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A SUGGESTION THAT THE TOXINS OF THE  
ALIMENTARY TRACT IN CHRONIC CONSTIPATION MAY HAVE  
AN INFLUENCE ON THE PATHOGENESIS OF LESIONS OF  
THE CENTRAL NERVOUS SYSTEM.

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A SUGGESTION "THAT THE TOXINS OF THE ALIMENTARY TRACT IN  
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OF LESIONS OF THE CENTRAL NERVOUS SYSTEM."

Intestinal toxæmia may be caused by (1) products of digestion, (2) bacterial endotoxins and exotoxins, (3) products of putrefaction, or (4) a combination of those.

The products of digestion are derivatives of either proteid, carbohydrate, or fat, arising from the chemical action of the various juices of the intestinal tract and the activity of certain bacteria present in the alimentary canal. The ultimate result is the formation of simple aromatic substances, which may in the healthy state be regarded as normal products of digestion; but in certain unhealthy states of the bowel further products may be formed which are departures from the normal.

Protein in digestion and putrefaction is split up into simple and aromatic amino-acids, the best known of which are Leucin (an acid), Tyrosin (a derivative) and Tryptophan. These under normal conditions are split up into small amounts of phenol and paracresol, with large amounts of indol and skatol. These appear later in the faeces unchanged and in the urine as ethereal sulphates. They are thus excreted. In abnormal digestive states, amino-acids, particularly leucin and tyrosin are found in the faeces.

The term fermentation is applied to the digestive changes in carbohydrate, the end products being the various fatty acids. Such as formic, acetic and butyric acids. They are partly formed by the action of *B. Lactis Aerogenes*, especially in the absence of oxygen. Butyric and acetic acids predominate in the healthy person. Propionic acid, carbon dioxide and alcohol are present in small quantity, and acetone and succinic acid are also formed in small quantity. The process takes place in the upper part of the gastro-intestinal canal. Two or more acids co-exist and one usually predominates. Lactic acid is formed in the stomach and intestine by *B. Ac.Lactis* and also by *B. Coli* types. In abnormal conditions acetic acid is got when fermentation is active. Butyric acid may also be formed from proteins by the action of bacilli when the hydrochloric acid secretion of the stomach is deficient. The products of carbohydrate fermentation are chiefly harmless.

Fats are acted on by the pancreatic juice, the process being one of saponification; if in excess they are also acted on lower in the canal by *B. Coli* in abnormal digestion. During normal digestion fats partly become transformed into soaps, without any bacterial action, the process commencing even in the stomach. The presence of bacteria does increase the breaking up of fats, so that acetic, lactic, butyric and succinic acids result in catarrhal conditions of the intestine. Excess of or deficient saponification depends on the rapidity of transit through the duodenum when saponification is diminished.

and on delay in the upper part of the colon when there is more saponification owing to the bacilli present.

In the decomposition of fat lecithin is formed, some of which may be absorbed as such, but the greater part is broken down in the alimentary canal into glycerophosphoric acid, fatty acids and cholin. Cholin may further be broken down into the highly poisonous muscarin, which yields the almost equally poisonous compound neurin.

It has become increasingly recognized that the rôle of bacteria in digestion is, from the chemical standpoint, a very important one. Active bacteria are numerous in the alimentary canal. They include bacteria, spores of fungi, yeast, and sarcinae. Many bacteria act on both protein and carbohydrate, and it is difficult to say how far the digestive process is influenced by the gland secretion and to what extent bacteria influence it. The latter, however, seem generally speaking to carry on the already altered state of the food to a further stage of disintegration. Whether this further stage reached is beneficial or not may be questioned.

Assuming the gastre-intestinal tract of a child, when born to be sterile, then bacteria are introduced by the mouth and nose from various sources, but chiefly with the food-stuffs. Of these some are destroyed in the stomach, while others pass on still in an active state and finding an ideal environment for growth beyond the alkaline level, adapt themselves to their surroundings. Their multiplication is great but is balanced

by the rapidity of transit in the upper bowel, a healthy state of the intestinal wall, and regular evacuation of the bowel contents. In this way the products formed are got rid of at regular intervals.

As regards biological characters, those of the protozoal inhabitants are little known. Of bacteria, certain growths have specially adapted themselves to the life conditions present in the intestinal canal. Such are the colon group, streptococci and certain anaerobes; which grow best at body temperature. The potential anaerobes have a high capacity for splitting up the various food-stuffs for their own use as food, with the resulting formation of waste products. These waste products are more or less poisonous and are formed from the food material itself by chemical action on the proteid, fat and carbohydrate; secondly, they are excreted from the bacilli as exotoxin, or from the decomposition of bacilli, when endotoxin is liberated; thirdly, they arise from the secretion, excretion and debris of epithelial cells of the intestinal wall. The latter source yields a considerable residue which undergoes putrefaction, as has been shown from the observations made on urine during starvation.

The numbers of bacteria vary at different levels of the canal, and may even carry the proteid-splitting process beyond the physiological requirements of the individual, and with certainty beyond the stage reached by the food-splitting ferments. Of those produced some may be useful to the host, while

others are known to be toxic.

Whilst it is difficult to prove that toxins are absorbed from the canal, as they have not been isolated and identified either before or after absorption, yet it is established that a very few produce soluble or exo-toxins which pass into the surrounding medium without decomposition of the bacterial body. These are the pre-eminently toxic bacteria, examples of which are the bacillus of diphtheria and tetanus, non-intestinal, and Van Ermigen's bacillus botulinus of hand poisoning, an intestinal bacillus. They give soluble and absorbable toxins. These chemical poisons are absorbed from the alimentary tract, are of known or unknown composition and, circulating in the blood, combine with and to a certain extent injure the cells of the body, for which they have a chemical affinity. If present in sufficient amount, clinical symptoms develop.

Toxins may be produced chemically by the action of the intestinal juices on the food, and in this way protein even in ordinary digestion may, without the action of bacteria, yield toxic products. The decomposition products of protein putrefaction, peptone, peptoses and polypeptids and amino-acids, are practically the same, whether formed by the action of bacteria or by enzymes in ordinary digestion. Hence it is considered that bacteria are useful in the organism. They then apparently live in symbiosis. It is known that they break down cellulose, which is unaffected by the digestive ferments. It is found that rapid peptonization is got by the B. Cloacae, or by

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symbiotic activity between B. Coli and proteins and the subtiloid group in milk. The solution of casein appears to make the lactose more accessible. At the same time the alkali formed by subtilis tends to neutralize the acid formed by B.Coli. B.Coli in itself seems to have practically no power to cleave and peptonize native proteins such as casein, but can energetically cleave peptones which have been prepared by other microorganisms. Hence, if there is good absorption of protein above the level where B. Coli becomes predominant, very little putrefactive decomposition can occur, no matter what the nature of the inhabitants of the colon may be; but if excess of protein be taken, so that native proteins find their way into the large intestine, and putrefactive anaerobes be present, they initiate peptonization, and the colon bacillus will then take an active part in breaking down and hydrolyzing products thus formed. This may be given as the non-beneficial action of bacilli, as it seems not unlikely that some such association of B. Coli with peptonizing bacteria may explain the nervous and other symptoms, as neurasthenia.

Products of putrefaction may be got by the action of putrefactive bacteria on either carbohydrate, fat or proteid. Those formed from carbohydrate are, even in quantity, chiefly harmless gases and organic acids, and those from fats are the fatty acids, which are later transferred into volatile acids, which, except in abnormal states of the intestinal canal are also chiefly harmless.



It is to the putrefactive process that proteid undergoes that infinitely more attention must be attached. These products are, to a great extent, toxic nitrogenous bases, which are likely to give rise to serious symptoms, when formed in abnormal excess. Even in healthy people a certain amount of protein decomposition goes on in the lower part of the intestine and chemical investigation may show that these products are increased considerably without there being any serious clinical symptoms. It is only when the putrefactive changes are so great, or have persisted such a length of time, as to overcome the defensive mechanisms of the organism that unequivocal clinical symptoms make their appearance.

Putrefactive bacilli are numerous, and break up the protein into fatty and amino-acids, such as leucin, tyrosin, indol and skatol; other aromatic bodies, as phenol and cresol; various ptomaines, as neurin, cholin, cadaverin, and other ammoniacal compounds; and various gases, such as sulphuretted hydrogen. Of the amino-acids, a few known to be produced in the intestinal canal by putrefaction are - tyrosin, which minus carbon dioxide gives the amine parahydroxyphenylethylamine; histidine which similarly transformed gives  $\beta$ -iminazoylethylamine; leucin which gives izoamylamine. The amines are poisonous, while their corresponding acids are not. Cadaverin and putrescin are closely allied to the diamino-acids lysin and ornithin, lysin minus carbon dioxide giving cadaverin, and ornithin, putrescin. But no organism has been found changing these,

although in cholera, cadaverin has been found in the stools, and it is now believed that they are formed within the organism from lysin and ornithin of protein, as the result of an inborn error of metabolism.

Of gases, ammonia has been found in the large intestine from putrefaction, and has been traced to the portal vein.

It is interesting to note that the organic acids produced from the decomposition of carbohydrate exercise an inhibiting influence on the putrefactive bacteria, and it has been shown that sugar added to the putrefying matter reduces the production of cadaverin and putrescin to 1/20th.

Different diets and different bacteria at different levels have a distinct influence on the production of toxic substances, Thus Herter and Kendall, experimenting with cats and monkeys, showed that with a protein diet the bacterial flora was of a strongly proteolytic character, while a change to a carbohydrate diet caused a rapid replacement of these organisms by others of a non-proteolysing type. This was associated with a change of the putrefactive products in the urine and the faeces.

In toxic poisoning from the alimentary canal, the recognized means of transit, after absorption, of toxic products is the blood stream. It is, therefore reasonable to assume that the vehicle may be affected, that the channel conveying the tainted fluid, and the organs through which the toxic blood circulates first to be purified, and later, should all toxic material not

be destroyed, the various tissues fed by that particular fluid may be more or less affected.

In considering these toxic affections, it may be argued that in a more or less mild intoxication, when the toxin can be dealt with before reaching the organs of excretion, as the bowel, kidney and skin, the effect will be seen in the blood constituents and the organs in close association with them; while in a sudden and severe intoxication of short duration, as from food poisoning, the toxin will reach the excretory organs in sufficient amount to set up disturbance there, resulting in a recognized toxic albuminuria of a transient nature, and in various skin affections.

In children who live under unhygienic conditions, and who are fed on unsuitable diet, one of the commonest symptoms during illness is a gastro-intestinal catarrh, followed by a more or less severe primary anaemia. This anaemia may be due partly to a deficiency in the blood-forming elements of the food, with a resulting lowering of the tone of the bowel, followed by absorption of toxic products, but can scarcely be the primary cause producing those toxic products. In such cases persistent increased fermentation of fats and carbohydrate gives vomiting and diarrhoea from fatty acid irritation, and often leads to anaemia, probably due to the oleic acid formed causing destruction of the red blood corpuscles. With increased carbohydrate fermentation there is often a consequent effect on proteid digestion, as shown by increased indicanuria,

and in association with these changes is found retarded growth and mental irritability, followed or accompanied by anaemia and muscular fatigue, which indicates protein putrefaction. Campbell claims that enteric catarrh of infancy, with which anaemia is associated, following an excessive sugar diet, is due to the formation of toxins formed by the Bac. Aerogenes Capsulatus. In adults, anaemia accompanies all cases where there is excessive indicanuria and indol in the faeces. The anaemia may be so pronounced as to be indistinguishable from pernicious anaemia. The increase of aromatic substances might be due to simple anaemia lowering the general condition of the individual, accompanied by decreased motor and secretory power of the intestine, the anaemia being the cause; but in many cases it appears to be due to the intestinal condition from putrefaction, with increased formation of aromatic substances and absorption of these leading to haemolysis. It has been shown that an ethereal extract of stools causes a haemolytic action on red blood corpuscles, but on the other hand Cohnheim points out that this may be due to haemolysin present in the pancreatic secretion.

In pernicious anaemia, a disease of adult life, of unknown cause, Hunter has shown from experimental work that the portal blood causes destructive (haemolytic) changes in red blood corpuscles, induced by some special haemolytic poison reaching the blood from the intestinal tract, and causing eventually a profound anaemia, which may go on to acute yellow atrophy of

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the liver and death from cholaemia. He says that this is enhanced by the constipation, which is always an increased source of portal toxæmia when there is a want of the protective mucous lining of the canal and want of intestinal muscular movements. The adventitious organisms are got through the mouth and nose, are not killed by the gastric juice, and are entirely saprophytic, and to those belong the causal agent in pernicious anaemia.

Hunter has shown that primary anaemias of the pernicious type are commonly associated with preponderance of the B. Aerogenes Capsulatus in the faeces. While there is no precise knowledge on the subject, it is possible that pernicious anaemia in the vast majority of cases, may result from the chronic absorption of toxins from some part of the alimentary tract, which destroy the red blood corpuscles, and that the atrophy of the stomach and of the intestinal mucous membrane is the result, and not the cause. The diarrhoea here may be caused by the toxin acting on the nerve secreting apparatus of the intestine.

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In ankylostomiasis there is an anaemic cachexia, induced by one of three intestinal nematodes. These cause, when sick or dead, a profound hydraemic plethora, due to an increase of plasma, and not to a shortage of haemoglobin. Here a chronic catarrh of the stomach is associated.

It is pointed out by Professor Dixon (Royal Society of Medicine 1913) that the amino-acids formed during digestion can

by a simple chemical change - decarboxylation - be transformed from non-poisonous acids to the corresponding poisonous amines. In 1906, Abeclus obtained from putrid horseflesh a substance the immediate action of which is on the vascular and muscular systems of the body. In 1907, Taylor and Dixon proved that extract of normal human placenta contained a pressor substance, later found to be due to an incipient putrefaction. In 1909, Barger and Walpole identified two of those substances with certainty as isoamylamine and parahydroxyphenylethylamine. Both have a similar action to adremalin, but the action is obtained when given either by mouth or subcutaneously. (Both are mentioned previously as derivatives of amino-acids.) Indolethylamine produces vaso-constriction, with rise of blood pressure, and a transient effect on the central nervous system causing clonic and tonic convulsions and tremors of the limbs. The histidine base is different, giving gastro-intestinal disturbance, with subsequent collapse and narcosis, and it gives direct stimulation of plain muscle. A curious feature is its depressor action on the circulation. It is the possible causal agent in asthma (Adams).

There is a wide spread belief that alimentary toxæmia is an important cause of the rise of blood pressure in later life, when there has been long continued absorption and weakened defence, and here we have an example of a definite pressor substance which can be produced by intestinal putrefaction. When B.Coli is dominant at a higher level than the lower ileum,

then the conditions necessary for the increase of its putrefactive properties exist, and we get the lower derivatives of protein putrefaction, i.e., indol, tyrosin, etc., which in the circulation cause hyperactivity of the medulla of the suprarenals, which suggests that hypertension of the blood-vessels (and arterio-sclerosis) may be dependent on unusual activity of B. Coli.

Lauder Brunton has pointed out that the symptoms of food-poisoning resemble the action of a paralysing narcotic, and are considered to be due to the dilatation of the gastro-intestinal vessels, with consequent anaemia of the brain.

Erythema, urticaria, and purpura are, in susceptible people, commonly developed after eating certain articles of diet, as shellfish. There is a recent tendency to regard these results as evidence of anaphylactic phenomena or hypersensitiveness to foreign proteid. When once they occur, then quite a small quantity of the same, or even of a different proteid will cause a second attack. They may not be due to alimentary toxæmia, and it is questioned whether similar symptoms could be got from toxins in the alimentary canal or from chemical products of defective digestion. Here it may be mentioned, that rashes following the use of diphtheria and tetanus antitoxin are not due to the antitoxin, but to the foreign proteid of the serum. In erythema there are abdominal symptoms which might be produced by the same kind of lesions as erythema in the intestinal canal, but the relationship between skin and toxin as between

bacillus and toxin must be established.

On the other hand, the group of "toxic erythemata" is considered to be symptomatic of general toxaemia, and is said to result from the presence of toxin in the blood-vessels causing changes in their walls, or from excretion causing a mild inflammation. It is noticed that after a saline enema in constipation, where the endotoxin of bacteria is presumably set free from scybala, and "enema" rash is got in many instances.

In certain errors of diet, various skin lesions may be got, varying from disturbance in blood-vessels, as in urticaria, to inflammation and scarring. In purpura, the coats of the vessels seem to suffer in some way, the result being haemorrhagic manifestations. A haemolysis may occur. in the case of purpura, attacks are more prone to occur where evidence of toxaemia and septicaemia become prominent. Generally, it may be said that ordinary food toxins of a proteid nature tend to cause cutaneous reactions, as urticaria, while ptomaines or bacterial toxins from some infective focus are liable to give rise to severe purpuric lesions.

Cirrhosis may be regarded as the result of some irritant causing the proliferation of connective tissue in certain organs. That the specific irritant may be of toxic origin is borne out by the aetiology of cirrhosis of the liver in children, of analogous conditions of the brain, and of toxic amblyopia.

Cirrhosis of the liver is found to be produced by a chronic poisoning by various agents, as lead and alcohol, in continued small doses. The liver, acting as a highly specialised tissue



in removing toxic substances from the portal circulation, and being at the same time little resistant itself to disease, becomes affected. In children, cirrhosis may be caused by highly seasoned foods, and "in recent years increasing attention has been directed to the occurrence of cirrhosis of the liver in children, under conditions in which alcohol in all its forms can be excluded. There are cases of subacute yellow atrophy which are in all probability due to a chronic infection from the intestine arising in association with a catarrhal condition of the duodenum." (Chalmers Watson, "Food in Health and Disease") In adults, on the other hand, alcohol is a common cause, and recently it has been pointed out that it may act by altering the bacterial flora, and thus causing a toxæmia in excess of that with which the liver can effectively deal. It may also arise from chronic intestinal fermentation, resulting from the use of a diet which favours abnormal fermentative and putrefactive changes in the bowel, and is usually associated with a certain amount of gastric catarrh.

In the pathogenesis of senile cataract, a sclerosis of the nucleus of the lens, one view (Burdon Cooper) is that the cataract is the result of a hydrolysis of the lens protein which results in the formation of tyrosin, a substance not present in the normal lens, but which is found in the aqueous and lens in cases of senile cataract.

Excess of carbohydrate food, and more particularly starch, is stated to cause intestinal disorder, either from excess of

carbohydrate or from want of fat, followed at times by an associated anaemia and possible toxic absorption. If the resistance, always less in children, cannot overcome the toxæmia, which may be in excess of lactic acid, leading to an excess of ammonia salts in the urine and to four or five times the normal excretion of calcium, causing calcium starvation, the result is rickets, from the resulting changes in the joints. The intestinal mucous membrane seems to be particularly affected, as in ulceration, and later the muscular coat, in constipation or stasis. Then in the absence of protective secretion, and delayed propulsion, the alimentary toxæmia may become progressive. Rickets is possibly the result of a toxæmia of the alimentary tract.

Arterio-sclerosis may be met at all ages, in young people as a sequel to infective fevers, in adults frequently following a continued high blood pressure and as the result of an absorption of certain poisons, as lead and alcohol. Besides this, it has been proved that certain substances, pressor bases, can be got from protein putrefaction (Dixon, R.S.M., "Alimentary Toxæmia", 1913), and can cause an increase in blood pressure. All this points to a toxæmic origin, which is generally in the intestinal canal. Premature senile decay and arterio-sclerosis occur in people with indol and urobilin in the stools, and who are fed on a diet beyond their caloric requirements. Their absorption of protein and fat is good, and it is considered that the aromatic substances act as poisons, causing tissue

waste.

Chambers Watson points out that defective feeding may cause it, as follows:- "by the action of toxins from the abnormal digestion of proteins, especially animal proteid foods, and more particularly in constipated people; by the action of toxins produced, either in the digestive system or in the tissues, from an excess of nutrient material or over-eating. Here also constipation is an important predisposing factor."

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Experimental arterial disease has been produced in a variety of ways. In 1889 Gilbert and Lyon showed that injected bacillus plus toxin produced a fibrocartilaginous change, especially if the vessels had been injured. In 1913 Josué called attention to the action of drugs in producing arterial disease. Adrenalin caused extensive change in the mid coat of arteries. In man, the first change here is a fatty degeneration, and it has been shown that any drug that can considerably raise the blood pressure, will, if injected into the blood of healthy animals, bring about changes in the mid coat of arteries, irrespective of age.

The toxic effects of some of the heavy metals on nerve structure are well known and definitely proved. It is interesting to note that in certain doses and in certain combinations the toxic effects differ for the same metal, as they also differ in their method of absorption. All in small enough doses have no appreciable effect, in larger doses are beneficial, and in continued or very large doses give toxic results. Thus lead

has a selective action on the peripheral nerves, the paralysis of the ulnar nerve being a classic result. It has also a special action leading to constipation and to colic and diarrhoea .

The constipation is believed to be the result of a paralysis of the splanchnic nerves which inhibit the automatic ganglia of the intestinal wall, the colic being merely an acute exacerbation of the intoxication.

Mercury has a selective action depending on the method of administration and absorption. When inhaled, as in workers in the metal, the toxic result is a fine tremor of the fingers, pointing to an impaired or delayed conduction in the nerve fibres. When absorbed from the bowel or cutaneous surface, the pathological condition following is different, and is chiefly limited to the gastro-intestinal tract.

Arsenic differs in toxic results according to whether it be given as an organic or inorganic preparation. The inorganic preparation in small doses has a selective action, generally exhibited in the peripheral nerves of the leg, leading to a neuritis and possibly later to a paralysis. In large doses it causes a very severe gastro-intestinal irritation, with later, should death not occur, expensive and hopeless paralysis of all the groups of muscles in the body. On the other hand, given as an organic preparation (atoxyl) it has caused a primary optic atrophy. This result seems to depend less on the size of the dose than on individual predisposition, and it is less dangerous to give one large dose than continued smaller doses.

Poisoning by inorganic arsenic preparations does not cause optic atrophy and amaurosis, but does cause a conjunctivitis and oedema of the eyelids, while organic preparations do not do so. (Swanzy, "Eye Diseases")

In considering the effect of organic toxins on the nerve system, we see that in chloroform anaesthesia the immediate effects are through the blood-stream, and act in a definite progressing manner, producing a paresis of the various muscles, while certain organs, as the heart and muscles of respiration, are affected later, and with a sufficient dose also come under the same influence. In long continued doses, there is fatty degeneration, possibly from deficient oxygenation. Like other toxins passing through the liver, it may cause a cirrhosis, finally ending in an acute yellow atrophy. Hunter says that prolonged anaesthesia in difficult patients causes a depression of the liver cells, allowing the portal blood to pass unchanged to the systemic circulation, with its consequent action on nerve cells. The toxic results may vary from slight headache to the toxic phenomena of poisoning, as in acidosis.

Alcohol may be regarded as an exotoxin, the product of the action of yeast on sugar. It is readily absorbed from the intestinal mucous membrane. Small doses cause excitement of the central nervous system, due to a deadening of the higher centres, with a consequent loss of control, and not to a real stimulation. Large doses paralyse the nervous system, beginning with the higher centres. It also causes paralysis of the blood-vessels,

and consequent dilatation. In chronic alcoholism, there is a special effect in the onset of a peripheral neuritis - a clear example of a nerve disease resulting from a toxin. But there is reason to believe that the deleterious effect of alcohol on the tissues has a more complex origin, and is in all probability due not only to the direct effects, but also to its indirect influence in promoting an abnormal bacterial activity in the intestinal canal, with the resulting absorption of toxins. Alcohol and tobacco are the chief causes of toxic amblyopia with gastric disturbance and optic nerve inflammation. Pathological findings prove an interstitial neuritis at the axis of the optic nerve, gradually leading to proliferation of connective tissue, and a secondary descending atrophy of one bundle of fibres - the papillo macular fibres - which are exceedingly vulnerable to the influence of certain toxic agents. These changes may be regarded as analogous to those which take place in the liver and brain as the result of chronic alcoholism in frequent small doses (Swanzy, "Eye Diseases"). Lauder Brunton points out that tobacco in small doses stimulates the vagus nerve, giving a slow cardiac rhythm, while in large doses it paralyses the vagus, causing a rapid beat. The effect of other organic toxins, as Atropin, is also well known.

As examples of bacterial toxins, those of tetanus and diphtheria are well known. Tetanus is a definite example of a disease resulting from the action of an exotoxin secreted at any distance in the body from the specific bacillus, which

itself remains at the infective spot. This toxin has the property of travelling along the nerve course to the central nervous system, and there selecting certain nerve centres for its pathological manifestations. These centres are stimulated, causing a tetanic contraction of certain groups of muscles, with characteristic results. It would appear from the results of antitetanus injection, that the toxin forms a stable combination with the nerve centre, as, when once established, the effect of anti-treatment is not appreciable.

In diphtheria, the effect seen is a paresis or paralysis of nerve, either at a distance from the focus or in its immediate vicinity. The toxic results seem to vary, and frequently the first symptom got is a diminished or absent knee-jerk. Later, the local effect is seen, sometimes some time after the focus of infection has apparently cleared up, as in the fauces. Frequently there results a paralysis or paresis of the lower limbs, and the extent of the lesion seems to have no relation to the severity of the paralysis following. It would appear from this that there is a pathogenic effect, probably from the exotoxin in the circulation, which affects fairly rapidly the nervous structures which are susceptible, as the heart nerve mechanism and that of the limbs, while the paralysis of the muscles of deglutition points to delayed infection, which may be associated with endotoxins as well, and possibly with the presence of other bacteria, as streptococci. Here, again, it appears that the toxin, once combined with the nerve substance,

forms a compound which is more or less stable.

There are some indefinite conditions affecting nerve structure which may be the result of a toxin affecting the selected agent, or which may be caused by tissue starvation. Thus we have conclusive evidence that certain articles of food and drink are for all practical purposes the causes of well-defined nerve diseases. Pellagra, a chronic disease of the spinal cord, characterised by digestive, cutaneous and nerve symptoms, is known to be the result of a toxin present in unripe maize, and would hence seem to be an intoxication. The pathological findings exhibit, amongst others, a sclerosis of the posterior and postero-lateral columns, and frequently meningeal inflammation. The peripheral nerves are not affected by the toxin. The lesions of the posterior column in diabetes may also be cited as a nervous affection intimately associated with diet. The causal agent in pellagra is probably an ultramicroscopic organism carried by the *Stomoxys Calcitrans*. There seems little doubt that food can become poisonous from the absence of certain principles, normally present, but which have been removed, or have disappeared during its preparation, from some action, probably chemical, during its keeping. Such occurs in rice, with the disease beri-beri possibly resulting.

Kidder and Williams (1913) and Hill (1914) in an article on Vitamines, point out that there are three bases of unknown chemical nature in food-stuffs. These are Vitamines, purines



and cholines. They exist in most food-stuffs, and are probably necessary for the growth and nutrition of the body. It has been shown that they can be destroyed under certain conditions (alkali action or heat); that the vitamine base is not the active curative agent in wet beri-beri; but that it immediately relieves the paralytic symptoms in dry beri-beri; that the therapeutic properties of alcoholic extract of rice polishings are greatly altered by hydrolysis, the non-hydrolysed extract being curative and non-poisonous, the hydrolysed extract being very poisonous in large and promptly curative in small doses. Kohlbrugger suggests an air-borne and acid-forming bacillus, the growth of which is favoured by warmth and moisture, and the favourite food of which is over-milled rice. Rice after cooking and exposure to air becomes acid. He claims to have recovered the bacillus from the crops of chickens suffering from polyneuritis. Such an origin of the toxin formed by hydrolysis is possible.

Certain nerve diseases are believed to be caused by bacteria or other toxins. Tabes and General Paralysis of the Insane are both diseases caused by the continued action of the virus of syphilis, or the continued use of alcohol, or both combined. The lesions of both seem to be similar, tabes dorsalis affecting the nerve cells of the cord and G.P.I. those of the brain. In both, when incipient or when once established, the accelerating factors of overwork, mental strain, or dissipation, are well known. The nerve cells, when injured

from any cause, seem to have to some extent lost their power of resistance. Optic atrophy is associated with other spinal amaurosis, especially in locomotor ataxia, less often with disseminated sclerosis and lateral sclerosis, which are possibly toxic in origin. Atrophy of the papilla may occur in G.P.I. The association of all with chronic constipation is well known.

The effect of alcohol on the intestinal tract in its relation to toxæmia is of great practical importance. The aetiology of such diseases as disseminated sclerosis and sub-acute combined sclerosis is unknown. All we know is that they are the result of some toxic condition of the blood. "If alcohol can act in this manner, it is possible that other defects in the diet, with their results, may be a factor of importance in the production of the toxic condition of the blood which is undoubtedly the cause of these chronic inflammatory infections of the central nervous system." (Chalmers Watson, "Diet in Health and disease"). In many of these disorders, the clinical history shows that a marked gastro-intestinal disturbance precedes the development of the nerve symptoms, the disturbance taking the form of flatulence, constipation and bilious attacks, while a septic condition of the intestinal tract is indicated by the ill-formed foetid stools while the diet has been of the nature which would conduce to abnormal bacterial activity in the intestinal canal. The same applies to chronic mental diseases which are regarded as the result of chronic auto-intoxications.

In certain diseases the thyroid gland shows signs of increased size, associated with increased secretory power. It is believed that the secretion is one agent counteracting, probably neutralizing or destroying toxins, and possibly it fulfils the same function in regard to toxins absorbed from the alimentary tract. Thus, in children who suffer from irritation in the gastro-intestinal tract, and in certain stomach cases, classical symptoms develop which are designated under the name of tetany. Langmead has described similar symptoms in dilatation of the colon with stagnation. The same condition is also found after excision of the thyroid gland, and especially if at the same time parathyroids have been removed or injured. There is a resulting and rapid toxaemia, if untreated, which can be overcome in stomach cases by washing out the organ, and in colon cases by colon lavage.

Since tetany occurs in rickety children, in whom the gastric and intestinal conditions are well known, and in whom it is always associated with an unhealthy condition of the stools, the cause points to an intestinal toxaemia. Bouveret and Deric have isolated a substance from such stomach cases which, when injected into animals, produces the classical picture of tetany.

In certain people, after attacks of pneumonia or typhoid fever, a peculiar mental condition develops. They exhibit extreme irritability of temper, with severe headache, sleeplessness, and at times slight mental irregularities. This is accompanied by changes in the urine which indicate a disturbance

of metabolism. In some cases the condition seems to be progressive, and may occur for the first time a considerable time after the causal attack. It has been pointed out by Flexner at the Rockefeller Institute (B.M.J. , 23rd. June, 1917, p. 846 ) that in poliomyelitis, meningeal irritation precedes the onset of the paralysis, and he continues, "the virus does not reach the central nervous system unless the meninges have first been injured in some way, as by the introduction into the meningeal sac of some substance which would set up an inflammation or irritation. The injection of normal horse serum (protein) into the theca a few hours previous to the injection of the virus into the blood is quite sufficient to admit of the virus penetrating into and infecting the central nervous system. The injection of an immune serum, however, does not allow the infection to take place. Even physiological saline, injected into the theca, will so alter the meninges that infection occurs. Undamaged meninges are extraordinarily efficient as a barrier against infection."

Various symptoms are known to be produced by constipation and toxæmia, such as headache, vertigo, neuralgia. Cephalalgia is commonly dependent on constipation, and is found associated with neurasthenia. Migraine, neuralgia and sciatica are due to many causes, one of the most common being anaemia, gastro-intestinal derangement, and arterio-sclerosis. The relation of these to each other and to proteid putrefaction has already been pointed out. Migraine is often found associated with

physical and mental depression and local vaso-motor disorders. The symptoms of haedache, aphasia, and transient hemianopsia followed by migraine of the opposite side, are probably due to disturbances of the circulation in the occipital lobe of the brain.

Herter has classified the symptoms of intestinal putrefaction, and describes them as Indolic where there is marked Indicanuria, with organisms of the baëillus coli type found, associated with chronic dyspepsia and incomplete digestion of proteid, and in adults with fatigue; Saccharobutyric, associated with Bac. Aerogenes Capsulatus and anaemia ; Skatolic, where nerve symptoms are unusually prominent ; and Mixed - the most common - where indicanuria is marked and nerve symptoms are nearly always present and predominate, while many cases present a characteristic neurasthenia.

In excessive indicanuria, melancholia and mental depression are found, and Herter found that frontal headache, irritability, and insomnia can be produced by feeding with indol, which he considers a toxic substance.

Neurasthenia has long been suspected to be due in the majority of cases to a toxic condition of the blood originating in an alimentary toxaemia; but definite proof is difficult to get. When the classical symptoms of chronic alcoholism are considered - a known toxic agent - and those of a neurasthenic case compared, there is a very close resemblance between them, both having the symptoms of restlessness, nervousness, hyper-

aesthesia, easy fatigue, and loss of concentration and memory. The bacteriological evidence points to an abnormal state of the intestinal flora, Bac. Coli acquiring pathogenic properties, and being replaced partly by Streptococci and coliform bacilli and Bac. lactis aerogenes. These on treatment and with improvement give place again to B. Coli.

It is probable that the toxins of the intestine have a special affinity for the nerve centres. Although neurasthenia may cause the intestinal wall to take on a lethargic condition, with a resulting constipation, yet the condition increases bacterial activity and possibly absorption of toxins, which may cause the increased nerve symptoms of neurasthenia. Here there is a great sense of fatigue, the patient being always tired. Sir Lauder Brunton says: "The B. Coli seems to have a special power of producing fatigue toxins, and many people in whose intestine it exists in great abundance suffer from constant weariness and a sense of fatigue."

The general conclusion is that the aromatic substances formed may be the cause of many of the symptoms of neurasthenia, which does accompany increased intestinal putrefaction. Experiments of Richards and Rowland seem to show that reduced oxidation in the tissues explains the more marked toxicity of indol in some individuals.

With the average mixed diet it is found that 85% to 95% is absorbed after being subjected to the normal intestinal changes, and the 5% to 15% mainly indigestible residue, passes

into the motions. The greater part of the faeces is derived from the gastro-intestinal secretions and excretions, and on an average  $\frac{2}{3}$  of the stools consist of these with débris of the mucous membrane and glands. Of the remaining  $\frac{1}{3}$  about  $\frac{1}{6}$  is bacteria. Hence, roughly,  $\frac{1}{3}$  of the faeces is contributed directly by the food. But when conditions favouring abnormal putrefaction and fermentation are present, the intestinal contents may increase in bulk by the proliferation of bacteria, which normally may be as much as  $\frac{1}{3}$  and in abnormal conditions, as in fermentative dyspepsia, may amount to  $\frac{1}{2}$  or  $\frac{5}{6}$  of the stools.

Hertz defines constipation as a condition in which none of the residue taken eight hours after defaecation is excreted within 48 hours. The distribution and activity of the intestinal flora no doubt influences the proportion of saponified and unsaponified fat in the faeces. Owing to the defensive mechanism of the stomach juices, and the rapid passage of the chyme through the upper part of the healthy intestine, comparatively few bacteria are met with until within one foot of the colon. Here and in the large intestine the bacteria rapidly increase in number and variety; so that a certain amount of fat-splitting goes on, normally due to the colon group. Delay here may, as in some cases of constipation, result in excessive saponification and absorption of fats; on the other hand, if hurried through both intestines, the fat may escape complete pancreatic digestion in the small intestine and hence give

excessive cleavage products of bacteria in the large intestine. At any part of the bowel where retention or other pathological condition occurs, there is apt to be an abnormal flora, owing to the rapidity with which bacteria multiply. This multiplication is more likely to be in the normal flora, with incidentally increased fermentative and absorptive effects, as in dilatation of the stomach and colon. When there is such bacterial decomposition and faecal retention in excess, with absorption, clinical symptoms may arise. As there is no increase of phenol and cresol in simple constipation, any urgent symptoms arising point rather to the cause being the decomposition products (endotoxins) of bacteria.

Poisoning from faecal stasis is got from bowel obstruction, but there is little evidence that mere faecal retention favours fermentation and putrefaction. This is probably so because of the solid nature of the contents. But there must be more bacterial decomposition with the liberation of endotoxin, which in most bacteria is a virulent poison. This occurs in that part of the bowel where absorption is a physiological result. There may also be an injury to the bowel resulting in an inflammation, or even ulceration from pressure of scybalae. Abnormal absorption would then tend to occur and be progressive, with the resulting pathological symptoms. Inflammation of the mucous membrane of the bowel is stated to favour the absorption of toxins. Where the mucous membrane is thin, as in infants and young animals, the permeability is greater, and it is



claimed that diphtheria antitoxins can be given successfully per rectum in infants. It is further found that various vegetable toxalbumins are not completely destroyed by the digestive juices, but diffuse through the intestinal wall into the blood. Ulceration is often the result of streptococcal action in the intestine.

The association of constipation with epileptic conditions is well known, and the benefit derived from aperients is appreciated in these cases. It is also found that the disease can be successfully treated by dieting alone. From this it may be argued that intestinal intoxication plays an important part in epilepsy in association with constipation. The disease may be accompanied with high blood pressure, and it is known that certain pressor bases are found in protein putrefaction which could cause the increased blood pressure. It is also known that the subcutaneous injection of potassium cyanide lowers the power of animal cells to take up oxygen, and that the absence of oxygen will cause cyanosis and vomiting, with twitching of the muscles in some cases under an anaesthetic. Kramen states that soluble toxins capable of producing nervous excitement followed by convulsions and general paralysis have been used in animals. In dogs the subcutaneous or intraperitoneal injection of indol or phenol (the indicator of putrefaction in constipation) will cause convulsions and muscular twitchings of greater intensity and longer duration than in control animals.

In epilepsy the nerve cells may be from hereditary conditions more susceptible to the action of poisons, which are produced as the result of toxæmia in constipation and may act either by stimulation of the nerve cell or by preventing the proper oxidation of toxic products formed in the cell, with the result that convulsions occur.

I may quote a case of Epilepsy Major associated with constipation. - Miss W. , aet. 28 years, single. Troubled with constipation since a baby, the quantity of faeces being deficient, as well as delayed in transit. Developed Epilepsy Major at 12 years of age, which continued, with one intermission of two years, at fairly regular intervals, until her present age (1913). The father developed Locomotor Ataxia, and the mother was highly nervous. The patient's blood was negative to the Wassermann reaction. She had received the usual bromide treatment without any permanent relief. Examination of the faeces showed B. Coli Communis, B. Coli Communior, B. Acid. Lactis, and two varieties of Streptococci. The blood was absolutely normal to the first two. The opsonic index to B. Acid. Lactis was quite abnormal (2.50), while it was low to Streptococci (0.75). There was also agglutination to B. Acid. Lactis. The patient was hence suffering from B. Ac. Lactis infection and probably also Streptococcal infection, two organisms commonly associated in the intestine. Streptococcal and B. Ac. Lactis vaccines were used together (Oct. 27th. 1913), and the dose increased and continued over three months. On

Dec. 3rd. 1913 there was a considerable improvement. Since then there has been no return of the condition (Jan. 1917) . An occasional aperient was given. One fit occurred after the vaccines were given, during the first fortnight.

In considering any varieties of bacteria found in any part of the gastro-intestinal tract, it is found that those in the mouth are 9/10 streptococci; the stomach and duodenum have very few when healthy; the small intestine harbours a few B. Coli and hardier streptococci with restriction of proteus. In the large intestine, B. Coli and cocci have very favourable conditions, and here anaerobic bacilli begin to assume prominence, while proteus and pyocyanus are not uncommon. Of the named varieties, B. Coli Cominus and B. Lactis Aerogenes are the most frequent inhabitants. Bac.Faecalis Alkaligenes and members of the Gaertner group are less common. Of Streptococci, the Streptococcus pyogenes is harmful. Our knowledge of anaerobes is imperfect. The most abundant are B. Aerogenes Capsulatus, B. Welchii, B. Enteritidis Sporogenes and the ordinary putrefying anaerobe, B. Cadaveris Sporogenes. In the absence of oxygen, their activity in proteid disintegration is very great. Others are streptococci and sarcinae, B. Proteus, and B. Pyocyanus, which forms soluble metabolic products.

Of these some do form toxic substances. B. Enteritidis Sporogenes, grown on albuminous material which has been subjected to tryptic digestion with sugar added, produces a sub-

stance strongly poisonous to animals, even in small doses, This method of growth corresponds to an abnormal digestive process. *B. Aerogenes Capsulatus* is intimately associated with anaemias, and produces haemolytic substances. *B. Coli* under certain conditions assumes virulent properties and may be a cause of changes in vessels and the symptoms of neurasthenia.

That it is possible for bacteria to change to a more pathogenic state is borne out by the evidence supplied in the Croonian Lecture (Lecture II) on Adaptation and Disease, by J.G. Adami. M.D. (B.M.J. , June 23rd., 1917). He points out that the virulence of bacteria may be exalted or depressed by methods known for some time; but what was more, that it was possible to make harmless and non-pathogenic bacteria into highly virulent and pathogenic forms. It was this direct adaptation that explained the origin of the infections. Recently a perfectly harmless soil bacterium - the *Bac. Mycoides* - was gradually educated to grow at body temperature. Use was then made of the principle of anaphylaxis, and the host (a guinea-pig) made increasingly susceptible to the influence of the bacillus. He was thus rendered incapable of destroying it. As a result, it multiplied and became accustomed to grow and to live in the tissues. Here is the important fact; simultaneously it gained the property of virulence, attacking and breaking down the tissues of the host.

The toxic substances, derivatives of protein putrefaction,

are possibly responsible for auto-intoxication. Thus the proteoses and simpler products of digestion, when injected directly into the circulation, can be rapidly eliminated by the kidneys, but since they lead to inhibition of coagulation of blood, and have a lymphagogue effect, they are apparently toxic. They also cause a fall in the arterial pressure, with a febrile reaction, and large doses in animals may even cause death. The epithelial cells of the intestinal wall seem to have the power of converting these back again into harmless protein, and it has been demonstrated that in health neither the proteoses nor the end products are found in the blood of the general circulation. With ulceration and other lesions of the intestinal canal, it is conceivable that they do reach the circulation; and if the quantity absorbed is larger than the liver can deal with, then their presence may explain many of the toxic symptoms periodically observed. Such ulceration is known to occur in sprue, which is now regarded as a gastro-intestinal intoxication. Here it is also observed that the symptoms vary according to the particular level of the intestine in which the ulceration occurs.

Putrescin and cadaverin have been found in cholera stools, Dambrowski has found cadaverin in health. These diamines in the canal would be easily absorbed, but are only to a small extent toxic, and the quantity found in the bowel is not very considerable.

7  
6  
Homogenthesic Acid, a product of the protein molecule

tyrosin in the intestine, is under normal conditions broken down after being absorbed in the general metabolism. The quantity of indol absorbed even in marked indicanuria would perhaps have very little effect on the tissues, unless long continued and associated with a diminished oxidation in the tissue. Sulphuretted hydrogen is found largely in elderly people, and may cause pathological symptoms by interfering with oxygenation of the blood, the sulphur molecule taking the place of the oxygen. The general symptoms are - headache, at times resulting in collapse, and if the interference be continued and combined with the influence of indol absorbed at the same time, may even lead to melancholia.

It is found that certain amines can produce a pharmacologi<sup>o</sup>g-ical effect. Thus the action of the pressor bases previously described is characteristic, and indolethylamine produces a transient effect on the central nervous system, causing clonic and tonic convulsions and tremors of the limbs, while the histidine base is possibly the causal agent in asthma, from its depressor effect on the vessels of the mucous membrane of the lungs resulting in dilatation and spasm of the bronchioles.

The evidence of normal products of intestinal putrefaction and fermentation producing disease is very small, but there are a few instances. On the other hand, there is widespread belief that many diseases depend on the absorption of toxins from the intestine. McKenzie Wallace has pointed out that it is possible that in excessive bacterial activity we may have a negative

as well as a positive result, and that tissue starvation may be got. Thus it is known that shatol is a derivative of tryptophan, and if this be an important element of protein, the excessive splitting up may have a detrimental effect, apart from toxic formation. The disease beri-beri may be such an example.

Toxins may act on nerve structure, either directly, as in diphtheria and tetanus, where there is evidently a chemical action and combination, with decreased physiological power of the affected tissue; or they may act indirectly through their effect on the blood constituents or blood-vessels, as in anaemia, atony, and hypertonicity of the blood-vessels. Here the secondary effect is seen on other tissues, from want of food supply, want of removal of toxic materials formed by their own metabolism, or want of oxygenation. The latter seems to be a powerful factor in any toxaemia.

Toxic substances may arise partly in the bowel and partly in the tissues in the bowel as nitrogenous poisons from microbial action. But the chief source may be due to an error of nitrogenous metabolism, the result of imperfect oxygenation or enzyme action. In any case, it arises from proteid food or proteid tissue.

The toxins after formation must, before they act on the various systems, pass unchanged, so far as their toxic properties go, through the various lines of defence in the body. Before the bacillus establishes itself in the intestine, it must be capable of resisting the stomach juices, either by its

own vitality or hidden in food-stuffs. Gastric secretion would, if deficient, tend to assist this. There are then many antagonistic bacteria in the intestinal canal, and even if the entrance of bacteria be easy, their growth is prevented by obligate bacteria such as B. Coli, B. Lactis Aerogenes and B. Bifidus, which discourage growth both of harmful and harmless species. How they do so is unknown. After toxin is formed, it can be got rid of by rapid elimination, deposition and fixation in tissues such as the liver; or chemically altered by oxidation, reduction, hydrolysis, or neutralization; or combined with substances formed or contained in the tissues, so that compounds of a harmless or less toxic nature result. Defence against inorganic toxins is chiefly by oxidation, but with more complex organic poisons protective combination is very often added. Such protective substances are chiefly alkalies, glyccoll, ures, sulphuric acid and glycuronic acid. Aromatic substances are generally combined with the last two, being excreted as ethereal sulphates and glycuronates, the quantity of these being the index of the amount of putrefaction, and possibly of toxaemia occurring. There may be said to be a triple line of defence; the intestinal mucous membrane; the liver, which then intercepts the toxic products passing the former, and transforms amines and ammonia into urea, besides combining the aromatic bodies with sulphuric acid and glycuronic acid to form comparatively soluble innocuous compounds; the thyroid, suprarenals and other ductless glands, dealing to some



extent with some toxins escaping the two former. Heger showed that the animal tissues had the power of destroying certain alkaloids, but that the power varied with the animal and its way of living. Thus a rabbit is tolerant to atropine. Lauder Brunton showed that the liver has considerable power of destroying diphtheria toxin, and recently Lee and Dixon pointed out that tolerance to nicotine depended on the activity of the tissues to destroy the alkaloid, the chief of those tissues being the liver. Lately Flexner has pointed out (v.a.) that the meninges act as a barrier if uninjured. The aromatic substances, such as indol (which is more or less toxic) etc., have been shown by Herter and Wakemann to be fixed in the living cells, forming a loose chemical combination, and are hence not recoverable by simple distillation. The liver cells are the most active; then the kidney, muscle, blood and brain, in this order.

Here are submitted seven cases, which seem to be closely related in their chemical symptoms to a toxæmia, in all probability from some part of the intestinal canal. Constipation of a chronic nature had been present in all, except the first, in whom the constipation was transient.

1. A.W. aet, 24 years, miner. Had severe pain over the stomach region, no vomiting or headache. Constipation present from the previous day, and continued over three days. Pain was described as shooting round his waist. Found to have a zone of hyperaesthesia at level of lower ribs and slight

rhombbergism. K.J. slightly increased. No eye symptoms, except lateral nystagmus. No syphilitic history, and no previous illness. Treated by Calomel gr. V. followed by  $\zeta$ .iv Magnes. sulph. daily for two days, after which the symptoms cleared up and have not returned.

II. T.H., aet. 37, hatter. Vomited blood several times a day; no appetite, very weak and anaemic, and later unable to walk from weakness. Teeth found to be very septic, and associated with ulceration of the mucous membrane of the gums. Tongue foul. Gastric contents revealed no organic condition. Bowels very constipated. Teeth were treated by a dentist, few being extracted, bowels regulated by aperients, and vaccine (Streptococcal from pockets in alveolus) given. The patient improved steadily, and was practically well in four weeks.

III. Mrs B., aet. 36, married. Had suffered from constipation, with slight abdominal pain, for many years. Had a sallow, anaemic appearance, with soft and flabby tissues. Examination of faeces gave cause as being a variety of B. Coli. Vaccines given, and aperient when necessary. The general condition of patient improved, and the neurasthenia and introspective mental condition from which she suffered showed considerable abatement at the end of two months. Patient has not been seen since.

IV. Miss W., Epilepsy - considered previously under that heading.

V. Mrs. M.O.aet, 32. married. Five children - two alive. One child died of maramus when three months old. Three abortions, all between second and third months. No illness during the first two pregnancies, but with the three abortions she had the same symptoms and results as described below. Admitted with occipital headache, diarrhoea, and sickness of two months' duration. Diarrhoea was occasional; at other times she was always constipated. Illness began in first month of pregnancy with occipital headache, causing the patient to retract her head, which position gave some relief. There was also diplopia, with left internal strabismus, weakness of arms and legs, rhombergism, and feeling as if walking on cotton wool. No Kernig's sign. Pupils were dilated, and reaction to light and accommodation delayed, but present. Fine tremors of hands were present. Examination of the fundus oculi revealed double chocked discs, with much exudate and some haemorrhage: swelling of the discs moderate - 2 D. Blood examination showed Hb. 85% R.B.C. 4 million. Whites 8500. Treated with Mist. Bismuthi Co., which cleared up the sickness in seven days. Oedema of the feet went in eight days with rest. Other signs did not improve under Potassium Iodide, but abortion occurred at the end of the fourth month, and ten days later all symptoms had gone. Since that time patient has been healthy, except for an appendicectomy done. The appendix removed showed old signs of inflammation, with adhesions to the right pelvic wall. Wassermann negative.

VI. W.M., aet. 27, single. Chancre Aug. 1912. Treated locally and with calomel. Secondary symptoms Oct. 1914. Wassermann positive + + . Four intravenous injections of .9 Noosalvarsan given at intervals of four days. Reaction was fairly severe. Sixteen days after last injection developed a scarlatinal rash on chest and back, and slight hyperaesthesia on soles of both feet; two days later oedema of face, and the following day rash spread all over body. A week later a "weeping eczema" developed, with a septic state of the throat and nose, and conjunctivitis. Seen by a skin expert, who diagnosed an acute exfoliative dermatitis, probably arsenical. The hands and nails were severely affected. The hyperaesthesia spread till it reached above the knees, and later was present up to the waist. Diplopia was present. Had three weeks later weakness of walking. Patient stated that he had been treated in hospital and had two antistreptococcal injections. He got well. A second attack developed two weeks after, and when seen he still had signs of the dermatitis. He was suddenly seized one cold morning with pain in both legs, which later went on to weakness in walking. On examination he was unable to stand and walk, the tongue was foul, the mucous membrane of the mouth tender, and the bowels very constipated (this was a chronic condition all his lifetime). Sensation to touch was diminished all over body, absent entirely on soles of both feet, and delayed in arms and legs. Heat and cold similar. Pain - a zone of hyperaesthesia at level of lower ribs and on soles of

feet, and here touch was described as pain; considerable tenderness of calves of both legs. The knee jerk was elicited only on reinforcement. and the response very feeble. Rhombergism absent. Gait stamping. Motor power of arms and legs about half normal; inco-ordination of hand movements. The blood and cerebro-spinal fluid gave a negative Wassermann reaction. No change in fundus oculi. Treated with Pot. Iodidi gr.  $\text{iii}$  t.i.d., inunction of Ungt. Hydrarg. Ammon., dil. with Pot. Iodidi gr. V. to  $\text{3i}$  in lower dorsal region and aperient Mag. Sulph.  $\text{3}$  iv. Notes of the case during the following six weeks reveal steady improvement. Three months after admission there was still slight anaesthesia in soles of feet, and k.j. slightly diminished, but after that date the patient followed his usual occupation. In June 1915 there was still arsenic.001 m.gram in 100 c.c. urine - no albumen. June 1916, he was very well, but easily fatigued. Nov. 1917. still well.

VII. J.J.aet. 21 years, brushmaker. 18th June 1914, evening, seized with violent frontal and occipital headache, followed by collapse, but not unconsciousness. Admitted 6. p.m. same evening. T.96.4. P. 68. feeble, but regular. R.24. At that time nothing elicited in the various systems except constipation. He displayed considerable reluctance to being interrogated, but could speak with an effort. There was no sign of a blow on the head. He complained of extreme occipital headache. The father, who accompanied him, gave a

history of constipation over three days, and stated that his son had suffered from constipation for three years. Calomel gr.vi. given. Six hours later T.98.2. P.63. full and bounding. R. 24.

19th June - head retracted, pain in muscles of neck and vertex of head, pupils dilated, reaction normal, body felt cold. K.J. increased. No Kernig. The same evening he developed Kernig's sign and passed urine involuntarily. No action of bowels. Saline aperient given, and later enema, with practically no result.

20th June - pain more intense, head more retracted, and back became arched;  $1\frac{1}{2}$  ozs. cerebro-spinal fluid withdrawn, colour red-brown, pressure slightly increased. The pathological report revealed no bacilli on direct examination or on culture. Hb. present. Urine S.G. 1034 - no abnormal constituents. Bowels opened well. Evening, slight improvement generally, and less pain.

21st. - 22nd. June. B.O. †. C.S. Fluid 3 vi withdrawn. Further examination of organ revealed nothing except Hb.

24th. June - C.S.Fluid 3 vi withdrawn; colour much lighter; less Hb. present. He then began to improve rapidly and steadily till discharged at the end of 27 days. Ophthalmic examination revealed slight papillitis and 1.5 D. Myopia. He was subsequently seen in August 1914, up to when there had been no recurrence; in February 1916. when he said he had had

attacks of dizziness, falling down on one occasion, and before the attack had double vision and constipation more marked than usual. He volunteered the statement that the attacks came on when the bowels did not move for two days. March 1917, attended O.P. department as the result of a relapse, and stated: "I had first a feeling of standing on something higher than my feet, and my fingers felt thick. I then felt dizzy and got near to a wall and leaned against it for a quarter-of-an-hour till better. I went home and had a cup of tea. At 2 a.m. I felt sick and vomited, then became half unconscious. I felt better in the morning, except for weakness. My bowels in spite of medicine, have given me more trouble lately. Next day there was a sensation of mist before my eyes and slight headache."

In considering the action of toxins on the nerve system, certain ones have a selective action on the peripheral nerve system, and others on the central nerve system. In the case of central nerve system diseases, the results are a sclerosis of that tissue followed by degeneration, the sclerosis following inflammatory changes induced by toxins. This may be caused by toxins acting on the blood-vessels, with consequent contraction, thickening or obliteration of the lumen, followed by degenerative changes in the part supplied or by direct action on nerve structure, as in certain known toxic conditions. It has been demonstrated that products of proteid putrefaction do cause tonic and clonic convulsions, and others cause a

sclerosis of the tissue, while certain nerve fibres are particularly vulnerable to their action. In botulism there is constipation or internal ophthalmoplegia following. Whether chronic mental disease is caused or simply associated with chronic constipation is not definitely settled. It is pointed out by Chalmers Watson - "that experimentally certain foods have an influence on the structure and function of the tissues of animals fed on those foods over a considerable time, and amongst these effects are the changes in nerve tissue. The structure and functions of the organs are modified, whilst some of the modifications are repeated in the offspring of animals primarily affected, and in them there is an increased susceptibility to disease, notably a catarrh of the different mucous membranes." The same may apply to human beings. It is recognized that certain people are born with tendencies to the reception and development of certain diseases. This has been called the influence of heredity. The various organs are thus "prepared" to receive the particular toxin to which they are susceptible, certain toxins having a selective action for certain cells, forming a more or less stable chemical combination. It would appear from the above that it is the cell that has the selective action, if any, and that the toxic product is a more or less chance acquaintance that may be avoided. The absorption of the toxin may even be due to an inherited susceptibility of the intestinal wall, and the same argument applied to the various other barriers and to the central nervous



system itself.

The great importance of free drainage from a surgical point of view has been demonstrated by Carrel in his experiments on growing tissue. He has demonstrated finally that toxins are produced, and that these cause pathological results from auto-intoxication, and that can be prevented by removal of the toxin as it is formed. The analogy between free drainage in toxin production and free ventilation may here be compared, and would mean the continuous removal of toxic products as they are formed. The conditions caused by constipation are the reverse of this. Whether constipation be the result or cause of bacterial infection does not alter the significance that elimination is hindered by stasis and the opportunities of toxic absorption enhanced. This may occur during increased absorption, which may be a cause of constipation, and Bayliss and Starling have shown that increased absorption is attended by increased secretion from the intestine to absorb food. If this occurs rapidly, then constipation would not be prevented, and toxins might at the same time be absorbed. As the condition also tends to cause inflammation of the mucous membrane of the intestines, and also ulceration, then the chances of absorption of toxins are greater. It has been shown that when the epithelial cells are destroyed, proteoses are not reconverted into protein, and then circulate in the blood stream causing clinical symptoms. "Hence the pathological basis is established for toxæmia by constipation, and is

associated with a catarrh of the large bowel, chiefly the caecum." (Ext, "Lancet", Sept., 25th.1914,Chalmers Watson). It is known that delay in transit gives toxic substances with clinical symptoms following, and that in constipation there is certainly a decomposition of bacteria and liberation of endotoxins. That inflammation and ulceration of the bowel are caused by constipation is known; that the chronic state of the disease tends to long-continued absorption, no matter how small the amount of toxin absorbed. Apart from this, it is definitely proved that toxalbumins are not destroyed by the intestinal mucous membrane. When toxins are absorbed into the blood, they can cause changes in most of the organs of the body, and although this action is reduced by a considerable quantity of them being destroyed or changed into harmless products, yet in time the organs effecting these changes themselves become changed in structure, usually by a process of sclerosis. This enables the further circulation of the toxin and extension of its field of influence, and in this case oxidation of other tissues has been reduced by the action of the toxin itself. It then causes tissue waste, which is stated to be seen more particularly in constipated subjects, whether produced in the gastro-intestinal tract or in the tissues themselves. The same applies to the central nervous system, where substances of putrefactive origin have been experimentally proved to cause nerve symptoms. Lastly, Flexner has proved that toxins cause injury to the meninges, resulting in changes in

them which cause that tissue to lose its barrier action - probably from inflammation - to the poison circulating in the blood. There is then free access to the central nervous system, and following a meningeal irritation, a paralysis has been found to occur in Poliomyelitis.

In considering the cases described in relation to toxic absorption, the following remarks may be made.

Case I. May have been due to an acute toxæmia followed by slight myelitis, caused by toxins in constipation more rapidly absorbed during hot weather (July, 1917)

Case II. Undoubtedly due to septic absorption from the mouth, the toxin causing a hæmolysis followed by anaemia, which in its turn led to gastric trouble and hæmorrhage.

Case III. The neurasthenia and slight mental condition - melancholia - was due to a virulent strain of B.Coli, which has been thought to cause this condition. Here constipation acted by preventing daily elimination of toxin, and probably there was inflammation and ulceration, leading to increased absorption.

Case IV. The resistance to certain bacteria was defective, and on this being increased there was definite improvement. Here it would appear that toxin did act as a causal agent of the epileptic condition, and that elimination was related to chronic constipation, as in other cases.

Case V. May have been due to pregnancy with toxic products absorbed from slight changes in the uterus, but here must be considered the constipation (diarrhoea present may be an acute

exacerbation of the toxaemia, as in lead-poisoning), which may not have caused the toxaemia, but which no doubt contributed to the delay in its excretion. The toxin could then be re-absorbed, and then the constipation was a causal factor in the pathogenesis of the central nervous symptoms resulting.

Case VI. Here the poisoning was undoubtedly due to arsenic. There is also the syphilitic poison to consider. It is interesting here to note that the organic preparation of arsenic caused a dermatitis and conjunctivitis, with oedems of the face, symptoms not usually observed with organic preparations, but with inorganic salts. This would lead one to consider a combination of causes. Syphilis may have caused the Myelitis and peripheral neuritis, but here again there was a second attack, similar to the first, which would point to a delay in elimination, and at the same time reabsorption from some part. This would most likely be through the intestinal mucous membrane and as constipation was very much present, the organic form of the arsenic may have been re-arranged or changed. Besides this, the poisoning, from whatever source, was rapid in onset, and the patient was undoubtedly susceptible to its influence. In this case constipation may have acted as a preventative of elimination, thus assisting in the onset of the nerve disease, taking arsenic as the toxin.

Case VII. The observations in this case led to the title of the present thesis, the others indicating such a possibility. Here the only apparent cause operating during his lifetime

was a chronic constipation. The patient stated voluntarily that he had always felt its effect in dizziness and headache, and that relief from these was got on the bowels acting well. An interesting statement is that the attacks up to his admission to hospital, before which he had no regular treatment for constipation, were getting more pronounced, and finally ended in a severe attack followed by collapse. After admission there is a beautiful picture of meningitis, developing during an attack of chronic constipation more obstinate than usual, and relieved by decompression and aperients, ending in complete recovery. In reviewing the development of the attack, there was sudden collapse, followed in order by cerebral irritation, meningismus, and later meningitis, with the presence of its classical symptoms. That the condition was purely toxic is brought into evidence in the examination of the cerebro-spinal fluid, when no causal agent was found on repeated examination. The presence of haemoglobin is also explained by a toxic origin, due to haemolysis and injury to the capillary walls. The repeated lumbar puncture got rid of the excess of toxin, while the treatment of the constipation removed its source. The eye condition was such as could be caused by a toxic origin, and it was found not to increase subsequently. In conclusion the possible analogy between this case and the experimental works of Flexner already mentioned may be pointed out. Adopting the same view it is found that there is a chronic toxic origin in the constipation. Absorption is got, which would reduce the barrier

action of the various organs. A sudden and severe toxaemia is got, which results in a quantity of the poison passing the various barriers unchanged, and finally reaching a slightly altered and less resistant meninges. Here inflammatory processes are again set up, resulting in increased toxin acting on the central nervous system and free to exert its potency there. Phobism as a possible cause is eliminated, since the attacks occurred at all times of the year.

The suggestion is therefore respectfully submitted, "that the toxins of the alimentary tract in chronic constipation may have an influence on the pathogenesis of lesions of the central nervous system."

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WORKS OF REFERENCE.

Transactions Royal Society of Medicine.

Vols. I & II, Intestinal Toxaemia - 1913.

Faeces - Cambridge.

Food in Health & Disease - Chalmers Watson.

(and Appendix)

System of Medicine - Nerve Diseases - Clifford Allbutt.

The Physiology of the Circulation - Lauder Brunton.

Diseases of the Eye - Swanzy.

Asthma - Jas. Adams.

Anaphylaxis - Richet.

The new Physiology - Rendell Short.

The British Medical Journal.

The Lancet.

Tropical Medicine - C.E. Brocke.

Inborn Errors of Metabolism - Garrod.

The Fluids of the Body - Starling.

The Nature of Enzyme Action - W.M. Bayliss.

Oxidations & Reductions in the Animal Body - H.B. Dakin.

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