THE "NEWER" VITAMINS.

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For the purpose of this review the "older" vitamins are defined as A, B, C and D. One of these, vitamin B, is a complex consisting of vitamin B₁ plus the B₂ complex. The latter in turn is made up of at least four components—

Nicotinic acid (pellagra-preventing factor).

Riboflavin.

Vitamin B₆ (adermin).

Chick-pellagra factor (pantothenic acid) and/or various "filtrate factors."

Also under the B "umbrella" have to be gathered certain less well-defined principles—

Vitamins B₃, B₄, B₅.

Pigeon heart-block factor.

All of the above are discussed in other papers in this series, and our task in this contribution is to deal with the "newer" vitamins, a list of which is given in Table 1.

TABLE 1.
LIST OF THE "NEWER" VITAMINS.

Name	Species in which the deficiency has been mostly studied	Effects of deficiency	Chemical nature	Whether chemical structure known	Whether synthesised	Principal sources	Whether of known use in clinical medicine
Vitamin E	Rats ..	Sterility	Fat-soluble, chroman-phytol derivs. (α- and β-tocopherols)	+	+	Green leaves, wheat-germ oil	+ (probably)
F	Rats ..	Dermatitis, caudal necrosis, kidney lesions, irregular ovulation, etc.	Nutritionally essential, unsaturated fatty acids (e.g. linoleic and/or linolenic acids)	+	—	Linseed oil, other vegetable oils	—
H	Rats ..	Seborrheic dermatitis ..	Protein derivative	?	—	Certain protein foods	—
J	Guinea pigs	Increased susceptibility to infection (viz. pneumonia)	Water-soluble ..	—	—	Orange juice	—
K	Fowls, rats, humans	Hæmorrhage associated with lack of prothrombin	Fat-soluble, naphthoquinone derivs. { K ₁ K ₂	+	+	Green leaves	+
L	Rats ..	Failure of lactation ..	—	—	—	Liver	—
M	Monkeys ..	Cytopenia	—	—	—	Yeast, liver	—
P	Guinea pigs	Scurvy-like symptoms, not curable by vitamin C	Flavone-glucosides (citrin, hesperidin)	+	—	Fruit juice	?

FACTOR U
W
Y

ADDITIONAL FACTORS:

CHOLINE

Achromitrichia Factor
Alimentary Exudative Factor
Anti-Anæmic Factors
Bios, Biotic Acid
Cartilage Factor
Chick Anæmic Factor
" Paralysis Factor
Cholic Acid
Chondroitin Sulphuric Acid (C.S.A.)
Encephalomalacia Factor
Extrinsic Factor (P.A.)
Gizzard Erosion Factor
Grass-Juice Factor
H Factor (Trout)
Heart-Block Factor
" Light White" Casein Factor
Muscular Dystrophy Factor
Myopathy Factor
Panmyelophthisis Factor
Physin
Rice Factor

See pages 43 to 45.

Of these "newer" vitamins only one, vitamin K, is known for certain to have a *role* in clinical practice. A second, vitamin E, almost certainly is of consequence for the physician, but final proof based on adequately controlled clinical trials is unfortunately still lacking. Claims have been made for a third, vitamin P; but the issue is still in the arena of controversy.

Vitamin H has not yet substantiated its case for a place in human therapeutics ; and the fanciful clinical applications proposed for vitamin F must be disallowed.

It will be best to discuss first the two vitamins, E and K, about which a clinical literature already exists.

Vitamin E.

About 20 years ago workers in three different laboratories in the U.S.A. found that rats failed to reproduce when restricted to artificial diets containing the four vitamins then known, A, B, C and D. Evans and Bishop of the University of California were the first to indicate clearly that a hitherto unknown vitamin was involved, and named it at first vitamin X, or later vitamin E. Evans and Burr in 1927 and Evans in 1932 published comprehensive monographs describing their pioneer investigations, and these provided the basis for further studies on the pathology of the deficiency, the distribution of the vitamin, methods for its assay, and its concentration from various natural sources.

In the female rat deficiency of vitamin E causes sterility : fertilisation and implantation proceed normally but gestation is interrupted by the resorption of the foetus at about the second week. If vitamin E is restored to the diet, the rat can once again bear live young. In the male deprived of the vitamin degeneration of the germ cells occurs. This is less readily curable, or incurable. More recently attention has been given to other symptoms of prolonged deficiency in the rat. These include muscular dystrophy, degeneration of muscle fibres leading to discoloration of the uterus and seminal vesicles, a characteristic degeneration of the convoluted tubules of the kidney and a so-called "alimentary exudative diathesis". Little work has been done on the avitaminosis in other species apart from the rat. Next to nothing is known about the mode of action of the vitamin ; the theory that it acts through the anterior pituitary has had some support but is not generally accepted.

The materials containing vitamin E in highest concentration include wheat-germ oil, rice-germ oil, cotton-seed oil, and green leaves. It is absent from cod-liver oil and apparently other fish-liver oils, which are so bountifully provided with the A and D vitamins. For purposes of assay a curative technique with female rats is generally used, but quantitative chemical tests with ferric chloride seem very promising (see Emmerie and Engel, 1939).

The isolation of crystalline vitamin E was accomplished in 1936 by Evans and his colleagues. They found that it occurred in two forms, which they named α -tocopherol and β -tocopherol (*=alcohol promoting child-birth*). The first-named

proves somewhat more active than the second in tests on rats. Recently the constitution of α -tocopherol has been established and it has been synthesised. It can be regarded as a derivative of duroquinol, with a side chain derived from the phytol molecule. The latter is of interest in that it enters also in the structure of vitamin K₁ (see below) and of chlorophyll. β -Tocopherol differs from α -tocopherol in having one less methyl

group in the benzene-ring system. Both α - and β -tocopherols may also be regarded as chroman derivatives. Certain closely related synthetic analogues have some degree of biological activity.

In its chemical properties vitamin E is marked by its solubility in fats and fat-solvents, and by its stability to heat and to many reagents. It is however fairly readily oxidised under some conditions and is destroyed during the development of rancidity in fatty menstrea, and by "autoxidative" processes or by ferric salts. It resembles vitamin A in the fact that "reserves" can be stored in the animal organism for considerable times.

Turning to clinical applications, it seems very reasonable to suppose that certain cases of habitual abortion, not attributable to other known causes, may have their origin in a deficiency, or conditioned deficiency (i.e. faulty utilisation), of vitamin E. Many claims have indeed been made for success in the treatment of habitual abortion, or threatened abortion, with the vitamin. Either wheat germ, or concentrates from wheat-germ oil, or, latterly, pure preparations of the vitamin have been used. Unfortunately, however, no one seems to have thought it worth while to *control* their trials, by leaving alternative cases untreated and comparing the results statistically in the positive and negative groups. Judgment must be suspended until this has been done; for as Malpas has pointed out, the chances of the next pregnancy being carried to term in the absence of specific treatment are, after one, two or three spontaneous abortions, 78, 62 and 27 per cent. respectively. Thus the success recorded by many writers may be nothing more than the natural tendency to recovery without treatment. In fact Boycott mentions that a series of seven negative control cases observed by him all recovered without vitamin E. A carefully controlled clinical trial is therefore urgently needed.

Recently the suggestion has been made, based on animal experience, that vitamin E may be of use also in muscular dystrophies. Even tabes have been mentioned in this connection. So far the evidence seems unconvincing.

In veterinary practice vitamin E has been largely used, particularly for habitual abortion in cattle. Here the consensus of opinion seems favourable; but again it may be doubted whether rigid statistical proof is available, based on adequately controlled material.

Readers interested in a more detailed account of modern work on vitamin E may consult a recent monograph (Vitamin E Symposium, 1939).

Vitamin K.

In 1934 H. Dam and F. Schönheyder of Copenhagen described a new deficiency disease in chickens which was characterised by subcutaneous intramuscular hæmorrhages, and by a diminished clotting power of the blood. It was soon found to be due to the lack of a specific vitamin, which was heat-resistant and fat-soluble: this latter conclusion was reached independently and almost simultaneously by Dam (1935) and by Almquist and Stokstad (1935) of the University of California. Systematic investigations by the two groups of workers established that the vitamin was present in high concentration in green leaves (alfalfa, cabbage, spinach, etc.) and in moderate amounts in other vegetable tissues, e.g., tomato, hempseed or soya-bean. Hog-liver fat is said to be a good source, but there is little in normal chicken liver and apparently in various other animal fats or in cod-liver oil (rich in A and D vitamins) or wheat-germ oil (potent source of vitamin E). The name "Koagulationsvitamin" was first suggested and this has later been abbreviated into Factor K, or Vitamin K.

When a chicken suffering from deficiency of vitamin K is treated with an intravenous injection of the vitamin or a concentrate, the clotting time of the blood is restored to normal remarkably rapidly, namely within 4—6 hours. The blood of the deficient chicken is found to have a subnormal content of prothrombin, and the latter is restored to normal upon cure. These phenomena are used as the basis for a method of determining the distribution of the vitamin in foodstuffs.

The precise rôle of vitamin K in the blood-clotting mechanism is not yet known. It has no action *in vitro* on blood from deficient chickens, nor do preparations of prothrombin possess any significant vitamin K activity.

Avitaminosis K has been described also in young geese and ducklings, and it can be produced, but far less readily, in rats and certain other mammals.

Chemical nature. Within the last two years, thanks to the work of Almquist, of Dam, of Doisy, and of Fieser and their respective collaborators, vitamin K has been isolated in a crystalline state and synthesised—or, as it would be more accurate to say, the two naturally occurring variants, vitamin K₁ (present in alfalfa leaves) and K₂ (in fish meal), have been isolated and synthesised. (For detailed bibliography of the very extensive literature see a recent review by the writer—Harris, 1939.) Both vitamins K₁ and K₂ are chemically related to 1:4-naphthoquinone. K₁ is the 2-methyl-3-phytol derivative, and K₂ may be, according to Fieser, the 2:3-difarnesyl derivative, or according to Binkley and others the 2-methyl-3-difarnesyl derivative. It appears that numerous relatively simple synthetic products, with either 2- or 2:3-substituents (and particularly those with a Me group in the 2-position) are biologically active. Several have a potency even greater than that of the natural products.

Vitamin K₁

2-Methyl-1 : 4-naphthoquinone (synthetic substitute, more active and more readily absorbed than K₁).

Clinical applications. In medicine vitamin K has found an important use in at least three hæmorrhagic states known to be associated with hypo-prothrombinæmia, viz. (1) in obstructive jaundice, particularly post-operative; (2) in hæmorrhages owing their origin to other similar obstructive or malabsorptive conditions, and (3) in the hæmorrhagic state in early infancy (Hypothrombinæmia hæmorrhagica neonatorum). In the first of these at least the failure in utilisation of vitamin K can be traced to the absence of bile within the intestine preventing the absorption of the vitamin. Thus the hæmorrhage of obstructive jaundice is due to a *conditioned* deficiency of the vitamin arising from the steatorrhœa. It is not surprising therefore that it has generally been found necessary when the vitamin is given by mouth to administer bile salts (or human bile) simultaneously. An alternative procedure much favoured by recent workers is to give the vitamin by intramuscular injection, in which case bile salts can be dispensed with. It has been found too that certain synthetic products, notably 2-methyl-1 : 4-naphthoquinone are more active, and more readily absorbed, than the more complex vitamin K₁ with its long side chain. Experiments are still in progress with certain water-soluble derivatives (vitamins K₁ and K₂ of course are fat-soluble) and it is hoped that these may prove serviceable when given by mouth even in absence of bile therapy.

In obstructive jaundice. The bulk of the clinical literature so far published relates to the use of vitamin K in the treatment or prevention of post-operative hæmorrhage in obstructive jaundice. Reports are almost unanimously favourable and it is clear that a valuable new weapon has here been forged in the fight against disease. The

prophesy which Dam and Glavind ventured so recently as 1938 has already been amply fulfilled :—

" We are aware that the experiments given in this preliminary communication must be supplemented by a careful clinical investigation, but the fact seems already to be secured that the treatment with parenteral introduction of vitamin K will completely substitute the old bile therapy."

An equally important development is the treatment of patients suffering from obstructive jaundice with vitamin K as a routine measure, not only after operation but as an accepted feature of *pre-operative preparation* (see Rhoads, 1939 ; Olson and Menzel, 1939 ; Feggetter and Potter, 1940).

" Of eleven patients with obstructive jaundice and hæmorrhagic tendency (indicated by prolonged plasma-clotting time) treated with vitamin K [+ bile salts] pre-operatively, 36 per cent. showed some post-operative bleeding (never serious). In contrast, post-operative bleeding occurred in 75 per cent. of twelve patients with obstructive jaundice and hæmorrhagic tendency not treated with vitamin K." (From abstract of paper by Olson and Menzel, 1939.)

Several writers have stressed the advisability of checking the results of such treatment by determinations of prothrombin in the patient's blood. Generally the restoration of the prothrombin value to normal is remarkably rapid, e.g. within twelve hours to two days, as found by Macfie and co-workers (1939) ; but it seems that the response is not necessarily uniform from one patient to another (see Rhoads, 1939). The technique for estimating the prothrombin value of human blood has been described by Dam and Glavind (1938) and by various later writers (e.g. Smith *et al.*, 1939). It appears that bleeding occurs in jaundice when the level of prothrombin drops to a point at about 20 to 50 per cent. of the normal amount. (These two values are given by Stewart (1939) and by the workers at the Mayo Clinic (1938), respectively.)

" The various studies made [at the Mayo Clinic] suggest that bleeding in jaundice occurs when the level of prothrombin reaches as low a point as 20 per cent. of the normal amount. This point is a critical one ; the transition from apparent normality to a hæmorrhagic state may be abrupt and may follow quite a small operative blood loss, owing to the body's inability to regenerate prothrombin in the absence of vitamin K." (Quoted by Lancet, 1938.)

In treatment of hæmorrhagic diatheses. The clinical literature is summarised in Table 2, and it will be seen that apart from obstructive jaundice, vitamin K has been used successfully for the hypo-prothrombinæmia, and consequent tendency to hæmorrhage, in various other analogous conditions—such as post-operative or chronic intestinal obstruction, intestinal fistula, prolonged diarrhœa, and in sprue. Obviously the deficiency of vitamin K in all these instances is a conditioned one ; and indeed it is only recently that the suggestion has been made that avitaminosis K may also be seen occasionally as a result of a direct dietary lack (Kark and Lozner, 1939).

An instructive clinical experiment has been described by Zuckerman and co-workers (1939). They were able to produce a hæmorrhagic tendency experimentally in a young female subject with a total external biliary fistula by restricting her for two weeks to a diet low in fat and deficient in vitamin K. The bleeding diathesis was not alleviated either by oral administration of bile or by administration of a concentrate of vitamin K. The use of both together caused a cessation of bleeding in five days and the return of the prothrombin value to normal in eight days.

TABLE 2.
CLINICAL LITERATURE ON VITAMIN K.

<i>Condition for which used.</i>	<i>Notes on method of administration, etc.</i>	<i>Result.</i>	<i>Reference.</i>
Obstructive jaundice due to cancer (3 cases)	Concentrate injected intramusc.	Prothrombin value or coagulation time restored to normal, and/or liability to hæmorrhage cured	Dam and Glavind (1938).
Obstructive jaundice (18 cases)	Concentrate <i>per os</i> , plus bile salts	Ditto	Mayo Clinic (1938).
" " (3 ")	Concentrate injected intramusc.	"	Dam and Glavind (1938).
" " (30 ")	Concentrate <i>per os</i> , plus bile salts	"	Snell <i>et al.</i> (1938).
" " (14 ")	" " "	Improvement in 11/14 cases	Stewart (1939).
" " "	2-Methyl-1 : 4-naphthoquinone	Successful	Rhoads (1939).
" " "	Ditto, intramusc. injec.	" (post operative)	Fernholz and Ansbacher (1939).
" " "	Diet rich in K (or concentrate) plus bile salts	" (pre-operative prophylaxis)	Macfie, Bacharach and Chance (1939).
" " "	" " "	" " "	Olson and Menzel (1939).
" " "	" " "	" " "	Feggetter and Potter (1940).
Hæmorrhage in sprue	Synthetic K Concentrate	Successful	Engel (1939).
" " "	"	Successful	Hult (1940).
Hypo-prothrombinæmia associated with— post-operative or chronic intestinal obstruction absence of bile intestinal fistula prolonged diarrhœa faulty fat absorption in non-tropical sprue post-operative hæmorrhage [4 out of 8 cases taken for treatment]	Concentrate by mouth, by enterostomy tube, or by intramuscular injection	Successful	Clark <i>et al.</i> (1939).
Hæmorrhagic tendency in newborn infants	Concentrate <i>per os</i> .	Successful	Dam, Tage-Hansen and Nygaard (1939); Waddell and Gurry (1939).
" " "	" "	Successful (curative or preventive)	Nygaard (1939).
Hæmorrhagic diatheses in infancy (icterus gravis neonatorum; anæmia neonatorum; hydrops congenitus)	Vitamin K plus bile-salt by mouth	Hypo-prothrombinæmia cured	Dam, Tage-Hansen and Nygaard (1939).
Direct dietary deficiency (4 adults)	Vitamin K orally	Hypo-prothrombinæmia cured	Kark and Lozner (1939).

There is no evidence that vitamin K is of use in hæmophilia, or in other hæmorrhagic diseases not associated with hypo-prothrombinæmia.

Vitamin K in early infancy. Dam and his co-workers (1939) have shown that in normal infants a moderate hypo-prothrombinæmia develops during the first or second day after birth and then disappears within a week. The cause must be an insufficient supply of vitamin K from the intestine, and the result is the commonly seen slight hæmorrhagic diathesis of the newborn. The fall in prothrombin can be prevented by giving the baby vitamin K by mouth or even by giving it to the mother for at least 24 hours before birth. Nygaard has reported successful treatment of three cases of hypo-prothrombinæmia hæmorrhagica neonatorum with vitamin K, the effect equalling that of blood transfusion. A recent editorial annotation in the *Lancet* discusses the rival merits of blood transfusion and vitamin K therapy for hæmorrhages of the newborn, and concludes that for the general practitioner the former is still to be preferred. "Vitamin K may, of course, justifiably be used in hospital, where it can be rapidly followed by blood transfusion if necessary. And by way of prophylaxis there is evidence

to support the routine administration of the vitamin to the mother for a short time before and after labour, the early commencement of feeding, and the intramuscular injection of 5 mg. of 2-methyl-1:4-naphthoquinone to the infant."

The explanation of this transient prothrombin deficiency in early infancy is probably to be found in a delay in the production of the vitamin by the intestinal micro-flora. There is good evidence that vitamin K may be synthesised by the bacteria in the intestine of various species, and to some extent may account for the differing needs as between one species and another. However this may be, returning to the problem of the infant and its requirements, it has to be added that supplementary feeding with cows' milk in addition to the breast is said to prevent the "physiological" fall in the prothrombin level. Thus, it is evident that the diet of the new-born infant, apart from bacterial synthesis, may play a part in the hæmorrhagic disease.

Vitamin H and Vitamin P.

Two other vitamins, vitamins H and P, have been the subject of clinical trials.

Vitamin H.* This is the "Haut Faktor" ("skin vitamin") described by Paul György (1931, 1935, 1939). In its absence rats maintained on a diet containing excess of raw or dried egg-white develop a severe dermatitis of a characteristic seborrheic nature. This peculiar effect of raw egg-white had earlier been described by Boas (1927). The vitamin seems to occur in nature as a constituent part of the protein molecule. The free vitamin is set free by autolysis or hydrolysis. It appears to be an ampholyte, probably an amino-acid or related substance with excess of acid groups (Birch and György, 1939). It is very stable to heat. The latest reports (György *et al.* 1940) indicate that it is probably identical with "biotin" and with "coenzyme R," growth factors for yeast and for organisms in the nodules of certain plant roots, respectively.

The seborrheic nature of the lesions in rats led György to suggest its trial in psoriasis, and in eczema, or in the so-called seborrheic dermatitis of infancy. So far results appear to have been disappointing, but there is little published literature.

Vitamin P. Szent-Györgyi and his co-workers (Bentsath *et al.*, 1936) contended that experimental scurvy as seen in guinea pigs is a combined deficiency of vitamin C and a new factor, vitamin P. The latter was described as a flavone or flavonol glucoside ("citrin," "hesperidin") found in red pepper and other vegetables. "It was called 'P' because of its effect on 'Permeability' and because of 'Paprika' ('Pepper')." [Szent-Györgyi]. It was stated that guinea pigs on a diet devoid of vitamin C but containing "vitamin P" survive longer than those suffering from a simple deficiency of vitamin C. Vitamin P was considered to regulate the permeability of the capillaries; and it was stated that clinical trials had given encouraging results in curing hæmorrhagic purpuræ in cases where vitamin C alone had proved ineffective. Unfortunately attempts in several other laboratories (Harris, Moll, Zilva) to repeat the experimental observations on guinea pigs failed; and later Szent-Györgyi's collaborator, Bentsath, was himself unable to corroborate his original findings on guinea pigs. What makes the matter the more puzzling is that several investigators have thought that they were able to detect a beneficial result attributable to vitamin P in patients suffering from diseases in which there is an increased permeability of the capillaries. Others however have had negative results clinically. As a recent reviewer (Wormall, 1938) remarks—"the time has not yet arrived for the full recognition of vitamin P". Szent-Györgyi himself suggests: "Maybe, a new and labile accessory food factor is hiding behind these discrepancies and I am afraid much work will be needed, till their final cause will be revealed". There the matter must rest for the present.

* Not to be confused with Factor H, p. 44. The term vitamin H was also used by Boohar (1937) in the sense of the factor now generally called vitamin B₆.

Vitamins F, J, L and M.

There remain several additional vitamins, dignified with letters of the alphabet, which appear to be needed either by rats or other species of experimental animals, but which are not as yet known to have any practical relation to human disease or to dietetics.

Vitamin F. If rats are raised on a "synthetic" basal diet rigorously freed from all traces of fat, a deficiency disease develops characterised by cessation of growth, the development of a dry scurfy skin and a scaly tail (and sometimes caudal necrosis), irregularities in the reproductive cycle, and lesions in the kidney and urinary tract (Burr and Burr, 1929, 1930; Burr *et al.*, 1932; Evans, Lepkovsky and Murphy, 1934). Two known constituents of fats, the highly unsaturated fatty acids, linoleic and linolenic, will prevent the deficiency even when provided in only minute amounts. For these essential unsaturated fatty acids the name Vitamin "F" [*F* for *Fat*] has been proposed. Other related unsaturated acids may have some degree of activity, and it appears that there is some close inter-relation between these substances and vitamin B₆ (another anti-dermatitis factor). Attempts to produce the deficiency experimentally in man by prolonged subsistence on diets almost devoid of fat have failed (e.g. Brown *et al.*, 1938). These same diets produced the fat-deficiency-syndrome in rats, and it seems very unlikely therefore that any natural human diets can in practice be so low in fat or in the essential fatty acids as to give rise to actual avitaminosis F in man. It is true that claims have been made that the incorporation of vitamin F in cosmetic preparations and ointment improve the complexion and prevent dandruff or eczematous conditions (Pacini, 1936), but these lack substantiation—and it is hard to see the connection between the scaly tail or caudal necrosis of the experimental rat reared on diets completely devoid of all traces of fat and the alleged beneficial action for normal human subjects of the vitamin when incorporated in toilet preparations!

Vitamin J. Vitamin J, or Factor J, is the name given by Euler and Malmberg (1934) to a hypothetical substance present in orange juice along with ascorbic acid and supposed to differ from the latter in conferring on guinea pigs increased resistance to pneumonic infection.

Vitamin L. Vitamin L (including L₁ and L₂ and possibly other components) is described by Nakahara *et al.* (1933, 1934, 1936) as necessary for lactation—whence its name—in rats.

Vitamin M. This is the name given by Day to a factor which prevents nutritional cytopenia in monkeys ["M" for "Monkey"]. Its possible relation to the newly recognised components of the vitamin B₆ complex, adermin, pantothenic acid and filtrate factors, may still have to be investigated. Reference—Langston *et al.*, 1938.

Factors U, W and Y.

As we approach the end of the alphabet there is a curious tendency to denote new dietary essentials as "Factors" rather than "Vitamins". Three such have been discussed in the literature, namely U, W and Y.

Factor U. (Stokstad and Manning, 1938) is described as a substance present in yeast, middlings, wheat bran and alfalfa, which has a growth stimulating action on chicks, and is distinct from other accessory factors hitherto recognised or needed by chicks (aneurin, riboflavin, nicotinic acid, filtrate factors, "gizzard-erosion" factor, and vitamins A, D, K, etc.).

Factor W. This is a growth factor for rats, distinct from vitamins B₁, B₂, B₆, riboflavin, filtrate factor, and considered to be related to the adenine nucleotides (Elvehjem *et al.*, 1936; Frost and Elvehjem, 1937, 1939; Emerson and Evans, 1938).

Factor Y. This term was used by Chick and Copping (1930) to denote a factor in yeast ("Y" for "Yeast") distinct from the B vitamins then known. It probably corresponds with what is now called vitamin B₆ (adermin) plus perhaps a residue of other B vitamins.

Choline.

In the past year or two it has come to be recognised that choline is an indispensable constituent in the diet of the rat. The story begins in 1934, when Best and his co-workers demonstrated that choline possesses a pronounced lipotropic action. In the absence of choline "fatty livers" develop and the deposition of cholesterol in the tissues is affected. Later it was found that the absence of choline from the diet might appreciably retard the growth rate of young rats (McHenry, 1935), although to demonstrate this effect conclusively it was necessary that the diet should contain a very high proportion of fat and a low concentration of protein (Best *et al.*, 1936). More recently the symptoms of deficiency of choline in the rat have been found to include hæmorrhagic degeneration of the kidneys, paralysis and impairment of lactation (Griffith and Wade, 1939; Sure, 1940).

The significance of these findings for human nutrition still remains to be discovered.

Various Unclassified Factors.

To conclude our survey, it only remains to make brief mention of some additional factors, not yet labelled with distinctive letters of the alphabet but designated rather by the effects of their deficiency or by their sources in nature. Some of them are as yet very poorly characterised, and others may be related to (or identical with) one or other of the better known factors already discussed. In no instance is there any clear connection with human disease. In the following list they are taken in alphabetical order. It must not be imagined that a good case has been made out for the separate existence of every one of the factors mentioned below. The list is given rather to provide the reader with a handy index for reference—also it will serve to convey an impression of the number, and in some instances the vagueness, of these additional factors and of the need for further research.

Achromotrichia Factor.—(Synonyms: Anti Gray-Hair Vitamin, Vitamin Bx.) Absence causes defective pigmentation of hair of rats, silver foxes, etc. Present in yeast and liver. Can be regarded as a "B" vitamin, but distinct from all known components of vitamin B₂ complex. Literature—Gorter, 1934; Lunde and Kringstad, 1939, 1 and 2; Oleson *et al.*, 1939).

Alimentary Exudative Factor. — Probably identical with vitamin E. (Dam and Glavind, 1939).

Anti-anæmic Factors.—Two anti-anæmic factors present in liver, the *Extrinsic Factor* and the *Macrocytic Anæmia Factor*, may be regarded as in the category of vitamins and are discussed below (pp. 44 and 45 respectively). Other anti-anæmic factors in liver include (1) the principle effective in Addisonian pernicious anæmia and (2) the principle shown by Whipple to influence secondary anæmia (see review in Lancet, 1938). Apparently the anti-pernicious-anæmia principle in hog stomach, "hæmopoietin," is distinct from that in liver (Klein and Wilkinson, 1934).

Bios, Biotic Acid, etc.—Factors required, in addition to pantothenic acid (p. 34) and other "known substances," for growth of yeast at maximum rate. Requirements of mammals for several such factors at present doubtful or unknown (see e.g. Wildiers, 1901; Eakin and R. J. Williams, 1939).

Cartilage Factor.—Growth factor for chicks, present in cartilage, kidney, brain, liver, wheat middlings, polished rice. Said to be distinct from chondroitin, *vide infra* (Hegsted *et al.*, 1939).

Chick Anæmia Factor.—Factor preventing anæmia and loss of weight in chicks (Hogan and Parrott, 1940).

Chick Paralysis Factor.—Absence causes paralysis in chicks. Fat-soluble. Present in unsaponifiable fraction of soya-bean oil, or alfalfa meal (Jukes and Babcock, 1938; see also Norris *et al.*, 1930; Hart *et al.*, 1930; Bethke *et al.*, 1931).

Cholic Acid.—See gizzard-erosion factor, *infra*.

Chondroitin Sulphuric Acid (C.S.A.).—Growth factor for chicks and rats, present in cartilage and various animal and vegetable tissues, thought by some to be identical with gizzard erosion factor—*vide infra* (Bird, Oleson, Elvehjem and Hart, 1938), but disputed by others (Robinson, Gray, Chesley and Crandall, 1939). See *Rice Factor*, below.

Encephalomalacia Factor.—Prevents "nutritional encephalomalacia" in chicks ("chick paralysis," "crazy chicks"), marked by severe pathological changes in central nervous system developing only during period of active growth of the brain (Pappenheimer and Goettsch, 1931, 1934, 1). Said to exist in two forms, water-soluble and fat-soluble. Fat-soluble form is identical with or can be replaced by synthetic vitamin E *dl*- α -tocopherol (Dam *et al.*, 1938). See also *Myopathy Factor*, *infra*.

Extrinsic Factor (preventive of pernicious anæmia).—The extrinsic factor of Strauss and Castle (1932) may be regarded as residing in the heat-stable vitamin B₁₂ complex, but it is distinct from any of the known constituents (Birch, György and Harris, 1935). The view that it is identical with the macrocytic anæmia factor, *vide infra*, has now been withdrawn (Wills and Evans, 1938).

Gizzard-Erosion Factor.—Prevents erosion of the lining of the gizzard in chicks (McFarlane *et al.*, 1931). First supposed to be identical with vitamin K (Dam, 1935; Schönheyder, 1935) but now regarded as distinct (Almquist and Stokstad, 1936; Bird *et al.*, 1936). Certain bile salts, viz., cholic acid or dehydrocholic acid (but not desoxycholic acid) are effective as preventive or curative agents (Almquist and Mecchi, 1938)—cf. vitamin K sparing action of bile salts (above, p. 38). Alleged identity with chondroitin sulphuric acid disputed (Crandall *et al.*, 1939).

Grass-Juice Factor.—This is described as "a relatively labile vitamin necessary for the normal growth of guinea pigs and rats" (Kohler, Elvehjem and Hart, 1936, 1938). It is found in grasses, lettuce, etc.

"H" Factor for Trout.—"A factor not included in the usual category of protein, carbohydrate, mineral matter and vitamins A, B, D [C or E] which is the major factor in the growth of trout." Thermolabile; present in yeast and dried skimmed milk (McCay *et al.*, 1927, 1928; McCay, 1938).

Heart-Block Factor.—Prevents bradycardia and heart block in pigeons. Differentiated from vitamin B₁ (Carter, 1930). Already mentioned under vitamin B₁₂ complex on p. 34, but entered again here as it is considered that "it does not yet seem clear that the heart-block factor is to be classed in the B group" (Carter, Kinnersley and Peters, 1930).

"Light White" Casein Factor.—Factor, present in "light white" casein but not in "vitamin free" casein, which stimulates growth of rats. Present also in fresh milk, lettuce, fresh or dried grass, ox muscle, liver and wheat embryo (Coward, Key and Morgan, 1929; Coward, Key, Dyer and Morgan, 1931).

Macrocytic Anæmia Factor.—A factor present in crude liver extracts which is curative in tropical macrocytic anæmia and in nutritional macrocytic anæmia in monkeys, and is distinct from the anti-anæmia extrinsic factor (Wills and Evans, 1938).

Muscular Dystrophy Factor.—Absence causes "progressive, highly selective and ultimately fatal dystrophy of the voluntary muscles" in guinea pigs and rabbits (Goettsch and Pappenheimer, 1931) and rats. A similar or identical abnormality can be prevented or cured by synthetic vitamin E (*α*-tocopherol) but it is sometimes thought that two distinct vitamins are concerned, only one of which is vitamin E. (Selection from recent literature:—Olcott, 1938; Morgulis *et al.*, 1938; Morgulis, 1938–9; Goettsch and Ritzmann, 1939; Shimotori, Emerson and Evans, 1939. Morgulis is the author of a detailed illustrated review, "Nutritional Muscle Dystrophy," 94 pp., 1938.)

Myopathy Factor for Ducklings.—Produced in ducks by the same diet which in chicks produces Nutritional Encephalomalacia (q.v.). The latter is a disorder of the central nervous system, but in the nutritional myopathy of ducks there are no changes in the C.N.S., but the birds "succumb to a remarkable and universal degeneration of the skeletal muscles" (Pappenheimer and Goettsch, 1934, 2)—cf. Muscular Dystrophy Factor, above.

Panmyelophthisis Factor.—Factor preventing so-called "panmyelophthisis" in rats—a disease characterised by severe anæmia, "together with symptoms of a hæmorrhagic diathesis, such as blood effusions in the skin, epistaxis, melena, hæmaturia, and, frequently, bilateral adrenal hæmorrhage" and said to be the counterpart of aplastic anæmia in man (György, 1937, 1938; György, Goldblatt, Miller and Fulton, 1937). Possible identity with nicotinic acid (p. 34) has been suggested (György, 1938).

Physin.—Factor present in fresh ox liver, which promotes growth, lactation and reproduction in rats and has a transmitted effect on the offspring (Mapson, 1932: cf. also Smith and Seegers, 1934). Has a similar action on swine (Dunlop, 1935). Cf. vitamin L, p. 42.

Rice Factor.—Growth-promoting factor for chicks, and prevents muscular dystrophy (cf. above). Present in polished rice. Appears to consist of two components, viz., glycine and chondroitin (see preceding page). Glycine is replaceable by creatinine, of which it is probably a precursor; and the active component of the chondroitin seems to be glucuronic acid (Almquist and co-workers, 1940).

The array of new names is indeed bewildering. None the less, a good case has been made out for the existence and reality of most of the deficiency *symptoms* described in the last section. Within the next year or two we may expect to see knowledge extend from the present vaguely descriptive basis, and reach a more exact definition and differentiation of the actual nature of the *preventive factors* concerned. No doubt several of the items now given separate entries above will be found to fall into a single category. (Consider in this connection vitamin E, the "two" muscular dystrophy factors, the encephalomalacia factor and the myopathy factor.) On the other hand some of the factors now considered single will almost certainly be found complex. For the time being the scientific worker may be content to imitate the standpoint recommended to churchmen who have intellectual doubts about points of dogma—

"Assent to formularies . . . should be understood as signifying general acceptance without implying detailed assent to every phrase or proposition thus employed. A member should not be held to be involved in dishonesty *merely* on the ground that, in spite of some divergence . . . he has assented to formularies . . . It is legitimate either to suspend judgment on the point, or alternatively to interpret the language in a purely symbolic sense." (Church of England Report of Commission on Doctrine, 1938.)

However that may be, the growing length of the vitamin alphabet undoubtedly puts a strain on the memory of the student. One almost begins to sympathise with the Chancellor of Cambridge University who, about a hundred years ago, at the time of the election of Prince Albert as Chancellor (see Bolitho, 1933) urged that "a century should pass before new discoveries in Science should be admitted into University instruction."

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