and phosphorus at a high rate was tried on two occasions (0·5 oz. of bone-flour per sheep twice weekly), no better growth rate resulted, although the amount and severity of rickets was reduced.

Conclusion

There is a relationship between a good season, more feed, greater growth by the sheep and high incidence of rickets, and it appears that the quantity of ultraviolet radiation is of less importance than the occurrence of some specific principle interfering with phosphorus metabolism in the growing sheep, found in highest concentration in green cereals.

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Imbalance of Fat-Soluble Vitamins

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Only a few instances are known in which the requirement for one fat-soluble vitamin has been found to be influenced by the intake of another vitamin of this group. If we interpret the scope of our title more comprehensively, however, we may consider the effects of toxic overdosage with one vitamin as being a form of imbalance, and may include also the effects of excess or deficiency of various other nutrients on the activity of the fat-soluble vitamins.

Vitamin A

Great excess of vitamin A when given to rats causes skeletal fractures and internal haemorrhages in various sites (Moore & Wang, 1945). The symptoms resemble those of scurvy, and it has been claimed that treatment with vitamin C is beneficial (Vedder & Rosenberg, 1938). Another link between these two vitamins might be inferred from the reduced synthesis of vitamin C in vitamin A deficiency (Sure, Theis & Harrelson, 1939), although others have found that this relationship is not specific (Mapson & Walker, 1948–9). Mayer & Krehl (1948), however, have claimed that the administration of vitamin C greatly prolongs the survival of rats kept on a diet deficient in vitamin A, and Bassett, Loosli & Wilke (1948) have reported that, by giving vitamin C to silver foxes kept on a diet deficient in vitamin A, symptoms of nervous inco-ordination were prevented. Experiments by the author and his colleagues have failed to indicate that ascorbic acid has any beneficial effect in deficiency or excess of vitamin A, and vitamin D also has been found ineffective in the treatment of hypervitaminosis A.

The report of Light, Alscher & Frey (1944) that a state of vitamin A excess induces in rats a low level of blood prothrombin which may be corrected by giving vitamin K

has been confirmed (Walker, Eylenburg & Moore, 1947). This treatment was found to ameliorate the haemorrhages without preventing skeletal fractures.

Deficiency of vitamin E was found by Moore, Martin & Rajagopal (1939) to lead to reduced liver stores of vitamin A in rats. Hickman, Harris & Woodside (1942) found that the effectiveness of small doses of carotene and vitamin A was increased by simultaneous dosing with vitamin E. It is clear that vitamin E may protect vitamin A by: (1) preventing oxidative changes in the fatty medium before dosing, for which purpose tocopherol is effective only as the free alcohol, and other anti-oxidants, such as hydroquinone, are equally protective; (2) preventing the destruction of carotene and vitamin A during their passage through the intestines; and (3) reducing the loss of vitamin A from the tissues.

Imbalance of vitamin A metabolism may result also from the defective absorption of carotene through the use of medicinal paraffin. In human subjects the habitual use of this drug may reduce the level of carotene in the plasma by 50% (Alexander, Lorenzen, Hoffman & Garfinkel, 1947). Infants may have difficulty in absorbing vitamin A even from marine liver oils, and absorption is greatly improved by giving the vitamin in the form of an aqueous emulsion (Lewis, Bodansky, Birmingham & Cohlan, 1947).

The action of certain cereal products, notably ergot of rye, in emphasizing the effects of vitamin A deficiency on the nervous system was observed by Mellanby (1930). The increased liability to injury was considered to result from an unduly rapid expenditure of vitamin A reserves rather than from the presence of a specific neurotoxic factor; the more recent discovery that nerve lesions in vitamin A deficiency are associated with malformation of the bones (Mellanby, 1939, 1941) would appear to strengthen this view.

A curious form of imbalance has been noticed by the author in rats which have been deprived of vitamin A and then cured with moderate doses of carotene. During acute deficiency the incisor teeth retain their normal brown colour, but some weeks after treatment has been started they often become completely depigmented. This apparent anomaly may be due to injury to the unerupted parts of the teeth during the period of acute deficiency.

Vitamin D

Imbalance of this vitamin has been discussed by other speakers, but the successful treatment of cutaneous tuberculosis with doses of calciferol verging on the toxic level (Charpy, 1943; Dowling & Thomas, 1945–6) may be mentioned as an example of vitamin imbalance being turned to practical advantage.

It is noteworthy that so far there has been little evidence that vitamin D is as susceptible as vitamin A to the effects of oxidized fats and anti-oxidants. This difference may be due to the somewhat greater chemical stability of vitamin D.

Vitamin E

Extensive experiments with animals have indicated that lack of vitamin E may cause many lesions besides failure in reproduction. The abnormalities found vary in different species and, in numerous instances, are affected by the supply of many other nutrients. Thus, deficiency of vitamin E may cause not only infertility through resorption of the

foetuses (Evans & Burr, 1927) or through testicular degeneration (Evans, 1925), but also muscular dystrophy (Olcott, 1938), brown pigmentation of the uterus, skeletal muscles, and adipose tissues (Martin & Moore, 1936, 1939; Dam & Granados, 1945), exudative diathesis (Dam & Glavind, 1938), encephalomalacia (Dam, Glavind, Bernth & Hagens, 1938), renal abnormalities (Martin & Moore, 1936, 1939), ceroid pigmentation of the liver (Victor & Pappenheimer, 1945), and the uneconomical use of protein

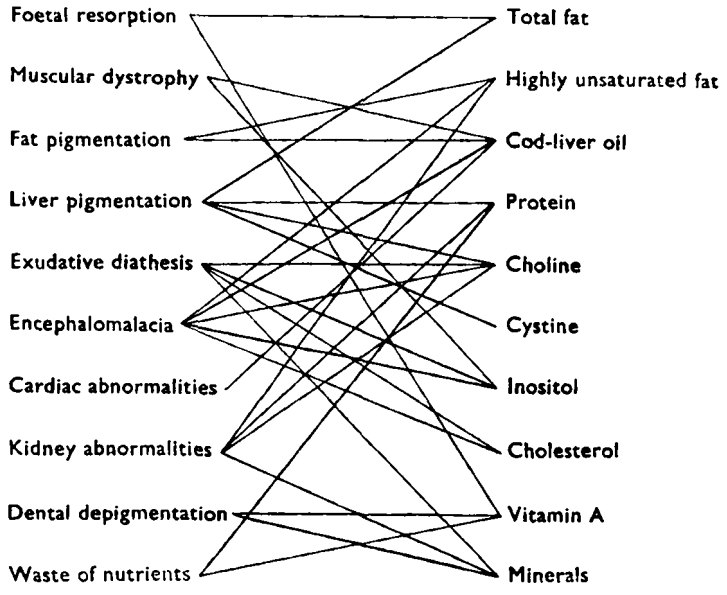

Fig. 1. Factors affecting the occurrence of lesions due to vitamin E deficiency. The diagonal lines indicate claims that deficiency or excess of the nutrient listed in the right-hand column interacts with deficiency of vitamin E to cause or aggravate the abnormality in the left-hand column with which the nutrient is linked.

(Dam, 1944*a*) and of vitamin A (Davies & Moore, 1941). Some of these abnormalities are influenced not by the supply of vitamin E only, but also by the amount, degree of unsaturation and character of the fat in the diet, by the protein allowance, and by all the participants in the complicated lipotropic systems, including choline, cystine, methionine, inositol and cholesterol. The result is a complicated network of interrelationships which will be fully clarified only by prolonged and carefully co-ordinated research. An attempt to suggest graphically the complexity of these interrelationships is made in Fig. 1.

Again, it is evident that vitamin E may be imbalanced by the presence of fats in distinctly different ways. For instance, although vitamin E protects fats from rancidity, it is equally true that all rancid fats will tend to destroy any vitamin E which is added to them. On the other hand, certain fresh fats, notably cod-liver oil and hog-liver fat, have been shown by Dam (1943, 1944*b*) to emphasize some effects of vitamin E deficiency. This property is lost when the fats become rancid, and thereby capable of destroying vitamin E in vitro. Dam concludes that highly unsaturated fats inhibit the action of vitamin E in the tissues by some mechanism which does not involve the general destruction of a vitamin.

Vitamin K

The inhibition of vitamin K by dicoumarol from spoilt sweet clover has been discussed by a previous speaker, but deserves further mention as an excellent example of the imbalance of a fat-soluble vitamin by a typical antivitamin under natural conditions (Stahmann Huebner & Link, 1941). In comparing the effects of dicoumarol poisoning in rats with those of vitamin A excess, Walker *et al.* (1947) found that, although dicoumarol readily lowered the prothrombin content of the blood, the animals remained free from skeletal fractures.

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