Greig, J. R. (1936). *Congr. int. Path. Comp.* III, **2**, 424.
Green, H. H. (1925). *Physiol. Rev.* **5**, 336.
Green, H. H. (1944). *Proc. Nutr. Soc.* **1**, 177.
Taylor, E. L. (1944). *Endeavour*, **3**, 150.
Theiler, A. (1919). *Fmr's Wkly, Bloemfontein*, 7 May.
Theiler, A. & Green, H. H. (1931–2). *Nutr. Abstr. Rev.* **1**, 359.
Theiler, A., Green, H. H. & du Toit, P. J. (1924). *J. Dep. Agric., S.Afr.*, **8**, 460.
Theiler, A., Green, H. H. & du Toit, P. J. (1927). *J. agric. Sci.* **17**, 291.

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ANTIVITAMINS IN FOOD

Chairman: SIR EDWARD MELLANBY, G.B.E., K.C.B., F.R.S.
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Antivitamins and Other Factors Influencing Vitamin Activity

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Development of the concept of antivitamins

When, at the end of the last century, Eijkman (1890, 1897, 1906) earned for himself the distinction of being the first to investigate a vitamin deficiency disease experimentally in an animal, namely beriberi in the hen, he did in fact also enunciate what amounted to the theory of a vitamin and its corresponding antivitamin, although of course he did not use these words. What he said was that beriberi was caused by an excess of carbohydrate in the diet, and that an antidote was present in the rice germ, which counteracted the effect of the excess of carbohydrate. This statement is quite unexceptionable, even as read to-day in the light of the most recent knowledge. We now know that the antidote, the vitamin B_1 in the rice germ, is indeed needed by the animal organism to enable it to metabolize carbohydrate, and also that carbohydrate is a beriberi-producing agent, in the sense that the more carbohydrate there is present in the diet, the more vitamin B_1 is needed with it. Thus, a rat can be cured of experimental beriberi either by giving it more vitamin B_1 or by replacing the carbohydrate in its diet by more fat. It is, therefore, quite legitimate to regard carbohydrate as an antivitamin factor, operating against vitamin B_1, the term antivitamin being used in its widest sense.

This concept of vitamins as mere antidotes, however, in the way that Eijkman regarded the curative substance in rice germ as an antidote, failed no doubt to emphasize

sufficiently another aspect of the vitamins, namely that they are also necessary components of all normal diets. It was the second of the two most eminent of the early pioneers, Sir Frederick Gowland Hopkins (1906, 1912), who was concerned particularly to bring out this point, and to stress that vitamins were more than antidotes, that disease can be caused by a simple deficiency, by a negative factor no less than by the more easily understood positive factor, that is, the toxin, or disease-producing agent.

When these two eminent and gifted pioneers, Eijkman and Hopkins, were rewarded in 1929 by the conferment on them jointly of the Nobel Prize for Medicine, Hopkins (1930), in his Prize Essay, elaborated the point of view to which I have just referred:

> 'Eijkman's own earlier teaching as based on his results was that the function of the substance in the cortex was to neutralize a nutritional error due to excess of carbohydrate in a diet of rice. A substance which functions in the neutralization of an error is not the same thing as a substance universally necessary, and it was to the existence of substances of the latter type that my own thoughts had turned. Eijkman did not at first visualise Beri-Beri clearly as a Deficiency Disease; but the view that the cortical substance in rice supplied a need rather than neutralised a poison was soon after put forward by Grijns and ultimately accepted by Professor Eijkman himself.'

This same emphasis on the mental approach to the problem of deficiency disease stands out in a passage inspired by Hopkins, which can be found in the early and influential Report on Vitamins prepared by the Accessory Food Factors Committee (Medical Research Council, 1924).

> 'The recognition of beri-beri and scurvy as deficiency diseases has provided good evidence...for the nutritive importance of what we have agreed to call accessory factors.
>
> The evidence from disease would have led sooner to a conception of these food constituents and their functions but for a not unnatural bias in thought. It is difficult to implant the idea of disease as due to deficiency.
>
> Disease is so generally associated with positive agents—the parasite, the toxin, the *materies morbi*—that the thought of the pathologist turns naturally to such positive associations and seems to believe with difficulty in causation prefixed by a *minus* sign. ...
>
> So in connexion with the newer conception of disease as due to dietetic deficiencies. Even when Eijkman, through his admirable studies, had clearly established more than twenty years ago that beri-beri arose during the consumption of decorticated and not of whole rice (making it clear, therefore, that something in the cortex was necessary to normal nutrition) he was led to suggest, not the simple view that the cortical substance was of direct use to the body, but rather that it was necessary to neutralize the otherwise deleterious effect of a diet over-rich in starch. Save for the mental bias just referred to it is very difficult to see why so roundabout an explanation should have been thought necessary.'

Looking back, we can see now that there was perhaps at this time the risk of almost too great a reaction, with the amount of attention then being given solely to the negative

factor, the deficiency, with the danger of overlooking the importance of a possible positive factor, the antivitamin or toxamin, to use the word coined by Mellanby, who from the start, and at first almost alone, taught the importance of the harmful positive factor.

In his paper on the nature of experimental rickets in puppies, Mellanby (1921) directed attention to the finding that cereals as such were rachitogenic. In 1922 he showed that certain cereal products such as oatmeal or wheat germ were more potent than others in producing rickets (Mellanby, 1922). In 1926 he introduced the word, toxamin, to describe this factor in cereals which exerts a harmful effect by antagonizing the vitamin D and calcium salts. A second toxamin, or neurotoxamin, was described also; it hastened degenerative changes in the nervous system (Mellanby, 1926) and was counteracted by vitamin A or carotene (Mellanby, 1930, 1931). An informative and stimulating essay on the theme of Toxamins in Food (Mellanby, 1937) will be found in the volume *Perspectives in Biochemistry*, containing thirty-one essays presented to Sir Frederick Gowland Hopkins by his past and present pupils in 1937.

The rickets-producing toxamin described by Mellanby, or as some would now call it the antivitamin factor, present in oatmeal and other cereals, has, as the result of later investigation, been identified with phytic acid, thanks to the work of Bruce & Callow (1934), McCance & Widdowson (1935), Harrison & Mellanby (1939), and others, and knowledge has been gained about its mode of action. It is now known that it interferes with the assimilation of calcium and phosphate salts, which it is the business of vitamin D to promote.

Various types of anti- and pro-vitamin factors

At the present time many factors are recognized which may influence the activity of a vitamin present in a foodstuff; and, as well as those factors which antagonize or inhibit vitamin action, an opposite set of agencies can operate to augment or intensify the activity of particular vitamins. In consequence, it is well appreciated by those who are concerned with the estimation of vitamins, that the chemical analysis, which tells us the amount of a vitamin present in a food, does not necessarily always give the same result as the biological test, which tells not the amount, but the potency, of the vitamin.

Some examples which will make this distinction clear are summarized in Table 1.

Examples of factors influencing the biological potency of vitamins present in foods

Vitamin D. In the biological test for vitamin D (see Table 1), the antirachitic activity of a food will depend not simply on the vitamin D content, but, e.g. will be antagonized by (1) the antivitamin factor, phytic acid. (2) The calcium and phosphorus content and ratio, and (3) the acid-base balance, also will profoundly and quantitatively influence the antirachitic action of the vitamin in one direction or the other. (4) Large excess of fat may act against the vitamin by precipitating calcium salts, and (5) lactose may act with it. Furthermore, (6) vitamin D_2, though approximately equal in potency to

vitamin D_3 for the rat, is less effective than vitamin D_3 for the chick, and this is another possible cause of discrepancy between biological and chemical tests.

Vitamin B_1. Similarly, vitamin B_1 activity is variously influenced:

(1) There are antivitamin factors working against the vitamin: (*a*) the enzyme, thiaminase; (*b*) other antivitamin agents present in ferns, and in grain, and elsewhere; (*c*) the synthetic antivitamin, pyrithiamin, a vitamin analogue about which more will be said later.

(2) Fat aids the vitamin.

(3) An increased intake of calories, or rather of carbohydrate, creates a greater need for the vitamin, and hence has an antivitamin effect.

Table 1. *Examples of dietary and other factors influencing the potency of vitamins in foods*

Vitamin D
Presence of an antivitamin (phytic acid)
Content and ratio of calcium and phosphorus
Acid-base balance
Presence of excess fat
Presence of lactose
Difference of potency for different species

$$\text{vitamin } D_2 \begin{cases} = \text{(rat)} \\ < \text{(chick)} \end{cases} \text{vitamin } D_3$$

Vitamin B_1
Presence of an antivitamin (thiaminase*; 'fern' factor†; 'grain' factor‡; 'mutton' factor§; pyrithiamin)
Amount of fat in the diet
Magnitude of calorie intake in the form of carbohydrate

Nicotinamide
Amounts of tryptophan and protein; existence of amino-acid imbalance
Presence of an antivitamin, e.g. in maize
Activity of biosynthesis

Vitamin A
Presence as vitamin A, or as β- or α-carotene, or as other carotenoids of differing value
Variability in absorption, utilization, conversion, storage and mobilization
Conditions of the biological test

● Green (1936, 1937); Green, Carlson & Evans (1942); Woolley (1941).
† Weswig, Freed & Haag (1946).
‡ Hart, McCollum, Steenbock & Humphrey (1911); Hart, Miller & McCollum (1916); Moore (1914); McCollum, Simmonds & Pitz (1916); Williams (1927); Bhagvat & Devi (1944*a*, *b*).
§ Radeleff (1945); Putney (1945).

Nicotinamide. The pellagra-preventing activity of a food for an animal is determined not only by its nicotinamide content, but also by the amount of tryptophan present (which spares the vitamin), by the amino-acid balance or imbalance, apparently also by an antivitamin factor in maize, and by the nature of the factors controlling synthesis of the vitamin by micro-organisms in the intestine of the test animal.

Vitamin A. (1) Vitamin A is not equal biologically to a molecular equivalent of β- or of α-carotene, and the same is true for other carotenoids or other forms of vitamin A.

(2) Another cause of discrepancy between the results of chemical and biological estimations is the variation in the degree of absorption, utilization, conversion of carotenoids to vitamin A, storage and mobilization, all of which are influenced by many different factors.

(3) The vitamin potency found in a biological test may depend on the actual conditions of that test (see further below, p. 367).

In Table 2 an attempt is made to analyse and classify the chief causes of divergence between the results of chemical tests and the value biologically determined.

Table 2. *Causes of divergence between the vitamin values for foods obtained by chemical and biological methods*

1. Differences in the forms of a given vitamin:
   (a) Differing activity of homologues (? and isomers)
   e.g. β-Carotene $= 2 \times$ (approx.) α-carotene
   Vitamin $D_2 \gtrless$ Vitamin D_3
   Vitamin $K_1 \neq$ Vitamin K_2
   (b) Differing activity of free and combined forms
   e.g. Vitamin B_1 ⎫
   Nicotinamide ⎬ cf. enzyme systems
   Riboflavin ⎭
2. Variations in availability (e.g. in solubility, absorption, utilization, storage, mobilization)
   e.g. β-Carotene in different food sources
3. Presence of antivitamin factors
   e.g. Vitamin D: phytic acid
   imbalance of calcium and phosphorus
4. Presence of vitamin 'enhancers'
   e.g. Vitamin B_1: fat
   Nicotinamide: tryptophan
5. Difference between responses of different animal species
   e.g. Vitamin D_2 (rat) $\neq$ vitamin D_2 (chick)
6. Difference of method of test
   e.g. Carotene: 'growth' and 'storage' methods
7. Activity of enzymes
   e.g. Ascorbic acid oxidase
8. Vitamin balance
   e.g. Vitamin A 'spared' by vitamin E
9. Intestinal microsynthesis
   e.g. B-vitamins; vitamin K

Similar considerations apply to microbiological tests; interfering substances may be of two kinds:

(a) Substances analogous to the vitamin in chemical structure, of which the standard instance is sulphonamide which blocks p-aminobenzoic acid.

(b) Substances affecting the metabolic activity or viability of the micro-organism; an example is furnished by the unsaturated fatty acids, studied by Kodicek & Worden (1945).

Chemical content of vitamins in food in relation to biological potency

After this brief examination of the nature of the factors conditioning vitamin activity, some general comments and conclusions may be useful about the relative validity of chemical and of biological tests.

The chemical method measures the amount of the vitamin, and not necessarily its potency.

The biological test, on the other hand, may be influenced by various additional factors, such as the presence of vitamin antagonists and supporters; moreover, it may

be applicable only for the particular species used in the biological test, and perhaps sometimes also only for the special conditions of the test, such as the method and level of dosing. For example, the vitamin A potency for a rat of a foodstuff containing carotene is not necessarily the same as for a human being, and for the rat may depend on the type of assay method chosen.

There is a moral to be drawn from the foregoing facts: it is essential that workers reporting the results of vitamin determinations should not be content with giving merely a numerical value, but should state also the conditions employed for the assay.

Table 3. *Alternative biological procedures for measuring vitamin activity of foods*

1. Measurement of total potency:
   e.g. (*a*) Vitamin D activity = vitamin D content + effect of inhibitors (e.g. phytic acid) + effect of enhancers (e.g. calcium:phosphorus ratio)
   (*b*) Vitamin B_1 activity = vitamin B_1 content + effect of inhibitors (e.g. antivitamins) + effect of enhancers (e.g. high fat content of diet)

2. Measurement of vitamin content:
   (*a*) Test of a purified extract, and not of the foodstuff itself, e.g. removal of fat from diet before a vitamin B_1 test
   (*b*) Equalization of conditions for animals receiving vitamin standard and test material, e.g. vitamin B_1: fat content of diet equalized
   vitamin D: calcium and phosphorus content of diet equalized

Only so will it be possible to interpret the meaning of their findings, and apply them to practical nutrition. Fortunately, in practice, the problem is not generally as difficult as it might appear from scrutiny of Tables 1 and 2 which, at first glance, look somewhat formidable. Provided we are told the total amounts of the different forms of a given vitamin which are present (whether, for instance, vitamin A occurs only as such or together with β-carotene) and also have information about any special factors which may augment or diminish potency (such as whether the source of carotene is a green vegetable or an oily solution) it should usually be possible to make a fairly reasonable approximation to the probable total potency. Indeed, from the Dunn Nutritional Laboratory some long lists of foodstuffs have been published, witnessing to the satisfactory agreement it has been possible to get between the biological and chemical values, e.g., for vitamin B_1 (Harris & Wang, 1941) and vitamin C (Harris & Olliver, 1942; Harris & Mapson, 1947).

For biological tests there are two main alternative procedures which give different kinds of answers (see Table 3).

The first is to measure the 'overall vitamin value' of the food. For example, in such a test for antirachitic potency, the result would indicate not only the amount of vitamin D in the food but also the influence of any vitamin inhibitors or antivitamins (phytic acid for instance in this case) or vitamin activators (such as a decrease in the calcium: phosphorus ratio). Similarly, for total vitamin B_1 potency, there would be taken into account the vitamin B_1-inhibiting effect of any antivitamin factor, and a vitamin B_1-enhancing effect if the foodstuff was rich in fat.

The second alternative in biological technique, and perhaps the preferable one, is not to measure the overall effect, but to attempt a discriminating measurement of the

specific amount of the vitamin present as such. For this second purpose one of two techniques may be used:

The first is to prepare an extract of the vitamin from the food, and test that, and not the food itself, on the animal, and thereby remove the effect of the interfering influences. For example, in measuring the vitamin B_1 content of any foodstuff which happens to be rich in fat, which is vitamin-sparing, a fat-free extract containing the vitamin would first be prepared for dosing, and that would be used instead of the food. The second technique is to equalize the dietary conditions for the animals receiving the test material

Table 4. *Classification of antivitamin factors according to their mode of action*

	Type of antivitamin factor		
Vitamin	Having related chemical structure and acting by blocking	Oxidative enzyme or other destructive agent	Exercising some other type of interference with action
Vitamin A	—	Heated fats	—
Vitamin B_1	Pyrithiamin	Raw fish (enzyme)	—
Vitamin C	Glucoascorbic acid	Ascorbic acid oxidase; copper	....
Vitamin D	—	—	Phytic acid; calcium : phosphorous ratio; excess fat and other factors
Vitamin E	Tocopherol quinone	—	—
Biotin	Desthiobiotin	Avidin	—
Vitamin K	Dicoumarol	—	....
p-Aminobenzoic acid	Sulphanilamide	—	—
Pantothenic acid	Pantoyltaurine	—	—
Nicotinamide	Sulphapyridine 3-Acetylpyridine	—	—
Pyridoxin (Vitamin B_6)	Desoxypyridoxin	—	—
Riboflavin	*Iso*riboflavin	—	—
Choline	—	—	Cystine
Inositol	γ-Hexachlorocyclo- hexane (Gammexane)	—	—
Folic acid	Methylfolic acid and others	—	—

and those having the standard preparation of the vitamin, so that these factors are eliminated as variables affecting the issue. For example, where the test material is a fatty food containing vitamin B_1, the animals receiving the vitamin standard will receive a diet with the percentage of fat adjusted to be the same as for those receiving the test material.

Similarly, in a vitamin D test, the calcium and phosphorus content of the diet would be equalized; and many other examples could be given.

Structural analogues as antivitamins

I have left to the end what is perhaps the most exciting of all the recent developments in this field of antivitamin factors: namely the recognition of a class of specific antivitamin analogues, or substances so closely resembling particular vitamins in structure as to function by blocking their action. A few of these are listed in the second

column of Table 4 which classifies the various types of antivitamin factors. Table 5 gives, in more detail, some typical examples of structural homologues which block vitamin action.

Table 5. *Examples of structural analogues acting as specific anti-vitamins to inhibit vitamin action*

Vitamin	Specific antivitamin	Species of organism shown to be affected by inhibition	Notes	References
p-Aminobenzoic acid	Sulphanilamide	Bacteria	Has clinical applications	Woods (1940); Woods & Fildes (1940)
	Sulphonamides	Bacteria	Have clinical applications	
Inositol	γ-Hexachlorocyclo-hexane (Gammex-ane)	Insects	Used as an insectide	Slade (1945); Kirkwood & Phillips (1946)
Vitamin B₁	Pyrithiamin	Mouse		Woolley & White (1943)
[Vitamin C]	[Glucoascorbic acid]	[Mouse, cotton rat]	[Action not reversed by addition of vitamin C]	[Woolley & Krampitz (1943)]
Vitamin E	Tocopherol quinone	Mouse	Regarded as analogue of vitamins K and E	Woolley (1945b)
Biotin	Desthiobiotin	Micro-organisms		Melville, Dittmer, Brown & du Vigneaud (1943); Lilly & Leonian (1944)
	Biotin sulphone	Micro-organisms		Dittmer & duVigneaud(1944)
Vitamin K	Dicoumarol	Various	Cause of spontaneous 'sweet clover disease' in cattle. Has clinical uses	Quick (1937); Roderick (1931); Stahmann, Huebner & Link (1941)
	Various homologues	Rabbit		Meunier, Mentzer, Buu Hoï & Cagniant (1943); Meunier (1948–9)
Pantothenic acid	Pantoyltaurine	Bacteria		McIlwain (1942)
		Mouse		Snell, Chan, Spiridanoff, Way & Leake (1943); cf. Unna (1943)
	Phenyl pantothenate	Bacteria		Woolley (1946b)
Nicotinamide	Sulphapyridine	Bacteria		West & Coburn (1940); Wood & Austrian (1942); West (1941); Anderson, Pilgrim & Elvehjem (1944)
		Dog		Elvehjem, Teply & Axelrod (1942); West (1941)
	3-Acetylpyridine	Mouse		Woolley (1945a; 1946a)
Pyridoxin	Desoxypyridoxin	Chick		Ott (1946)
Riboflavin	Phenazine analogues	Bacteria, mouse		Woolley (1944)
	ᴅ-Araboflavin	Rat		Euler & Karrer (1946)
Choline	Triethyl analogue of choline	Mouse, frog (isolated muscle)		Keston & Wortis (1946)
Folic acid	Various	Bacteria		Woolley & Pringle (1948)
	4-Aminopteroyl-glutamic acid	Bacteria, chick, rat		Oleson, Hutchings & Sub-barow (1948)

Sulphanilamide and p-*aminobenzoic acid*. Sulphanilamide must take pride of place as the first and classical example of an antivitamin. The story began with the discovery that sulphanilamide itself, or other related substances containing the sulphonamide group, inhibited the growth of certain pathogenic micro-organisms. This finding was followed by the clinical application of the drug to the treatment

Sulphanilamide (antivitamin)   p-Aminobenzoic acid (vitamin)
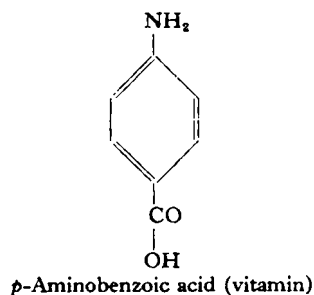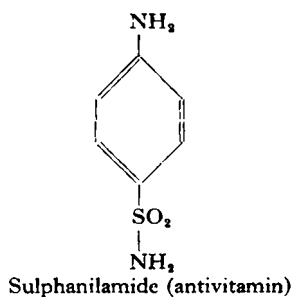
of streptococcal infections, and of some types of pneumonia, with the remarkably successful cures known to many of us by personal experience. Laboratory studies by Woods then brought to light the no less remarkable fact that the way in which the sulphonamide drug acted was by competing with an essential nutrient needed by the micro-organism. The nutrient was later identified with p-aminobenzoic acid, which had not previously been suspected of being a vitamin or essential nutrient at all. The idea of a competitive action, developed by Quastel & Wooldridge (1928) in their studies on the dehydrogenating enzymes of bacteria, has thus proved most fruitful in this direction, as in others.

Other antivitamins for bacteria. Naturally enough this fine work on the sulphonamides, and its immense practical importance, quickly caused a rush to find other similar antibacterial substances. The following are a few examples of those now known:

Vitamin	Corresponding antivitamin
Vitamin B$_1$	Pyrithiamin
Riboflavin	*Iso*riboflavin
Nicotinic acid	Pyridine-β-sulphonic acid
Pantothenic acid	Pantoyltaurine

Some of these may function as antivitamins, in respect of these same vitamins, for mammals as well as bacteria, and this aspect will be considered again later.

Great hopes were entertained that other antivitamins might be used therapeutically, like the sulphonamides, but the hopes have so far been mostly disappointed. The reason may be, as the work of McIlwain & Hawking (1943) suggests, that when the anti-vitamin is administered to the human subject it is counteracted by the corresponding vitamin present in his blood stream. For example, antivitamin B$_1$ might not be able to exert its bacteriostatic action on an invading micro-organism unless the human host was already depleted of vitamin B$_1$, that is, had developed beriberi.

γ-Hexachlorocyclohexane: an insect antivitamin? No less interesting than the elucidation of the action of these antibacterial substances, is the suggestion that a well-known insecticide, Gammexane (Imperial Chemical Industries Ltd.), the γ-isomer of hexachlorocyclohexane, may owe its toxic action to its interference with the metabolism of the nutrient, inositol, to which it is structurally closely related (see Kirkwood & Phillips, 1946).

Inositol (hexahydroxy*cyclo*hexane)   Gammexane (γ-hexachloro*cyclo*hexane)
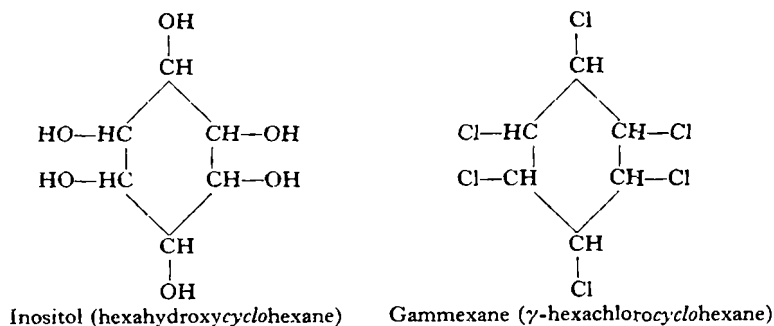
Incidentally, it is of interest to note that inositol itself can act, as previously mentioned, as a vitamin antagonist when it is in the form of phytic acid, and that it can also, as just explained, function as a vitamin in its own right for bacteria and perhaps insects.
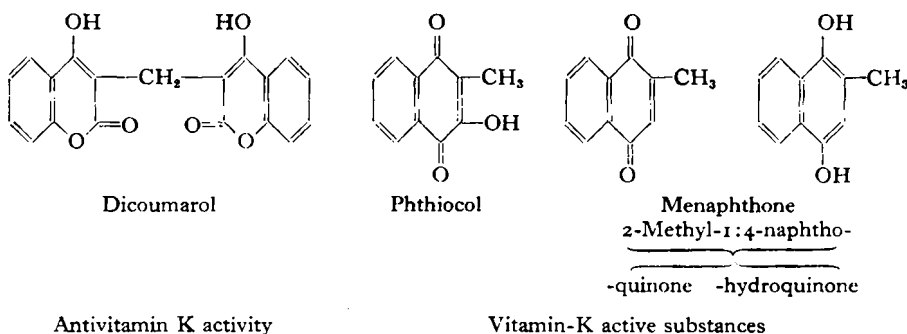
Antivitamins for mammals. The most prominent worker, in the preparation of structural analogues antagonistic to vitamin action, has been D. W. Woolley. Those which have been described include the following:

Pyrithiamin (antivitamin B_1). Synthetic product, precipitating vitamin B_1 deficiency in mice; competes quantitatively with vitamin B_1 (Woolley & White, 1943).

Glucoascorbic acid (antivitamin C). Synthetic product, causing scurvy-like symptoms in mice and cotton rats, but not counteracted by vitamin C (Woolley & Krampitz, 1943). The non-reversibility of the effect poses the question whether it should be regarded as a true antivitamin analogue.

DL-α-*Tocopherol quinone (antivitamin* E). Synthetic product, causing reproductive failure in female mice, prevented by administration of vitamin K but not of α-tocopherol. Regarded as structural analogue of both vitamin E and vitamin K (Woolley, 1945 *b*).

Dicoumarol (naturally occurring antivitamin K). Present in spoiled sweet clover, and the cause of a spontaneous, endemic haemorrhagic disease of cattle. There has been some discussion about the mode of action of dicoumarol as an antivitamin. However, its structural resemblance to the K group of vitamins is at least suggestive of a possible competitive or blocking action. It is worth noting that dicoumarol has been used in human medicine, to increase the blood-clotting time, in the prevention and treatment of post-operative thrombosis.

Dicoumarol   Phthiocol   Menaphthone
2-Methyl-1:4-naphtho-

-quinone   -hydroquinone

Antivitamin K activity   Vitamin-K active substances

Vitamin K *homologues.* These, including another naturally occurring analogue, will be dealt with in Prof. Meunier's (1948–9) communication (vide infra).

Pantoyltaurine (antipantothenic acid). Synthetic product, said to cause symptoms of pantothenic acid deficiency in mice (Snell, Chan, Spiridanoff, Way & Leake, 1943), but apparently not in rats (Unna, 1943).

Sulphapyridine (antinicotinamide). Synthetic product, belonging to the sulphonamide class of drugs, said to block nicotinamide (West & Coburn, 1940; Wood & Austrian, 1942) by preventing formation of coenzyme systems (Anderson, Pilgrim & Elvehjem, 1944; West, 1941), both in nutrition of micro-organisms and in blacktongue of dogs (Elvehjem, Teply & Axelrod, 1942; West, 1941). There has been some difference of opinion as to the specificity of sulphapyridine as an antinicotinamide factor.

3-*Acetylpyridine* (*antinicotinamide*). Synthetic product, precipitating nicotinamide deficiency in mice (Woolley, 1945*a*, 1946*a*).

Desoxypyridoxin (*antivitamin* B_6). Synthetic product, antagonizing pyridoxin in the chick (Ott, 1946).

Phenazine-flavin analogue (*antiriboflavin*). Synthetic, 2:4-dinitro-7:8-dimethyl-10-ribityl-5:10-dihydrophenazine, a structural analogue of riboflavin, producing symptoms of riboflavin deficiency in mice (Woolley, 1944).

D-*Araboflavin* (*antiriboflavin*). Has been used similarly for inducing riboflavin deficiency in rats (Euler & Karrer, 1946).

Triethyl analogue of choline (*anticholine*). Has been reported to be toxic to mice, but to be completely antagonized by choline. It also blocked the action of choline in pharmacological tests on isolated frog muscle (Keston & Wortis, 1946).

Folic acid structural analogues. Various analogues have been described by Woolley and others, which antagonize folic acid in the nutrition of microorganisms. 4-Amino-pteroylglutamic acid has lately been used for procuring the deficiency in rats and chicks (Oleson, Hutchings & Subbarow, 1948).

In conclusion, one point stands out: namely, that with almost the solitary exception of dicoumarol and perhaps another antivitamin K factor, the structural analogues which are described above and which function as antivitamins in mammalian nutrition, are synthetic products. The future has still to show whether any of these analogues, or perhaps some related substances, may occur as such in natural foods. In this connexion it may be recalled that several vitamins (nicotinic acid, ascorbic acid, riboflavin) had already been isolated and characterized long before they were recognized to be vitamins at all. It may be that history will repeat itself with the antivitamins.

REFERENCES

Anderson, E. G., Pilgrim, F. J. & Elvehjem, C. A. (1944). *Proc. Soc. exp. Biol., N.Y.*, **55**, 39.
Bhagvat, K. & Devi, P. (1944*a*). *Indian J. med. Res.* **32**, 123.
Bhagvat, K. & Devi, P. (1944*b*). *Indian J. med. Res.* **32**, 131.
Bruce, H. M. & Callow, R. K. (1934). *Biochem. J.* **28**, 517.
Dittmer, K. & Vigneaud, V. du (1944). *Science*, **100**, 129.
Eijkman, C. (1890). *Geneesk. Tijdschr. Ned.-Ind.* **30**, 295.
Eijkman, C. (1897). *Virchows Arch.* **149**, 187.
Eijkman, C. (1906). *Arch. Hyg., Berl.*, **58**, 150.
Elvehjem, C. A., Teply, L. J. & Axelrod, A. E. (1942). *Fed. Proc.* **1**, 108.
Euler, H. v. & Karrer, P. (1946). *Helv. chim. Acta*, **29**, 353.
Fildes, P. (1940). *Lancet*, **238**, 955.
Green, R. G. (1936). *Minnesota Wild Life Dis. Invest.* **2**, 106.
Green, R. G. (1937). *Minnesota Wild Life Dis. Invest.* **3**, 83.
Green, R. G., Carlson, W. E. & Evans, C. A. (1942). *J. Nutrit.* **23**, 165.
Harris, L. J. & Mapson, L. W. (1947). *Brit. J. Nutrit.* **1**, 7.
Harris, L. J. & Olliver, M. (1942). *Biochem. J.* **36**, 155.
Harris, L. J. & Wang, Y. L. (1941). *Biochem. J.* **35**, 1068.
Harrison, D. C. & Mellanby, E. (1939). *Biochem. J.* **33**, 1660.
Hart, E. B., McCollum, E. V., Steenbock, H. & Humphrey, G. C. (1911). *Res. Bull. Wis. agric. Exp. Sta.* no. 17.
Hart, E. B., Miller, W. S. & McCollum, E. V. (1916). *J. biol. Chem.* **25**, 239.
Hopkins, F. G. (1906). *Analyst*, **31**, 395.
Hopkins, F. G. (1912). *J. Physiol.* **44**, 425.
Hopkins, F. G. (1930). *The Earlier History of Vitamin Research. Prix Nobel* 1929.
Keston, A. S. & Wortis, S. B. (1946). *Proc. Soc. exp. Biol., N.Y.*, **61**, 439.

Kirkwood, S. & Phillips, P. H. (1946). *J. biol. Chem.* **163**, 251.
Kodicek, E. & Worden, A. N. (1945). *Biochem. J.* **39**, 78.
Lilly, V. G. & Leonian, L. H. (1944). *Science*, **99**, 205.
McCance, R. A. & Widdowson, E. M. (1935). *Biochem. J.* **29**, 2694.
McCollum, E. V., Simmonds, N. & Pitz, W. (1916). *J. biol. Chem.* **25**, 105.
McIlwain, H. (1942). *Brit. J. exp. Path.* **23**, 95.
McIlwain, H. & Hawking, F. (1943). *Lancet,* **244**, 449.
Medical Research Council (1924). *Spec. Rep. Ser. med. Res. Coun., Lond.,* no. 38, 2nd ed.
Mellanby, E. (1921). *Spec. Rep. Ser. med. Res. Coun., Lond.,* no. 61.
Mellanby, E. (1922). *Brit. med. J.* ii, 849.
Mellanby, E. (1926). *J. Physiol.* **61**, xxiv.
Mellanby, E. (1930). *Brit. med. J.* i, 677.
Mellanby, E. (1931). *Brain,* **54**, 247.
Mellanby, E. (1937). *Toxamins in Food.* In *Perspectives in Biochemistry,* p. 318 [J. Needham and D. E. Green, editors]. Cambridge: University Press.
Melville, D. B., Dittmer, K., Brown, G. B. & Vigneaud, V. du (1943). *Science,* **98**, 497.
Meunier, P. (1948–9). *Brit. J. Nutrit.* **2**, 396.
Meunier, P., Mentzer, C., Buu Hoï & Cagniant (1943). *Bull. Soc. Chim. biol., Paris,* **25**, 384.
Moore, P. H. (1914). *Rep. exp. Fms Can.,* p. 21.
Oleson, J. J., Hutchings, B. L. & Subbarow, Y. (1948). *J. biol. Chem.* **175**, 359.
Ott, W. H. (1946). *Proc. Soc. exp. Biol.,* **61**, 125.
Putney, W. W. (1945). *J. Amer. vet. med. Ass.* **106**, 164.
Quastel, J. H. & Wooldridge, W. R. (1928). *Biochem. J.* **22**, 689.
Quick, A. J. (1937). *Amer. J. Physiol.* **118**, 260.
Radeleff, R. D. (1945). *Vet. Med.* **40**, 280.
Roderick, L. M. (1931). *Amer. J. Physiol.* **96**, 413.
Slade, R. E. (1945). *Chem. & Ind.* **64**, 314.
Snell, E. E., Chan, L., Spiridanoff, S., Way, E. L. & Leake, C. D. (1943). *Science,* **97**, 168.
Stahmann, M. A., Huebner, C. F. & Link, K. P. (1941). *J. biol. Chem.* **138**, 513.
Unna, K. (1943). *Proc. Soc. exp. Biol., N.Y.,* **54**, 55.
West, R. (1941). *Proc. Soc. exp. Biol., N.Y.,* **46**, 369.
West, R. & Coburn, A. F. (1940). *J. exp. Med.* **72**, 91.
Weswig, P. H., Freed, A. M. & Haag, J. R. (1946). *J. biol. Chem.* **165**, 737.
Williams, R. R. (1927). *Biochem. J.* **21**, 1349.
Wood, W. B. Jr. & Austrian, R. (1942). *J. exp. Med.* **75**, 383.
Woods, D. D. (1940). *Brit. J. exp. Path.* **21**, 74.
Woods, D. D. & Fildes, P. (1940). *Chem. & Ind.* **59**, 133.
Woolley, D. W. (1941). *J. biol. Chem.* **141**, 997.
Woolley, D. W. (1944). *J. biol. Chem.* **154**, 31.
Woolley, D. W. (1945a). *J. biol. Chem.* **157**, 455.
Woolley, D. W. (1945b). *J. biol. Chem.* **159**, 59.
Woolley, D. W. (1946a). *J. biol. Chem.* **162**, 179.
Woolley, D. W. (1946b). *J. biol. Chem.* **163**, 481.
Woolley, D. W. & Krampitz, L. O. (1943). *J. exp. Med.* **78**, 333.
Woolley, D. W. & Pringle, A. (1948). *J. biol. Chem.* **174**, 327.
Woolley, D. W. & White, A. G. C. (1943). *J. biol. Chem.* **149**, 285.

Anti-B-Vitamins

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The classic concept of vitamin deficiencies, that disease arises solely from the lack of an essential vitamin, has been modified by new developments. Thus, it is now realized that not only the absence of vitamins, but also the presence of 'toxamins' which interfere in some way with the essential nutrient cause symptoms of a deficiency. This concept is not new, having been put forward by Mellanby (1926) more than 20 years ago, but more recently an accumulation of evidence has emphasized its far-reaching