CHAPTER XI

VITAMINS

An outline of historical review. The disease *Scurvy* is said to have afflicted the Crusadors. During 1400's and 1500's it was one of the prevalent diseases in Europe. Scurvy was reported by Vasco de Gama during his sea voyages, and Jacques Cartier in 1535 reports loss of 25% of his sailing crew due to scurvy. As early as 1601 ships of the East India Company carried oranges and lemons to prevent scurvy on the recommendation of the English privateer, Sir James Lancaster. In 1720 Kramer, an Austrian Army Physician, had written about the disease scurvy and its cure after the intake of oranges or green vegetables. In 1753 Captain Lind of the British Navy proved that Scurvy could be cured by oranges and lemons. In 1882 Admiral Takaki, Director-General of the Medical Service in Japan, observed that *Beriberi* could be cured by increasing fresh vegetables, meat, fish and other proteins in the diet. In 1890 Eijkman in Dutch East Indies found out that birds fed with polished rice developed *Polyneuritis* along with other signs similar to that of Beriberi. Dr. Casimir Funk of the Lister Institute of London isolated the antiberiberi substance in pure form and as it was thought to be an *amine*, and at the suggestion of Dr. Max Nierenstein the term **vitamine** was used. In 1888 Lunin and Professor Bunge of Basle observed that life was not sustained by diet containing purified proteins, carbohydrates, fats and minerals, but when such food was supplemented by milk the *normal growth* and *longivity* are maintained. So they concluded that there must be some substances, besides carbohydrate, protein, fat and minerals, which are essential for nutrition. In 1915 McCollum and Davis established the presence of essential factors for growth in milk and egg-yolk. (*a*) 'Fat-soluble A' found in eggs and butter, (*b*) 'Water-soluble B' in milk, etc. In 1920 Professor J. C. Drummond suggested the term for the essential factor (vital) as **vitamin** after dropping the word **e.**

So the *vitamins may be defined as potent organic compounds which is found in foods in variable and minute quantity, and must be supplied to the animal organisms from external sources, so that specific physiological functions, vital to life, may go on normally.* They are neither oxidised to supply energy nor used to build tissue structures. However, it is difficult to give a proper definition which would be concise and complete due to the diverse and incomplete knowledge regarding these substances.

The general characteristics of the vitamins are given below:

1. **Distribution.** The vitamins are widely distributed in nature—both in the animal and vegetable kingdoms. *All vitamins are manufactured in plants.* The animals can manufacture a few only but can store all to some extent. Almost all common articles of food contain more than one vitamin.

2. **Daily requirement.** Vitamins can perform their work in very low concentration. Hence, the total daily requirement is usually very small. The daily need of any vitamin for any individual is not a fixed quantity. It varies according to the rate of metabolism. In people undergoing heavy muscular work, in hyperthyroidism, pregnancy, lactation, growing children, i.e., in all cases where metabolism is very high, the vitamin requirement is proportionally more. Generally, a man doing ordinary work, can obtain enough vitamin from his balanced mixed diet.

3. **Store.** Vitamins can be stored in the body to some extent, for example, the fat-soluble vitamins are stored in the liver and the subcutaneous tissue, vitamin C in adrenal cortex, etc.

4. **Fate.** Vitamins are partly destroyed and are partly excreted.

5. **Synthesis in the body.** Some vitamins are synthesised in the body, viz., vitamin A from provitamin carotene and vitamin D from ultra-violet irradiation of vitamin D-precursors, e.g., ergosterol. Some members of the

vitamin B complex are synthesised by micro-organisms in the intestinal tract. Vitamin C is also synthesised in some animals, e.g., rat.

6. **Vitamins are not destroyed in the digestive process** and are, therefore, absorbed as such. Hence, all vitamins are effective when administered orally.

7. **Mode of action.** Not exactly known in all cases. Several of them have been proved to act as a coenzyme of other metabolic enzymes. Since the enzyme system of a tissue is specific in nature, it is quite probable that, a particular vitamin acts selectively upon one tissue (i.e., acts as a coenzyme of the specific enzymes of these tissues). This conception will help one to explain why the deficiency of a particular vitamin, specially affects some tissues and systems and leaves others more or less untouched.

8. **Essential constituent of diet.** Although they are essential for life, yet all vitamins are not required for all the species of animals. One which is required for rats may not be so for man. The physiological requirement is met with the synthesis of a particular vitamin in the organism.

9. **Non-antigenic.** Vitamins are not antigenic.

10. **Solubility.** Some of them are soluble in water and others in fats and fat-solvents.

11. **Artificial synthesis.** Most of the vitamins have been artificially synthesised.

The vitamins and their functions in brief are given below:

FAT-SOLUBLE

- **A (Retinol)**—*Antixerophthalmic* factor
  - A_1 (Retinol$_1$), A_2 (Retinol$_2$) — Regeneration of visual purple, prevents night-blindness and keratinisation of epithelial tissues.
- **D (Calciferol)**—*Antirachitic* factor
  - D_2—Ergocalciferol (activated ergosterol or viosterol)—prevents rickets.
  - D_3—Cholecalciferol or natural vitamin D—essential for bone development and also prevents rickets.
- **E—Tocopherols** (α, β, γ)—*Antisterilitic* factor—prevents sterility and muscular dystrophy.
- **K**—Methyl phytyl naphthoquinone (quinoid structure): *Antihaemorrhagic* factor—essential for the formation of prothrombin of blood, hence essential for blood clotting and prevents haemorrhage.

WATER-SOLUBLE

VITAMINS OF B COMPLEX

1. **Thiamine** (**Aneurine**, vitamin B_1)—*Antineuritic* factor or *Antiberiberi* substance—acts as the coenzyme of pyruvate carboxylase.
2. **Lipoic acid** (Thio-acetic acid)—*Acetate-replacement* factor and a cofactor in oxidative decarboxylation of α-keto acids.
3. **Riboflavin** (vitamin B_2, Lactoflavin)—closely concerned with oxidative processes in the cells. Prevents cheilosis. Acts as coenzyme for flavoprotein enzymes in the body. Deficiency produces loss of appetite and weight, corneal vascularisation, etc.

WATER-SOLUBLE (contd.)

4. **Nicotinic acid (Niacin)** and **Nicotinamide (Nicotinic acid amide, Niacinamide)**—prevents human pellagra, hence called *antipellagra* factor or *pellagra-preventing* factor (P–P factor) acts as a coenzyme for the two enzymes NAD and NADP.
5. **Pantothenic acid** (vitamin B_3)—*Chick antidermatitis* factor, *Filtrate* factor. Functionally related to CoA.
6. **Pyridoxine** (vitamin B_6)—*Rat antidermatitis* factor. Acts as a coenzyme for transaminases or aminotransferases, decarboxylases, deaminases or dehydrases, desulphydrases, etc.
7. **Folic acid** (Pteroylglutamic acid)—*Fermentation residue* factor, prevents macrocytic anaemia in human being. **Folinic acid** also known as Citrovorum factor, or Leucovorin is also intimately connected with the functions of folic acid. Both folic acid and cyanocobalamin are intimately related to one-carbon metabolism.
8. **Cyanocobalamin** (vitamin B_{12})—*Antipernicious anaemia* factor, *Castle's extrinsic* factor.
9. **Biotin** (vitamin H)—*Anti-egg-white-injury* factor, prevents dermatitis in rats and dogs. Experimental deficiency in man causes peculiar dermatitis. Absence of biotin produce lassitude and sometimes gastro-intestinal symptoms. It also acts as a coenzyme.
10. **Choline** and **Lipotropic factor**—methyl donor; synthesis of acetylcholine, phospholipids, etc. Not essential for man because it can be synthesised in the body.
11. **Para-amino-benzoic acid** (PABA)—prevents premature greying of hair in rats.
12. **Inositol**—*Mouse anti-alopecia* factor.
13. B_4 } Essential for the growth of pigeons. Their value in
14. B_5 } human dietary is not yet proved.

Vitamin C (Ascorbic acid)—*Antiscorbutic* factor, i.e., prevents human scurvy. Involved in many other important physiological functions.

Vitamin P (Citrin, Rutin, Hesperidin)—*Permeability* factor—closely related to vitamin C and helps its action. Prevents capillary fragility.

FAT-SOLUBLE VITAMINS

VITAMIN A (RETINOL)
(Antixerophthalmic factor)

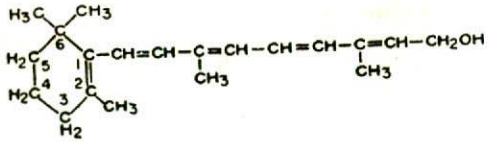
Historical review. In 1912 Hopkins reported normal and continued growth when whole milk was added to purified rations in young rats, and this study ultimately led up to the discovery of this vitamin by McCollum. In 1915 McCollum and Davis established the essential factors in eggs, butter and milk, i.e., 'fat-soluble A' in eggs and butter, and 'water-soluble B' in milk. 'Fat-soluble A' cured *Xerophthalmia*.

Components. Includes A_1 and A_2. A_2* is functionally almost similar

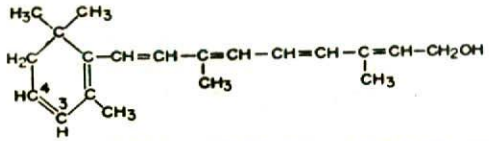
* **Vitamin A_2.** Found chiefly in the livers of fresh-water fishes. Apart from other functions, it takes part in the cyclical breakdown and resynthesis of a pigment, called *Porphyropsin* which replaces rhodopsin in the rods of certain fresh-water fishes.

to A_1. Chemical structure is slightly different. Vitamin A_2 has one more double-bond. It is a dehydrovitamin A_1 and also known as 3-dehydro-retinal. Its potency is 40% that of vitamin A_1. Vitamin A_1 may be derived from β-carotene by cleavage at the midpoint of the carotene molecule.

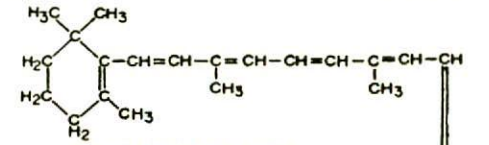
Chemistry. Unsaturated primary alcohol (-ioninol). Empirical formula of vitamin A_1 (**retinol$_1$**) is $C_{20}H_{29}OH$ and of vitamin A_2 (**retinol$_2$**) is $C_{20}H_{27}OH$. Structure closely similar to plant pigments *carotenes*, the provitamin A. Since β-ionone ring is essential part of vitamin A molecule and as β-carotene contains two β-ionone rings and α- and γ-carotenes contain β-ionone ring, so α- and γ-carotenes give one molecule of vitamin A but β-carotene gives two. The chemical structure of β-carotene, vitamins A_1 and A_2 are shown below:



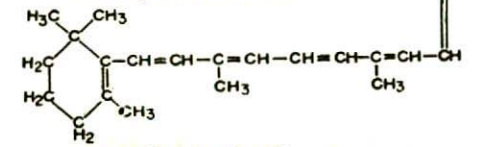
Vitamin A_1 (Retinol$_1$) ($C_{20}H_{29}OH$)



Vitamin A_2 (Retinol$_2$ or 3-dehydroretinal) ($C_{20}H_{27}OH$)



A RING (β-IONONE RING)



B RING (β-IONONE RING)

β-carotene ($C_{40}H_{56}$)

Vitamin A exists naturally in several isomeric forms. This is a *cis-trans isomerism* which arises from configurational differences about the double bonds in the side chain. The most naturally occurring form of vitamin A is the *all-trans isomer.*

Retinene (Retinal) is the aldehyde form of vitamin A.

Absorption. In the small intestine, the vitamin A esters of food are hydrolysed to fatty acids and free vitamin. Vitamin A_1 and carotene are absorbed through the lymphatics and appear in the blood plasma as the ester, indicating re-esterification in the intestinal wall. Presence of fats and bile salts helps the process. Vitamin A_1 is more quickly and completely

absorbed than carotene and the latter which is not converted to vitamin A here is carried to the blood. The simultaneous presence of tocopherols and other antioxidants protects them against destruction in the intestinal lumen.

Storage. Chiefly in the liver (95%) as esters. Slightly in the lungs, lactating breasts, kidney, skin, etc. In liver vitamin A seems to be associated with lipoprotein.

In Blood. The values for vitamin A and carotenes in the blood of normal subjects vary widely. Approximate concentrations are—vitamin A, 18 to 60 μ gm (60 to 200 i.u.) per 100 ml serum; carotenoids, 100 to 300 μ gm per 100 ml serum, carried mainly in the β-lipoprotein fraction.

Excretion. Mainly in the faeces.

Synthesis. In the body from carotene. One molecule of β-carotene gives two molecules of vitamin A. Hence, carotene is called **provitamin A.** Conversion takes place in the intestinal mucosa by the enzyme *carotinase* in rats, pigs, goats, sheep, etc., although the liver may also participate. In man the liver is believed to be the only organ which performs this conversion. It has also been artificially synthesised.

Properties. Soluble in fat-solvents, insoluble in water. Ordinarily it is a viscid colourless oil but by careful fractionation it has also been isolated as pale yellowish needles. Heat-stable, provided contact with air is prevented. Easily destroyed on exposure to air or ultra-violet rays. It gives a characteristic absorption band in the ultra-violet spectrum at 328 mμ.

Test. Gives blue colour with antimony trichloride in chloroform. This colour reaction is used as a basis for both colorimetric and spectrophotometric methods. The reaction is known as **Carr-Price reaction.**

Distribution. Vitamin A is present only in lipids of animal sources and carotenoid, in vegetable ones. *Animal sources*—Cod-liver oil (400–4,000 i.u. per gm); halibut-liver oil (20,000 i.u. per gm); milk (2,000 i.u. per 600 ml); butter (20–50 i.u. per gm); one egg (200 i.u.). Fishes are also rich sources. *Vegetable sources*—Vegetable oils contain very little. Substances which are rich sources of carotene, e.g., carrots (20 i.u. per gm); spinach (100 i.u. per gm). Green leaves, yellow fruits such as mangoes, tomatoes, etc., are also good sources.

Functions. (1) Essential for growth. (2) It is a component of rhodopsin, hence essential for night vision (*vide* 'Rhodopsin'). (3) Maintains the integrity and activity of epithelial tissues and glands. (4) Prevents infection (secondary to normal epithelial tissues). (5) It plays some part in protein synthesis. (6) Controls the action of the bone cells, so that normal growth and shape of bone are maintained. (7) Vitamin A is directly concerned both in the formation of mucopolysaccharides and also in the sulphation of it. (8) Helps in keeping normal fertility. (9) Vitamin A participates in reactions which affect the stability of cell membranes, and membranes of subcellular particles. (10) It also plays a stabilising role on the normal permeability of lysozymes and mitochondria. (11) It is probable, that vitamin A has some specific functions on carbohydrate metabolism. (12) Prevents the condition known as urolithiasis where urinary calculi in the form of calcium phosphate is present.

The protein carrier of vitamin A is similar to that of *copper-carrying protein*, **ceruloplasmin,** and both are stored predominantly in the liver. It has been observed that there may be inverse relationship between the vitamin and the metal. This indicates that there may be

some reciprocating interplay between vitamin A and copper in their metabolism and mode of action.

Deficiency signs. General growth—failure of growth. **Eye**—(1) Night-blindness (*Nyctalopia*). The **rhodopsin** or visual purple is a chromoprotein containing the carotenoid pigment **retinene** which is same as vitamin A aldehyde or retinal as a prosthetic group and a protein **opsin.** It is present in the outer limbs of the rods only. When exposed to light rhodopsin is split up into the (*a*) yellow compound retinene and (*b*) colourless protein opsin. The *retinene* is actually retinene$_1$ (vitamin A$_1$ aldehyde). Under the influence of light, rhodopsin is converted to orange-red compound **lumirhodopsin** which becomes changed to **metarhodopsin,** ultimately forming a yellow mixture of *trans*-**retinene** and **opsin.** *In vitro*, *trans*-retinene is converted to *cis*-**retinene** on exposure to blue light. But in the eye, *trans*-retinene is rapidly converted to *trans*-**vitamin A** by retinene reductase and NADH. In dim light, during the process of resynthesis of rhodopsin, **active** *cis*-**vitamin A** enters the retina from blood and is oxidised to *cis*-retinene by **retinene reductase** and NAD. This *cis*-retinene couples with opsin to give rhodopsin (FIG. 490). *Degree of vitamin A deficiency can be measured by the delay in dark adaptation.* [*Vide Dark Adaptation.*] (2) Degeneration of lachrymal glands. (3) Redness, abnormally dry and lustreless condition of the eye-ball (*Xerophthalmia*) (FIG. 491) with consequent keratinisation and degeneration of cornea (*Keratomalacia*). **Epithelial tissues**—(*a*) *Skin*—thickening and keratinisation, follicular and papular eruptions (Phrynoderma or Toad skin), sebaceous and sweat glands degenerate. (*b*) *Alimentary tract*—the glands present in the alimentary tract and the epithelial linings degenerate. (*c*) *Kidney and Urinary tract*—epithelium degenerates and becomes cornified, hence favours formation of renal stone.* (*d*) *Respiratory passages*—the

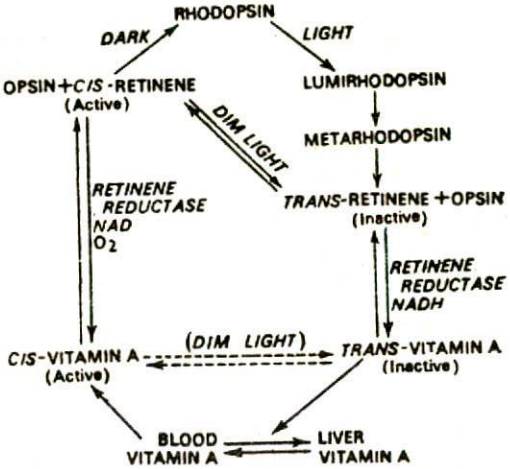


FIG. 490. Block diagram showing cyclical role of rhodopsin.

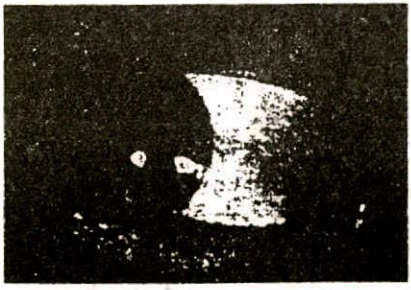


FIG. 491. Conjunctival changes (*Xerophthalmia*) in deficiency of vitamin A.

* **Formation of kidney stones.** Diet with high calcium and low vitamin A favours formation of calcium phosphate stone in the kidney and bladder.

epithelium becomes stratified and degenerates. (*e*) *Cornea*—mentioned above. These degenerative changes of the epithelial tissues decrease the resistance of the local cells, hence infection in these regions easily takes place. *For this reason vitamin A is called anti-infective vitamin.* **Nervous system**—degeneration of the nervous system specially affecting the afferent tracts (resembles subacute combined degeneration). Retina also shows degenerative changes. **Bones**—abnormal bone growth in certain parts of vertebral column and skull. It is believed that effects on nervous system are partly due to the abnormal type of growth giving pressure effect on nerves. **Reproduction**—in rats reproduction becomes defective. Interferes with the normal process of ovulation although it is not proved in man.

International unit. Equivalent to the activity of 0·6 micro-gram of carotene (same as 0·344 micro-gram of pure preparation of vitamin A_1 acetate).

Daily requirement. 5,000 i.u. for adults. For growing children and during puberty, lactation and pregnancy—6,000–8,000 i.u.

Hypervitaminosis A. In growing rats large doses (4,000 units per day) cause (1) loss of weight, (2) atrophy of skin, (3) loss of hair, (4) ulcerations in the eyes, (5) haemorrhage, (6) decalcification of bones with (7) spontaneous fracture, (8) lowering of plasma prothrombin, (9) reduction of ascorbic acid content of the tissues. Administration of vitamins K and C prevents these changes of hypervitaminosis A. Effects in man include drowsiness, sluggishness, severe headache, vomiting and peeling of skin of mouth and elsewhere. **Vitamin interrelationship**—The haemorrhagic manifestations associated with hypervitaminosis may be prevented by simultaneous administration of vitamin K. The effect may be due to interference with bacterial synthesis of vitamin K in the intestine. The antioxidant action of tocopherols is probably responsible for its sparing action on vitamin A and carotene. This protective effect of vitamin E is enhanced by other antioxidants, e.g., ascorbic acid, etc.

VITAMIN D (CALCIFEROL)

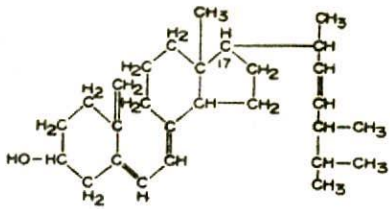
(Antirachitic factor)

Historical review. In 1782 it was found out that cod-liver oil cured *rickets*. In 1918 Mellanby produced experimental rickets in animals and confirmed the conception which was so far prevalent that ricket was due to deficiency of vitamin D. Since then further advancement has been made and it is now established that synthesis of vitamin D occurs in the body under the influence of the ultra-violet rays of the sunlight. The amount of vitamin D thus formed is greatest during summer months and low amount in the winter.

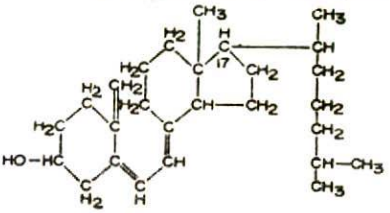
Components. There is a group of vitamin D of which D_2 and D_3 are chief for nutritional purposes. **Calciferol** is applied to a number of chemically related thermostable compounds, all of which, have physiological property of curing or/and preventing rickets.

Chemistry. All the members are sterol compounds. D_2 or **activated ergosterol** or **ergocalciferol** or **viosterol** is an isomer of ergosterol. This vitamin is very thermostable. The structure of vitamin D_3 or **cholecalciferol** (also known **activated 7-dehydrocholesterol**) is the same as that of D_2, except that the side chain on position 17 is that of cholesterol. The structures of vitamin D_2 and D_3 are given below.

Synthesis. D_2 is obtained when plant sterol, **ergosterol,** is activated by irradiation with ultra-violet rays. The epidermal cells of the skin of man and animals contain large amounts of provitamin D (7-dehydrocholesterol), which can be converted to vitamin D_3 by exposure of the skin to sunlight. D_3 is also made by ultra-violet irradiation of 7-dehydrocholesterol and is the form that occurs in natural foods. Man and other mammals can synthesise provitamin D_3 in the body. D_3 is also a close isomer of cholesterol. But it is less potent than D_2. Vitamin D_2 is a powerful antirachitic compounds for man and rat, whereas vitamin D_3 is more potent for chicken.



Vitamin D_2 (Ergocalciferol)—$C_{28}H_{43}OH$



Vitamin D_3 (Cholecalciferol)

Absorption. It is absorbed in the intestine while bile and fatty acids are present.

Properties. D_2 is a white, crystalline material, soluble in fat and fat-solvent, stable in heat, acids and alkalis, and resistant to oxidation. D_3 is also a white, odourless, crystalline compound, soluble in fats and common fat-solvents such as ether, chloroform, and acetone.

Distribution. *Fish-liver oils are the richest sources.* For instance, *cod-liver oil*—100 *i.u. per gram; halibut-liver oil*—1,000 *i.u. per gram.* Mammalian liver almost nil. Butter, milk and eggs moderate quantities. Vegetable oils negligible. One mgm calciferol=40,000 i.u. and one mgm D_3=24,000 i.u.

Functions and mode of action. (1) Favours calcium absorption from the intestine. The rate of active transport of calcium across the intestinal wall is increased by vitamin D. (2) It promotes the absorption of phosphate if there is increased absorption of calcium. (3) As calciferol increases indirectly the resorption of calcium from fully calcified bone so it helps in the calcification of new bone. Vitamin D maintains normal structure of bone and assists to govern the equilibrium between bone calcium and blood calcium. Calciferol in small amounts increase the excretion of calcium by kidneys and in large doses excretion of phosphate also. (4) Helps in the development of the normal teeth. In *deficiency* of vitamin D the formation of the teeth becomes defective and leads to the development of *dental caries* (FIG. 492). (5) It influences the handling of phosphate by the kidney. In the parathyroidectomised animals, vitamin D increases the

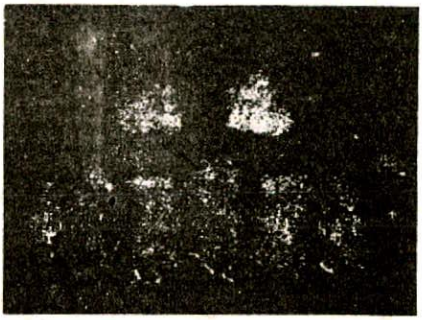


FIG. 492. Dental caries in deficiency of vitamin D.

clearance of phosphate and promotes lowering of serum phosphate. It may act in connection with alkaline phosphatase, liberating inorganic phosphate which influences the deposition of calcium phosphate in ossification process. (6) It is necessary for proper bone growth perhaps by promoting endochondral growth of long bones. (7) Probably, vitamin D controls the retention of calcium and parathyroid regulates the level of blood calcium by controlling mobilisation of calcium from the bones. Thus vitamin D and parathyroid help each other in Ca metabolism and bone formation. (8) It lowers the pH in the colon, caecum, ileum, etc., and increases the urinary pH simultaneously. This may be a secondary effect due to absorption of Ca. (9) In physiological doses, it increases the citrate content of bone, blood and other tissues as well as urinary excretion. (10) It counteracts the inhibitory effect of calcium ions on the hydrolysis of phytate (inositol hexaphosphate). The **mode of action** is mainly by promoting the transport of calcium and secondarily phosphate in the blood stream. *On the whole the function of vitamin D is to cause increased absorption, longer retention and better utilisation of calcium and phosphorus in the body.*

Deficiency signs. The fundamental change in this vitamin deficiency is an *increased loss of calcium and phosphate* in the faeces. This leads to a fall in their blood level, and hence not available for bone formation. Due to this reason, the children suffer from **rickets** (*wrickken* = to twist), and adults from **osteomalacia.**

In **rickets** the bones remain soft due to less deposition of calcium salts. So the long bones remain cartilagenous and easily bend under the weight of the body (Fig. 493). There is defective ossification at the epiphyseal line. The epiphyseal line remains wide and irregular and there is irregular proliferation of the cartilage cells. Due to defective ossification there is malformation of the chest and pelvis, and changes in the spinal curvature (**scoliosis**), softness in parietal bones (**craniotabes**), etc. Rickets occur in children between 6 and 18 months of life during the period of skeletal growth.



Fig. 493. Bowing of the legs due to deficiency of vitamin D—rickets. H = healthy; R, R = rachitic; three children of the same age.

Osteomalacia is a form of adult ricket. It is due to deficiency of vitamin D and calcium salts in the diet. It occurs in women during pregnancy and lactation when a large amount of calcium is depleted from the pregnant woman (mother).

International unit. Equivalent to activity of 0·025 micro-gram of calciferol.

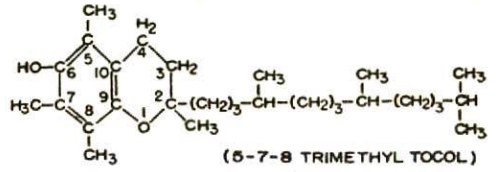
Daily requirement. Exogenous vitamin D is required throughout the period of skeletal growth, i.e., to adult life. The recommendations for infants under 1 year are 400–800 i.u. daily, and for children and adolescents up to 20 years—400 i.u. This should be simultaneously supplemented

with adequate intake of calcium and phosphorus. In the latter half of pregnancy and throughout lactating period, the dose should be 400–800 i.u.

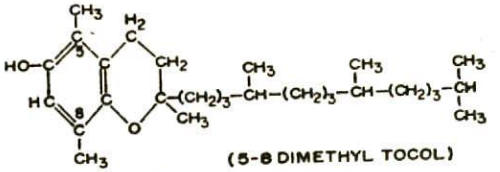
Poisoning action (Hypervitaminosis D). Poisoning action has been noted after large doses of vitamin D. It causes loss of weight, reduced excretion of calcium and phosphorus, increased blood calcium, various other toxic symptoms like nausea, vomiting, headache and drowsiness. Extensive deposit of calcium is found in the soft regions which are not normally calcified, such as kidney, heart, artery, etc. The signs of renal failure may appear.

VITAMIN E (TOCOPHEROLS)
(Antisterilitic factor)

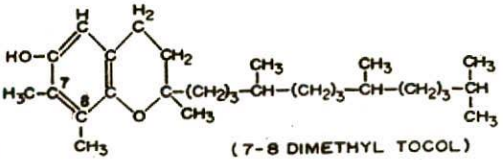
Historical review. Since 1922 effects of vitamin E deficiency was studied in rats. When Bishop and Evans announced the existence of a substance X, the absence of which in the diet, results failure in the reproductive capacity of rats. In 1936 Evans and Emerson isolated and synthesised vitamin E from the unsaponifiable fraction of wheat-germ oil which was found to be a mixture of three closely related compounds. A fourth was discovered in 1955, and recently two other compounds have been detected.



α-Tocopherol—$C_{29}H_{50}O_2$



β-Tocopherol—$C_{28}H_{48}O_2$



γ-Tocopherol

Chemistry. There are three varieties of **tocopherol**—(*Tokos*=child-birth, *Phero*=to bear, suffix *Ol* signifies alcohol)—α, β and γ. They are unsaturated alcohols. The most active compound is α-tocopherol, $C_{29}H_{50}O_2$. β-tocopherol contains one less methyl group—$C_{28}H_{48}O_2$. The composition of γ-tocopherol is the same as β-tocopherol. Recently δ-tocopherol and few more compounds have been isolated.

Properties. They are soluble in fat and fat-solvents, heat-stable and exists naturally as a yellow oil. These tocol types of vitamin can stand cooking and they are extraordinarily stable in heat in the absence of oxygen, and withstand acids at elevated temperatures. The vitamin activity is destroyed by ultra-violet light as well as by oxidation. They are excellent antioxidants. They prevent other vitamins present in food (e.g., vitamin A) from oxidative destruction.

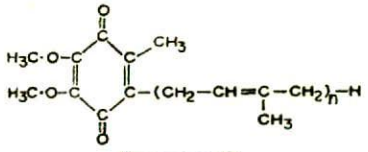
Absorption. Free tocopherols and their esters are readily absorbed from the small intestine. Bile acids are necessary for absorption.

Distribution. This vitamin remains in blood in the α-lipoprotein

fraction. The average blood level is 1·0 mgm per 100 ml of serum. *Animal sources*—Egg, milk, fish and muscles contain this vitamin. *Vegetable sources*—It is abundantly present in vegetable seed oils, especially wheat, soyabean, corn and leafy vegetables. It has also been synthetically prepared.

Functions and mode of action. (1) Tocopherols have got *anti-oxidative* effects and prevent unwanted oxidation in the body. (2) Required for the normal reproductive function in rats. (3) Essential for normal function of muscle. Deficiency produces muscular dystrophy. (4) The increased uptake of O_2 in the dystrophic muscles produced by the deficiency of this vitamin is prevented by administration of tocopherols. (5) Peroxidation and brown pigmentation due to formation of highly unsaturated fatty acids are prevented by the tocopherols. (6) Massive hepatic necrosis produced by deficiency of sulphur-containing amino acids and selenium are also prevented by tocopherols. (7) The development of *encephalomalacia* in chicks (cerebellar disorder) and exudative *diathesis* is due to deficiency of vitamin E and is relieved by administration of tocopherols. (8) It acts as a cofactor in the electron transfer system operating between cytochromes *b* and *c*.

Deficiency signs. In the female rats implantation of the ovum occurs, but after some time the foetus dies (*resorption sterility*). The changes however are reversible. Vitamin E therapy is of some promise in the prevention of habitual miscarriage in women. In rats there are increased metabolic rate, development of *muscular dystrophy*, electrocardiographic changes in cardiac muscle indicating degenerative lesions. Excessive intake does not increase fertility but may cure sterility. Male rats show atrophy of testes and spermatogenic failure and both of which are irreversible in prolonged deficiency. Erythrocytes are affected in vitamin E deficiency. Combined deficiency of this vitamin and selenium (Se) produces *hepatic necrosis*. Goat, sheep and rabbit do not show deficiency signs. Probably they may synthesise sufficient quantities. Vitamin E also remain stored in the tissues. It has been observed that members of the coenzyme Q group* have protective action against vitamin E deficiency in some species of animals.



Coenzyme Q

Daily requirement. Average daily intake through normal diet is about 15 to 20 mgm, which satisfies the requirement.

VITAMIN K
(Antihaemorrhagic factor)

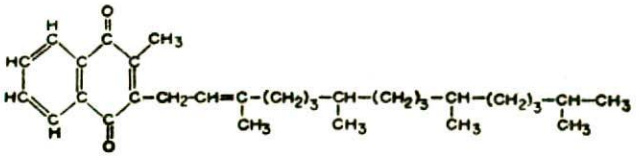
Historical review. Dam discovered this vitamin after studying haemorrhagic disease in chickens between the years 1930 and 1933.

Chemistry. It is a naphthoquinone derivative.

It is reported that more than one member of the K family, such as K_1, K_2, etc., are synthesised by green plants and bacteria. The artificially synthetic product (menadione), 2-methyl-1,4-naphthoquinone (K_3) without any side chain is 3 times more potent than the natural variety.

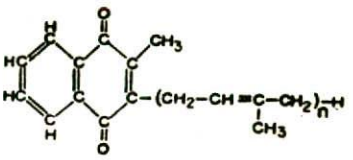
* **Coenzyme Q group (Ubiquinones).** It is isolated from cardiac mitochondria (Crane et al, 1957) and has been found to play an important role in electron transport system. Several members (Q_6, Q_7, Q_8, Q_9) have been found to exist.

Two naturally-occurring vitamins K are vitamin K_1 (**phylloquinone, phytonadione**) having a phytyl chain attached at position 3 of menadione nucleus, and vitamin K_2 (**flavinoquinone, farnoquinone**) having a difarnesyl chain attached at position 3. Activity is apparently related to the presence of methyl group at 2 position in the quinonoid ring. Synthetic vitamin K is called **vitamin K_3** (commercially **menadione**).



Vitamin K_1 (Phylloquinone)—$C_{31}H_{46}O_2$

Properties. It is fat-soluble, heat-stable, and can stand cooking. Vitamin K_1 is a yellow viscid oil, but vitamin K_2 is a yellow, crystalline solid. The K vitamins are readily destroyed by light, alkali and alcohol.



Vitamin K_2 (Farnoquinone) in which n may be 6, 7, 9 ($C_{41}H_{56}O_2$).

Distribution. *Vegetable sources* are rich, such as cabbage, spinach, alfalfa, tomato, soyabean, etc. It is absorbed from the intestine with the help of bile salts. Most putrefied animals and plants contain considerable amount of vitamin K. It has also been produced synthetically. Under normal circumstances, adequate amounts are synthesised by normal intestinal bacteria. Excessive amount of vitamin A administration in certain species produces interference with bacterial synthesis of vitamin K in the intestine producing prothrombinaemia and haemorrhagic manifestations.

Functions. It helps to maintain the formation of normal prothrombin and factor VII in the blood and thus takes part in normal coagulation. It has been postulated that vitamin K acts as the prosthetic group to an *apoenzyme* to produce a *holoenzyme* which is involved in the clotting reactions. Prothrombin and factor VII are formed in the liver. The principal overall effect of vitamin K is to shorten the prothrombin time. It is also postulated that vitamin K_1 is an essential component of phosphorylation in both the processes of photosynthesis in green plants and animal tissues, as a cofactor necessary in oxidative phosphorylation. Loss of activity of vitamin K by ultra-violet radiation impairs oxidative phosphorylation in the mitochondria.

Bile salts are necessary for the absorption of vitamin K. In *jaundice* and in certain diseases of liver, when the bile secretion is defective, vitamin K fails to be absorbed resulting haemorrhages. Hepatic disease also produces *hypoprothrombinaemia* which is corrected by vitamin K administration. The haemorrhagic disease in the new-born is believed to be due to lack of vitamin K, since vitamin K deficiency in the new-born is due to absence of bacteria in their gut. An important therapeutic use of vitamin K is as an antidote to the anticoagulant drugs such as **dicumarol.**

Deficiency signs. Defective blood coagulation and haemorrhages.

Daily requirement. Normal mixed diet supplies this vitamin in

adequate amount. In the treatment of haemorrhagic diseases produced as a result of vitamin K deficiency, 5 mgm is given either orally or by injection. It is believed that in adults, quite a good amount of vitamin K is synthesised by the bacteria in the gut.

WATER-SOLUBLE VITAMINS

THE VITAMINS OF B COMPLEX

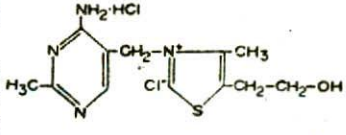
The vitamins of B complex comprises about a dozen of chemical substances.

THIAMINE (ANEURINE, VITAMIN B_1)

(Antineuritic factor, Antiberiberi substance)

Historical review. Beriberi, a disabling condition, was endemic for centuries in the Orient and Pacific islands and this was finally proved to be deficiency disease. An analogous condition was produced artificially in hens in 1890 when Eijkman found out that birds fed with polished rice developed *polyneuritis*. In 1911 Dr. Casimir Funk cured polyneuritis in birds by administering concentrate of rice polishings. In 1926 this vitamin in pure form was isolated by Jansen and Donath and in 1936 the vitamin was synthesised by Williams and his coworkers.

Chemistry. Free thiamine is a basic substance containing a pyrimidine and a thiazole ring. It is generally prepared as a thiamine hydrochloride. In yeast it is found combined with a pyrophosphate. It contains sulphur and a primary amino group.



Thiamine hydrochloride (vitamin B_1)—$C_{12}H_{17}Cl.N_4OS.HCl$

Properties. It is a white, crystalline substance, water-soluble and destroyed at elevated temperature unless the pH is low; but can stand short boiling up to 100°C. Hence, it is only partly lost in cooking or canning processes. Autoclave, long boiling or boiling with *alkali*, destroys it. But it is stable in acid medium. On oxidation it produces **thiochrome** which gives fluorescence and its oxidation, under controlled condition, has become the basis of assay of this vitamin.

Distribution. *Vegetable sources*—cereals (in the husk and embryo) pulses, nuts and green vegetables, i.e., beets, carrots, turnips, lettuce, cauliflower, pears, beans, etc., are rich sources. Polished rice and white flour are poor in this vitamin content. *Animal sources*—generally poor. Yeast and egg-yolk contain fair amount (100 i.u.).

Free thiamine is absorbed readily from the small intestine. It is not much stored in the body. About 25% of the ingested vitamin B_1 is excreted in the urine. It has also been produced synthetically. An international unit of thiamine is equal to 3 μ gm of thiamine hydrochloride.

Functions. (1) The pyrophosphate ester of thiamine is a coenzyme (*cocarboxylase*) and being bound to a specific protein (*apoenzyme*) together with α-lipoic acid and Mg^{++} forms the active enzyme *carboxylase*, which is responsible for the oxidative decarboxylation of pyruvic acid, α-ketoglutaric acid and other keto acids. It is an essential step in the final oxidation of sugar in the tissues and brain. In the absence of this vitamin, pyruvic and lactic acids fail to be broken down, and hence, accumulate in blood

and tissues. Most of the deficiency signs are due to the abnormal accumulation of these acids (pyruvic and lactic acids). (2) It also helps the enzyme system which is responsible for the synthesis of fats from carbohydrates and proteins. Thiamine pyrophosphate is also a coenzyme for the transketolase reaction in the phosphogluconate oxidative pathway of carbohydrate metabolism.

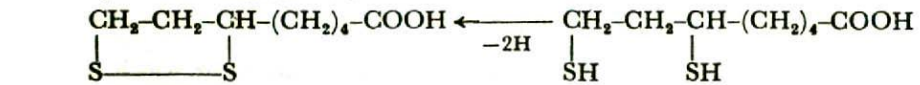
Deficiency signs. Beriberi may be classified as dry, wet, cardiac or mixed type. (*i*) *Dry beriberi* is associated with disorders of the nervous system. (*ii*) In *wet beriberi*, the polyneuritis is accompanied by oedema. (*iii*) *Cardiac beriberi* is associated with signs of congestive cardiac and circulatory failure. (*iv*) The *mixed type* in which any combinations of the above may be found. The general manifestations in Beriberi are as follows: (1) There is oedema specially in the legs. (2) Loss of appetite, atony of the gastro-intestinal tract, hypochlorhydria, etc. All these are due to lack of energy derived from the imperfect metabolism of carbohydrate. (3) Blood changes—*lactic and pyruvic acids accumulate in blood.* (4) Same changes are found to take place in peripheral nerves, brain and cerebrospinal fluid. The peripheral neuritis or *polyneuritis*, with the tenderness of muscles of feet and legs, ataxia and muscular weakness, is a characteristic feature. These defects are due to diminished utilisation of carbohydrate and production of energy. Pyruvic acid accumulates in the brain stem, brain and cerebrospinal fluid. (5) Heart also becomes weak and enlarged, which is obviously due to accumulation of pyruvic acid. Cardiac failure may also occur in some subjects. In rats, marked bradycardia occurs. (6) Cerebral beriberi has also been reported. In this disease the grey matter of the cerebrum round the third ventricle is affected. In certain fishes there are heat-labile enzymes which destroy thiamine. Foxes, fed with raw uncooked **fishes,** develop a type of spastic paralysis (**Chastek paralysis**). This has been attributed to presence of a thiamine-splitting enzyme in raw fishes.

Daily requirement. About 1·8 mgm for a diet producing 3,000 calories. The requirement is increased in pregnancy, lactation, heavy muscular work, high carbohydrate diet, etc. Daily intake for children range from 0·4 mgm for infants to 1·3 mgm for pre-adolescents. Requirement of thiamine increases in shock, haemorrhage, serious illness or injury, during oral administration of antibiotics, etc.

LIPOIC ACID (THIOCTIC ACID)

For a certain micro-organism and protozoa, α-lipoic acid is a growth factor which is usually classified among the vitamin B complex. This acid is also known as **acetate-replacement factor, pyruvate oxidation factor** or **protogen.**

Chemistry. It is sulphur-containing fatty acid and chemically it is 6,8-dithio-octanoic acid.



α-Lipoic acid (oxidised form) α-Lipoic acid (reduced form)

Properties. This compound is soluble in fat.

Distribution. Widely distributed in natural sources.

Functions. Lipoic acid is required along with thiamine and some

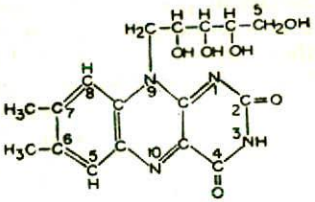
other members of vitamin B in the oxidative decarboxylation of pyruvic acid to acetyl CoA and α-ketoglutaric acid to succinyl CoA.

Deficiency signs. Has not been shown to be required in the diet of higher animals and deficiency signs not yet demonstrated.

RIBOFLAVIN (VITAMIN B_2, LACTOFLAVIN)

Historical review. In 1932 Warburg and Christian were able to isolate *yellow enzyme* from yeast. The yellow enzyme was named riboflavin. In 1935 it was synthesised.

Chemistry. A flavin derivative riboflavin is an orange-yellow compound containing D-*ribitol* (α-ribose alcohol) and a heterocyclic substance—isoalloxazine (flavin). The one-carbon of the ribityl group is attached at position 9 of isoalloxazine. In the living cell it combines with phosphoric acid and a specific protein radicle. As prosthetic group of a number of enzymes, riboflavin acts either as a mono- or di-nucleotide.



Riboflavin—$C_{17}H_{20}N_4O_6$

Flavin mononucleotide (FMN) is formed as:

$$\text{Riboflavin} + \text{ATP} \xrightarrow[Mg^{++}]{\textit{Flavokinase}} \text{Flavin mononucleotide} + \text{ADP}$$

Flavin adenine dinucleotide (FAD) is formed as:

$$\text{Flavin mononucleotide} + \text{ATP} \xrightarrow[Mg^{++}]{\textit{Flavin nucleotide pyrophosphorylase}} \text{Flavin adenine dinucleotide} + \text{PPi}$$

It has been artificially synthesised in 1935. *Normally riboflavin is phosphorylated in the intestinal mucosa* and adrenal cortical hormone plays a major regulatory role in this mechanism.

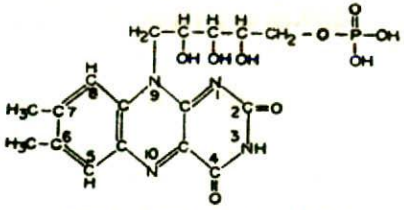
Properties. It is orange-yellow crystals, soluble in water to a limited degree and insoluble in fat-solvents. It is heat-stable in neutral and acid media, but sensitive to light, unstable in alkaline solutions, stands ordinary cooking and canning. Aqueous solutions are unstable to visible and ultra-violet light. On exposure to light the ribityl residue splits off, forming a compound—**lumiflavin** in alkaline solution and **lumichrome** in acid or neutral solution, and this reaction is irreversible. However, riboflavin readily undergoes reversible reduction by thiosulphate, H_2S and H_2 to colourless compound—**leucoriboflavin,** which is the functional basis related to catalysing *cellular oxidation-reduction reactions.* This vitamin produces a yellow solution having a yellow-green fluorescence.

Distribution. *Animal sources*—milk (*lactoflavin*), liver, kidney, muscle, eggs. *Vegetable sources*—whole grain, green leafy vegetables. It has also been synthetically prepared.

Functions. (1) Essential for growth. (2) Both FMN and FAD in combination with protein (*apoenzyme*) play major role in a number of enzyme system and the enzyme containing this vitamin called *flavoprotein.* Riboflavin present in various enzyme systems in its two forms:

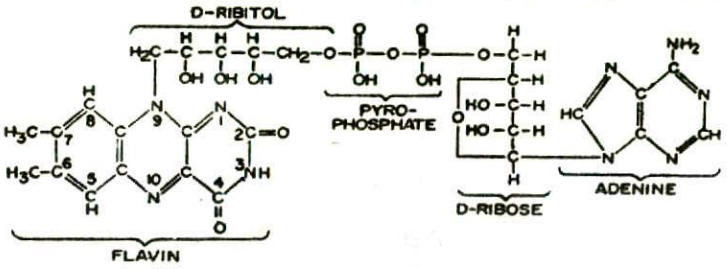
(*a*) In the form of riboflavin phosphate (FMN=flavin mononucleotide). FMN is a constituent of yellow enzyme of Warburg and Christian, cytochrome *c* reductase, L-amino acid dehydrogenase.

(*b*) In the form of FAD=flavin adenine dinucleotide. A great number of enzymes like xanthine oxidase, diaphorase, a synthetic enzyme of Warburg and Christian, fumaric dehydrogenase, liver aldehyde oxidase, Haas enzymes, glycine oxidase, etc., contain FAD as prosthetic group and the enzyme *xanthine oxidase* also contains iron and molybdenum.



Riboflavin phosphate or FMN

(3) Riboflavin is related to the metabolic process of proteins. (4) It is also an integral part of the prosthetic group of acyl-CoA dehydrogenase—the enzyme which mediates the first oxidative step in the oxidation of fatty acids. (5) A suggestion has been



FAD (FADN)

made that riboflavin play some part in cornea and deficiency produces corneal vascularisation. But this is still controversial.

Deficiency signs. The tissues which have originated from ectoderm (e.g., nervous system, skin, eye) are first affected. In man—(1) *Mouth*—(*a*) Cheilotic fissures at the corner of the mouth and ulcers on the lips (FIG. 494), (*b*) Angular stomatitis, (*c*) Glossitis (magenta tongue). (2) *Eye*—Keratitis, corneal opacities, vascularisation of cornea and photophobia. (3) *Skin*—Loss of hair and dry and scaly skin. (4) Arrested growth occurs.

Daily requirement. 1·5 to 1·8 mgm in adults. The daily requirement of riboflavin can be calculated in term of protein intake, i.e., 0·025 mgm of riboflavin per 1 gm of protein.

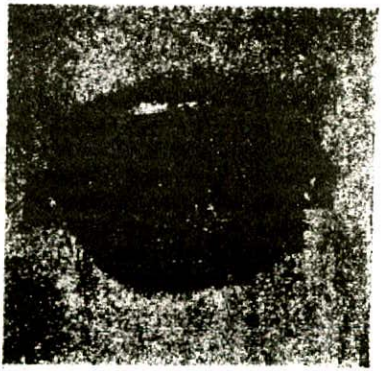


FIG. 494. Oral fissures due to deficiency of riboflavin.

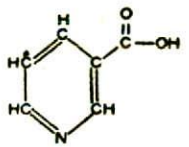
NICOTINIC ACID (NIACIN) AND NICOTINAMIDE (NICOTINIC ACID AMIDE, NIACINAMIDE)

(Pellagra-preventing factor, P-P factor of Goldberger)

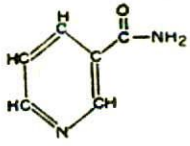
Historical review. Pellagra was first described by Casal of Spain

in 1735. Dr. Goldberger and his associates studied it between the years 1874 and 1929 and showed that food rich in vitamin B cured pellagra. In 1926 Smith and Hendrick identified that vitamin B contains heat-labile and heat-stable factors. The latter one cured pellagra. Dr. Goldberger named it as P–P factor.

Chemistry. Nicotinic acid or niacin is known now as pyridine-3-carboxylic acid. It occurs in tissues principally as amide of nicotinic acid. In the body nicotinic acid is converted into the amide before it becomes active. In tissues, nicotinamide is present largely as a dinucleotide. Two well-defined coenzymes contain nicotinamide which acts with a large group of hydrogen-transport enzymes. These two compounds are: (1) Diphosphopyridine nucleotide (DPN) or coenzyme I (Co I) or nicotinamide adenine dinucleotide (NAD), (2) Triphosphopyridine nucleotide (TPN) or coenzyme II (Co II) or nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are soluble in water, stable in acid but not in alkali.



Nicotinic acid (Niacin) —$C_6H_5O_2N$

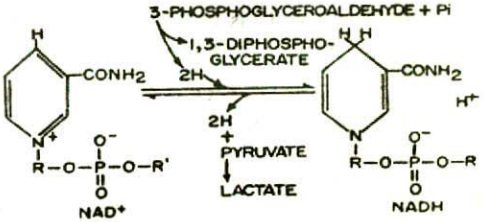


Nicotinamide (Nicotinic acid amide or niacinamide)—$C_6H_6ON_2$

Properties. Nicotinic acid is a white crystalline substance and is moderately soluble in water but quite soluble in alkali (salt formation), alcohol and glyceride. It is heat-stable and not lost during cooking or canning.

Distribution. *Vegetable sources*—the husk of the cereals, green vegetables, peas, beans, tomatoes, etc., are rich in this vitamin. Whole wheat meal contains fair amount (maize or white flour negligible amount). *Animal sources*—meat, fish, liver, milk, yeast, etc., contain fair amount. It has also been produced synthetically. Body can synthesise this vitamin from tryptophan.

Mode of action. In the living tissue it remains as a part of at least two enzyme systems: (*i*) NAD or DPN or Co I, (*ii*) NADP or TPN or Co II. Niacinamide in combination with two molecules each of ribose and phosphoric acid and one molecule of adenine forms NAD. The reduced form of NAD and NADP are NADH and NADPH respectively (Fig. 495). This set of coenzymes takes part in various oxidation-reduction reactions in the body.



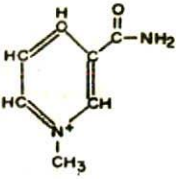
(Oxidised form) (Reduced form)

Fig. 495. Reduction of NAD in the *para*-position.

Functions. (1) Essential for growth. (2) Takes essential part in metabolism and tissue oxidation. (3) Helps in the formation of fats from carbohydrates. Niacin may reduce the plasma lipid concentration in certain cases of hyperlipaemia, the mechanism being not known. (4) Prevents pellagra. (5) It has a stimulating effect on central nervous system. (6) In therapeutic doses, niacin produces the pronounced transient vasodilatation with flushing of the face. This

is accompanied by an increase in peripheral blood flow and skin temperature.

Excretion. 2–8 mgm of this vitamin is excreted daily through the urine in adults, fed with average mixed diet as a methylated derivative—N^1-methylnicotinamide—at the expense of labile methyl groups of the body.



N^1-methylnicotinamide

Deficiency signs. *In man*—**Pellagra.** The cardinal symptoms of this condition is generally known as the three D's, i.e., **dermatitis, diarrhoea,** and **dementia.** Deficiency results characteristic dermatitis, specially on the exposed parts of the body. The dermatitis begins with *erythema* resembling sun-burnt areas. Gradually these areas become reddish-brown, rough, scaly and keratotic (FIG. 496). Gastro-intestinal disorders, polyneuritis and various forms of mental disorders are observed. Cerebral manifestations include headache, irritability, confusion, etc. General effects are inadequate growth for children, loss of weight and strength and anaemia. *In dogs*—Black tongue.



FIG. 496. Nicotinic acid deficiency—Dermatitis of Pellagra.

Daily requirement. 12–18 mgm for adult males and a little less in adult females. Requirement varies with the protein content of diet as amino acid **tryptophan** gives rise to niacin in the body. The requirement for niacin increases in increased calorie intake or expenditure, in acute illness, after severe infection, injury, etc.

PANTOTHENIC ACID (VITAMIN B_3)
(Chick antidermatitis factor, Filtrate factor)

Historical review. In 1901, a growth factor for yeast, **bios** was described by Wildiers. In 1933 Williams and his coworkers isolated the crystalline product and called it **pantothenic acid** because of universal distribution. It was synthesised in 1940 by Stiller and others.

Chemistry. It is peptide-like compound of β-alanine and α-γ-dihydroxy-β,β-dimethyl butyric acid. The empirical formula of vitamin B_3 is $C_9H_{17}O_5N$.

$[HO.CH_2.C(CH_3)_2.CHOH.CO.NH.CH_2.CH_2.COOH.]$

Properties. The free acid is a viscous, yellow oil, soluble in water and ethyl acetate but insoluble in $CHCl_3$. It is heat-labile and destroyed in acid and alkali. Its calcium salt is a white, crystalline substance, highly soluble in water and hygroscopic and insoluble in alcohol. It is quite stable, although autoclaving destroys activity.

Distribution. It is widely distributed in small amounts. (1) *Animal sources*—liver, kidney, egg-yolk, yeast, milk, etc. are the rich sources of this vitamin. (2) *Vegetable sources*—molasses, wheat bran, peas, sweet potatoes, etc., contain this vitamin in appreciable amount. It has also been produced synthetically. **Blood** contains 19–32 μ gm per 100 ml.

Functions. The physiologically active form of pantothenic acid is coenzyme A (CoA). It is essential for several basic reactions of metabolism.

(1) Acetyl CoA, also known as **active acetate,** takes part in the citric acid (TCA) cycle, in combination with choline forms acetylcholine and

also acts as an intermediate in the biosynthesis of cholesterol, fatty acids, etc. (2) Coenzyme A plays an essential part in lipid metabolism. Activation which occurs by formation of a coenzyme A derivative is the first step in fatty acid oxidation. (3) Pantothenic acid is not present mainly in CoA. A good amount of pantothenic acid is present in the protein-bound form. This protein-bound pantothenic acid is the **acyl-carrier protein** (ACP) and is required for the biosynthesis of fatty acids (*vide* pp. 569–70). (4) Although this coenzyme is required in the biosynthesis of fatty acids, but coenzyme A is mainly concerned with fatty acid catabolism. (5) Being a precursor of cholesterol, acyl coenzyme A may produce steroid hormone. (6) CoA in combination with succinate forms **active succinate** and helps in the biosynthesis of haemoglobin. (7) It might activate some amino acids.

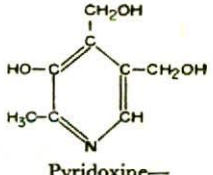
Deficiency signs. Dermatitis, fatty liver, degeneration of spinal cord, myelin degeneration of peripheral nerves, and involution of thymus in chicks occur by the deficiency of this vitamin. Various tissues are also affected, including gastro-intestinal disturbances, alopecia, cornification of the skin and hypofunction of adrenal cortex.

Daily requirement. Not exactly known. Average daily diet contains 10 mgm which satisfies this vitamin requirement.

PYRIDOXINE (VITAMIN B_6)
(Rat antidermatitis factor)

Historical review. In 1934 Györgyi observed that an extract of yeast cured dermatitis in rats which was not curable with other members of B vitamins. Isolated from natural sources in 1938. Stiller and others characterised its structure in 1939.

Chemistry. It is a pyridine derivative which was synthesised in 1939 by Harris et al independently, and by Kuhn and others.



Pyridoxine—
$C_8H_{11}O_3N$

Two allied compounds, *pyridoxal* and *pyridoxamine*, (natural) and synthetic, have the same action. All the three varieties are known as vitamin B_6. *Pyridoxal phosphate* is the active form.

Properties. This vitamin is a white, crystal, soluble in water and *heat-stable* in both acidic and alkaline solutions.

Distribution. Rich sources are: (1) *Vegetable*—germs of various grains and seeds, leafy vegetables, etc. (2) *Animal*—liver, egg-yolk, meat, kidney, yeast, etc. Traces are present in all common articles of food. It has also been produced synthetically.

Functions. Essential for lower mammals. May be important for man but not definitely known. The functions are as follows:

(1) It takes part in normal tryptophan metabolism. Because (*a*) Kynurenine and xanthurenic acid are excreted by rats made deficient in pyridoxine. The above products are not on the main metabolic pathway of tryptophan metabolism and considered as products of side reactions. (*b*) The enzyme *kynureninase*, responsible for the breakdown of kynurenine to anthranilic acid and 3-hydroxykynurenine to 3-hydroxyanthranilic acid requires pyridoxal phosphate as a coenzyme. (2) Pyridoxal phosphate also acts as a *coenzyme* for the following enzyme systems: (*a*) **Transaminases** or **aminotransferases** which are responsible for the transfer of amino

groups from amino to keto acids. (*b*) **Decarboxylases** which decarboxylate tyrosine, arginine, glutamic acid, 3,4-dihydroxyphenylalanine (DOPA), etc. (*c*) **Deaminases** or **dehydrases,** e.g., serine and threonine dehydrases. (*d*) **Desulphydrases,** responsible for transfer of sulphur group. (3) Pyridoxal phosphate in some way is related to the formation of long chain polyunsaturated fatty acids. (4) Helps in the synthesis of fats from proteins and carbohydrates. [3 and 4 possibly explain—rat acrodynia in vitamin B_6 deficiency.] (5) It plays some part in the interconversion of serine and glycine where there is involvement of tetrahydrofolic acid also. (6) Helps in transulphurase and thionase reactions converting homocysteine and cystathionine to cysteine. (7) The coenzyme is required in the synthesis of δ-amino levulinic acid—an intermediate in porphyrin synthesis. (8) Pyridoxal phosphate is an intimate component of phosphorylase-*a* of muscle. (9) It is suggested that pyridoxine is involved in the active transport of amino acids and certain metallic ions across cell membranes. (10) There is increased evidence that vitamin B_6 is intimately concerned with the metabolism of the central nervous system.

Thus it is indicated that it definitely takes part in protein metabolism and possibly also in fat and carbohydrate metabolism.

Deficiency signs. Peculiar dermatitis (*acrodynia*), reduced growth, degeneration of the nerves, reproductive failure and hypochromic microcytic anaemia, weakness of muscles and convulsive seizures occur in absence of this vitamin. In 1951, deficiency of this vitamin was noted in infants due to destruction of this vitamin in a preparation of baby food which produced epileptic type of convulsions. In subjects suffering from Pellagra and Beriberi, synthetic B_6 can easily cure insomnia, irritability, abdominal pain, difficulty in walking and such other symptoms—which fail to be cured by other vitamins. This vitamin seems to be essential also for lower animals, bacteria and mosquito larva. The drug **isonicotinic acid hydrazide** (INH) used in the treatment of tuberculosis has similar chemical structure as **pyridoxal** and acts as an antivitamin to pyridoxal kinase reaction.

Daily requirement. In infants 0·3 mgm and in adults 2 mgm per day. It is sufficiently present in normal diet.

FOLIC ACID (PTEROYLGLUTAMIC ACID)
(Fermentation residue factor)

Historical review. The existence of this nutritional factor was suggested by Day. It was named folic acid (L. *folium*) by Mitchell, Snell and Williams, because of its isolation from spinach leaf. The chemical structure was established in 1945. It has also been known as vitamin M, vitamin B_c, Liver Lactobacillus casei factor and Streptococcus lactis R (SLR) factor.

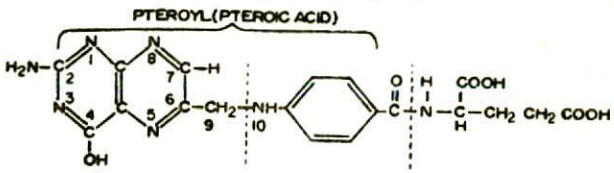
Chemistry. Folic acid is a group of chemically different compounds. The simplest form of *pteroylglutamic acid* (PGA) contains a pterin derivative residue connected to para-amino-benzoic acid and glutamic acid.

Folic acid or *folacin* is converted into tetrahydro derivative in the body which after taking up a formyl (—CHO) group forms **folinic acid** and also known as **citrovorum factor** (CF).

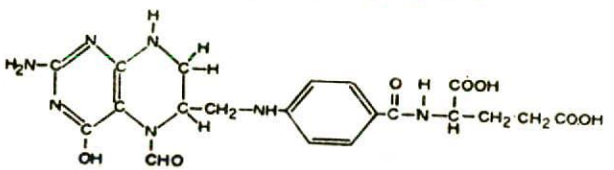
Properties. It is a yellow compound, slightly soluble in water and destroyed by light. It is soluble in dilute alcohol and can be precipitated as barium or lead salt.

Distribution. Liver, kidney, green-leafy vegetables and cauliflower are good sources of this vitamin.

Functions. (1) Folinic acid acts as a coenzyme (coenzyme F) in the transfer of formyl and hydroxymethyl groups in different biological



Folic acid (PGA)—$C_{19}H_{19}N_7O_6$



Folinic acid (CF), N^5-formyl FH_4

systems (e.g., in the biosynthesis of purine, synthesis of the methyl group of methionine, etc.) in the one-carbon metabolism. (2) It is indispensable for the synthesis of *deoxyribonucleic acid* in the nuclei of the cells. *Takes part in the formation and maturation of the red cells.* Along with vitamin B_{12} it helps in the synthesis of nucleic acid. Deficiency causes disturbances in the synthesis of deoxyribonucleic acid (DNA) and metabolism of the nucleated red cells resulting in megaloblastic or macrocytic anaemia. (3) It is used in the treatment of megaloblastic anaemia.

Deficiency signs. *In rats and monkeys*—Arrested growth, anaemia, leukopenia and agranulocytosis. *In man*—Megaloblastic anaemia especially occurring during pregnancy.

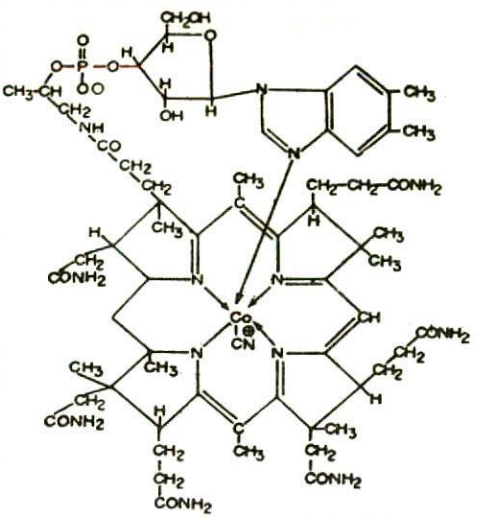
Daily requirement. Not exactly known. Average daily diet of adults contains about 50 micro-gram, which seems to be adequate.

CYANOCOBALAMIN (VITAMIN B_{12}, COBAMIDE)
(Antipernicious anaemia factor, Extrinsic factor of Castle)

Historical review. In 1948 Smith and Parker isolated cyanocobalamin from the liver. In 1955 its complex structure was determined.

Chemistry. The central portion of the molecule consists of four reduced and extensively substituted pyrrol rings surrounding a single cobalt atom. The central structure is referred to as a *corrin* ring and is similar to that of the porphyrins except that two pyrrol rings are joined directly. Below the ring system it contains the base *dimethylbenziminazole* linked with ribose and phosphoric acid, so that one end is connected to the central cobalt atom and the other through ribose phosphate and aminopropanol to a side chain on ring IV of the tetrapyrrole nucleus. Different cobalamin compounds possessing common prosthetic group have vitamin B_{12} activity. A cyanide group (—CN) co-ordinately

bound to cobalt atom may be removed giving the compound *cobalamin*. Addition of cyanide gives *cyanocobalamin*, substitution of cyanide with hydroxyl group (—OH) gives *hydroxycobalamin*, B_{12a} and with nitro group—*nitrocobalamin*. All of these have similar biologic action although hydroxycobalamin is more active enzymatically. In vitamin B_{12} containing coenzymes, *cobamides*, the cyanide (cyano) group is replaced by an adenine deoxy nucleoside. Co is present in this prosthetic group in a similar way as Fe in haemoglobin. The empirical formula of vitamin B_{12} has been suggested as $C_{63}H_{88}O_{14}N_{14}$ PCo.



Vitamin B_{12} (Cyanocobalamin)

Properties. Red crystalline substance, soluble in water. Contains metalloporphyrin nucleus and **cobalt** (4·5%). Molecular weight is 1,500 approximately.

Distribution. Absent in plants, but present in almost all animal tissues. Rich sources are liver (1 unit of liver extract contains approximately 1 micro-gram of B_{12}), kidney, egg, beef extract, milk, etc. It is synthesised by microfloral fermentation in the alimentary tract of ruminants. This vitamin is found in the fungus *Streptomyces griseus*. Hence vitamin B_{12} is obtained as a by-product in the manufacture of Streptomycin.

Absorption and excretion. Absorption takes place from the ileum. Intrinsic factor (IF) present in normal gastric juice is essential for the proper absorption of vitamin B_{12}. It is stored in the liver. From the liver it passes to the bone-marrow and helps in the maturation of red cells. The absorption and excretion have been studied by using vitamin B_{12} containing *radioactive cobalt*. Vitamin B_{12} is excreted in the faeces and urine.

Functions. (1) Essential for the formation and maturation of red blood cells. Recent idea is that the vitamin B_{12} is Castle's extrinsic factor, which combines with the *intrinsic factor* present in normal gastric juice and is absorbed. The intrinsic factor has not been identified as yet but is a non-dialysable, thermolabile substance possibly a mucoprotein. [*Vide* pages 165, 438 for details.] (2) It plays an essential role in the synthesis of nucleic acid. Deficiency causes a disturbance of the deoxyribose nucleic acid metabolism. (3) Increases the white cell count and the platelets through its action in the bone-marrow. (4) Concerned with the maintenance of normal health and activity of certain parts of the nervous system. Vitamin B_{12} not only cures the pernicious anaemia but also the neurological manifestations of pernicious anaemia, e.g., subacute combined degeneration of the spinal cord. [Folic acid cures only the pernicious anaemia.] (5) As it helps in the growth of micro-organism called the *Lactobacillus lactis* so this vitamin can be assayed by studying the growth of

this micro-organism. (6) Biosynthesis of methyl group is increased by vitamin B_{12} and it is said that vitamin B_{12} plays an enzymatic role in one-carbon metabolism and synthesis. (7) This vitamin has also a role in transmethylation process. (8) Formation of lipid from carbohydrate is influenced by vitamin B_{12}. (9) A coenzyme of vitamin B_{12} helps in isomerisation (e.g., that of glutamic acid to β-methyl aspartate). This is clearly observed in the isomeric reaction where methyl malonyl CoA is converted to succinyl CoA. (10) Hyperglycaemia due to vitamin B_{12} deficiency can be corrected after administration of vitamin B_{12} or glutathione (GSH).

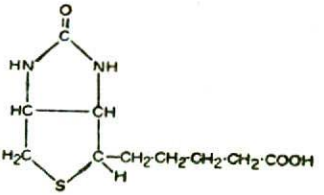
Deficiency signs. Pernicious or macrocytic or megaloblastic anaemia is produced. Brings about hyperglycaemia. Slow growth as well as nervousness and irritability are observed in pigs and rats. Deficiency might occur as a result of (*a*) lack in diet, (*b*) lack of intrinsic factor as in pernicious anaemia, (*c*) defective absorption due to intestinal disease (malabsorption syndrome), (*d*) infection with micro-organisms which have affinity for vitamin B_{12} and thus destroy it in the intestinal tract. (*e*) Other important features in vitamin B_{12} deficiency in man are mucosal atrophy and inflammation of tongue, mouth, etc., degenerative lesions of the posterior and lateral columns of the spinal cord.

Daily requirement. The requirement is very small. A daily intake of 1·0 μ gm is sufficient to prevent deficiency. However, it is not known accurately as yet.

BIOTIN (VITAMIN H)
(Anti-egg-white-injury factor)

Historical review. In 1916, Bateman observed that a diet containing high percentage of egg-white was toxic to animals. In 1941, *avidin* the protein isolated from egg-white was found to prevent absorption of biotin. Allison and others (1933) isolated another growth factor and named it coenzyme R which was later found to be identical to biotin. Its structure was identified in 1942 and synthesised in 1943.

Chemistry. Biotin is a heterocyclic, s-containing monocarboxylic acid, a valeric acid derivative containing two five-sided rings (thieno and imidazole) fused together. Biotin acts as coenzyme for carboxylase enzyme that helps in carbon dioxide fixation. It is suggested that biotin coenzyme is tightly bound to *enzyme protein* by an amide linkage between the biotin carboxyl group and the terminal (*epsilon*) nitrogen of the lysine in the enzyme protein (apoenzyme) (Fig. 497). In naturally-occurring biotin, **biocytin** has been identified as a lysine-biotin conjugate—ε-N-biotinyl lysine.



Biotin (vitamin H)—$C_{10}H_{16}O_3N_2S$

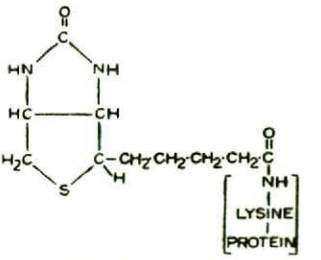


Fig. 497. Biotin coenzyme attached to apoenzyme through lysine nitrogen.

Properties. It is soluble in *water* and *alcohol*, *heat-stable* and resistant to acids and alkalis. It contains *sulphur*.

Distribution. Present in all common articles of food—specially in yeast, egg-yolk,

kidney, liver, cauliflower, peas, etc. Raw egg-white contains **avidin** which antagonises biotin and thus the animal suffers from this vitamin deficiency. Hence, raw egg-white is antibiotin in nature.

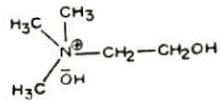
Functions. (1) Biotin acts as coenzyme for carboxylase, so as to help in carboxylation reactions (CO_2 fixation), viz., in urea formation and biosynthesis of pyrimidines and fatty acids. It also helps in deamination of threonine, serine and aspartic acid. (2) An important function of biotin is in the coenzyme activity related to carbamyl phosphate synthesis and reaction related to it. (3) In micro-organisms, biotin is related to purine synthesis. (4) Biotin enzyme plays a specific role in lipid synthesis in animals. (5) Prevents dermatitis in rats and dogs.

Deficiency signs. In dogs and rats—*dermatitis*. Experimental deficiency in man also causes (1) a peculiar dermatitis of the extremities, pallor of skin and mucous membranes. (2) Symptoms resembling thiamine deficiency and (3) rise of blood cholesterol occur. (4) In rats, deficiency produces spectacle-eyed appearance; thinning of fur (alopecia) in mouse, pig, etc.; and perosis or slipped tendon disease in fouls. (5) Deficiency does not occur normally but may be induced either by (*a*) feeding raw egg-white which contains an antivitamin avidin able to form a non-absorbable complex with biotin, (*b*) administration of sulpha drugs which interferes with normal synthesis of this vitamin by micro-organisms in the intestine.

Daily requirement. In human beings it is 150–300 micro-gram per day on the average. Average daily diet contains sufficient amount.

CHOLINE AND LIPOTROPIC FACTOR

Choline and methionine exert lipotropic action. For **chemistry** of choline and other details *vide* pages 572, 603.



Choline—$C_5H_{15}O_2N$

Properties. It is water-soluble and a component of lecithin, acetylcholine, and other phospholipids. Essential for rats and chicken, if intake of methionine is low.

Distribution. Rich sources are butter, nervous tissues, eggs, etc.

Functions. (1) It has got a lipotropic action. [*Vide* page 572]. (2) It is required for synthesis of lecithin, sphingomyelin, acetylcholine, etc. (3) It acts as a methyl donor in transmethylation (*vide* page 581).

Deficiency signs. (1) It produces fatty liver in rats, (2) causes haemorrhagic necrosis in kidneys, (3) anaemia, (4) hypoproteinemia in mammalian species.

Daily requirement. Not essential for man, because it is freely synthesised in the body.

PARA-AMINO-BENZOIC ACID (PABA)

Chemistry. Empirical formula ($COOH\text{-}C_6H_4NH_2$) structurally similar to sulphonamides.



PABA—$COOH\text{-}C_6H_4NH_2$

Properties. It is a white crystalline substance and slightly soluble in water but highly soluble in alcohol.

Distribution. It is widely distributed in animal tissues and also found in wheat germ, rice bran and polishings and milk.

Functions. (1) Essential for the growth of micro-organisms. It has similar chemical structure as that of sulphonamides so it prevents the bacteriostatic properties of the drug. (2) It maintains growth and lactation in albino rats and preserves hair colour in black rats. (3) It forms a portion of folic acid. (4) Its role in human nutrition is not definitely established.

Deficiency signs. (1) Might be responsible for achromotrichia in man due to changes in intestinal microflora. (2) Production of gray hair has also been postulated.

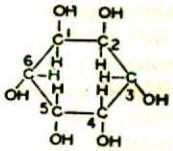
INOSITOL

(Mouse anti-alopecia factor)

Chemistry. Hexahydroxycyclohexane. Empirical formula $(CH_2O)_6$.

Properties. It is soluble in water and sweet taste. [But not a carbohydrate.] The natural variety is optically inactive and is known as *mesoinositol.*

Distribution. Rich sources are muscles (hence, called *muscle sugar*), liver, kidney, brain, etc. In cereals it is present as *phytic acid* (*hexaphosphate*).



Inositol—$(CH_2O)_6$

Functions. (1) It has a lipotropic action like choline in rat and might play some part in fat metabolism. (2) In hamsters, inositol is essential for normal reproduction. (3) In mice, chicks and rats, it is required for normal growth. (4) Its function in man is not definitely known.

Deficiency signs. (1) Alopecia in mice. (2) A peculiar eye in rats known as 'spectacle eye' condition.

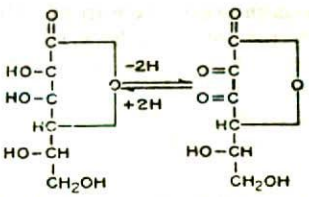
Daily requirement. Human requirement not known, but daily diet contains about 1·0 gm which seems enough.

VITAMIN C (ASCORBIC ACID)

(Antiscorbutic factor)

Historical review. In 1753 Captain Lind of the British Navy showed that the disease *Scurvy* which was common in sailors could be cured by giving them lemons and oranges. Captain Cook (1772–75) kept the sailors free from scurvy by giving them fresh food. In 1907 scurvy was experimentally produced in guinea-pigs by Holst and Frölich, and effects of vitamin C was studied on them. It was isolated by Szent-Györgyi (1928) and synthesised by Reichstein (1933).

Chemistry. Ascorbic acid is an enediol isomer of 2-keto-L-gulonolactone with a configuration similar to that of L-glucose. The natural variety is the laevo form; the dextro form is physiologically inactive. Oxidation of ascorbic acid gives rise to dehydroascorbic acid. This reaction is reversible. Both forms are physiologically active. This reaction has provided the basis of oxidation and reduction process (biological oxidation).



Ascorbic acid—$C_6H_8O_6$ Dehydroascorbic acid—$C_6H_6O_6$

Properties. It is white crystal, soluble in water, (insoluble in fat-solvents) and *heat-labile.* Easily oxidised at 100°C. in presence of oxygen. Alkali and copper salts help destruction. Hence, *cooking and canning destroy it.* Slow cooking is more destructive than rapid cooking, even at high temperature. It can be saved if cooking or canning is carried out anaerobically. It is an actively reducing substance present in the living tissues. Ascorbic acid reduces silver nitrate, ferricyanide, methylene blue, 2,6-dichlorophenol indophenol, etc. This vitamin can be assayed either chemically or histochemically by this property of ascorbic acid. The oxidation product is dehydroascorbic acid, which also has the biological activity of the vitamin. In the animal system dehydroascorbic acid can again be reduced to ascorbic acid with the help of a tripeptide glutathione. Ascorbic acid is readily absorbed from the intestine and is stored specially in liver, adrenals, pituitary and corpus luteum.

Distribution. *Vegetable sources*—fresh fruits, mainly citrus fruits, e.g., emblic myrobalan (amlaki), orange, lemon, tomato, pine-apple, papaya, etc.; fresh vegetables, e.g., cabbage, cauliflower, lettuce, spinach, green peppers, beans, etc.; properly sprouted pulses, germinating grams, etc., are

also rich sources. Potato and seeds are poor, but rich during germination. *Animal sources*—generally poor. In the animal body the adrenal cortex contains a good amount. Cow's milk, meat and fish contain a little. Milk is the only food for infants, so their diet should be supplemented with a good source of ascorbic acid, e.g., orange juice or synthetic ascorbic acid. **Blood serum** contains 0·8 mgm of ascorbic acid per 100 ml, but in deficiency only 0·4 mgm or less. It is not much stored in the body. *Most of the ingested vitamin C is promptly excreted*, although vitamin C is a high threshold substance. **Daily excretion** *in urine is* 30–50 *mgm.* The aqueous and vitreous humours are very rich in it.

Biosynthesis of ascorbic acid. Man, primates, guinea-pigs and birds cannot synthesise this vitamin. They presumably lack the enzyme system necessary to convert L-gulonic acid to ascorbic acid. So they require an external supply to meet their body needs. All other animals are capable of synthesising this vitamin either in liver or in kidney, and do not suffer from ascorbic acid deficiency. The stages of biosynthesis are glucose⟶glucuronic acid⟶2-keto-L-gulonolactone⟶ascorbic acid.

Functions and mode of action. (1) Ascorbic acid regulates oxidation-reduction potential inside the cell probably by acting as a hydrogen-carrier. (2) It helps in the oxidation of *p*-hydroxyphenyl pyruvic acid to homogentisic acid which is the intermediate product of *tyrosine* metabolism. (3) Ascorbic acid is related to carbohydrate metabolism. Deficient production of *insulin* takes place in ascorbic acid deficiency. On the other hand, after injection of dehydroascorbic acid in animals diabetic condition is produced. (4) *It is essential for the proper functioning of the formative cells* of various tissues, such as fibroblasts, osteoblasts, etc. (5) It is, at the same time, necessary to *maintain the normal state of the intercellular substance* (mucoprotein and collagen) in different tissues like bone, cartilage, teeth, skin and connective tissue; also the cementing substance of the capillary endothelium. (6) It helps in the development of the *protein matrix*, i.e., by synthesising collagen with special reference to the synthesis of hydroxyproline from a proline precursor. Hydroxyproline is a characteristic constituent of collagen, and it also helps in deposition of calcium and phosphate in the bones. (7) It plays an important role in wound repair. It lays down connective tissues which help in healing of wounds. (8) *It takes part in the maturation of red cells.* It helps in the mobilisation of iron from its storage form ferritin. The delayed blood clotting, delayed clot retraction and anaemia as seen in vitamin C deficiency, can be explained from this standpoint. (9) Due to the reducing properties of ascorbic acid, it helps in the absorption of iron from the intestine. (10) It helps in the conversion of folic acid to folinic acid. (11) This vitamin possibly has some role in enhancing the resistance of animals against different toxins and stress conditions. (12) It may be involved in the synthesis of adrenal cortical and gonadal hormones. It is observed that the adrenal cortex contains a large amount of vitamin C which is rapidly depleted when it is stimulated by ACTH.

Deficiency signs. *Scurvy*—(1) Increased fragility of capillaries causing haemorrhages—under the skin (FIG. 498), periosteum, intestine, kidney, etc. The gums show erosion of the mucous membrane at their margins and due to the increased fragility of the capillaries there is frequent bleeding (FIG. 499). (2) Malformations of bones and teeth. The osteoblasts remain functionless. Many of them are reverted to fibroblasts. There is

irregular deposition of bone salts and decrease in the density of long bones. Teeth also show similar changes. The functions of the odontoblasts are impaired. New dentine is not formed and the tissue becomes spongy and porous. (3) Increased brittleness of bones leading to fracture. (4) Anaemia—number of red cells and platelets are reduced. (5) Delayed blood clotting and clot retraction. (6) Skin eruptions. (7) Increased susceptibility to infections. (8) Impaired healing of wounds. (9) Disturbance in carbohydrate metabolism. (10) Reproductive failure both in males and females.



FIG. 498. Petechial haemorrhages in Scurvy.



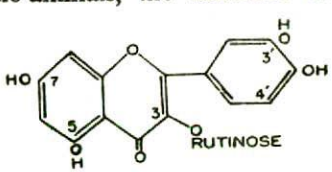
FIG. 499. Changes of gums in Scurvy.

Daily requirement. A daily intake of about 100 mgm is adequate to maintain the normal plasma level. Recommended intakes for children are 30 mgm to 80 mgm (adolescents), 75 mgm for adults, 100 mgm during pregnancy and 150 mgm during lactation. Large doses of vitamin C produce no observable ill effects in normal individuals.

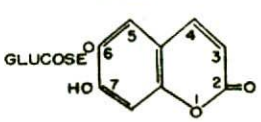
VITAMIN P (CITRIN, RUTIN, HESPERIDIN)

(Permeability factor)

When crude extracts of ascorbic acid were more effective than the pure substance in prolonging lives of scorbutic animals, the existence of another vitamin was suggested. The name of this vitamin has come from the paprika, and hence this vitamin is known as P. Of the several compounds with vitamin P activity **rutin** and **esculin** have been formed to be most effective.



Rutin



Esculin

Chemistry. Rutin is obtained from buckwheat and it is 3,5,7,3′,4′-pentahydroxyflavone-3-rutinoside. Rutinose contains glucose and rhamnose and is a disaccharide. **Esculin** is obtained from chestnuts and it is 6,7-dihydroxycoumarin-6-glucoside.

Property. They are water-soluble.

Distribution. These are always of plant origin and remain in association with vitamin C.

Mode of action. The substances possessing vitamin P activity have a direct constrictor action on vascular capillaries and reduce their fragility and permeability.

Functions. It is widely used for a variety of therapeutic reasons although the status of this is not well established. It is generally used in treating capillary bleeding and increased capillary fragility. Hence,

these substances maintain normal permeability and resistance of vascular capillaries and promote the action of vitamin C.

Deficiency signs. The haemorrhage of scurvy is believed to be due to deficiency of vitamin P. If vitamin P is given along with vitamin C, the haemorrhage is cured in most cases.

ROLE OF VITAMINS ON METABOLISM

Following vitamins are related to metabolism: (1) Vitamin B complex—(*a*) Thiamine (vitamin B_1), (*b*) Lipoic acid (Thioctic acid), (*c*) Riboflavin (vitamin B_2), (*d*) Nicotinic acid (Niacin), (*e*) Pantothenic acid (vitamin B_3), (*f*) Pyridoxine (vitamin B_6), (*g*) Folic acid (PGA), (*h*) Cyanocobalamin (vitamin B_{12}), (*i*) Biotin (vitamin H). (2) Vitamin C (Ascorbic acid). (3) Vitamin D. (4) Vitamin A. (5) Vitamin E.

Thiamine (vitamin B_1). *Relation with carbohydrate metabolism*—Thiamine acts as a coenzyme of the carboxylase which helps in the oxidative decarboxylation of α-keto acids, viz., pyruvic acid and α-ketoglutaric acid. It also acts as a coenzyme in the reaction of transketolation. It is an essential step in the oxidation of sugar in the tissues including brain. In the absence of this vitamin, pyruvic and lactic acids fail to be degraded and hence, they are accumulated in blood and tissues. The polyneuritis with tenderness of the muscles of the feet and legs, ataxia and muscular weakness which occur in Beriberi, are all due to diminished utilisation of carbohydrate. Pyruvic acid accumulates in the brain stem and cerebrospinal fluid. Heart also becomes weak and enlarged due to accumulation of pyruvic acid. *Relation with fat and protein metabolism*—Thiamine also helps the enzyme system which is responsible for the synthesis of fats from carbohydrates and proteins.

Lipoic acid (Thioctic acid). It takes part in the oxidative decarboxylation of pyruvic acid and α-ketoglutaric acid along with other members of B vitamins to acetyl CoA and succinyl CoA respectively.

Riboflavin (vitamin B_2). *Relation with tissue oxidation and protein, carbohydrate and fat metabolism*—Riboflavin containing coenzyme flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) takes part in a number of enzymatic reactions (for details *vide* riboflavin on page 681). This vitamin is also related with the metabolism of protein. It helps in the general metabolic processes mainly related to dehydrogenation.

Nicotinic acid (Niacin). *Relation with tissue oxidation, carbohydrate and fat metabolism*—Nicotinic acid remains as a part of at least two enzyme systems: (i) Nicotinamide adenine dinucleotide (NAD) and (*ii*) Nicotinamide adenine dinucleotide phosphate (NADP). The reduced form of NAD and NADP are NADH and NADPH respectively. They all take part in various oxidation-reduction reactions of the body. Niacin helps in the general metabolic processes relating to the dehydrogenase system.

Pantothenic acid (vitamin B_3). *Relation with carbohydrate and fat metabolism*—Pantothenic acid as coenzyme A (CoA) is transformed into *acetyl CoA* or *active acetate*, a pivot on which transfer of acetyl mechanism depends. For various metabolic functions involving acetyl CoA *vide* p. 684. *Active succinate* and *acyl-carrier protein* (ACP), other derivatives of pantothenic acid take part in fatty acid metabolism.

Pyridoxine (vitamin B_6). *Relation with protein, fat and carbohydrate metabolism*—Pyridoxine is essential for lower mammals. This vitamin takes

part in the normal tryptophan metabolism being a coenzyne of the enzyme **kynureninase,** in the reaction of kynurenine to anthranilic acid and 3-hydroxy kynurenine to 3-hydroxy anthranilic acid. It also acts as a coenzyme for the following enzymes: (*a*) transaminases, (*b*) decarboxylases, enzymes which decarboxylate tyrosine, arginine, glutamic acid, 3,4-dihydroxyphenylalanine (DOPA), etc., (*c*) deaminases, and (*d*) desulphydrases. It is related to the metabolism of long-chain polyunsaturated fatty acids. It helps in the synthesis of fats from proteins and carbohydrates. All these show that pyridoxine definitely takes part in protein metabolism and possibly also in fat and carbohydrate metabolism.

Folic acid. *Relation with nucleoprotein metabolism*—Folinic acid, derived from folic acid, acts as a coenzyme in the transfer of formyl and hydroxymethyl group in the biosynthesis of purines, etc.

Cyanocobalamin (vitamin B_{12}). *Relation with nucleoprotein metabolism*—Vitamin B_{12} plays an essential role in the synthesis of nucleic acid. Deficiency causes a disturbance of the deoxyribose nucleic acid (DNA) metabolism. *Relation with protein metabolism*—This vitamin influences protein metabolism as it helps in the biosynthesis of methyl group, in the process of transmethylation and also in isomerisation as that of glutamic acid. *Relation with carbohydrate and fat metabolism*—When a diet, high in carbohydrate but low in fat, fed to a weanling rat, there is an increased requirement of vitamin B_{12}. Dietary deprivations of vitamin B_{12} results decrease in reduced glutathione content, enzymatic degradation of glucose to ribose in the red blood cells and in the hepatic $NADH+H^+$ as well as in the increase of CoA. After administration of vitamin B_{12} or glutathione (GSH), hyperglycaemia can be corrected. These results show that vitamin B_{12} plays an important role in the conversion of carbohydrate to fat (*vide* p. 550).

Biotin (vitamin H). *Relation with protein metabolism*—It acts as a coenzyme and helps in carboxylation reactions taking place in urea cycle, in the process of biosynthesis of pyrimidines, fatty acids, etc. It also helps in the deamination of threonine, serine and aspartic acid.

Vitamin C (Ascorbic acid). *Relation with carbohydrate, protein and fat metabolism*—Ascorbic acid is related to carbohydrate metabolism. After injection of dehydroascorbic acid in animals diabetic condition is produced. Vitamin C takes part in the tissue oxidation probably by acting as hydrogen-carrier. It helps in the oxidation of *p*-hydroxyphenyl pyruvic acid to homogentisic acid which is the intermediate metabolic product of tyrosine metabolism. It also helps in the development of protein matrix and deposition of calcium and phosphate in the bones.

Vitamin D. *Relation with calcium and phosphorus metabolism*—Vitamin D helps in the bone formation by an indirect action on bone cells and in the development of the normal teeth. It attacks the tissue phospholipids and liberates their phosphoric acids. The phosphoric acids combine with calcium and are deposited as calcium phosphate in bones. This vitamin also activates the enzyme alkaline phosphatase in bone and soft tissues.

Vitamin A. It plays some part in protein synthesis. It is directly concerned in the formation of mucopolysaccharides and has some specific function on glucose synthesis by stimulating enzymes concerned.

Vitamin E. It acts as a cofactor in the electron transport system operating between cytochromes *b* and *c*.

INTERRELATION BETWEEN VITAMINS AND ENDOCRINES

Evidence is fast accumulating, indicating that some of vitamins and hormones act in close co-ordination in exerting their action on different physiological aspects. Major examples are indicated below:

VITAMIN A. (*a*) **Adrenal cortex**—A fall in the synthesis of adrenal cortical steroids has been observed in vitamin A deficiency which results depressed neoglucogenesis. It is possible that vitamin A or some losely related molecule acts as a coenzyme for the enzyme, concerned in some steps in the synthesis of one or more cortical hormones controlling a triose→glucose reaction. It can be corrected after administration of this vitamin. (*b*) **Gonads**—Testicular atrophy develops in vitamin A deficiency which can be corrected by administration of this vitamin. There is also disturbance in oestrous cycle during deficiency of this vitamin. Administration of vitamin A has been observed to improve fertility in cattles. (*c*) **Thyroid**—Thyroid hormone is required for the conversion of carotene to vitamin A. Hypertrophy of the thyroid gland results in vitamin A deficiency and atrophy in hypervitaminosis. Rate of formation of thyroxine decreases in vitamin A deficiency. As vitamin A is directly related to growth, naturally it seems that it may be concerned with thyroid activity.

VITAMIN D. **Parathyroid**—Vitamin D and parathyroid act synergistically on calcium metabolism. So both cause resorption of bone and increased transport of calcium through intestinal and renal epithelium.

VITAMIN E. **Sex glands**—Although vitamin E itself does not affect the normal process of ovulation, fertilisation or implantation in female rats, guinea-pigs or mice but it causes defective development of placenta and thereby death of foetus and its resorption take place. In male animals degeneration of seminiferous tubules in testes has been noted in vitamin E deficiency.

PANTOTHENIC ACID. (*a*) **Adrenal cortex**—It appears that there is a close functional relationship between pantothenic acid and adrenal cortex. In deficiency of pantothenic acid, adrenal necrosis have been noted. This vitamin has been found to protect rats from the harmful effects of excessive stress and to maintain adrenalectomised rats in good condition along with NaCl. (*b*) **Gonads**—Impaired reproduction has been noted in deficiency of this vitamin.

PYRIDOXINE. **Gonads**—The foetus has a high requirement of vitamin B_6 and for this reason this vitamin should be supplied in larger amounts during pregnancy.

VITAMIN B_{12}. **Thyroid**—Vitamin B_{12} can correct the growth retardation of adult or young rats placed on diet supplemented with the thyroid hormone. **Gonads**—This vitamin is also important for normal reproduction in some classes of laboratory animals.

FOLIC ACID. **Sex glands**—Folic acid is required for the maintenance of normal pregnancy.

ASCORBIC ACID. (*a*) **Insulin**—The synthesis of insulin in the β-cells of islets of Langerhans is impaired during vitamin C deficiency, resulting in hyperglycaemia and disturbance in carbohydrate metabolism. (*b*) **Adrenal cortex**—Hypertrophy of the adrenal cortex has been noted in scurvy which might be due to its increased activity.

THIAMINE. This vitamin is concerned with the synthesis of cortical hormones which regulate the level of blood cholesterol.

SUMMARY OF VITAMINS ACTING ON DIFFERENT SYSTEMS

The following is a brief summary of the various vitamins acting on different tissues and systems. It must be remembered that, like the endocrines, vitamins also act in close co-operation with one another. The functions of a particular vitamin are not independent, but depend upon the proper activity of other vitamins.

VITAMINS ACTING ON NERVOUS SYSTEM—(1) **Vitamin A.** (2) **Vitamin B**—(*a*) Thiamine, (*b*) Nicotinic acid (Niacin), (*c*) Pantothenic acid, (*d*) Pyridoxine, (*e*) Choline. (3) **Vitamin D**—indirectly through its action on bones.

VITAMINS ACTING ON ALIMENTARY SYSTEM—(1) **Vitamin A**—on the epithelium, glands and secretions. (2) **Vitamin B**—Thiamine (tone, appetite and secretion), Riboflavin (ulcer mouth), Nicotinic acid (Niacin) (gastro-intestinal disorders in pellagra). (3) **Vitamin C** (malformations of teeth, haemorrhages from the gums, intestine, and increased susceptibility to infections of the gastro-intestinal tract, etc.).

VITAMINS ACTING ON CIRCULATORY SYSTEM AND BLOOD—(1) **Vitamin B**—(*a*) Thiamine (cardiac damage of beriberi, increased blood lactate), (*b*) Folic acid, (*c*) Cyanocobalamin (vitamin B_{12}), (*d*) Pyridoxine. (2) **Vitamin C.** (3) **Vitamin D** (on blood calcium). (4) **Vitamin K.** (5) **Vitamin P.**

VITAMINS ACTING ON BONE FORMATION—(1) **Vitamin A,** (2) **Vitamin C,** (3) **Vitamin D.**

VITAMINS ACTING ON EPITHELIUM, SKIN AND HAIR—(1) **Vitamin A** (2) **Vitamin B**—(*a*) Riboflavin, (*b*) Nicotinic acid (Niacin), (*c*) Biotin, (*d*) Pyridoxine, (*e*) Inositol, (*f*) Para-amino-benzoic acid (PABA). (3) **Vitamin C.**

VITAMINS ACTING ON REPRODUCTIVE SYSTEM—(1) **Vitamin A.** (2) **Vitamin B**—(*a*) Pyridoxine, (*b*) Folic acid, (*c*) Pantothenic acid, (*d*) **Vitamin B_{12}.** (3) **Vitamin C.** (4) **Vitamin E.**

VITAMINS ACTING ON GROWTH—(1) **Vitamin A.** (2) **Vitamin B_1,** (3) **Vitamin B_1 complex** (including B_{12}). (4) **Vitamin C.** (5) **Vitamin D.**

ANTIVITAMINS

The term **antivitamin** is losely used and it refers to substances which have got any of the following three kinds of actions interfering with the normal utilisation of this vitamin. These are as follows:

1. These substances have got structural and chemical groups similar to vitamins but without any physiological action. In fact they act as antagonists and in most cases produce deficiency symptoms when given simultaneously with the vitamin. Some of these antivitamins have been prepared, such as pyrithiamine—pyridine analogue of thiamine. Experimentally and clinically they are of some use.

2. Substances which destroy vitamins, e.g., the enzyme thiaminase destroying thiamine.

3. Some chemical substances make the vitamins ineffective, such as *avidin* found in raw egg-white which binds and prevents the action of biotin.

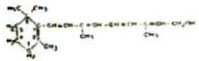
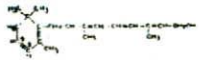
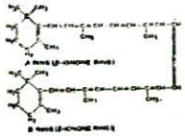
Substances having antivitamin activity in case of thiamine are pyrithiamine, oxythiamine and the 2-N-butyl homologue of thiamine (in case of rats).

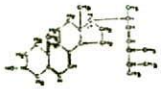
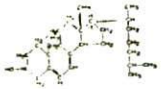
Galactoflavin is a potent riboflavin inhibitor. Other compounds are the diethyl derivative, flavin monosulphate, etc., which act as the antagonist to riboflavin in different species.

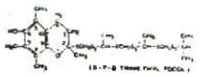
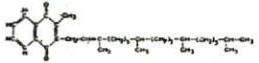
Niacin antagonists are pyridine-3-sulphonic acid and 3-acetyl pyridine and 6-aminoniacinamide which produce niacin deficiency symptoms in rats.

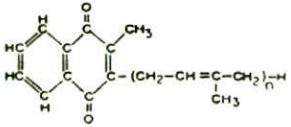
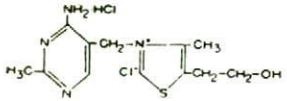
Pantoyltaurine and ω-methyl pantothenic acid are the examples of pantothenic acid antagonists. Deoxypyridoxine plays a potent antagonistic action against pyridoxine. Other examples are methoxypyridoxine and toxopyrimidine. One of the most important inhibitors of folic acid is aminopterin. Amethopterin also produces deficiency of the vitamin folic acid.

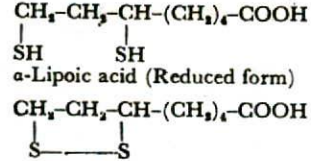
SYNOPSIS OF FAT-SOLUBLE AND WATER-SOLUBLE VITAMINS

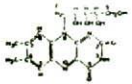
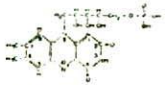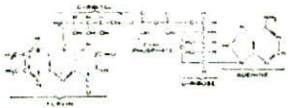
Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Vitamin A  A_1 (Retinol$_1$)— $C_{20}H_{29}OH$  A_2 (Retinol$_2$)— $C_{20}H_{27}OH$  β-Carotene (Provitamin A)— $C_{40}H_{56}$	Soluble in fat-solvents. Insoluble in water. Ordinarily it is a viscid colourless oil but by careful fractionation it has also been isolated as pale yellowish needles. Heat-stable in absence of air. Easily destroyed on exposure to air or ultra-violet rays.	*Animal sources* — cod-liver oil, halibut-liver oil, milk, butter, eggs, fishes. *Vegetable sources* — (as carotene) carrots, spinach, vegetable oils, green leaves, yellow fruits, e.g., mangoes, tomatoes, etc.	Essential for growth. It is a component of rhodopsin, hence essential for night vision. Helps in the preservation of structural integrity and the normal permeability of membranes: cellular, mitochondrial, lysosomal, etc. Maintains the health and activity of epithelial tissues and glands. Prevents infection. Maintains nutrition and functions of the nervous tissue. Controls the action of the bone cells, formation and sulphation of mucopolysaccharide. Helps in normal fertility. Helps in glucose synthesis by stimulating enzymes concerned.	Night-blindness (Nyctalopia). Xerophthalmia. Keratinisation of skin and mucous membrane with increased susceptibility to infections entering by way of epithelial tissues. Retardation of growth in children. Defective growth of bone and teeth.	5,000 i.u. for adults. 6,000–8,000 i.u. for growing children and during puberty, lactation and pregnancy.

Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Vitamin D (Calciferol)  D_2 (Ergocalciferol)— $C_{28}H_{43}OH$  D_3 (Cholecalciferol)	Soluble in fat-solvents but insoluble in water. Heat-stable. There are a group of D vitamins of which D_2 (ergocalciferol) and D_3 (cholecalciferol) are chief. D_2 is obtained when ergosterol is activated by irradiation with ultra-violet rays, D_2 is a white, crystalline material, soluble in fat and stable in heat, acids and alkalis, and oxidation. D_3 is made by ultra-violet irradiation of 7-dehydrocholesterol (provitamin D) and is also close isomer of cholesterol. D_3 is also a white, odourless, crystalline compound, soluble in fats and in common fat-solvents. D_3 is less potent than D_2.	Richest sources are fish-liver oils, e.g., cod-liver oil, halibut-liver oil, etc. Butter, milk, eggs, liver, etc.	Favours calcium and phosphorus absorption from the intestine. Related to calcium and phosphorus metabolism. Helps in the bone formation by direct action on bone cells. Helps in the development of the normal teeth. Activates the alkaline phosphatase in bone, kidney and intestine.	Defective bone growth, condition known as rickets in infants and children and osteomalacia in adults. The formation of teeth becomes defective and leads to the development of dental caries. Tetany in infants.	400–800 i.u. in growing children and during pregnancy and lactation.

Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Vitamin E (tocopherols)  α-Tocopherol—$C_{29}H_{50}O_2$  β-Tocopherol—$C_{28}H_{48}O_2$  γ-Tocopherol—$C_{28}H_{48}O_2$	Soluble in fat and fat-solvents. Heat-stable. Exists naturally as a yellow oil. In food, acts as an antioxidant and prevents vitamin A, etc., from oxidative destruction. There are three varieties of tocopherols α, β and γ. The most active compound is α-tocopherol.	*Animal sources*—egg, milk, fish and muscles. *Vegetable sources* — vegetable seed oils, especially wheat, soyabean and corn. It has also been produced synthetically.	Tocopherols act as a cofactor in the electron transport system acting between cytochromes *b* and *c* and have got antioxidative effects and prevent oxidation (unwanted in the body). Prevent sterility. Essential for foetal development. Required for normal function of muscles. Maintains the physiological equilibrium in vascular and nervous system.	In the female rats implantation of the ovum occurs, but after some time the foetus dies. Vitamin E therapy is of some promise in the prevention of habitual miscarriage in women. In rats there is increased metabolic rate and development of muscular dystrophy. Male rats show atrophy of testes and changes in germinal epithelium.	Average daily intake in diet is about 15 to 20 mgm, which satisfies the requirement.
Vitamin K  K_1 (Phylloquinone)—$C_{31}H_{46}O_2$	Fat-soluble. Heat-stable. More than one member of K family, such as K_1, K_2, etc., which are synthesised by green plants and bacteria. The synthetic product is 2-methyl-1 : 4-naphthoquinone(K_3).	*Vegetable sources* — cabbage, spinach, alfalfa, tomato, soyabean, etc. It has also been produced synthetically.	It catalyses the formation of prothrombin and factor VII in the blood and helps in the normal coagulation of blood. It has been suggested that this vitamin acts as a coenzyme for some enzymes responsible for	Defective blood coagulation due to reduction of prothrombin and factor VII in the blood causes haemorrhages. The haemorrhagic disease in the new-born is believed to be due to lack of vitamin K.	Normal mixed diet supplies adequate amount. In the treatment of certain haemorrhagic diseases, 5 mgm is given either orally or by injection.

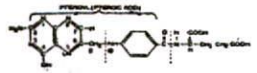
Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Vitamin K (*contd.*)  K_2 (Flavinoquinone) in which n may be 6, 7, 9 ($C_{41}H_{56}O_2$)	K_1 is a yellow viscid oil, but K_2 is a yellow, crystalline solid.		normal clotting reactions. It plays an important role in oxidative phosphorylation in the mitochondria. Bile salts are necessary for the absorption of vitamin K.		
Thiamine **(aneurine, vitamin B_1)**  Thiamine hydrochloride— $C_{12}H_{17}Cl.N_4OS.HCl$	White, crystalline substance. Water-soluble. Heat-labile. Unstable at high temperature and in alkaline medium. Stable in acid medium. On oxidation it gives a yellowish dye with fluorescence known as *thiochrome*.	*Vegetable sources* — cereals (in the husk and embryo), pulses, nuts, yeast, beets, carrots, turnips, lettuce, cauliflower, pears, beans, etc. Polished rice or white flour is poor in this vitamin. *Animal sources* — egg-yolk contains fair amount. It has also been produced synthetically.	Acts as a coenzyme of the carboxylase which helps in the oxidative decarboxylation of pyruvic acid (α-keto acid). It is an essential step in the oxidation of sugar in the tissues and brain. In tissues thiamine exists as thiamine pyrophosphate and helps in oxidative decarboxylation of α-ketonic acid as a coenzyme. In the absence of this vitamin, pyruvic and lactic acids fail to be broken down, and accumulate in blood and tissues.	Beriberi—dry, wet, cardiac or mixed type. (*a*) Dry beriberi is associated with disorders of nervous system, (*b*) Cardiac beriberi is associated with signs of congestive cardiac and circulatory failure, (*c*) In wet beriberi, polyneuritis is accompanied by oedema, (*d*) In mixed beriberi there is a combination of the above conditions. Loss of appetite, atony of the gastro-intestinal tract and hypochlorhydria. In addition to these	About 1·8 mgm for a diet producing 3,000 calories. The requirement is increased in pregnancy, lactation, heavy muscular work, high carbohydrate diet, etc.

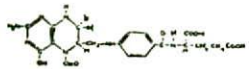
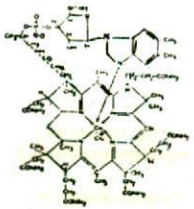
Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
			Helps the enzyme system for the synthesis of fats from carbohydrates and proteins. It helps in transketolation reaction. It is also called *antineuritic* factor.	signs heart becomes weak and enlarged and oedema of the legs occurs. Cardiac failure may also occur in some subjects. In rats, marked bradycardia occurs. Cerebral beriberi has been reported where the grey matter of the cerebrum round the third ventricle is affected.	
Lipoic acid (Thioctic acid)  α-Lipoic acid (Reduced form) α-Lipoic acid (Oxidised form)	6,8-dithio-octanoic acid. Sulphur-containing fatty acid.	Widely distributed in nature.	Along with thiamine and some other members of vitamins B helps in the oxidative decarboxylation of pyruvic acid and α-ketoglutaric acid to acetyl CoA and succinyl CoA respectively.	Deficiency signs not known in higher animals.	Probably not required from the dietary source in higher animals.
Riboflavin (Vitamin B_2, Lactoflavin)	Yellow crystals. Sparingly soluble in water. Heat-stable in neutral and acid media. Destroyed by light.	*Animal sources* — milk (lactoflavin), liver, kidney, muscle, raw egg-white, etc. *Vegetable sources* — whole grains and	Essential for growth. Constituent of 'yellow enzyme' of Warburg, hence essential for tissue oxidation. In the	In man—oral fissures at the corners of the mouth —Cheilosis. Ulcers on the lips. Angular stomatitis. Glossitis.	In adults—1·5 to 1·8 mgm. The requirement of riboflavin can be calculated in term of the protein intake, i.e.,

Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Riboflavin (*contd.*)  $C_{17}H_{20}N_4O_6$  Riboflavin phosphate or FMN  FAD (FADN)		green-leafy vegetables. It has been synthetically produced.	tissues, riboflavin exists as flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). These two coenzymes in combination with protein are termed flavoprotein which have a major functional role as a number of enzyme system act as hydrogen-carrier to the cytochromes which further carry the same to the molecular oxygen where hydrogen finally combines with it to form H_2O. It is also related to carbohydrate, fat and protein metabolism.	Keratitis, corneal opacities, vascularisation of cornea and photophobia. Loss of hair. Skin becomes dry and scaly. Arrest of growth	0·025 mgm of riboflavin per 1·0 gm of protein.
Nicotinic acid (**Niacin**)  Niacin—$C_6H_5O_2N$	White, crystalline substance. Moderately soluble in water. Heat-stable.	*Vegetable sources* — dried legumes, peas, beans, tomatoes, whole wheat meal, green vegetables, etc.	Acts as a *pellagra-preventing* factor. Essential for growth. Remains as a part of at least two	Dermatitis, diarrhoea and dementia. Pellagra — characteristic dermatitis specially on the exposed parts of the	12–18 mgm for adult males and a little less in adult females. Requirement varies with the protein

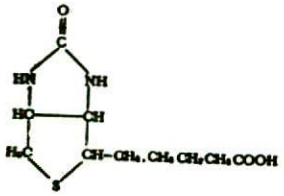
Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Nicotinic acid amide (Niacinamide, Nicotinamide)  Nicotinamide— $C_6H_6ON_2$		*Animal sources* — meat, fish, liver, milk, eggs, yeast, kidneys, heart, etc. It has been produced synthetically.	enzymes — NAD (DPN) and NADP (TPN). They act along with dehydrogenase and take part in tissue oxidation. Helps in the formation of fats from carbohydrates. Stimulates the central nervous system.	body. The dermatitis begins with erythema resembling sunburnt areas. Gradually these areas become reddish-brown, rough, scaly and keratotic. Gastro-intestinal disorders. Polyneuritis. Various forms of mental disorders. In dogs — black tongue.	content of diet, as amino acid tryptophan gives rise to niacin.
Pantothenic acid (vitamin B_3)—$C_9H_{17}O_5N$ [$HO.CH_2.C(CH_3)_2.CHOH.CO.NH.CH_2.CH_2.COOH$.]	White, crystalline substance. Highly soluble in water. Hygroscopic. Heat-stable.	*Animal sources* — liver, kidney, egg-yolk, meat, milk, yeast, etc. *Vegetable sources* — molasses, wheat bran, peas, sweet potatoes, etc. It has also been produced synthetically.	Plays a fundamental role in the metabolism as co-enzyme A (CoA). Its acetyl derivative (acetyl CoA) called *active acetate*, a pivot on which transfer of acetyl mechanism depends. In combination with succinate forms *active succinate* and helps in the biosynthesis of haemoglobin.	Various tissues affected, e.g., gastro-intestinal disturbances, alopecia, cornification of the skin and hypofunction of adrenal cortex.	Not exactly known. Average daily diet contains 10 mgm.

Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
			The protein-bound pantothenic acid, called *acyl-carrier protein* (ACP) helps in the biosynthesis of fatty acids.		
Pyridoxine (vitamin B_6)  $C_8H_{11}O_3N$	Two allied compounds — *pyridoxal* and *pyridoxamine*, (natural) and synthetic, have the same action and the three vitamins are known as vitamin B_6. White crystal, soluble in water. Heat-stable in both acidic and alkaline solutions.	*Vegetable sources* — germs of various grains and seeds, leafy vegetables, etc. *Animal sources* — liver, egg-yolk. meat, kidney, yeast, etc. It has been produced synthetically.	Essential for lower mammals. Pyridoxal phosphate acts as a coenzyme for the enzyme kynureninase, which breaks down kynurenine to anthranilic acid and 3-hydroxykynurenine to 3-hydroxyanthranilic acid and so helps in the normal metabolism of tryptophan. Acts as a coenzyme for (*a*) transaminases or aminotransferases, (*b*) decarboxylases, (*c*) deaminases or dehydrases, and (*d*) desulphydrases. Related to the metabolism of unsaturated fatty acids.	Peculiar dermatitis (*rat acrodynia*) and hypochromic microcytic anaemia. Weakness of muscles and convulsive seizures. In man its role is not exactly known. But in subjects suffering from pellagra and beriberi, synthetic B_6 can easily cure insomnia, irritability, abdominal pain, difficulty in walking, etc., which cannot be cured by other vitamins.	0·3 mgm per day in infants and in adults 2·0 mgm daily. Sufficient in normal diet.

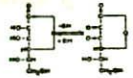
Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Pyridoxine (vitamin B_6) (*contd.*)			Helps in the synthesis of fats from proteins and carbohydrates. It is also called *antidermatitis* factor.		
Folic acid *Pteroylglutamic acid* (*PGA*)  (*Pterin derivative residue*— $C_7H_6ON_5$ *Para-amino benzoic acid*— C_7H_5ON *Glutamic acid*— $C_5H_9O_4N$ Folic acid (PGA)—$C_{19}H_{19}O_6N_7$ (folacin)	Yellow compound. Slightly soluble in water, and destroyed by light.	*Animal sources* — liver, kidney, etc. *Vegetable sources* — widely distributed in plants, and in green vegetables.	Essential for the synthesis of deoxyribonucleic acid (DNA) in the nuclei of the cells. Along with vitamin B_{12} it helps in the synthesis of nucleic acid.	In rats and monkeys — anaemia, leukopenia and agranulocytosis. In man — Megaloblastic anaemia, especially occurring during pregnancy. Combined system disease, i.e., pernicious anaemia and neurological symptoms, i.e., pernicious anaemia may develop as a result of deficiency of this vitamin along with vitamin B_{12} deficiency.	Exact requirement not known. Average daily diet of adults contains about 50 microgram, which seems to be adequate.

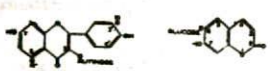
Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Leucovorin  Folinic acid (CF), N^5-formyl FH_4			Reduced form of folic acid, i.e., tetrahydrofolic acid (FH_4) is converted into **folinic acid** in the body, a formyl derivative of FH_4 (single carbon carrier) which acts as a coenzyme in the transfer of formyl and hydroxymethyl group in various biological systems. Related to phospholipid metabolism (choline synthesis) and amino acid metabolism.		
Cyanocobalamin (vitamin B_{12})  $C_{63}H_{88}O_{14}N_{14}PCo$	Red crystalline substance. Soluble in water. Contains metalloporphyrin nucleus and cobalt. Three different cobalamin compounds having common prosthetic group possess vitamin B_{12} activity which are as follows:	Absent in plants but present in almost all animal tissues. Rich sources are liver, kidney, eggs, beef extract, milk, etc. Also found in fungus — *Streptomyces griseus*. Hence vitamin B_{12} is obtained as a by-product in	*Antipernicious anaemia* factor. Essential for the formation and maturation of red blood cells. Recent idea is that vitamin B_{12} is Castle's extrinsic factor. The intrinsic factor helps in its absorption from the intestine. Plays an essential	Pernicious or Macrocytic anaemia. Brings about Hyperglycaemia. In pigs or rats, marked reduction in growth as well as nervousness and irritability observed.	The requirement about 1 μ gm per day is very small.

Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Cyanocobalamin (vitamin B_{12}) *(contd.)*	(*i*) Cyanocobalamin, in which cobalt attached to cyanide group. (*ii*) *Hydroxycobalamin*, (B_{12a}) in which cyanide group is replaced by hydroxyl group. (*iii*) Nitrocobalamin in which cyanide group is replaced by nitro group. B_{12a} is must active and enzyme system requiring B_{12}.	the manufacture of *Streptomycin*.	role in the synthesis of nucleic acid. Increases the white cell count and the platelets through its action in the bone-marrow. Concerned with the maintenance of normal health and activity of certain parts of nervous system. Cures pernicious anaemia and also neurological manifestations of pernicious anaemia. Helps in the growth of *Lactobacillus lactis*. Helps in the biosynthesis of methyl group and also in transmethylation. Hyperglycaemia due to deficiency of B_{12} can be corrected after administration of vitamin B_{12} or glutathione (GSH). Related to nucleoprotein, protein, carbohydrate and fat metabolism.		

Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Biotin (vitamin H)  $C_{10}H_{16}O_3N_2S$	It is a valeric acid derivative. Soluble in water and alcohol. Heat-stable. Resistant to acids and alkalis. It contains sulphur.	Widely distributed in all common articles of food—specially in yeast, egg-yolk, kidney, liver, cauliflower, peas, etc. Raw egg-white contains **avidin** (antivitamin of *biotin*) which antagonises and prevents its action.	Biotin acts as coenzyme in CO_2 fixation for the urea (carbamyl phosphate) formation as well as for the biosynthesis of pyrimidines and fatty acids. Helps in deamination of threonine, serine and aspartic acid. Prevents dermatitis in rats and dogs.	In dogs and rats—dermatitis. Experimental deficiency in man causes (1) peculiar dermatitis, (2) symptoms resembling thiamine deficiency, and (3) rise of blood cholesterol. Deficiency does not occur normally but may be induced by either (1) feeding raw egg-white or (2) intake of sulphur drugs which interferes with the biosynthesis of this vitamin in the intestine.	Average in human 150–300 microgram daily. Average daily diet contains sufficient amount.
Choline and Lipotropic factor  Choline—$C_5H_{15}O_2N$	Water-soluble. Component of lecithin and other phospholipids, acetylcholine, etc.	Butter, nervous tissues, eggs, etc.	Lipotropic action. Synthesis of lecithin, sphingomyelin, acetylcholine, etc. Acts as a methyl donor in transmethylation.	In rats fatty liver. Cause anaemia, hypoproteinaemia, and haemorrhagic necrosis of kidney, etc.	Not essential for man, because freely synthesised in the body.

Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Para-amino-benzoic acid (PABA)  $COOH–C_6H_4NH_2$	White crystalline substance. Slightly soluble in water but highly soluble in alcohol.	Widely distributed in animal tissues. Also found in wheat germ, rice bran and polishings and milk.	Prevents the bacteriostatic properties of sulpha drugs due to structural similarities.	Might produce (1) achromotrichia in man due to changes in intestinal microflora. (2) premature graying of hair. (3) Some rickettsial infection.	—
Inositol  *Myo*-inositol or *Meso*-inositol $—C_6H_{12}O_6$	Soluble in water. Sweet taste. The natural variety is known as *meso*-inositol or *myo*-inositol (i.e., inositol present in muscle) or muscle sugar.	Rich sources are muscles, liver, kidney, brain, etc. In cereals present as phytic acid.	It has a lipotropic action like choline in rat and plays some part in fat metabolism. Although its role in human nutrition is not definitely known, but inositol is found to be responsible for normal reproduction in hamsters and for normal growth in mice and rats.	Alopecia in mice. Peculiar eye condition known as 'Spectacle eye', in rats.	Human requirement not known. Daily diet contains about 1 gm which seems enough.

Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Ascorbic acid (vitamin C)  Ascorbic acid— $C_6H_8O_6$ Dehydroascorbic acid— $C_6H_6O_6$	White crystals. Soluble in water. Insoluble in fat-solvents. Heat-labile. Easily oxidised at 100°C. in presence of oxygen. Cannot stand cooking and canning. Destroyed by alkali and copper salts. Good reducing agent. Reduces silver nitrate, ferricyanide, 2, 6-dichlorophenol indophenol, etc.	*Vegetable sources* — fresh (citrus) fruits, e.g., emblic myrobalan (amlaki), orange, lemon, tomato, etc. Fresh vegetables, e.g., cabbage, cauliflower, lettuce, etc. Properly sprouted pulses, germinating grams, etc. *Animal sources* — generally contains a negligible amount, e.g., adrenal.	Regulates oxidation - reduction potential inside the cell, probably by acting as hydrogen-carrier. It helps in the oxidation of *p*-hydroxyphenyl pyruvic acid to homogentisic acid which is the intermediate metabolic product of tyrosine metabolism. Related to carbohydrate metabolism. In ascorbic acid deficiency, reduced production of insulin takes place. On the other hand, dehydroascorbic acid (oxidation product of this vitamin), when injected in animals produces diabetes. Essential for the proper functioning of the formative cells of various tissues, such as	*Scurvy* — Increased fragility of the capillaries causing haemorrhages — under the skin, periosteum, intestine, kidney, etc The gums show erosion of the mucous membrane at their margins and due to increased fragility of the capillaries there is frequent bleeding. Malformations of bones and teeth. The osteoblasts remain functionless. Many of them are reverted to fibroblasts. There is irregular deposition of bone salts. The functions of the odontoblasts are impaired. New dentine is not formed and the tissue becomes spongy and porous.	In adults normally 75 mgm on the average, during pregnancy, lactation and adolescence 100–150 mgm approximately.

Name of Vitamins, Empirical and Structural Formulae	Properties	Distribution	Functions	Effects of Deficiency	Daily Requirement
Ascorbic acid *(contd.)*			fibroblasts, osteoblasts, etc. Maintains the normal state of the intercellular substance, mucoprotein and collagen and the cementing substance of capillary endothelium. Helps in the development of *proteinious matrix* and deposition of calcium and phosphate in the bones. Plays a role in wound repair. Helps in the formation of red cells. It may be involved in cortical steroid metabolism. In some way related to the synthesis of steroid hormones.	Anaemia — number of red cells and the platelets are reduced. Delayed blood clotting and clot retraction. Skin eruptions. Increased susceptibility to infections. Impaired healing of wounds. Disturbance in carbohydrate metabolism. Reproductive failure both in males and females.	
Vitamin P (citrin, rutin, hesperidin)  Rutin Esculin	Water-soluble.	Remains always in association with vitamin C, i.e., citrus fruits specially more in rind than in juice.	Maintains normal permeability and resistance of vascular capillary.	**Haemorrhage of scurvy.**	

MILK

Milk is the secretion of the mammary glands. The importance of the chemical composition of milk arises from the fact that it is the sole foodstuff of sucklings (viviparous) and it provides for adequate nutrition during the suckling stage. Although it is not a perfect food but it supplies many of the essential nutrients with few exceptions like copper, iron, etc. The fluid secreted in the first three days after labour, is called **colostrum.** It is thick, yellowish in colour and very rich in proteins and salts. It contains large granular cells called *colostrum corpuscles*. The higher protein content is due mainly to the presence of globulins which are apparently identical with the γ-globulins of the blood plasma. The protein content gradually falls with simultaneous steady rise in the fat and carbohydrate content until the true milk level is attained. It is coagulated by heat or even spontaneously on standing. The milk formed after this period and up to four weeks, is called the **intermediate milk** (or **transition milk**). The **mature milk** is secreted after one month. The general properties and composition of mature milk of all mammals are more or less same. They differ in details. The general characteristics of cow's milk are described below:

Cow's milk is an opaque white fluid, having a peculiar smell and a sweetish taste. Its specific gravity lies between 1·028–1·034, pH—6·6–6·8 (slightly acid), contains no bicarbonates, but is rich in buffers. It does not coagulate on boiling unless it is already sour. It is coagulated by rennin.

Milk is an emulsion of finely divided fat particles which remain uniformly suspended in milk fluid. The reason why the fat droplets do not run together, lies in the fact that the protein of milk makes a thin covering on each fat globule and thus prevents them from running together (protective action of colloids).

The bile pigments and generally, the micro-organisms are not excreted in milk. Hence, milk is a sterile product. But many drugs, taken by the mother, are excreted in the milk, viz., alcohol, belladonna, opium, iodide, bromide, mercury (when continued for long period) and occasionally salicylates and arsenic.

Composition of milk. The average percentage composition of the human milk and cow's milk is given below (all the constituents are shown in grams per 100 gm of milk):

Milk	Protein	Fat	Carbohydrate	Ash	Water
Human	1·2–1·8	3·6	6·8	0·20–0·25	88·0
Cow	3·3	3·5	4·7	0·75	88·0

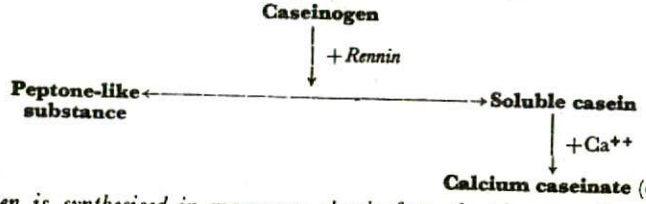
On comparing, it is seen that human milk is poorer in protein (1/2), poorer in salts (nearly 1/3rd), but richer in sugar (nearly 1½) than cow's milk. The fat content is almost same. Regarding vitamins, both cow and human milk contain sufficient quantity of vitamin A, thiamine, vitamin D, etc. Vitamin C content is very poor. When compared between the two, most vitamins are present in higher concentration in cow's milk, exceptions being vitamins C, D, nicotinic acid and inositol.

A short account of the chief ingredients of milk is given below:

Proteins. Three types of proteins are present in milk: **caseinogen, lactalbumin, lactglobulin.**

Caseinogen—is the chief protein of milk. Cow's milk is very rich in it (2·7%). It is much less in human milk (0·3%). It is a phosphoprotein, precipitated by weak acids but is dissolved in weak alkalis. It is a 'first class' protein or protein of 'high biological value', rich in almost all essential amino acids. It is not coagulated by heat. Rennin coagulates it. Under the influence of milk-clotting (curdling) enzymes, e.g., rennin, pepsin, and chymotrypsin, casein is hydrolysed to soluble paracasein which in the presence of Ca^{++} is converted to insoluble casein (calcium paracaseinate) or **milk** curd. The residual clear fluid in 'whey'. The casein of cow's milk is **more** readily precipitated by acid and coagulated by rennin than that of human milk. The curd formed in human milk is more flocculent and more readily digested.

Clotting of milk. Rennin coagulates milk in presence of calcium ion. It seems that caseinogen is at first split up by rennin into two parts: **soluble casein** and another peptone-like substance. Calcium then combines with soluble casein and forms insoluble **calcium caseinate.** This is the clot. The process can be represented as follows:



Caseinogen is synthesised in mammary glands from the plasma amino acids and proteins. The relative concentration of caseinogen and lactalbumin in cow's milk and human milk differ considerably. The *caseinogen-lactalbumin ratio* in cow's milk is roughly 6/1, that in human milk is 1/2. Human caseinogen also slightly differs chemically from that of cow's milk. On the whole, cow's milk contains over six times more caseinogen than human milk.

Lactalbumin and Lactglobulin. They resemble very closely the albumin and globulin of blood plasma. Globulin is found only in minute traces. They are *synthesised* in the mammary glands from the plasma amino acids. They are coagulated on heating.

Milk protein is rich in essential amino acids and has a high biological value. In underdeveloped countries where low amount of milk is produced, the young children from the poorer class have to depend on a diet high in carbohydrate and poor in protein, leading to a protein deficiency disease known as **kwashiorkor.**

Fat. As already mentioned, fats remain as a stable emulsion in milk. It contains neutral fat, free fatty acids, traces of lecithin and cholesterol. It is synthesised from neutral fat of the blood and partly from acetate.

The neutral fat is chiefly triolein, tripalmitin and tristearin. But small amounts of the triglycerides of other saturated (even carbon) fatty acids,—from butyric (C_4) to lignoceric (C_{24}), are present. The glycerides of various unsaturated acids are also found. Cow's milk contains eight times as much free fatty acids as human milk. Milk has a greater proportion of fatty acids of low molecular weight than is present in any other natural fats.

The fats of human milk differ from cow's milk in their fatty acid concentration. Oleic acid predominates in both, and in about 10% of human

milk, fatty acids are highly unsaturated while cow's milk has about only 0·5%. Moreover human milk contains no short-chain fatty acids (below C_{10}) whereas they form 5 to 10% of the fatty acids of cow's milk. Available evidence suggests that milk fat is synthesised in the lactating breast, chiefly from glucose by the process of intermediary metabolism. Very small amount is contributed by the blood fats or other lipids.

Carbohydrate. The carbohydrate of milk is **lactose.** It is a specific constituent of milk manufactured in the mammary glands. It is synthesised from blood glucose. At first galactose is formed which combines with glucose to form lactose. Lactose is present in the milk of all species and is absent in all other food materials. Souring of milk is due to conversion of lactose to lactic acid. As human milk contains more lactose than that of cow's milk, so dairy milk is usually fortified with some form of carbohydrate before it is fed to babies. Milk sugar (lactose) helps in the absorption of calcium.

Galactosaemia. Galactosaemia is the condition when a large amount of galactose accumulates in the blood and excreted in the urine. Sometimes galactose also accumulates in the red blood cells of galactosaemic subjects. In this rare congenital disease an enzyme (galactose-1-phosphate-uridyl transferase) responsible for normal metabolism of galactose is lacking. Feeding of milk leads to enlargement of liver, spleen, etc. Withdrawals of dietary milk and milk products from the diet have got great improvement. Alternatively, galactose may be consumed through UDP-galactose pyrophosphorylase.

Minerals (Ash). Cow's milk contains nearly three times as much minerals as that of human milk. On the whole, milk is rich in minerals, specially calcium, potassium, sodium, chlorine and phosphorus. The ratio, in which *the calcium and phosphorus* are present, is ideal for their proper absorption and assimilation and consequently for bone formation along with vitamin D. Presence of inadequate amounts of iron and copper makes the milk an incomplete food. As the iron content of milk is very low, the baby from three months of age, should be fed additional amount of iron. Proper amount of iron if not supplied, there is iron deficiency resulting anaemia in infants. All the minerals are derived from blood stream. The phosphorus compounds are derived from the inorganic phosphate of blood.

Vitamins. Under satisfactory dietary conditions milk contains adequate vitamin A and carotenes. It is low in vitamin B complex except riboflavin and pantothenic acid, and poor in vitamin D. Vitamin C content is relatively low and is further reduced by pasteurisation.

FACTORS AFFECTING COMPOSITION OF MILK

(1) **Age of the mother**—In younger women the milk is more rich. [Milk is not affected by the return of menstruation.] (2) The **number of days after delivery**—One month after delivery, the milk becomes mature having average normal composition. Before this period, milk is always richer. (3) A **superabundant diet** does neither increase the total quantity nor the richness of the milk unless the protein quantity is also increased. (4) If the diet is **insufficient** in amount, it is seen that at first milk is not reduced, because the body tissues are utilised to manufacture milk and the mother loses weight. But later on, milk is reduced in quantity.

If the quantity of protein is reduced much below the normal, the total quantity of milk, the fat content and also the protein content, will fall within a few hours. Hence, *in order to increase the quantity and richness of the milk the lactating mother should have a high protein diet.* (5) The concentration of milk fat depends upon blood fat which in its turn depends upon the fatty acid content in the diet. (6) The **vitamin** content of milk is directly proportional to the vitamins supplied in diet.

Humanisation of cow's milk. Since the constituents of human milk differ both in quality and quantity from those of cow's milk, it is not possible to humanise cow's milk fully. But for artificial infant feeding, often it becomes necessary to convert cow's milk into human milk approximately. It is done by adding equal volume of water to cow's milk (to make the protein concentration same as that of human milk) and also by adding appropriate amounts of cream, lactose, vitamins and iron.

NORMAL DIET

In general terms, an adequate diet is one which permits normal growth, maintenance and reproduction. The following points should be taken into consideration while estimating adequate diet for an individual:

Essential constituents of diet. Normal diet must contain the following six items: (1) *proteins*, (2) *fats*, (3) *carbohydrates*, (4) *vitamins*, (5) *minerals*, (6) *water*. The first three are for energy production, growth and maintenance of tissues, and the last three are essential for chemical mechanisms, i.e., for the utilisation of energy, synthesis of various necessary metabolites, viz., enzymes, hormones, etc.

Quantity of food. Energy for physiological processes is provided by the combination of carbohydrates, fats and proteins. The daily energy requirement or the daily calorific need is the sum of the basal energy demands *plus* that required for the additional work of the day. The energy is quantitatively expressed as units of heat which in this case is the kilocalorie. It is the amount of heat required to raise the temperature of a litre of water by 1° Centigrade at a range around 15° to 16° Centigrade. However, recent convention, has been agreed to have the joule as the unit of energy and to convert 1 Kcal ≡ 4·19 K joules (or 1 kilocalorie is equal to 4184 or 4188·5 or 4186·8 joules).

The quantity of food will be proportional to the total energy requirement of the individual. The total energy requirement can be calculated from the following data:

(*a*) **B.M.R.** B.M.R. can be determined from the surface area (*vide* B.M.R.). On the whole, an average adult male has a surface area of 1·8 sq. metres and a B.M.R. of about 72 C per hour or 40 C per sq. metre of body surface.

(*b*) **Nature of work done** by the individual—Work involves expenditure of energy, over and above the basal metabolic rate. The following is a rough estimate: (*i*) *Sedentary work*—without any muscular effort (such as the brain workers)—20–25% (about 400 C). (*ii*) *Light work*—30–40% (700 C). (*iii*) *Moderate exercise*—50–60% (1,000 C). (*iv*) *Heavy work*—100% or more (2,000 C). The total energy requirement will be B.M.R. *plus* these figures.

(*c*) **Allowance for growth.** Infants, growing children, pregnant women, lactating mothers, athletes and convalescent patients require at

least 50% more food over and above their actual B.M.R. This additional amount is necessary to provide for active growth.

(*d*) **During waking hours** ingestion of food stimulates metabolism by 5–10%.

The basal calorie requirement of an individual is 40 calorie per sq. metre per hour. Thus in an average adult male, having a surface area of 1·8 sq. metre, the total energy requirement during 24-hour period may be obtained by calculating as follows:

8 hours' sleep = $(40 \times 1{\cdot}8) \times 8 = 576$ C.

8 hours' awake = basal + 30% (i.e., 10% for stimulating action of food + 20% for minor activities, etc.) = 576 C + 174 C = 750 C.

8 hours' moderate work = basal (576 C) + 1,000 C = 1,576 C.

Total = (576 + 750 + 1,576) C = 2,902 C (roughly about 3,000C). To provide for the 10% loss in cooking and faulty absorption, the purchased value of the food should have 300 calories more, i.e., total 3,300 C.

The average calorific requirement of a man doing light work is 3,000 C net or 3,300 C as purchased. The average housewife needs about 10% less (i.e., 2,700 C net), a lady doing more active work has the same requirement as the average male. Men doing hard work should receive up to 4,000 C. The requirements of the children are suggested to be as follows:

Age in years	1–2	2–3	3–6	6–8	8–10	10–12	12–14
Calories	1,000	1,250	1,550	1,850	2,150	2,550	2,900

It is to be noted that children of 12 and over require as much food as an adult. Girls between 14 and 18 should have 2,800–3,000 C. For boys of the same age—3,000–3,400 C. [A little over the requirements of an adult light worker.]

According to Lusk the following are the energy requirements for different age groups in the young people. [1·0 represents 3,000 C or 1 adult unit (called **Man value**)] Age 0–6 = 0·5 (i.e., 1,500 C). Age 6–10 = 0·7 (i.e., 2,100 C). Age 10–14 = 0·83 (i.e., 2,500 C). Boys 14–20 = 1 (i.e., 3,000 C). Girls 14–20 = 0·83 (i.e., 2,500 C).

Distribution of calories in the diet. (*a*) The **protein requirement** must be carefully maintained. A minimal amount of protein is indispensable in the diet to provide for the replacement of tissue proteins which undergo wear and tear. If the protein content of diet is in excess, the remainder is utilised to produce energy. The requirement of protein is not only quantitative, but also qualitative, since metabolic aspect of protein is intimately connected with its amino acid composition. The essential amino acids must be supplied in the dietary protein which is the basis of the qualitative aspect of protein material. First class proteins contain more essential amino acids than others. For adults the adequate maintenance dose is 1 *gm of protein per Kg of body weight per day. To provide enough margin of safety* 100 *gm per day is advocated. One-half of it must be given in the form of 'first class' proteins* or proteins of 'high biological value'. For infants and growing children 3–4 grams of proteins per Kg of body weight per day; for school boys and girls, pregnancy, lactation, etc., 2–3 gm per Kg of body weight per day.

To provide for the specific dynamic action of proteins on the average the S.D.A. is approximately 5–10% of B.M.R. This is to be provided for by adding proportional amount of carbohydrates and fats.

(*b*) **Fat requirement.** Fat produces high energy and serves as a vehicle for the fat-soluble vitamins A, D, E and K. It also contains essential fatty acids, i.e., linoleic, linolenic and arachidonic acids. Out of the total energy requirement 20–30% should come from fats of the diet. The daily intake of fat should be between 50–100 gm per day.

(*c*) **Carbohydrate requirement.** There should be sufficient carbohydrate in the diet to prevent ketosis. Out of the total energy requirement 60–70% should come from carbohydrates.

(*d*) **Loss during digestion, absorption and cooking.** The full calorific value of the purchased food is not physiologically available. During preparation and cooking about 5% of the energy of the food is lost. Another 5% loss takes place due to incomplete absorption of food. The total loss is 10%. So that, to obtain 1,000 C, the diet should be equivalent to 1,100 C approximately as purchased from the market.

The proportion of fat, protein and carbohydrate. A correct proportion of these three constituents is essential to avoid ketosis (*vide* page 560).

This can be done in two ways: (1) The first method is that of the ratio between protein, fat and carbohydrate should be approximately 1 : 1 : 4, i.e., if 100 gm of protein be given, fat should also be 100 gm and carbohydrate 400 gm. But considerable variations, specially of carbohydrates, may be done without any harm. In India fat consumption is much less. (2) The second method is that of the total energy requirement, 10–15% *should come from proteins*, 20–30% *from fats and* 60–70% *from carbohydrates.* This principle has got more in favour than the other one. In this way the three constituents should be distributed.

Mineral requirement. All salts are adequately supplied in normal diet. In lactating and expectant mothers as well as in infants additional amounts of iron, phosphorus and calcium should be given. In people who undergo a lot of sweating extra quantity of salts should be given.

Choice of foodstuff. The articles of food should be selected keeping in view the following facts: (*a*) *Digestibility*—Certain articles cannot be digested by human beings. For instance, elastin and cellulose. Hence, they should not be taken into account for calculating the calorific value of that particular food, but the presence of cellulose in the diet to be considered as they give bulk and provide adequate roughage for prevention of constipation. (*b*) *Age*—An infant before six months does not develop starch-splitting enzymes specially the pancreatic amylase. Hence, starch should be given in moderation before this age. (*c*) *Habit*—Articles should be selected in such a way that the subject is generally accustomed to it. Unaccustomed diet cannot be easily digested. (*d*) *Religious and Social factors*—Certain classes of people and certain religions have certain restrictions on animal proteins. (*e*) *Cost*—It is needless to emphasise that the articles should be selected in such a way that the subject can easily afford to buy.

Value of cooking. Cooking has certain advantages as well as certain disadvantages. The *advantages* are that (*a*) the food is sterilised, (*b*) the food is partly digested (as a result of hydrolysis) and (*c*) it is made palatable (which stimulates gastric secretion and thereby digestion). Addition of spices and condiments also serve this purpose. The *disadvantages* are—(*a*) some quantity of vitamin is lost, (*b*) a small part of energy of the food (about 5%) is lost. Hence, to avoid this loss of vitamin by cooking, certain amount of uncooked fresh food should be taken (fruits, green vegetables and milk).

From the above principles, the diet of any individual, viz., adult male or female, lactating or expectant mother, children, infants, etc., may be calculated. It should be specially remembered that *in infants before six months*

age, starch should be given in moderation and milk should be the chief diet, with added amounts of minerals and vitamins. As a matter of fact it is not definitely known how much food is just adequate for infants and children. A little excess over the calculated value is always desirable. The following few actual examples may be helpful:

I. **A man weighing 70 Kilograms** and with an energy requirement of 3,000 C should have the following diet: Protein—70 gm (or to provide for a margin of safety—100 gm). This will yield $100 \times 4{\cdot}1 = 410$ C. Fats —same amount as proteins, i.e., 100 gm. This will yield $100 \times 9{\cdot}3 = 930$ C. Total of these two is 1,340 C. The remaining, i.e., $3{,}000 - 1{,}340 = 1{,}660$ C should come from $1{,}660/4 = 415$ gm of carbohydrates. Thus he will have 100 gm of proteins, 100 gm of fats and 415 gm of carbohydrates. However for practical purposes, it is usually presumed that 1 gm of carbohydrate yields 4 C, 1 gm of protein 4 C and 1 gm of fat 9 C, and necessary adjustments are made in the calculation of calorific requirement in the diet.

II. **A man in nitrogen equilibrium** excrets 12 gm of nitrogen per day. His total calorific requirement is 3,000 C. His diet chart should be as follows: Protein requirement $= 12 \times 6{\cdot}25 = 75$ gm. This is his actual protein requirement. This will yield $75 \times 4{\cdot}1 =$ about 308 C. Fats approximately same quantity, i.e., 75 gm. This will yield $75 \times 9{\cdot}3 =$ about 698 C. These two make up 1,006 C. The remaining $3{,}000 - 1{,}006 = 1{,}994$ C should be supplied by $1{,}994/4 =$ about 500 gm of carbohydrates.

It has been observed that an average adult can maintain his nitrogen equilibrium by taking as low as 35–45 gms of protein daily. In economically backward countries the total Calorie obtained from a combination of protein and fat is usually as low as 15–25 per cent.

III. **Diet of school student.** For school student (age 10–15) the calorific requirement is same as that of an adult. The protein requirement is high and is about 2·5 gm per Kilogram of body weight per day. Rest of the calculations should be done in the above method.

IV. **Diet of an infant.** *For infants before six months*, the total calorific supply should be aimed at between 700–1,000 C. [May be approximately calculated from the above mentioned principles.] *It should receive small amounts of polysaccharide.* Whole of his diet should preferably be given in the form of milk till the fourth month, and after that it can be supplemented with some form of semi-solid food. The amount of milk can be calculated from the percentage composition of cow's milk, from which its calorific value per ounce can be known. The protein requirement should not be less than 4 gm per Kilogram of body weight per day. It is to be noted that the fat content of this milk diet is in large excess than the accepted standard for adults. This is very helpful in infants whose B.M.R. is very high. Because, it supplies enough energy in comparatively small volume.

V. **Diet for the aged.** The calorific requirement should be reduced as the age advances according to the following:

3·0%	reduction	between 30 and 50	years
7·5%	,,	,, 50 and 70	,,
10·0%	,,	,, 70 and 80	,,

VI. **Diet for pregnant or lactating mothers.** Additional allowance over the normal requirements: During pregnancy 500 extra Calorie and 20 gm extra protein, during lactation 1,000 C and 40 gm protein.

Extra amount of iron, calcium and different vitamins should also be provided.

VII. **Lactovegetarian diet.** Protein should be given from milk and pulses. Other same as above.

PERCENTAGE COMPOSITION OF THE ORDINARY ARTICLES OF DIET

For prescribing diet charts where actual articles of food have to be mentioned, the following facts are helpful. According to some nutritionists there are in all seven basic food groups: (1) bread and cereals, (2) dairy foods, (3) meats, fish, eggs, (4) butter, oils, (5) green-leafy and yellow vegetables, (6) citrus fruits, (7) potatoes and other vegetables, while others suggest four main groups, such as (1) breads and cereals, (2) milk food, (3) meats, fish, eggs, (4) vegetables and fruits. However, whatever the grouping, the diet should be balanced, containing all the items of food in adequate proportions which will supply the required energy in the body as well as maintain proper growth, normal cytoarchitecture and functioning of the body.

For proteins, the following articles should be selected: *fish, meat, milk, eggs* ('first class' proteins or proteins of 'high biological value'), and *pulses* ('second class' proteins or proteins of 'low biological value'). The protein contents of the other varieties of foodstuffs are so low that for practical purposes they can be neglected. The *protein content of fresh fish is roughly* 20% (fats 1·5%); *that of meat is roughly* 25% (fats about 15%); *that of pulses is approximately* 15–20%. *Whole egg contains* 12·8% *protein* (*fat* 11·3%) *and yolk only has* 15·5% (*fat* 33·3%) *of it. Rice and wheat contains* 7–8% *and* 10–11% *protein respectively on the average.* Although rice contains less protein than that of pulses, its biological value is higher.

For fats—*vegetable vils, ghee, butter* (all of which are pure fat) and *milk* (fat approximately 4%) should be selected.

For carbohydrates—*cereals* (*mainly rice and wheat*) *and root vegetables* (e.g., *potatoes*) contribute the major portion of dietary carbohydrate. All these contain approximately 70–80% carbohydrates (and 6–10% proteins).

Qualitative and quantitative composition of diet with approximate calorific value

Qualitative composition of diet	*Corresponding quantitative values*	*Corresponding calorific value*
Protein ..	70 gm	2,500 calories
Fat ..	50 „	
Carbohydrate ..	440 „	
Calcium ..	0·8 „	
Phosphorus ..	1·4 „	
Iron ..	40 mgm	
Vitamin A ..	7,300 i.u.	
Thiamine (vitamin B_1)	1·8 mgm	
Vitamin C ..	200 „	

Balanced diets for Adult Man*

Dietary articles	Sedentary work		Moderate work		Heavy work	
	Vegetarian (gm)	Non-vegetarian (gm)	Vegetarian (gm)	Non-vegetarian (gm)	Vegetarian (gm)	Non-vegetarian (gm)
Cereals	400	400	475	475	650	650
Pulses	70	55	80	65	80	65
Green-leafy vegetables	100	100	125	125	125	125
Other vegetables	75	75	75	75	100	100
Roots and tubers	75	75	100	100	100	100
Fruits	30	30	30	30	30	30
Milk	300	100	300	100	300	100
Fats and oils	40	35	45	40	50	45
Meat and fish	—	30	—	50	—	60
Egg	—	30	—	30	—	30
Sugar and jaggery	30	30	40	40	55	55
Groundnuts	—	—	—	—	50†	50†

Balanced diets for Adult Woman*

Dietary articles	Sedentary work		Moderate work		Heavy work		Additional allowance during	
	Vegetarian (gm)	Non-vegetarian (gm)	Vegetarian (gm)	Non-vegetarian (gm)	Vegetarian (gm)	Non-vegetarian (gm)	Pregnancy‡ (gm)	Lactation (gm)
Cereals	300	300	350	350	475	475	50	100
Pulses	60	45	70	55	70	55	—	10
Green-leafy vegetables	125	125	125	125	125	125	25	25
Other vegetables	75	75	75	75	100	100	—	—
Roots and tubers	50	50	75	75	100	100	—	—
Fruits	30	30	30	30	30	30	—	—
Milk	200	100	200	100	200	100	125	125
Fats and oils	35	30	40	35	50	45	—	15
Meat and fish	—	30	—	30	—	50	—	—
Egg	—	30	—	40	—	30	—	—
Sugar and jaggery	30	30	30	30	40	40	10	20
Groundnuts	—	—	—	—	40**	40**	—	—

* Adapted from Tables on Balanced Diets as given the Report of the Nutrition Expert Group, Indian Council of Medical Research (1968).

† An additional 30 gm of fats and oils can be included in the diet in place of groundnuts.

‡ An additional amount of vitamins and Fe salts to be added.

** An additional 25 gm of fats and oils can be included in the diet in place of groundnuts.

Balanced diets for Children*

Dietary articles	Pre-school Children				School Children			
	1–3 years		4–6 years		7–9 years		10–12 years	
	Vegetarian (gm)	Non-vegetarian (gm)	Vegetarian (gm)	Non-vegetarian (gm)	Vegetarian (gm)	Non-vegetarian (gm)	Vegetarian (gm)	Non-vegetarian (gm)
Cereals	150	150	200	200	250	250	320	320
Pulses	50	40	60	50	70	60	70	60
Green-leafy vegetables	50	50	75	75	75	75	100	100
Other vegetables, Roots and tubers	30	30	50	50	50	50	75	75
Fruits	50	50	50	50	60	60	60	60
Milk	500	200	400	200	500	200	400	200
Fats and oils	20	20	25	25	30	30	35	35
Meat and fish, Egg	—	30	—	30	—	40	—	50
Sugar and jaggery	30	30	40	40	50	50	50	50

Balanced diets for Adolescent Boys and Girls*

Dietary articles	Boys				Girls	
	13–15 years		16–18 years		13–18 years	
	Vegetarian (gm)	Non-vegetarian (gm)	Vegetarian (gm)	Non-vegetarian (gm)	Vegetarian (gm)	Non-vegetarian (gm)
Cereals	430	430	450	450	350	350
Pulses	70	50	70	50	70	50
Green-leafy vegetables	100	100	100	100	150	150
Other vegetables	75	75	75	75	75	75
Roots and tubers	75	75	100	100	75	75
Fruits	30	30	30	30	30	30
Milk	500	200	400	150	400	150
Fats and oils	35	40	45	50	35	40
Meat and fish	—	60	—	70	—	80
Egg	—	30	—	30	—	30
Sugar and jaggery	30	30	40	40	30	30
Groundnuts	—	—	50†	50†	--	—

* Adapted from Tables on Balanced Diets as given the Report of the Nutrition Expert Group, Indian Council of Medical Research (1968).

† An additional 30 gm of fats and oils can be included in the diet in place o groundnuts.

REGULATION OF FOOD INTAKE

A good number of factors operate together as a complex mechanism for regulating food intake (FIG. 501).

Food intake regulation. Since eating is a voluntary act so conscious sensation (*hunger* and *appetite*) indicating whether food is needed or not, is a prerequisite for the regulation of food intake (eating). Hunger is aroused by the physical need of the food whereas appetite is the emotional (psychic) desire to which may or may not be associated with the need of food.

Hunger, i e. desire for taking food, is controlled by a centre in the hypothalamus, i e., lateral hypothalamic area. There is another centre, i e., ventromedial hypothalamic nuclei (FIG. 500) in

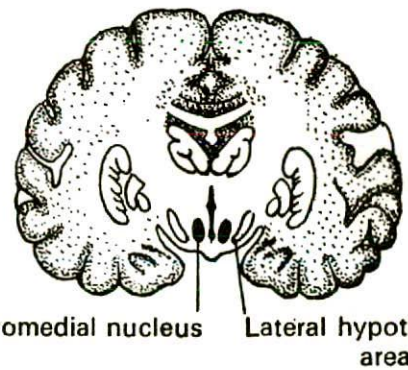


Fig. 500. Showing the anatomical positions of ventromedial nuclei and lateral areas of the hypothalamus in which satiety centre and hunger centre are situated respectively (diagrammatic).

tuber cinerium called *satiety* centre, which inhibit the hunger centre when it is satisfied with the amount of food appropriate to calorific requirement resulting loss of desire for taking food. Reversely when the satiety centre is not satisfied with the amount of food appropriate to calorific requirement, then this centre is not satisfied to inhibit the centre so the hunger centre is not inhibited resulting the desire for food.

Appetite, on the other hand, is conditional and not dependent to calorific need.

The mode of activation of these centres has not been established as yet. Several theories have been put forward suggesting the regulatory activity of the appetite centre or appestat. They are as follows :

1. Concentration of blood glucose. Low glucose concentration stimulates the lateral hypothalamic nucleus producing increased hunger and food intake. When glucose concentration increases after

intake of food, the ventromedial centre of the hypothalamus is satisfied and hunger centre is inhibited Thus the animal stops eating.

2. **Temperature variation of blood.** Low temperature from normal stimulates food intake and *vice versa.*

3. The **proportionate amounts of active fat** in fat cells to passive fat also acts in a regulatory manner.

4. **The concentration of serum amino acids** also regulates the hunger centre.

Other factors also play some part. The hypothalamic hunger centre receives projection from the cortex, so it is under voluntary control. Emotional stress, such as worry, tension, etc. also play a major part (Fig. 501).

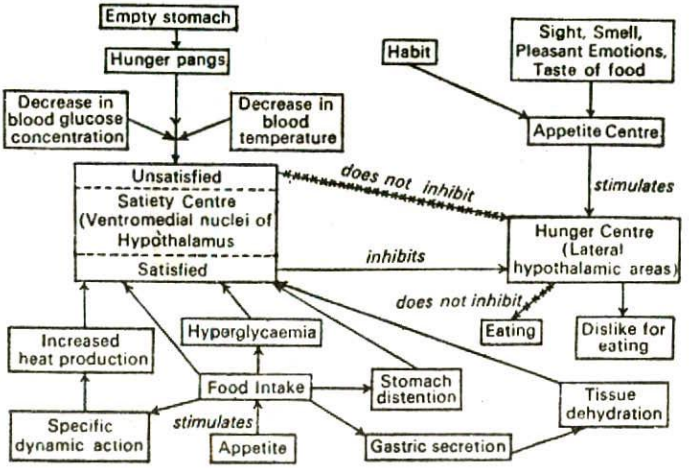


Fig. 501. Schematic representation of factors influencing the hunger and appetite centres present in the hopothalamus.

The satiation achieved by food intake and its regulatory role are partly dependent also on the digestive tract. The feeling of fullness after a heavy meal may depend on the distention of the stomach, which may be brought about by proprioception. Other nervous projections may also play a part.

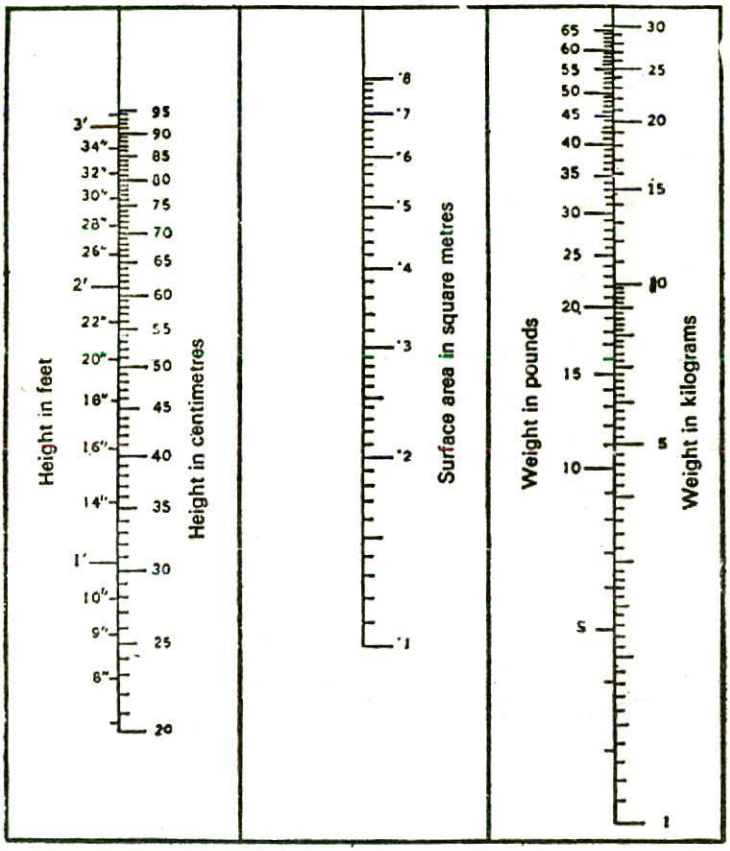


Fig. 503. Nomogram for estimating surface area of infants and young children. To determine the surface area of the indi vidual it can be drawn a straight line between the point representing his height on the left-hand vertical scale to the point representing his weight on the right-hand vertical scale. The point at which this line intersects the middle vertical scale represents the individual's surface area in square metres.

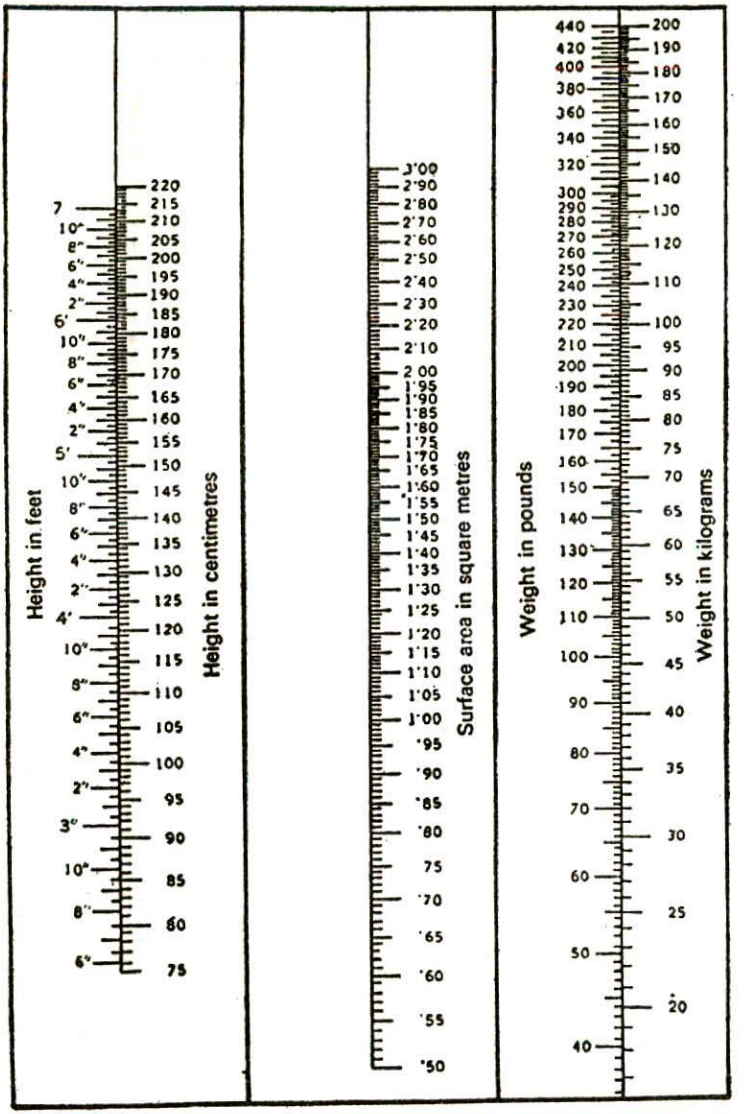


Fig. 504. Nomogram for estimating surface area of older children and adults. The description is same as in Fig. 503.