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ALL THE VITAMINS

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Q.—Please give a list of vitamins with all their different names and with notes on the signs and symptoms of deficiency.

A.—The answer would take more space than can be allowed in "Any Questions?" and at the request of the Editor the following article has been contributed.

The vitamins which so far have been shown to be needed by man, or to be of undoubted clinical significance, are the following: vitamin A, vitamin B₁, three components of the vitamin B₂ complex—namely, nicotinic acid, riboflavin, and folic acid—vitamins C, D, and K, together with several different forms and modifications of most of them.

The significance of some other vitamins for human nutrition is still somewhat uncertain: these include two additional "B₂ vitamins" (biotin—vitamin H—and choline), and also vitamins E, F, and P.

A third group of vitamins comprises those which have so far been demonstrated only by means of animal experiments. These consist of four vitamins of the B₂ group (vitamin B₆—pyridoxin—pantothenic acid, inositol, *p*-aminobenzoic acid). The vitamins will be described in three groups in the above order.

I. Vitamins Needed by Man

Vitamin A

These include vitamin A proper (otherwise called vitamin A₁ or axerophthol) and the principal provitamin, β -carotene. There are several other forms of vitamin A—namely, vitamin A₂, anhydro-vitamin A, subvitamin A—and several other active carotenoids also serve as provitamins in addition to β -carotene—for example, α - and γ -carotene, kryptoxanthine, leprotene, echinenone, myxoxanthine, aphanene, aphanicene—but none of these have any special medical interest. The signs and symptoms of deficiency of vitamin A may include: diminished powers of dark adaptation (this is the earliest and most delicate diagnostic sign), progressing to night blindness; xerosis and keratinization of various membrane tissues, giving rise to a liability to local infections; a keratinized follicular papular eruption in the skin; xerotic changes in the conjunctiva and cornea (best detected by slit-lamp inspection or examination of corneal scrapings for keratinized cells), leading to "Bitot's spots" and to xerophthalmia and, in advanced cases, keratomalacia. In experimental animals other changes observed in deficiency include renal calculi, degenerative changes in the central nervous system, periodontal hyperplasia, overgrowth of bone, failure in reproduction, and of course impaired growth rate. (Among

the first signs of inadequate intake, of this or any other vitamin, is poor growth.) The best sources of vitamin A include halibut-liver and cod-liver oils, mammalian liver, and milk (or fortified margarine); as carotene it occurs abundantly in green leafy vegetables and in carrots; eggs and butter contain both carotene and vitamin A. The League of Nations standard of requirement is 3,000 i.u. (1 i.u.=0.6 microgram of β -carotene), but carotene is only about one-half or one-third as well utilized by the animal body compared with an equal amount of vitamin A.

B Group of Vitamins

This comprises the heat-labile vitamin B₁, and the heat-stable vitamin B₂ complex of vitamins (see below).

Vitamin B₁ (aneurin hydrochloride or thiamin hydrochloride) occurs also in nature as the pyrophosphate ester or co-carboxylase. This is the anti-beriberi or antipolyneuritic vitamin. Beriberi, common in the East among populations subsisting too exclusively on diets of "polished" (white) rice, is characterized by polyneuritis of the peripheral nerves (typical manifestations being the patches of paraesthesia in the lower limbs, diminished knee-jerks, wrist-drop, high-stepping gait), by cardiac irregularities (shortness of breath, dyspnoea, tachycardia, dilatation of the right side of the heart), muscular weakness, anorexia, and sometimes emaciation ("dry beriberi") or oedema ("wet beriberi"). The disease may follow several different forms depending on whether the polyneuritic, cardiac, or oedematous symptoms predominate.

Conditioned deficiency of vitamin B₁ (secondary polyneuritis), as distinct from the endemic deficiency seen in the Orient, occurs from time to time in Western countries—as in polyneuritis arising from gastro-intestinal obstruction (which causes faulty absorption of the vitamin), in alcoholic polyneuritis, and in the polyneuritis of pregnancy. In infants and children suboptimal intake of vitamin B₁ has been thought to lead to inadequate growth and gastro-intestinal hypotonia.

The national wheatmeal loaf (about 80–85% extraction) has been an important source of vitamin B₁ in Great Britain since the beginning of the second world war, white flour (72% extraction) containing negligible amounts. The best foods for vitamin B₁ include: dried brewers' yeast (c. 1,000–2,000 i.u. per 100 g.), wheat germ, rice germ, barley germ (c. 1,000), oatmeal (c. 300), wholemeal wheat flour, peas, haricot beans, egg yolk (c. 100). The League of Nations standard of requirement for vitamin B₁ is 300 i.u. per day (1 i.u.=3 μ g.=0.000,003 g.).

Vitamin B₂ when first recognized was thought to be a single factor, and defined as the "heat-stable, water-soluble fraction present in extracts of yeast which prevents pellagra in man, black-tongue in dogs, and a so-called pellagra-like dermatitis in rats and is needed also for promotion of health and growth in rats." As so defined, vitamin B₂ is in reality a complex of at least nine vitamins (including nicotinamide, riboflavin, pyridoxin, pantothenic acid, *p*-aminobenzoic acid, inositol, choline, biotin, and folic acid). The term is sometimes used, but less accurately, as synonymous with riboflavin.

B₂ Vitamins Needed By Man

(a) *Nicotinamide* (otherwise called nicotinic amide, or niacin amide, or "P-P," or pellagra-preventing, vitamin). The parent substance, nicotinic acid (or niacin), is likewise active, being doubtless converted to the amide in the animal body. In the combined form, in living tissues, nicotinamide occurs as a component of certain enzyme systems—namely, as the two "pyridine coenzymes" (1) codehydrogenase I, or "Euler's cozymase," diphosphopyridine nucleotide, and (2) codehydrogenase II, or "Warburg's enzyme," triphosphopyridine nucleotide.

The signs and symptoms of pellagra in man may be summarized under four headings: (1) The characteristic glossitis and stomatitis, including the "beefy tongue." (2) There develops a persistent diarrhoea. (3) Most typical are the skin lesions. These begin as an erythema resembling sunburn, and progress into a deeper dermatitis, followed by a pigmentation and a great thickening of the dermis. The pathognomonic feature of these eruptions is that they are bilaterally symmetrical, possess a well-defined pigmented border, and occur especially on the parts of the body exposed to the sun or to friction, including the back of the hands and wrists, the face, the upper part of the chest, and the perineal region. (4) Mental symptoms develop as the disease progresses, and in the absence of treatment insanity results.

"Secondary pellagra," or "conditioned deficiency" of nicotinamide, with symptoms similar to the above, is caused by faulty absorption or assimilation of the vitamin, as, for example, in the pellagra of chronic alcoholism or in gastro-intestinal obstruction.

The daily requirement of nicotinamide (preventive) is probably about 10–12 mg. The best sources in food include yeast and liver (or yeast and liver extracts), fish (e.g., canned salmon), meat, pulses, whole wheatmeal or bran, but there is practically none in white flour.

(b) *Riboflavin* was formerly called lactoflavin (or oboflavin, or hepatoflavin, etc., according to its origin) and is still sometimes known as B₂: (More strictly speaking, this term was correctly used when riboflavin was the only known "B₂" vitamin, before it was found to be a complex.) In living tissues riboflavin occurs in the combined form as a coenzyme—namely, iso-alloxazine-adenine-dinucleotide, a component of the enzyme systems known as flavoproteins.

Riboflavin deficiency in man causes a typical "cheilosis" (lesions of the lips) and an angular stomatitis characterized by cracks, scaliness, and maceration at the corners of the mouth, developing into a deep fissuring. Corneal changes, opacity, and vascularization have also been described; but probably both oral and ocular symptoms lack full specificity. In experimental animals the deficiency is likewise marked by corneal lesions and dermatitis, as well as by growth failure. In addition, in birds, deficiency results in a condition described as "curled toe," and is of much practical importance in poultry husbandry. In dogs a condition described as "yellow liver" has been produced.

The daily requirement (preventive) is probably about 1–2 mg. Foods rich in riboflavin include yeast, liver, kidney, milk, and egg-white.

(c) *Folic acid* is probably identical with or closely related to factors known severally as the grass juice factor (for guinea-pigs), vitamin B₁₂ (anti-anaemia factor for chicks), vitamin M (for monkeys), and the growth factors for the micro-organism *Lactobacillus casei* and for *Streptococcus lactis R*. In chemical structure it is built from glutamic acid, *p*-aminobenzoic acid, and pterin residues; and certain other pterin derivatives may also be active. Folic acid has been shown to produce a haematopoietic response in Addisonian pernicious anaemia and in some other macrocytic anaemias in man; it is, however, apparently ineffective in controlling cord degeneration in pernicious anaemia. Remarkable success is said to have followed its use in treatment of sprue. A possible anticarcinogenic action is being examined experimentally in animals.

Vitamin C

Vitamin C, or *L*-ascorbic acid (formerly known also in the U.S.A. as cevitamic acid), is the anti-scurvy (antiscorbutic) vitamin. The closely related, and somewhat unstable, reversibly oxidized derivative, dehydroascorbic acid, is also active, and several artificially prepared chemical analogues show some varying degree of activity. Characteristic symptoms of scurvy in the adult are the haemorrhagic manifestations, particularly the spongy gums and the petechiae in the trunk or limbs. Among the early signs may be a follicular hyperkeratosis. In advanced cases there is a pronounced secondary anaemia. Bronchitis and other infections often occur as a complication. The associated symptoms may include sallowness, lassitude and mental depression, pains in the lower limbs, and hardening of the calf muscle due to haemorrhage. In infantile scurvy the diagnostic features include: (1) a tenderness in the lower limb as a result of which the child adopts a characteristic attitude, dreading to be touched; (2) subperiosteal haemorrhage with swelling, e.g., near the lower end of the femur; and (3) the radiological appearance of the long bones, showing a cessation of osteogenesis; the oral lesions may be absent. In scurvy there is an extreme degree of depletion of ascorbic acid from the tissues, as shown by the number of test doses needed before an overflow of the excess into the urine, where it can be estimated by chemical test.

The League of Nations standard requirement is 30 mg. per day. The best sources of the vitamin include, among fresh fruits (in decreasing order): blackcurrants, strawberries, oranges, lemons, grapefruit, gooseberries; there is relatively little in pears, plums, grapes, or some varieties of apples. The richest vegetables include (also in decreasing order): Brussels sprouts, cauliflower, cabbage, and new potatoes. During the cooking of vegetables the loss of vitamin C can be minimized by avoidance of such conditions as the use of excessive amounts of cooking water, an undue prolongation of the time of heating, too much shredding of the vegetable before cooking, and overmuch keeping hot or re-cooking before serving.

Vitamin D

Vitamin D is the antirachitic vitamin. The two most important forms are: (1) vitamin D₂, or calciferol, prepared artificially by ultra-violet irradiation of ergosterol and present also in certain irradiated plant materials; and (2) vitamin D₃ or irradiated 7-dehydrocholesterol (cholestadien-3-ol), present naturally in fish-liver oils, including halibut, tunny, and cod. Other D vitamins, of little more than academic interest, are the following: irradiated heated

cholesterol; cholesterolene sulphonate; irradiated 22-dihydroergosterol; irradiated 7-dehydrositosterol. Rickets (vitamin D deficiency) is characterized particularly by deficient calcification of the bones, especially in the newly forming bone at the epiphysis, where the zone of provisional calcification is increased in breadth and inadequately mineralized. The consequent irregular growth of soft osteoid tissue causes the typical swellings at the epiphyseal junctions ("rachitic metaphysis"). The bending of the inadequately calcified bones and the overgrowth of osteoid tissue in turn give rise to the well-recognized deformities bow-legs, knock-knees, rachitic pelvis, "green-stick" fractures, the enlargement of the ends of the bones, and the beading of the ribs. Active rickets is characterized by a deficiency level of inorganic phosphate in the blood and sometimes of calcium, causing spasmodophilia (tetany), and by an increase in blood phosphatase. The fundamental chemical lesion in vitamin D deficiency is excessive loss of phosphate and/or calcium in the faeces, with a concurrent drop in their levels in the blood and consequent inadequate calcification of bony tissues. Severe rickets is of course readily detected by the clinical signs, but mild cases of rickets may need x-ray diagnosis.

Legitimate "pharmacological" uses of vitamin D—i.e., in the absence of rachitic signs—are: (1) to maintain the level of the blood calcium after parathyroidectomy, and (2) in the treatment of lupus vulgaris by massive local injection. Vitamin D occurs in fish-liver oil (halibut, cod, tunny, etc.) and in smaller quantity in egg yolk and in vitaminized margarine and butter. The international unit is 0.02 μ g. of calciferol, the protective dose in early childhood about 500 to 1,500 i.u. per day, and an effective curative dose 1,500 to 3,000 i.u. per day; larger doses may be toxic. For nursing and expectant mothers 1,000–2,000 i.u. daily may be prescribed in order to improve the assimilation of calcium and phosphate and to make good the losses of these elements to the foetus and in the milk.

Vitamin K

Vitamin K includes vitamin K₁ (2-methyl-3-phytyl-1,4-naphthoquinone) and vitamin K₂ (2-methyl-3-difarnesyl-1,4-naphthoquinone). Active homologues include various other 2-methyl-1,4-naphthoquinone derivatives—for example, phthiocol (2-methyl-3-hydroxy-1,4-naphthoquinone) and the parent substance itself, 2-methyl-1,4-naphthoquinone. The last-mentioned, because of its solubility and ease of absorption, is the form of vitamin K most favoured in medicine. In experimental chicks and other species, deficiency of vitamin K causes a lowering of the prothrombin value of the blood, and this results in a haemorrhagic syndrome. In clinical practice vitamin K has been of great service in controlling those haemorrhagic conditions that are due specifically to hypoprothrombinaemia—namely, (a) in haemorrhagic disease in the newborn, associated with a transient hypoprothrombinaemia; (b) after surgical treatment of obstructive jaundice; and (c) in the hypoprothrombinaemia associated with steatorrhoea, sprue, and intestinal obstruction. It is believed that in (a) the transient hypoprothrombinaemia can be attributed to the fact that symbiotic microflora, which normally synthesize vitamin K, have not yet become established in the intestine of the infant through the ingestion of food. In (b) and (c) a faulty absorption of vitamin K is considered to be responsible for the deficiency. In treatment, 1 to 4 mg. of 2-methyl-1,4-naphthoquinone daily is commonly used, given either by injection or by mouth. In the prophylaxis of hypoprothrombinaemia in the newborn the vitamin may be administered as a prenatal routine to the mother, or to the child at birth.

II. Vitamins of Probable or Possible Significance for Humans

Biotin, a growth factor for yeast and other micro-organisms, is identical with the so-called vitamin H (= *Haut* [skin] *Faktor*, or anti-eggwhite injury factor for rats and other animals) and with coenzyme R (growth factor for micro-organisms in the nodule of legumes). It protects rats and other experimental animals from seborrhoeic skin lesions and other abnormalities when they are fed on a special diet containing raw egg-white as an ingredient. The latter contains a protein-like substance or antivitamin, "avidin," which inactivates the vitamin and is destroyed by cooking. Clinical relations are still obscure, although biotin deficiency has been produced experimentally in the human subject by means of a diet of raw egg-white, and there is at least one record of a primary deficiency having been described.

Choline functions in chemical physiology as a trans-methylating agent, and as such is replaceable by the amino-acid methionine, or by betaine. In experimental animals choline deficiency results in a fault in fat transport and consequently in fatty liver (sometimes accompanied by necrosis), as well as by haemorrhages in the kidney, paralysis, and other ill effects. Possible clinical applications still remain to be defined, although its use has been proposed to control a negative nitrogen balance in conditions similar to those in which methionine or a high-protein diet has been found effective.

Vitamin E includes α -tocopherol (5,7,8-trimethyl-tocol), β -tocopherol (5,8-dimethyl-tocol), γ -tocopherol (7,8-dimethyl-tocol), and several related synthetic derivatives. In rats or other experimental animals deficiency of vitamin E causes: (1) reproductive failure, due in the female to resorption of the foetuses during gestation, and in the male to degeneration of the germ cell; (2) muscular dystrophy; (3) degeneration of muscle fibres, leading to discoloration of the uterus and other tissues; (4) degeneration of the epithelium of the convoluted tubules of the kidney; (5) an "exudative diathesis"; and (6) dental depigmentation. Many claims have been made for the successful use of vitamin E in treatment of habitual abortion in women, but adequately controlled experiments still seem to be lacking. The supposed effectiveness of vitamin E in treatment of muscular dystrophies lacks confirmation. The richest sources of vitamin E include wheat-germ and rice-germ oils, cotton-seed oil, and green leaves. In contrast with vitamins A and D it is absent from cod-liver oil and other fish-liver oils.

"*Vitamin F*" is a synonym for the nutritionally essential unsaturated fatty acids—namely, linoleic acid, linolenic acid, and arachidonic acid. Symptoms of deficiency in rats include a scaliness of the tail sometimes leading to caudal necrosis, irregularities in reproduction, and kidney lesions. Deficiency of "vitamin F" has not been recognized to occur in the human, but claims have been made for its use in eczematous conditions.

Vitamin P, a group of substances including citrin (hesperidin glucoside), is claimed to be concerned in controlling fragility of capillary blood vessels, and to be needed as an adjunct to vitamin C in the cure of some symptoms associated with scurvy: this, however, is disputed.

III. Vitamins Needed by Experimental Animals : Significance for Humans Uncertain

Pyridoxin (adermin, vitamin B₆) prevents a deficiency disease in rats characterized by a florid symmetrical dermatitis of the extremities. Another sign in rats, as also in pigs, may be the occurrence of fits. Pyridoxin is thought

to be concerned in the synthesis of fats from protein, and perhaps in tryptophan metabolism. Biologically active derivatives also include pyridoxal (concerned in tyrosine decarboxylation and possibly in biochemical transaminations) and pyridoxamine. Another derivative, pyridoxic acid, is described as a dietary factor for chicks. The need of man for pyridoxin has been questioned: symptoms of deficiency are, however, said to include cheilosis resembling that seen in deficiency of riboflavin. Pyridoxin has recently been used in the treatment of agranulocytosis.

Pantothenic acid (formerly called "chicken pellagra factor" or "filtrate factor") prevents a characteristic dermatitis in birds. It is needed also by dogs and pigs. Signs of deficiency in rats include growth failure, dermatitis, nose-bleeding, depilation about the nose, occurrence of a sticky exudate in the eyelids, and achromotrichia, together with adrenal lesions. It is also a growth factor for micro-organisms. Pantothenic acid is thought to be probably needed by humans, but its significance is still obscure.

Inositol is identical with bios I, needed for growth of yeast and other micro-organisms. An experimental deficiency in rats or mice is said to cause alopecia. Deficiency in man is unknown, but inositol may possibly be a "secondary nutrient"—that is, it may stimulate the intestinal microflora to synthesize other nutrients essential to the host.

Para-aminobenzoic acid (or "Paba") is a growth factor for various micro-organisms, and is said to prevent achromotrichia in some experimental species. It may be a "secondary nutrient" (see above) for man. Its special interest is that drugs of the sulphonamide type exert their bacteriostatic action by "blocking" the bacterium's supply of Paba. Conversely, Paba can negative the bacteriostatic action of the sulpha-drugs. Recent work suggests that large doses of Paba itself may exert an anti-infective action in animals in some circumstances.

"Q" FEVER

A SEROLOGICAL INVESTIGATION OF A GROUP OF CASES PREVIOUSLY REPORTED AS PRIMARY ATYPICAL PNEUMONIA

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Derrick (1937) first described "Q" fever in Australia, and the causative agent was isolated by injection of the blood and urine into guinea-pigs. Burnet and Freeman (1937) showed that the infective agent was a rickettsia, which was subsequently named *Rickettsia burneti*. In the winter of 1944 an epidemic of so-called primary atypical pneumonia occurred among New Zealand troops in the Cassino area (Adams and Porteous, personal communication). Later in 1944 Turner (1945) recorded a similar epidemic of 280 cases from the Naples area. During the same year an outbreak of primary atypical pneumonia occurred among German troops in Greece, and was referred to by them as the "Balkan gripe." Dr. Caminopetros, at the Pasteur Institute in Greece, was able to establish the infection in guinea-pigs by injection of blood taken from cases in the early stages of the infection. Subsequently, blood taken from these guinea-pigs was investigated at the laboratories of the Commission on Acute Respiratory Diseases at Fort

Bragg, North Carolina (1946), and *R. burneti* was isolated. In the winter of 1945 an epidemic of "atypical pneumonia" occurred among New Zealand and British troops in the Naples and Caserta area. Similar epidemics arose among British and American troops in the Mediterranean theatre of operations. Detailed studies of some of these epidemics have recently been reported by Robbins and Rustigian (1946). In a British parachute regiment, probably infected in Athens before being transferred to Italy, serological tests later established the diagnosis of "Q" fever. Four epidemics among U.S. troops in Northern Italy were fully investigated. *R. burneti* was isolated from the blood of some of these cases, and by serological tests it was demonstrated that 75% of the cases of "atypical pneumonia" in the same area were in fact cases of "Q" fever.

In May, 1945, an epidemic of "atypical pneumonia" occurred in mid-Atlantic amongst a group of airmen who had recently been stationed at Grottaglie Air Base in Southern Italy, in the Taranto area. These were fully investigated when the airmen arrived at Camp Patrick Henry, Virginia (Feinstein *et al.*, 1946). Epidemiological and aetiological studies were made, and it was demonstrated that the infective agent was the "Balkan gripe" strain of *R. burneti* (Commission on Acute Respiratory Diseases, 1946).

Clinically the epidemic of so-called primary atypical pneumonia recorded by Adams *et al.* (1946) was very similar to the cases recorded by Robbins and Rustigian (1946) and by Feinstein *et al.* (1946), in which the aetiological agent was established as *R. burneti*. On this account it was decided to attempt to establish the infective agent in the New Zealand Hospital cases.

Clinical Features

For complete clinical details of the cases readers are referred to the original report of Adams *et al.* (1946). The main clinical features may be summarized for the sake of completeness.

The epidemic occurred between February and April, 1945, and during this period 511 cases were reported in the Naples-Caserta area, 161 of which were treated at the 2nd N.Z. General Hospital. Of these, 50 consecutive cases were studied in detail clinically and by serial pathological and radiological investigations.

In brief, the clinical picture was as follows. In most cases there was a prodromal period of about six days. The actual onset was abrupt in 96%, and severe headache, malaise, lassitude, and anorexia were the most constant symptoms. Pyrexia from the onset averaged 8.6 days, was over 103° F. (39.4° C.) in 70% of cases, and defervescence was by lysis in 86%. The pulse followed the temperature, though it showed a tendency to a relative bradycardia. The respiratory rate was little affected. Cough was present in 94%, but was not an outstanding feature; it occurred about the fifth day. Sputum was scanty and in 28% contained blood. Chest pains occurred in 46% of the cases, and in 26% of these a pleural rub was detected.

Physical Signs.—Severe toxæmia was a feature of some, and one-third showed generalized rhonchi on admission, but the most characteristic sign was a localized patch of sticky persistent crepitations, which were heard on an average on the sixth day from the onset of the acute symptoms. Usually there was enlargement of glands, and the spleen was palpable in 36% of cases. Scanty small pink macules fading on pressure were observed on the chest, back, and flanks in the early stages in 34% of cases.

Laboratory Investigations.—The results of serial pathological investigations can be summarized in brief. The white cell count revealed a slight polymorphonuclear

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