abnormality and the lack of the factor for any vitamin other than aneurin (vitamin B_1). We have now at last a final proof that aneurin pyrophosphate is the actual factor missing in the avitaminous brain (Banga, Ochoa and Peters, 1939). It has taken long to reach this. Always the physiology will take the longest. The fact is that chemistry and biochemistry have rushed ahead lately and we must not be disappointed if the true nutritional work takes rather longer to do, because it involves physiology. Today we shall be discussing our subject from the dual aspects of pure biochemistry and of nutrition.

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The Vitamin B Complex: Introductory Survey

Dr. L. J. Harris and Dr. E. Kodicek (Dunn Nutritional Laboratory, Cambridge)

The title of today's conference, "The Vitamin B Complex," covers a very wide field. At least a dozen well defined components of the vitamin B complex are now recognized (Table 1). It is obvious, therefore, that

TABLE 1

COMPONENTS OF THE VITAMIN B COMPLEX

B complex	Heat labile (B_1)		ANEURIN, vitamin B_1
	Heat stable (B_2 complex)	Adsorbable	NICOTINAMIDE, P.P. factor
			*RIBOFLAVIN
			*PYRIDOXIN, vitamin B_6
		Filtrate factors	*PANTOTHENIC ACID
			p-AMINOBENZOIC ACID
			INOSITOL
			CHOLINE
		Others or unclassified	BIOTIN
			"FOLIC ACID"
			GRASS JUICE FACTOR
			ETC.

* At first confused with the P.P. factor.

only a few selected aspects can be considered in the course of a one day meeting. Our object in this opening paper must be to give a preliminary survey of the field as a whole, although in the short time allowed it will have to be somewhat cursory.

TABLE 2

VITAMIN B COMPLEX: EXTENT OF PRESENT KNOWLEDGE

Name	Structural formula	Biochemical action	Needed by		Deficiency disease in man	Approximate minimum daily human requirement mg.	Methods of estimation		
			experimental animals	man			Chemical	Biological	Microbiological
Aneurin, thiamin, vitamin B_1 ..	+	Co-carboxylase	+	+	Beriberi	1	+	+	+
Nicotinamide	+	Co-dehydrogenase	+	+	Pellagra	12	+	+	+
Riboflavin	+	„	+	+	Cheilosis	1·8	+	+	+
Pyridoxin, pyridoxal, pyridoxamine, vitamin B_6	+	Amino-acid decarboxylation ?Transamination	+	—	—	—	+	+	+
Pantothenic acid	+	—	+	—	—	—	—	+	+
p-Aminobenzoic acid	+	—	(+)	—	—	—	+	—	+
Inositol	+	—	(+)	—	—	—	+	—	+
Choline	+	Transmethylation	[+]	[+]	—	—	+	—	+
Biotin, vitamin H	+	—	+	+	—	—	—	+	+
"Folic acid"	—	—	+	—	—	—	—	+	+
Grass juice factor	—	—	+	—	—	—	—	—	—

( ) = ? secondary accessory. [ ] = replaceable.

In Table 2 the attempt is made to give a bird's eye view of the extent of, as well as of the gaps in, our present knowledge. From this it will be seen that the structural formulae are known for about nine of the B vitamins; that a biochemical role in some specific enzyme reaction is recognized for about five of them; that about five have been proved to be needed by man; that in two instances classical deficiency diseases are caused by their absence; that in about three instances some approximate idea of the human requirement is known; and that various alternative methods for making chemical, biological and microbiological estimations have been, or are being, worked out.

Next we must turn to a discussion of the individual factors in a little more detail.

Vitamin B_1

Of vitamin B_1, the antiberiberi vitamin, little need be said here, since the history is so well known, beginning with the discovery of experimental beriberi by Eijkman (1897) and leading eventually to the isolation of the vitamin (Jansen and Donath, 1926), the elucidation of its structural formula (Windaus, Tschesche and Grewe, 1935; Williams, 1936; Grewe, 1936) and finally its synthesis (Williams and Cline, 1936; Todd and Bergel, 1937). The structural formula is given in Figure 1.

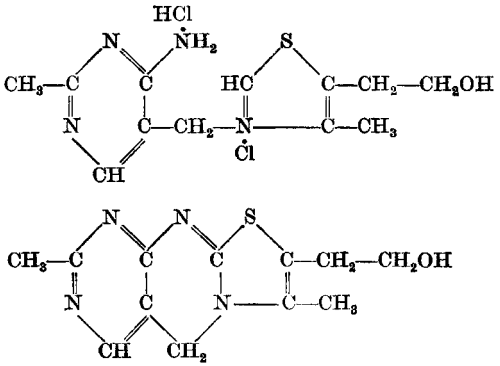

FIGURE 1. STRUCTURE OF VITAMIN B_1 (ABOVE), SHOWING RELATION TO THIOCHROME (BELOW).

The high degree of specificity is to be noted, a very small change in chemical structure causing loss of biological activity (Bergel and Todd, 1937, 1938; Price and Pickel, 1941; Buchman and Richardson, 1945).

On the side of the biochemical action of the vitamin, Peters and his collaborators were the pioneers in showing that the influence of vitamin B_1 could be demonstrated *in vitro*, by its power to restore an impaired oxygen uptake to avitaminous tissues (Gavrilescu, Meiklejohn, Passmore and Peters, 1932). One of the first clues to the precise function of the vitamin in metabolism was the detection in the tissues of deficient animals and men of abnormal amounts of lactic acid (Collazo, 1922; Bickel, 1924; Inawashiro and Hayasaka, 1928), and later of pyruvic acid (Thompson and Johnson, 1934, 1935; Platt and Lu, 1935, 1936). Pyruvic acid then came right into the centre of the picture when Lohmann and Schuster (1937, 1, 2) disclosed that the co-enzyme in yeast responsible

for the breakdown of pyruvic acid, that is co-carboxylase, is the pyrophosphate ester of vitamin B_1 (Figure 2), and controls the reaction

$$CH_3CO.COOH \longrightarrow CO_2 + CH_3.CHO$$

Dr. Quastel (1946) in the next paper will develop the theme of the vitamin's mode of action from this starting point, and will, no doubt, tell us of the numerous reactions in which it is concerned either directly or indirectly and of how complicated and interrelated they may be. Perhaps he will say whether or not he would agree with the thesis that in all these reactions decarboxylation or carboxylation may be involved at some stage

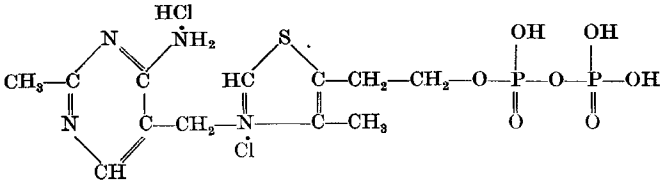

FIGURE 2. CO-CARBOXYLASE (ANEURIN PYROPHOSPHATE ESTER).

as the essential feature. If this is true it would at least bring some kind of unity into the mechanism of the action of vitamin B_1.

Concerning clinical relations there is only time here for a passing reference to beriberi and its cure with crystalline vitamin B_1 when given early enough and in sufficiently large doses (see, *e.g.*, Platt, 1938). Mention must be made too of the various conditioned deficiencies of vitamin B_1, as seen in polyneuritis associated with pregnancy, with gastro-intestinal obstruction and with alcoholism. In ruminants, as also in refected rats, a symbiotic synthesis of B vitamins occurs in the gastro-intestinal tract and this is of consequence in that it prevents their developing the corresponding deficiency diseases. Studies have been begun of the conditions under which, as has been found, there may be some partial synthesis of B vitamins by human beings. Drs. Platt and Webb (1946) will speak of this in their paper.

As for methods of estimation, the organizers of this meeting have decided that there will be no opportunity today for any detailed consideration of methods of determining the B vitamins. The suggestion has been made, however, that a special conference of The Nutrition Society should be held, devoted to a discussion of the relative merits and demerits of biological as compared with chemical methods of test. It is very much to be hoped that this will be done. All that need be said now is that in our laboratory we are satisfied that for estimating vitamin B_1 various chemical and biological methods are now available which yield reliable and concordant results (Harris and Wang, 1941,1).

Assessment of Nutritional Status

Work at the Cambridge Nutritional Laboratory has shown that subjects with low intakes of vitamin B_1 have a low excretion of the vitamin in their urine, and show also a lessened or delayed response in excretion after a test dose. This offers the basis for a test (Harris and Leong, 1936; Harris, Leong and Ungley, 1938; Wang and Harris, 1939; Harris

and Wang, 1941, 1, 2; Wang and Yudkin, 1940; Najjar and Holt, 1940, 1942; Melnick and Field, 1942, 1, 2; Ruffin, Cayer and Perlzweig, 1944). Another possibility for assessing nutritional status arises from the finding of Banerji and Harris (1939) confirmed in McCollum's laboratory (Shils, Day and McCollum, 1941) and elsewhere, that a rat, even when suffering from only a slight partial degree of deficiency, excretes in its urine an increased amount of bisulphite binding substances provided it has been loaded first with a product of intermediate metabolism, namely lactate given orally. For man the most promising procedure appears to be a loading test with glucose, followed by measurement of tolerance curves in the resulting rise of bisulphite binding substances in blood or urine (Bueding, Stein and Wortis, 1941; Harris, 1940; Williams, Mason and Wilder, 1943).

Vitamin B_2 Complex

Differentiation of the P.P. Factor

Leaving vitamin B_1 we now come to the vitamin B_2 complex. The first point is the differentiation of the pellagra preventing vitamin from certain other B_2 factors. This immediately raises the question of nomenclature. It was at first thought that only one single vitamin was concerned and thus when the term "vitamin B_2" was introduced (for history of terminology see Birch, György and Harris, 1935) it was regarded, by definition, as the heat stable water soluble fraction present in extracts of yeast, which served to prevent pellagra in human beings, blacktongue in dogs and a so called pellagra-like dermatitis in rats, and was needed also for the promotion of health and growth in rats.

Therefore, when Kuhn, György and Wagner-Jauregg (1933) showed that riboflavin had vitamin B_2 activity for rats, in the sense that it was a heat stable component of yeast which stimulated growth, they at first regarded it as simply synonymous with vitamin B_2, including in its functions the prevention of so called rat pellagra, of the true pellagra of human beings, and of canine blacktongue. Further work from various laboratories including our own (György, 1934, 1935; Harris, 1935; Chick, Copping and Edgar, 1935) soon showed, however, that the factor preventing rat pellagra was not riboflavin at all but a second B_2 factor first called B_6 and now renamed pyridoxin. The differentiation continued and it was next proved (Birch *et al.*, 1935) that the true P.P. factor, the one preventing pellagra in human beings and blacktongue in dogs, was yet a *third* component, distinct from riboflavin and vitamin B_6. Later the so called chicken pellagra factor, which Koehn and Elvehjem (1937) had at first considered to be identical with the true pellagra factor, had likewise to be differentiated from it (Dann, 1937; Dann and Subbarow, 1938), and its identity was established (Jukes, 1939; Woolley, Waisman and Elvehjem, 1939) with what we now know as pantothenic acid.

Nicotinamide

In the identification of the P.P. factor, it was the knowledge that nicotinic acid was the component of certain enzyme systems which prompted Elvehjem's team (Elvehjem, Madden, Strong and Woolley, 1937) to test it on their dogs suffering from blacktongue, and with spectacular success. Very soon afterwards several laboratories reported

equal success in treating human pellagra with nicotinic acid (Fouts, Helmer, Lepkovsky and Jukes, 1937; Harris and Hassan, 1937; Smith, Ruffin and Smith, 1937).

Nicotinic acid, then, or it would be better to say the amide (Figure 3), is the P.P. factor for man, and the antiblacktongue factor for dogs.

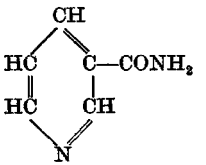

FIGURE 3. NICOTINAMIDE.

It prevents also a corresponding disease in monkeys described by one of us (Harris, 1937, 1938), as well as the remarkable deficiency disease in pigs studied by Sir Charles Martin and his collaborators (Birch, Chick and Martin, 1937; Chick, Macrae, Martin and Martin, 1938).

Rats on the other hand are able to synthesize nicotinic acid, and thus do not need it in their diets and the same is apparently true of ruminants. In man, Ellinger and Benesch (1945) have recently reported evidence of its synthesis in the gut. Nicotinic acid is a nutrient of universal significance, and its properties as a growth factor for various micro-organisms will be discussed by Dr. Knight (1946).

As to the mode of action of nicotinamide, we know it to be a component of two enzyme systems (Figures 4 and 5) in which it acts as hydrogen

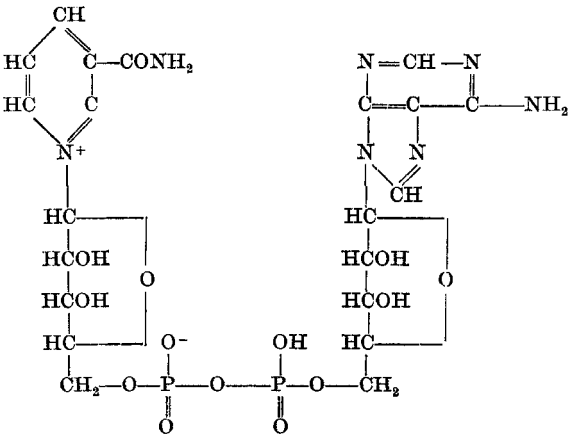

FIGURE 4. CO-DEHYDROGENASE I.

transporter, and concerning this we are no doubt to hear more from Dr. Quastel (1946).

For its estimation a choice of methods is available, microbiological (Snell and Wright, 1941), chemical (Swaminathan, 1938, 1944; Harris and Raymond, 1939; Wang and Kodicek, 1943; Perlzweig, Levy and Sarret, 1940: Dann and Handler, 1941) and biological. But here we

can do no more than draw attention to the fact that in *plant* tissues there is a chromogen, or precursor, as shown by Kodicek (1940) and others (Waisman and Elvehjem, 1941; Krehl and Strong, 1944) and, therefore,

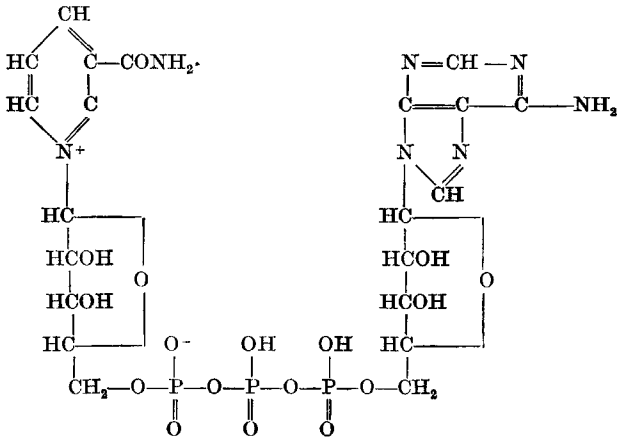

FIGURE 5. CO-DEHYDROGENASE II.

special methods of hydrolysis are accordingly needed in order to include it in the determination, since it is biologically active (Krehl, Elvehjem and Strong, 1944).

There is general agreement that, for assessment of nutritional status, the measurement of nicotinic acid in blood is unfortunately of little or no use. The best procedure appears to be to give test doses of nicotinamide by mouth, and estimate the amount of methylated products which are then excreted in the urine. They can be estimated colorimetrically, together with other N-methyl pyridinium compounds (Kodicek and Wang, 1941; Kodicek, 1941) or, alternatively after suitable chemical treatment of the urine, whereby the methylated substance, nicotinamide methochloride, or some related product, is converted to a fluorescent substance called F_2. Here I refer to the valuable work of Najjar and his collaborators (Najjar and Holt, 1941; Najjar, White and Scott, 1944), of Huff and Perlzweig (1943), and of Ellinger and his collaborators (Ellinger, Glock and Platt, 1942; Ellinger and Coulson, 1943, 1944).

Riboflavin

Riboflavin (Figure 6), like nicotinamide, functions as a hydrogen transporter, in this instance in a great variety of different enzymes. Clinically, riboflavin has been said to prevent cheilosis (angular stomatitis) and corneal vascularization in man, but its clinical connexions are still somewhat obscure.

For estimating riboflavin two main alternatives are available, microbiological (Snell and Strong, 1939), and fluorimetric (Hodson and Norris, 1939; Conner and Straub, 1941; Wang and Kodicek, 1946). Biological methods are also being used (El-Sadr, Macrae and Work, 1940; Copping, 1943). Of the microbiological test all that need be said at the moment

is that further critical examination seems to be needed of the effects of the various interfering factors, which may act as inhibitors (Kodicek and Worden, 1944, 1945) or as accelerators (Bauernfeind, Sotier and Boruff,

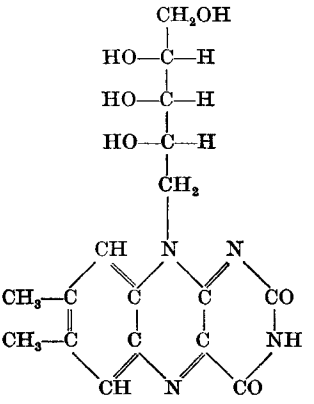

FIGURE 6. RIBOFLAVIN.

1942). In the fluorimetric method the main difficulty of estimation lies in the very small amount of riboflavin present in most tissues.

For the assessment of nutritional status, estimation of urinary excretion after test dosing seems applicable along the lines previously described for the other vitamins (Ruffin *et al.*, 1944).

Other B_2 Vitamins

The remaining vitamins will have to be dismissed here with a sentence or two apiece, and Mr. Robinson (1946) will have time to develop some of the detail in his paper.

Vitamin B_6 or pyridoxin (Figure 7) as before mentioned is needed by rats to prevent a florid dermatitis. A connexion with protein metabolism seems indicated by recent work which shows it to have an effect

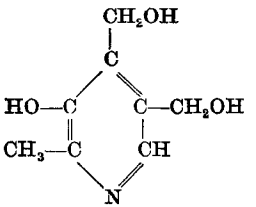

FIGURE 7. VITAMIN B_6 (ADERMIN, PYRIDOXIN)
(2-methyl-3-hydroxy-4 : 5-di(hydroxymethyl)pyridine).

in the synthesis of fat from protein (McHenry and Gavin, 1941) and in the metabolism of tryptophane (Reid, Lepkovsky, Bonner and Tatum, 1944). A derivative, pyridoxal, is concerned in tyrosine decarboxylation (Gunsalus, Bellamy and Umbreit, 1944), and both this substance and another derivative, pyridoxamine, are said to be connected with biological transaminations (Schlenk and Snell, 1945). Dr. Quastel will no doubt give his views on that. Another derivative, 4-pyridoxic acid, excreted in urine (Huff and Perlzweig, 1944), is said to promote growth and prevent

microcytic anaemia in chicks when vitamin B_c, discussed below, is present in the diet (Scott, Norris, Heuser and Bruce, 1945).

Pantothenic acid (Figure 8), a substance which had been previously recognized as needed by numerous micro-organisms, was later identified

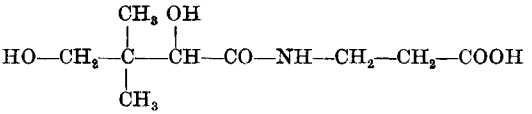

FIGURE 8. PANTOTHENIC ACID
($\alpha\gamma$-dihydroxy-$\beta\beta$-dimethyl-butyryl-β-alanine).

with the vitamin preventing the so called pellagra of chicks. It is needed also by rats and mice for growth and to prevent greying of the fur and occurrence of adrenal lesions. Little or nothing is yet known about its mode of action (see review by Williams, 1943).

p-Aminobenzoic acid (Figure 9) at first presented a truly confusing picture, with various claims and counterclaims being made about the production

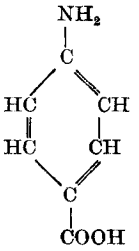

FIGURE 9. *p*-AMINOBENZOIC ACID.

or non-production of grey hairs and other alleged ill effects (Anonymous, 1944). The explanation may well be that it is what we are venturing to term a "secondary accessory," a substance not directly needed by mammals but stimulating their intestinal microflora to the production of certain other vitamins which are needed by the host.

Inositol (Figure 10), needed by micro-organisms, and later considered as necessary for the prevention of alopecia in mice, may perhaps be

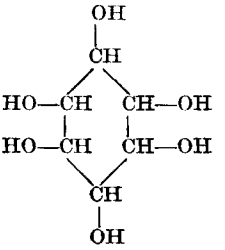

FIGURE 10. INOSITOL.

similarly regarded as a "secondary accessory," although there are accounts of a possible direct action in metabolism manifested in its lipotropic properties for rats (Anonymous, 1944).

Choline (Figure 11) is to be regarded as a biological methylating agent and the fact that it is replaceable by methionine and other substances,

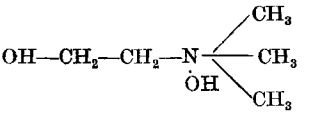

FIGURE 11. CHOLINE.

and that the dose needed is relatively high, has raised philosophic doubts as to the propriety of including it in the category of vitamins (see review by Best and Lucas, 1943).

Biotin or vitamin H (Figure 12) prevents the development of a peculiar seborrhoeic dermatitis in rats fed on diets containing raw egg white.

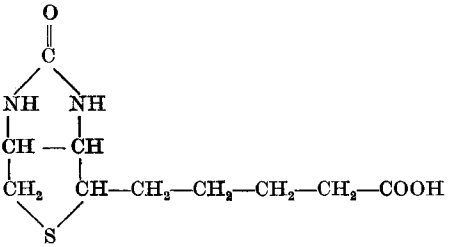

FIGURE 12. BIOTIN (VITAMIN H).

The egg white serves as a source of the antivitamin, avidin, a protein which inactivates biotin by combining with it. Biotin is apparently needed by man as well as by yeasts and bacteria (see review by Hofmann, 1943).

Folic acid and other so called "grass" factors. Under this heading a complex of related substances seems to be involved comprising the following: growth factors for *Lactobacillus casei* and *Streptococcus lactis* R, the so called monkey vitamin or vitamin M, vitamin B_c, and perhaps xanthopterin, functioning as a precursor (see review by Luckey, Teply and Elvehjem, 1944). Mr. Robinson (1946) will develop this theme and Miss Wills (1946) will tell us about the apparent relations of vitamin B_c, for example, to anaemia.

Other anti-anaemia factors. Miss Wills will also, no doubt, give us her views on the so called extrinsic factor for pernicious anaemia which, according to the theory of Castle, is present in foods in association with the vitamin B_2 complex, and interacts with the intrinsic factor secreted in the stomach to give rise to the liver substance curative of pernicious anaemia; we shall also hear her views about the possible relationship, or lack of relationship, of this extrinsic factor to the dietary factors concerned in the prevention of tropical macrocytic anaemias.

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Role of Members of the Vitamin B Complex in Enzyme Systems

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Aneurin

The work of Peters and his colleagues (Gavrilescu, Meiklejohn, Passmore and Peters, 1932; Passmore, Peters and Sinclair, 1933; Peters and Sinclair, 1933; Sinclair, 1933; Thompson, 1934; Peters, Rydin and Thompson, 1935; Kinnersley, O'Brien and Peters, 1935; Rydin

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