**VITAMINS**

A vitamin is defined as an organic compound that is required in the diet in small amounts for the maintenance of normal metabolic integrity. Deficiency causes a specific disease, which is cured or prevented only by restoring the vitamin to the diet. However, **vitamin D,** which is formed in the skin from 7-dehydrocholesterol on exposure to sunlight, and **niacin,** which can be formed from the essential amino acid tryptophan, do not strictly comply with this definition.

The lipid-soluble vitamins (ADEK) are hydrophobic compounds that can be absorbed efficiently only when there is normal fat absorption. Like other lipids, they are transported in the blood in lipoproteins or attached to specific binding proteins.

The water-soluble vitamins are composed of the B vitamins and vitamin C; they function mainly as enzyme cofactors. Folic acid acts as a carrier of one-carbon units. Deficiency of a single vitamin of the B complex is rare, since poor diets are most often associated with multiple deficiency states.

**LIPID-SOLUBLE VITAMINS**

**VITAMIN A**

Two groups of compounds have vitamin A activity. (1) Retinoids comprise **retinol, retinaldehyde,** and **retinoic acid** (preformed vitamin A, found only in foods of animal origin); and (2) carotenoids, found in plants, are composed of carotenes and related compounds; many are precursors of vitamin A, as they can be cleaved to yield retinaldehyde, then retinol and retinoic acid.

**Functions of Vitamin A**

**Vitamin A Has a Function in Vision -** In the retina, retinaldehyde functions as the prosthetic group of the light-sensitive opsin proteins, forming **rhodopsin** (in rods) and **iodopsin** (in cones). Any one cone cell contains only one type of opsin, and is sensitive to only one colour. In deficiency, both the time taken to adapt to darkness and the ability to see in poor light are impaired.

**Retinoic Acid Has a Role in the Regulation of Gene Expression and Tissue Differentiation -** A major role of vitamin A is in the control of cell differentiation and turnover. Like the thyroid and steroid hormones and vitamin D, retinoic acid binds to nuclear receptors that bind to response elements of DNA and regulate the transcription of specific genes.

**Vitamin A Deficiency Is a Major Public Health Problem Worldwide**

Vitamin A deficiency is the most important preventable cause of blindness. The earliest sign of deficiency is a loss of sensitivity to green light, followed by impairment to adapt to dim light, followed by night blindness. More prolonged deficiency leads to **xerophthalmia:** keratinization of the cornea and blindness. Vitamin A also has an important role in differentiation of immune system cells, and even mild deficiency leads to increased susceptibility to infectious diseases. Also, the synthesis of retinol binding protein is reduced in response to infection, decreasing the circulating concentration of the vitamin, and further impairing immune responses.

**Vitamin A (Hypervitaminosis A) Is Toxic in Excess**

There is only a limited capacity to metabolize vitamin A, and excessive intakes lead to accumulation beyond the capacity of binding proteins, so that unbound vitamin A causes tissue damage. Symptoms of toxicity affect the central nervous system (headache, nausea, ataxia, and anorexia, all associated with increased cerebrospinal fluid pressure); the liver (hepatomegaly with histologic changes and hyperlipidaemia); calcium homeostasis (thickening of the long bones, hypercalcemia, and calcification of soft tissues); and the skin (excessive dryness, desquamation, and alopecia).

**VITAMIN D (CHOLECALCIFEROL)**

Vitamin D is not strictly a vitamin, since it can be synthesized in the skin, and under most conditions that is the major source of the vitamin. Only when sunlight exposure is inadequate is a dietary source required.

7-Dehydrocholesterol (an intermediate in the synthesis of cholesterol that accumulates in the skin) undergoes a nonenzymic reaction on exposure to ultraviolet light, yielding previtamin D. This undergoes a further reaction over a period of hours to form cholecalciferol, which is absorbed into the bloodstream.

Cholecalciferol, either synthesized in the skin or from food, undergoes two hydroxylations to yield the active metabolite, 1,25-dihydroxyvitamin D or calcitriol (Figure 44–4). Ergocalciferol from fortified foods undergoes similar hydroxylation to yield ercalcitriol. In the liver, cholecalciferol is hydroxylated to form the 25-hydroxyderivative, calcidiol. This is released into the circulation bound to a vitamin D binding globulin, which is the main storage form of the vitamin. In the kidney, calcidiol undergoes either 1-hydroxylation to yield the active metabolite 1,25-dihydroxy-vitamin D (calcitriol).

**Functions of Vitamin D**

The principal function of vitamin D is to maintain the plasma calcium concentration. Calcitriol achieves this in three ways: it increases intestinal absorption of calcium; it reduces excretion of calcium (by stimulating resorption in the distal renal tubules); and it mobilizes bone mineral.

In addition, calcitriol is involved in insulin secretion, synthesis and secretion of parathyroid and thyroid hormones, inhibition of production of interleukin by activated T-lymphocytes and of immunoglobulin by activated B-lymphocytes, differentiation of monocyte precursor cells, and modulation of cell proliferation.

**Vitamin D Deficiency Affects Children & Adults**

In the vitamin D deficiency disease **rickets,** the bones of children are undermineralized as a result of poor absorption of calcium. Similar problems occur as a result of deficiency during the adolescent growth spurt. **Osteomalacia** in adults results from the demineralization of bone, especially in women who have little exposure to sunlight, especially after several pregnancies.

**Vitamin D Is Toxic in Excess (Hypervitaminosis D)**

Some infants are sensitive to intakes of vitamin D as low as 50 g/day, resulting in an elevated plasma concentration of calcium. This can lead to contraction of blood vessels, high blood pressure, and **calcinosis** —the calcification of soft tissues. Although excess dietary vitamin D is toxic, excessive exposure to sunlight does not lead to vitamin D poisoning, because there is a limited capacity to form the precursor, 7-dehydrocholesterol, and prolonged exposure of previtamin D to sunlight leads to formation of inactive compounds.

**VITAMIN E (TOCOPHEROL)**

Vitamin E is the generic descriptor for two families of compounds, the **tocopherols** and the **tocotrienols**. The different vitamers have different biologic potency; the most active is D - -tocopherol, and it is usual to express vitamin E intake in terms of milligrams D - -tocopherol equivalents.

**Function of Vitamin E**

The main function of vitamin E is as a chain-breaking, free-radical-trapping antioxidant in cell membranes and plasma lipoproteins by reacting with the lipid peroxide radicals formed by peroxidation of polyunsaturated fatty acids.

**Vitamin E Deficiency**

Dietary deficiency of vitamin E in humans is unknown, although patients with severe fat malabsorption, cystic fibrosis, and some forms of chronic liver disease suffer deficiency because they are unable to absorb the vitamin or transport it, exhibiting nerve and muscle membrane damage. Premature infants are born with inadequate reserves of the vitamin. The erythrocyte membranes are abnormally fragile as a result of peroxidation, leading to haemolytic anaemia.

**VITAMIN K (PHYLLOQUINONE)**

Three compounds have the biological activity of vitamin K: **phylloquinone,** the normal dietary source, found in green vegetables; **menaquinones,** synthesized by intestinal bacteria, with differing lengths of side-chain; and **menadione** and menadiol diacetate, synthetic compounds that can be metabolized to phylloquinone. Menaquinones are absorbed to some extent, but it is not clear to what extent they are biologically active as it is possible to induce signs of vitamin K deficiency simply by feeding a phylloquinone-deficient diet, without inhibiting intestinal bacterial action.

**Functions of Vitamin K**

1. Vitamin K plays an important role in blood clotting. A high dose of vitamin K is the antidote to an overdose of warfarin (an anticoagulant).
2. Vitamin K Is Important in Synthesis of Bone Calcium-Binding Proteins **-** Treatment of pregnant women with warfarin can lead to foetal bone abnormalities known as foetal warfarin syndrome. It is therefore contraindicated in the first trimester.

**WATER-SOLUBLE VITAMINS**

**VITAMIN B1 (THIAMINE)**

**Thiamine** has a central role in energy-yielding metabolism, and especially the metabolism of carbohydrates. **Thiamine diphosphate** is the coenzyme for three multi-enzyme complexes that catalyze oxidative decarboxylation reactions:

* pyruvate dehydrogenase in carbohydrate metabolism;
* ketoglutarate dehydrogenase in the citric acid cycle; and
* the branched-chain keto-acid dehydrogenase involved in the metabolism of leucine, isoleucine, and valine

Thiamine triphosphate has a role in nerve conduction; it phosphorylates, and so activates, a chloride channel in the nerve membrane.

**Thiamine Deficiency Affects the Nervous System & the Heart**

Thiamine deficiency can result in three distinct syndromes: a chronic peripheral neuritis, **beriberi,** which may or may not be associated with **heart failure** and **oedema;** acute pernicious (fulminating) beriberi (shoshin beriberi), in which heart failure and metabolic abnormalities predominate, without peripheral neuritis; and **Wernicke encephalopathy** with **Korsakoff psychosis,** which is associated especially with alcohol and narcotic abuse.

**VITAMIN B2 (RIBOFLAVIN)**

Riboflavin provides the reactive moieties of the coenzymes **flavin mononucleotide (FMN)** and **flavin adenine dinucleotide (FAD)**. FMN is formed by ATP-dependent phosphorylation of riboflavin, whereas FAD is synthesized by further reaction with ATP in which its AMP moiety is transferred to FMN. The main dietary sources of riboflavin are milk and dairy products. In addition, because of its intense yellow colour, riboflavin is widely used as a food additive.

**Riboflavin Deficiency Is Widespread But Not Fatal**

Although riboflavin is centrally involved in lipid and carbohydrate metabolism, and deficiency occurs in many countries, it is not fatal, because there is very efficient conservation of tissue riboflavin. Riboflavin released by the catabolism of enzymes is rapidly incorporated into newly synthesized enzymes. Deficiency is characterized by cheilosis, desquamation and inflammation of the tongue, and a seborrheic dermatitis.

**VITAMIN B3 (NIACIN)**

Niacin was discovered as a nutrient during studies of **pellagra.** It is not strictly a vitamin since it can be synthesized in the body from the essential amino acid tryptophan. Two compounds, **nicotinic acid** and **nicotinamide,** have the biologic activity of niacin; its metabolic function is as the nicotinamide ring of the coenzymes **NAD** and **NADP** in oxidation/reduction reactions.

**Pellagra Is Caused by Deficiency of Tryptophan & Niacin**

Pellagra is characterized by a photosensitive dermatitis. As the condition progresses, there is dementia and possibly diarrhoea. Untreated pellagra is fatal. Although the nutritional aetiology of pellagra is well established, and tryptophan or niacin prevents or cures the disease, additional factors, including deficiency of riboflavin or vitamin B6, both of which are required for synthesis of nicotinamide from tryptophan, may be important. In most outbreaks of pellagra, twice as many women as men are affected, probably the result of inhibition of tryptophan metabolism by oestrogen metabolites.

**Niacin Is Toxic in Excess**

Nicotinic acid has been used to treat hyperlipidemia when of the order of 1–6 g/day are required, causing dilatation of blood vessels and flushing, along with skin irritation. Intakes of both nicotinic acid and nicotinamide in excess of 500 mg/day also cause liver damage.

**VITAMIN B6 (PYRIDOXINE)**

Six compounds have vitamin B6 activity: **pyridoxine, pyridoxal, pyridoxamine,** and their 5'- phosphates. The active coenzyme is pyridoxal 5'-phosphate. Some 80% of the body's total vitamin B6 is pyridoxal phosphate in muscle, mostly associated with glycogen phosphorylase. This is not available in deficiency, but is released in starvation, when glycogen reserves become depleted, and is then available, especially in liver and kidney, to meet increased requirement for gluconeogenesis from amino acids.

**Vitamin B6 Deficiency Is Rare**

Although clinical deficiency disease is rare, there is evidence that a significant proportion of the population have marginal vitamin B6 status. Moderate deficiency results in abnormalities of tryptophan and methionine metabolism. Increased sensitivity to steroid hormone action may be important in the development of **hormone-dependent cancer** of the breast, uterus, and prostate, and vitamin B6 status may affect the prognosis.

**In Excess, Vitamin B6 Causes Sensory Neuropathy**

The development of sensory neuropathy has been reported in patients taking 2–7 g of pyridoxine per day for a variety of reasons.

**VITAMIN B12 (CYANOCOBALAMIN)**

Although it is synthesized exclusively by microorganisms, for practical purposes vitamin B12 is found only in foods of animal origin, there being no plant sources of this vitamin. This means that strict vegetarians (vegans) are at risk of developing B12 deficiency. The small amounts of the vitamin formed by bacteria on the surface of fruits may be adequate to meet requirements, but preparations of vitamin B12 made by bacterial fermentation are available.

Vitamin B12 is absorbed bound to **intrinsic factor,** a small glycoprotein secreted by the parietal cells of the gastric mucosa. Gastric acid and pepsin release the vitamin from protein binding in food and make it available to bind to **cobalophilin,** a binding protein secreted in the saliva. In the duodenum, cobalophilin is hydrolyzed, releasing the vitamin for binding to intrinsic factor. **Pancreatic insufficiency** can therefore be a factor in the development of vitamin B12 deficiency, resulting in the excretion of cobalophilin-bound vitamin B12. Vitamin B12 is absorbed from the distal third of the ileum via receptors that bind the intrinsic factor-vitamin B12 complex, but not free intrinsic factor or free vitamin.

**Vitamin B12 Deficiency Causes Pernicious Anemia**

Pernicious anemia arises when vitamin B12 deficiency impairs the metabolism of folic acid, leading to functional folate deficiency that disturbs erythropoiesis, causing immature precursors of erythrocytes to be released into the circulation (megaloblastic anemia). The most common cause of pernicious anemia is failure of the absorption of vitamin B12 rather than dietary deficiency. This can be the result of failure of intrinsic factor secretion caused by autoimmune disease affecting parietal cells or from production of anti-intrinsic factor antibodies.

**FOLIC ACID/FOLATE (VITAMIN B9)**

The active form of folic acid (pteroyl glutamate) is tetrahydrofolate. The folates in foods may have up to seven additional glutamate residues linked by gamma-peptide bonds. Tetrahydrofolate can carry one-carbon fragments attached to *N* -5 (formyl, formimino, or methyl groups), *N* -10 (formyl) or bridging *N* -5–*N* -10 (methylene or methenyl groups). 5-Formyl-tetrahydrofolate is more stable than folate, and is therefore used pharmaceutically (known as **folinic acid**), and the synthetic (racemic) compound **(leucovorin).**

**Folate Deficiency Causes Megaloblastic Anemia**

Deficiency of folic acid itself or deficiency of vitamin B12, which leads to functional folic acid deficiency, affects cells that are dividing rapidly because they have a large requirement for thymidine for DNA synthesis. Clinically, this affects the bone marrow, leading to megaloblastic anemia.

**BIOTIN (VITAMIN H/VITAMIN B7/8)**

Biotin is widely distributed in many foods as biocytin, which is released on proteolysis. It is synthesized by intestinal flora in excess of requirements. Deficiency is unknown, except among people maintained for many months on total parenteral nutrition, and a very small number who eat abnormally large amounts of uncooked egg white, which contains avidin, a protein that binds biotin and renders it unavailable for absorption.

**PANTOTHENIC ACID (VITAMIN B5)**

Pantothenic acid has a central role in acyl group metabolism when acting as the pantetheine functional moiety of coenzyme A or acyl carrier protein (ACP). The pantetheine moiety is formed after combination of pantothenate with cysteine, which provides the–SH prosthetic group of CoA and ACP. CoA takes part in reactions of the citric acid cycle, fatty acid oxidation, acetylations and cholesterol synthesis. ACP participates in fatty acid synthesis. The vitamin is widely distributed in all food-stuffs, and deficiency has not been unequivocally reported in humans except in specific depletion studies.

**VITAMIN C (ASCOBIC ACID)**

Ascorbic acid has specific roles in the copper-containing hydroxylases and the alpha-ketoglutarate-linked iron-containing hydroxylases. It also increases the activity of a number of other enzymes in vitro, although this is a nonspecific reducing action. In addition, it has a number of nonenzymic effects as a result of its action as a reducing agent and oxygen radical quencher.

**Vitamin C Deficiency Causes Scurvy**

Signs of vitamin C deficiency include skin changes, fragility of blood capillaries, gum decay, tooth loss, and bone fracture, many of which can be attributed to deficient collagen synthesis.