU day^{-1}; 4–10 years, 100–200 IU day^{-1}; and >10 years, 200–400 IU day^{-1}; in water-soluble form. Vitamin K deficiency has not been adequately studied, but the current recommendations are: ages 0–12 mo, 2.5 mg $week^{-1}$ or 2.5 mg twice a week if on antibiotics; ages >1 year, 5.0 mg twice weekly when on antibiotics or if cholestatic liver disease is present. Iron deficiency is fairly common in cystic fibrosis patients but iron supplementation is not usually recommended because of concern that higher iron levels in the blood might encourage systemic bacterial infections. Calcium levels in the blood are usually normal. However, since calcium absorption is probably suboptimal, it is important to make certain that the diet provides at least RDA levels of calcium.

Littlewood, J. M., and MacDonald, A. Rationale of modern dietary recommendations in cystic fibrosis. *J. R. Soc. Med.* 80(Suppl. 15):16, 1987; and Ramsey, B. W, Farrell, P. M., and Pencharz, P. Nutritional assessment and management in cystic fibrosis; a consensus report. *Am J. Clin. Nutr.* 55:108, 1992.

there is little or no dietary requirement for vitamin D. The best dietary sources of vitamin D_3 are saltwater fish (especially salmon, sardines, and herring), liver, and egg yolk. Milk, butter, and other foods are routinely fortified with **ergocalciferol (D_2)** prepared by irradiating ergosterol from yeast. Vitamin D potency is measured in terms of milligrams of cholecalciferol (1 mg cholecalciferol or ergocalciferol = 40 IU).

Both cholecalciferol and ergocalciferol are metabolized identically. They are carried to the liver where the 25-hydroxy derivative is formed. **25-Hydroxy-cholecalciferol** [25-(OH)D] is the major circulating derivative of vitamin D, and it is in turn converted into the biologically active **1-α,25-dihydroxychole-calciferol** (also called calcitriol) in the proximal convoluted tubules of kidney (see Clin. Corr. 28.2).

The compound 1,25-$(OH)_2$D acts in concert with **parathyroid hormone (PTH),** which is also produced in response to low serum calcium. Parathyroid hormone plays a major role in regulating the activation of vitamin D. High PTH levels stimulate the production of 1,25-$(OH)_2$D, while low PTH levels induce formation of an inactive 24,25-$(OH)_2$D. Once formed, the 1,25-$(OH)_2$D acts

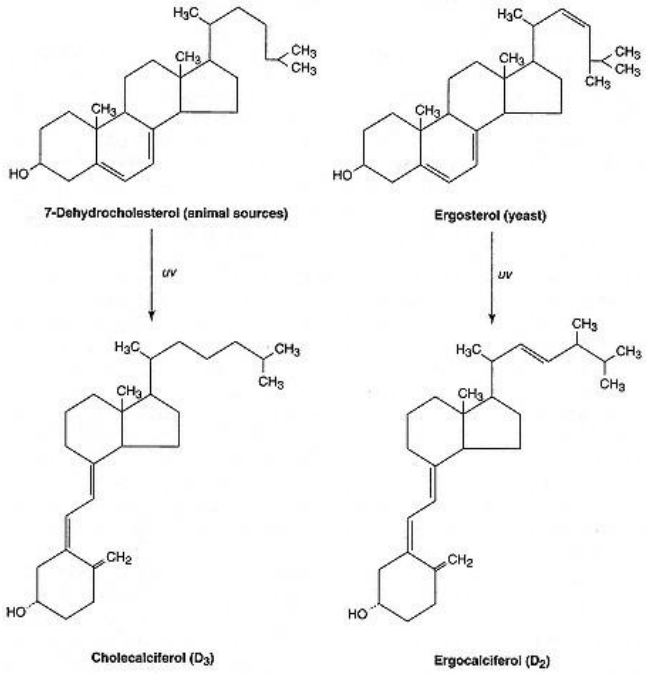

Figure 28.4
Structures of vitamin D and related compounds.

CLINICAL CORRELATION 28.2

Renal Osteodystrophy

In chronic renal failure, a complicated chain of events leads to a condition known as renal osteodystrophy. The renal failure results in an inability to produce 1,25-$(OH)_2$D, and thus bone calcium becomes the only important source of serum calcium. In the later stages of renal failure, the situation is complicated further by increased renal retention of phosphate and resulting hyperphosphatemia. The serum phosphate levels are often high enough to cause metastatic calcification (i.e., calcification of soft tissue), which tends to lower serum calcium levels further (the solubility product of calcium phosphate in the serum is very low and a high serum level of one component necessarily causes a decreased concentration of the other). The hyperphosphatemia and hypocalcemia stimulate parathyroid hormone secretion, and the resulting hyperparathyroidism further accelerates the rate of bone loss. One ends up with both bone loss and metastatic calcification. In this case, simple administration of high doses of vitamin D or its active metabolites would not be sufficient since the combination of hyperphosphatemia and hypercalcemia would only lead to more extensive metastatic calcification. The readjustment of serum calcium levels by high calcium diets and/or vitamin D supplementation must be accompanied by phosphate reduction therapies. The most common technique is to use phosphate-binding antacids that make phosphate unavailable for absorption. Orally administered 1,25-$(OH)_2$D is effective at stimulating calcium absorption in the mucosa but does not enter the peripheral circulation in significant amounts. Thus patients with severe hyperparathyroidism may need to be treated with intravenous 1,25-$(OH)_2$D.

Johnson, W. J. Use of vitamin D analogs in renal osteodystrophy. *Semin. Nephrol.* 6:31, 1986; McCarthy, J. T., and Kumar, R. Behavior of the vitamin D endocrine system in the development of renal osteodystrophy. *Semin. Nephrol.* 6:21, 1986; and Delmez, J. M., and Siatopolsky, E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. *Am. J. Kidney Dis.* 19:303, 1992.

alone as a typical steroid hormone in intestinal mucosal cells, where it induces synthesis of a protein, calbinden, required for calcium transport. In the bone 1,25-$(OH)_2D$ and PTH act synergistically to promote bone resorption (demineralization) by stimulating osteoblast formation and activity. Finally, PTH and 1,25-$(OH)_2D$ inhibit calcium excretion in the kidney by stimulating calcium reabsorption in the distal renal tubules. The overall response of calcium metabolism to several different physiological situations is summarized in Figure 28.5. The response to low serum calcium levels is characterized by elevation of PTH and 1,25-$(OH)_2D$, which act to enhance calcium absorption and bone resorption and to inhibit calcium excretion (Figure 28.5*a*). High serum calcium levels block production of PTH. The low PTH levels allow 25-(OH)D to be metabolized to 24,25-$(OH)_2D$ instead of 1,25-$(OH)_2D$. In the absence of PTH and 1,25-$(OH)_2D$ bone resorption is inhibited and calcium excretion is enhanced. High levels of serum calcium and phosphate increase the rate of bone mineralization (Figure 28.5*b*). Thus bone is a very important reservoir of the calcium and phosphate needed to maintain homeostasis of serum levels. When vitamin D and dietary calcium are adequate, no net loss of bone calcium occurs. However, when dietary calcium is low, PTH and 1,25-$(OH)_2D$ will cause net demineralization of bone to maintain normal serum calcium levels. Vitamin D deficiency also causes net demineralization of bone due to elevation of PTH (Figure 28.5*c*).

The most common symptoms of **vitamin D deficiency** are **rickets** in young children and **osteomalacia** in adults. Rickets is characterized by continued formation of osteoid matrix and cartilage, which are improperly mineralized, resulting in soft, pliable bones. In the adult demineralization of preexisting bone takes place, causing the bone to become softer and more susceptible to fracture. This osteomalacia is easily distinguishable from the more common osteoporosis, by the fact that the osteoid matrix remains intact in the former, but not in the latter. Vitamin D may be involved in more than regulation of calcium homeostasis. Receptors for 1,25-$(OH)_2D$ have been found in many tissues including parathyroid gland, islet cells of pancreas, keratinocytes of skin, and myeloid stem cells in bone marrow. The role of vitamin D in these tissues is the subject of active investigation.

Because of fortification of dairy products with vitamin D, dietary deficiencies are very rare. The cases of dietary vitamin D deficiency that do occur are most often seen in low-income groups, the elderly (who often also have minimal exposure to sunlight), strict vegetarians (especially if their diet is also low in calcium and high in fiber), and chronic alcoholics. Most cases of vitamin D deficiency, however, are a result of diseases causing **fat malabsorption** or severe liver and kidney disease (see Clin. Corr. 28.1 and 28.2). Certain drugs also interfere with vitamin D metabolism. For example, corticosteroids stimulate the conversion of vitamin D to inactive metabolites and have been shown to cause bone demineralization when used for long periods of time.

Vitamin D can also be toxic in doses 10–100 times the RDA. The mechanism of **vitamin D toxicity** is summarized in Figure 28.5*d*. Enhanced calcium absorption and bone resorption cause hypercalcemia, which can lead to metastatic calcification. The enhanced bone resorption also causes bone demineralization similar to that seen in vitamin D deficiency. Finally, the high serum calcium leads directly to hypercalciuria, which predisposes the patient to formation of renal stones.

Vitamin E Is a Mixture of Tocopherols

For many years **vitamin E** was described as the "vitamin in search of a disease." While vitamin E deficiency diseases are still virtually unknown, its metabolic role in the body has become better understood in recent years. Vitamin E occurs in the diet as a mixture of several closely related compounds, called tocopherols.

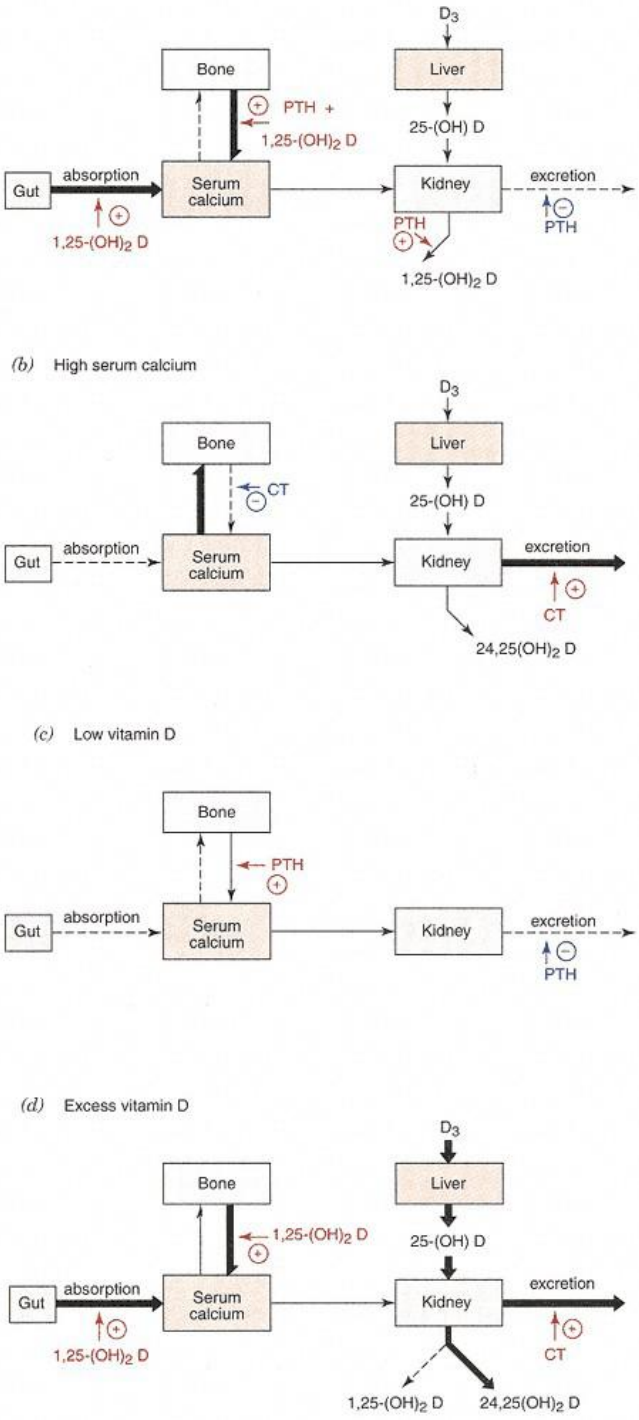

Figure 28.5
Vitamin D and calcium homeostasis.
Dominant pathways of calcium metabolism under each set of metabolic conditions are shown with heavy arrows. The effect of various hormones on these pathways is shown by red arrows for stimulation or blue arrows for repression. PTH, parathyroid hormone; D, cholecalciferol; 25-(OH)D, 25-hydroxycholecalciferol; and 1,25-$(OH)_2$D, 1-α,25-dihy-droxycholecalciferol.

α-Tocopherol is the most potent and is used as the measure of vitamin E potency (1 α-tocopherol equiv = 1 mg α-tocopherol).

First and foremost, vitamin E is an important naturally occurring **antioxidant.** Due to its lipophilic character it accumulates in circulating lipoproteins, cellular membranes, and fat deposits, where it reacts very rapidly with molecular oxygen and free radicals. It acts as a scavenger for these compounds, protecting unsaturated fatty acids (especially those in the membranes) from peroxidation reactions. Vitamin E appears to play a role in cellular respiration, either by stabilizing coenzyme Q or by helping transfer electrons to coenzyme Q. It also appears to enhance heme synthesis by increasing the levels of -aminolevulinic acid (ALA) synthetase and ALA dehydratase. Most of these vitamin E effects are thought to be an indirect effect of its antioxidant potential, rather than its actual participation as a coenzyme in any biochemical reactions. For example, an important role of vitamin E in humans is to prevent oxidation of **LDL,** since it appears to be the oxidized form of LDL that is atherogenic. Finally, neurological symptoms have been reported following prolonged vitamin E deficiency associated with malabsorption diseases.

Studies on the recommended levels of vitamin E in the diet have been hampered by the difficulty of producing severe vitamin E deficiency in humans. In general, it has been assumed that the vitamin E levels in the American diet are sufficient, since no major vitamin E deficiency diseases have been found. However, vitamin E requirements increase as intake of polyunsaturated fatty acids (PUFAs) increases. While the recent emphasis on high PUFA diets to reduce serum cholesterol may be of benefit in controlling heart disease, the propensity of PUFA to form free radicals on exposure to oxygen may lead to an increased cancer risk. Thus it appears only prudent to increase vitamin E intake in high PUFA diets.

Premature infants fed on formulas low in vitamin E sometimes develop a form of hemolytic anemia that can be corrected by vitamin E supplementation. Adults suffering from fat malabsorption show a decreased red blood cell survival time. Hence vitamin E supplementation may be necessary with premature infants and in cases of fat malabsorption. In addition, recent studies have suggested that supplementation with at least 100 mg day^{-1} of vitamin E may decrease the risk of heart disease. This is well above the current RDA and is far greater than can be obtained from even a very well balanced diet. These findings have rekindled the debate as to whether dietary recommendations should consider optimal levels of nutrients rather than the levels needed to prevent deficiency diseases. As a fat-soluble vitamin, E has the potential for toxicity. However, it does appear to be the least toxic of the fat-soluble vitamins. No instances of toxicity have been reported at doses of 1600 mg day^{-1} or less.

Vitamin K Is a Quinone Derivative

Vitamin K is found naturally as **K_1** (phytylmenaquinone) in green vegetables and **K_2** (multiprenylmenaquinone), which is synthesized by intestinal bacteria. The body converts synthetically prepared menaquinone (menadione) and a number of water-soluble analogs to a biologically active form of vitamin K. Dietary requirements are measured in terms of micrograms of vitamin K_1 with the RDA for adults being in the range of 60–80 g day^{-1}.

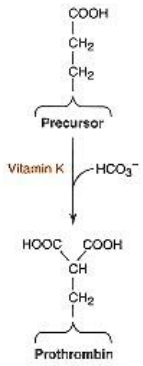

Figure 28.6
Function of vitamin K.

Vitamin K_1 is required for the conversion of several **clotting factors** and **prothrombin** to the active state. The mechanism of this action has been most clearly delineated for prothrombin (see p. 970). Prothrombin is synthesized as an inactive precursor called preprothrombin. Conversion to the active form requires a vitamin K-dependent **carboxylation** of specific glutamic acid residues to **γ-carboxyglutamic acid** (Figure 28.6). The γ-carboxyglutamic acid residues are good chelators and allow prothrombin to bind calcium. The prothrombin-Ca^{2+} complex in turn binds to the phospholipid membrane, where

proteolytic conversion to thrombin can occur *in vivo*. The mechanism of the carboxylation reaction has not been fully clarified but appears to involve the intermediate formation of a 2,3-epoxide derivative of vitamin K. **Dicumarol,** a naturally occurring anticoagulant, inhibits the reductase, which converts the epoxide back to the active vitamin.

Recently, vitamin K has been shown to be essential for the synthesis of γ-carboxyglutamic acid residues in the protein **osteocalcin,** which accounts for 15–20% of the noncollagen protein in the bone of most vertebrates. As with prothrombin, the γ-carboxyglutamic acid residues are responsible for most of the calcium-binding properties of osteocalcin. Because osteocalcin synthesis is controlled by vitamin D and osteocalcin is thought to play an important role in bone remodeling, vitamin K may be important for bone formation.

The only readily detectable symptom of **vitamin K deficiency** in humans is increased coagulation time, but some studies have suggested that vitamin K deficiency may be a factor in **osteoporosis** as well. Since vitamin K is synthesized by bacteria in the intestine, deficiencies have long been assumed to be rare. However, recent studies have suggested that intestinally synthesized vitamin K may not be efficiently absorbed and marginal vitamin K deficiencies may be more common than originally thought. The most common deficiency occurs in newborn infants (see Clin. Corr. 28.3), especially those whose mothers have been on anticonvulsant therapy (see Clin. Corr. 28.4). Vitamin K deficiency also occurs in patients with **obstructive jaundice** and other diseases leading to severe **fat malabsorption** (see Clin. Corr. 28.1) and patients on long-term **antibiotic therapy** (which may destroy vitamin K-synthesizing organisms in the intestine). Finally, vitamin K deficiency is sometimes seen in the elderly,

CLINICAL CORRELATION 28.3

Nutritional Considerations in the Newborn

Newborn infants are at special nutritional risk. In the first place, this is a period of very rapid growth, and needs for many nutrients are high. Some micronutrients (such as vitamins E and K) do not cross the placental membrane well and tissue stores are low in the newborn infant. The gastrointestinal tract may not be fully developed, leading to malabsorption problems (particularly with respect to the fat-soluble vitamins). The gastrointestinal tract is also sterile at birth and the intestinal flora that normally provide significant amounts of certain vitamins (especially vitamin K) take several days to become established. If the infant is born prematurely, the nutritional risk is slightly greater, since the gastrointestinal tract will be less well developed and the tissue stores will be less.

The most serious nutritional complications of newborns appear to be hemorrhagic disease. Newborn infants, especially premature infants, have low tissue stores of vitamin K and lack the intestinal flora necessary to synthesize the vitamin. Breast milk is also a relatively poor source of vitamin K. Approximately 1 out of 400 live births shows some signs of hemorrhagic disease. One milligram of the vitamin at birth is usually sufficient to prevent hemorrhagic disease.

Iron is another potential problem. Most newborn infants are born with sufficient reserves of iron to last 3–4 months (although premature infants are born with smaller reserves). Since iron is present in low amounts in both cow's milk and breast milk, iron supplementation is usually begun at a relatively early age by the introduction of iron-fortified cereal. Vitamin D levels are also somewhat low in breast milk and supplementation with vitamin D is usually recommended. However, some recent studies have suggested that iron in breast milk is present in a form that is particularly well utilized by the infant and that earlier studies probably underestimated the amount of vitamin D available in breast milk. Other vitamins and minerals appear to be present in adequate amounts in breast milk as long as the mother is getting a good diet. Recent studies have suggested that in situations in which infants must be maintained on assisted ventilation with high oxygen concentrations, supplemental vitamin E may reduce the risk of bronchopulmonary dysplasia and retrolental fibroplasia, two possible side effects of oxygen therapy. Studies have also suggested that anemia of prematurity may respond to supplemental folate and vitamin B_{12}.

In summary, most infants are provided with supplemental vitamin K at birth to prevent hemorrhagic disease. Breast-fed infants are usually provided with supplemental vitamin D, with iron being introduced along with solid foods. Bottle-fed infants are provided with supplemental iron. If infants must be maintained on oxygen, supplemental vitamin E may be beneficial.

Barness, L. A. Pediatrics. In: H. Schneider, C. E. Anderson, and D. B. Coursin (Eds.), *Nutritional Support of Medical Practice*, 2nd ed. New York: Harper & Row, 1983, pp. 541–561; Huysman, M. W., and Sauer, P. J. The vitamin K controversy. *Curr. Opin. Pediatr.* 6:129, 1994; Worthington-White, D. A., Behnke, M., and Gross, S. Premature infants require additional folate and vitamin B_{12} to reduce the severity of anemia of prematurity. *Am. J. Clin. Nutr.* 60:930, 1994; and Mueller, D. P. R. Vitamin E therapy in retinopathy of prematurity. *Eye* 6:221, 1992.

CLINICAL CORRELATION 28.4

Anticonvulsant Drugs and Vitamin Requirements

Anticonvulsant drugs such as phenobarbital or diphenylhydantoin (DPH) present an excellent example of the type of drug–nutrient interactions that are of concern to the physician. Metabolic bone disease appears to be the most significant side effect of prolonged anticonvulsant therapy. Whereas children and adults on these drugs seldom develop rickets or severe osteomalacia, as many as 65% of those on long-term therapy will have abnormally low serum calcium and phosphorus and abnormally high serum alkaline phosphatase. Some bone loss is usually observed in these cases. While the cause of the hypocalcemia and bone loss is thought to be an effect of the anticonvulsant drugs on vitamin D metabolism, not all of the studies have shown decreased levels of 25-(OH) D and 1,25-$(OH)_2$D in patients on these drugs. However, supplemental vitamin D in the range of 2000–10,000 units per day appears to correct both the hypocalcemia and osteopenia. Anticonvulsants also tend to increase needs for vitamin K, leading to an increased incidence of hemorrhagic disease in infants born to mothers on anticonvulsants. In addition, anticonvulsants appear to increase the need for folic acid and B_6. Low serum folate levels are seen in 75% of patients on anticonvulsants and megaloblastic anemia may occur in as many as 50% without supplementation. By bio-chemical parameters, 30–60% of the children on anticonvulsants exhibit some form of B_6 deficiency. Clinical symptoms of B_6 deficiency are rarely seen, however. From 1 to 5 mg of folic acid and 10 mg of vitamin B_6 appear to be sufficient for most patients on anticonvulsants. Since folates may speed up the metabolism of some anticonvulsants, it is important that excess folic acid not be given.

Moslet, U., and Hansen, E. S. A review of vitamin K, epilepsy and pregnancy. *Acta Neurol. Scand.* 85:39, 1992: Rivery, M. D., and Schottelius, D. D. Phenytoin-folic acid: a review. *Drug Intelligence Clin. Pharm.* 18:292, 1984; and Tjellesen, L. Metabolism and action of vitamin D in epileptic patients on anticonvulsant treatment and healthy adults. *Dan. Med. Bull.* 41:139, 1994.

who are prone to poor liver function (reducing preprothrombin synthesis) and fat malabsorption. Clearly, vitamin K deficiency should be suspected in patients demonstrating easy bruising and prolonged clotting time.

28.5— Water-Soluble Vitamins

Water-soluble vitamins differ from fat-soluble vitamins in several important aspects. Most are readily excreted once their concentration surpasses the renal threshold. Thus toxicities are rare. Deficiencies of these vitamins occur relatively quickly on an inadequate diet. Their metabolic stores are labile and depletion can often occur in a matter of weeks or months. Since the water-soluble vitamins are coenzymes for many common biochemical reactions, it is often possible to assay vitamin status by measuring one or more enzyme activities in isolated red blood cells. These assays are especially useful if one measures both the endogenous enzyme activity and the stimulated activity following addition of the active coenzyme derived from that vitamin.

Most of the water-soluble vitamins are converted to coenzymes, which are utilized either in the pathways for energy generation or hematopoiesis. Deficiencies of the energy-releasing vitamins produce a number of overlapping symptoms. In many cases the vitamins participate in so many biochemical reactions that it is impossible to pinpoint the exact biochemical cause of any given symptom. However, it is possible to generalize that because of the central role these vitamins play in energy metabolism, deficiencies show up first in rapidly growing tissues. Typical symptoms include **dermatitis, glossitis** (swelling and reddening of the tongue), **cheilitis** at the corners of the lips, and **diarrhea.** In many cases nervous tissue is also involved due to its high energy demand or specific effects of the vitamin. Some of the common neurological symptoms include **peripheral neuropathy** (tingling of nerves at the extremities), depression, mental confusion, lack of motor coordination, and **malaise.** In some cases demyelination and degeneration of nervous tissues also occur. These deficiency symptoms are so common and overlapping that they can be

considered as properties of the energy-releasing vitamins as a class, rather than being specific for any one.

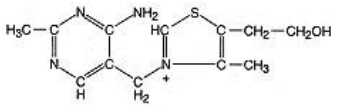

Figure 28.7
Structure of thiamine.

28.6— Energy-Releasing Water-Soluble Vitamins

Thiamine (Vitamin B_1) Forms the Coenzyme Thiamine Pyrophosphate (TPP)

Thiamine (Figure 28.7) is rapidly converted to the coenzyme **thiamine pyrophosphate (TPP),** which is required for the key reactions catalyzed by pyruvate dehydrogenase complex and α-ketoglutarate dehydrogenase complex (Figure 28.8). Cellular energy generation is severely compromised in thiamine deficiency. TPP is also required for the transketolase reactions of the pentose phosphate pathway. While the pentose phosphate pathway is not quantitatively important in terms of energy generation, it is the sole source of ribose for the synthesis of nucleic acid precursors and the major source of NADPH for fatty acid biosynthesis and other biosynthetic pathways. Red blood cell transketolase is also the enzyme most commonly used for measuring thiamine status in the body. TPP appears to function in transmission of nerve impulses. TPP (or a related metabolite, thiamine triphosphate) is localized in peripheral nerve membranes. It appears to be required for acetylcholine synthesis and may also be required for ion translocation reactions in stimulated neural tissue.

Although the biochemical reactions involving TPP are fairly well characterized, it is not clear how these biochemical lesions result in the symptoms of **thiamine deficiency.** The pyruvate dehydrogenase and transketolase reactions are the most sensitive to thiamine levels. Thiamine deficiency appears to selectively inhibit carbohydrate metabolism, causing an accumulation of pyruvate. Cells may be directly affected by lack of available energy and NAPDH or

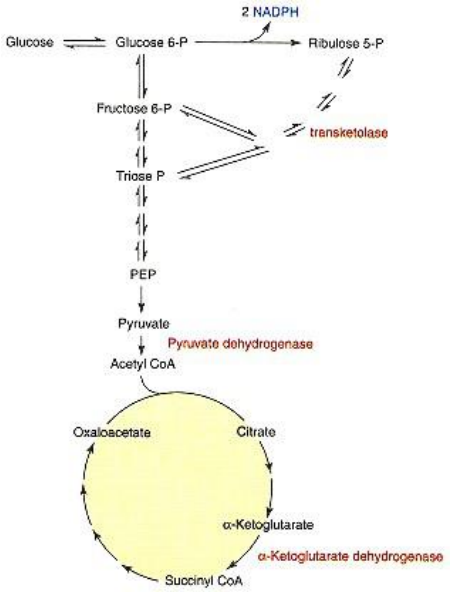

Figure 28.8
Summary of important reactions involving thiamine pyrophosphate.
The reactions involving thiamine pyrophosphate are indicated in red.

may be poisoned by the accumulated pyruvate. Other symptoms of thiamine deficiency involve the neural tissue and probably result from the direct role of TTP in nerve transmission.

Loss of appetite, constipation, and nausea are among the earliest symptoms of **thiamine deficiency.** Mental depression, peripheral neuropathy, irritability, and fatigue are other early symptoms and probably directly relate to the role of thiamine in maintaining healthy nervous tissue. These symptoms of thiamine deficiency are most often seen in the elderly and low-income groups on restricted diets. Symptoms of moderately severe thiamine deficiency include **mental confusion, ataxia** (unsteady gait while walking and general inability to achieve fine control of motor functions), and **ophthalmoplegia** (loss of eye coordination). This set of symptoms is usually referred to as **Wernicke–Korsakoff syndrome** and is most commonly seen in chronic **alcoholics** (see Clin. Corr. 28.5). Severe thiamine deficiency is known as **beriberi.** Dry beriberi is characterized primarily by advanced neuromuscular symptoms, including atrophy and weakness of the muscles. When these symptoms are coupled with edema, the disease is referred to as wet beriberi. Both forms of beriberi can be associated with an unusual type of heart failure characterized by high cardiac output. Beriberi is found primarily in populations relying exclusively on polished rice for food, although cardiac failure is sometimes seen in alcoholics as well.

The thiamine requirement is proportional to caloric content of the diet and is in the range of 1.0–1.5 mg per day for the normal adult. This requirement should be raised somewhat if carbohydrate intake is excessive or if the metabolic rate is elevated (due to fever, trauma, pregnancy, or lactation). Coffee and tea

CLINICAL CORRELATION 28.5

Nutritional Considerations in the Alcoholic

Chronic alcoholics run considerable risk of nutritional deficiencies. The most common problems are neurologic symptoms associated with thiamine or pyridoxine deficiencies and hematological problems associated with folate or pyridoxine deficiencies. The deficiencies seen with alcoholics are not necessarily due to poor diet alone, although it is often a strong contributing factor. Alcohol causes pathological alterations of the gastrointestinal tract that often directly interfere with absorption of certain nutrients. The liver is the most important site of activation and storage of many vitamins. The severe liver damage associated with chronic alcoholism appears to interfere directly with storage and activation of certain nutrients.

Up to 40% of hospitalized alcoholics are estimated to have megaloblastic erythropoiesis due to folate deficiency. Alcohol appears to interfere directly with folate absorption and alcoholic cirrhosis impairs storage of this nutrient. Another 30% of hospitalized alcoholics have sideroblastic anemia or identifiable sideroblasts in erythroid marrow cells characteristic of pyridoxine deficiency. Some alcoholics also develop a peripheral neuropathy that responds to pyridoxine supplementation. This problem appears to result from impaired activation and increased degradation of pyridoxine. In particular, acetaldehyde (an end product of alcohol metabolism) displaces pyridoxal phosphate from its carrier protein in the plasma. The free pyridoxal phosphate is then rapidly degraded to inactive compounds and excreted.

The most dramatic nutritionally related neurological disorder is Wernicke–Korsakoff syndrome. The symptoms include mental disturbances, ataxia (unsteady gait and lack of fine motor coordination), and uncoordinated eye movements. Congestive heart failure similar to that seen with beriberi is also seen in a small number of these patients. While this syndrome may only account for 1–3% of alcohol-related neurologic disorders, the response to supplemental thiamine is so dramatic that it is usually worth consideration. The thiamine deficiency appears to arise primarily from impaired absorption, although alcoholic cirrhosis may also affect the storage of thiamine in the liver.

While those are the most common nutritional deficiencies associated with alcoholism, deficiencies of almost any of the water-soluble vitamins can occur and cases of alcoholic scurvy and pellagra are occasionally reported. Chronic ethanol consumption causes an interesting redistribution of vitamin A stores in the body. Vitamin A stores in the liver are rapidly depleted while levels of vitamin A in the serum and other tissues may be normal or slightly elevated. Apparently, ethanol causes both increased mobilization of vitamin A from the liver and increased catabolism of liver vitamin A to inactive metabolites by the hepatic P450 system. Alcoholic patients have decreased bone density and an increased incidence of osteoporosis. This probably relates to a defect in the 25-hydroxylation step in the liver as well as an increased rate of metabolism of vitamin D to inactive products by an activated cytochrome P450 system. Dietary calcium intake is also often poor. In fact, alcoholics generally have decreased serum levels of zinc, calcium, and magnesium due to poor dietary intake and increased urinary losses. Iron-deficiency anemia is very rare unless there is gastrointestinal bleeding or chronic infection. In fact, excess iron is a more common problem with alcoholics. Many alcoholic beverages contain relatively high iron levels, and alcohol appears to enhance iron absorption.

Hayumpa, A. M. Mechanisms of vitamin deficiencies in alcoholism. *Alcohol. Clin. Exp. Res.* 10:573, 1986; and Lieber, C. S. Alcohol, liver and nutrition. *J. Am. Coll Nutr.* 10:602, 1991.

contain substances that destroy thiamine, but this is not a problem for individuals consuming normal amounts of these beverages. Routine enrichment of cereals has assured that most Americans have an adequate intake of thiamine on a normal mixed diet.

Riboflavin Is Part of FAD and FMN

Riboflavin is the precursor of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), both of which are involved in a wide variety of redox reactions. The flavin coenzymes are essential for energy production and cellular respiration. The most characteristic symptoms of **riboflavin deficiency** are angular cheilitis, glossitis, and scaly dermatitis (especially around the nasolabial folds and scrotal areas). The best flavin-requiring enzyme for assaying riboflavin status appears to be erythrocyte glutathione reductase. The recommended riboflavin intake is 1.2–1.7 mg day^{-1} for the normal adult. Foods rich in riboflavin include milk, meat, eggs, and cereal products. Riboflavin deficiencies are quite rare in this country. When riboflavin deficiency does occur, it is usually seen in chronic **alcoholics.** Hypothyroidism has recently been shown to slow the conversion of riboflavin to FMN and FAD. It is not known whether this affects riboflavin requirements, however.

Niacin Is Part of NAD and NADP

Niacin is not a vitamin in the strictest sense of the word, since some niacin can be synthesized from tryptophan. However, conversion of tryptophan to niacin is relatively inefficient (60 mg of tryptophan is required for the production of 1 mg of niacin) and occurs only after all of the body requirements for tryptophan (protein synthesis and energy production) have been met. Since synthesis of niacin requires thiamine, pyridoxine, and riboflavin, it is also very inefficient on a marginal diet. Thus most people require dietary sources of both tryptophan and niacin. Niacin (nicotinic acid) and niacinamide (nicotinamide) are both converted to the ubiquitous oxidation–reduction coenzymes NAD^+ and $NADP^+$ in the body.

Borderline **niacin deficiencies** are first seen as a glossitis (redness) of the tongue, somewhat similar to riboflavin deficiency. Pronounced deficiencies lead to **pellagra,** which is characterized by the three Ds: dermatitis, diarrhea, and dementia. The dermatitis is characteristic in that it is usually seen only in skin areas exposed to sunlight and is symmetric. The neurologic symptoms are associated with actual degeneration of nervous tissue. Because of food fortification, pellagra is a medical curiosity in the developed world. Today it is primarily seen in **alcoholics,** patients with severe **malabsorption** problems, and **elderly** on very restricted diets. Pregnancy, lactation, and chronic illness lead to increased needs for niacin, but a varied diet will usually provide sufficient amounts.

Since tryptophan can be converted to niacin, and niacin can exist in a free or bound form, the calculation of available niacin for any given food is not a simple matter. For this reason, niacin requirements are expressed in terms of niacin equivalents (1 niacin equiv = 1 mg free niacin). The current recommendation of the Food and Nutrition Board for a normal adult is 13–19 niacin equivalents (NE) per day. The richest food sources of niacin are meats, peanuts and other legumes, and enriched cereals.

Pyridoxine (Vitamin B_6) Forms the Coenzyme Pyridoxal Phosphate

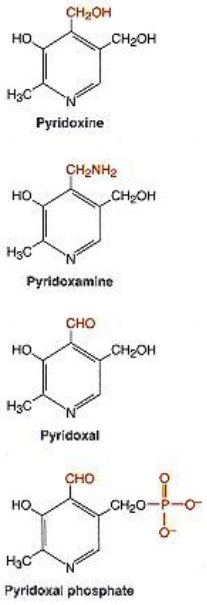

Figure 28.9
Structures of vitamin B_6.

Pyridoxine, pyridoxamine, and **pyridoxal** are all naturally occurring forms of vitamin B_6 (Figure 28.9). All three forms are efficiently converted by the body to **pyridoxal phosphate,** which is required for the synthesis, catabolism, and interconversion of amino acids. The role of pyridoxal phosphate in amino

acid metabolism has been discussed previously (see p. 449). While pyridoxal phosphate-dependent reactions are legion, there are a few instances in which the biochemical lesion seems to be directly associated with the symptoms of **B_6 deficiency** (Figure 28.10). Pyridoxal phosphate is essential for energy production from amino acids and can be considered an energy-releasing vitamin. Thus some of the symptoms of severe B_6 deficiency are similar to those of the other energy-releasing vitamins. Pyridoxal phosphate is also required for the synthesis of the neurotransmitters **serotonin** and **norepinephrine** and for synthesis of the sphingolipids necessary for myelin formation. These effects are thought to explain the irritability, nervousness, and depression seen with mild deficiencies and the peripheral neuropathy and convulsions observed with severe deficiencies. Pyridoxal phosphate is required for the synthesis of -aminolevulinic acid, a precursor of heme. B_6 deficiencies occasionally cause **sideroblastic anemia,** which is characteristically a microcytic anemia seen in the presence of high serum iron. Pyridoxal phosphate is also an essential component of glycogen phosphorylase; it is covalently linked to a lysine residue and stabilizes the enzyme. This role of B_6 may explain the decreased glucose tolerance associated with deficiency, although B_6 appears to have some direct effects on the glucocorticoid receptor as well. Vitamin B_6 is also required for the conversion of homocysteine to cysteine, and **hyperhomocysteinemia** appears to be a risk factor for cardiovascular disease. Finally, pyridoxal phosphate is one of the cofactors required for the conversion of tryptophan to NAD. While this may not be directly related to the symptomatology of B_6 deficiency, a tryptophan load test is a sensitive indicator of vitamin B_6 status (see Clin. Corr. 28.6, p. 1124).

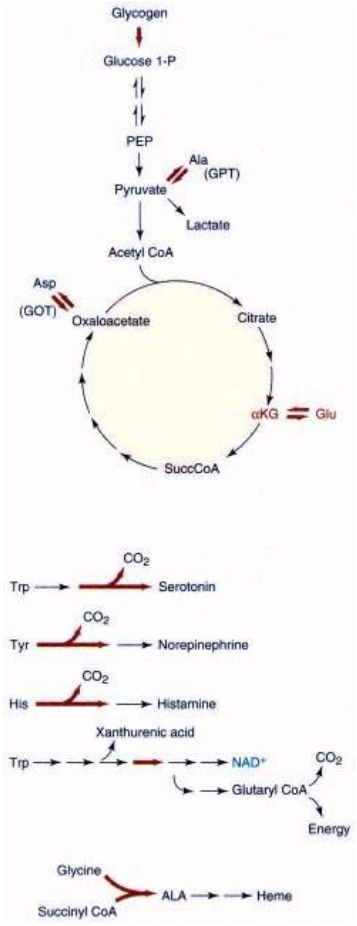

Figure 28.10
Important metabolic roles ofpyridoxal phosphate.
Reactions requiring pyridoxal phosphate are indicated with red arrows. ALA, -aminolevulinic acid; αKG, α-ketoglutarate; GPT, glutamate pyruvate aminotransferase; and GOT, glutamate oxaloacetate aminotransferase.

The requirement for B_6 in the diet is roughly proportional to the protein content of the diet. Assuming that the average American consumes close to 100 g of protein per day, the RDA for vitamin B_6 has been set at 1.4–2.0 mg day^{-1} for a normal adult. This requirement is increased during pregnancy and lactation and may increase somewhat with age as well. Vitamin B_6 is fairly widespread in foods, but meat, vegetables, whole-grain cereals, and egg yolks are among the richest sources.

Evaluation of B_6 nutritional status has become a controversial topic in recent years. Some of this controversy is discussed in Clin. Corr. 28.6. It has usually been assumed that the average American diet is adequate in B_6 and it is not routinely added to flour and other fortified foods. However, recent nutritional surveys have cast doubt on this assumption. A significant fraction of the survey population was found to consume less than two-thirds of the RDA for B_6.

Pantothenic Acid and Biotin Are Also Energy-Releasing Vitamins

Pantothenic acid is a component of coenzyme A (CoA) and the phosphopantetheine moiety of fatty acid synthase and thus is required for the metabolism of all fat, protein, and carbohydrate via the citric acid cycle. More than 70 enzymes have been described to date that utilize CoA or its derivatives. In view of the importance of these reactions, one would expect pantothenic acid deficiencies to be a serious concern in humans. This does not appear to be the case for two reasons: (1) pantothenic acid is very widespread in natural foods, probably reflecting its widespread metabolic role, and (2) most symptoms of pantothenic acid deficiency are vague and mimic those of other B vitamin deficiencies.

Biotin is the prosthetic group for a number of carboxylation reactions, the most notable being pyruvate carboxylase (needed for synthesis of oxaloacetate for gluconeogenesis and replenishment of the citric acid cycle), acetyl-CoA carboxylase (fatty acid biosynthesis), and propionyl-CoA carboxylase (methione, leucine, and valine metabolism). Biotin is found in peanuts, chocolate, and eggs and is synthesized by intestinal bacteria.

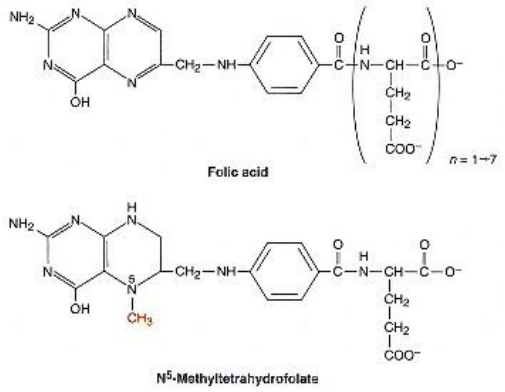

Figure 28.11
Structure of folic acid and N^5-methyltetrahydrofolate.

28.7— Hematopoietic Water-Soluble Vitamins

Folic Acid (Folacin) Functions As Tetrahydrofolate in One-Carbon Metabolism

The simplest form of **folic acid** is pteroylmonoglutamic acid. However, folic acid usually occurs as polyglutamate derivatives with from 2 to 7 glutamic acid residues (Figure 28.11). These compounds are taken up by intestinal mucosal cells and the extra glutamate residues are removed by **conjugase,** a lysosomal enzyme. The free folic acid is then reduced to **tetrahydrofolate** by the enzyme dihydrofolate reductase and circulated in the plasma primarily as the free N^5-methyl derivative of tetrahydrofolate (Figure 28.11). Inside cells, tetrahydrofolates are found primarily as polyglutamate derivatives, and these appear to be the biologically most potent forms. Folic acid is also stored as a polyglutamate derivative of tetrahydrofolate in the liver.

Various one-carbon tetrahydrofolate derivatives are used in biosynthetic reactions (Figure 28.12). They are required, for example, in the synthesis of choline, serine, glycine, purines, and dTMP. Since adequate amounts of choline and the amino acids can usually be obtained from the diet, the participation of folates in purine and dTMP synthesis appears to be metabolically the most

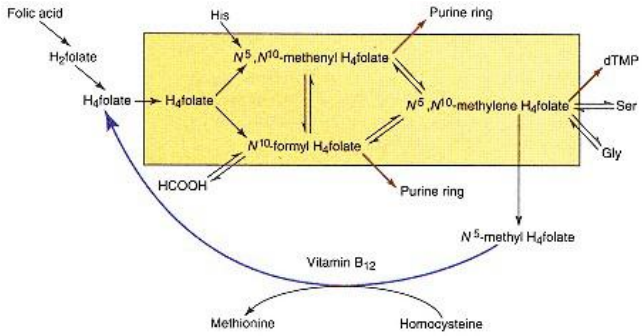

Figure 28.12
Metabolic roles of folic acid and vitamin B_{12} in one-carbon metabolism.
The metabolic interconversions of folic acid and its derivatives are indicated with black arrows. Pathways relying exclusively on folate are shown with red arrows. The important B_{12}-dependent reaction converting N^5-methyl H_4folate back to H_4folate is shown with a blue arrow. The box encloses the "pool" of C_1 derivatives of H_4folate.

CLINICAL CORRELATION 28.6

Vitamin B_6 Requirements for Users of Oral Contraceptives

The controversy over B_6 requirements for users of oral contraceptives best illustrates the potential problems associated with biochemical assays. For years, one of the most common assays for vitamin B_6 status had been the tryptophan load assay. This assay is based on the observation that when tissue pyridoxal phosphate levels are low, the normal catabolism of tryptophan is impaired and most of the tryptophan is catabolized by a minor pathway leading to synthesis of xanthurenic acid. Under many conditions, the amount of xanthurenic acid recovered in a 24-h urine sample following ingestion of a fixed amount of tryptophan is a valid indicator of vitamin B_6 status. When the tryptophan load test was used to assess the vitamin B_6 status of oral contraceptive users, however, alarming reports started appearing in the literature. Not only did oral contraceptive use increase the excretion of xanthurenic acid considerably but the amount of pyridoxine needed to return xanthurenic acid excretion to normal was 10 times the RDA and almost 20 times the level required to maintain normal B_6 status in control groups. As might be expected, this observation received much popular attention in spite of the fact that most classical symptoms of vitamin B_6 deficiency were not observed in oral contraceptive users.

More recent studies using other measures of vitamin B_6 have painted a slightly different picture. For example, erythrocyte glutamate pyruvate aminotransferase and erythrocyte glutamate oxaloacetate aminotransferase are both pyridoxal phosphate-containing enzymes. One can also assess vitamin B_6 status by measuring the endogenous activity of these enzymes and the degree of stimulation by added pyridoxal phosphate. These types of assays show a much smaller difference between nonusers and users of oral contraceptives. The minimum level of pyridoxine needed to maintain normal vitamin B_6 status as measured by these assays was only 2.0 mg day^{-1}, which is slightly greater than the RDA and about twice that needed by nonusers.

Why the large discrepancy? For one thing, it must be kept in mind that enzyme activity can be affected by hormones as well as vitamin cofactors. Kynureninase is the key pyridoxal phosphate-containing enzyme of the tryptophan catabolic pathway. The activity of kynureninase is regulated both by pyridoxal phosphate availability and by estrogen metabolites. Even with normal vitamin B_6 status most of the enzyme exists in the inactive apoenzyme form. However, this does not affect tryptophan metabolism because tryptophan oxygenase, the first enzyme of the pathway, is rate limiting. Thus the small amount of active holoenzyme is more than sufficient to handle the metabolites produced by the first part of the pathway. However, kynureninase is inhibited by estrogen metabolites. Thus with oral contraceptive use its activity is reduced to a level where it becomes rate limiting and excess tryptophan metabolites are shunted to xanthurenic acid. Higher than normal levels of vitamin B_6 overcome this problem by converting more apoenzyme to holoenzyme, thus increasing the total amount of enzyme. Since the estrogen was having a specific effect on the enzyme used to measure vitamin B_6 status in this assay, it did not necessarily mean that pyridoxine requirements were altered for other metabolic processes in the body.

Does this mean that vitamin B_6 status is of no concern to users of oral contraceptives? Oral contraceptives do appear to increase vitamin B_6 requirements slightly. Several dietary surveys have shown that a significant percentage of women in the 18-24-year age group consume diets containing less than 1.3 mg of pyridoxine per day. If these women are also using oral contraceptives, they are at some increased risk for developing a borderline deficiency. Thus, while the tryptophan load test was clearly misleading in a quantitative sense, it did alert the medical community to a previously unsuspected nutritional risk.

Bender, D. A. Oestrogens and vitamin B_6—actions and interactions. *World Rev. Nutr. Diet*. 51:140, 1987; and Kirksey, A., Keaton, K., Abernathy, R. P., and Grager, J. L. Vitamin B_6 nutritional status of a group of female adolescents. *Am. J. Clin. Nutr*. 31:946, 1978.

significant of those reactions. In addition, tetrahydrofolate and vitamin B_{12} are required, along with vitamin B_6, for the conversion of homocysteine to methionine. As mentioned earlier, this may also be significant because **hyperhomocysteinemia** appears to be a risk factor for cardiovascular disease. Methionine, of course, is also converted to *S*-adenosylmethionine, which is used in many methylation reactions.

The most pronounced effect of **folate deficiency** is inhibition of DNA synthesis due to decreased availability of purines and dTMP. This leads to arrest of cells in S phase and a characteristic "megaloblastic" change in size and shape of nuclei of rapidly dividing cells. The block in DNA synthesis slows down maturation of red blood cells, causing production of abnormally large "macrocytic" red blood cells with fragile membranes. Thus a **macrocytic anemia** associated with megaloblastic changes in the bone marrow is characteristic of folate deficiency. In addition, **hyperhomocysteinemia** is fairly common in the elderly population and appears to be due to inadequate intake and/or decreased utilization of folate, vitamin B_6, and vitamin B_{12}. Elevated homocysteine levels usually respond to supplementation with RDA levels of those vitamins.

There are many causes of **folate deficiency,** including inadequate intake, impaired absorption, increased demand, and impaired metabolism. Some dietary surveys have suggested that inadequate intake may be more common than previously supposed. However, as with most other vitamins, inadequate intake is probably not sufficient to trigger symptoms of folate deficiency in the absence of increased requirements or decreased utilization. Perhaps the most common example of increased need occurs during **pregnancy and lactation.** As the blood volume and the number of rapidly dividing cells in the body increase, the need for folic acid increases. By the third trimester the folic acid requirement has almost doubled. In the United States almost 20–25% of otherwise normal pregnancies are associated with low serum folate levels, but actual megaloblastic anemia is rare and is usually seen only after multiple pregnancies. However, recent studies have shown that inadequate folate levels during the early stages of pregnancy increase the risk for **neural tube defects,** a type of birth defect. Normal diets seldom supply the 400 g of folate needed during pregnancy, so most physicians routinely recommend supplementation for women during the child-bearing years. Folate deficiency is common in **alcoholics** (see Clin. Corr. 28.5). Folate deficiencies are also seen in a number of malabsorption diseases and are occasionally seen in the elderly, due to a combination of poor dietary habits and poor absorption.

There are a number of drugs that also directly interfere with folate metabolism. **Anticonvulsants** and **oral contraceptives** may interfere with folate absorption and anticonvulsants appear to increase catabolism of folates (see Clin. Corr. 28.4). Oral contraceptives and estrogens also appear to interfere with folate metabolism in their target tissue. Long-term use of any of these drugs can lead to folate deficiencies unless adequate supplementation is provided. For example, 20% of patients using oral contraceptives develop megaloblastic changes in the cervicovaginal epithelium, and 20–30% show low serum folate levels.

Vitamin B_{12} (Cobalamine) Contains Cobalt in a Tetrapyrrole Ring

Pernicious anemia, a megaloblastic anemia associated with neurological deterioration, was invariably fatal until 1926 when liver extracts were shown to be curative. Subsequent work showed the need for both an **extrinsic factor** present in liver and an **intrinsic factor** produced by the body: **vitamin B_{12}** was the extrinsic factor. Chemically, vitamin B_{12} consists of **cobalt** in a coordination state of six—coordinated in four positions by a tetrapyrrole (or corrin) ring, in one position by a benzimidazole nitrogen, and in the sixth position by one of several different ligands (Figure 28.13). The crystalline forms of B_{12} used in supplementation are usually hydroxycobalamine or cyanocobalamine. In foods B_{12} usually occurs bound to protein in the methyl or 5 -deoxyadenosyl forms. To be utilized the B_{12} must first be removed from the protein by acid hydrolysis in the stomach or trypsin digestion in the intestine. It then must combine with **intrinsic factor,** a protein secreted by the stomach, which carries it to the ileum for absorption.

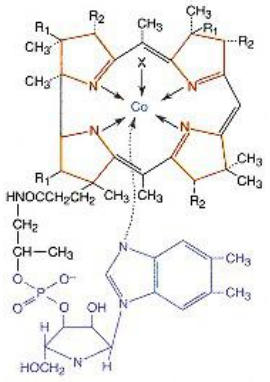

Figure 28.13
Structure of vitamin B_{12} (cobalamine).

In humans there are two major symptoms of B_{12} deficiency (hematopoietic and neurological), and only two biochemical reactions in which B_{12} is known to participate (Figure 28.14). Thus it is very tempting to speculate on exact cause and effect mechanisms. The methyl derivative of B_{12} is required for conversion of homocysteine to methionine and the 5-deoxyadenosyl derivative is required for the methylmalonyl-CoA mutase reaction (methylmalonyl CoA succinyl CoA), which is a key step in the catabolism of some branched-chain amino acids. The neurologic disorders seen in B_{12} deficiency are due to progressive demyelination of nervous tissue. It has been proposed that the

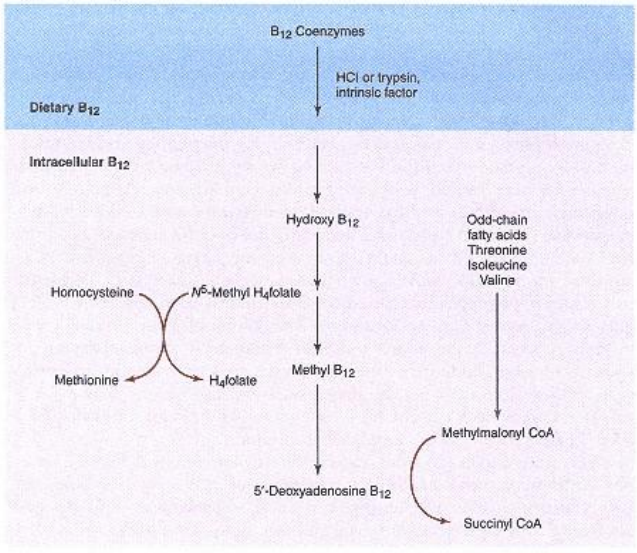

Figure 28.14
Metabolism of vitamin B_{12}.
Metabolic interconversions of B_{12} are indicated with light arrows, and B_{12}-requiring reactions are indicated with red arrows. Other related pathways are indicated with a blue arrow.

methylmalonyl CoA that accumulates interferes with myelin sheath formation in two ways.

1. Methylmalonyl CoA is a competitive inhibitor of malonyl CoA in fatty acid biosynthesis. Since the myelin sheath is continually turning over, any severe inhibition of fatty acid biosynthesis will lead to its eventual degeneration.

2. In the residual fatty acid synthesis, methylmalonyl CoA can substitute for malonyl CoA in the reaction sequence, leading to branched-chain fatty acids, which might disrupt normal membrane structure. There is some evidence supporting both mechanisms.

Megaloblastic anemia associated with B_{12} deficiency is thought to reflect the effect of B_{12} on folate metabolism. The B_{12}-dependent homocysteine to methionine conversion (homocysteine + N^5-methyl THF methionine + THF) appears to be the only major pathway by which N^5-methyltetrahydrofolate can return to the tetrahydrofolate pool (Figure 28.14). Thus in B_{12} deficiency there is a buildup of N_5-methyltetrahydrofolate and a deficiency of the tetrahydrofolate derivatives needed for purine and dTMP biosynthesis. Essentially all of the folate becomes "trapped" as the N^5-methyl derivative. Vitamin B_{12} also may be required for uptake of folate by cells and for its conversion to the biologically more active polyglutamate forms. High levels of supplemental folate can overcome the megaloblastic anemia associated with B_{12} deficiencies but not the neurological problems. Hence caution must be taken in using folate to treat megaloblastic anemia.

Vitamin B_{12} is widespread in foods of animal origin, especially meats. Liver stores up to a 6-year supply of vitamin B_{12}. Thus **deficiencies** of B_{12} are extremely rare. They are occasionally seen in older people due to insufficient production of intrinsic factor and/or HCl in the stomach. B_{12} deficiency can also be seen in patients with severe malabsorption diseases and in long-term **vegetarians.**

28.8— Other Water-Soluble Vitamins

Ascorbic Acid Functions in Reduction and Hydroxylation Reactions

Vitamin C or ascorbic acid is a six-carbon compound closely related to glucose. Its main biological role is as a reducing agent in several important hydroxylation reactions in the body. Ascorbic acid is required for the hydroxylation of lysine and proline in protocollagen. Without this hydroxylation protocollagen cannot properly cross-link into normal collagen fibrils. Thus vitamin C is obviously important for maintenance of normal connective tissue and for wound healing, since the connective tissue is laid down first. Vitamin C is also necessary for bone formation, since bone tissue has an organic matrix containing collagen as well as the inorganic, calcified portion. Finally, collagen appears to be a component of the ground substance surrounding capillary walls, so vitamin C deficiency is associated with **capillary fragility.**

Since vitamin C is concentrated in the adrenal gland, especially in periods of stress, it may be required for hydroxylation reactions in synthesis of some corticosteroids. Ascorbic acid has other important properties as a reducing agent, which appear to be nonenzymatic. For example, it aids in **absorption of iron** by reducing it to the ferrous state in the stomach. It spares vitamin A, vitamin E, and some B vitamins by protecting them from oxidation. Also, it enhances the utilization of folic acid, either by aiding the conversion of folate to tetrahydrofolate or the formation of polyglutamate derivatives of tetrahydrofolate. Finally, vitamin C appears to be a biologically important antioxidant. The National Research Council has recently concluded that adequate amounts (RDA levels) of antioxidants such as β-carotene and vitamin C in the diet reduce the risk of **cancer.** The data for other naturally occurring antioxidants such as vitamin E and selenium are not yet conclusive.

Most of the symptoms of **vitamin C deficiency** can be directly related to its metabolic roles. Symptoms of mild vitamin C deficiency include easy bruising and formation of petechiae (small, pinpoint hemorrhages in skin) due to increased capillary fragility and decreased immunocompetence. **Scurvy** is associated with decreased wound healing, osteoporosis, hemorrhaging, and anemia. Osteoporosis results from the inability to maintain the collagenous organic matrix of the bone, followed by demineralization. Anemia results from extensive hemorrhaging coupled with defects in iron absorption and folate metabolism.

Since vitamin C is readily absorbed, deficiencies almost invariably result from poor diet and/or increased need. There is uncertainty over the need for vitamin C in periods of stress. In severe stress or trauma there is a rapid drop in serum vitamin C levels. In these situations most of the body's supply of vitamin C is mobilized to the adrenals and/or the area of the wound. Does this represent an increased demand for vitamin C, or merely a normal redistribution to those areas where it is needed most? Do the lowered serum levels of vitamin C impair its functions in other tissues in the body? The current consensus seems to be that the lowered serum vitamin C levels indicate an increased demand, but there is little agreement as to how much.

Smoking causes lower serum levels of vitamin C. In fact, the 1989 RDAs recommend that smokers consume 100 mg of vitamin C per day instead of the 60 mg day^{-1} needed by nonsmoking adults. **Aspirin** appears to block uptake of vitamin C by white blood cells. **Oral contraceptives** and **corticosteroids** also lower serum levels of vitamin C. While there is no universal agreement as to the seriousness of these effects, the possibility of marginal vitamin C deficiencies should be considered with any patient using these drugs over a long period of time, especially if dietary intake is less than optimal.

The most controversial question surrounding vitamin C is its use in megadoses to prevent and cure the **common cold.** Ever since this use of vitamin C was first popularized by Linus Pauling in 1970, the issue has generated

considerable controversy. However, some double-blind studies have suggested that while vitamin C supplementation does not appear to be useful in preventing the common cold, it may moderate its symptoms. The mechanism by which vitamin C ameliorates the symptoms of the common cold is not known. It has been suggested that vitamin C is required for normal leukocyte function or for synthesis and release of histamine during stress situations.

While **megadoses of vitamin C** are probably no more harmful than the widely used over-the-counter cold medications, some potential side effects of high vitamin C intake should be considered. For example, oxalate is a major metabolite of ascorbic acid. Thus high ascorbate intakes could theoretically lead to the formation of oxalate kidney stones in predisposed individuals. However, most studies have shown that excess vitamin C is primarily excreted as ascorbate rather than oxalate. Pregnant mothers taking megadoses of vitamin C may give birth to infants with abnormally high vitamin C requirements. Earlier suggestions that megadoses of vitamin C interfered with B_{12} metabolism have proved to be incorrect.

28.9— Macrominerals

Calcium Has Many Physiological Roles

Calcium is the most abundant mineral in the body. Most is in bone, but the small amount of calcium outside of bone functions in a number of essential processes. It is required for many enzymes, mediates some hormonal responses, and is essential for **blood coagulation.** It is also essential for muscle contractility and normal neuromuscular irritability. In fact, only a relatively narrow range of serum calcium levels is compatible with life. Since maintenance of constant serum calcium levels is so vital, an elaborate homeostatic control system has evolved (see pp. 862 and 1112). Low serum calcium stimulates formation of 1,25-dihydroxycholecalciferol, which enhances calcium absorption. If dietary calcium intake is insufficient to maintain serum calcium, 1,25-dihydroxychole-calciferol and parathyroid hormone stimulate bone resorption. Long-term dietary calcium insufficiency, therefore, almost always results in net loss of calcium from the bones.

Dietary **calcium requirements,** however, vary considerably from individual to individual due to the existence of other factors that affect availability of calcium. For example, vitamin D is required for optimal utilization of calcium. Excess dietary protein may upset calcium balance by causing more rapid excretion of calcium. Exercise increases the efficiency of calcium utilization for bone formation. Calcium balance studies carried out on Peruvian Indians, who have extensive exposure to sunlight, get extensive exercise, and subsist on low-protein vegetarian diets, indicate a need for only 300–400 mg calcium day^{-1}. However, calcium balance studies carried out in this country consistently show higher requirements and the RDA has been set at 800–1200 mg day^{2+}.

The chief symptoms of **calcium deficiency** are similar to those of vitamin D deficiency, but other symptoms such as muscle cramps are possible with marginal deficiencies. A significant portion of low-income children and adult females in this country do not have adequate calcium intake. This is of particular concern because these are the population groups with particularly high needs for calcium. For this reason, the U.S. Congress has established the WIC (Women and Infant Children) program to assure adequate protein, calcium, and iron for indigent families with pregnant/lactating mothers or young infants.

Dietary surveys show that 34–47% of the over-60 population consumes less than one-half the RDA for calcium. This is the group most at risk of developing **osteoporosis,** characterized by loss of bone organic matrix as well as progressive demineralization. Causes of osteoporosis are multifactorial and

largely unknown, but it appears likely that part of the problem has to do with calcium metabolism (see Clin. Corr. 28.7). Recent studies have also suggested that inadequate intake of calcium may result in elevated blood pressure. Although this hypothesis has not been conclusively demonstrated, it is of great concern because most low-sodium diets (which are recommended for patients with high blood pressure) severely limit dairy products, the main source of calcium for Americans.

Magnesium Is Another Important Macromineral

Magnesium is required for many enzyme activities and for neuromuscular transmission. Deficiency is most often observed in conditions of alcoholism, use of certain diuretics, and metabolic acidosis. The main symptoms of magnesium deficiency are weakness, tremors, and cardiac arrhythmia. There is some evidence that supplemental magnesium may help prevent the formation of calcium oxalate stones in the kidney.

CLINICAL CORRELATION 28.7

Diet and Osteoporosis

The controversies raging over the relationships between calcium intake and osteoporosis illustrate the difficulties we face in making simple dietary recommendations for complex biological problems. Based on the TV ads and wide variety of calcium-fortified foods on the market, it would be easy to assume that all an older woman needs to prevent osteoporosis is a diet rich in calcium. However, that may be like closing the barn door after the horse has left. There is strong consensus that the years from age 10 to 35, when the bone density is reaching its maximum, are the most important for reducing the risk of osteoporosis. The maximum bone density obtained during these years is clearly dependent on both calcium intake and exercise and dense bones are less likely to become seriously depleted of calcium following menopause. Unfortunately, most American women are consuming far too little calcium during these years. The RDA for calcium is 1200 mg day^{-1} (4 glasses of milk per day) for women from age 11 to 24 and 800 mg day^{-1} (2 glasses of milk per day) for women over 24. The median calcium intake for women in this age range is only about 500 mg day^{-1}. Thus it is clear that increased calcium intake should be encouraged in this group.

But what about postmenopausal women? After all, many of the advertisements seem to be targeted at this group. Do they really need more calcium? The 1994 NIH consensus panel on osteoporosis recommended that postmenopausal women consume up to 1500 mg of calcium per day, but this recommendation has been vigorously disputed by other experts in the field. Let's examine the evidence. Calcium balance studies have shown that many postmenopausal women need 1200–1500 mg of calcium per day to maintain a positive calcium balance (more calcium coming in than is lost in the urine), but that does not necessarily mean that the additional calcium will be stored in their bones. In fact, some recent studies have failed to find a correlation between calcium intake and loss of bone density in postmenopausal women while others have reported a protective effect. All of those studies have been complicated by the discovery that calcium intake may have different effects on different types of bones. Calcium intakes in the range of 1000–1500 mg day^{-1} appear to slow the decrease in density of cortical bone, such as that found in the hip, hand, and some parts of the forearm. Similar doses, however, appear to have little or no effect on loss of density from the trabecular bone found in the spine, wrist, and other parts of the forearm. At least some of the confusion in the earlier studies appears to have resulted from differences in the site used for measurement of bone density. Thus the effect of high calcium intakes alone on slowing bone loss in postmenopausal women remains controversial at present. It is clear that elderly women should be getting at least the RDA for calcium in their diet. With the recent concern about the fat content of dairy products, calcium intakes in this group appear to be decreasing rather than increasing. Furthermore, even with estrogen replacement therapy, calcium intake should not be ignored. Recent studies have shown that with calcium intakes in the range of 1000–1500 mg day^{-1}, the effective dose of estrogen can be reduced significantly.

While the advertisements and much of the popular literature focus on calcium intake, we also need to remember that bones are not made of calcium alone. If the diet is deficient in other nutrients, the utilization of calcium for bone formation will be impaired. Vitamin C is needed to form the bone matrix and the macrominerals magnesium and phosphorus are an important part of bone structure. Recent research has also shown that vitamin K and a variety of trace minerals, including copper, zinc, manganese, and boron, are important for bone formation. Thus calcium supplements may not be optimally utilized if the overall diet is inadequate. Vitamin D is important for absorption and utilization of calcium. It deserves special mention since it may be a particular problem for the elderly (see Clin. Corr. 28.9). Finally, an adequate exercise program is just as important as estrogen replacement therapy and an adequate diet for preventing the loss of bone density.

Schaafsma, G., Van Berensteyn, E. C. H., Raymakers, J. A., and Dursma, S.A. Nutritional aspects of osteoporosis. *World Rev. Nutr. Diet.* 49:121, 1987; Heaney, R. P. Calcium in the prevention and treatment of osteoporosis. *J. Intern. Med.* 231:169, 1992; and National Institutes of Health. Optimal calcium intake. *NIH Consens. Statement*, 12 (Nov. 4), 1994.

28.10— Trace Minerals

Iron Is Efficiently Reutilized

Iron metabolism is unique in that it operates largely as a closed system, with iron stores being efficiently reutilized by the body. Iron losses are minimal (<1 mg day^{-1}), but iron absorption is also minimal under the best of conditions. Iron usually occurs in foods in the ferric form bound to protein or organic acids. Before absorption can occur, the iron must be split from these carriers (a process that is facilitated by the acid secretions of the stomach) and reduced to the ferrous form (a process that is enhanced by ascorbic acid). Only 10% of the iron in an average mixed diet is usually absorbed, but the efficiency of absorption can be increased to 30% by severe iron deficiency. Iron absorption and metabolism have been discussed in Chapter 24 and are summarized in Figure 28.15.

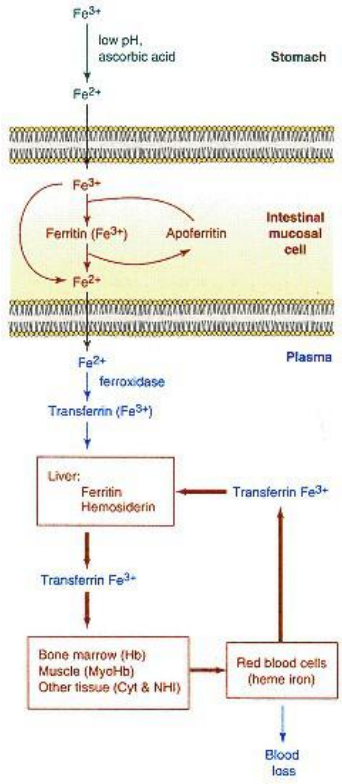

Figure 28.15
Overview of iron metabolism.
This figure reviews some of the features of iron metabolism discussed previously in Chapter 24. The red arrows indicate that most of the body's iron is efficiently reutilized by the pathway shown. Hb, hemoglobin; MyoHb, myoglobin; Cyt, cytochromes; and NHI, nonheme iron.

Iron plays a number of important roles in the body. As a component of hemoglobin and myoglobin, it is required for O_2 and CO_2 transport. As a component of cytochromes and nonheme iron proteins, it is required for oxidative phosphorylation. As a component of the essential lysosomal enzyme myeloperoxidase, it is required for proper phagocytosis and killing of bacteria by neutrophils. The best-known symptom of iron deficiency is a **microcytic hypochromic** anemia. Iron deficiency is also associated with **decreased immunocompetence.**

Assuming a 10–15% efficiency of absorption, the Food and Nutrition Board has set a recommended dietary allowance of 10 mg day^{-1} for normal adult males and 15 mg day^{-1} for menstruating females. For pregnant females this allowance is raised to 30 mg day^{-1}. While 10 mg of iron can easily be obtained from a normal diet, 15 mg is marginal at best and 30 mg can almost never be obtained. The best dietary sources are meats, dried legumes, dried fruits, and enriched cereal products.

Iron-deficiency anemia is considered the most prevalent nutritional disorder in the United States. Young children and pregnant females need enough iron for a continuing increase in blood volume. Menstruating females lose iron through blood loss and lactating females through production of lactoferrin. Thus iron deficiency anemia is primarily a problem for these population groups. This is reflected in dietary surveys, which indicate that 95% or more of children and menstruating females are not obtaining adequate iron in their diet. It is also reflected in biochemical measurements of a 10–25% incidence of iron deficiency anemia in this same group. Iron-deficiency anemia is also occasionally a problem with the elderly due to poor dietary intake and increased frequency of achlorhydria.

Because of the widespread nature of iron-deficiency anemia, government programs of nutritional intervention such as the WIC program have emphasized iron-rich foods. There has also been discussion of more extensive iron fortification of foods. There is concern among some nutritionists that iron deficiency has been overemphasized. Some recent studies suggest that **excess iron** intake may increase the risk of cardiovascular disease. Thus iron supplementation and the consumption of iron-fortified foods may be inappropriate for adult men and postmenopausal women. Excess iron can also lead to a rare condition called **hemochromatosis** in which iron deposits are found in abnormally high levels in many tissues. This can lead to liver, pancreatic, and cardiac dysfunction as well as pigmentation of the skin. This condition is usually only seen in hemolytic anemias and liver disease.

Iodine Is Incorporated into Thyroid Hormones

Dietary **iodine** is efficiently absorbed and transported to the **thyroid** gland, where it is stored and used for synthesis of the thyroid hormones triiodothyro-

nine and thyroxine. These hormones function in regulating the **basal metabolic rate** of adults and the growth and development of children. Saltwater fish are the best natural food sources of iodine and in earlier years population groups living in inland areas suffered from the endemic deficiency disease **goiter**. The most characteristic symptom of goiter is the enlargement of the thyroid gland to the point where a large nodule is visible on the neck. Since iodine has been routinely added to table salt, goiter has become relatively rare. However, in some inland areas, mild forms of goiter may still be seen in up to 5% of the population.

Zinc Is a Cofactor for Many Enzymes

Zinc absorption appears to be proportional to **metallothionein** levels in intestinal mucosa cells. The exact function of metallothionein in zinc transport is uncertain, but it may serve as a buffer for zinc ions as the metal transverses the intestinal cells. Over 300 zinc metalloenzymes have been described to date, including a number of regulatory proteins and both RNA and DNA polymerases. **Zinc deficiencies** in children are usually marked by poor growth and impairment of sexual development. In both children and adults zinc deficiencies result in poor wound healing. Zinc is also present in **gustin**, a salivary polypeptide that appears to be necessary for normal development of taste buds. Thus zinc deficiencies also lead to decreased taste acuity.

The few dietary surveys that have been carried out in this country have indicated that zinc intake may be marginal for many individuals. However, few symptoms of zinc deficiency other than decreased taste acuity can be demonstrated in those individuals. Severe zinc deficiency is seen primarily in **alcoholics** (especially if they have cirrhosis), patients with **chronic renal disease** or severe malabsorption diseases, and occasionally in people after long-term parenteral nutrition (TPN). The most characteristic early symptom of zinc-deficient patients on TPN is dermatitis. Zinc is occasionally used therapeutically to promote wound healing and may be of some use in treating gastric ulcers.

Copper Is Also a Cofactor for Important Enzymes

Copper absorption may also be dependent on the protein **metallothionein**, since excess intake of either copper or zinc interferes with the absorption of the other. Copper is present in a number of important metalloenzymes, including cytochrome *c* oxidase, dopamine β-hydroxylase, superoxide dismutase, lysyl oxidase, and ^{9}-desaturase. ^{9}-Desaturase is responsible for converting stearic acid (a C_{18} saturated fatty acid) to oleic acid (a C_{18} monounsaturated fatty acid). This may be responsible for the fact that dietary stearic acid does not have the cholesterol-raising property of the other saturated fatty acids. Lysyl oxidase is necessary for the conversion of certain lysine residues in collagen and elastin to allysine, which is needed for cross-linking. Some of the symptoms of **copper deficiency** include **hypercholesterolemia**, demineralization of bones, leukopenia, anemia, fragility of large arteries, and demyelination of neural tissue. Anemia appears to be due to a defect in iron metabolism. The copper-containing enzyme ferroxidase is necessary for conversion of iron from the Fe^{2+} state (in which form it is absorbed) to the Fe^{3+} state (in which form it can bind to the plasma protein transferrin). The bone demineralization and blood vessel fragility can be traced directly to defects in collagen and elastin formation. The hypercholesterolemia may be related to increases in the ratio of saturated to monounsaturated fatty acids of the C_{18} series due to reduced activity of the C_{18}, ^{9}-desaturase.

Copper balance studies carried out with human volunteers seem to indicate a minimum requirement of 1.0–2.6 mg day^{-1}. The RDA has been set at 1.5–3 mg day^{-1}. Most dietary surveys find the average American diet provides only 1 mg at <2000 cal day^{-1}. This remains a puzzling problem. Few symptoms of

copper deficiency have been identified in the general public. It is not known whether there exist widespread marginal copper deficiencies, or whether the copper balance studies are inaccurate. Recognizable symptoms of copper deficiency are usually seen only as a result of excess zinc intake and in **Menkes' syndrome**, a relatively rare X-linked hereditary disease associated with a defect in copper transport. **Wilson's disease**, an autosomal recessive disease, is associated with abnormal accumulation of copper in various tissues and can be treated with the naturally occurring copper chelating agent penicillamine.

Chromium Is a Component of Glucose Tolerance Factor

Chromium probably functions primarily as a component of **glucose tolerance factor (GTF),** a naturally occurring coordination complex between chromium, nicotinic acid, and the amino acids glycine, glutamate, cysteine, or glutathione. GTF potentiates the effects of insulin, presumably by facilitating its binding to cell receptor sites. The chief symptom of **chromium deficiency** is impaired glucose tolerance, a result of the decreased insulin effectiveness. The frequency of chromium deficiency is unknown. The RDA for chromium has been set at 50–200 g for a normal adult. The best current estimate is that the average consumption of chromium is around 30 g day^{-1} in the United States. Unfortunately, the range of intakes is very wide (5–100 g) even for individuals otherwise consuming balanced diets. Those most likely to have marginal or low intakes of chromium are individuals on low-caloric intakes or consuming large amounts of processed foods. Some concern has been voiced that many Americans may be marginally deficient in chromium.

Selenium Is a Scavenger of Peroxides

Selenium functions primarily in the metalloenzyme glutathione peroxidase, which destroys peroxides in the cytosol. Since the effect of vitamin E on peroxide formation is limited primarily to the membrane, both selenium and vitamin E appear to be necessary for efficient scavenging of peroxides. Selenium is one of the few nutrients not removed by the milling of flour and is usually thought to be present in adequate amounts in the diet. The selenium levels are very low in the soil in certain parts of the country, however, and foods raised in these regions will be low in selenium. Fortunately, this effect is minimized by the current food distribution system, which assures that the foods marketed in any one area are derived from a number of different geographical regions.

Manganese, Molybdenum, Fluoride, and Boron Are Other Trace Elements

Manganese is a component of pyruvate carboxylase and probably other metalloenzymes as well. **Molybdenum** is a component of xanthine oxidase. **Fluoride** is known to strengthen bones and teeth and is usually added to drinking water. **Boron** may also play an important role in bone formation.

28.11— The American Diet: Fact and Fallacy

Much has been said about the supposed deterioration of the American diet. How serious a problem is this? Clearly Americans are eating much more processed food than their ancestors. These foods differ from simpler foods in that they have a higher caloric density and a lower nutrient density than the foods they replace. However, these foods are almost uniformly enriched with iron, thiamine, riboflavin, and niacin. In many cases they are even fortified (usually as much for sales promotion as for nutritional reasons) with as many as 11–15 vitamins and minerals. Unfortunately, it is simply not practical to replace all of

the nutrients lost, especially the trace minerals. Imitation foods present a special problem in that they are usually incomplete in more subtle ways. For example, imitation cheese and imitation milkshakes that are widely sold in this country usually contain the protein and calcium one would expect of the food they replace, but often do not contain the riboflavin, which one would also obtain from these items. Fast food restaurants have also been much maligned in recent years. Some of the criticism has been undeserved, but fast food meals do tend to be high in calories and fat and low in certain vitamins and trace minerals. For example, the standard fast food meal provides over 50% of the calories the average adult needs for the entire day, while providing <5% of the vitamin A and <30% of biotin, folic acid, and pantothenic acid. Unfortunately, much of the controversy in recent years has centered around whether these trends are "good" or "bad." This simply obscures the issue at hand. Clearly it is possible to obtain a balanced diet which includes processed, imitation, and fast foods if one compensates by selecting foods for the other meals that are low in caloric density and rich in nutrients. Without such compensation the "balanced diet" becomes a myth.

28.12— Assessment of Nutritional Status in Clinical Practice

Figure 28.16
Factors affecting individual nutritional status.
Schematic representation of three important risk factors in determining nutritional status. A person on the periphery would have very low risk of any nutritional deficiency, whereas people in the green, orange, purple, or center areas would be much more likely to experience some symptoms of nutritional deficiencies.

Having surveyed the major micronutrients and their biochemical roles, it might seem that the process of evaluating the **nutritional status** of an individual patient would be an overwhelming task. It is perhaps best to recognize that there are three factors that can add to nutritional deficiencies: poor diet, malabsorption, and increased nutrient need. Only when two or three components overlap in the same person (Figure 28.16) do the risks of symptomatic deficiencies become significant. For example, infants and young children have increased needs for iron, calcium, and protein. Dietary surveys show that many of them consume diets inadequate in iron and some consume diets that are low in calcium. Protein is seldom a problem unless the children are being raised as strict vegetarians (see Clin. Corr. 28.8). Thus the chief nutritional concerns for most children are iron and calcium. **Teenagers** tend to consume diets low in calcium, magnesium, vitamin A, vitamin B_6, and vitamin C. Of all these nutrients, their needs are particularly high for calcium and magnesium during the teenage years, so these are the nutrients of greatest concern. **Young women** are likely to consume diets low in iron, calcium, magnesium, vitamin B_6, folic acid, and zinc—and all these nutrients are needed in greater amounts during pregnancy and lactation. **Adult women** often consume diets low in calcium, yet they may have a particularly high need for calcium to prevent rapid bone loss. Finally, the elderly have unique nutritional needs (see Clin. Corr. 28.9) and tend to have poor nutrient intake due to restricted income, loss of appetite, and loss of the ability to prepare a wide variety of foods. They are also more prone to suffer from malabsorption problems and to use multiple prescription drugs that increase nutrient needs (Table 28.1).

TABLE 28.1 Drug-Nutrient Interactions

Drug	*Potential Nutrient Deficiencies*
Alcohol	Thiamine Folic acid Vitamin B_6
Anticonvulsants	Vitamin D Folic acid Vitamin K
Cholestyramine	Fat-soluble vitamins Iron
Corticosteroids	Vitamin D and calcium Zinc Potassium
Diuretics	Potassium Zinc
Isoniazid	Vitamin B_6
Oral contraceptives and estrogens	Vitamin B_6 Folic acid and B_{12}

Illness and metabolic stress often cause increased demand or decreased utilization of certain nutrients. For example, diseases leading to fat malabsorption cause a particular problem with absorption of calcium and the fat-soluble vitamins. Other malabsorption diseases can result in deficiencies of many nutrients depending on the particular malabsorption disease. Liver and kidney disease can prevent activation of vitamin D and storage or utilization of many other nutrients including vitamin A, vitamin B_{12} and folic acid. Severe illness or trauma increases the need for calories, protein, and possibly some micronutrients such as vitamin C and certain B vitamins. Long-term use of many drugs in the treatment of chronic disease states can affect the need for certain micronutrients. Some of these are summarized in Table 28.1.

Who then is at a nutritional risk? Obviously, the answer depends on many

CLINICAL CORRELATION 28.8

Nutritional Considerations for Vegetarians

A vegetarian diet poses certain problems in terms of micronutrient intake that need to be recognized in designing a well-balanced diet. Vitamin B_{12} is of special concern, since it is found only in foods of animal origin. Vitamin B_{12} should be obtained from fortified foods (such as some brands of soybean milk) or in tablet form. However, surprisingly few vegetarians ever develop pernicious anemia, perhaps because an adult who has previously eaten meat will have a 6–10-year store of B_{12} in their liver.

Iron is another problem. The best vegetable sources of iron are dried beans, dried fruits, whole grain or enriched cereals, and green leafy vegetables. Vegetarian diets can provide adequate amounts of iron provided that these foods are regularly selected and consumed with vitamin C-rich foods to promote iron absorption. However, iron supplementation is usually recommended for children and menstruating women.

When milk and dairy products are absent from the diet, certain other problems must be considered as well. Normally, dietary vitamin D is obtained primarily from fortified milk. While some butters and margarines are fortified with vitamin D, they are seldom consumed in sufficient quantities to supply significant amounts of vitamin D. Although adults can usually obtain sufficient vitamin D from exposure to sunlight, dietary sources are often necessary during periods of growth and for adults with little exposure to sunlight. Vegetarians may need to obtain their vitamin D from fortified foods such as cereals, certain soybean milks, or in tablet form. Riboflavin is found in a number of vegetable sources such as green leafy vegetables, enriched breads, and wheat germ. However, since none of these sources supply more than 10% of the RDA in normal serving sizes, fortified cereals or vitamin supplements may become an important source of this nutrient. The important sources of calcium for vegetarians include soybeans, soybean milk, almonds, and green leafy vegetables. Those green leafy vegetables without oxalic acid (mustard, turnip, and dandelion greens, collards, kale, romaine lettuce, and loose leaf lettuce) are particularly good sources of calcium. None of these sources, however, is equivalent to cow's milk in calcium content, so calcium supplements are usually recommended during periods of rapid growth.

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CLINICAL CORRELATION 28.9

Nutritional Needs of Elderly Persons

If current trends continue, one out of five Americans will be over the age of 65 by the year 2030. With this projected aging of the American population, there has been increased interest in defining the nutritional needs of the elderly. Recent research shows altered needs of elderly persons for several essential nutrients. For example, the absorption and utilization of vitamin B_6 has been shown to decrease with age. Dietary surveys have consistently shown that B_6 is a problem nutrient for many Americans and the elderly appear to be no exception. Many older Americans get less than 50% of the RDA for B_6 from their diet. Vitamin B_{12} deficiency is also more prevalent in the elderly. Many older adults develop a condition called atrophic gastritis, which results in decreased acid production in the stomach. That along with a tendency toward decreased production of intrinsic factor leads to poor absorption of B_{12}. Recent research has suggested that elevated blood levels of the amino acid homocysteine may be a risk factor for atherosclerosis. Homocysteine is normally metabolized to methionine and cysteine in reactions requiring folic acid, B_{12} and B_6. Vitamin D can be a problem as well. Many elderly do not spend much time in the sunlight and to make matters worse the conversion of both 7-dehydrocholesterol to vitamin D in the skin and 25-(OH)D to 1,25-$(OH)_2$D in the kidney decreases with age. These factors often combine to produce significant deficiencies of 1,25-$(OH)_2$D in the elderly, which can in turn lead to negative calcium balance. These changes do not appear to be the primary cause of osteoporosis but they certainly may contribute to it.

There is some evidence for increased need for chromium and zinc as well. Chromium is not particularly abundant in the American diet and many elderly appear to have difficulty converting dietary chromium to the biologically active glucose tolerance factor. The clinical relevance of these observations is not clear but chromium deficiency could contribute to adult-onset diabetes. Similarly, dietary surveys show that most elderly consume between one-half and two-thirds the RDA for zinc. Conditions such as atrophic gastritis can also interfere with zinc absorption. Symptoms of zinc deficiency include loss of taste acuity, dermatitis, and a weakened immune system. All of these symptoms are common in the elderly population and it has been suggested that zinc deficiency might contribute.

Not all of the news is bad, however. Vitamin A absorption actually increases as we age and the ability of the liver to clear vitamin A from the blood decreases, so it remains in the circulation for a longer time. In fact, not only does the need for vitamin A decrease as we age, but the elderly also need to be particularly careful to avoid vitamin A toxicity. While this does not restrict their choice of foods or multivitamin supplements, they should generally avoid separate vitamin A supplements.

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factors. Nutritional counseling is an important part of treatment for infants, young children, and pregnant/lactating females. A brief analysis of a dietary history and further nutritional counseling are important when dealing with high-risk patients.

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Questions

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1. Recommended dietary allowances (RDAs):

   A. are standards for all individuals.

   B. meet special dietary needs arising from chronic diseases.

   C. include all nutritional needs.

   D. define optimal levels of nutrients.

   E. are useful only as general guides in evaluating the adequacy of diets.

2. The effects of vitamin A may include all of the following EXCEPT:

   A. prevention of anemia.

   B. serving as an antioxidant.

   C. cell differentiation.

   D. the visual cycle.

   E. induction of certain cancers.

3. All of the following organs are associated with vitamin D metabolism or effects of vitamin D on calcium metabolism EXCEPT:

A. bone.

B. erythrocytes.

C. gut.

D. kidney.

E. liver.

Refer to the following for Questions 4–8:

A. vitamin A

B. vitamin K

C. niacin

D. vitamin D

E. vitamin B_{12} (cobalamine)

4. Requirement may totally be supplied by intestinal bacteria.

5. Precursor is synthesized by green plants.

6. Tryptophan is a precursor.

7. Deficiency may be seen in long-term adherence to a strict vegetarian diet.

8. Is required for normal regulation of calcium metabolism.

9. Ascorbic acid may be associated with all of the following EXCEPT:

A. iron absorption.

B. bone formation.

C. acute renal disease when taken in high doses.

D. wound healing

E. participation in hydroxylation reactions.

10. In assessing the adequacy of a person's diet:

A. age of the individual usually has little relevance.

B. trauma decreases activity, and hence decreases need for calories and possibly some micronutrients.

C. a 24-h dietary intake history provides an adequate basis for making a judgment.

D. currently administered medications must be considered.

E. intestine is the only organ whose health has substantial bearing on nutritional status.

Refer to the following for Questions 11–15:

A. calcium

B. iron

C. iodine

D. copper

E. selenium

11. Absorption is inhibited by excess dietary zinc.

12. Excess dietary protein causes rapid excretion.

13. Risk of nutritional deficiency is high in young children.

14. Unsupplemented diets of populations living in inland areas may be deficient.

15. Essential component of glutathione peroxidase.

Answers

1. E A: RDAs are designed for most individuals; exceptions occur. B: Diseases often change dietary requirements. C: Some nutritional needs may be unknown; the requirements for all known nutrients are not even clear. D: Optimal levels of nutrients are hard to define; it depends on the criterion for optimal. (See pp. 1108–1109.)

2. E Vitamin A deficiency is linked to increased susceptibility to certain cancers. A: Retinyl phosphate serves as a glycosyl donor in the synthesis of certain glycoproteins (p. 1110), including transferrin (p. 1111). B: β-Carotene functions as an antioxidant. See p. 1110. C: Retinol and retinoic acid may function like steroid hormones (p. 1110). D: Retinol cycles between the ^{11}-cis and all-trans forms in the visual cycle (p. 1111).

3. B A: Calcium mobilization from bone is increased by 1,25-$(OH)_2$D. C: 1,25-$(OH)_2$D regulates calcium absorption by the gut. D: Kidney converts inactive 25-(OH) D to the active 1,25-$(OH)_2$D or to the inactive 24,25-$(OH)_2$D. E: Liver converts D to 25-(OH)D. See Figure 28.5 and p. 1114.

4. B See p. 1117.

5. A β-Carotene, from green plants, is converted to vitamin A (p. 1110).

6. C See p. 1121.

7. E This vitamin is from animal sources (p. 1126).

8. D 1,25-Dihydroxyvitamin D is required for calcium absorption and, along with parathyroid hormone, regulates bone resorption and calcium excretion.

9. C There has been speculation, not borne out by studies designed to shed light on the issue, that high levels of ascorbic acid could lead to oxalate kidney stones. A: Ascorbic acid aids in iron absorption by reducing iron. B: Ascorbic acid is essential for collagen synthesis, which is critical in bone formation. D and E: Ascorbic acid is required for the hydroxylation of lysine and proline residues in protocollagen and, therefore is required for wound healing. (See pp. 1127–1128.)

10. D Corticosteroids stimulate vitamin D inactivation. (p. 1114). A: Dramatic differences may occur at different ages. B: Trauma increases caloric requirements and probably requirements for specific micronutrients. C: You cannot be sure that any 24-h diet history is either accurate or representative of the individual's typical diet. E: While the intestine must function well enough to absorb nutrients, further metabolic changes are typically required. The metabolism of vitamin D by the liver and kidney (p. 1115) and the conversion of β-carotene to vitamin A exemplify these interorgan interrelations.

11. D See p. 1131.

12. A See p. 1128.

13. B Rapid growth in children causes high demands for iron (p. 1130).

14. C The problem is rare in the United States due to the common use of iodized salt (p. 1131).

15. E See p. 1132.