THE VITAMIN B COMPLEX.*

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In moving a motion recently in the House of Commons Commander Locker-Lampson suggested that this was a war of well-being and our slogan might be "March upon Milk," and our motto "Vitamins for Victory"; seconding the motion, Sir M. Sueter suggested rum might be added to the milk "to make the vitamins more lively." To some people vitamins appear to be a panacea for all ills, to others a mystical group curing rare diseases such as pellagra, scurvy, rickets or xerophthalmia. Some medical scientists have claimed that vitamin B₁ cures such different conditions as lead neuritis, subacute combined degeneration of the cord, disseminated sclerosis and sciatica; others have stated that beriberi is almost unknown in this country and therefore deficiency of vitamin B₁ rarely, if ever, occurs here. Since about one paper is published on the vitamin B complex alone each day of the year it is not surprising that the medical practitioner cannot keep abreast of the scientific advances in this field. And his attempt to do so is discouraged by the fact that most of these papers will not stand a critical analysis, and therefore ought not to have been published. The object of this article is briefly to summarize recent work, done mainly upon animals, on the vitamin B complex, and to indicate the applications of this work to disease in man.

The term "water-soluble B" was originally used for the vitamin that cured beriberi in man or the similar disease produced in fowls by Eijkman in 1897. Vitamin B₂ was distinguished in 1926 as a factor that prevented pellagra and was more heat-stable than vitamin B₁. Vitamins B₃, B₄, B₅ and B₆ were various water-soluble fractions of yeast that were believed at intervals to be necessary for the nutrition of pigeons or rats. The terminology, always confused, became chaotic in 1933. It was known that rats fed on a diet deficient in vitamin B₂ failed to grow and developed a dermatitis, and this was believed to be analogous to pellagra. When the fluorescent compounds called flavins were discovered by Kuhn in 1933, it was found that one of these (riboflavin) could be isolated from preparations of vitamin B₂ and would promote growth in rats deficient in this factor; Kuhn therefore claimed that riboflavin was vitamin B₂. But since riboflavin was found to have no effect upon this dermatitis of rats or upon human pellagra, it was obvious that vitamin B₂ must consist of more than one factor. In 1935 vitamin B₆ was shown to cure rat dermatitis; but since riboflavin together with vitamin B₆ did not cure human pellagra, the original "vitamin B₂" fraction of yeast consisted of at least three components. The third component, the P-P (pellagra-preventive) factor, was shown in 1937 to be nicotinic acid. These three factors are all adsorbed on fuller's earth, and there are two factors that are not adsorbed—the "filtrate factor" which is necessary for the growth of rats, and pantothenic acid which prevents dermatitis in chickens, and has just been synthesized ($\text{CH}_2\text{OH}.\text{C}(\text{CH}_3)_2.\text{CHOH}.\text{CO}.\text{NH}(\text{CH}_2)_2.\text{COOH}$). These five factors comprise the vitamin B₂ complex, and it is wrong to use the term "vitamin B₂" to denote a single vitamin: the term should, in fact, be abandoned.

Vitamins B₃, B₄ and B₅, as well as the "filtrate factor," pantothenic acid and other possible factors (such as choline, and the factor that prevents achromotrichia in rats or grey hair in silver foxes), are not yet known to have any clinical significance and

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will not be further considered here. The evolution of the more important factors is indicated in the accompanying diagram (Fig. 1).*

FIG. 1.

Vitamin B₁.

This, the "antineuritic vitamin," is also called aneurin, thiamin and torulin. Extensive chemical work in various laboratories led finally to the synthesis of the vitamin by Williams and others in 1936. The molecule (Fig. 2) will be seen to contain two rings: the left-hand one is the pyrimidine ring and the sulphur-containing one is the thiazole ring. It may be thought that the elucidation of the structure of the vitamin and its

Vitamin B₁

FIG. 2.

final synthesis are of mere academic interest. Such a view is wholly erroneous. A knowledge of the structure has helped, and will ultimately explain, the action of the vitamin in living cells; and the synthesis has made the cheap commercial preparation of the vitamin possible. For instance, five years ago the most efficient method of preparing the vitamin was the large-scale extraction from yeast devised by Peters; this took 14 days for the preparation of a few milligrams, and the cost of the yeast alone was £200 for 1 g. of pure vitamin. Now 1 g. of the vitamin can be synthesized for £1, and the cost could no doubt be lowered to a tenth of this if private commercial interests were eliminated. The vitamin is stable to heat in acid solution, but if boiled in an alkaline medium it is rapidly destroyed. If the processes are properly carried out little or no destruction occurs during the pasteurisation of milk, the canning of foods and the cooking of vegetables unless alkali is added (for example, the addition of soda to preserve the colour of boiled cabbages or of canned spinach); but it must be

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remembered that the vitamin is very soluble in water, and therefore after boiling a cabbage most of the vitamin is in the water, which is usually thrown away. It cannot be too strongly emphasized that it is not the inclusion of a particular food in a diet that is important but the nutritional value of that food when it is consumed, or better when it has been absorbed from the gut.

Few common foods are rich in the vitamin. Wholemeal bread, which contains about 0.25 mg. per 100 g., is a good source and contains about ten times as much as white bread and twice as much as brown. Oatmeal, liver, kidney, peas, broad beans and nuts, eggs and pork are all fairly good, but milk is rather poor and beer contains little. The minimum required to prevent symptoms of beriberi in an adult man is not less than 0.5 mg. a day, and the optimum intake is probably about 2 mg. But several factors alter the requirement. It is proportional to the body weight, the total metabolism and the energy value of the ingested carbohydrate. Anything that increases metabolism—such as muscular work, fever, or hyperthyroidism—increases the amount of the vitamin required; this amount is tripled during pregnancy. As will be shown later, the vitamin is necessary for the oxidation of carbohydrate and for its conversion into fat. A diet high in fat spares vitamin B₁, but beriberi has sometimes followed diets very high in carbohydrate but otherwise normal. Deficiency may also be produced by failure to assimilate the vitamin B₁ in the diet, and this may be caused by three factors: destruction in the gut, failure of absorption from the gut or failure of phosphorylation (since, as stated below, the vitamin must be converted into its diphosphate ester, cocarboxylase, before it acts in the body). It has already been mentioned that the vitamin is stable in acid but destroyed in alkaline solution. Incubation with achlorhydric gastric or duodenal juice causes destruction, whereas with normal juice there is no destruction; but in presence of hæmin destruction occurs even in an acid medium. Therefore patients with achlorhydria—and particularly ones that have pyloric stenosis in addition—tend to develop deficiency of vitamin B₁, and the same is true of cases of ulcer or carcinoma with bleeding into the stomach; several cases of “gastrogenous polyneuritis” have been described (see Laurent & Sinclair, 1938). Failure of absorption from the gut occurs in various conditions: chronic diarrhoea is one such cause (Dann & Cowgill, 1938) and extensive resection of the small intestine is another. These various factors tending to produce deficiency can be summarized as follows and are more fully discussed in the paper from which this table is taken (Sinclair, 1939).

A. Inadequate ingestion.

(1) *Unbalanced diet.*

Alcoholism, “glucose-lemonade,” gastric ulcer diets.

(2) *Increased requirement.*

High carbohydrate diets—(diabetes mellitus).

Increased metabolism	{	Muscular work and rapid growth. Delirium, and manic type of manic-depressive psychosis. Pregnancy and childbirth. Fever. Hyperthyroidism.
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Diuresis, Lactation.

Possibly leucocytosis and polycythæmia.

B. Failure of assimilation.

- (1) *Destruction in the gut.*—Achlorhydria. Pyloric stenosis, carcinoma of the stomach, gastric ulcer.
- (2) *Failure of absorption.*—Diarrhoea: steatorrhoea; ulcerative colitis; bacillary dysentery. Gastro- and entero-enterostomy.
- (3) *Failure of phosphorylation.*—Possibly steatorrhoeas. Possibly diseases of the liver, adrenal cortex and of reticulo-endothelial tissue.

The way in which the vitamin acts in the body has been worked out by Peters (1936, 1938). Using pigeons and rats he has shown that in deficiency of vitamin B₁ lactic and pyruvic acids accumulate in the body because they are formed from carbohydrate but cannot be completely broken down because Vitamin B₁ is necessary for the degradation of pyruvic acid in the body.

This work on lower animals has been confirmed upon patients with beriberi, for they have an abnormally large amount of pyruvic acid in blood (Platt & Lu, 1936). The biochemical change occurs particularly in nerve cells and in the heart, both of which depend for energy mainly upon the oxidation of carbohydrate; deficiency therefore produces peripheral neuritis and cardiac symptoms. Carbohydrate also cannot be converted into fat in absence of vitamin B₁ probably because pyruvate is a step in this conversion. Vitamin B₁ is not only necessary throughout the animal kingdom: higher plants, yeast, bacteria and fungi need it. In the course of alcoholic fermentation, yeast converts sugar into pyruvic acid, which is then converted into acetaldehyde and CO₂ by the enzyme carboxylase. This enzyme requires a coenzyme, and in 1937 Lohmann showed that this coenzyme—cocarboxylase—was vitamin B₁ combined with two phosphate molecules. This discovery further confirmed Peters' work, and he has more recently shown that in the animal body also the vitamin acts as a coenzyme only after phosphorylation (which takes place mainly in the liver, the kidney and in nucleated cells derived from reticulo-endothelial tissue). The probable way in which the vitamin is metabolized may be summarized as follows. It is absorbed from the gut into blood in the unphosphorylated form and as such diffuses into cells. It is then phosphorylated to form cocarboxylase and becomes combined with protein. Blood contains about 1 μg. free vitamin B₁ per 100 ml. and 7 μg. cocarboxylase, all the latter being combined with protein inside the blood cells; plasma or cerebrospinal fluid contains 1 μg. or less vitamin B₁ per 100 ml. and no cocarboxylase. The vitamin is excreted in urine in the unphosphorylated form.

It has already been mentioned that in deficiency of vitamin B₁ the biochemical lesion occurs mainly in nerve cells and in the heart. Although it is rare to find one system affected without some alteration occurring in the other, it is customary to recognize three types of beriberi according as the lesion falls predominantly upon the nervous or cardiovascular system: first, dry beriberi, which is an ascending symmetrical peripheral neuritis; second, wet beriberi, characterized by dilatation of the heart and of peripheral arterioles, with serous effusions and oedema; third, acute fulminating beriberi ("shōshin") with sudden onset of severe cardiac symptoms which rapidly proved fatal before the introduction of crystalline vitamin B₁. Symptoms of deficiency begin and progress somewhat as follows. First there is loss of appetite, with lack of energy, muscular weakness and "heaviness" of the legs; this is followed by tenderness of the calf muscles (a very valuable sign), and burning sensations in the soles of the feet with loss of vibration sense in the

legs. The paræsthesiæ in the legs become more marked, the weakness increases and is perhaps accompanied by intermittent claudication, and the ankle and patellar reflexes become weak and later absent. Menstruation ceases. The weakness in the legs spreads to the extensors of the toes, then of the foot and next to the extensors and flexors of the leg; toe and foot-drop are therefore found. At the same time hyperæsthesia followed by anæsthesia advances up the legs. Atrophy of the skin and muscles occurs. The upper extremity is usually affected later. The central nervous system and sphincters are rarely involved, but there may be forgetfulness, irritability and headache.

Cardiovascular symptoms include tachycardia, fatigue and "palpitations" on exertion, and dyspnœa. Later the heart dilates, particularly to the right; "tic-tac" or gallop rhythm, and "pistol-shots" over the peripheral arteries are heard. The liver is enlarged and tender. The arterial pressure is usually normal and the pulse pressure slightly increased. The circulation rate is increased because the peripheral vessels are dilated. This dilatation is the most probable cause of the œdema, which may be mild or extreme and occurs without obvious renal changes or alteration of the plasma proteins. It must be distinguished from war (or famine or hunger) œdema which is due to deficient ingestion of protein and is therefore accompanied by bradycardia and low plasma protein; and from epidemic dropsy, which is frequently accompanied by fever, hæmorrhages and glaucoma.

At autopsy few pathological changes are usually found. The heart is dilated, particularly on the right side. The vessels in the walls of the gut are dilated, and punctuate hæmorrhages may occur in the stomach and duodenum; hæmorrhagic pancreatitis may be found. The spinal cord shows degeneration of the medullary sheaths particularly in the posterior columns and in the anterior and posterior nerve roots. The axis cylinder may be fragmented, and congestion and hæmorrhages are sometimes found. In peripheral nerves degeneration of the myelin sheath is constant; this occurs first in the long nerves of the leg.

Extravagant and fantastic claims have been made for the therapeutic use of vitamin B₁. It has previously been mentioned that diseases as dissimilar as lead neuritis, subacute combined degeneration of the cord, disseminated sclerosis, and sciatica have been alleged to respond to therapy with vitamin B₁. The œdema and cardiac dilatation of wet beriberi respond dramatically to such therapy. The neuritis is quickly cured in the early stages before degeneration of the axis cylinder has occurred; but long-standing cases may obtain little or no improvement. Some at least of the cases of nutritional, "alcoholic," gastrogenous, gestational, diabetic and "infective" polyneuritides are caused by deficiency of vitamin B₁; but in true cases of infective polyneuritis and in most cases of diabetic neuritis no improvement can be expected with vitamin therapy. Cases of cardiac dilatation and tachycardia without any obvious signs of organic heart disease, and cases of œdema not of cardiac or renal origin and with normal plasma proteins, might reasonably be treated with vitamin B₁. Evidence recently accumulated suggests that deficiency of vitamin B₁ may play a part in the causation or cure of Wernicke's encephalopathy, of pink disease and of tic douloureux. Of topical interest are the claims of Champy and Goujard that deficiency of vitamin B₁ causes "trench foot" and of Sliosberg that it is useful in the treatment of painful amputation stumps.

During the last four years I have carried out analyses of vitamin B₁ in the blood of over 500 cases. Significantly low values have been found in most or all cases of the following: nutritional, gastrogenous and alcoholic polyneuritides; beriberi heart

(10 cases), aplastic anaemia, alcoholic cirrhosis of the liver, scurvy, pink disease. Half or more of the cases of the following have been deficient: oedema of obscure origin, thyrotoxicosis, pellagra, anorexia nervosa, depression, inoperable carcinoma of the stomach, ulcerative colitis, diabetic and gestational polyneuritides, pernicious and idiopathic hypochromic anaemias and macrocytic anaemia accompanied by steatorrhea. Low values were also given by a third of 32 poor women attending an antenatal clinic, and by a third of 27 cases of polyneuritis of unknown aetiology. Similar results have been obtained by estimations of cocarboxylase in blood (Goodhart and Sinclair, 1940). Though gross deficiency is rare in this country, mild and sub-clinical degrees are undoubtedly quite common. Pure vitamin B₁ is available for therapeutic use, either orally or parenterally, and there is no danger of over-dosage. In definite cases of deficiency it is wise to start treatment with intramuscular or intravenous injection of very large doses—20 to 50 mg. daily. Later the same amount may be given orally or the injections decreased to 10 mg. or less daily. But the problem of *preventing* deficiency—particularly subclinical cases—is an urgent one, especially in time of war. Two German experts, Stutz and Weispfennig, have recently been investigating at the Baltic Sea marine station the vitamin requirements of sailors; they recommend a combined use of vitamins B₁ and C for men at sea. In America Cowgill has brought forward cogent arguments for adding synthetic vitamin B₁ to bread. It is now possible to manufacture artificially at least eight of the most important vitamins. There is no reason why these should not be added to basic artificial foods such as bread and margarine; there would be no danger of over-dosage, and since even in time of peace many thousands of people in this country suffer from mild vitamin deficiencies the result would be entirely beneficial. This would diminish the nutritional problem, but would not abolish it since it is mainly an economic problem. Alternatively, these important vitamins could be supplied in the form of a free biscuit to the whole population. The consumption of such a biscuit would ensure that the person had obtained the minimum daily requirement of eight of the most important vitamins.

Vitamin B₂ Complex.

It has been pointed out above that this complex consists of at least five factors of which at least three—nicotinic acid, riboflavin and vitamin B₆—are of importance in human nutrition. Before considering the aetiology of pellagra it would be well to define these three factors more closely.

Riboflavin, which has been synthesized and has the formula shown in Fig. 3, is necessary for the growth of animals and probably of man. It prevents certain disorders in rats (such as conjunctivitis, alopecia, cataract and even pediculosis); it is present

Riboflavin

FIG. 3.

in yeast, milk, eggs and liver, and is destroyed by light. To Sebrell belongs the credit for having first recognized the clinical manifestations of riboflavin deficiency: they consist essentially of cheilosis and seborrhœic excrescences around the nose. In 1938 Sebrell and Butler fed eighteen women on a purified diet; after about one hundred days ten of the subjects developed the characteristic signs. These begin as a pallor of the mucosa of the lip in the angles of the mouth, soon followed by maceration and then superficial transverse fissures, which may extend on to the skin. At the same time there is a superficial denudation of mucosa making the lips abnormally red along the line of closure. In addition "there was also seen a fine, scaly, slightly greasy desquamation on a mildly erythematous base in the nasolabial folds, on the alæ nasi, in the vestibule of the nose and on the ears." These lesions were alleviated by synthetic riboflavin, but not by nicotinic acid. The conclusion of Sebrell that they are due to deficiency of riboflavin is justified, and the work of other authors as well indicates that this deficiency is not uncommon in the U.S.A. Like vitamin B₁, riboflavin acts in the body combined with phosphate, and the significance of this will be discussed below.

Vitamin B₆ was synthesized last year and has the structure shown in Fig. 4. In rats it prevents an extensive symmetrical dermatitis which is called "rat acrodynia" because it is alleged to resemble pink disease in children; Miss Chick has shown that

FIG. 4.

such rats are also prone to have "fits," similar to those occurring as a result of magnesium deficiency. Dogs and rats deficient in this factor develop a microcytic anaemia. Pathologically, the histological lesions consist of hyperkeratosis and a great increase in the vascularity of the skin, with little or no change in the cells of the basal layer; there are no characteristic microscopical changes in the liver or brain.

Vitamin B₆ plays a rôle in the growth of plants as well as of animals, and is no doubt important throughout nature. Deficiency in man has not yet been recognized; but Spies and his colleagues have claimed improvement in health in four cases of nutritional deficiency: the intravenous administration of vitamin B₆ is alleged to have cured within 24 hours their irritability, nervousness, insomnia, vomiting, weakness, and wide-based reeling gait.

Nicotinic acid, which, like vitamin B₆, is a pyridine derivative (Fig. 4), was first prepared three-quarters of a century ago, and it was first isolated from biological material by Japanese workers in 1912. Its common occurrence with the antineuritic vitamin led to several attempts to use it or closely related compounds for the cure of avian polyneuritis. These attempts were not successful, although in 1926 nicotinic acid and its amide were alleged to preserve weight and stimulate appetite. A very important advance was made in 1935 when Warburg and Christian showed that nicotinic acid amide occurred in coenzyme II of blood, and in the same year it was also isolated from coenzyme I. Shortly afterwards nicotinic acid was shown to cause slightly increased

growth in rats and pigeons, and to be important in the nutrition of micro-organisms. In 1937 Elvehjem and his colleagues showed that it cured canine black-tongue (a disease analogous to pellagra), and in the same year its successful use in pellagra was shown by a number of clinicians.

Pellagra is common in some parts of America, but is very rarely recognised in this country where it can most commonly be found accompanying ulcerative colitis or in patients in mental hospitals. The early symptoms are weakness, lassitude, anorexia and diarrhoea. These are followed by sore ulcerations of the mouth and an ulcerated atrophic tongue of a fiery red, mental changes and typical cutaneous lesions. The latter consist of a very characteristic dermatitis on the exposed surfaces, of lesions about the genitalia, seborrhoea on the face and neck, and hyperkeratoses over bony prominences; the lesions are aggravated by sunlight. The acute mental symptoms—which vary from slight confusion to delirium or mania—respond dramatically to nicotinic acid, usually clearing up overnight; the oral manifestations and the cutaneous erythema disappear in a few days. Nicotinic acid is cheap, and the dose recommended by Spies is 500 mg. a day, given by mouth in doses of 50 mg. It must be emphasized that nicotinic acid, unlike vitamin B₁, is definitely toxic: large amounts produce flushing, burning and itching of the skin, and increased motility of the stomach.

It is most satisfactory to restrict the term pellagra to the condition caused by deficiency of nicotinic acid. As thus defined pure pellagra is seldom found. Many pellagrins suffer from peripheral neuritis, and this has been shown by Spies and Aring to be due to deficiency not of nicotinic acid but of vitamin B₁; many suffer from cheilosis which is cured by riboflavin and not by nicotinic acid. Korsakov's psychosis sometimes accompanies pellagra, and this is believed by some to be due to deficiency of vitamin B₁; the typical mental changes of pellagra are due to the same pathological process as causes Wernicke's encephalopathy, and this is stated by Jolliffe to be cured by large doses of nicotinic acid. This mixture of deficiencies is not surprising since it is unlikely that a patient will be deficient in only one vitamin. Therefore it is seldom justifiable to treat a case of, say, beriberi or scurvy with one purified vitamin without paying due attention to the underlying dietary fault.

Anæmia and the Vitamin B Complex.

A relation between the vitamin B complex and various forms of anæmia has repeatedly been claimed since 1929. Castle and Strauss (1932) stated that "vitamin B₁₂" or a closely related substance was the extrinsic factor in pernicious anæmia, but this view was later discarded. Pigeons on a synthetic diet develop an anæmia that is cured by yeast but not by vitamins B₁ or B₆ or riboflavin, and the filtrate factor is alleged to cure nutritional anæmia in monkeys. György has produced aplastic anæmia with symptoms of a hæmorrhagic diathesis in rats by dietary means and cured it with nicotinic acid; others have produced severe microcytic hypochromic anæmia in puppies by a diet deficient in vitamin B₆, and recently Hogan has produced macrocytic hyperchromic anæmia in chicks by a diet deficient in an entirely new member of the vitamin B complex. At present these facts are difficult to correlate, and it is not known what relation they have to human anæmia. Pernicious anæmia, unlike the macrocytic anæmia of pregnancy, does not usually respond to high doses of the vitamin B complex. Tropical macrocytic anæmia is due to dietary deficiency, and appears to exist in at least two forms. The first is a non-hæmolytic type, common in India, which responds to crude liver preparations or to filtrate-factor concentrates, but not to anahæmin (Wills and Evans); this is probably similar to the macrocytic anæmia of sprue and analogous

to nutritional macrocytic anæmia in monkeys. Secondly, there is a hæmolytic type, common in Macedonia, which responds to anahæmin but not to filtrate-factor concentrates; in addition, there is a macrocytic anæmia, associated with an enlarged spleen and free gastric hydrochloric acid, that is very common in males in Macedonia, and does not respond to crude liver extracts (Foy and Kondi).

If in a case of anæmia, or any other case, deficiency of some part of the vitamin B complex is suspected, yeast is a convenient therapeutic agent to use since it contains the whole complex. Dried powdered brewer's yeast is cheap, and is easily administered stirred into milk, or in warm water with salt; about 30 g. daily is a convenient dose for an adult.

Catalytic Nature of the Vitamin B Complex.

Recent biochemical work upon respiratory enzymes has not only given the clue to the nature of the pellagra-preventive vitamin but has also shed much important light upon the actual way in which vitamins of the B complex act in the body. The nuclei of all cells, both animal and plant, contain large amounts of nucleoproteins. The non-protein part of these compounds consists of four nucleotides, and a nucleotide is formed by the combination of a nitrogenous base (usually purine or pyrimidine) with a pentose and phosphate. These substances are of great importance in nature; some crystalline viruses are known to be nucleoproteins; and uric acid, caffeine and the pterins (the white pigment in the wings of butterflies and the yellow pigment of the bodies of wasps and hornets) are typical purines. A nucleotide derivative (adenyl pyrophosphate) is of immense importance in carbohydrate metabolism (in fermentation by yeast, in muscular contraction, and in the production of lactic acid and oxidation of pyruvic acid). Further, it has recently been shown that certain coenzymes that are essential for transporting hydrogen during the oxidation of foodstuffs in cells are nucleotides. When a compound is oxidised in the body to provide energy, hydrogen is removed from it by an enzyme ("dehydrogenase") which itself becomes reduced; this reduced enzyme is oxidised by a further enzyme, and the hydrogen is passed from enzyme to enzyme until finally it is united with oxygen brought (usually) by the cytochromes and water is formed. These respiratory enzymes consist of nucleotides (or coenzymes) combined with protein. One such coenzyme ("cozymase" or "coenzyme I") consists of the nucleotide adenylic acid combined with another "nucleotide" in which nicotinic acid amide is the nitrogenous base; "coenzyme II" differs from this compound in having an extra phosphate molecule. Other respiratory enzymes consist of riboflavin phosphate combined with protein, and since riboflavin phosphate has very nearly the structure of a nucleotide, these enzymes can also be considered as a nucleotide combined with protein. Further, vitamin B₁ contains a pyrimidine nucleus and becomes combined with phosphate to form the coenzyme cocarboxylase; this probably combines with protein to form the enzyme carboxylase which oxidises pyruvic acid. In all these cases the vitamin concerned combines with phosphate to form a coenzyme, and then probably with protein to form an enzyme; various respiratory enzymes are formed in this way, the specificity depending in large part upon the particular protein to which the coenzyme is attached. We have therefore seen that at least three vitamins of the B complex probably form the active group of certain important respiratory enzymes. If there is deficiency of one or other of these vitamins an enzyme or enzymes cannot be formed, and interference with the respiration of cells that depend upon the enzyme will cause deficient production of energy and failure of function. We are still far from understanding the exact way in which the particular biochemical lesion in the cells produces the signs

and symptoms of the relevant disease, but the goal is in sight and will be reached by the combination of clinical observation and laboratory biochemical research that has proved so useful in the earlier stages.

Summary.

1. Four members of the vitamin B complex are believed to be important in human nutrition: vitamin B₁, nicotinic acid, riboflavin and vitamin B₆. All have been synthesized.

2. Deficiency of vitamin B₁ causes disorders of the nervous and cardio-vascular systems which in their extreme forms constitute beriberi. The symptoms and signs of deficiency are briefly described. The causes of deficiency are discussed, and the frequency of mild states of deficiency in this country is emphasized.

3. Nicotinic acid cures pellagra—a disease found more commonly in this country than is generally supposed; the symptoms and nature of the disease are briefly discussed.

4. Deficiency of riboflavin causes cheilosis and seborrhoea around the nose.

5. There is an ill-defined relation between the vitamin B complex and anæmia.

6. The members of the vitamin B complex are probably parts of enzymes or coenzymes necessary for the respiration of certain cells. In their absence the metabolism of the cell becomes deranged. Yeast is a convenient therapeutic source of the vitamin B complex.

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