Vitamins and Vitamin-containing Drugs

Vitamins are organic substances, not synthesized within the body, that are essential in small amounts for the maintenance of normal metabolic functions. They do not furnish energy and are not utilized as building units for cellular structure. The lack of specific vitamins leads to distinctive deficiency states such as beriberi, rickets, scurvy, and xerophthalmia, or to conditions without definitive symptoms.

The term vitamin was derived in 1911 when an amine thought to prevent beriberi was isolated from rice bran; this essential or vital amine was called a vitamin. The term has been retained even though it is technically incongruous. Not all vitamins are amines; vitamins A, C, D, E, K, and inositol lack a nitrogen function of any type. The vitamins are diverse chemically, ranging from a simple molecule such as niacin to a complex molecule such as cyanocobalamin.

Biologic diversity is also noted with the vitamins. Vitamin B_2, niacin, and pantothenic acid function as coenzymes. Vitamin B_{12} and folic acid are involved in the biosynthetic transfer of 1-carbon units, and vitamin C is required for the biosynthesis of hydroxyproline, an essential component of collagen. Vitamins B_1 and B_6 are involved in the metabolism of carbohydrates and amino acids, respectively, and biotin has a function in metabolic carboxylation. Vitamins D and E selectively influence membrane transport. A number of vitamins (A, B_2, B_{12}, C, E, and niacin) are involved, directly or indirectly, in metabolic oxidation-reduction reactions.

Vitamins are distributed widely and are normally ingested as constituents of various food substances. Fresh fruits, leafy vegetables, whole grains, eggs, and liver are rich dietary sources of vitamins. Standardized, partially purified concentrates and isolated vitamins can be obtained for commercial purposes from a variety of animal, microbial, and plant sources; however, chemical synthesis is more feasible for many of the vitamins. Vitamins obtained from natural sources and those prepared synthetically are indistinguishable biochemically, nutritionally, and therapeutically.

Vitamins may be used as special dietary supplements or as drugs. Vitamin supplements are technically foods for special dietary needs and are unnecessary in most cases in which there is a balanced diet. Vitamins are considered drugs if they are taken to treat a condition of vitamin deficiency or to prevent imminent development of a disease. Deficiency conditions are the classic therapeutic uses for vitamins, but recognition of their utility in a

variety of hereditary conditions (inborn errors of metabolism) is increasing.

Situations in which vitamin supplementation is frequently indicated to prevent development of deficiency states can be grouped into four general categories. Inadequate dietary intake is encountered among alcoholics, the aged, and the impoverished. Increased metabolic requirements are associated with pregnancy, lactation, major surgery, and severe infections. Impaired intestinal absorption creates a problem in severe GI disorders, surgical resection, old age, obstructive jaundice, and cystic fibrosis. Iatrogenic situations, such as prolonged use of broad-spectrum antibiotics, isoniazid, total parenteral nutrition, or even oral contraceptives, sometimes require supplemental vitamin intake.

Accurate assessment of vitamin nutritional status can be very difficult, and self-diagnosis is the rule rather than the exception. These factors have contributed to the common daily ingestion of a multivitamin product by a large percentage of the American population. The risks to health associated with daily ingestion of unnecessary vitamins is undoubtedly less than with over ingestion of caloric foods, but the pharmacist and other health professionals must be alert to the need for detailed diagnostic assessment if an actual deficiency is suspected.

The U.S. Food and Drug Administration requires that vitamin products be labeled to show the percentage of the U.S. recommended daily allowance (US RDA) for each ingredient. The actual dietary needs depend on a number of variables, including age, illness, sex, stress, and weight. The US RDA guidelines are set sufficiently high to compensate for individual variations in the normal person. Extra strength formulations are frequently employed in situations of special need, such as pregnancy. When individual vitamins are used to treat inborn errors of metabolism, the dosage regimens are not related to the US RDA estimate. The US RDA values, which must be used for official labeling purposes, should not be confused with the recommended dietary allowances (RDA), values determined by the Food and Nutrition Board of the National Research Council. RDA values are considered to be good indicators of dietary needs for adequate nutrition in most healthy persons and are used widely by nutritionists, but they differ somewhat from the US RDA figures.

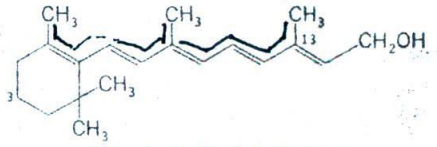
It is convenient for a number of purposes to classify the vitamins as fat soluble or water soluble.

FAT-SOLUBLE VITAMINS

Vitamins A, D, E, and K are fat soluble. Their absorption from the intestinal tract is associated with that of lipids, and a deficiency state may be caused by conditions that impair fat absorption. These conditions include pathologic situations such as biliary cirrhosis, cholecystitis, and sprue, and therapeutic situations such as cholestyramine regimens and excessive use of mineral oil laxatives.

Vitamin A

Vitamin A is a term applied to all derivatives of β-ionone, other than the carotenoids, that possess the biologic activity of all-*trans* retinol. Retinol is the major natural form of the vitamin, but known forms include the acetate and palmitate esters of the alcohol and such oxidation products as retinal, retinoic acid, and 3-dehydroretinol. The ester forms have good stability characteristics, and the acetate and palmitate esters of synthetically prepared all-*trans* retinol are the major commercial forms of vitamin A.



Vitamin A Alcohol (Retinol)

Retinol is readily absorbed (80 to 90%)

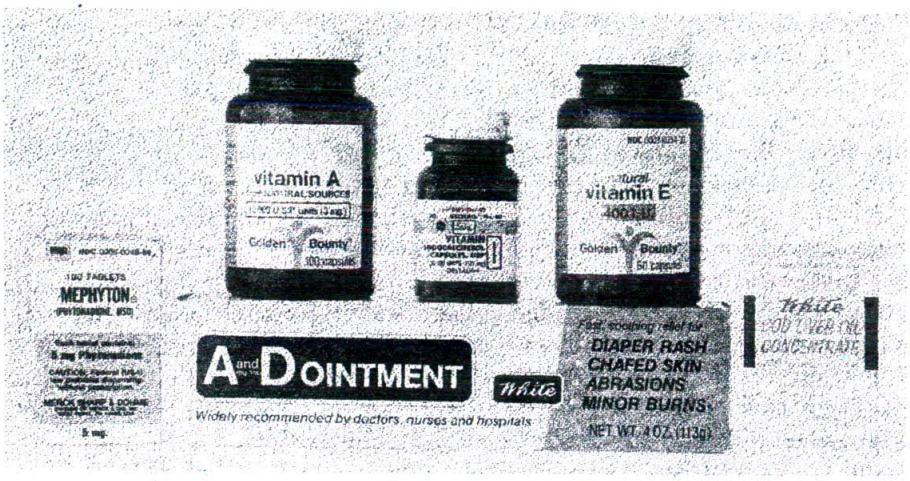


Fig. 11–1. Representative fat-soluble vitamin products.

from the normal intestinal tract and is stored in body tissues, especially the liver. An estimated one third of the ingested vitamin A is stored under normal circumstances. Fish liver oils are the richest known natural sources of the vitamin and formerly were its primary commercial sources.

Common dietary sources of vitamin A are animal organs (heart, kidney, liver), eggs, dairy products, and fish. Vitamin A activity is also derived from some plant carotenoids that occur in carrots and green leafy vegetables. Only carotenoids that possess at least one unhydroxylated β-ionone ring (α-, β-, and γ-carotene and cryptoxanthin) can be converted to vitamin A. *Beta*-carotene and related carotenoids (provitamin A substances) are cleaved by β-carotene oxygenase in mucosal cells of the intestine to yield retinal, most of which is promptly reduced in the presence of NADH to retinol.

Vitamin A is involved in vision, growth, and tissue differentiation. A deficiency of this vitamin can result in a variety of conditions, including nyctalopia (night blindness), xerophthalmia, hyperkeratosis of the skin, growth retardation, and decreased resistance to infection. Activation of the visual pigment rhodopsin involves retinal (retinol is probably oxidized in situ). The function of vitamin A in tissue differentiation may relate to the synthesis of specific glycoproteins (cell receptors or regulators); retinyl phosphate plays an essential role in transferring sugars to glycoprotein. Evidence suggests that vitamin A is biochemically involved in many other essential processes, but details of its molecular involvement need clarification. For example, observations suggest that a deficiency of vitamin A prompts a decline in the plasma level of a macroglobulin that is an inhibitor of collagenases and other proteinases in the cornea; the consequence can be the development of corneal lesions.

Vitamin A is indicated specifically for the treatment of a deficiency of this vitamin, a situation rarely encountered in practice. The vitamin is used primarily for prophylactic purposes when normal dietary intake is inadequate or when normal absorption is compromised. This vitamin has not been implicated in any genetic errors of metabolism, but high doses of some analogs, especially 13-*cis* retinoic acid, have shown interesting promise in retarding the development of certain preneoplastic lesions. The particular advantage of 13-*cis* retinoic acid relates to the fact that it is not stored in the body, thus avoiding some of

the toxicity potential of high doses of retinol. The efficacy of high doses of vitamin A in the treatment of acne has not been established and should be avoided.

Acute toxicity, usually manifest as increased intracranial pressure (hydrocephalus) within 8 to 12 hours, has been observed with high doses of vitamin A, and a hypervitaminosis A syndrome has occurred with chronic overuse of the vitamin. Symptoms of this syndrome include fatigue, night sweats, abdominal discomfort, anorexia, and vomiting. Competent medical supervision and caution should be exercised with extended usage of daily adult doses of 25,000 units or more.

The usual US RDA of vitamin A for adults and children over 4 years of age is 5000 units (sometimes expressed as 1000 retinol equivalents). The US RDAs are 1500 units for infants, 2500 for children under the age of 4, and 8000 units for pregnant and lactating women. Units and equivalents originally represented biologic standards, but a spectrophotometric assay is employed currently; 1 unit is equal to 0.3 μg of retinol.

The usual adult dose of vitamin A for treatment of a deficiency is 10,000 to 25,000 units per day for 1 to 2 weeks or until improvement occurs. In cases of xerophthalmia, the usual daily adult dose is 25,000 to 50,000 units, and up to 100,000 units may be used with close medical supervision in the treatment of corneal lesions caused by hypovitaminosis A. The usual pediatric dose for treatment of a deficiency is 5000 units per kg of body weight per day.

Vitamin A is usually taken orally, but it may be administered intramuscularly. Therapy may be discontinued when liver storage of the vitamin is determined to be adequate. Vitamin A equivalent to an adult requirement for 2 years is normally stored in the hepatic tissues of persons receiving a balanced diet.

Vitamin A is a yellow to red oily liquid that may solidify when refrigerated and that should be protected from air and light. It may be nearly odorless or may have a slightly fishy odor. It has no rancid odor or taste. It may be diluted with edible oils, or it may be incorporated in solid, edible carriers or excipients, and product formulations may contain suitable antimicrobial agents, dispersants, and antioxidants. Capsule, tablet, oral solution, and injection dosage forms are available.

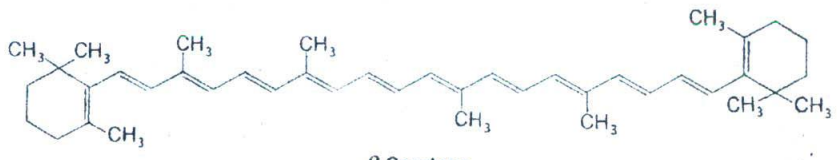
PROPRIETARY AND PRESCRIPTION PRODUCTS. Alphalin® and Aquasol A®.

Tretinoin or all-*trans* retinoic acid is available in several formulations (cream, gel, and solution) for topical purposes. It appears to increase epidermal cell mitosis and epidermal cell turnover and is used to treat acne vulgaris.

PRESCRIPTION PRODUCT. Retin-A®.

Isotretinoin or 13-*cis* retinoic acid is available for oral use in special situations. It is approved for use in severe recalcitrant cystic acne. It is also used sometimes in keratinization disorders of the skin, which are frequently preneoplastic. Use of the drug must be closely monitored since adverse reactions are common and may require its discontinuation. It should not be used by women who are pregnant, and contraception should be continued for at least one month after termination of therapy.

The recommended dosage regimen for cystic acne is 1 to 2 mg per kg of body weight per day, in two divided doses, for 15 to 20 weeks. A second course of therapy,



β-Carotene

if needed, may be initiated after a vacation period of at least 8 weeks.

PRESCRIPTION PRODUCT. Accutane®.

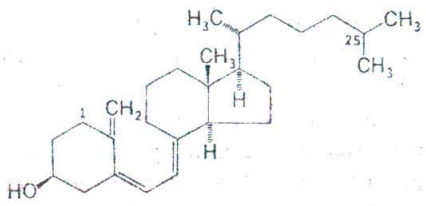
***Beta*-carotene,** in addition to being a provitamin A substance, is effective in reducing photosensitivity in individuals with erythropoietic protoporphyria. It does not act as a sunscreen in normal individuals and should not be used for that purpose. However β-carotene does provide a novel and safe approach to the treatment of a specific type of photosensitivity. When ingested over a period of several weeks, the drug produces carotenemia, a yellowing of the skin often first observed in the palms of the hands or on the soles of the feet. The mode of action has not been established, but it is no doubt related to the pigmentation of the skin. During the course of therapy, elevated blood carotene levels are observed, but vitamin A levels do not rise above normal.

The usual adult dose of β-carotene is 30 to 300 mg per day, adjusted according to the severity of the symptoms and to the response of the patient. Increased exposure to sunlight should not occur until the patient first appears carotenemic, 2 to 6 weeks after initiation of therapy. The protective effect is not total and varies with each individual.

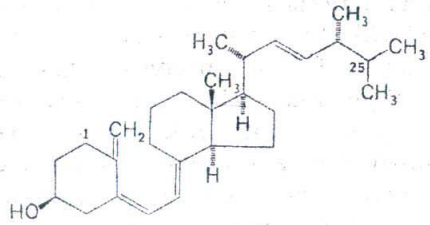
PRESCRIPTION PRODUCT. Solatene®.

Vitamin D

Vitamin D is a term that is used for several related steroids and their metabolites that are essential for the absorption and utilization of calcium. Cholecalciferol, or vitamin D_3, is the primary form of the vitamin encountered in zoologic species; it is stored in a number of tissues, including the liver and skin. Fish liver oils are a rich natural source of this material. Ergocalciferol, or vitamin D_2, is derived from ergosterol, a plant steroid. It is the form of this vitamin normally used to fortify such foods as milk, bread, and cereals.



Vitamin D_3 (Cholecalciferol)



Vitamin D_2 (Ergocalciferol)

Vitamin D has been called the sunshine vitamin since ultraviolet light is involved in the conversion of provitamin substances to vitamins D_2 and D_3. 7-Dehydrocholesterol is converted to cholecalciferol in the skin upon exposure to the ultraviolet rays in sunlight, and ergosterol is converted to ergocalciferol in vitro by controlled exposure to ultraviolet irradiation. If the irradiation process is not adequately controlled, ergocalciferol becomes contaminated with undesirable reaction products, including lumisterol, tachysterol, toxisterol, and supresterols.

Cholecalciferol and ergocalciferol undergo metabolic hydroxylations in the body to yield molecular forms with greater physiologic activity. The initial activation reaction occurs in the liver and involves formation of 25-hydroxyl derivatives (calcifediol and 25-hydroxyergocalciferol, respectively). The second hydroxylation reaction occurs in the kidney and involves the 1-position; the resulting calcitriol and 1,25-dihydroxyergocalciferol are considered to be the most active molecular forms of this vitamin.

Dihydrotachysterol, a substance prepared by synthetic reduction of tachysterol, is closely related to ergocalciferol and possesses useful vitamin D activity. This

compound undergoes hydroxylation in the liver to give an active 25-hydroxyl metabolite; no kidney metabolism occurs or is required for full activity.

Vitamin D is absorbed readily from the small intestine of normal individuals, but deficiencies caused by malabsorption are known. Cholecalciferol is absorbed with somewhat greater efficiency than ergocalciferol. Bile salts are required for absorption of the latter material.

The body's requirements for vitamin D are normally satisfied by dietary sources and by the activating action of sunlight (ultraviolet component) on the skin. Butter, cream, and liver are good natural sources of vitamin D, and milk and cereals are usually fortified with this vitamin.

Vitamin D aids in the utilization of calcium and phosphate and is essential to the development and maintenance of strong teeth and bones. Deficiency states lead to rickets in children and osteomalacia in adults. Calcitonin and parathyroid hormone (see page 269) are also involved in calcium homeostasis. Vitamin D increases serum calcium and phosphate concentrations by stimulating absorption of these ions from the small intestine and by mobilizing calcium resorption from bone. The enhanced serum levels of calcium and phosphate normally promote bone mineralization, and the vitamin effect on bone resorption of calcium becomes significant only in hypocalcemic conditions, in which it helps prevent muscular tetany.

Vitamin D, the antirachitic vitamin, is indicated specifically for the prevention and treatment of deficiency states. Such conditions are rarely encountered in persons receiving a balanced diet and some exposure to sunlight. However, deficiencies are sometimes encountered in patients with intestinal malabsorption of various etiologies, in those on strict vegetarian diets (no dairy products), in which cholesterol and vitamin intake is inadequate, and in those with renal impairment, in which activation of the vitamin is precluded. Vitamin D is also used to treat familial hypophosphatemia and hypoparathyroidism and to supplement the diet in therapeutic regimens involving long-term use of cholestyramine or anticonvulsant drugs. Calcitriol has special utility in patients with kidney failure.

Individuals vary in their sensitivity to vitamin D, and some infants may show hyperactivity even with low doses. However, most toxicities are associated with prolonged ingestion of high doses and can be serious. Chronic vitamin D–induced hypercalcemia may result in soft-tissue calcification, including lethal vascular calcification and nephrocalcinosis. Common symptoms may include gastrointestinal disturbances and hypertension. The serum calcium levels of patients receiving 50,000 units of ergocalciferol per day should be monitored closely; serum calcium concentrations should be maintained at 8 to 9 mg per 100 ml.

The US RDA for vitamin D is 400 units per day; there is no variation for age and no other special considerations. One unit is equal to 0.025 μg of cholecalciferol or ergocalciferol. The usual dose of cholecalciferol and ergocalciferol for treatment of a deficiency is 1000 to 4000 units per day, the dose being reduced to 400 units per day when appropriate. Much higher doses of ergocalciferol are employed in the treatment of familial hypophosphatemia (50,000 to 100,000 units per day), hypoparathyroidism (50,000 to 200,000 units per day), and vitamin D–dependent rickets (3000 to 10,000 units per day, up to 50,000 units per day in resistant cases, for infants; 10,000 to 60,000 units per day, up to 500,000 units per day in resistant cases, for children and adults). Vitamin D substances are usually taken orally, but ergocalciferol is available for intramuscular injection in cases of intestinal malabsorption.

Cholecalciferol, vitamin D_3, or 9,10-secocholesta-5,7,10(19)-trien-3β-ol is a white, water-insoluble substance that is affected by air and light. It is available as 400- and 1000-unit tablets.

PROPRIETARY PRODUCT. Delta-D®.

Ergocalciferol, vitamin D_2, or 9,10-secoergosta-5,7,10(19),22-tetraen-3β-ol is a white, water-insoluble substance that is affected by air and light. Capsule (25,000 and 50,000 units), tablet (50,000 units), oral solution (8000 units per ml), and injection (100,000 and 500,000 units per ml) dosage forms are available.

PROPRIETARY AND PRESCRIPTION PRODUCTS. Calciferol®, Deltalin®, and Drisdol®.

Calcifediol or 25-hydroxycholecalciferol is a normal metabolite of cholecalciferol that is used in the management of metabolic bone diseases and hypocalcemia in patients on chronic renal dialysis. The usual initial adult dose is 300 to 350 μg per week administered on a once-a-day or alternate-day schedule, the dosage being increased, if necessary, at monthly intervals. It is available as 20- and 50-μg capsules.

PRESCRIPTION PRODUCT. Calderol®.

Calcitriol or 1,25-dihydroxycholecalciferol is the most active normal metabolite of cholecalciferol. It is used in the management of hypocalcemia in patients on chronic renal dialysis. The usual initial dose is 0.25 μg per day, the dosage being increased in increments of 0.25 μg every 2 to 4 weeks, if necessary, up to a maximum of 3 μg per day, depending on the condition being treated. Calcitriol is available as 0.25- and 0.5-μg capsules.

PRESCRIPTION PRODUCT. Rocaltrol®.

Dihydrotachysterol or 9,10-secoergosta-5,7,22-trien-3β-ol is a white, water-insoluble substance with vitamin D activity; 1 mg of dihydrotachysterol is approximately equivalent to 3 mg of ergocalciferol. It is used in the treatment of acute, latent, and chronic forms of postoperative tetany, idiopathic tetany, and hypoparathyroidism. The usual initial dose is 0.8 to 2.4 mg daily for several days, then a daily maintenance dose of 0.2 to 1.0 mg, as required for normal serum calcium levels. Capsule (0.125 mg), tablet (0.125, 0.2, and 0.4 mg), and oral solution (0.25 mg per ml) dosage forms are available.

PRESCRIPTION PRODUCTS. DHT® and Hytakerol®.

Oleovitamin A and D is a solution of vitamin A and vitamin D in fish liver oil or in an edible vegetable oil.

The product label must indicate the content of vitamins A and D in mg per g and μg per g, respectively; the content of these vitamins may also be expressed in units per g. The label must further state whether the product contains cholecalciferol, ergocalciferol, or vitamin D from a natural source.

Oleovitamin A and D is available as a capsule, usually containing 10,000 units of vitamin A and 400 units of vitamin D (e.g., Super D Perles®). It is used as a dietary supplement. Vitamins A and D are also available in a number of topical emollients for temporary relief of minor burns, sunburn, windburn, abrasions, chapped skin, and other skin irritations (e.g., Andoin®, Balmex®, Caldesene Medicated®, Clocream®, Comfortine®, Desitin®, Lobana®, and Primaderm®).

Cod liver oil is the partially destearinated, fixed oil obtained from the fresh livers of *Gadus morrhua* Linné and other species in the family Gadidae. The generic name *Gadus* is from the Greek *gados*, meaning codfish, and *morrhua* is the Latin name of the codfish.

Codfish inhabit the northern Atlantic Ocean, and cod liver oil is a by-product of the fishing industry. The livers are removed during the fish processing, taking care to exclude the gallbladders, and frozen until subjected to a steaming process to remove the oil. The steaming takes place in closed containers in a carbon dioxide atmosphere to prevent oxidation. The separated oil is chilled to a temperature below −5° C; the precipitated stearin is separated from the lighter vitamin-containing oil by decantation and filtration. Finally, the oil is adjusted to a definite vitamin content by admixture, if necessary, of different lots with higher or lower vitamin levels.

Cod liver oil is a thin, oily liquid that has a distinctive, slightly fishy but not rancid

odor and a fishy taste. Medicinal grade cod liver oil must contain, in each gram, not less than 255 μg of vitamin A (850 units) and not less than 2.125 μg (85 units) of vitamin D. It may be flavored by the addition of not more than 1% of a suitable flavoring agent or a mixture of such substances. The oil also contains glyceryl esters of unsaturated (about 85%) and saturated (about 15%) fatty acids. (A sterile solution of the sodium salts of the fatty acids, sodium morrhuate injection, is employed as a sclerosing agent; see page 97.) The unsaturated acids include oleic, linoleic, gadoleic, and palmitoleic. Myristic and palmitic acids are the major saturated acids; only traces of stearic acid remain in the oil. Bile salts and the alkaloids, morrhuine and aselline, should be absent; presence of the former indicates contamination of the livers with gallbladders, and presence of the latter indicates decomposition.

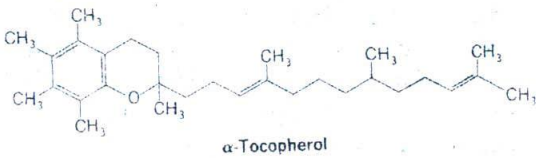
Cod liver oil was introduced into medicine during the middle of the 18th century. Fish liver oils were the predominant therapeutic sources of vitamins A and D for years. Pure, laboratory-prepared vitamins A and D have substantially replaced the fish liver oils, but cod liver oil still finds some use as a dietary supplement. The usual daily dose is 5 ml containing 1170 μg (3900 units) of vitamin A and 9.7 μg (386 units) of vitamin D. The oil may also be used in formulating oleovitamin A and D products and topical emollients containing these vitamins.

Vitamin E

Vitamin E is a term that refers to various forms of α-tocopherol, including the dextrorotatory isomer, the racemic mixture, and their acetate and acid succinate esters. The free alcohol forms are readily subject to oxidation, but the esters are more stable. Several structurally related tocopherol analogs also occur in nature, including β-, γ-, and δ-tocopherols, but these substances possess only low levels of vitamin E activity.

Vitamin E requires bile salts and dietary lipids for efficient absorption from the intestinal tract. The vitamin is stored extensively in adipose tissues of the body; the stored vitamin E in normal situations represents up to 4 years' requirements. Thus, it is not surprising that no defined adult deficiency state is known. Severe deficiency conditions characterized by muscular dystrophy, coronary disease, and sterility can be induced experimentally in animals, and many of the more common human uses are prompted by such studies.

Vitamin E is widely distributed in nature, and the body's requirements are normally satisfied by dietary sources. Plant oils, green vegetables, whole grains, egg yolks, and meats are common dietary sources of this vitamin. Wheat germ oil is a traditional natural source of vitamin E for therapeutic purposes.



α-Tocopherol

The exact biochemical function of vitamin E is unknown, but the antioxidant properties of the vitamin have been implicated. The vitamin may help preserve the integrity of cellular membranes, including those of red blood cells, by preventing free-radical attack and peroxidase cleavage of unsaturated bonds of lipid membrane components. It may also act as a cofactor in some enzyme systems.

Vitamin E is used primarily for prophylactic purposes to prevent the development of deficiency states in conditions in which reduced absorption is likely. Such conditions include diseases of the small intestine, pancreatic insufficiency, postgastrectomy states, and prolonged therapeutic regimens involving cholestyramine or min-

eral oil. It is also used to treat a syndrome sometimes encountered in premature infants that may actually represent a deficiency state. The beneficial effect of vitamin E in cancer, fibrocystic disease of the breast, intermittent claudication, sickle-cell disease, and pollution-associated lung toxicity has been suggested, but further evidence is required to establish efficacy. A large number of unsubstantiated claims have been made for vitamin E; the promotion of high doses of vitamin E to increase physical endurance or sexual ability, to prevent arteriosclerosis or aging, and to treat loss of hair or the menopausal syndrome must be considered fraudulent.

Vitamin E is generally considered to lack significant acute or chronic toxicity when ingested in normal therapeutic doses. However, very high doses of the vitamin (higher than 800 units per day) may cause adverse reactions, including increased bleeding tendencies in vitamin-K–deficient patients.

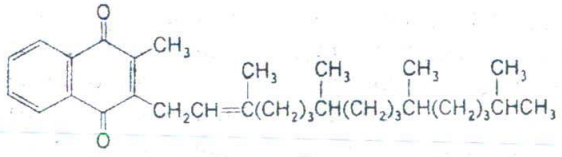
The US RDA for vitamin E is 30 units for adults and children over 4 years of age, 10 units for children under 4 years of age, and 5 units for infants. It should be noted that these figures are significantly higher than the actual daily dietary requirements. One unit is equal to 1 mg of *dl*-α-tocopheryl acetate. The equivalents for 1-mg quantities of the other forms of α-tocopherol are *dl*-α-tocopheryl acid succinate, 0.89 units; *dl*-α-tocopherol, 1.1 units; *d*-α-tocopheryl acetate, 1.36 units; *d*-α-tocopheryl acid succinate, 1.21 units; and *d*-α-tocopherol, 1.49 units. Products containing vitamin E must be labeled to indicate the form and amount of the vitamin they contain; the amount is usually expressed in units, but it may be expressed in milligrams.

The usual adult dose of vitamin E for prophylactic purposes is 30 units per day; 60 to 75 units per day are used to treat a deficiency. The usual pediatric dose to treat a deficiency is 1 unit per kg of body weight per day. Vitamin E is usually administered orally, but it may be given intramuscularly in cases of severe absorption problems. Capsule (30 to 1000 units), tablet (100, 200, and 400 units), chewable tablet (200 and 400 units), oral solution (50 units per ml), and injection (200 units per ml) dosage forms are available. Vitamin E is also incorporated into a number of topical emollient products for control of dry or chapped skin or for temporary relief of minor skin disorders.

PROPRIETARY AND PRESCRIPTION PRODUCTS. Aquasol E®, CEN-E®, E-Ferol®, E-Vital®, Epsilan-M®, Pheryl-E®, and Viterra E®.

Vitamin K

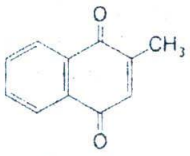
Vitamin K is a term that refers to 2-methyl-1,4-naphthoquinone and derivatives of this compound that exhibit an antihemorrhagic activity. The naturally occurring forms of vitamin K possess large aliphatic substituents at position 3. Phytonadione (vitamin K_1) occurs in green leafy vegetables; synthetically prepared phytonadione is used for therapeutic purposes. Vitamin K_2 (prenylmenaquinone-7) has a larger aliphatic side chain than phytonadione (35 carbons compared to 20 carbons). It has been isolated from putrefied fish meal and other natural sources, but vitamin K_2 and its related naturally occur-



Phytonadione

ring analogs are not commercially available for medicinal use. Menadione or 2-methyl-1,4-naphthoquinone, sometimes called vitamin K_3, is a synthetic material with vitamin K activity. Menadiol (vitamin K_4), a reduced form (hydroquinone) of menadione, is another synthetic form of this vitamin that is used therapeutically.

Menadiol is oxidized to menadione in the body. Menadione is alkylated metabolically to yield menaquinone-4 or other physiologically active molecules; the alkylation process may involve geranyl pyrophosphate, farnesyl pyrophosphate, or geranylgeranyl pyrophosphate.



Menadione

Phytonadione is absorbed from the intestinal tract only in the presence of bile salts. Menadione and menadiol are absorbed directly. The lymphatic system is the major means of transporting vitamin K to the liver where it tends to concentrate. This vitamin is metabolized hepatically and eliminated readily. There is no significant storage of vitamin K in the body tissues, in distinct contrast with the other fat-soluble vitamins.

Vitamin K is distributed widely in dairy products and many fruits and vegetables, green leafy vegetables being especially good dietary sources. The intestinal microflora also provide a significant portion of the normal human supply of this vitamin. The latter factor presumably explains the infrequent occurrence of deficiency conditions; no recommended daily or dietary allowances are recognized for vitamin K. Intestinal microbial synthesis of vitamin K is particularly important in poultry. It has been observed that when low levels of antibiotics are added to chicken feed to enhance growth efficiency, dietary supplementation with substances possessing vitamin K activity is often necessary to prevent hemorrhagic conditions.

Vitamin K is necessary for normal clotting of blood. The vitamin promotes the hepatic formation of prothrombin (factor II), other essential clotting factors (VII, IX, X), and some proteins of unknown physiologic significance. Details of the action of vitamin K need considerable clarification, but a vitamin-K–dependent carboxylase seems to be involved.

Hemorrhage is the most common symptom in vitamin K deficiency, and this vitamin is used in coagulation disorders characterized by impaired formation of factors II, VII, IX, and X. Disruption in the formation of the clotting factors may result from a deficiency of vitamin K, usually related to intestinal malabsorption, or from interference with vitamin K activity, including hypoprothrombinemia caused by oral anticoagulants, salicylates, and some antibiotics.

Allergic or hypersensitive reactions are encountered occasionally upon administration of vitamin K. Serious hyperbilirubinemia has been associated with its use in premature infants who often lack adequately developed hepatic function. Erythrocyte hemolysis may occur in patients with a deficiency of glucose-6-phosphate dehydrogenase who receive menadione and menadiol. Neither of these forms of the vitamin should be given to women during the last few weeks of pregnancy or to newborn infants.

Phytonadione, phylloquinone, phytylmenaquinone, 2-methyl-3phytyl-1,4-naphthoquinone, or vitamin K_1 is administered by subcutaneous or intramuscular injection when possible. The usual dose to treat hypoprothrombinemia attributable to anticoagulant drugs, malabsorption, or other causes is 2 to 25 mg for adults, 2 to 10 mg for children, and 1 to 2 mg for infants; the response of prothrombin time should be monitored, and the dose may be repeated after 6 to 8 hours if necessary. A 1-mg dose is frequently given to neonates

to prevent hemorrhagic disease since placental transfer of vitamin K is low and an intestinal microflora has not yet been acquired.

Tablets (5 mg) are available for oral use. The usual dose is 2.5 to 10 mg and may be repeated after 12 to 48 hours if necessary. Phytonadione decomposes when exposed to sunlight and must be properly protected.

PRESCRIPTION PRODUCTS. aqua-MEPHYTON®, Konakion®, and Mephyton®.

Menadione, menaquinone, 2-methyl-1,4-naphthoquinone, or vitamin K_3 is a yellow, crystalline, synthetic material with prothrombogenic properties. It is affected by sunlight and has irritating properties. Tablets (5 mg) of menadione are available for oral use, the usual dose being 5 to 10 mg daily. Administration to infants is not recommended.

Menadiol or 2-methyl-1,4-naphthalenediol is available as the water-soluble bis (dihydrogen phosphate) tetrasodium salt. Tablet (5 mg) and injection (5, 10, and 37.5 mg per ml) dosage forms are used. The usual oral dose for treatment of hypoprothrombinemia secondary to obstructive jaundice, biliary fistulas, or administration of certain drugs is 5 to 10 mg per day. The usual intramuscular or subcutaneous dose is 5 to 15 mg once or twice daily for adults or 5 to 10 mg once or twice daily for children; intravenous administration is used occasionally for a faster response.

PRESCRIPTION PRODUCT. Synkayvite®.

WATER-SOLUBLE VITAMINS

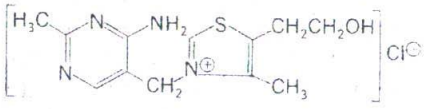
The water-soluble vitamins are dominated by the vitamin B complex, but this solubility classification also includes ascorbic acid (vitamin C), biotin, and such physiologically questionable substances as *p*-aminobenzoic acid, the bioflavonoids (see page 73), choline, and inositol. The vitamin B complex includes thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), folic acid (B_9), and cyanocobalamin (B_{12}). Liver and yeast are recognized as rich sources of the B vitamins.

The water-soluble vitamins range from simple to complex chemical molecules, play diverse physiologic roles, and have a wide scope of therapeutic applications.

Vitamin B Complex

Vitamin B_1

Thiamine or vitamin B_1 has substituted pyrimidine and thiazole rings linked by a methylene bridge. Final steps in both the biosynthesis and chemical synthesis of this vitamin involve linkage of the two ring systems. Commercial supplies of thiamine are prepared by chemical synthesis, and it is usually used as the hydrochloride salt. The vitamin is stable in an acidic environment but decomposes readily above pH 5.0. It is estimated that about 50% of the vitamin in foods is destroyed during cooking.



Thiamine

Whole grains, legumes, and meats are good dietary sources of thiamine. Although the substance is absorbed readily from the small intestine, alcohol inhibits its absorption. Beriberi is the classic dietary deficiency state; however, most of the commonly observed deficiency conditions (symptoms include emotional hypersensitivity, loss of appetite, fatigue, and muscular weakness) involve malabsorption in alcoholics. Thiamine is associated with several infrequently encountered genetic-based deficiencies or inborn errors of metabolism, including lactic acidosis due to pyruvate carboxylase deficiency, branched-chain aminoacidopathy, and the Wernicke-Korsakoff syndrome. There is no appreciable storage of the vitamin in the body; it is metabolized hepatically and eliminated renally.

Thiamine is required for carbohydrate metabolism (approximately 0.2 to 0.3 mg

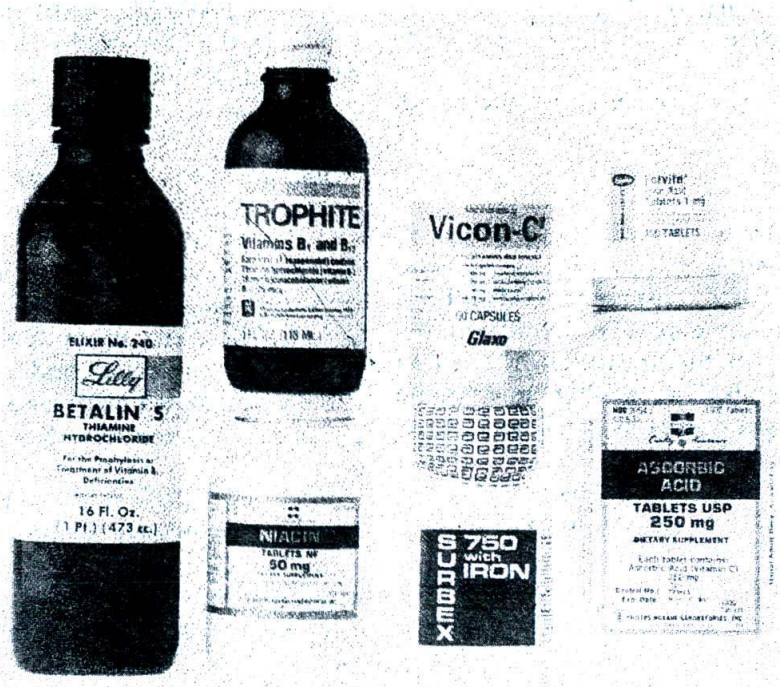


Fig. 11–2. Representative water-soluble vitamin products.

per 1000 calories) and for some neurologic functions. It is phosphorylated in the body to give thiamine diphosphate or cocarboxylase, its active form. Cocarboxylase functions biochemically as a coenyzme for α-ketoacid decarboxylases (acetylcoenzyme A formation and acetate metabolism) and transketolase (hexose monophosphate shunt).

The US RDA of thiamine is 1.5 mg for adults and children over 4 years of age, 0.7 mg for children under 4 years of age, 0.5 mg for infants, and 1.7 mg for pregnant and lactating women. The actual requirements vary somewhat with body weight, caloric intake, and carbohydrate content of the diet. The maximum daily absorption of thiamine upon oral ingestion is usually 5 to 15 mg, so megadose oral regimens of this vitamin are rarely justified. Hypersensitivity is encountered occasionally with exogenously administered thiamine, but the vitamin is considered to possess a very low risk of toxicity, especially with oral ingestion.

Thiamine is used to supplement an inadequate diet (rare) and to treat deficiency conditions resulting from intestinal malabsorption of various etiologies, and from certain genetic errors. There is no substantive evidence to support its use as an insect repellant or an appetite stimulant or to treat dermatitis, chronic diarrhea, fatigue, mental disorders, multiple sclerosis, or ulcerative colitis.

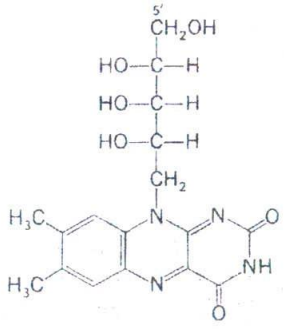
Thiamine is used as the hydrochloride and mononitrate salts and is available in tablet (5 to 500 mg), elixir (usually 1 mg per 5 ml), and injection (usually 100 mg per ml) dosage forms. The usual adult oral doses are 1 to 2 mg per day for dietary supplementation, 5 to 10 mg three times a day until improvement occurs in general deficiency conditions, 40 mg per day in alcohol-induced deficiency, and 10 to 20 mg per day in genetic enzyme-deficiency diseases. Parenteral administration is reserved for critical deficiency conditions; the adult dose is 5 to 100 mg three times a day

by intramuscular or slow intravenous injection. Pediatric doses are proportionally lower.

PROPRIETARY AND PRESCRIPTION PRODUCTS. Betalin S® and Biamine®.

Vitamin B_2

Riboflavin or vitamin B_2 is a yellow, heat-stable substance that is slightly soluble in water. It is sensitive to light and will change into lumichrome or lumiflavin, depending on whether the irradiated solution is acidic or alkaline; neither lumichrome nor lumiflavin possesses physiologic activity. Riboflavin can be synthesized chemically, but bacterial synthesis is more convenient and economical for commercial purposes.



Riboflavin

Yeast is the richest natural source of riboflavin. Dairy products, eggs, legumes, and meats are the main dietary sources of this vitamin. Small amounts are provided by cereal grains, fruits, and green vegetables. Riboflavin is stable during cooking in the absence of light.

Riboflavin occurs in foods in the free form and as riboflavin 5'-phosphate (flavin mononucleotide or FMN) and flavin adenine dinucleotide (FAD). The nucleotides are hydrolyzed to riboflavin in the upper gastrointestinal tract. Free riboflavin is absorbed readily into cells of the intestinal mucosa by an active transport system that is enhanced by bile salts. The riboflavin is phosphorylated by mucosal flavokinase, and the FMN is bound to plasma albumin and transported to the liver where it is converted to FAD. The heart, kidneys, and especially the liver are the primary storage sites for bound riboflavin (flavoproteins). Free riboflavin is rapidly eliminated by the kidneys; peak blood concentrations occur within 2 hours following ingestion of large doses of the vitamin.

FMN and FAD function as coenzymes in the transfer of electrons in a number of important biologic oxidation-reduction reactions. These enzyme systems cover both aerobic and anaerobic conditions, and are usually designated oxidases and dehydrogenases, respectively. Key riboflavin-containing enzyme systems include glucose oxidase (Warburg's old yellow enzyme), α-aminoacid oxidases, xanthine oxidase, cytochrome reductase, succinic dehydrogenase, acyl-coenzyme A dehydrogenases, and erythrocyte glutathione reductase. The last enzyme is a useful biochemical indicator of riboflavin deficiency.

Riboflavin deficiency is rarely encountered in healthy persons receiving a balanced diet, but symptoms of deficiency may occur in cases of inadequate nutrition, intestinal malabsorption, and a few specific drug regimens (phenothiazines, tricyclic antidepressants, and probenecid). It should be noted that alcohol inhibits intestinal absorption of riboflavin. Deficiency symptoms are usually dermatologic in nature, including cheilosis, glossitis, seborrheic dermatitis, and corneal vascularization.

Although riboflavin seldom causes toxicity in those with normal renal function, yellow discoloration of the urine may cause concern in patients taking high doses of the vitamin. Hemodialysis removes riboflavin but more slowly than normal renal excretion.

The US RDA of riboflavin is 1.7 mg for adults and children over 4 years of age, 0.8 mg for children under 4 years of age, 0.6 mg for infants, and 2.0 mg for pregnant and lactating women. The actual requirements for riboflavin vary somewhat with

caloric intake. There is no evidence to justify ingestion of megadoses of this vitamin.

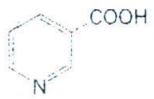
Riboflavin is used to supplement an inadequate diet and to treat symptoms of riboflavin deficiency of any cause. It has not been proved effective for treatment of acne, migraine headaches, or muscle cramps. The usual dose to treat a deficiency is 5 to 30 mg per day orally, in divided doses for several days, followed by a 1 to 4 mg per day dietary supplemental dose. The usual initial pediatric dose is 3 to 10 mg orally for several days, then 0.6 mg per 1000 calories ingested for dietary supplementation. Intramuscular administration is reserved for deficiency situations in which oral administration is not acceptable; the usual adult parenteral dose is 50 mg.

Riboflavin is available in tablet (5, 10, 25, 50, and 100 mg) and injection (50 mg per ml) dosage forms. It is usually formulated as the free riboflavin, but niacinamide or some other suitable solubilizing agent must be added to the injectable product. The more soluble riboflavin 5'-phosphate sodium is also available commercially. A number of proprietary products are marketed under the generic designations riboflavin and vitamin B_2.

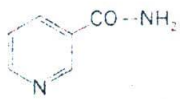
PRESCRIPTION PRODUCT. Riobin-50®.

Niacin

Niacin, nicotinic acid, or vitamin B_3 is a simple, naturally occurring pyridine derivative that prevents pellagra. **Niacinamide or nicotinamide** also occurs naturally, has antipellagra activity, and is used for dietary and therapeutic purposes. The terms niacin and niacinamide are usually employed, except in the chemical literature, since they do not have the phonetic similarity to nicotine. These compounds can be prepared easily by chemical synthesis. They are readily absorbed from the gastrointestinal tract under normal circumstances.



Niacin



Niacinamide

Lean meats, fish, and dairy products are good dietary sources of niacin; the vitamin is stable during cooking. Cereal grains and a number of other foods contain appreciable quantities of niacin that is present in a bound form and thus is not readily bioavailable. The roasting of coffee beans results in the release of a significant quantity of niacin as well as in the development of a characteristic flavor. Tryptophan is also converted to niacin in the body (Fig. 11–3). It is estimated that 60 mg of tryptophan is approximately equivalent to 1 mg of niacin and that such metabolic synthesis may account for up to one half of the body's requirement for this vitamin.

Niacin is metabolized to niacinamide which is a component of nicotinamide adenine dinucleotide (NAD), or coenzyme I, and nicotinamide adenine dinucleotide phosphate (NADP), or coenzyme II. These coenzymes are involved in electron transport in a large number of essential enzyme systems associated with glycogenolysis, lipid metabolism, and tissue respiration.

Pellagra is the classic niacin-deficiency condition. Symptoms of the deficiency involve the nervous system, the skin, and the gastrointestinal tract and are sometimes summarized as the 3D's—dementia, dermatitis, and diarrhea. Oral lesions, especially angular stomatitis, cheilosis, and red tongue, are more distinctive than the other symptoms.

Several genetic errors have been associated with niacin. The best documentation is found with Hartnup's disease, an inherited condition that is characterized by a defective intestinal absorption of tryptophan and thus an impaired in-vivo synthesis of niacin. A NAD-dependent schizophrenia and a niacin-responsive familial hypercholesterolemia have also been recognized; the

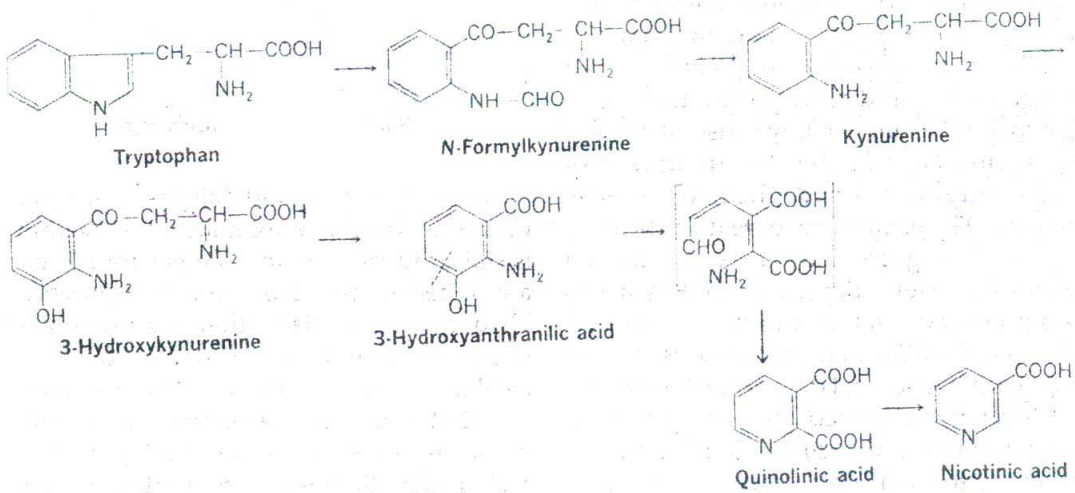


Fig. 11–3. Biosynthetic pathway from tryptophan to nicotinic acid.

former appears to involve an enzymatic block between tryptophan and NAD.

Niacin causes direct peripheral vasodilation. It may cause cutaneous flushing and a sensation of warmth, especially in the area of the face, neck, and ears. Because gastrointestinal upset is sometimes encountered with this vitamin, it should be taken with meals or milk. Niacinamide lacks the vasodilating property, a distinction of therapeutic significance.

The US RDA of niacin is 20 mg for adults and children over 4 years of age, 9 mg for children under 4 years of age, and 8 mg for infants. There is no justification for ingestion of megadoses of this vitamin, except for limited therapeutic use in hyperlipidemia.

Niacin and niacinamide are used to prevent or treat deficiency conditions. Such conditions may result from inadequate nutrition, intestinal malabsorption, or genetic errors of metabolism. Niacin, but not niacinamide, is also used as adjunctive therapy in some patients with primary hyperlipidemia. Niacin is not useful in the treatment of mental disorders, including schizophrenia, or for the prevention of heart attacks; it has not proved effective for the treatment of acne, motion sickness, or peripheral vascular disease.

The usual oral doses of niacin and niacinamide are 10 to 20 mg per day for dietary supplementation; up to 500 mg per day, usually in divided doses, for treatment of pellagra; and 50 to 200 mg per day in Hartnup's disease. Antihyperlipidemic use of niacin involves a usual adult oral dosage of 1 to 2 g, 3 times per day. Parenteral administration of niacin and niacinamide is reserved for cases in which oral administration is not acceptable; the usual dose by slow intravenous infusion (not exceeding 2 mg per minute) is 25 to 100 mg, 2 or more times per day.

Niacin is available in elixir (10 mg per ml), tablet (25, 50, 100, and 500 mg), sustained release (125, 150, 250, 300, 400, and 500 mg), and injection (50 and 100 mg per ml) dosage forms.

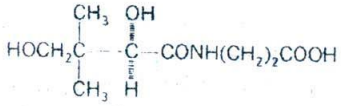
PROPRIETARY AND PRESCRIPTION PRODUCTS. Niac®, Nico-400®, Nicobid®, Nicolar®, Nico-Span®, Nicotinex®, Span-Niacin-150®, and Tega-Span®.

Niacinamide is available in tablet (50, 100, and 500 mg) and injection (100 mg per ml) dosage forms.

Pantothenic Acid

Pantothenic acid or vitamin B_5 is a component of the vitamin B complex that is sometimes known as the "chick antider-

matitis factor" (based on a prior bioassay procedure). Pantothenic acid is a naturally occurring compound that on hydrolysis yields β-alanine and pantoic acid, a substituted butyric acid derivative. Biosynthetic evidence reveals that pantothenic acid is derived from β-alanine and α-ketoisovaleric acid.



Pantothenic Acid

Pantothenic acid is a viscous, oily liquid, so it is usually used as the calcium salt. It is readily synthesized. Both the racemic mixture and the dextrorotatory isomer are available commercially, the former having approximately one half the physiologic activity of the latter. **Panthenol,** a synthetic racemic mixture of the alcohol analog of pantothenic acid, is also available as a crystalline substitute for the acid; presumably panthenol is oxidized in vivo to pantothenic acid.

Pantothenic acid is a precursor of coenzyme A, a cofactor that is essential for metabolism of carbohydrates, lipids, and proteins. Coenzyme A is involved in the synthesis of fatty acids and sterols, the oxidation of fatty acids, pyruvic acid, and α-ketoglutaric acid, as well as in direct biologic acetylations.

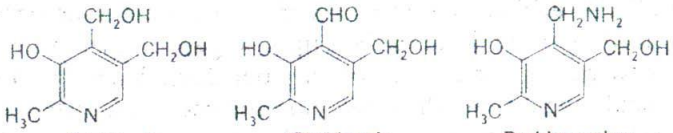
Animal organs (heart, kidney, and liver) and cereal grains are rich dietary sources of pantothenic acid, but this vitamin is so widely distributed that deficiency conditions are encountered only following deprivation or experimental induction. The most distinctive of the deficiency symptoms are paresthesias of the extremities or "burning foot" syndrome.

The US RDA for pantothenic acid is 10 mg for adults and children over 4 years of age, 5 mg for children under 4 years of age, and 3 mg for infants. However, it is recognized that there are no reliable data on the body's actual requirements for this vitamin. Adverse reactions are unknown upon ingestion of the usual dose (5 to 10 mg per day). There is no known justification for use of megadoses.

Tablets of pantothenic acid (50 mg to 1 g) and calcium pantothenate (10 to 250 mg) are available, but this vitamin is more commonly taken for dietary supplementation as a component of multivitamin preparations. Pantothenic acid, calcium pantothenate, and panthenol are used in various multivitamin products. This vitamin has not been proved effective for treating diabetic neuropathy, preventing arthritis, gray hair, or stress-related diseases, or improving mental processes. **Dexpanthenol,** the alcohol analog of *d*-pantothenic acid, is available as an intramusuclar injection (250 to 500 mg; Ilopan® and Panol®) for prevention or treatment of postoperative adynamic ileus and as an oral tablet with choline bitartrate (50 and 25 mg, respectively; Ilopan-Choline®) to help relieve intestinal gas retention of various etiologies. Dexpanthenol is also available in emollient preparations (Panthoderm®) for relief of itching and minor skin irritations.

Pyridoxine

Vitamin B_6 is a term that is applied to pyridoxol, pyridoxal, and pyridoxamine, three closely related, naturally occurring, highly substituted pyridine derivatives with comparable physiologic activity. **Pyridoxine** is the term that is usually used for pyridoxol in pharmacy and medicine. This alcohol is the predominant form of the vitamin in plant materials. Pyridoxal and pyridoxamine occur in animal tissues. Because pyridoxine is the most stable of these substances, synthetically prepared pyridoxine is the material usually used for exogenous dietary supplementation and therapeutic purposes.



Pyridoxol (Pyridoxine) Pyridoxal Pyridoxamine

Pyridoxine is readily absorbed in the jejunum, but the vitamin synthesized by the microflora of the colon is largely excreted in feces. Pyridoxine is converted to pyridoxal in erythrocytes; pyridoxal 5-phosphate or codecarboxylase is the main physiologically active form of the vitamin. Pyridoxamine 5-phosphate also functions to a lesser extent as an enzyme cofactor. Although pyridoxal 5-phosphate is protein bound, it is ultimately metabolized in the liver. The estimated biologic half-life of the vitamin is 15 to 20 days.

Codecarboxylase is involved in many reactions of carbohydrate, lipid, and protein metabolism. As a cofactor for aminotransferases, dehydratases, and decarboxylases, it is particularly important in amino acid metabolism. It is involved in a number of reactions, including the conversion of tryptophan to niacin and the biosynthesis of porphyrins.

Meats, bananas, whole cereal grains, nuts, and potatoes are good dietary sources of vitamin B_6. Up to 40% of its activity may be lost during cooking, but deficiency conditions are encountered in persons receiving a balanced diet only in such special situations as intestinal malabsorption, drug-induced (iatrogenic) requirements, and inborn errors of metabolism. A number of drugs, including chloramphenicol, cycloserine, hydralazine, isoniazid, and oral contraceptives, act as pyridoxine antagonists or increase its renal excretion. When they are used, intake of this vitamin must be increased. Congenital metabolic dysfunctions associated with vitamin B_6 include pyridoxine-dependent infantile convulsions, sideroblastic anemia, xanthurenic aciduria, homocystinuria, and cystathioninurea.

Symptoms of vitamin B_6 deficiency somewhat resemble those of niacin and riboflavin deficiencies. They include neurologic abnormalities (confusion, irritability, and convulsive seizures), skin lesions (glossitis, seborrheic dermatitis, and stomatitis), and hypochromic microcytic anemia. An oral loading dose of tryptophan can be used for diagnostic purposes; high urinary elimination of xanthurenic acid, normally a minor tryptophan metabolite, is indicative of a deficiency state.

The US RDA for pyridoxine is 2 mg for adults and children over 4 years of age, 0.7 mg for children under 4 years of age, 0.4 mg for infants, and 2.5 mg for pregnant and lactating women. Actual dietary requirements depend on the protein component of the diet as well as on genetic and iatrogenic factors.

Pyridoxine is used to supplement dietary intake and to treat deficiency states, congenital metabolic dysfunctions, and poisonings caused by cycloserine and isoniazid. There is no substantive evidence to support the beneficial use of pyridoxine in acne, alcohol intoxication, mental disorders, migraine headaches, morning sickness, or premenstrual tension.

The usual dose of pyridoxine is 10 to 20 mg per day for dietary supplementation, 10 to 300 mg per day for drug-induced deficiencies, and 100 to 600 mg per day for hereditary deficiencies. When a pyridoxine dependency syndrome is encountered, it is treated with an initial adult dosage regimen of 30 to 600 mg per day, followed by a 50-mg daily maintenance dose for life.

Poisoning cases may justify doses of 1 g or more. Pyridoxine is usually administered orally; parenteral administration is reserved for infantile convulsions, poisoning cases, and patients in whom oral administration is not acceptable.

Adverse reactions are rarely encountered with pyridoxine at doses of 25 mg per day or less. Ataxia and paresthesia have been noted in patients taking higher doses, and a pyridoxine dependency syndrome is sometimes induced in patients consuming 200 mg or more daily for periods exceeding a month. Because doses as small as 5 mg per day will stimulate decarboxylation of levodopa in peripheral tissues, patients taking this drug for parkinsonism should use a pyridoxine-free vitamin product.

Pyridoxine is available as the hydrochloride salt in tablet (5 to 500 mg), sustained release (5 to 500 mg), and injection (50 and 100 mg per ml) dosage forms. Pyridoxine should be protected against exposure to light.

PROPRIETARY AND PRESCRIPTION PRODUCTS. Beesix®, Hexa-Betalin®, Nestrex®, and Vitabee-6®.

Folic Acid

Folic acid, folacin, pteroylglutamic acid, and occasionally **vitamin B_9** are terms that refer to a material with antianemia properties; it is a conjugate of a pteridine derivative, *p*-aminobenzoic acid, and glutamic acid (Fig. 11–4). A number of other related metabolites with antianemia properties also exist in nature, but synthetically prepared folic acid is the most common commercial form of this vitamin. Dihydrofolate reductase in the liver and plasma reduces folic acid to tetrahydrofolic acid, the physiologically active form of the vitamin. N^5-Formyltetrahydrofolic acid (folinic acid or leucovorin) is a naturally occurring biochemical metabolite of folic acid that finds special use in an anticancer drug regimen employing folate antagonists.

Leafy vegetables (origin of the term "folic") and liver are good dietary sources of pteroylpolyglutamates (folates), the primary dietary forms of this vitamin. Up to 90% of dietary folates are lost during the cooking process; raw liver has been recommended in deficiency conditions, and a raw spinach salad is superior to cooked spinach as a dietary source. The pteroylpolyglutamates do not cross mammalian cell membranes but are hydrolyzed to pteroylmonoglutamate by γ-glutamylhydrolase prior to absorption in the jejunum. Polyglutamate metabolites that are resynthesized within mammalian cells are the in-vivo storage form of this vitamin. Human tissue storage of folates is estimated to be 5 to 10 mg. About one half of this amount is normally stored in the liver.

Tetrahydrofolic acid functions via a series of folate coenzymes that are acceptors and donors of 1-carbon units in amino acid (e.g., methionine) and nucleotide (e.g., purine and pyrimidine) metabolism. These coenzymes are essential in processes, such as erythropoiesis, leukopoiesis, and nucleoprotein synthesis, which are characterized by a high rate of cell turnover and metabolism.

Deficiency of folic acid is rarely encountered in the absence of intestinal malabsorption or impaired hepatic function (including alcoholism). Clinical symptoms of a deficiency state include megaloblastic and macrocytic anemias and glossitis.

Folic acid is used to treat deficiency states and to supplement dietary intake. Increased dietary supplementation may be required in chronic diseases of the liver and small intestine, prolonged stress and infection, a number of inborn errors of metabolism, and long-term use of medications such as anticonvulsants, oral contraceptives, and glucocorticosteroids. Folic acid has not been proved effective for relief of stress or prevention of mental disorders.

Although folic acid will correct the megaloblastic anemia associated with vitamin B_{12} deficiency, it will not stop the progressive neurologic lesions. Thus, pernicious

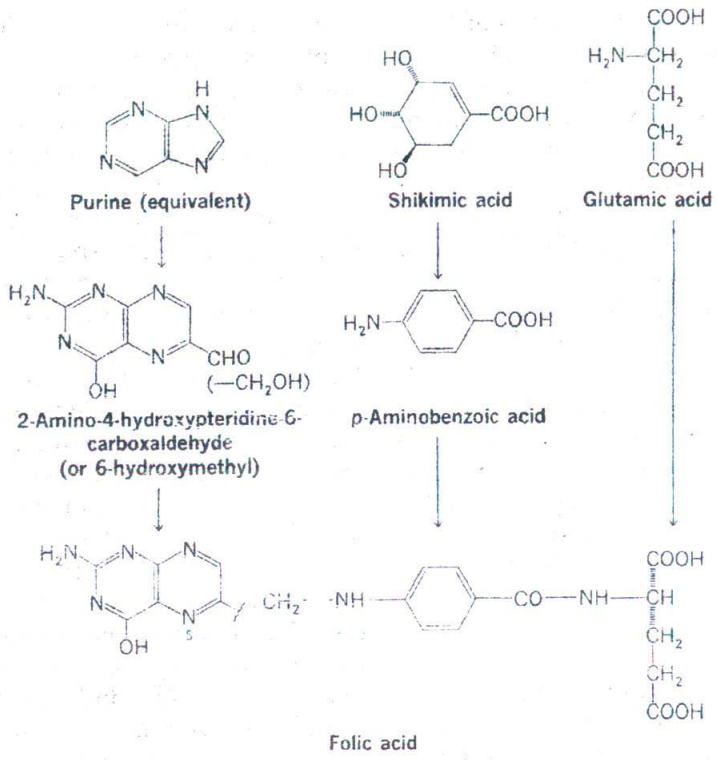


Fig. 11–4. Biosynthesis of folic acid.

anemia should be excluded before more than 0.4 mg per day of folic acid is taken; this precaution will avoid masking a key hematologic indication of pernicious anemia. Folic acid is generally considered to be free of other serious adverse reactions, but there is no justification for use of megadoses of this vitamin.

The US RDA of folic acid is 0.4 mg for adults and children over 4 years of age, 0.2 mg for children under 4 years of age, 0.1 mg for infants, and 0.8 for pregnant and lactating women.

The usual dose of folic acid for treating a deficiency condition is 0.25 to 1.0 mg per day until a hematologic response occurs. The usual doses for dietary supplementation parallel the US RDA values, but these doses may be increased slightly, if necessary. Parenteral (intramuscular, intravenous, or deep subcutaneous) administration is reserved for cases of intestinal malabsorption or other situations in which oral administration is not acceptable.

Folic acid is available as tablet (0.1, 0.4, 0.8, and 1 mg) and injection (5 mg and 10 mg per ml) dosage forms. It must be packaged in well-closed, light-resistant containers. Most folic acid products are available by prescription only, but products containing 0.4 mg or less (0.8 mg or less if intended for pregnant and lactating women) may be sold over-the-counter.

PRESCRIPTION PRODUCT. Folvite®.

Folinic acid or leucovorin is available as the calcium salt in tablet (5 and 25 mg) and injection (3 and 5 mg per ml) dosage forms. It is used as the "folinic acid rescue" antidote in chemotherapeutic regimens employing a potent folate antagonist such as methotrexate.

PRESCRIPTION PRODUCT. Wellcovorin®.

Vitamin B_{12}

Vitamin B_{12} and cobalamins are terms that refer to a series of porphyrin-related

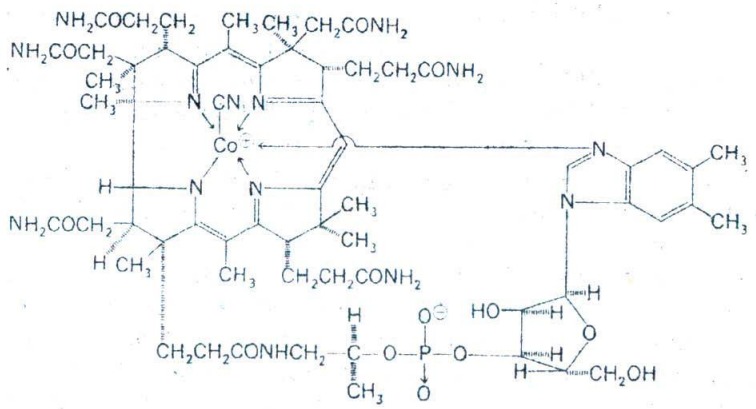
corrinoid derivatives that function as extrinsic factors to prevent pernicious anemia. These macromolecules contain cobalt, and the corrin nucleus is derived biosynthetically via a pathway that is similar to that for the porphyrin nucleus of heme. **Cyanocobalamin,** a red crystalline material, is the most stable of the cobalamins; consequently, it is the form of vitamin B_{12} most frequently utilized in therapy. **Hydroxocobalamin** also finds some therapeutic use; in it the cyano group is replaced with a hydroxyl substituent. The physiologically active in vivo forms of the vitamin are 5′-deoxyadenosylcobalamin (coenzyme B_{12}) and methylcobalamin.

Cyanocobalamin has been synthesized in a monumental chemical effort, but commercial supplies of the vitamin are obtained semisynthetically using microorganisms, especially *Streptomyces griseus*. The total cobalamin fraction obtained by fermentation is readily converted to cyanocobalamin by controlled treatment with cyanide. Cyanocobalamin can be converted, if desired, to hydroxocobalamin.

Vitamin B_{12} is stored in the liver (the liver half-life is estimated to be 400 days), and liver extract has been the classic source of this vitamin. Meat, seafood, eggs, dairy products, and fermented foods, such as soy sauce, are good dietary sources of the vitamin. Because vegetables are a poor dietary source of vitamin B_{12}, deficiency conditions have been associated with some strict vegetarian diets (no soy sauce or other fermented foods).

Vitamin B_{12} is absorbed in the lower half of the ileum. Two distinct mechanisms of absorption exist for this vitamin. A diffusion-type mechanism is operative when the amount of vitamin is large, but an active absorption process involving a glycoprotein (intrinsic factor) is more significant. Intrinsic factor is secreted by the parietal cells of the gastric mucosa. A vitamin B_{12}-intrinsic factor complex is formed in the stomach and passes into the intestine where it binds to receptor sites on the ileal mucosa. Calcium ion appears to be involved in breaking the vitamin-intrinsic factor complex at the receptor site. The absorbed vitamin is then transported in the plasma bound to transcobalamin I or transcobalamin II. Although the normal excretion process is biliary, with 65 to 75% reabsorption, nutritionally excessive quantities of cobalamins are excreted renally.

The cobalamins are essential to cell reproduction, growth, hematopoiesis, and synthesis of myelin and nucleoprotein. These cofactors participate in folate recycling, lipid metabolism, and methylation reactions. The adenosylcobalamin coenzyme is involved in a number of rearrangement reactions mediated by mutase and dehydrase enzymes; methylcobalamin is essential for the methyltransferase enzyme that catalyzes tetrahydrofolate regeneration.



Cyanocobalamin

Deficiency of vitamin B_{12} is usually associated with intestinal malabsorption or increased requirements for the vitamin in certain iatrogenic situations or in some pathologic states. Nutritional deficiency is rare, developing very slowly as a result of high liver storage and efficient enterohepatic recycling. Symptoms of vitamin B_{12} deficiency usually involve rapidly dividing cells of the hematopoietic system (e.g., megaloblastic anemia) and irreversible neurologic damage (e.g., defective myelin nerve sheaths); they include irritability, weakness, memory loss, mood swings, and a sensation of tingling or numbness of the arms and legs. A number of drugs, including the aminoglycoside antibiotics, *p*-aminosalicylic acid, many anticonvulsants, cholestyramine, and colchicine, interfere with intestinal absorption of the cobalamins. These medications may require dietary supplementation with the vitamin. The need for cobalamin supplementation may also be associated with a number of chronic clinical conditions, including hyperthyroidism, stress, malignancy of the pancreas, hepatic-bilary disease, and diseases of the small intestine. A deficiency in transcobalamin II and a failure to synthesize one or both of the active coenzyme forms of the vitamin are recognized as rare inborn errors of metabolism.

The US RDA of vitamin B_{12} is 6 μg for adults and children over 4 years of age, 3 μg for children under 4 years of age, 2 μg for infants, and 8 μg for pregnant and lactating women.

Oral cyanocobalamin (1 to 25 μg per day for adults) is taken for nutritional supplementation when intestinal absorption is normal. Intramuscular or subcutaneous administration of cyanocobalamin or hydroxocobalamin is employed in cases of intestinal malabsorption and in the treatment of pernicious anemia. The initial parenteral dosage regimen is 30 to 100 μg of either cyanocobalamin or hydroxocobalamin per day for 5 to 10 days, followed by a maintenance dose of 100 to 200 μg once a month for life.

Serious adverse reactions are uncommon with the therapeutic use of vitamin B_{12}. Hypokalemia can occur when megaloblastic anemia is converted to normal erythropoiesis under the influence of the vitamin. Patients with hereditary optic atrophy (Leber's disease) suffer an accelerated rate of atrophy when treated with cyanocobalamin. Hydroxocobalamin is the preferred therapeutic agent in the latter situation, but some patients develop antibodies to the hydroxocobalamin-transcobalamin II complex.

Hydroxocobalamin has also been used to prevent and treat cyanide toxicity associated with sodium nitroprusside. The cobalamins have no proven efficacy in the treatment of a number of conditions, including acute viral hepatitis, aging, mental disorders, multiple sclerosis, sterility, trigeminal neuralgia, and other neuropathies.

Cyanocobalamin is available as tablet (10 μg to 1 mg) and injection (30 μg, 100 μg, and 1 mg per ml) dosage forms. It must be packaged and stored in light-resistant containers.

PROPRIETARY AND PRESCRIPTION PRODUCTS. Bay Bee-12®, Berubigen®, Betalin 12®, Cabadon-M®, Cobex®, Crystimin-1000®, Cyanoject®, Cyomin®, Kaybovite 1000®, Pernavit®, Redisol®, Rubesol 1000®, Rubramin PC®, Sytobex®, and Vibal®.

Hydroxocobalamin is available only as an injection dosage form (100 μg and 1 mg per ml). It also must be packaged and stored in light-resistant containers.

PRESCRIPTION PRODUCTS. Alphamin®, AlphaRedisol®, Codroxomin®, Droxomin®, Hybalamin®, Hydrobexan®, Hydro-Cobex®, Hydroxo-12®, LA-12®, and Vibal LA®.

Although products containing crystalline cyanocobalamin are preferred for treating vitamin B_{12} deficiency, preparations containing a partially purified liver extract are available for oral and parenteral use.

The liver extract contains a number of vitamins, including folic and folinic acids; its potency, however, is expressed on the basis of vitamin B_{12} activity. An oral product (Biopar Forte®) also contains intrinsic factor concentrate, a concentrate prepared from the mucosal glands of porcine stomach walls. Parenteral products are usually fortified with crystalline cyanocobalamin plus either thiamine (Reticulogen® and Reticulogen Fortified®) or folic acid (Crysti-Liver®, Folabee®, Fol-Li-Bee Forte®, Hepfomin®, Hyliver Plus®, Lifolbex Improved®, Lifolex®, Lifomin®, Livroben®, Sanguis®, and Vifex®).

Parenteral cobalamins are preferred for the treatment of pernicious anemia, but a number of oral products containing cyanocobalamin and intrinsic factor concentrate, as well as iron and other vitamins (ascorbic acid, folic acid, niacin, riboflavin, and thiamine), are still available for dietary supplementation. Such products include Chromagen®, Contrin®, Eviron®, Ferotrinsic®, Heptuna Plus®, Lextron®, Omnihemin®, Perihemin®, Pronemia®, Reticulex®, TriHemic 600®, Trinsicon®, and Tri-Tinic®.

Cyanocobalamin Co 57 and cyanocobalamin Co 60 are substances that contain radioactive cobalt in their molecular structures. The specific activity of these materials is not less than 0.5 μCi per μg of cyanocobalamin. They are used as diagnostic aids in determining pernicious anemia. Absorption of the radioactive cyanocobalamin following oral ingestion is less than normal in patients with pernicious anemia. However, it may be normalized by concurrent administration of intrinsic factor, thus differentiating pernicious anemia from other causes of cyanocobalamin malabsorption.

Cyanocobalamin Co 57 and cyanocobalamin Co 60 are available as capsules and oral solutions. The usual test dose is 0.5 to 1 μCi at least 24 hours after ingestion of any other cobalamin-containing preparation. When calculating dosage, a correction should be made for radioactive decay because the radioactive half-life of ^{57}Co is 270 days and that of ^{60}Co is 5.27 years. The expiration date of these products is not later than 6 months after the date of standardization.

PRESCRIPTION PRODUCTS. Rubratope-57® and Rubratope-60®.

Dried Yeast

Yeasts are unicellular organisms that are well-known for their ability to metabolize sugar into alcohol and carbon dioxide. They have a long history of use in the baking and fermentation industries. Yeast cells contain a number of enzymes, other proteins, and B vitamins, so dried yeast was used medicinally at an early date as a source of the vitamin B complex. Pure vitamin substances are normally used at the present time although dried yeast is still used on occasion, especially by individuals with a strong preference for natural products.

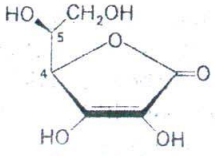
Brewer's yeast, *Saccharomyces cerevisiae* Hansen (Fam. Saccharomycetaceae), or torula yeast, *Candida utilis* (Henneberg) Loder and Kreger-Van Rij (Fam. Cryptococcaceae), is grown in suitable nutrient media in large fermentation tanks, and the cell mass is recovered. If the cell mass is a by-product of beer production, the cells must be washed thoroughly, usually using one or more alkaline solutions, to remove the insoluble acidic bitter resins from the hops. The yeast cells are dried and marketed as a granular powder or compressed tablets.

Representative dried yeast contains approximately 45% protein and, in each gram, 120 μg of thiamine, 40 μg of riboflavin, and 300 μg of niacin, plus detectable quantities of various other vitamins. When dried yeast is used as a dietary supplement, the usual dose is 10 g, 4 times a day.

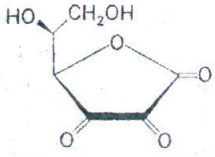
Vitamin C

Vitamin C or L-ascorbic acid is a naturally occurring vitamin substance that pre-

vents scurvy and has useful antioxidant properties. It occurs in equilibrium with dehydro-L-ascorbic acid, an oxidized form, which also has antiscorbutic properties. Vitamin C is the least stable of all the vitamins. Dehydro-L-ascorbic acid is irreversibly oxidized to the inactive 2,3-diketo-L-gulonic acid; alkaline conditions enhance this oxidation.



L-Ascorbic Acid



Dehydro-L-Ascorbic Acid

L-Ascorbic acid is derived biosynthetically from D-glucose, D-galactose, or other sugars with the correct chiral centers at C-2 and C-3 to yield the appropriate stereochemistry at C-4 and C-5 of ascorbic acid. L-Ascorbic acid can be isolated, using appropriate precautions to prevent oxidative inactivation of the molecule, from citrus fruits, rose hips, or other natural sources. Nevertheless, most commercial supplies of this vitamin are obtained by chemical synthesis starting with D-glucose. The physiologic properties of naturally occurring and synthetically prepared L-ascorbic acid are indistinguishable.

Exogenous vitamin C is required for primates (including humans), guinea pigs, fruit bats, some birds, and certain fish that lack the ability to form the material biosynthetically. This vitamin is essential for proper formation of collagen and other intercellular materials in tissues, especially in bones, skin, and teeth; it has been implicated in the hydroxylation of such collagen components as proline and lysine. It also appears to be associated with hydroxylases that act on cholesterol and tyrosine to produce corticosteroids and catecholamines, respectively. Vitamin C likewise is involved in biologic oxidation-reduction reactions (hydrogen and electron transport).

Good dietary sources of ascorbic acid include citrus fruits, tomatoes, strawberries, and other fresh fruits and vegetables. Although the vitamin content is preserved on freezing, up to 50% of the vitamin C content is lost upon cooking. Intestinal absorption involves a Na^+-dependent transport mechanism; the maximum intestinal absorption capacity is about 1200 mg per 24 hours. A normal healthy adult has an ascorbate body pool in excess of 1500 mg. This pool must drop below 300 mg before clinical signs of scurvy appear, a depletion process that usually takes several months with a vitamin C–deficient diet. Deficiency symptoms include fatigue, muscular pain, increased susceptibility to infection and stress, skin lesions, bleeding gums, and other signs of collagen degeneration.

The US RDA for ascorbic acid is 60 mg for adults and children over 4 years of age, 40 mg for children under 4 years of age, and 35 mg for infants. It is estimated that pregnant and lactating women may require 100 mg per day. Medications such as barbiturates, salicylates, and tetracycline may increase the requirements for this vitamin. Patients who smoke or who have gastrointestinal disease, cancer, peptic ulcer, hyperthyroidism, stress, or severe burns also may require increased vitamin C supplementation. The need for enhanced dietary supplementation is usually related to increased metabolic turnover or to reduced efficiency of intestinal absorption; for example, smokers have a daily turnover of approximately 100 mg (60 mg is normal) and intestinal absorption in the 63 to 80% range (78 to 88% of ingested ascorbic acid is normal).

Ascorbic acid is used to prevent or treat deficiency conditions and to enhance wound healing. High doses of the vitamin have been used as a urinary acidifier to enhance the effectiveness of methenamine, and it has been used with deferoxamine in iron toxicities to increase the excretion of the iron. Ascorbic acid is predominantly metabolized to carbon dioxide and oxalic acid prior to renal elimination, except upon

ingestion of high doses. The vitamin is generally considered free of serious adverse reactions or toxicities. When problems are encountered, they usually involve high doses and relate to undesirable urinary acidification or interference with diagnostic tests (e.g., serum lactic dehydrogenase and transaminase, occult blood in the stools, and urinary glucose).

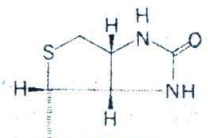
The usual doses of ascorbic acid for dietary supplementation are 50 to 100 mg per day for adults and 20 to 50 mg per day for infants. For treatment of a deficiency, the usual doses are 100 to 250 mg, 1 to 3 times a day for adults and 100 to 300 mg per day in divided doses for infants. The usual dosage regimen to enhance wound healing is 300 to 500 mg daily for 7 to 10 days. Doses of 4 to 12 g per day, in divided doses every 4 hours, are used in adults for urinary acidification. A potential role for vitamin C in prevention and treatment of cancer has been suggested, but efficacy has not been proved. Claims for the benefit of megadoses of vitamin C for the amelioration or prevention of the common cold, for the prevention of vascular thrombosis, and for the treatment of atherosclerosis, hypercholesterolemia, infertility, mental depression, and ulcers remain unsubstantiated.

Ascorbic acid is available in tablet (25 mg to 1 g), chewable tablet (100 mg to 1 g), effervescent tablet (1 g), extended-release tablet (250 mg to 1 g), extended-release capsule (250 and 500 mg), oral solution (35 and 100 mg per ml), syrup (20 and 100 mg per ml), and injection (50 to 500 mg per ml) dosage forms. Calcium ascorbate and sodium ascorbate are available as sugar-free powders and in tablet (equivalent to 500 mg of ascorbic acid) and injection (calcium salt: equivalent to 100 mg per ml; sodium salt: equivalent to 200, 250, and 500 mg per ml) dosage forms.

PROPRIETARY AND PRESCRIPTION PRODUCTS. Arco–Cee®, Ascorbicap®, C-Caps 500®, C-Span®, Ce-Vi-Sol®, Cecon®, Ceebate®, Cemill®, Cenolate®, Cetane®, Cevalin®, Cevi-Bid®, Dull-C®, Flavorcee®, and Vita-C®.

Biotin

Biotin, D-biotin, or vitamin H is a physiologically active substance that consists of fused imidazolidone and tetrahydrothiophene rings and a valeric acid side chain. Egg yolk, liver, cereal grains, and milk are good dietary sources of biotin, but commercial supplies are prepared by chemical synthesis.



Biotin

Even though biotin is produced by the intestinal microflora, evidence of the nutritional significance of enterically produced biotin is equivocal. It is known that biotin deficiency is rarely encountered and that biotin excreted in the feces is 2 to 5 times greater than the dietary intake. When biotin deficiency is encountered, it is usually caused by avidin, a glycoprotein in raw egg whites that forms a nonabsorbable avidin-biotin complex, or by inborn metabolic errors.

This vitamin functions as a carboxyl-carrying cofactor in several carboxylase and decarboxylase enzyme systems. Propionic acidemia, lactic acidosis, and 3-methylcrotonyl glycinuria encountered in some infants represent inborn errors in the metabolism of propionyl-CoA carboxylase, pyruvate carboxylase, and 3-methylcrotonyl-CoA carboxylase, all of which are biotin-dependent carboxylases.

Symptoms of biotin deficiency include alopecia, erythroderma desquamativa (Leiner's disease), and seborrheic dermatitis. Circumstantial evidence has linked biotin deficiency with the sudden infant death syndrome, but conclusive documentation is lacking.

The US RDA for biotin is 300 μg for

adults and children over 4 years of age, 150 μg for children under 4 years of age, and 50 μg for infants.

Biotin is generally considered to be well tolerated by humans and free of side effects, even at high doses. It is used to prevent or treat deficiency conditions and is available as an ingredient (usually 30 to 300 μg) in some multiple vitamin products.

VITAMIN-RELATED FACTORS

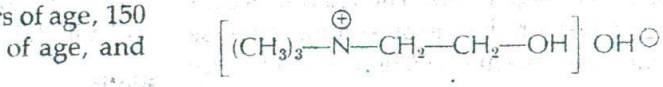
Para-aminobenzoic Acid

***Para*-aminobenzoic acid or PABA**, a precursor of folic acid, occurs in nature. Although sometimes grouped with the vitamin B complex, it is not an essential nutrient for humans and should not be considered a vitamin.

It is added as an accessory food factor (usually 15 to 100 mg) to a few multiple vitamin and mineral products. Because PABA may increase salicylate serum levels when taken concomitantly, it is sometimes used (500 mg, 4 to 6 times a day) for this purpose in rheumatic fever and other conditions benefiting from salicylate therapy. PABA interferes with the antibacterial action of sulfonamides, and they should not be taken concurrently. PABA is also used, either as the acid or various esters, as an ultraviolet sunscreen in a number of topical preparations.

Choline

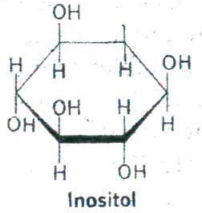
Choline or β-hydroxyethyltrimethylammonium hydroxide is a component of lecithin, a phospholipid, and a precursor of acetylcholine, a neurotransmitter. Choline is widely distributed in nature, occurring in egg yolk, animal organs (brains, heart, liver, and thymus), fish, milk, cereal grains, fruits, and root vegetables. It is known to be an essential nutrient in certain higher animals, but no proof exists for a dietary need in humans. Thus, it is technically not a vitamin, even though it is frequently associated with them.



Choline is available as the bitartrate, chloride, and dihydrogen citrate salts. As such, it is added (20 to 240 mg) to a number of multiple vitamin products. Choline has been associated, at least by implication, with fatty infiltration of the liver; it is sometimes used (usually 250 mg to 1 g per day) as a lipotropic agent in conditions such as liver cirrhosis, Huntington's chorea, presenile dementia, and tardive dyskinesia. However, its beneficial effect as a lipotropic agent has not been unequivocally established.

Inositol

Inositol, *meso*-inositol, myoinositol, or *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol is a sweet-tasting, optically inactive substance that is sometimes associated with the B vitamins. However, because dietary deficiency is unknown in humans, it is technically not a vitamin. Sources of inositol include endogenous synthesis and the normal American diet, which is estimated to provide 900 mg per day of exogenous inositol. It is distributed ubiquitously in food substances; particularly rich dietary sources are legumes, cereal grains, nuts, and animal organs, including liver and kidney. Inositol occurs free and as a component of phospholipids in animals but is bound to phosphate as phytate in plants.



Inositol

The biologic function of inositol appears to be related to its role as a phospholipid component of membranes and lipoproteins. It has been implicated in membrane

transport of amino acids and potassium and sodium ions.

Inositol is added (5 to 250 mg) to a number of multiple vitamin products. It is also sometimes used (1 to 3 g daily in divided doses) as an unproven lipotropic agent. The compound is metabolized to glucose in the kidney. Although inositol is free of serious adverse reactions, large doses may cause moderate diarrhea.

MULTIVITAMIN THERAPY

Diets deficient in one vitamin are likely to be deficient in several, and conditions that hinder the absorption of one vitamin may likewise interfere with the absorption of others. Inadequate vitamin intake can result not only from a poor diet but also from alcoholism, increased needs during pregnancy and lactation, prolonged broad-spectrum antibiotic therapy, and the course of parenteral nutrition. Poor absorption of ingested vitamins occurs frequently in elderly persons, chronically ill persons, and others who suffer from infections, reduced bile flow, intestinal disease, diarrhea, and the like. For these reasons, the supplementation of diets with multivitamin preparations does have a rational basis in certain circumstances.

Decavitamin capsules and decavitamin tablets serve as model multivitamin preparations, providing 10 vitamins for which recommended dietary allowances (RDA) have been established and one vitamin for which there is no such recommendation. Each capsule or tablet contains the labeled amounts of vitamins A, B_1, B_2, B_6, B_{12}, C, D, E, calcium pantothenate, folic acid, and niacinamide. The usual dose is 1 capsule or tablet daily.

PROPRIETARY PRODUCTS. (Some of these may differ slightly from the composition of Decavitamin.) Dayalets®, Multicebrin®, One-A-Day®, Sigtab®, Theracebrin®, Theragran®, Unicap®, Vigran®, and Zymacap®.

Hexavitamin capsules and hexavitamin tablets each contain the following specified amounts of 6 vitamins: vitamin A, 1.5 mg; B_1, 2 mg; B_2, 3 mg; C, 75 mg; D, 10 μg; niacinamide, 20 mg.

PROPRIETARY PRODUCT. Hepicebrin®.

A wide variety of other combination proprietary products is available. Such preparations may be grouped, for purposes of summation, into the vitamin B complex (Betalin Compound®, Becotin®, Lederplex®, and Surbex®), the vitamin B complex with C (Allbee with C®, Cebenase®, and Stresscaps®), multivitamins with iron (Dayalets Plus Iron®, Poly-Vi-Sol with Iron®, Unicap Plus Iron®, and Vi-Daylin Plus Iron®), multivitamins with calcium and iron (En-Cebrin®, Natabec®, Natafort®, and Natalins®), and multiple vitamins with iron and other minerals (Eldec®, Mi-Cebrin®, Myadec®, and Theragran-M®).

READING REFERENCES

Baker, B.M., and Bender, D.A.: *Vitamins in Medicine*, 4th ed., Vols. 1–2, London, Heinemann Medical Books Ltd., 1980–1982.

Botez, M.I., and Reynolds, E.H., eds.: *Folic Acid in Neurology, Psychiatry, and Internal Medicine*, New York, Raven Press, 1979.

Dolphin, D., ed.: *B_{12}*, New York, John Wiley & Sons, Inc., 1982.

Everse, J., Anderson, B., and You, K.-B., eds.: *The Pyridine Nucleotide Coenzymes*, New York, Academic Press, Inc., 1982.

Goodhart, R.S., and Shils, M.E., eds.: *Modern Nutrition in Health and Disease*, 6th ed., Philadelphia, Lea & Febiger, 1980.

Kumar, R., ed.: *Vitamin D*, The Hague, M. Nijoff Publishing, 1984.

Lubin, B., and Machlin, B., eds.: *Vitamin E: Biochemical, Hematological, and Clinical Aspects*, New York, New York Academy of Sciences, 1982.

Machlin, M.E., ed.: *Handbook of Vitamins*, New York, Marcel Dekker, Inc., 1984.

Nobile, S., and Woodhill, J.M.: *Vitamin C*, Hingham, Massachusetts, MTP Press, 1981.

Sable, H.Z., and Gubler, C.J., eds.: *Thiamin: Twenty Years of Progress*, New York, New York Academy of Sciences, 1982.

Silverman, H.M., Romano, J.A., and Elmer, G.: *The Vitamin Book*, New York, Bantam Books, 1985.

Sporn, M.B., Roberts, A.B., and Goodman, D.S., eds.: *The Retinoids*, Vols. 1–2, Orlando, Academic Press, Inc., 1984.

Tryfiates, G.P., ed.: *Vitamin B_6—Metabolism and Role in Growth*, Westport, Connecticut, Food & Nutrition Press, Inc., 1980.