

were three further reports on the condition in South Africa; one by Dr. J. W. Johnson, Assistant Surgeon to the 85th Regiment, saying "Haematuria prevails to some extent among children of the civil community of Natal;" one by Mr. George Saunders, Staff Surgeon, saying "While in Port Elizabeth I was struck with the number of cases of haematuria in young boys and, on enquiry, was informed that the disease was very common in Uitenhage. I have never met with haematuria at Grahamstown, which is 95 miles from Port Elizabeth, nor at Fort Beaufort or Alice, 50 miles up country;" and Mr. Robert Speedy, of the 45th Regiment, added further to this account that "Haematuria is not prevalent either at East London or Kingwilliamstown."

In 1870, Cobbold experimented with ova obtained from South African patients suffering from haematuria. His object was to establish the life cycle of the parasite. Although he was not successful in his efforts, the credit for being the first to attempt this goes to him.

Some observations as to the mode of entry of the parasite were contributed in 1888, by Allen, Medical Officer of the Corporation of Pietermaritzburg. Writing in the *Practitioner* of that year he said, "The parasite is practically confined to those who bathe, some streams being more dangerous than others," and in this view he was supported by most authorities.

As early as 1893, Sir Patrick Manson suggested that there may be two forms of eggs, one with a terminal spine and the other with a lateral spine, the former only having been obtained from South Africa, while both forms were found in Egypt. The problem was finally solved in 1902, when he found only lateral spined eggs in a West Indian patient. To this form, Sambon gave the name of *Schistosoma mansoni*.

The second great advance in the Bilharzia question took place in 1915, when Leiper, as a result of brilliant researches, worked out the life cycle of the parasite and isolated the intermediate hosts in Egypt. Soon afterwards, Dr. J. G. Becker collected specimens of snail from a bathing pool in Nylstroom which was known to be infected. He was able to identify Bilharzial cercariae and to reproduce from these the life cycle of the worm in a guinea pig. The mollusc found infected were of the species *Physopsis africana*. In the same year,

Dr. Cawston reported the finding of cercariae in numerous other molluscs, including *Planorbis pfeifferi* and *Limnaea natalensis*, recovered from the Tollgate brickfield in Durban, and the Umzinduzi River, Pietermaritzburg.

In 1920, Dr. Annie Porter incriminated *Limnaea natalensis* as harbouring *Schistosoma haematobium* and soon afterwards reported the presence of *S. mansoni* in 2 out of 1,050 specimens of *Physopsis africana*, and in a specimen of *Planorbis pfeifferi* obtained from pools in Mayville, Natal. In the following year, Cawston reported finding the ova of *Schistosoma bovis* in the urine of a man who was also passing ova of *S. haematobium*. In the same year, too, he reported the finding of ova of *S. mansoni* in the dejecta of a boy bathing in pools at Sydenham, Natal. In 1926, the finding of *S. spindalis* was reported in South Africa.

At this time was established the first treatment camp in Zeerust. Following the principle of mass treatment, as applied by the mobile hospital units in Egypt, infected school children were collected into holiday camps, and were there treated for the Bilharzia. The value of these camps lay, not so much in the curative results among the children, but as propaganda for enlightenment of the population as to the dangers of Bilharzia, its treatment and prevention. Since then, numerous other camps have been held in the Transvaal, warning notices against bathing in infected pools are being erected near likely bathing spots, the public is being educated against the danger by means of lectures and pamphlets and there are hopeful signs of awakening interest in the subject which bids fair for the future health of the nation.

THE NEWER KNOWLEDGE OF THE VITAMINS.

L. F. LEVY.

The story of the discovery of the vitamins, of how infinitely minute quantities of substances in our food are necessary to health besides the commonly regarded constituents of the diet—proteins, carbohydrates, fats and mineral salts—is one of the most fascinating in the history of biochemistry. Research in this field is now-a-days so intensive and the literature so vast that it is becoming

increasingly difficult to keep up-to-date. In the following brief summary it is intended to indicate the extent of the progress achieved. Before 1928, the vitamins were thought to be somewhat mystical in character, but they are now recognized as definite chemical entities. Whereas only three factors were known in 1918 (the fat-soluble vitamin A, the water-soluble vitamin B and the antiscorbutic vitamin C), at least thirteen are now established, and of these, four have been artificially prepared, three from simple chemicals, and one from a well-known naturally occurring sterol, and two others isolated in very highly purified form. The Vitamin B Complex has been subdivided into six factors. As a result of obtaining the vitamins in pure condition, their specificity of action has been considerably narrowed down.

Vitamin A—

The belief that the only source of the anti-xerophthalmic and growth promoting vitamin was fish liver oils and fats has been dispelled by the discovery that green vegetables are highly active. From spinach and carrots has been extracted a deeply coloured crystalline substance, carotene, which readily cured rats suffering from vitamin A deficiency, and on examining the livers of the treated animals, a considerable storage of vitamin A was found. This indicated that carotene splits up into vitamin A *in vivo*, a change which could be followed with the spectroscope. Carotene, which is thus a vitamin A precursor, has been found to exist in three isomeric forms, α -, β - and δ - carotenes, the β - isomer being twice as active as the other two. Analysis showed the carotenes to be $C_{40}H_{56}$, and controlled oxidative processes proved β - carotene to possess the structure I. Vitamin A ($C_{20}H_{30}O$; structure II) is formed *in vivo* by fission of the long carotene in the centre. α -carotene differs from β -carotene by the displacement of one double bond, and δ -carotene by the opening of one ring). (Researches of Kuhn and Karrer independently).

The slight activity of maize is due to the presence of cryptoxanthin which produces *in vivo* one molecule of vitamin A.

The vitamin has been obtained in 80 per cent purity by fractional distillation of halibut liver oil, the final stages being affected at pressure below 0.00001 mm.

It has long been known that xerophthalmia is one of the results of vitamin A deficiency

in man and animals, this being a case of avitaminosis, but now states of chronic hypovitaminosis manifesting themselves as disorders of the epidermis are being recognized. A peculiar type of dermatosis has been observed in Uganda (Loewenthal 1933) which makes its appearance in vitamin A-deficiency before xerophthalmia. The first visible signs are dryness of the skin with a papular eruption. This was cured by vitamin A administration in one to nine weeks, while cases of xerophthalmia side by side took much longer. Similar lesions were observed in China as 'keratinized papules at the site of the hair follicles in the limb and trunk,' and in Ceylon (Nicholls, 1933 and 1934) as 'toad skin' and 'sore mouth.'

It has been shown that the vitamin has no effect on the incidence of general infections. The chief evidence for the previously held view of the importance of vitamin A in this respect has been the geographical distribution of diets poor in the vitamin and the correlated distribution of certain diseases, particularly skin diseases. Donaldson and Tasker (1930) tested its anti-defective action on pneumonia with mine natives on the Crown Mines, but the mortality was not significantly decreased. However, there are indications that in vitamin A-deficiency it is possible for *Streptococcus pyocyanus* to become more virulent.

Mellanby (1934) has suggested that vitamin A-deficiency may also be the cause of the degenerative changes in the nerves in beriberi, pellagra, disseminated sclerosis, pernicious anaemia and other diseases.

Vitamin A is only one of the factors for growth promotion, as concerted action of all is necessary.

Vitamin B₁—

By absorbing extracts of foodstuffs rich in the antipolyneuritic vitamin on fuller's earth and then following a long process of purification, Jansen and Donath (using rice polishings) and Windaus and Peters (independently using yeast extracts) have succeeded in isolating a pure crystalline hydrochloride of a base, $C_{12}H_{17}ON_4ClS$. The structure III which was assigned to the vitamin has now been confirmed by complete synthesis (Williams and Kline, August 1936). The activities of the natural and synthetic substances are identical, daily doses of 0.005 mg. curing polyneuritis in rats. The vitamin is now called 'Aneurin.'

By means of this crystalline material,

Peters and Thompson (1934) have shown that the true function of the vitamin in clearing up the acute opisthotonus symptoms (beri-beri) in pigeons may be characterized by its coenzyme action in the oxidation of lactic and pyruvic acids in the central nervous system. It appears that vitamin B₁-deficiency gives rise to an accumulation of these acids, particularly the latter, causing paralysis. On addition of minute amounts of aneurin crystals in vitro to the avitaminous (not normal) brain tissue of a pigeon or a rat, it was found that the diminished tissue respiration was restored. It has also been shown that the low heart rate in rats suffering from this deficiency was correlated with an accumulation of lactic acid. (Birch and Harris, 1934). This finding was used in the quantitative assay of vitamin B₁ in foodstuffs.

Vitamin B₅ has been found to be needed together with aneurin for the maintenance of weight, while vitamin B₃ is also needed to restore the weight to the maximum.

Vitamin B₂ Complex—

Vitamin B₂ has been defined in the past as the more heat-stable, water-soluble dietary factor found necessary for the maintenance of growth and health and prevention of characteristic skin lesions in rats, also being concerned with the prevention of human pellagra. Recently it has been shown that the vitamin is a complex of at least two factors.

(a) *Vitamin B₂—*

Kuhn, György and Wagner-Jauregg (1933) isolated from 5,400 litres of the whey of milk, one gram of a yellow water-soluble dyestuff, having the formula C₁₇H₂₀N₄O₆, which they called Lactoflavin, and this substance was found to promote the growth of rats in doses of 0.0008 mg. per day, giving rise to 40 g. increase in 30 days. The substance could not prevent pellagra, however, and was given the designation vitamin B₂, the pellagra-preventing vitamin being renamed Vitamin B₆. Egg white and liver extract were also found to contain flavin.

Warburg and Christian (1932) discovered a yellow oxidation ferment in yeast, which on irradiation in alkaline solution produced a dyestuff Lumiflavin C₁₃H₁₂N₄O₂ (structure V). exactly the same substance was obtained by Kuhn by similarly treating lactoflavin. This gave a clue to the chemical constitution of the vitamin, and the substance was synthesized

independently by Kuhn and Karrer (structure IV). Kuhn has now shown that not only is synthetic lactoflavin 5'-phosphoric ester physiologically active, but also that the yellow ferment itself is actually a saturated solution of this ester in a colloidal medium. The synthetic ferment was equally as active as the naturally occurring substance in catalyzing the assimilation of oxygen. Thus the newly isolated substance was proved to be a coenzyme-like material intimately connected with the assimilation of free oxygen. Two dyestuffs, therefore, occur in milk with vitamin activity carotene and lactoflavin.

(b) *Vitamin B₆—*

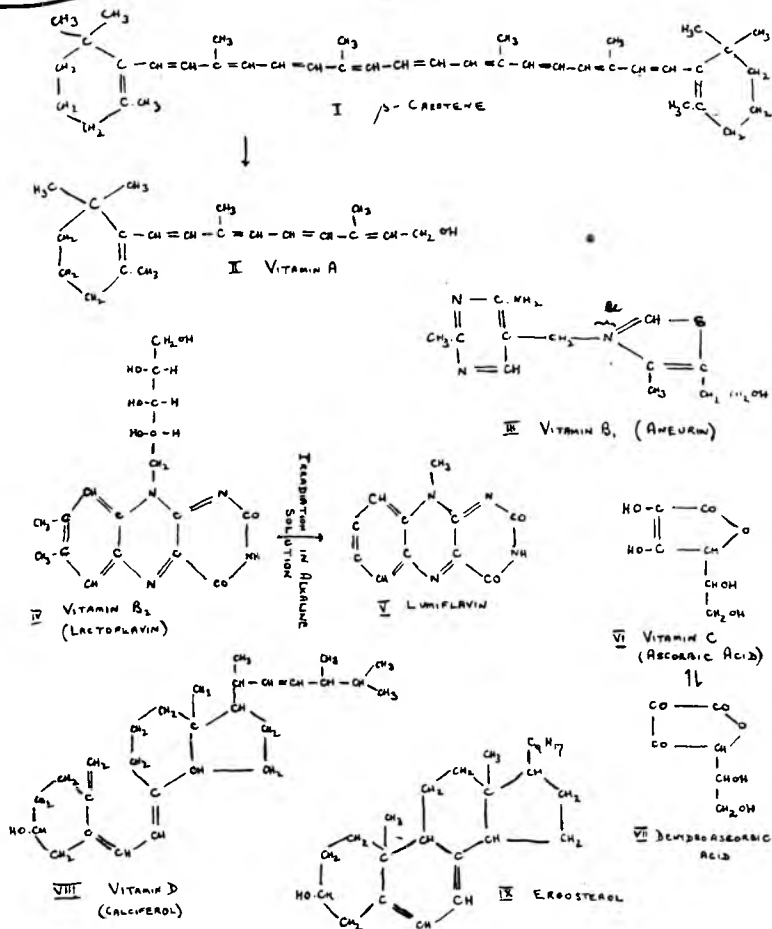
The chemistry of the pellagra-preventing vitamin is still unknown. It is thought by some that there are two types of this disease, one in animals and the other in man, since the skin appearances are somewhat different, and that each type has its own factor. Pellagra is very prevalent in the United States among the negroes, and is generally suspected to be connected with a diet consisting mainly of maize, but this view is incompatible with the comparative rareness of the disease among the Bantu in this country. The cause of such outbreaks might be the 'civilized' idea of milling to produce a meal as white as possible. During this 'purification' process the embryo containing the vitamin besides other very nutritious materials is thrown out as cattle food!

(c) *Anti-anaemia Factors—*

Experimental work on pernicious anaemia at the present time suggests that this condition is intimately associated with one or other of the vitamin B₂ factors.

Firstly, a deficiency in vitamin B₂ in experimental animals may lead to a pathological picture having certain features in common with that seen clinically in pernicious anaemia. Miller and Rhoads (1934) report that dogs exhibit symptoms of glossitis, stomatitis and gastrointestinal disturbance, anaemia being present in 60 per cent of the cases, and there were changes in the bone marrow resembling those of pernicious anaemia or sprue. Other authors confirm this finding.

Secondly, there are clinical analogies to be found between the symptoms seen in pellagra and in pernicious anaemia. For example, many workers have demonstrated the occurrence of achlorhydria in pellagra.



Thirdly, Strauss (1934) found that his anti-anaemia 'extrinsic factor' had a distribution resembling that of the pellagra preventing factor, and, like it, was heat-stable.

Vitamin B₄—

Barnes, O'Brien and Reader (1932) confirmed the finding by one of them of a water-soluble, thermo-stable nutritional factor, distinct from vitamins B₁ and B₂, and named it Vitamin B₄. This substance of which peanuts was an excellent source, prevented the development of paralytic symptoms in chicks similar to those seen in encephalomalacia, a disease which developed in the animal receiving a diet containing adequate amounts of vitamin B₁. The symptoms could also be produced in rats.

Vitamin C—

Waugh and King (1932) isolated from lemon juice a crystalline substance with very high antiscorbutic activity, and this proved to be

identical with the 'hexuronic acid' of Szent-Györgyi (1928) obtained from adrenal glands. Although the substance possessed the very powerful reducing activity of lemon juice, it was some time before this property was actually associated with vitamin C, and the isolated crystals recognized as the vitamin, which has been renamed ascorbic acid. Large quantities of vitamin were isolated by Szent-Györgyi from *Iris germanica* and *Capsicum anuum* (Hungarian red pepper) which enabled the chemist firstly to elucidate the chemical constitution (C₆H₈O₆; structure VI), and then to synthesize the substance. (Laboratories of Haworth and Reichstein). The cost of manufacture is now actually less than the price of oranges containing an equivalent amount of ascorbic acid. It is now on the market for therapeutic use.

By utilizing the reducing action of the substance on indophenol dyestuffs, Birch, Harris and Ray (1933) have introduced a

method whereby the vitamin can be chemically estimated in foodstuffs. The procedure is not perfect, as indophenol reduction is not absolutely specific for the vitamin. However, when carried out under special conditions, the method gives results which are in very good agreement with those obtained biologically with guinea pigs. The distribution of the antiscorbutic vitamin in the foodstuffs of many countries and in the organs and tissues of animals, both healthy and diseased, is now known.

Ascorbic acid, on treatment with indophenol, iodine, controlled hydrogen peroxide, or best of all with norite charcoal, is converted into a reversibly oxidized form, dehydroascorbic acid (VII), which is also antiscorbutically active to the same degree. This oxidation also takes place enzymatically, especially on extracting such foodstuffs as potatoes and cauliflower (having almost neutral reaction) with water. An enzyme has been found in hubbard squash which is specific for vitamin C. The dehydroascorbic acid may be reconverted into ascorbic acid by means of hydrogen sulphide. The reduction of this acid also takes place enzymatically in the human body. Ascorbic acid is found in human urine, a large intake at one time increasing the daily excretion of the vitamin. On ingestion of a large amount of dehydroascorbic acid, however, only ascorbic acid in an increased amount is excreted, which conversion must be due to enzymatic reduction.

This property of being susceptible to reversible oxidation by means of enzymes indicates the part which ascorbic acid plays in the living cell. The vitamin appears to serve as an agent for the transference of hydrogen between unidentified metabolites (it being thereby converted into dehydroascorbic acid) or the transference of free oxygen (ascorbic acid being reformed) by means of two or more oxidase enzyme systems. Most gross effects of severe scurvy may be explained on the basis of this respiratory function and on its action in regulating the colloidal condition of intercellular substances.

Crystalline ascorbic acid has been used in the treatment of scurvy by intravenous injection with excellent results. Numerous papers have appeared dealing with the relationship of vitamin C-deficiency to infection, particularly with regard to diphtheria

and tuberculosis, but it is still too early to state anything definite. Injection of ascorbic acid has been found of great benefit in the healing of stubborn wounds in cases of 'vitamin C-subnutrition.'

Vitamin P—

Szent-Györgyi and Rusznyak (1936) have demonstrated that ascorbic acid is accompanied in the cell by a second factor with related activity, which prevents a vascular type of haemorrhagic purpura. This disease could not be cured by administration of crystalline ascorbic acid, but the desired effect was obtained with extracts of *Capsicum anuum* or lemon juice. On fractionating these extracts a pure flavin or flavinol glucoside, not similar to lactoflavin, was obtained, 40 mg. of which given intravenously to man restored the normal capillary resistance in a fortnight.

Vitamin K—

A deficiency disease in chicks resembling scurvy which cannot be prevented by ascorbic acid, has been ascribed to the lack of a particular fat-soluble anti-haemorrhagic vitamin found in hog liver, hemp seed, certain cereals and vegetables. The disease could not be cured by large amounts of purified vitamins A (carotene), D and E. Other animals are being tested to see if the disease is specific for chicks or not. (Dam and Schnheyder 1936).

Vitamin D—

The finding of Rosenheim and Webster (1927) that ergosterol which occurs along with cholesterol in the body, on irradiation with ultra-violet light was converted into a substance having similar antirachitic activity to vitamin D was a just reward for a long series of researches. Reerink and van Wijk (1931) succeeded in crystallizing irradiated ergosterol which was obtained as fine needles melting at 115-117°. On analysis the substance proved to possess the empirical formula $C_{27}H_{42}O$. Other workers also obtained a crystalline substance on distillation of irradiated ergosterol and called it Calciferol. The chemical constitutions of calciferol and ergosterol have not yet been quite settled, but formulae VIII and IX are very close representations of them.

The surprising observation has been made that not only are calciferol and vitamin D probably not identical, but other very powerful antirachitic substances also exist. In order to produce bone of normal composition in chicks 144 times more vitamin in the form of calciferol

is required in the form of cod liver oil, whilst with infants the opposite effect has been found, calciferol having greater activity than an equal number of rat units in the fish liver oil. However, all evidence of variation in potency between the two substances has been based on responses of different species, and insufficient attention may have been paid to effects caused by the unequal adsorption and utilization of the vitamin, as well as to the possibility of secondary rachitic influences of other major constituents of the diet. Thus the vitamin A in the fish oil might have a powerful effect in the assimilation of vitamin D and might also account for the finding by Ender that the chemical and physical properties of the two active substances differ slightly.

Other substances with antirachitic activity to a lesser degree are 22:23-dihydroergosterol after heating and 7:8 dehydrocholesterol after irradiation.

Vitamin D is the one case so far established where hypervitaminosis is a real danger, when overcalcification of bone and the calcification of soft tissue result.

Reproductive Vitamins—

It now appears that more than one vitamin is essential for the efficient functioning of the reproductive processes.

(a) *Vitamin E—*

Evans, Emerson and Emerson (1936), by fractional distillation of wheat-germ oil have succeeded in isolating a pale yellow oil with very high activity in enabling vitamin E-deficient rats to bear young, to which they ascribe the formula $C_{29}H_{50}O_2$. The substance which has proved to be an alcohol and has been renamed α -Tocopherol is also suspected of being related to the sterols.

The reports that pregnant women with a previous history of abortion for no apparent cause have been successfully treated enabling them to complete gestation in over 80 per cent of cases indicate the probable importance of the vitamin therapeutically. The extract, however, has been found to have no effect in the treatment of sterility. (Watson and Tew 1936).

(b) *Vitamin F—*

Evans, Lepkovsky and Murphy (1934) report the existence of essential fatty acids, to which is given the designation vitamin F. In the absence of this factor a failure in the repro-

ductive function always results. It is marked by a peculiar and characteristic prolongation of the gestation period, due, apparently, to a derangement of the birth mechanism. The addition of vitamin F (contained in lard and butter) to the diet enables the young to thrive normally, but lactation is still not normal.

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AN INVESTIGATION INTO THE INCIDENCE OF HIGH BLOOD PRESSURE IN THE NATIVE.

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In the European under the age of 40 years, the normal blood pressure is generally recognised to be in the neighbourhood of 120 to 130mm. Hg., systolic, and 80 to 90 mm. Hg., diastolic; the extremes of the normal range of the systolic pressure appearing to be 110 and 140 mm., respectively. Over this age a gradual elevation of these figures is found, and with the advance of years and the onset of arterio-sclerotic changes in the vascular system, pressures of 150 to 200 mm. are commonly observed, occasionally without any associated abnormal symptoms being present.