AUTO-INTOXICATION AND LIVER INADEQUACY.

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The subject of this paper is one which has caused great interest to pathologists and chemists, more especially in the last decade, during which time undoubted evidence of many cases of disease, produced by this cause, have been brought forward. The appreciation of this factor in disease even now is not fully given its true place in clinical medicine, and for this reason I venture to put forward some recent views on the subject. Looking back on past clinical experience it is evident that many cases of sickness, due to this cause, have been overlooked and called by one or other of the names which may cover such a multitude of the unknown, as malaria, simple continued fever, or even enteric. In the first place, how are we to define auto-intoxication? The name itself explains the meaning to a great extent, but briefly we may say that the term is used to embrace those cases of disease in which a patient is suffering from the effects of poisons or toxins manufactured in his own person. The wide subject of toxins derived from food containing the poison when ingested will not be discussed. Again, what do we mean by the name toxin? It must include substances which are known under the terms ptomaine, leucomaine, animal alkaloid, &c. The definition may be put down as "an alkaloid produced by the decomposition of some animal substance," or "an organic base derived from some animal source." Originally, the term was applied only to an alkaloid derived from cadaveric decomposition, but it now includes also alkaloids of animal origin formed during life, as the result of changes brought about by some agent acting within the body. The term leucomaine was introduced to distinguish the latter. It would seem best to class all these toxins together under the name of animal alkaloid, in order to differentiate them from the vegetable alkaloids. Many of these alkaloids, vegetable and animal, are quite harmless, others are of a highly poisonous nature, a few derived from animal sources possessing the most powerful poisons known to science; many of the vegetable derivatives are well established as therapeutical agents.

The animal body may be considered as a laboratory, in which are being manufactured all kinds of products, resulting either from the breaking up of food material in the processes of digestion, or

from the breaking down of the body cells in metabolic katabolism. Let us deal first of all with the normal healthy body and see briefly what these processes are which take place. To do so, it will be necessary to follow out the changes which certain of the foodstuffs undergo before they become absorbed as part of the body substance, and then to trace what happens to the cast-off or waste material from the body cells. Regarding these changes in foodstuffs, more especially the proteid, a vast amount of research has been carried out during the last two years, relating to the end-products resulting from the action of the intestinal and intracellular juices; and we now know that a very much more complicated series of reactions takes place than was formerly imagined. These investigations have been confined almost entirely to the chemical aspect, but a certain amount of enquiry has also taken place regarding the *rôle* of bacterial action. Finality has by no means been reached, and there still remains a vast problem for elucidation. Turning first to the chemical side of the question, we will trace the history of a proteid substance as dealt with and made use of by the body.

The proteid molecule is a heavy and complex one, which by a process of hydrolysis in digestion becomes split up into smaller and smaller molecules. Under the action of the four digestive proteolytic ferments, pepsin, trypsin, erepsin and arginase, the albuminous matter is converted into primary crystalline dissociation products, the amino-acids, &c. Most of these may be included under the following heads: (1) The base ammonia; (2) the mono-amino acids, such as glycin, alanin, leucin, asparagin, aspartic acid and glutamic acid; (3) the diamino-acids, such as arginin, lysin, ornithin and histidin; (4) the aromatic amino-acids, such as phenyl-alanin, tyrosin and tryptophane; (5) the mono-amino acids, containing sulphur, cystein and cystin; (6) the chromogenic group, such as indol and pyrol derivatives; (7) the purin bases, such as adenin, guanin, hypo-xanthin and xanthin. The pyrimidin bases, such as cytosin, thymin and uracil.

Such a formidable list as the above must bring home to one's mind the highly complex nature of the original proteid molecule, which is built up out of the nuclei of all these dissociation products, linked together in more or less intricate groups. It appears now to be the general opinion that all proteid matter ingested must undergo this complete hydrolysis before absorption from the intestinal tube can take place, but there are still some observers who maintain that a certain amount of the albuminous matter can be absorbed in the form of albumoses, peptones and peptids. Such changes in the

proteid molecule are analogous to those which we know happen to the starch molecule. This heavy molecule becomes split up by digestion into smaller and smaller molecules. First the dextrins are produced (analogous to albumoses and peptones); on these follow the molecules of maltose (analogous to the polypeptids), to result in the simple molecules of glucose (analogous to the amino-acids).

Now a word as regards the part played by bacteria in digestion. It seems scarcely likely that Nature would provide such varied types of bacteria in the intestine without some special purpose. We know that the intestinal contents of the new-born child are generally sterile, but within a very few hours, and after the first few feeds, many kinds of the bacteria found in after-life make their appearance. It is only common-sense to say that these bacteria must have some very definite share in the normal processes of the intestinal tract, but their exact sphere or duty has not yet been worked out.

Experimental evidence shows that such organisms as *B. coli*, streptococci, *Proteus vulgaris*, and some forms of the yeasts, have certain very definite reactions on albumen. At first their action simulates exactly that of a digestive ferment, such as trypsin. The albumin is broken down into albumose, peptones, and subsequently amino-acids. The amino-acids are further differentiated into their corresponding simple acids, such as acetic, propionic, butyric, caproic and valerianic acids, &c., or they are split up with the separation of carbon dioxide and the formation of certain diamines, such as cadaverin, putrescin and phenylethylamin. It would seem but reasonable to suppose that identical changes take place in the animal gut, but actual proof of such being the case cannot be definitely stated.

It is only necessary for us to glance over the list of end-products which may be produced in the intestine, to grasp the fact that herein lies the origin of grave danger to the organism should these products pass on to the general circulation in an unmodified condition, for many of them are well known to us to possess the power of active and poisonous animal alkaloids. Experimental evidence also proves this quite clearly. The blood coming direct from the intestine and containing the products of absorption is very toxic. On extirpation of the liver or on tying its vessels in animals, it was found that they quickly succumbed, with all the symptoms of an acute toxic poisoning. Again, when a fistula was made, diverting the blood from the portal vein direct into the vena cava, so cutting off its passage through the liver, the same train of

symptoms developed. Further, if the blood from the portal vein of one animal is passed into the circulation of another of the same species, toxic symptoms quickly ensue; while the blood from the vena cava injected in the same manner has little effect. We are, then, bound to admit that we are at all times making the best endeavours in our unconscious inner workings to bring about self-destruction. What agent stands in the way of such self-poisoning taking place, and what agent is it that modifies, changes or neutralises these poisonous products of normal digestion? We know without doubt that this important function lies with the largest organ of the body, the liver. Up to within quite recent times this organ was looked upon as an addendum of the digestive apparatus, and its chief function was considered to be that of secreting a fluid, the bile, to aid in the processes of digestion. This idea has been a difficult one to eradicate, partly because the liver was known to originate from the entoderm, and therefore was looked upon as a necessary adjunct and help to the digestive apparatus, and partly on account of its position in proximity to the other organs of digestion. At the present day it is necessary for us to dismiss from our minds all idea of the bile taking any active part in digestion; it is now well known that it has no such action, outside the passive ones of lubricant and dialyser. The main function of the liver is that of a filter or a neutralising agent, combined with certain modifying reactions on some of the food products.

A word now in reference to the products of katabolic metabolism of the living tissues, and the disposal of their waste material. Each cell, in its cycle of vital activity, casts off the waste products of its existence; these products are of a toxic character. Three normal fatigue substances are now recognised, namely, paralactic acid, mono-potassium phosphate, and carbon dioxide. A muscle, when irrigated with a weak solution of any of these substances in physiological salt, and compared with a companion muscle irrigated with physiological salt solution only, is already, in some degree, fatigued, and on stimulation shows an earlier and more pronounced development of each successive stage of fatigue up to complete exhaustion. Similar effects have also been proved by the experiments on living animals in reference to fatigue toxin. It has been clearly shown that when the blood from a fatigued animal is injected into the circulation of a normal animal of the same species the latter suffers from fatigue effects. These effete products of the metabolic activity of the body cells must be eliminated as quickly

as possible if the normal equilibrium of the system is to be maintained. This duty, again, is carried out to a very large extent by the liver, which eliminates this waste material as it passes through the hepatic circulation.

It can now be seen how extremely diverse and complicated are the duties which the liver is called upon to perform, if that organ is to save the body from the effects of toxins derived either from the end-products of digestion, or from those of cell waste. It is only necessary to remember its size, to understand the amount of work which it undertakes, and to be reminded that the quantity of bile excreted equals in amount the urine daily passed by the kidneys. If the statement is correct, that the liver acts as a filter or neutraliser of toxic material, we should expect to find that its excretion contained some poisonous properties. Such is undoubtedly the case. The bile, when injected hypodermically or intravenously into animals, is powerfully toxic; and yet, when poured into the intestine in the normal process of excretion, it has no harmful effect. This can be explained by the fact that the bile salts are precipitated in the intestine, and its deleterious constituents are not then capable of absorption. We can, therefore, state that the chief functions of the liver are the following: (1) To act as a filter and eliminator of the harmful end-products of normal digestion and cell metabolism; (2) to act as a toxin reducer; (3) to elaborate certain of the end-products of digestion, changing their constitution, so that they may be in a suitable condition to be eliminated by other organs of the body; (4) to elaborate certain of the end-products of digestion, and store them up for future energy.

The first duty named above has been enlarged upon. The second, also, has to some extent been dealt with, but there remains for elucidation under this head the power to deal with toxins produced by pathogenic organisms. The third duty embraces the changes brought about by the liver cells in the elaboration of such substances as urea and uric acid from the ultimate products of digestion. The fourth duty refers to the elaboration of the complex molecule glycogen, or animal starch, from the simple starch molecule.

Having now considered this question from its normal physiological side, it remains to discuss its bearing in some of the phases of disease. We have seen that in the animal body processes are going on which have the power, should their normal balance be upset, of entailing disaster on the individual. Let us discuss first of all a very simple case, where a patient makes the only too common error of exceeding his proper food supply. What happens

in many cases? Symptoms are produced which we know by the name of dyspepsia, a term which includes a multitude of ills. What has really taken place? The food remains in a semi-digested condition in the gut, and is the prey of bacterial action, with the production of toxic material. This passes to the liver, which is called upon to cope with the neutralisation of these toxins. It may have the power to do so, but if not the well-known symptoms are produced of headache, lassitude, and general uneasiness. Again, we will take it that the powers of digestion are able to grapple with the excess of food. The end-products are carried to the liver for elaboration or elimination. It may have the power to carry this through, but if not, we get the well-known symptoms of plethora, from the passing on of certain of the end-products unchanged; followed in aggravated cases by symptoms which we call "torpid liver," "biliousness," or by some other vague term. Again, let us imagine that the liver, for some reason, either from chronic irritation by toxic material from the gut or from some poisonous infective agent, loses the power of coping with the materials circulating through its substance. What follows? Let us instance such conditions as gout and uræmia. When considering these two diseases it is natural to think at once of the kidneys being primarily at fault; but is this really so? Recent work would point very markedly to the liver as being the primary factor in the disease. We know that urea and uric acid, when ingested by, or injected into, animals are quite harmless; and yet the precursors of these substances, such as ammonium carbamate or carbamic acid in the case of urea, the nucleins and xanthin bases in the case of uric acid, are extremely toxic. It is the duty of the liver to convert these end-products, ammonium carbamate, xanthin, hypoxanthin, adenin, guanin, &c., into harmless substances, such as urea and uric acid, which are forthwith eliminated by the kidneys. Should the liver fail, a certain amount of these materials passes through to the general circulation, but is not in a suitable condition to be eliminated by the kidneys, and therefore is left to accumulate and poison the body. The kidneys in all probability really suffer from secondary irritation. Uræmia should, then, be looked upon as anuræmia, and the patient as suffering from non-formation of urea, and therefore poisoned by the unchanged end-products of his food and body metabolism. Such is the case, too, in puerperal eclampsia. The liver, during pregnancy, is called on for a great increase in the elimination of effete material, and should the woman herself be careless in diet, the balance may just be upset, the liver overtaxed in its power, toxic material passed on, and the well-known

symptoms supervene. The kidneys have not been primarily to blame, the liver has been called on for too great a task and has failed.

At a recent meeting of the Medical Society of London (December, 1906), Sir Lauder Brunton opened a discussion on "Hepatic Inadequacy in Relation to Gout," and brought forward experiments showing that the liver possessed the power of converting uric acid or urates into urea. Dr. Luff stated that he wished to raise his voice against the present fetishism of uric acid, as he was unable to recognise that uric acid could in any sense be considered a poison. He regarded uric acid as a comparatively harmless by-product of the human economy, which in many quarters had been most dangerously exploited as a poison. The liver was an important organ in regard to gout, but though it was capable of converting uric acid into urea, that amount of conversion had no part or parcel in the pathology of gout. Gout was an auto-intoxication, but he believed that might be due to the bacteria present in the intestinal tract, which, under certain conditions, became altered and caused the toxin of gout. The liver could destroy that toxin, but if the functions of the liver fell below par, then the toxin would cause gout. What amount of truth there may be in this theory of Luff's is for the future to prove, but that both gout and uræmia are conditions caused primarily by inadequacy of liver action in failing to deal with the toxic end-products from the gut, and changing them to harmless substances, appears now to be beyond all doubt.

There are many observers who are of the firm opinion that overloading of the gut with foodstuffs, more especially of the proteid type, plays a large part in preparing the body for the attacks of the organisms of disease. This may be brought about to some extent by the local condition of the gut, which becomes the breeding-ground of putrefactive bacteria; but also, and to a still greater extent, by the constant overloading of the liver with effete material, which it is powerless to neutralise; consequently the system becomes saturated and a ready prey to disease. A typical instance of this condition may be cited in so-called "simple continued fever" of the soldier, a term looked upon formerly as a cloak for the diagnosis of the ignorant; but it is undoubtedly a well-marked condition, and not always due to the invasion of the *Bacillus typhosus*, or *B. paratyphosus*, as would be claimed by some. The condition meant is that of a patient suffering from continued or irregular fever for seven or eight days, with foul tongue, headache and general malaise. We suspect enteric at once in the Tropics, but the fever falls and

everything clears up. What are these cases? In vulgar language they can be described as "putrid gut." Toxic material has been absorbed in large amount from the bowel, into which unsuitable or overmuch food has been introduced; and the liver has been overtaxed, allowing the toxic substances to pass on; the patient suffers from auto-intoxication, until either Nature or medicine rids him of his incubus.

Now let us glance at the effects of microbial invasion, and we will take first the case of the common cold. As a relic of custom we are inclined to attribute the common cold to draught or chill, whereas we know in our own minds that the invasion of bacteria is the true cause in nearly all cases. Why should we feel seedy with a cold? It appears a simple affair enough. Look at it from a common-sense aspect, and we see that the invading bacteria are manufacturing some waste material or toxin which overtaxes the powers of the body filter and we are being poisoned by their products. The same series of symptoms are produced by the specific infective organisms, each having its special train of effects, but in nearly all cases the results are similar. It would be too bold a statement to make, that as long as the liver can perform its functions no toxin can have effect; but the fact remains that in nearly all cases where toxic poisoning takes place and ends in death, the last train of symptoms is of very similar type, such as drowsiness, coma, Cheyne-Stokes breathing, and convulsions, the classical signs of poisoning from the retention in the system of metabolic products.

The sources of toxins, as developed by the animal organism, have been briefly dealt with, and an endeavour has been made to indicate that on liver efficiency lies, to a very great extent, our immunity to injury by these dangerous products. That intoxication by these self-made agents takes place there can be no doubt, if we consider the subject in a rational manner. Our petty ills are to a large extent due to this flooding of the liver with effete material: the graver effects are masked by the initial disease process. Cases of acute auto-intoxication are not common, but once seen are not quickly forgotten. Such a case was seen by the writer some two years ago, in which the patient, a man of robust constitution and perfect health, was attacked and succumbed in forty-eight hours. An impression such as this brings home to one the ignorance there is in certain branches of study. The subject was a strange one to me at that time, and thinking that others may be in like ignorance, this somewhat discursive article has been brought forward, in the hope that reference may be made to, and knowledge gained by reading, some of the literature mentioned below.

As regards clinical work, can we glean any hints with respect to treatment if we accept these views on auto-intoxication as reasonable? Most certainly we can do so. The indications would enhance still further the importance of the maxim of treatment in the Tropics, viz., to keep the gut in as clean a state as possible. This maxim should not only be applicable in disease, but also in health. We are mostly agreed that the European soldier in the Tropics does not conform to an ideal standard as regards his diet. This, to a great extent, is controlled by his habit of living, but there can be no question that the sooner our soldier, and officer too, can break away from the idea that a large consumption of food, more especially of the proteid variety, is necessary to his existence, the sooner will be brought about a diminution of disease, certainly of its intestinal forms.

In our treatment of disease the indications point to either clearing the gut of offensive matter by calomel or some other smart purgative, thereby cutting off the supply of noxious and effete matters, or to neutralising further fermentation and putrefaction by the aid of non-poisonous disinfectants.

Some observers scoff at all idea of rendering the gut contents less offensive by the administration of disinfectants, but the proof lies with results, and very many clinicians have claimed great benefit from the treatment. To what extent the more powerful disinfectants now available will effect this desirable object is a matter of conjecture and trial. That enteric patients do suffer very markedly from auto-intoxication there can be no question, and if the contents of the gut can in any way be relieved of the putrefactive conditions, a very marked change for the better in the symptoms supervenes.

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