[Discussion on alimentary toxaemia] / H.D. Rolleston.

Dr. H. D. Rolleston: As the uninjured skin is comparatively impervious, the other surface covering of the body or the mucous membranes constitutes the main inlet for microbes and poisons; and of the various mucous tracts, that of the alimentary is much the largest, and further, is much the most exposed to infection and intoxication. It is true that the exposed condition of the alimentary canal is specially protected by the acid gastric juice against microbic activity and by the liver against poisons, but these lines of defence may be overwhelmed and broken down. It is easy to argue that a very large number of the diseases to which flesh is heir are due to intestinal toxæmia, but the state of our present knowledge makes caution necessary. Still, although it may be difficult to prove the widespread influence of alimentary toxæmia, it is unwise to put aside possibilities until they can be definitely ruled out.

A difficulty about a wide assumption as to the existence of alimentary toxæmia in the sense in which it is employed in this discussion—namely, effects in other parts of the body due to poisons apart from micro-organisms—is that many of the effects assumed to be toxic may be due to the passage of micro-organisms in small numbers into the circulation and so into the tissues. The hypothesis of such an escape of micro-organisms has long been before us in Adami's sub-infection with *Bacillus coli*, which he suggests plays some part in the production of cirrhosis, hæmochromatosis, and pernicious anæmia. With the improvements in our methods of blood culture, bacteriæmia is now more commonly recognized, and in the future transient and comparatively non-virulent forms may be found to be more common than is generally realized. It is quite reasonable to believe that toxæmia and bacteriæmia of intestinal origin may occur simultaneously; this is illustrated by the frequent association of chronic pancreatitis with portal cirrhosis, for chronic pancreatitis is most readily explained as due to an ascending infection from the intestine, whereas hepatic cirrhosis appears to be the result of poisons absorbed from the portal system.

Another point to be borne in mind in this discussion is that the same result, for example, nephritis, neuritis, or arthritis, may be brought about in different ways by different forms of toxæmia, of which alimentary toxæmia is one. Therefore, in considering the influence of alimentary toxæmia it is not necessary to argue that it is the exclusive cause of certain conditions: to take an extreme instance, we need not join Mr. Arbuthnot Lane[1] in the *obiter dictum* that gynæcologists are solely due to intestinal stasis; and further the title of alimentary toxæmia to ætiological importance in a morbid condition is not necessarily rendered invalid because in some instances other factors are proved to exert a causal influence. Thus, exogenous oxaluria, due to the consumption of rhubarb, is not disproved because oxaluria may also result from metabolic disturbances which eventually result in diabetes.

[1] *Vide* Discussion (part i), p. 101.

The large subject of alimentary toxæmia may be divided in the first place into the results due to (1) alterations in the quality and quantity of the foodstuffs introduced into the intestine; (2) the activity of micro-organisms in the intestine.

Alterations in the Quality and Quantity of the Foodstuffs.

To refer in the first place to idiosyncrasies to certain foods, it is true that the hypersensitiveness may depend on changes in the blood and tissues, the intestine being merely the passive transmitter; but on the other hand, the digestive processes may be congenitally so modified or the circumstances so altered by a change of the intestinal flora as to produce poisons out of ordinary food—e.g., an abnormal cleavage of proteins and other bodies. Thus, family periodic paralysis might conceivably be due to a congenital metabolic defect, which in the presence of unsuitable food gives rise to the formation of poisons in the intestine (Gardner[2]). This subject has, I find, been discussed by Dr. Vaughan Harley,[3] who suggests that the idiosyncracy of some persons to eggs,

[2] Gardner, *Brain*, Lond., 1913, xxxv, p. 243.

[3] *Vide* Discussion (part i), p. 33.

which is now commonly quoted as an example of anaphylaxis, is due to the cleavage of lecithin into cholin, which may eventually yield the poisonous body neurin. In this connexion I may mention that a medical man with neurasthenic symptoms and a belief during the morning that he was ruined, recovered after he left off taking an egg for breakfast.

Apart from any active toxic properties, alteration in the quality and quantity of the foodstuffs may so modify metabolism that morbid changes and symptoms are produced. Our knowledge of "the nutritional importance of the presence in dietaries of minute amounts of certain accessory substances[4] which may possibly activate metabolism is only in its infancy. It has recently been shown that tropical beri-beri is due to feeding with polished rice, which is deficient in a nitrogenous substance, small amounts of which are essential for the metabolism of the nervous system, and that beri-beri, thus experimentally produced, can be cured by supplying the aqueous extract of rice polishings. Scurvy and infantile scurvy are also due to an analogous deficiency in the food; and it has been shown that dietaries composed of the proteins, carbohydrates, fats, and salts capable of keeping adult rats in good health entirely fail to promote growth in young rats, although they remain healthy. The addition to the diet of the milk from which the protein had been eliminated was followed by normal growth (Osborne and Mendel). These experimental results justify hesitation in employing for lengthy periods artificial milks made by the combination of the constituents of milk in appropriate proportions (percentage system) for infants who cannot take ordinary milk. To turn to the more commonplace results of excessive quantities of food, an excess in the intake of proteins is commonly regarded as one of the causes of arterio-sclerosis by raising the blood-pressure either (1) through toxic constriction of the peripheral field, or (2)—and this hypothesis will be referred to later—by

[4] *Vide* review of the subject by A. E. Cooper, *Brit. Med. Journ.*, 1913, i, p. 722, which is fully utilized here.

primarily acting on the suprarenals or the thyroid. It has recently been suggested that an excessive protein diet is specially prone to produce change in the gastro-intestinal vessels, so causing angina abdominis. In rare instances common salt in excessive quantities has produced œdema in healthy persons, just as it is known to do in nephritis. Rodriguez [5] has recently argued than an occasional intake of salt may,

[5] Rodriguez, *Rev. de méd.*, Par , 1913, xxxiii, p. 136.

by its influence on metabolism, cause some cases of diabetes. An excess of carbohydrate food favours fermentation, and in children may cause fever. How far an habitual excess of proteins or carbohydrates can, by wearing out the assimilative powers of the tissues, lead to metabolic disorders underlying gout and diabetes is a question which is perhaps hardly within the limits of a discussion on alimentary toxæmia.

Results due to Toxæmia Depending on the Activity of Micro-organisms in the Intestine.

In connexion with this, which is the most obvious aspect of the subject, I shall only refer to some rather debatable problems. The condition of intestinal infantilism due to chronic diarrhœa might be explained merely as the result of malnutrition. Herter and Kendall, however, have found that the condition is associated with large numbers of a micro-organism—*Bacillus infantilis*—in the stools. The suggestion that toxæmia of intestinal origin may produce widespread effects, such as neurasthenia and liability to other infections, is in harmony with views put forward by Mr. Lane and others. It is an attractive hypothesis that changes in the ductless glands, either in the direction of proliferative reaction, as in exophthalmic goitre, or of degeneration, as in myxœdema and pluri-glandular insufficiency, may in certain cases be due to toxins absorbed from the intestine. Personally, I quite anticipate that proof will eventually be forthcoming. There are some points compatible with the view that exophthalmic goitre may in some instances be the result of alimentary toxæmia. Digestive disturbances are very frequent, a protein diet usually aggravates the symptoms, indicanuria has in my experience been common. The evidence recently brought by McCarrison [6]

[6] McCarrison, "The Etiology of Endemic Goitre," 1913 (John Bale, Sons and Danielsson, Ltd.).

to prove that endemic goitre is due to alimentary toxæmia may well suggest that some other form of intestinal toxæmia may induce exophthalmic goitre. In both these diseases the blood shows a relative lymphocytosis, a change which may be due to intestinal disturbance.

The relation between synovitis and other forms of arthritis on the one hand, and the alimentary canal on the other hand, provides scope for considerable discussion. A. E. Garrod [7] argues that the transient

[7] Garrod, A. E., *Lancet*, Lond., 1911, i, p. 1411.

joint manifestations accompanying erythemas, purpura, and urticaria are, like the cutaneous changes, toxic. The influence of alimentary toxæmia in the production of skin lesions has been fully discussed, and it does not seem unreasonable to suppose that transient attacks of synovitis may be similarly explained. The synovitis of acute rheumatism is so transient, and leaves so little or no change, that in the presence of the conflicting accounts as to the sterile or infected condition of the joints it may be toxic, and due to the products of streptococci in the alimentary canal. The condition of chronic rheumatoid arthritis may be secondary to focal infection in various parts of the alimentary canal, and pending more convincing evidence that micro-organisms are constantly present in the articular and peri-articular tissues, the lesions may be referred to here. Pemberton's [8] preliminary report on the metabolism of such cases when

[8] Pemberton, *Amer. Journ. Med. Sci.*, Philad., 1912, cxliv, p. 474.

treated by colon lavage and a restricted diet, at first consisting mainly of buttermilk, is of considerable interest from several points of view. Cases which improve on this treatment may show an increased output of fæcal bacteria and of ethereal sulphates in the urine. The increase in the fæcal bacteria was thought to be due to bacilli of the lactic acid type. The increase in the ethereal sulphates is puzzling, but as it coincided with improvement it suggests that intestinal putrefaction of proteins is not an important factor in the disease, in which indeed Pemberton believes that carbohydrates play an important part. The retraction of the head and other symptoms of meningism sometimes seen in cases of severe infective diarrhœa in young children appears to be due to the action of poisons absorbed from the alimentary canal. A form of intestinal toxæmia in the newborn, due to bacterial infection of the meconium within the first forty-eight hours has recently been described by Morse.[9] Incomplete evacuation favours absorption of

[9] Morse, *Amer. Journ. Dis. Child.*, Chicago, 1912, x, p. 229.

putrefactive products from the meconium. The infant rather suddenly becomes seriously ill about the third to the fifth day, has moderate fever, and commonly cyanosis, twitching, general rigidity, and even convulsions. If the bowels are thoroughly opened, all food stopped for a time, and water freely given, recovery is usually rapid and complete.

The Alimentary Origin of Blood Diseases.

That the intestinal tract is primarily at fault in enterogenous cyanosis seems clear; but whether or not it is invariably a toxæmia only is not established. For in G. A. Gibson and Douglas's case, which was described as "microbic cyanosis," *Bacillus coli* was found in the blood when the cyanosis was well marked. In bothriocephalus anæmia, and in some cases of pernicious anæmia, poisons absorbed from the alimentary canal can be reasonably invoked. Clinically it is difficult to avoid the conclusion that in young children intestinal toxæmia is sometimes the cause of anæmia; but whether by hæmolysis or by inhibiting the formation of red blood corpuscles there is not sufficient evidence to show. In leukæmia and polycythæmia in which there is violent stimulation of the leucoblastic and erythroblastic elements respectively of the bone marrow, the cause is unknown, but alimentary toxæmia has been

suggested in polycythæmia, and by parity of reasoning might be invoked in leukæmia. It is most dangerous to argue from isolated cases, but J. H. Drysdale's remarkable case of acute myeloid leukæmia in which a cure for two years followed administration of naphthalene tetrachloride given with this view has a bearing on this point; and I have seen improvement in cases of leukæmia treated on these lines. Needless to say, great caution must be maintained with regard to the influence of alimentary toxæmia. Years ago Sir Andrew Clark urged that chlorosis was a copræmia due to constipation, but the absence of any evidence of excessive putrefaction in the intestine and of hæmolysis in the tissues has rendered this untenable. Again, the view that hæmochromatosis is the result of chronic but widespread hæmolysis, probably of intestinal origin, has recently been challenged on the ground that examination of the blood fails to show anæmia, hæmolysins, or evidence of hæmolysis, and it has been suggested that the disease is a metabolic disorder causing pigmentary degeneration of the parenchymatous cells (Sprunt).[1]

[1] Sprunt, *Arch. Int. Med.*, Chicago, 1911, viii, p. 75; *Journ. Exper. Med.*, New York, 1912, xvi, p. 607.

As the condition of hæmolytic jaundice now seems to be established, the absence of jaundice is an argument against hæmolysis as the underlying factor in hæmochromatosis.

Intestinal Toxæmia and Metabolic Disorders.

So far the results of alimentary toxæmia referred to have been those directly due to the action of poisons absorbed from the alimentary canal, for example, hepatic cirrhosis. But they may be indirect only, or depend on disturbances of metabolism which are caused by poisons derived from the alimentary tract. The part played by intestinal toxæmia in the production of metabolic diseases such as gout and diabetes is difficult to estimate accurately. While any bald statement that they are direct manifestations of alimentary toxæmia would be an exaggeration rightly calling for criticism, it would be equally unwise to assert that they are entirely independent of it, for it is obvious that when these disorders of metabolism are established their progress is intimately related to variations in the dietary. In some instances, especially in gout, the metabolic disorders appear to be hereditary, in other cases the derangement is acquired and in these instances, or in some of them, errors in the quantity of food or in its digestion may, when persistent for long periods, play a causal part. The methods by which intestinal toxæmia may disturb metabolism are various, and as illustrating the complexity of the subject, Woolley and Newburgh's[2]

[2] Woolley and Newburgh, *Journ. Amer. Med. Assoc.*, Chicago, 1911, lvi, p. 1796.

explanation of the ætiology of diabetes may be quoted; as they found that the injection of indol produced hypertrophy of the medulla of the suprarenals, they suggest that such hypertrophy, if lasting for a considerable time, may, by causing a change in the chromaffin-pancreas equilibrium, set up diabetes. That there is an inter-relation between the pancreas and adrenals is shown experimentally by (1) Pemberton and Sweet's[3] observations, that intravenous injections of adrenin inhibit

[3] Pemberton and Sweet, *Arch. Int. Med.*, Chicago, 1912, x, p. 169.

the flow of pancreatic juice, that removal of the adrenals induces a flow of pancreatic juice which can be inhibited by injections of adrenin, and (2) the production of glycosuria by painting the pancreas with adrenin, and also, though not so certainly, by its injection into the circulation. Reference may be made here to the possibility that changes in the suprarenals due to alimentary toxæmia may be instrumental in the production of arterio-sclerosis. It has long been an article of faith that continued indiscretions in diet and over-eating cause chronic arterial and renal disease; more recently it has been noted that the suprarenals are large in granular kidney and arterio-sclerosis, and it might again be suggested that indol and other bodies absorbed from the intestine cause hypertrophy of the suprarenal medulla, and so high blood-pressure, and ultimately arterio-sclerosis and granular kidneys. Metchnikoff, as the result of the experimental administration of paracresol, phenol, and indol, products of the activity of *Bacillus coli*, induce arterial changes. Schur and Weisel stated that they identified adrenin in the blood serum of patients with chronic nephritis by means of the Meltzer-Ehrmann frog pupil reaction, but other observers, and quite recently Janeway and Park[4] have failed to find any evidence of

[4] Janeway and Park, *Journ. Exper. Med.*, New York, 1912, xvi, p. 541.

adrenin or other pressor substances in the blood of persons with high blood-pressure. This suggestion as to the mechanism by which alimentary toxæmia causes arterio-sclerosis, is tempting, but as yet non-proven.

Another remote way in which alimentary toxæmia may conceivably set up arterio-sclerosis is conceivable—namely, by inducing thyroid insufficiency. If the normal blood-pressure is maintained by a balance between the pressor and the depressor internal secretions, and the activity of the thyroid, which is the chief depressor ductless gland, be diminished the blood-pressure should rise, and as a result of this arterio-sclerosis would eventually follow.