Toxamins in food / by Sir Edward Mellanby.

which is responsible for the potential changes and the passage of the impulse may be substances as familiar and as 'non-specific' as potassium or lactate.

Whatever view we take of the mechanism of cerebral activity, it is thus almost certain that the final solution can be expressed in terms of chemical change. The most obvious step towards investigating its nature will be to determine the increase in gaseous metabolism, if any, which occurs as the result of activity. So far as we may place reliance on the results of the study of brain tissue *in vitro*, they indicate that the oxidative mechanisms—dehydrogenases, as well as the pigment cytochrome and the cytochrome oxidase—are far more abundant in grey matter than in white. In the term 'grey matter', we include nerve cells, non-medullated fibres, and synapses. Since the nerve cells of the posterior root ganglia (in which no synapses are present) are but little better equipped than white matter with this oxidizing machinery, it is just possible that the synapse is the point at which most of the metabolic events take place. And it is to the synapse that physiological theory attributes those characteristics which distinguish conduction in the central nervous system as opposed to conduction in peripheral nerve.

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Toxamins in Food

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It is curious how biological research is influenced by vogues and fashions: probably not to the extent of dress, but still greatly. Nor is this altogether a bad thing. It means that a profitable idea is often pressed until it looks like a squeezed lemon, but, unlike the lemon, it is not really dry and is only put aside and not thrown away. After a moribund period the original line of investigation is taken up from another angle, the old fashion is revived, and all the workers in the subject are after it again.

In nutritional investigations this phenomenon is particularly apparent. Chatin(1) in 1850 put forward the first instance of deficiency disease, though he did not give it this name, when he ascribed simple goitre to a deficient intake of iodine in food and drink. His excellent work was discredited, partly by the French Académie des Sciences, and partly by the success of the Pasteur investigations on micro-organisms which led the medical world to believe that all disease is due to a *materies morbi*. Only in 1895, with the discovery of iodine in the thyroid gland by Baumann(2), was Chatin's original view of iodine deficiency and goitre revived and established.

When Eijkman(3) discovered the preventive and curative effects of rice polishings on polyneuritis gallinarum and beri-beri in 1897, he suggested that both diseases were due to the toxic effect of carbohydrate on the nervous system and that this toxicity was normally antagonized by a chemical agent in the rice pericarp. The suggestion that beriberi was purely a deficiency disease due to the absence from the diet of a chemical agent present in the silver skin of rice and other substances, which could be easily destroyed by moist heat, was advanced

by Grijns(4) in 1901. Eijkman in his earlier work could not shed the idea of a disease independent of a positive agent either of the nature of a toxin or a bacterium. Grijns' theory of deficiency disease has indeed been fruitful, and was followed by the establishment of scurvy by Holst & Frölich(5), of xerophthalmia by Osborne & Mendel(6), of rickets by E. Mellanby(7), of defective teeth structure by May Mellanby(8), and a number of other conditions as having a similar aetiology.

Now the pendulum swung towards the deficiency theory of nutritional disease with a vengeance, and well has the theory served its purpose. The object of the present contribution, however, is to swing the pendulum back a bit and emphasize the view that some so-called deficiency diseases are not simply due to the deficient intake of dietetic entities but depend also on the action of certain positive toxic factors which are normally present in food. Such a view is not only justified by experimental results, but is to my mind essential both for the control and elimination of certain nutritional diseases and also for the light it sheds on the normal working of the body. It is also a view which extends the idea of the nature of 'protective' foods from that advanced by McCollum when he introduced this terminology. It is of interest to note that the words 'protective substances' were previously read by Grijns in his paper on Polyneuritis Gallinarum (1901) to describe the antineuritic factor in food. A protective food, for McCollum, was one which supplied chemical factors missing from the rest of the diet, thus making it complete. According to my view, protective foods not only do this, but in some cases supply a really protective mechanism against toxic agents actually present in certain foods. That is to say, perfect nutrition is a condition in which, as the result of a conflict between harmful and defensive chemical mechanisms, the defensive mechanisms win. As in many battles, the defensive side can only win if its forces are superior in numbers or in strategy, so that generally more protective foods are necessary when the offending forces are greater.* This introduces a difficulty, often insurmountable,

* Thus the greater the amount of porridge consumed, the more milk is necessary to ensure good calcification of bones and teeth.

because the body can only receive a limited amount of combating elements in the form of ordinary food.

In 1926, as the result of investigations on nutritional causes of rickets and demyelination of nerve fibres in the nervous system, I introduced the word 'toxamin' as descriptive of two unknown factors in cereals(9), the first which interfered with bone calcification and the second which hastened degenerative changes in the nervous system. The name simply implied substances which produced harmful effects, each of which could be antagonized by a specific vitamin. Nothing could be said at the time about their chemical constitution; they might be simple or complicated. In the case of the rickets-producing toxamin, its effect on bones and teeth could be largely antagonized by vitamin D and to some extent by calcium salts. In the case of the neurotoxin, I could not name the antagonizing fat-soluble vitamin at the time, but later I showed that both vitamin A and carotene were effective agents(10).

The anti-calcifying toxamin of cereals

Even in 1921(7) I did not regard rickets as a simple deficiency disease, but called it a deficiency disease of growth, so that the greater the growth of an animal, the more antirachitic vitamin and calcium were necessary for the proper formation of bone. The effect of cereals at that time I ascribed to the greater growth produced when added to the diet. Only in 1922(11), when it became clear that equal quantities of different cereals varied greatly in their rickets-producing qualities and that those with higher calcium and phosphorus content, such as oatmeal and wheat germ, interfered more potently with bone calcification than those containing less of these substances, such as rice and white flour, did it seem necessary to introduce the idea of a chemical constituent of cereals which actually interfered with calcification.

In spite of many attempts to get some idea of the nature of this rickets-producing substance, I failed to do so. In this work, however, I did not try the effects of what now appears ought to have been tried, namely, phytin. This omission was made good to some extent in 1934, when Bruce & Callow(12) published

their work, in which they showed that phytin (Ca Mg inositolhexaphosphate) and sodium inositolhexaphosphate failed to prevent rickets when administered to rats on a high calcium, low phosphorus and low vitamin D diet. Since simple inorganic phosphates greatly mitigated the disease when added to the same diets, it was clear that the phosphorus of the phytic acid salts was not available to the animals under these experimental conditions. Bruce & Callow therefore concluded that the rickets-producing effect of cereals was due to the unavailability of much of their phosphorus because it was in the inositolhexaphosphate form.

McCance & Widdowson(13) found by direct experiment that the phosphorus of phytin—Ca Mg inositolhexaphosphate—may be as much as 50 per cent unavailable when added to human diets. The investigations have also been continued by Steenbock and his colleagues, who showed that phytin phosphorus is but poorly available as compared with that of phosphoric acid and sodium glycerophosphate when given to rats on a high calcium, low phosphorus and low vitamin D diet. In experiments using maize, they also confirmed an observation published by May Mellanby(14) in 1929, that when oats are allowed to germinate and then autolyse, they lose their rachitogenic qualities. Templin & Steenbock(15) found that germinated autolysed maize was much less rachitogenic than maize itself, and Lowe & Steenbock(16) later showed that this loss of rachitogenic action of germinated autolysed maize was accompanied by a conversion of organic phosphorus to an inorganic form. They assumed, therefore, that this change was due to the action of the phytase in maize, which broke down the phytin and converted the unavailable organic phosphorus to available inorganic phosphorus.

Important as all this work is, especially in giving an indication of the ultimate solution to the problem, it does not clinch the matter. All that it establishes is that the phosphorus of phytic acid salts is only partially available. What it does not show is that phytin in cereals actually produces rickets by interfering with calcium retention, an action which is the fundamental property of the rachitogenic toxamin.

Prof. D. C. Harrison and I, in work which will be published later, have studied the problem from this direct angle and tested the effect of phytic acid compounds on bone calcification of dogs on moderate rickets-producing diets. We have found that phytic acid itself under these conditions does actually increase rickets and osteoporosis. Phytin, on the other hand, does not interfere with bone calcification and indeed may have a slight antirachitic effect. Phytin in cereals, therefore, cannot account for their rachitogenic effect, nor is there any good evidence that phytic acid as such is present in cereals.

It is difficult to avoid the conclusion, however, that a substance having its phosphorus in organic combination affords the true explanation of the action. It seems likely that a phytic acid complex is present in cereals from which the acid is liberated on digestion. If, for instance, phytic acid is combined in a protein complex, as May Mellanby(14) suggested the rachitogenic toxamin would be found, the facts as at present known may be explained. Whether this is the real explanation, however, can only be settled by further work.*

Even those who have accepted the view that cereals have an anti-calcifying effect have regarded the subject as academic and of no practical importance in child nutrition. Since the discovery of the antirachitic vitamin in 1918, most of the attention of medical men and of biochemists has been centred, so far as rickets and defective formation of teeth are concerned, on the positive calcifying action of vitamin D, either as the natural product cod-liver oil or in the synthetic form. I shall now therefore give another instance of the anti-calcifying effect of some cereals.

On the basis of clinical evidence, including the histopathology of the bones and the curative effect of cod-liver oil, it has come to be assumed that adolescent rickets and osteomalacia have a similar aetiology to rickets in children. So far as I am aware, no experimental studies of osteomalacia in animals have been made, and the condition has not been experi-

* Another possible explanation is that the rachitogenic action of cereals does not depend only on its phytic acid content, but also on the amount of calcium in the diet relative to this phytic acid.

mentally produced in adult animals. I have recently been able to show that osteomalacia can be readily produced in adult dogs by giving a diet rich in cereals of powerful anti-calcifying action and poor in calcium and vitamin D. If cereals of less anti-calcifying action be eaten, then it seems impossible under these experimental conditions to produce any great defect in bone structure in adult dogs, beyond osteoporosis.

A number of adult dogs in normal health and physical condition were given different diets with the object of seeing whether osteomalacia could be produced. All these diets were rich in cereal, white flour in some cases, oatmeal in some cases, and maize in others. Other variables tested were the fat-soluble vitamin content, by giving cod-liver oil, butter or peanut oil in different cases; the quantity of meat and other proteins, and the effect of the addition of calcium carbonate and sometimes of calcium phosphate. After keeping the animals on constant diets for seven months to a year, they were killed and their bones examined chemically and histologically. The outstanding results can be described in a few words. Deformity of the bones was only produced in the animals whose diets included large quantities of those cereals with intense anti-calcifying action, i.e. maize or oatmeal. When white flour or rice were the cereals eaten, little or no deformity of bone appeared. The maize-eating dogs had bones with much osteoid tissue and very low calcium content, and oatmeal had a somewhat similar effect. The white flour and rice dogs had much better calcified bones with little osteoid tissue. In other words, maize diets produced severe osteomalacia. If, however, cod-liver oil or calcium carbonate was added to the diets, no osteomalacia developed and the bones remained relatively hard. Calcium phosphate had some preventive effect but not as much as calcium carbonate. It is evident from these experiments that a deficiency of calcium and of vitamin D is not sufficient for producing osteomalacia in adult dogs under the conditions of these experiments; in addition, the diet must be rich in the anti-calcifying toxamin found so abundantly in maize and oatmeal, but not to the same extent in white flour and rice. The ingestion of the toxamin deprived the bones of their stores of calcium

and made them soft and deformed. This excessive robbing of the bone of the calcium and phosphorus took place even though the intake of these elements was greater in the dogs eating oatmeal or maize.

Photographs of the costo-chondral junctions of some of these dogs are shown in Figs. 1 to 4, and it will be seen how deformed are the bones of the dogs eating maize (Figs. 1 and 2) as compared with those eating white flour (Fig. 3) or rice (Fig. 4).

I have long preached to medical men the importance of this aspect of nutrition in relation to the development of rickets and teeth structure in children. My words, based on experimental results, have gone practically unheeded. Probably now, when it can be shown that even adult bones are robbed of their calcium and phosphorus by cereals, they will be more ready to accept the statement and to reduce the cereal intake of infants and children, especially in early life, and of pregnant women.

The question of a neurotoxic 'toxamin'

Whereas the presence of an anti-calcifying toxamin in cereals can be regarded as established, the same cannot be said of the toxamin in cereals which I suggested might partially explain nerve degeneration found in some of my experimental animals. I am less certain now, after several years' further work, that there is a substance with this specific effect. I do not mean by this that there is no toxic substance, but only that I doubt whether it has the neurotoxic effect as specifically as the anti-calcifying substance has on bone and teeth calcification. The fact is that vitamin A deficiency in animals, and especially in all young animals tested, is so potent in producing pathological changes in the nervous system that any toxic agent which hastens the loss of the vitamin A stores from the body will increase the intensity of nerve degeneration in such animals. Zimmerman(17) has indeed shown that a synthetic diet not containing cereals but devoid of vitamin A and carotene produces the characteristic demyelination changes of nerve fibres in rats. This I have also found to be the case. On the other

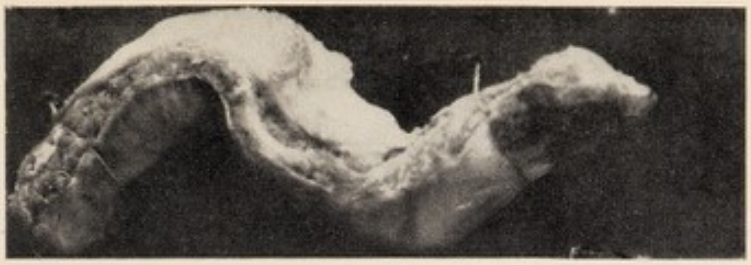

Fig. 1. Maize.

Fig. 2. Maize.

Fig. 3. White flour.

Fig. 4. Rice.

Photographs of ribs of four dogs whose diets were composed mainly of cereals for a period after full growth.

hand, I attempted to produce degeneration of the nervous system in a young dog by feeding it on a synthetic diet without cereals, vitamin A and carotene, and only produced a small amount of degeneration. From this it would appear that cereal in the diet hastens the pathological degenerative changes, for it is an easy matter to produce profound demyelination in young dogs by giving a diet rich in cereals and deficient in vitamin A and carotene. Almost any cereal will do except yellow maize, which is rich in carotene. I have made many attempts to classify cereals according to their nerve-degenerating effects in the same way as I classified the cereals in their rachitogenic qualities. On the whole these experiments have failed in their object, partly no doubt because of the great differences in the stores of vitamin A in different dogs at the beginning of the feeding. These stores are present for the most part in the liver and body fat, and have largely to be used up before the demyelination process in the nerves begins. Similarly, attempts to concentrate the hypothetical toxamin in cereals have failed, probably for the same reason. This work, however, is gradually bringing me to the belief, mentioned above, that the toxic agent is not a specific neurotoxin, but one which in its general effect hastens the discharge or using up of the stores of vitamin A in the body.

It may be remembered that one of the cereal products which I studied in this connexion was ergot of rye(10), and that the choice of this substance was made because of the similarity between the widespread degenerative changes in the nervous system of dogs produced experimentally and those of convulsive ergotism of human beings, a disease which often occurred at one time in epidemic form in countries, especially in times of famine, where rye is extensively eaten. Ergot of rye certainly hastens and intensifies the nerve disorder when added to diets deficient in vitamin A and carotene, and can be eaten with impunity by animals, so far as the nervous system is concerned, when vitamin A or carotene is present in the food. It is an interesting fact that, whereas most dogs loathe their food if ergot in small quantities is a constituent and vitamin A-containing substances are absent, they eat it with relish if vitamin A or

carotene is added, even in the presence of comparatively large quantities of ergot. Any biochemist interested in the relation between chemical composition of food and appetite might well study this particular problem.

An effort was also made to concentrate and isolate the chemical substance in ergot responsible for the accelerating effects of diets devoid of vitamin A on nerve degeneration, but this failed. The offending substance seemed to be unconnected with the total alkaloids in ergot, but beyond this no progress was made. The tracking down of a chemical agent in ergot, which has a pronounced toxic effect on the nervous system only when the animal's body is deprived of its vitamin A reserves, is obviously most difficult, especially as the mere deprival of these reserves makes the animal ill, apart from feeding with ergot.

Evidence was obtained that the toxic agent in ergot was also present in small quantities in rye germ, for the addition of rye germ intensified the nerve degenerative changes. It would be interesting if it should prove that the toxic agent in other cereals was the same as that in ergot of rye but present in smaller concentration. In this connexion it may be mentioned that one example of the concentration of a substance in ergot of rye was also found in the relatively large quantities of vitamin D it contains, as compared with the smaller quantities of this vitamin present in rye embryo not infected with *Claviceps purpurea*(18). The idea, therefore, that the neurotoxic agent in ergot of rye is the same as that present in non-ergotized rye germ is not beyond possibility.

One of the best pieces of evidence of the toxic action of cereals on the nervous system in the absence of vitamin A is obtained by comparing animals brought up on cereal-rich diets devoid of vitamin A and carotene with animals of the same litter given the same diets but with their cereals replaced by potato. Usually, the potato-eating animals are extremely active as compared with those eating cereals, and the nerve degeneration is either absent or only develops to a small degree. To what extent this great contrast is due to the carotene present in the potato cannot be stated, but direct estimations showed it to be

small in the potatoes used in the experiments and not much greater than that present in the cereals. The small quantity of carotene in unbleached wheaten flour, although it delays the onset of nerve degeneration when compared with bleached flour, does not prevent the nerve degeneration.

It seems to me probable that this aspect of biochemistry and pathology is well worth more extensive and intensive study. Its practical bearing on health, especially in view of the large part played by cereals in diet, may be more profound even than we know. From the point of view of bone and tooth formation it is certainly important. From that of the nervous system it may be equally so, not so much on account of the nerve degeneration actually produced, but because cereals under less unbalanced dietetic conditions may have detrimental effects on the nervous system short of actual degeneration and rather of an inhibitory effect on full development. Such harmful effects might be expected under present dietetic conditions where the cereal intake is high and the fat-soluble vitamin intake is low, especially in the diets of working-class people.

Even as regards the gross degenerative changes in the nervous system that can be easily produced in animals, there is good evidence that in pellagra, at least, cereals play a large part in the nerve pathology of the disease. The nerve lesions and even insanity that develop in many parts of the world, due to pellagra, are still great, and appear to be growing in Africa. Convulsive ergotism has fortunately largely disappeared from the world, the last epidemic reported being that in Russia in 1926. It is interesting to remember that the patients were treated with purgatives and sudorifics. Some milk and butter would be much more effective both in preventing and curing the disease.

An allied disease showing similar nerve degeneration is seen in lathyrism, a disease which attacks many people in parts of India following drought and famine, and is associated with the eating of akta, a form of lathyrous pea.

In all these conditions, there is reason to believe that toxic agents associated with maize, ergotized rye, and certain lathyrous peas respectively, are playing a part in the degeneration of

the nervous system. There is also good evidence that these toxic effects do not occur when the diet is rich in protective foods, especially those containing vitamin A and probably other vitamins, such as those of the vitamin B complex.

As regards the general position of nutrition, both in its physiological and pathological aspects, it seems likely that future investigations which take into account the potential harmful effect of certain food ingredients may well be profitable.

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