AUTO-INTOXICATION IN DISEASE

WITH SPECIAL REFERENCE TO

GASTRO - INTESTINAL TOXAEMIA.

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by

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Within recent years there has been a growing tendency among many physicians to regard certain abnormal conditions of the body as being due to the production and retention within the organism of certain normal or abnormal substances. Of these substances some have been definitely described, while others are of purely hypothetical nature. The theory of auto-intoxication is now so widespread that the term is frequently used as a convenient explanation of many abnormal states, but convenient only in the sense of concealing our ignorance. That such a condition as auto-intoxication exists, is undoubted. The study of Physiology teaches us that in the animal organism many normal processes are accompanied by the production of substances which may be inimical to the organism, while from Pathology and Clinical Medicine we learn that physiological products may be retained within the system and that abnormal processes may result in the formation of abnormal substances which may also be retained within the system.

If we define auto-intoxication as "an etiological factor in the production of certain abnormal conditions due to the retention within the body of physiological substances, or to the production and retention of pathological substances," we must clearly understand that this does not mean that the

mere presence of a poison within the body constitutes a state of intoxication. We must remember the power of toleration of the organism. To establish an intoxication there must be some disturbance in the function of the body.

The term auto-intoxication is apt to be used in a too limited sense, for it not only includes toxic states produced by the retention of normal and abnormal substances, i.e. products of metabolism, but also includes many infectious diseases which present phases dependent not upon the action of the specific bacterial toxins, but dependent upon the metabolism of the bacteria, whereby a condition of exaggerated autolysis is set up. The production of intoxication in this way is worthy of careful study. Some writers even state that the harmful effects of many micro-organisms are due purely to the production of an auto-intoxication.

Classification of Auto-intoxications.

The whole question of auto-intoxication in disease is still in such a chaotic state that any attempt at a proper classification would of necessity be futile, but in order to discuss the subject rationally it will be wise to make some sort of distinction between the probable forms of intoxication. The following provisional classification is merely an attempt to set forth the main types of supposed auto-intoxications and will perhaps serve as a suitable means of viewing the subject broadly. It is not a classification of abnormal states due to auto-intoxication but rather a grouping of the different ways in which auto-intoxication may arise. Its incompleteness and speculative nature will at once be evident, but no claim is made either for its completeness or accuracy. For a more definite knowledge of the subject the investigator in this field will have to direct his attention to bio-chemical problems of great complexity. Further researches on metabolism, and on the nature of internal secretions, enzymes, fermentations, toxins, toxic action and immunity are urgently required.

Classification.

I. Metabolic intoxications.

a. Produced by the retention of physiological products of metabolism, e.g. Bile, perspiration,

CO_2, faeces, urine.

b. Produced by the formation and retention of pathological products of metabolism. This includes many clinical conditions such as Gout, oxaluria, diabetes, uraemia, acidosis and other rarer conditions as cystinuria and alkaptonuria.

c. Produced by diseases of special organs, e.g. Thyroid, Supra-renals, Pituitary body, Pancreas, Liver, etc.

d. Produced by other disorders of metabolism depending on the existence of fever, infections and neoplasms.

II. Parasitic intoxications.

a. Produced by a systemic or general blood infection, e.g. The infectious diseases.

b. Produced by absorption from localised bacterial processes.

(1) Absorption from retained pus.

(2) Absorption from the gastro-intestinal tract, i.e. gastro-intestinal auto-intoxication.

A large number of diseases supposed to originate in an auto-intoxication might be added to the above list, e.g. simple anaemia, chlorosis, pernicious anaemia, the leukaemias, rickets, certain skin affections, arterio-sclerosis, tetany, rheumatoid arthritis, etc. but the true nature of most

of these affections is at present unknown and the auto-toxic origin is of course largely speculative. Bearing in mind then the limited state of our knowledge and the difficulties to be overcome in attempting to improve our knowledge, let us refer briefly to some of the work which has already been done in this field.

Bouchard[1] of Paris by experimentation with animals has elaborated certain views with regard to the production and nature of many toxic states. He probably takes an extreme view of the subject by stating that man is always producing poisons within himself and is therefore standing, as it were, constantly on the brink of self poisoning. Some of his results, however, are valuable and instructive. He proves that normal urine is toxic, and that a definite mass of living matter can be killed by a definite quantity of the poisons excreted in the urine of a healthy man.

He further shows that the urine contains many poisons, at least seven in number, (1) a diuretic substance (urea), (2) a narcotic substance, (3) a substance that produces salivation, (4) a substance that contracts the pupil, (5) a substance that lowers the temperature, (6) an organic convulsive substance, (7) an inorganic convulsive substance (chiefly potass.).

He then propounds the theory that Uraemia is an intoxication due to the retention within the system of these normal poisons, and in support of this theory he points out that the urine of uraemic patients is practically non-toxic. All the above poisons are not incriminated in the production of uraemia, for example, no blame is attached to urea. The colouring matter, he says, is responsible for three-tenths of the toxaemia, the extractive matter for one-tenth to two-tenths, while the potash and other minerals are responsible for four-tenths to five-tenths. As these inorganic substances play so important a part in the production of the poisoning, this theory of Bouchard is now generally spoken of as the Saline Theory of the French School, a theory which has been much discussed and discredited by many. Following on these investigations, further observations were made by Bouchard on morbid conditions caused by the exaggerated formation of these poisons in certain conditions, viz. dilatation of the stomach, constipation and intestinal obstruction.

"Dilatation of the stomach," he says, "gives rise to many other disorders, particularly to chronic albuminuria. The dilatation sets up gastric fermentation and excessive intestinal putrefaction, resulting in the formation of poisons (especially

acetic acid) which vitiate the nutrition of the osseous tissue and produce nodose rheumatism, osteomalacia, and perhaps rachitis." Poisoning by jaundice, he states, is two-fold. Bile contains two poisons, (1) The colouring matter and (2) the Bile salts. The colouring matter acts in disturbing the working of the nerve cells, while the Bile salts increase disassimilation, destroy muscle cells and blood corpuscles, and thus set free organic and mineral poisons, particularly potass. Acetonuria he demonstrated not only in glycosuric patients but also in certain cases of dyspeptic coma, cancer of the stomach, pernicious anaemia, leukaemia, dilatation of stomach and typhoid fever.

Von Noorden[2] in his studies on acid intoxication points out that the organism always tends to maintain the alkalinity of the blood, and that any reduction in the alkaline reaction of the blood serum is fraught with serious consequences. Alkali, he says, can be withdrawn experimentally from the body in two ways.

(1) The ingestion of the alkali with the food can be reduced or altogether stopped. This does not as a rule cause any particular derangement of metabolism, but in the dog, after a time it produces spasms and death, and in mice causes death sooner than in dogs. Bunge says the cause of death is intoxication with

sulphuric acid. (a product of protein metabolism.)

(2) Large quantities of acid can be exhibited. This in herbivorous animals leads to a rapid loss of alkali in the urine in consequence of a decrease of the alkalinity of the blood. At first the respirations become more rapid but grow slower towards the end of life. The pulse rate is also increased and the blood pressure is increased in the beginning, but falls off later in the course of the intoxication, the animals become atáxic, then convulsions set in and finally coma and death. In dogs the intoxication runs a different course. Quantities of acid that are three times as great as the fatal dose for a rabbit (tabulating the dose per kilo of animal) are borne by a dog without any particular impairment of the general health. The loss of alkali in the urine is slight and the alkalinity of the blood is only slightly reduced. In the urine the quantity of acid corresponding to the amount administered appears, and at the same time more ammonia. Thus the organism of carnivorous animals is protected against acid intoxication by the power it possesses of manufacturing ammonia from its proteids and of excreting this substance through the urine. Man shares this advantage with carnivorous animals of being able to manufacture ammonia in almost unlimited

quantities and of neutralising acid products in his body. Acid intoxication occurs in man in certain cases of perverted metabolism, the abnormal accumulation of acids being brought about either by a reduction in their excretion or by their increased formation, or it may be by a combination of both these conditions. Diminished secretion is not of much importance alone, unless perhaps, in cardiovascular diseases and gout where there is a reduced elimination of CO_2 and Uric acid respectively. Increased production is pathologically much more important and the acids to be considered in this connection are sarcolactic acid, carbaminic acid, aliphatic acid, oxalic acid, uric acid, aromatic oxy-acids, and above all B-oxy butyric acid, diacetic acid and acetone. These last threesubstances constitute the so called acetone bodies. Von Noorden believes that the poisonous effects of B-oxybutyric acid in diabetic coma are not due to any specific toxic properties but to its acid character in general and to the power it possesses as an acid of withdrawing alkali from the organism. Acetonuria, he states, is not to be always regarded as a morbid phenomenon. It is found in many clinical conditions and is always produced by the same cause, viz. lessened carbohydrate feeding.

On the subject of Gastro-intestinal auto-intoxication much has already been written. The products of normal or abnormal intestinal fermentation and putrefaction are said to be responsible for the production of such diverse conditions as epilepsy, tetany, chlorosis, pernicious anaemia, rickets, rheumatoid arthritis, certain skin affections, the so-called toxaemia of pregnancy, etc. Bouchard is a firm believer that in many cases of auto-intoxication the poisons are absorbed principally from the gastro-intestinal tract. Hemmeter[3], however, is in doubt as to the reality of some of the accepted forms of gastro-intestinal auto-intoxication, because in these cases, he states, the toxins have never been demonstrated in the blood of the patients. But it must be pointed out that gastro-intestinal toxins are capable of producing morbid phenomena in two distinct ways, (1) Directly in which the toxins are absorbed either unchanged or more or less modified and exert their deleterious effects directly on the tissues of the body, (2) Indirectly in which the toxins, modified or unmodified, produce some unanalysable alteration of metabolism which is only manifested in the establishment of a definite morbid phenomenon.

Metchnikoff[4], again, has endeavoured to prove that many diseases, particularly the degenerative changes of old age, are produced by poisons absorbed from the gastro-intestinal tract.

Many other opinions might be here cited, but it is unnecessary, I think, to do so, and I shall therefore pass on to a brief discussion of several points of great importance in the study of auto-intoxications.

The Blood Plasma in its Physiological and Pathological aspects.

The Blood Plasma is a straw coloured fluid of alkaline reaction and containing about 90% of water and 10% of solids. The colour is due to a yellow lipochrome. The chief solids are serum albumin, serum globulin, fibrin ogen, glucose, fats, urea, uric acid, creatin, chloride of sodium, carbonate of sodium, alkaline sodium phosphate, and traces of calcium, potassium, and magnesium compounds. Of the gases in the blood, oxygen is present in small quantity dissolved in the plasma but the bulk of this gas is present in combination with the haemoglobin. CO_2 is also present dissolved in the plasma, as well as nitrogen. In addition there are the internal secretions of the various organs of the body (Hormones) and the more complex substances described by bacteriologists, complement, opsonins, etc.

We thus see that the blood plasma is a highly complex fluid. As Campbell[5] says, "It is, in very truth, by far the most subtly complex fluid in nature, containing hundreds - nay, thousands - of substances, all in themselves highly complex, and for the most part, unanalysable." While all these complex substances are essential for the normal functioning of the body, we must not too hastily conclude that alterations in the composition of the plasma are necessarily of morbid significance, for the plasma may vary considerably within normal limits, depending upon age, sex, season, climate, diet, amount of exercise, etc.

Now, these variations in the plasma must lead to corresponding variations in the body metabolism, for the metabolism of all the cells of the body depends largely on the plasmic environment of the cells, the words blood plasma and tissue or cellular plasma being synonymous. The variations of blood plasma clearly have a direct bearing on the question of auto-intoxication, for the production of an auto-intoxication may depend altogether on an alteration in the blood plasma, sufficient to produce an abnormal metabolism. This is merely a re-statement of the fact that to produce an intoxication there must be a disturbance of function. It may be argued that an abnormal

metabolism might be primary to plasmic alteration, e.g. where fixed body cells are acted upon by nerve influences, dependent upon external stimuli. For the present argument, however, I wish merely to emphasise the importance of the composition of the blood plasma in the production of disease, and bearing this in mind, we may now pass on to a discussion of the methods by which plasma may be so altered as to set up abnormal metabolism, i.e. the production of a pathological plasma.

A pathological plasma may be produced in the following ways:

(1) The normal constituents may be altered.
(a) Excess, (b) Deficiency, (c) Perversion.

(2) Abnormal constituents may be present and these may be derived from (a) Morbid metabolism, (b) Gastro-intestinal disorders, (c) The action of Micro-organisms, (d) Exogenous sources.

(1) Alteration of normal constituents. We know that in certain pathological states the blood may contain an excess of one or more of its normal constituents. This may be due to overproduction, to insufficient elimination or to both combined.

Deficiency of normal constituents is usually due to a diminution in production while perversion of

normal constituents may usually be traced to some derangement in production.

(2) Presence of abnormal constituents.

The nature of many of these is shrouded in mystery. Their actual presence is even sometimes a matter of pure speculation. They may possibly originate, however, in morbid metabolism, e.g. acid substances producing the clinical condition described as acidosis, though the morbid metabolism may in itself depent on some obscure plasmic alteration. In gastro-intestinal disorders a large number of substances may be absorbed such as ethereal sulphates, ptomaines, etc. Finally, from bacterial activity toxins may be thrown directly into the blood stream or secondary intoxications may arise by the production of an exaggerated autolysis, giving rise to the formation of poisonous enzymes. Toxins of exogenous source we need not here consider.

Metabolism, normal and abnormal.

Metabolism is the name given to the chemical changes which are constantly taking place throughout the body. These changes are of two kinds, (1) Katabolic or destructive, and (2) Anabolic or constructive. The processes involved are highly complex and their study covers a large part of the field of Physiology. Briefly stated, the following

conditions would appear to be necessary for a normal metabolism:

(a) Normal or healthy organs and tissues.

(b) A normal or healthy condition of the fluids of the body, especially of the blood plasma.

(c) A suitable supply of food.

(d) A suitable environment.

Conversely, abnormal metabolism may arise from:

(a) Abnormal organs or tissues, the abnormality being in structure or function.

(b) Abnormal body fluids especially abnormal blood plasma.

(c) An unsuitable food supply, e.g. where the food materials are deficient or in excess, or contain poisonous materials.

(d) An unsuitable environment, e.g. excessive cold, excessive heat, vitiated atmosphere, etc.

In speaking of normal metabolism let us pause for one moment and think of the many complex phenomena involved therein, phenomena depending upon the chemical processes necessary for the digestion and assimilation of food stuffs, upon oxidation and distoxication, upon the secretory and excretory activity of glandular structures and upon many other processes all acting in unison and controlled more

or less by the nervous system. Is it to be wondered then that serious consequences sometimes follow even a slight derangement of one of these processes?

The Production and Elimination of Poisons by the organism.

It requires no great amount of argument to demonstrate the fact that the body constantly contains a large number of self induced poisons. These originate in several ways. Physiological secretions such as bile, saliva, the digestive juices and the secretions of the ductless glands may all possess poisonous properties under certain conditions. The products of digestion may also be of a toxic nature while intestinal putrefaction and disturbances of metabolism may be followed by the production of a variety of pathological toxins. There can be little doubt that many of these toxins circulate in the blood stream, yet direct demonstration of this fact is greatly needed. Some workers, however, have made interesting observations in this direction. Planer[6] has found H_2S in the blood of the portal vein. Carter has found indigo in the portal vein of animals suffering from intestinal derangements, while Bouchard and Gautier have demonstrated the presence of alkaloids in the circulating blood. When we remember that many poisons, whose existence

in the body is known, are excreted in the urine either in their original form or modified, we can surely assume that they must have passed through the blood stream. How then does the body protect itself against the action of these numerous poisons? It protects itself in two ways, first by simply excreting the poisons, and secondly, by bringing into play certain defensive processes with which the body is naturally well equipped. Our knowledge of these natural defences is at present somewhat limited and the subject is one which demands accurate investigation.

Natural Defences of the Body against Disease.

The recent advances of the science of Bacteriology have lead to the discovery of many defences in the body against the action of micro-organisms and their toxins; such defences are the acidity of the gastric juice and of the vaginal secretion, the bactericidal properties of blood serum and the phagocytic action of the leucocytes and fixed tissue cells. These defensive agencies, however, are connected chiefly with the subject of bacterial immunity and need not be further discussed. More important for us is the investigation of the defensive action of many of the glandular structures of the body.

The Liver is an important defensive organ. In the dog, when the portal circulation is directed

into the inferior vena cava symptoms resembling those of uraemia supervene, especially if the animal be given much proteid. Nenchi[7] has shown that the symptoms are mostly due to Carbamate of Ammonia. If, in addition, the hepatic artery be ligated, death occurs within a few hours under a most excessive acidosis[8].

The kidneys not only act as excretory organs but by some are believed to possess an act of catabolism whereby some intermediary product of metabolism is converted into an end product. According to some, this function depends upon the presence of an internal secretion. Abolition of this function would lead to metabolic disturbances and intoxication.

The Pancreas possesses an internal secretion which must have a profound influence on body metabolism. Extirpation of the organ leads to Diabetes, but if a small portion be left, the Diabetes does not occur.

The Thyroid is supposed to have an important defensive action. There are many views on the function of the thyroid, e.g.

(1) That it destroys products of renal insufficiency and substances that induce oedema, low temperature and debility.

(2) Notkin[9] has removed two substances from the

gland, (a) Thyro-protein - a toxin, and (b) Thyro-iodine. Thyro-protein is toxic. When injected into animals it causes symptoms analogous to those observed in Cachexia Strumipriva. This substance represents the colloid material of the gland and is believed to be, not a product of secretion, but an effete substance which the gland eliminates. Thyro-iodine is a substance formed by the gland itself from the iodine elements of the food and according to Baumann is the active principle of the Thyroid gland. Normally, the thyro-iodine which contains an enzyme destroys the thyro-protein, but after thyrodectomy the latter accumulates in the body and causes symptoms.

(3) Morktonne[10] believes that the thyroid collects mucin contained in the blood and transforms it synthetically into nucleo-albumen. After thyrodectomy this transformation ceases, mucin collects in various parts of the body and gives rise to myxoedema.

(4) Charrin[11] believes that the gland has a double function, (a) the removal from the blood of a phosphorated nucleo-albumen which has a slightly acid reaction, and (b) the secretion

of an alkaloidal leucomaine or thyro-antitoxin which neutralises the nucleo-albumen and forms with it a new substance necessary for the nutrition and development of the body. That is, the function is partly antitoxic and partly nutritive.

(5) Bunge[12] believes that the thyroid simply produces a ferment that influences the metabolism of the body.

(6) Blum[13] is of opinion that the function of the thyroid is not so much to form an internal secretion which passes into the blood as to seize upon and render harmless certain toxic substances that are formed in the intestine and find their way into the circulation. These toxins, - enterotoxins as they are called - are produced by the action of bacteria upon food. When the thyroid is absent or is diseased the absorbed enterotoxins produce changes in the body resembling myxoedema, tetany, cretinism, and other neuroses. He further states that the circulating enterotoxins are seized by the thyroid gland and converted by it into a new toxic substance called by him "Thyreotoxalbumen," a substance which closely corresponds

with the artificially isolated iodothyrin. The above theory was formulated on observations made on thyrodectomised dogs, some of which were fed on meat and some on milk. The experiments served at least to show that on a milk diet the production of enterotoxins is limited, while a meat diet favours their production.

The Pituitary Body is known to influence the body metabolism materially. Its removal in an animal causes death in two or three days. It is supposed to have a complex function, (a) To control bodily growth, In acromegaly the anterior part is enlarged, (b) to distoxicate certain products of intermediary metabolism, (c) to produce substances which have the following actions when injected, viz. raise blood pressure, dilate renal vessels and promote diuresis.

The Suprarenals according to Zucco, Lupino, and Albanese protect the body against muscular poisons. They are supposed to remove worn out pigments from the blood, and either to store them up as Chromogens or transform them so that they can be eliminated by the urine.

The Spleen. If a toxic substance which produces disintegration of blood cells, e.g. Potassium chlorate, be administered to dogs, splenic enlargement follows

(Dawein)[14], and the amount of enlargement is proportional to the number of cells destroyed. The splenic enlargement is due to its acting as a grave for the broken down cells and this sets up hyperaemia and hyperplasia. In a rapidly progressing anaemia therefore, splenic enlargement should be looked for. In chlorosis of course, we do not find any enlargement of the organ as we have here to deal notwith destruction of blood cells but with destruction and diminished production of Haemoglobin. In the leukaemias with great increase of the white cells the spleen sometimes becomes enormously enlarged owing to its being packed with dead leucocytes.

It has recently been pointed out that there is some interaction between some of the glands of the body, e.g. between the thyroid and pituitary, the thyroid and ovary or testis. Cretinism is usually associated with testicular atrophy; Menstruation and pregnancy are sometimes accompanied by a temporary enlargement of the thyroid; the pituitary body is often found enlarged after removal of the thyroid, also in goitre and cretinism. Iodine, too, is found in the pituitary.

The Toxic effects of substances produced within the body.

It is possible to deal with only a few of these.

Bile is a poison if absorbed into the blood stream. Its poisonous effects are due to (a) the pigment, and (b) the bile salts, glycocholate and taurocholate of soda. The pigment disturbs the working of the nerve cells and produces a depression of body temperature. The salts act as tissue poisons, particularly to renal, hepatic and muscle cells. Also, they exert a haemolytic action. In jaundice, therefore, the following symptoms might be said to be due to bile toxaemia, - low temperature, somnolence, albuminuria, slow pulse, and evidences of haemolysis.

Carbon Dioxide. It is doubtful if this gas acts as a direct poison. Dyspnoea is not necessarily due to excess of CO_2. It can be produced by a variety of chemical substances, by bacterial toxins, and it is a common symptom in certain diseases in which there is no excess of CO_2, e.g. uraemia, diabetic coma and hepatic coma. In asphyxia also, death is not due to excess of CO_2 but to the lack of oxygen. It is possible, however, that excess of CO_2 in the blood might give rise to some metabolic disturbance.

In June 1910 an interesting experiment was carried out at the London Hospital. Six students were enclosed in a hermetically sealed case until the CO_2 of the contained air reached 4%. At this point it was noticed that symptoms were present as long as the air remained stagnant and moist, while fanning of

the air was followed by a disappearance of the symptoms.

Perspiration. The general opinion now held is that normal perspiration possesses feeble toxicity.

Urine. The toxicity of normal urine as demonstrated by Bouchard, has already been painted out.

Substances produced in the gastro-intestinal tract. The action of these will be discussed under "Gastro-intestinal toxaemia."

Gastro-intestinal Toxaemia.

In the domain of Clinical Medicine there is at present probably no more confusing subject than that of gastro-intestinal toxaemia. This is clearly evident from the fact that authorities of the highest repute hold such widely different views on the subject. Some are inclined almost to treat the matter with ridicule, while others would have us believe that the vast majority of diseases in which a bacterial origin has not been demonstrated, are due to the action of gastro-intestinal poisons. Recent investigations, however, have brought to light many interesting and important facts in support of the theory. Bouchard was one of the first to investigate the subject scientifically and while he certainly elucidated many important facts, all his deductions and conclusions cannot be accepted unreservedly. Valuable work has been carried on by other investigators chiefly in France, Germany, and Switzerland. A perusal of the literature of the subject is somewhat disappointing, because the experimental work is of a highly technical nature and the conclusions to be drawnfrom these experiments are frequently of only academic interest.

Investigators of this subject will have to endeavour to formulate definite statements with regard

to the nature and action of gastro-intestinal poisons and the symptoms and signs they produce, in order that the physician may be able to recognise the condition by clinical observation and if possible by the use of ordinary clinical tests. The aim of the following pages is to place the matter in such a light.

Nature and Origin of Gastro-intestinal Toxins.

We know from our physiological studies that the gastro-intestinal tract normally contains substances (ferments) which are poisonous when circulating in the blood stream. We also know that in fermentation and putrefaction, which are normal digestive processes, materials are formed which if injected into the blood stream would prove highly toxic. In other words, the gastro-intestinal tract normally contains poisons. We shall further see that abnormal digestive processes may be accompanied by the production of abnormal poisons.

What then are the possible sources of gastro-intestinal poisons?

(1) Substances produced normally within the gastro-intestinal tract.

(2) Substances produced by normal digestion.

(3) Substances produced by abnormal digestion.

(1) Substances produced normally within the gastro-intestinal tract. These are the digestive fluids and secretions including Bile.

(2) Substances produced by normal digestion. It is unnecessary here to enter into a detailed discussion of the physiology of digestion. A description of the products of normal digestion will be sufficient for our purpose. These products are derived from two sources, (a) from the action of the digestive ferments on the food, and (b) from the action of the bacteria that normally inhabit the digestive tract.

(a) From the action of the digestive ferments on the food.

From the Proteins.

(i) Non-crystalline bodies - albumoses and peptones.

(ii) Ammonia.

(iii) Amino-acids.

(a) Mon-amino acids:-

Aromatic Series:- tyrosin, tryptophan, and phenylalanin.

Fatty Series:- leucin, glycocol, alanin, glutamic acid, aspartic acid and amido-valerianic acid.

(b) Di-amino acids:- lysin, arginin, histidin.

From Carbohydrates.

Saccharides (Mono- and di- saccharides).

From Fats.

Glycerine and Fatty acids.

(b) From the action of the bacteria that normally inhabit the digestive tract.

From the fermentation of Carbohydrates.

Formic, acetic, butyric, propionic, valerianic, lactic, succinic, and traces of oxalic acids.

From the bacterial action on Fats.

The fatty acids are not easily subjected to fermentation, hence products from this source may be disregarded. Theoretically, the same acids as are formed from carbohydrate fermentation could be formed from fatty acid fermentation, with the addition of oxy - acids, but this to only a very slight extent.

From the putrefaction of the Proteins.

Combe[15] gives the following table:

(1) Non-crystalline bodies:- albumoses and peptones.

(ii) Ammonia.

(iii) Diamino-acids:- lysin, arginin, histidin.

(iv) Mon-amino-acids:-

(a) Aromatic series:- tyrosin, tryptophane, phenylalanin.

(b) Fatty series:- leucin, alanin, glycocol, aspartic acid, glutamic acid, amidovalerianic acid.

(v) Fatty bodies.

(a) Butyric, caproic, and valerianic acids.

(b) Ptomaines.

(vi) Bodies of the aromatic series:-

(a) Oxy-acid group:- paraoxy-phenylacetic acid and paraoxy-phenylpropionic acid.

(b) Phenol group:- phenol and paracresol.

(c) Group of the indoxyls:- indol and skatol.

(vii) Gases:-

methane, hydrogen, carbonic acid, sulphuretted hydrogen and methyl-mercapton.

(3) Substances formed by abnormal digestion.

(a) Abnormal ferment digestion.

From the Proteins:- There is no known deviation of protein ferment digestion ~~resembling~~ resulting in the formation of substances of a possibly toxic nature.

From Fats:- The only abnormal deviation as yet recognised is the possible formation of B-oxy-butyric acid and diacetic acid.

From Carbohydrates. Theoretically, a gastro-intestinal oxaluria is possible, the oxalic acid

being derived from glucose.

(b) Abnormal bacterial disintegration.

From the Proteins. There is an increase of the substances normally formed and in this connection increased formation of Ptomaines should be specially borne in mind. In addition, certain Bases may be formed. Some of these belong to the pyridin group, others give the reactions of chinolin, while others resemble muscarin.

From Fats and Carbohydrates. Abnormal bacterial disintegration only results in an increased production of the substances normally formed.

We thus see that the gastro-intestinal tract is verily a reservoir of a great variety of substances of highly complex nature and we must now enquire, in the light of our present knowledge, as to how far these substances may, by absorption, produce deleterious effects upon the organism.

The Digestive Secretions. Theoretically these, if absorbed, might produce toxic effects; some of them (pepsin, trypsin, erepsin) when injected into the circulation produce cellular degenerations, but the question arises; Are they ever absorbed? Pepsin may be, as its presence has been demonstrated

in the urine, but probably the ferments are for the most part destroyed in the gastro-intestinal tract. Ferments are easily subjected to hydrolysis and experimentally the products of their hydrolysis are amido-acids. Briefly stated, there is no direct proof that any of the digestive secretions ever produce such deleterious effects as might be termed auto-intoxication.

The Products of ferment digestion.

Albumoses and Peptones when injected hypodermically produce fever, leucocytosis, alterations in the coagulability of the blood, haemolysis and cellular degenerations. Normally these substances are not found in the blood, though in certain febrile conditions, in acute yellow atrophy of the liver and in some other conditions, albumose is found in the blood plasma. But is the albumosaemia in these conditions of gastro-intestinal origin? Recent research tends to show that peptones are absorbed only as crystalline bodies.

Ammonia:- According to Bouchard[16] ammonia is toxic; it produces convulsions and a great fall of temperature. Normally, the intestinal ammonia passes into the blood of the portal vein and combines with the fatty acids derived from the fermentation of the carbohydrates, or with the Carbonic acid and prevents the

diminution of the blood's alkalinity (Combe)[17].
The ammoniacal salts when they reach the liver are transformed into urea. Salaskin[18] states that during digestion a variable amount of ammonia is found in the portal vein, but always more than in the rest of the body, also that the arterial blood contains an almost constant proportion of ammonia.

Mon-amino acids.

Tyrosin. Bouchard[19] states that it is non-toxic. In the intestine it is decomposed into Phenols and cresols.

Tryptophane is decomposed into indol and skatol.

Leucin is normally found in the pancreas, spleen, thyroid, salivary glands, and kidneys. It is non-toxic.

Glycocol, alanin, glutamic acid, aspartic acid, amidovalerianic acid, and the Diamo-acids. No known effects are produced by these substances.

Products of the digestion of Fats and Carbohydrates.

There is no known toxic action which can be ascribed to these products.

We are thus forced to conclude that in the processes connected with ferment digestion many complex substances are formed, but there is no direct evidence that any of them are absorbed and produce toxic symptoms. If, therefore, such a condition as gastro - intestinal toxaemia really exists we must look for the

toxic substances among those produced by the microbic disintegration of food stuffs.

From the fermentation of Carbohydrates and Fats, acid products are formed which may all be toxic in virtue of their acidity but none of them possess any toxicity per. se except oxalic acid.

From the putrefaction of the proteins.

Volatile Fatty acids. The general consensus of opinion is that these bodies are produced in quantities, too small to give rise to intoxication.

Ptomaines. These are basic bodies produced by the microbic decomposition of the diamino acids[20]. Some are harmless, while others are extremely toxic. The first ptomaine to be analysed and described was Collidin. Nencki discovered this body in 1876. It is obtained by the putrefaction of animal gum. Others of a similar nature, as pyridin and parolin, are closely allied in composition to the alkaloids, but the composition of many of them is unknown. Several ptomaines belong to the fatty series and are of known composition, e.g. ethylendiamin, trymethylen-diamin ($C_3H_{10}N_2$), tetramethylendiamin or putrescin (C_4H12N_2), pentamethylendiamin or cadaverin ($C_5H_{14}N_2$), hexamethylendiamin ($C_6H_{14}N_2$), etc. The presence of ptomaines in the body, has been demonstrated by the examination of the excreta (urine and faeces),.

Garcia[21] found putrescin, cadaverin, and hexamethylendiamin in the stools and states that they are produced by the putrefaction of proteins in intestinal digestion. Roos[22] also found diamines in the stools of patients suffering from cholera and malaria. Baumann and Van Udranszky[23] found putrescin and cadaverin in the stools of patients with cystinuria. Quite a number of observers have demonstrated the presence of ptomaines in the urine.

In considering these facts then we may conclude that intestinal putrefaction results in the formation of ptomaines, that at least some of these ptomaines are absorbed, that some are of known composition while others are of obscure nature, and finally that some are harmless while others appear to be of highly toxic nature. The next question which naturally presents itself is, What harmful effects do the ptomaines produce? It is highly probable that any changes produced in the tissues as well as the symptoms are analogous to the known tissues changes and symptoms produced by bacterial toxins and certain drugs, e.g. inflammations, cellular degenerations, metabolic disturbances, e.tc.

It is impossible, however, to make any definite statements in this connection as our present knowledge of the nature and actions of ptomaines is too limited,

and, moreover, we have no accurate methods for estimating their dosage.

Aromatic substances:- These, as already stated, are produced by protein putrefaction.

Oxy-acids. There is no evidence to show that the oxy-acids in the great quantities in which they are produced in the intestine are capable of setting up an auto-intoxication. Increased urinary excretion of oxy-acids simply means increased protein putrefaction in the intestine.

Phenol group. Phenol normally is produced in the intestine and the quantity produced is proportional to the degree of protein putrefaction. Jaffe also has shown that its production is increased in stasis of the large intestine. Phenol may be formed outside the intestine, e.g. in septic conditions such as empyaemia, putrid bronchitis, cancerous ulceration, pyaemia, puerperal fever, etc. Increased phenoluria, therefore, may be found in any of these conditions. It is extremely doubtful if phenol in the greatest amount in which it can possibly be produced in the intestine is capable of giving rise to toxic phenomena.

The Indoxyl Group.

Indol is practically non-toxic. Herter[24] administered it in large quantities to three medical

students for periods ranging from six to thirteen days. On one occasion 2 grams were consumed in 24 hours. Only with the larger doses were symptoms noted, viz. disturbance of sleep and headache. Although the amount of indol produced in the intestine is very small compared with the amount administered by Herter to his students, yet it is possible that this small amount might produce symptoms in susceptible patients. It must be remembered that Herter's students were all healthy young men.

Indol is excreted in the urine as indican and increased indicanuria is often regarded as a sign of auto-intoxication but it is not necessarily so. It only means that there is either an increased putrefaction of proteins going on in the intestine or as several observers have pointed out[25] that there is some condition producing stagnation of the contents of the small intestine.

Skatol appears under the same conditions as indol. It increases and diminishes parallelly with indican and what has been said with regard to indol applies equally to skatol.

Intestinal Gases.

The only gas of any importance produced by intestinal protein putrefaction is sulphuretted hydrogen. This gas is certainly toxic. Several cases are

recorded where death followed the breathing of the gas. Glaister[26] states that it combines with the haemoglobin of the blood and forms a sulph-haemoglobin. Strauss[27] has examined six cases of H_2S poisoning, all of gastric origin (the hydrothionaemia of Senator), In these cases there was ulcerated carcinoma, and dilatation of the stomach with motor insufficiency. Combe[28] states that the bacterial cause of H_2S ~~does~~ formation is nearly always the Colon Bacillus. H_2S, however, can probably ~~not~~ only ~~sometimes~~ produce toxic effects, ~~though only~~ when it is manufactured in large quantities.

We thus see that in the gastro-intestinal tract are produced many substances of which only a few are of definitely toxic nature, that some of these toxic substances are of unknown nature and that we are as yet unable to define accurately all the pathological changes which may be ascribed to any one particular poison. Many workers in this subject have described lesions and symptoms of supposed toxaemic origin, but in many cases without being able to define the actual causative toxin or toxins.

Local Conditions controlling the production of Gastro-intestinal toxins.

The Diet. The degree of protein putrefaction will depend to a certain extent on the amount of protein in the diet. A diet too rich in animal food (meat) will increase protein putrefaction while a mixed diet will tend to lessen putrefaction. On a pure milk diet putrefaction will be reduced to a minimum.

The Intestinal Juices. The gastric juice in virtue of its acidity possesses a certain degree of antiseptic power. The biliary acids, according to Maly and Emich[29], are capable of exercising an important antitoxic action, while the pancreatic juice as pointed out by Charrin and Levaditi neutralises a large number of toxins. Thus, we see how a diminution of these natural secretions may favour a gastro-intestinal toxaemia.

The acid reaction of the Small Intestine. The small intestine normally contains the products of carbohydrate fermentation if carbohydrates have been ingested, and these products consisting chiefly of fatty acids maintain an acid reaction of the contents of the small intestine in spite of the alkalinity of the secretions poured into them. According to

MacFayden, Sabor and Nencki this acid reaction is capable of diminishing protein putrefaction. Tissier and Martelly[30] have demonstrated that these acid products are produced by the disintegration of lactose by the Bacillus Coli and Bacillus lactis aerogenes. It is evident therefore that any conditions which diminish or abolish the acidity of the contents of the small intestine will favour protein putrefaction.

The Flora of the Large Intestine.

Of the organisms found in the normal colon aerobic bacteria or facultative anaerobes preponderate. Strict anaerobes are either absent or in very small quantity. Combe[31] points out that in intestinal toxaemia the aerobes are diminished (i.e. B. Coli and B. lactis) and the proteolytic anaerobes (proteus putrificans, mesentericus, etc.) which are the bacteria of putrefaction are present in large quantities. Hence, any conditions which produce this alteration of the intestinal flora will favour putrefaction and toxaemia. Combe[32] gives the following as the commonest causes which bring about this result.

(1) Diet too nitrogenous. especially if it consists of meat and "high" game.

(2) Conditions which produce a fluid or semifluid state of the contents of the large bowel, e.g.

acute and chronic inflammatory affections.

The Natural Defences of the Body against the Action of Gastro-intestinal Poisons.

There is no doubt that the organism is protected from the action of gastro-intestinal poisons through the agency of certain defences. These defences are as follows: (1) The gastro-intestinal mucous membrane, (2) The liver, (3) The ductless glands, (4) The excretory organs.

The gastro-intestinal mucous membrane is capable of affording protection in virtue of (a) the chemical and mechanical action of its secretions and (b) the antitoxic function of its cells. That these two protective functions exist has been ample demonstrated by Charrin and others. Charrin has showed that toxins (bacterial) which are fatal when injected into the circulation are practically non-toxic when administered by the mouth. The antitoxic action is not due to the gastric juice nor to the intestinal juices, for with alkalinization of the former and removal of the latter the same result is obtained. Also, after removal of the superficial layer of intestinal mucous membrane, oral administration of toxin (a dose sufficient to kill intravenously) is followed by a fatal result. Any conditions of the mucous membrane, therefore, which diminish or abolish

this antitoxic function will naturally favour the absorption of toxins. Such conditions would be inflammation, necrosis or atrophy of the mucous membrane.

The Liver. One of the chief functions of the liver is to arrest and distoxicate poisons which have been absorbed into the portal vein. This is brought about by a two-fold action, (a) Chemical, and (b) Toxicolytic. The chemical changes which take place are (1) the formation of urea (which is practically non-toxic) from amino-acid and ammonia, the latter of which is definitely toxic, (2) the formation of uric acid from nucleas and purin bases. Bouchard states that the formation of these two substances, urea and uric acid reduces to one-fourth the toxicity of the materials to be eliminated by the kidneys, (3) the conversion of aromatic bodies into harmless compounds by their combination with sulphuric and glycuronic acids. The toxicolytic action of the liver is a most important defensive function. Schupper[33] has shown that the toxicity of the alkaloids particularly atropine, pilocarpine, cocaine and apomorphine is diminished 50 to 75% by the activity of the hepatic cells. Ligature of the portal vein increases the toxicity of the urine while the diversion of the blood

of the portal vein into the vena cava is followed by a grave toxaemia. According to Charrin the intestinal mucous membrane exerts its protective action chiefly against the colloids, the albumoses and the toxins, while the liver acts upon the alkaloids and ammoniacal compounds. Thus we see how abolition of this function of the liver, could induce a state of intoxication.

The Ductless Glands. The functions of these glands have been already discussed. Many theories have been propounded and many investigators have endeavoured to demonstrate an antitoxic function. The thyroid especially is supposed to possess the power of destroying entero-toxins. Our knowledge of the physiological properties of these glands, however, is as yet too limited to make any definite statements, though the evidence seems to favour the view that some of them at least do possess an antitoxic function.

The Excretory Organs afford an important protection against the establishment of gastro-intestinal toxaemia. The lungs, for example, excrete CO_2, ammonia and acetone, while the salivary glands are able to excrete bromides, iodides and potassium salts, even urea, leucin and the xanthin bodies.

The skin is capable of excreting urea and ammonia, and other substances have been found in small quantities in the sweat such as volatile fatty acids, cholesterin, kreatinin, sulpho-ethers, phenols, skatol, the aromatic oxy-acids and indican. May it not be possible for entero-toxins to be excreted by the same channel? The important organs of elimination are the kidneys and the intestines themselves. The kidneys are able to excrete all the substances formed by intestinal putrefaction and which may be absorbed into the blood stream. The intestines likewise eliminate the substances formed by putrefaction but it must be clearly understood that insufficient excretion through the intestines does not necessarily lead to a condition of intoxication even if the products of putrefaction are present in excess. For the production of a toxaemia absorption of toxins must first take place. Yet retention of poisons within the intestine may result in increased absorption but that need not produce toxaemia if the protective organs are active.

Pathological Lesions produced by Gastro-intestinal Toxins.

Certain pathological lesions have been described as being due to the action of gastro-intestinal toxins. The demonstration of these changes is as a rule easier

than the demonstration of the actual causative toxins. In the Blood the changes to be found are those of destruction of Haemoglobin and blood cells. In chlorosis in which there is probably some destruction of haemoglobin as well as diminished formation and in pernicious anaemia in which there is a destruction of erythrocytes, the existence of some gastro-intestinal abnormality is frequently demonstrable.

In the Circulatory Organs changes in the arteries occur of the nature of fibrosis and some of the capillaries become so altered that blood extravasations easily occur. Changes in the heart are described in the form of thickening or degeneration of the myocardium.

In the Liver haemorrhages, and degenerations of the hepatic cells are found, while the

Spleen may show alterations in the Malpighian corpuscles and signs of haemolysis in the splenic pulp which results in the deposition of haemosiderin in the liver.

In the Nervous System, inflammations of the peripheral nerves are found and Charrin has described congestions in the spinal meninges and haemorrhages in the brain and its coverings. Among mental experts the idea is ~~easily~~ gaining ground that many psychic states are due to gastro-intestinal toxaemia. In

support of this view is the fact that many abnormal mental states can be controlled or improved by treatment directed mainly to the gastro-intestinal tract.

Conditions favouring the production of Gastro-intestinal Toxaemia.

Let us bear in mind the fact that while the gastro-intestinal tract normally contains poisons capable of setting up a toxaemia, the body is admirably equipped with certain defences which either minimise or completely prevent any harmful effects from these poisons. Let us also bear in mind that these defences are capable of protecting the body from the effects of quantities of poison much greater than are normally present. But there must be a limit to this protective influence. We may, therefore, assume that a toxaemia may arise (1) when the quantity of toxins produced and absorbed is excessive, (2) when the defensive processes are weakened or abolished. Of these two conditions I am of opinion that the latter is by far the more important. Excessive production of poisons does not of itself necessarily give rise to a toxaemia unless the amount produced is so great that the defensive processes break down under the strain, while a primary breakdown of the defensive processes may determine a toxaemia with a normal production of poisons. It is highly probably that

in many cases of gastro-intestinal toxaemia these two conditions of increased formation of poisons and weakening of the defensive processes exist side by side.

Excessive production of Poisons. This may occur under any conditions which increase intestinal putrefaction and the conditions to be considered are, (1) The nature of the diet, (2) the existence of functional alimentary derangements, (3) The presence of certain pathological lesions in the gastro-intestinal tract, (4) Alterations in the intestinal flora.

(1) The nature of the diet.

It has already been pointed out that on a milk diet putrefaction is reduced to a minimum and that on a diet rich in animal food putrefaction is increased. Increased putrefaction will also result from excessive eating especially if the food be unsuitable.

(2) Functional alimentary derangements.

These derangements are of the nature of Dyspepsias, gastric and intestinal. The most important are those associated with deficiency of the digestive secretions, gastric or intestinal. Deficiency of digestive secretions increases toxin formation in two ways, (1) by the diminution of their antiseptic or antitoxic properties, (2) by leaving a larger residue of undigested food material to be decomposed by the intestinal bacteria. Of other functional conditions,

constipation is often quoted as a cause of intestinal toxaemia but it is very doubtful if simple constipation per se, is capable of producing such a condition. In the first place, increased indicanuria is not always found in constipation; in fact, diminished indicanuria is fairly common, while Strasburger[34] has pointed out that the total number of dead and living bacteria in the faeces is less in constipation than under normal conditions. Many constipated people are quite free of any symptoms suggestive of toxaemia, but on the other hand, many do suffer from certain symptoms which appear to be due to the action of entero-toxins and relief is as a rule obtained by clearing out the bowel. How such a toxaemia is produced is as yet unknown. There are four possibilities.

(1) The delayed passage of faeces through the intestine gives a longer time for, and consequently may increase, the absorption of toxins. If the defensive processes are active it is difficult to see how intoxication can arise in this way.

(2) The constipation may be associated with some lesion of the intestinal mucosa, whereby increased absorption of toxins is permitted and in addition the antitoxin function of the intestinal mucosa (the first line of defense) is weakened.

(3) The other defenses of the body may be affected.

(4) It has recently been suggested that one of the functions of the intestinal mucosa is to secrete toxic substances and that in constipation these substances are either retained and reabsorbed or the intestinal mucosa fails to secrete them.

(3) The Presence of Certain Pathological Lesions in the Gastro-intestinal Tract.

In the stomach, pyloric stenosis will result in stagnation of the food material and consequently increased fermentation. Later, a condition of gastric dilatation may be produced with a further increase of fermentation or putrefaction. In the intestines such conditions as enteroptosis, dilatation of the colon and other localised dilatations will give rise to increased putrefaction, partly by producing a stagnation of intestinal contents and partly by the influence of the catarrh usually associated with these conditions. Other intestinal lesions which increase putrefaction are acute and chronic inflammatory processes especially muco-membranous enteritis[35].

(4) Alterations in the Intestinal Flora.

As already pointed out a too nitrogenous diet or the existence of pathological lesions in the intestine will increase the proteolytic anaerobes with consequent increased toxin formation.

Weakening or Abolition of the Defensive Processes is a most important factor in the production of gastro-intestinal toxaemia. The subject has already been partially discussed (p. 42-43) when it was pointed out that there are four lines of defence, viz.:

(1) The gastro-intestinal mucosa. This defence may be weakened by all forms of inflammation, ulceration and atrophy.

(2) The Liver is the chief line of defence and its protective influence may be weakened (hepatic insufficiency) in the following ways, (a) Congenital hepatic insufficiency is found in children whose mothers during pregnancy have been affected with alcoholism, saturnism, tuberculosis, syphilis, enteric fever, influenza, pneumonia, rheumatism, etc., (b) Acquired hepatic insufficiency may be produced (1) By the action on the hepatic cells of such poisons as alcohol, lead, and the poisons of the infectious fevers, (2) By the action of excessive amounts of intestinal poisons, i.e. the hepatic cells acting on the defensive are overcome by the invading army of entero-toxins, (3) In pregnancy, (4) By structural alterations in the liver itself, such as tumours, degenerations involving the hepatic cells, hepatitis and cirrhosis.

(3) The Ductless Glands.

If we assume that these glands do possess an anti-toxic function it is conceivable that this function might be disturbed by the pathological changes which these glands are liable to undergo.

(4) Diminished elimination of toxins may arise from diseases of the excretory organs. The kidneys if diseased may fail to excrete gastro-intestinal toxins sufficiently and a toxaemia may result. It is quite possible that this may be an important factor in the production of anaemia. An imperfectly acting skin also may aid in the production of a toxaemia though a very small proportion of intestinal poisons is normally excreted through the skin.

The Symptoms of Gastro-intestinal Toxaemia.

If a search be made throughout medical literature, nearly every symptom from which man is liable to suffer can be traced to originate in gastro-intestinal toxaemia. Some writers even present the symptomatology of the whole subject in a classified form with groups and sub-groups of symptoms, all possessing certain peculiarities and given in a cut and dry manner. As a result of many clinical observations, I have formed the opinion that while these descriptions may contain many truths, yet there is not sufficient evidence to

warrant such definite conclusions. Consequently, I have endeavoured to study the symptomatology of gastro-intestinal toxaemia on the basis of the pathogenesis of the condition which I have already discussed.

In many abnormal conditions of toxaemic origin, the symptoms and signs may be very definite but few in number, hence, it will be of great value to know exactly the symptoms or signs of gastro-intestinal toxaemia which will enable us to recognise the condition readily. It is very important to remember that in the great majority of cases, gastro-intestinal toxaemia is merely one factor in the production of an abnormal state. As a clinical entity it must be rare. Many so called acute cases are in reality produced by exogenous poisons, e.g. poisonous food, though, of course, acute symptoms may arise and frequently do arise in the course of a chronic intoxication. These acute symptoms are often of the nature of crises.

General Symptoms.

Persons suffering from gastro-intestinal toxaemia frequently complain of general weakness; the complexion is pale or muddy and the general nutrition is affected. If the affection sets in during childhood the growth of the body is interfered with.

Charrin has experimentally produced dwarfism in young animals by injecting intestinal products either

into the pregnant mother or into the young animals soon after birth. The bodily temperature is often affected. In some cases there is persistent sub-normal temperature while in others pyrexia is present. The fever is often of the intermittent type and is frequently also of the inverse type, i.e. rises in the morning and falls in the evening.

Skin affections are liable to occur, such as purpura and urticaria.

Gastro-intestinal symptoms.

Many gastro-intestinal symptoms are described such as peculiarities of the appetite, abdominal pains, altered appearance of the tongue and symptoms related to the abdominal viscera, but I venture to suggest that many of these symptoms are due to definite lesions of the gastro-intestinal tract, which in the first place aid in the excessive production of toxins and in the second place aid in the production of an intoxication on account of the weakening of the first line of defense. Thus, these symptoms may be due to gastritis, atrophy of the gastric or intestinal mucous membrane, dilatation of the stomach, enteritis, dilatation of the colon, chronic appendicitis, etc. Now, these lesions will probably be associated with toxaemic symptoms, but all the symptoms will not be toxaemic and therefore it is our duty to find out what the toxaemic symptoms are.

The evidences of the excessive formation of gastro-intestinal toxins do not necessarily prove the existence of a toxaemia, but it is very essential to be able to recognise the existence of such a condition as excessive toxin formation. Of course, one can readily understand that the presence of toxins in the gastro-intestinal tract may set up local inflammatory affections which might be included under the term auto-intoxication, though the term should be restricted to abnormal conditions following absorption of toxins. What then are the evidences of excessive toxin formation? The chief evidences are to be found in the examination of the stools, which are usually constipated and very foetid and to the naked eye are often seen to consist of undigested food particles, and much mucus. Bacteriological examination reveals the presence in excess of the organisms associated with nitrogenous putrefaction, - Bacillus mesentericus, putrificus, proteus vulgaris, etc. Chemical examination reveals the presence of the toxic substances produced by the nitrogenous putrefaction of these organisms, viz. ptomaines, etc.

We have now to consider the definite gastro-intestinal symptoms. These are of the nature of crises and may be regarded as attempts on the part of nature to get rid of large quantities of toxin. Thus, we have crises associated with the salivary glands,

with the stomach and with the intestines.

(a) Salivary Crises are rare. They take the form of periodic attacks of sialorrhoea, in which large quantities of saliva are poured into the mouth.

(b) Gastric crises are common and take the form of periodic attacks of vomiting, or epigastric pain, or both. These attacks are specially common in children.

(c) Intestinal Crises of the nature of attacks of diarrhoea are also common.

(d) Gastro-intestinal Crises in which both vomiting and diarrhoea occur and in which larger quantities of bile are found in the vomitus and stools.

When these crises do occur they usually set in suddenly and without any apparent cause. One noteworthy feature is their periodicity.

One other symptom remains to be mentioned, viz. the state of the liver. If it has to neutralise large quantities of toxin, fatigue is likely to set in, which may result in a definite enlargement of the organ and in the production of hepatic insufficiency, the signs of which will be described under the urinary system.

Circulatory System.

We have already seen that gastro-intestinal toxins

are capable of producing pathological changes in the heart muscle and the natural conclusion is that certain cardiac symptoms may arise in the course of a toxaemia. It is well known that toxic substances su ch as tea, coffee, tobacco and alcohol, give rise to definite cardiac symptoms such as palpitation, arrhythmia, tachycardia and bradycardia, and it is highly probable that gastro-intestinal toxins may give rise to similar symptoms. But just as these known toxins do not always give rise to symptoms, so also with the gastro-intestinal toxins. In addition to those symptoms, gastro-intestinal toxins may sometimes be responsible for the production of two well recognised conditions, viz. paroxysmal tachycardia and pseudo-angina, and these may be regarded as forms of Cardiac Crises. The primary effect of gastro-intestinal toxins on the blood vessels is to produce a condition of spasm of the arterioles and as a result the arterial blood pressure is raised. Later on, arterial fibrosis may appear. According to Metchnikoff, ~~Secondary~~ arterio-sclerosis is produced by intestinal toxins.

Perhaps the most marked change in the blood vessels is that which produces the tendency to haemorrhage in consequence of which we frequently observe epistaxis haematemesis, menorrhagia, etc., symptoms often present

in pernicious anaemia and leukaemia. Stockman believes that the deposition of haemosiderin in the liver in pernicious anaemia is due to repeated small capillary haemorrhages. This is a very likely thing to happen as the capillaries ofthe portal circulation will be affected by all the toxins which we believe are absorbed from the gastro-intestinal tract in pernicious anaemia. Cutaneous haemorrhages are liable to occur in gastro-intestinal toxaemia producing purpura, etc.

Respiratory System.

Respiratory symptoms are rare and I am doubtful if gastro-intestinal toxins are capable of setting up any definite respiratory disorders. Several writers regard asthma in some of its forms as having a gastro-intestinal origin, hence the name Dyspeptic Asthma, but it is just as likely that the exciting gastro-intestinal cause in these forms of asthma is of reflex nature for the attacks frequently occur during constipation or after over-eating. The only point in favour of the toxic origin of Dyspeptic Asthma is the nature of the attacks; they are of the nature of crises.

Nervous System.

The nervous system is highly susceptible to the action of toxins circulating in the blood stream and

there can be little doubt that there exists a close relationship between disorders of the nervous system and gastro-intestinal toxaemia. It is highly probable that gastro-intestinal toxins can produce symptoms of a disordered nervous system just as a poison like alcohol may, and it is also probable that structural alterations may be found in the nervous system due to the direct action of those toxins. It must be admitted, however, that our knowledge of the etiology of many nervous diseases is as yet unknown, still, in many cases the theory of auto-intoxication as a contributory factor at least, seems very feasible, and has many advocates. We already know that normal urine contains substances which when injected into animals produce, narcosis, convulsions, contraction of the pupils, etc.

The effects of gastro-intestinal toxins on the nervous system are manifested by the production of two groups of symptoms.

(a) General Nervous symptoms. Those most commonly met with are, Headaches, neuralgias, vertigo, Nervousness, Insomnia and diminution or abolition of the tendon reflexes, a condition I have occasionally observed. Many nervous symptoms common to children are stated to depend on gastro-intestinal toxaemia. Such symptoms are, nervous irritibility, headaches, anaemia, lassitude, fever, night terrors, teeth grinding,

failure to gain weight, or even loss of weight, albuminuria, etc. Now, in children who suffer from these symptoms there are usually evidences of gastric- or intestinal dyspepsia, frequently associated with constipation. Moreover, enquiry will often elicit a history of faulty dieting. Many of these children are highly neurotic. They inherit unstable nervous systems which can easily be upset purely by reflex irritation, originating in the gastro-intestinal tract. Treatment of these children by dieting and by measures directed to the removal or prevention of constipation is frequently followed by a rapid disappearance of the nervous symptoms. These clinical facts point rather to a purely reflex origin in many cases presenting the above mentioned symptoms, but it must be admitted that cases do occur which depend on a gastro-intestinal toxaemia and in these cases the more definite signs of a toxaemia will be usually found, viz. albuminuria and gastric crises in the form of periodic attacks of vomiting.

The relationship between mental symptoms and gastro-intestinal toxaemia is now occupying the attention of many observers, and the general opinion now held is that many abnormal mental states are dependent on toxins circulating in the blood, that these toxins may be formed in the body in various ways, but that in the

large majority of cases they originate in the gastro-intestinal tract. What evidence is there in favour of such a view?

(1) In many cases there is a history of gastro-intestinal disorder preceding the onset of the mental symptoms. An accurate enquiry into the gastro-intestinal symptoms will often reveal a history of dyspepsia with constipation. When the abnormal mental condition is established gastro-intestinal symptoms are commonly met with, such as, aseptic condition of the mouth from curious teeth, furred tongue, sordes, etc. loss of appetite, vomiting, constipation or occasionally diarrhoea. Further, treatment directed solely to the gastro-intestinal tract with the object of eliminating and ~~of~~ diminishing the formation of toxins, is often followed by a rapid improvement in the mental condition.

(2) In conjunction with these gastro-intestinal symptoms other evidences of toxaemic can often be demonstrated, viz. fever, albuminuria with diminished excretion of waste products, and blood changes, particularly leucocytosis and the presence of agglutinins. Moreover, the mental symptoms are often of the nature of crises. These will be considered under Nervous toxaemia Crises.

(3) Analagous symptoms occur from toxins of known

nature, such as alcohol and bacterial toxins, as those of staphylococcus and streptococcus.

(b) Nervous Toxaemic Crises. Under this heading we have to consider Paroxysmal Migraine, Epilepsy, Tetany and Certain Mental Disorders.

Paroxysmal Migraine. Some forms of migraine are characterised by remarkable periodicity. The attacks come on at regular intervals of one, two, or more weeks. They may be preceded by prodromal symptoms, they are usually accompanied by sickness and vomiting, and sometimes by severe epigastric pain. The symptoms are often relieved by clearing out the gastro-intestinal tract and in many cases strict attention to the diet and the avoidance of constipation will be followed by beneficial results. Many patients who suffer from this affection are definitely neurotic and heredity undoubtedly plays an important part in some cases. While it must be admitted that all cases of migraine are not of toxaemic origin, as a great many other factors may enter into the causation of the attacks, yet it seems highly probable that in many cases the exciting cause is a gastro-intestinal toxaemia.

Epilepsy. What has been said with regard to Paroxysmal Migraine applies equally to some forms of epilepsy, many cases of which are characterised by periodic attacks, preceded by prodromal symptoms and

accompanied by gastro-intestinal disorders. Constipation is a frequent accompaniment though not always present. When it is present the regular administration of purgatives will often control the number of convulsions. Even the carrying out of certain dietetic rules will in some cases influence the course of the disease beneficially. These facts are well known to most medical men who have to deal with epileptic patients. The association of gastro-intestinal disorders with epilepsy does not by any means prove that the former is the cause of the latter through the agency of a toxaemia, because it is quite possible to have convulsions produced purely by reflex irritation from the gastro-intestinal tract. The following facts, however, suggest that at least some forms of epilepsy are of toxic origin, and if of toxic origin everything points to the gastro-intestinal canal as the source of the toxins. The facts are:

(1) According to Bruce[36] the temperature in epileptics is irregular and fever is often present at intervals, independently of any outward bodily or mental symptoms. The pulse also is liable to be irregular and intermittent.

(2) According to the same observer, leucocytosis is frequently present, the increase occurring in the

polymorphonuclear cells. These observations, it should be noted, were carried out in insane patients.

(3) Normal urine contains convulsive substances and several foreign workers have demonstrated that the urine of epileptic patients if withdrawn during a fit and injected into an animal will produce convulsions.

(4) Krainsky[37] has injected defibrinated blood, withdrawn from epileptics during a fit, into the venous circulation of rabbits and true epileptic fits resulted. He regards the toxic agents as carbonic acid and ammonia, both of which are present in excess in the blood of epileptic patients, before, during, and after an epileptic attack.

I think it is as yet impossible to say what the toxic substance in epilepsy is. We must remember that an epileptic fit is a complex phenomenon in the production of which toxins probably only play a part.

Tetany. This affection may be produced by a variety of causes. Osler[38] in discussing the etiology distinguishes seven different groups of causes, among which one group comprises gastric and intestinal disorders, such as, dyspepsia, gastrectasis, diarrhoea, helminthiasis, and dilatation of the stomach. Of these conditions, the only one in which a definitely toxaemic cause has been demonstrated

is dilatation of the stomach. Halliburton and McKendrick in an interesting paper[39] have dealt with this subject at length. They state that the poison of gastric tetany is an acid substance soluble in alcohol and normal saline and when injected into animals causes, directly or indirectly, reflex excitation of the cardio-inhibitory centre and probably of other centres in the brain and spinal cord. The authors do not give the toxic substance a name. Other writers, however, have expressed definite opinions with regard to the nature of this substance. Thus, Brieger, Bouveret and Devic believe that it is a peptotoxin, whereas Gumbrecht says it is an albumose.

In connection with the subject of tetany, perhaps the most important fact to remember is that the direct cause lies in parathyroid insufficiency and that all other causes only act ~~indirectly~~ secondarily. Removal or atrophy of the parathyroids produces tetany and it is now believed that the function of these little glands is to neutralise a poison or poisons produced during metabolism. Now, if metabolic poisons are produced in excessive quantities and especially if large quantities of poison are being absorbed from the gastro-intestinal tract, the parathyroids may be unable to neutralise such quantities and hence a state of parathyroid insufficiency is produced. It is

interesting to note that in tetany the symptoms can be controlled by the nature of the diet, e.g. a diet containing extractives of meat and fat accentuates the symptoms, whereas a vegetable diet diminishes them.

Mental Disorders. It is now believed by many mental experts that gastro-intestinal toxaemia is an important factor in the causation of insanity. In support of this view are the facts that gastro-intestinal disorders are frequently associated with the mental symptoms and that if treatment be carried out with the object of diminishing toxin formation or of eliminating existing toxins, rapid improvement frequently takes place. It is well known that acute outbursts in the course of a mental disorder (Crises) can often be controlled by the timely use of purgatives. These facts, of course, do not prove anything with regard to the etiology of insanity. They merely support the view that gastro-intestinal toxaemia may be an exciting cause. Other toxic substances may be responsible, and as Bruce[40] points out, it is highly probable that in all cases there is some degree of hepatic and renal insufficiency, the liver failing to arrest and destroy the toxins and the kidneys failing to excrete the toxins by the urine.

The weakness of these defences, he states, is probably as much a part of nervous heredity as an unstable brain. This view seems a very reasonable one and it coincides with the statement which I have already made and which I again emphasise, viz. that the production of a toxaemia of gastro-intestinal origin depends largely on the insufficiency of one or more of the defensive agencies of the body.

The Blood and Ductless Glands.

We have already noted that some of the products of intestinal digestion are capable of producing cellular degenerations. Such being the case, it is conceivable that the cells of the blood and bone marrow might be acted upon by these poisons and thus gross changes in the composition of the blood might be produced. It is now generally believed that the cause of some forms of anaemia, particularly pernicious anaemia, is a gastro-intestinal toxaemia. There is much to be said in favour of this view. Hunter believes that pernicious anaemia depends on a progressive haemolysis produced by a chronic septic infection often associated with a specific glossitis, and oral, gastric and intestinal sepsis. Now, in many cases, carious teeth and a septic condition of the mouth are to be found. Other gastro-intestinal

symptoms are common, such as sickness, vomiting, and diarrhoea, the latter often appearing periodically (Crises). Hunter further believes that the haemolysis takes place in the portal circulation, and, therefore, there results the deposition of haemosiderin in the liver. He has isolated from the urine of patients suffering from perhicious anaemia two ptomaines identical with cadaverin and putresein. These facts seem to point to the probability of Hunter's view being correct, but there are other facts almost as important.

Thus the following facts may be regarded as supporting the view of the gastro-intestinal toxaemic origin of pernicious anaemia.

(1) Gastro-intestinal symptoms are common, such as, carious teeth, septic mouth, nausea, vomiting, and diarrhoea, which is ~~the latter~~ often periodic.

(2) On post mortem examination there are evidences of haemolysis having recurred in the portal circulation.

(3) Certain symptoms are common which, I have already pointed out are often associated with a gastro-intestinal toxaemia, viz. intermittent fever and the occurrence of haemorrhages.

(4) The urinary symptoms are often characteristic e.g. Spirits of polyuria (crises) are common, often there is excess of urobilin and as already stated

Hunter has extracted from the urine certain ptomaines.

(5) The blood picture of pernicious anaemia has been produced experimentally by certain German workers by feeding dogs with toxic substances in small repeated doses.

(6) A similar disease is known to occur with the presence of certain parasites in the intestine, notably Ankylostoma duodenale, and Combe[41] by injecting into rabbits poisons isolated from the urine of patients suffering from this parasitic anaemia was able to reproduce the disease.

(7) The injection into animals of a haemolytic serum produces a blood picture resembling that of pernicious anaemia[42].

(8) Some cases will improve rapidly with treatment directed solely to the gastro-intestinal tract, such as dieting, intestinal antiseptics, etc. without the exhibition of Arsenic.

Assuming that pernicious anaemia depends on a gastro-intestinal toxaemia, the question naturally arises, - What is the nature of the toxaemia? Is it simply an overproduction of poisons normally present in the gastro-intestinal tract? Or, is there a production of a substance or substances not normally present and, if so, is there a specific poison for pernicious anaemia? If there is a specific poison, is it due to

the presence of a specific organism which might be termed a haemolytic organism? And finally, is there any other important factor in the production of the condition, such as a weakening of the defences?

It is impossible to answer these questions directly though I am inclined to the belief that the causative toxins are more or less specific and that they are aided in their action by a weakening of the defensive processes of the body. Such a weakening is often evident in the gastro-intestinal symptoms present during life, and in the pathological changes found post-mortem.

We possess no definite knowledge of the etiology of other blood diseases, such as chlorosis and the leukaemias, but there is some evidence in favour of the view that these diseases are dependent to some extent at least on the action of gastro-intestinal poisons.

In chlorosis, gastric symptoms and constipation are common, but it is now regarded as more probable that these symptoms are caused by the anaemia instead of causing the anaemia. On the other hand, constipation might easily accentuate an existing anaemia and might do so by means of an auto-intoxication. Further, there is every reason to believe that certain intestinal toxins like other toxins are

capable of destroying haemoglobin.

The leukaemias present symptoms which have been already described as liable to occur in gastro-intestinal toxaemia, viz. gastro-intestinal symptoms, such as vomiting and diarrhoea, fever, spurts of polyuria and haemorrhages. We know the effect of some toxins in producing a leucocytosis. Is it not possible that certain toxins might be produced in the gastro-intestinal tract, capable of acting on the leucocytes in a similar way?

With regard to diseases connected with the ductless glands it is impossible to get beyond mere speculative statements, because our knowledge of the Physiology of these organs is as yet too limited.

The Urinary Symptoms.-

The absorption of gastro-intestinal poisons and their secretion through the kidneys may lead to albuminuria, a condition which is now well recognised and sometimes spoken of as alimentary albuminuria. The albuminuria appears to be due to the irritation produced by the toxins in their passage through the kidneys. In many of the conditions which I have described, albuminuria is frequently mentioned and I have no hesitation in saying that albuminuria is very frequently found in gastro-intestinal toxaemia, though not always. The amount of albumen is usually small and microscopical examination as a rule fails

to reveal the presence of tube-casts. If the toxins are very irritating or if their action be prolonged a true nephritis may result.

The quantity of urine is important. As a rule the daily excretion is below the normal even though the patient is consuming an ordinary amount of fluid. But perhaps a more important feature is the periodic attacks of polyuria to which these patients are liable.

In spite of the fact that the daily excretion of urine is diminished, it will usually be found that the Specific Gravity and total amount of solids are below the normal. Combe[43] points out that chemical examination will usually reveal a diminution in the proportion of the Nitrogen of urea, uric acid and purin bases to the total Nitrogen, and a diminished excretion of Phosphoric acid, Sulphuric acid and Sodium chloride. There is also an increased excretion of the aromatic bodies and urobilin. He also describes certain alterations in the ratios of many of the urinary constituents but the methods required for demonstrating these changes are too complicated for ordinary clinical work.

Perhaps the most valuable information to be gained is that which points to the existence of hepatic insufficiency. The urinary signs of hepatic insufficiency are, a diminution in the amount of urea

with an increase in the amount of ammonia and uric acid, and the presence of xanthin, hypoxanthin leucin and tryosin.

Ptomaines may be separated from the urine but the methods necessary are complicated.

Lastly, a positive Diazo reaction can sometimes be demonstrated, though it is uncommon.

Illustrative Cases.

Case 1.

J.J. miner age 24, was seen in August 1909. He complained of severe frontal headache and vertigo of twelve days duration. The illness began with vomiting which occurred at intervals for twenty-four hours, then stopped and returned four days later and continued for three days. The previous health of the patient was excellent. He had never been subject to any gastro-intestinal disorders. No definite cause could be found to account for the onset of the present illness, unless the eating of onions the day previously. While under observation he had intense frontal headache, vertigo on assuming the erect posture, nausea, slight albuminuria, absent knee jerks, and sluggish plantar reflexes. The temperature was normal and the average pulse rate 60. These symptoms pointed to gastro-intestinal toxaemia and appeared to be due to the absorption of some poison from the intestine, the production of which probably originated in a dietetic error. The patient was kept on a milk diet and small doses of calomel were administered. Within a few days all his symptoms had disappeared.

Case 2.

I.G. male, 30, consulted me in March 1911. He was a healthy man but admitted that he had an

abnormally big appetite. He complained of intense frontal headache which appeared early one morning without any apparent cause. The headache lasted for nearly two days. Albuminuria was present to a slight degree and it persisted for nearly a fortnight. No tube-casts were found in the urine. For several days after the disappearance of the headache he had neuralgic pains in the left forearm and in one of the right intercostal spaces.

Case 3.

Miss D. age 44, seen in October 1910. Her illness began with a sudden attack of vomiting and diarrhoea without apparent cause. For several months previously had suffered from 'dyspeptic' symptoms. After the diarrhoea and vomiting had stopped it was noted that the urine contained a trace of albumen and she had marked bradycardia which persisted for two to three weeks. The pulse rate at one time was only 40 per minute. The heart, otherwise, seemed normal. She also complained of intercostal neuralgia and vertigo.

These symptoms, viz. the albuminuria, bradycardia, vertigo and neuralgia were, I think, of toxic origin, while the attack of diarrhoea and vomiting appeared to be of the nature of a gastro-intestinal crisis. The patient made an excellent recovery.

Case 4.

Miss M. age 43, first seen about the beginning of 1911. Two years previously she had an acute abdominal illness which was regarded as appendicitis. There was great pain on the right side of the abdomen, extending from the region of the appendix up to the pylorus. She has now been under observation for fourteen months. On physical examination she presents the signs of a moderate degree of gastric dilatation. Her diet consists of milk, milk foods, fish, etc. Any indiscretion is followed by nausea and vomiting. She has at times complained of transient attacks of dyspnoea, flushing and redness of the nose and cheeks, but perhaps the most characteristic feature is the onset of periodic attacks of epigastric pain (crises) These attacks come on nearly every fortnight, they are preceded by a period during which the patient does not feel so well. The attack usually lasts a day and when over she feels very well.

Case 5.

M.K. male, age 18, on physical examination presents the signs of gastric dilatation. He has been ill for over two years, his chief complaint being vomiting after food. He suffers very little from nausea and he never has epigastric pain. His general nutrition

is affected and he is undersized. He has a definite but slight albuminuria.

Case 6.

R.W. male, age 45, seen May 1909. He had been ill for six weeks with sickness and vomiting. A test meal showed the absence of free HCl., the reaction was faintly alkaline and there were signs of complete absence of digestion. He was under observation for nearly two weeks, and during this time it was noted that the temperature remained for the most part subnormal and albuminuria was present. Blood examination showed Haemoglobin 88%, Red cells 5,000,000 per c.m., White cells 10,000 per c.m., Colour index .88. The condition was regarded as one of gastric dilatation but the cause could not be ascertained. In spite of the most careful medical treatment the patient steadily grew worse and a gastro-enterostomy was performed. At the operation nothing was found beyond a dilated stomach with the mucous membrane apparently much atrophied. The patient died a few days after operation but an autopsy was not performed.

Case 7.

P.McM. was admitted to the Glasgow Royal Infirmary on 21st July 1909. His illness which dates from one year before admission began with diarrhoea which lasted

for three or four weeks. He had several similar attacks during the year. For two days before admission he had great sickness and vomiting. He had never vomited blood nor passed any by the bowel.

On examination. Tongue clean, most of the teeth absent. He complained of abdominal pain, a tumour mass could be felt in the epigastrium; the stomach was dilated. Pulse high tension, plantar and patellar reflexes sluggish.

Urine contained albumen and pus. Microscopically pus cells and hyaline casts were seen.

Anaemia was very marked. Blood examination showed Hb. 25%, Red cells 1,030,000, Whites 6,250, Colour index 1.25.

Films showed marked poikilocytosis, reds variable in size, megalocytes abundant, polychromatophilia marked. No nucleated reds were seen.

The patient at first improved but six weeks after admission he began to vomit large quantities of blood. The bleeding continued at intervals and he gradually sank and died after being four months in hospital.

At the autopsy the stomach was found atrophied. An old simple ulcer was found in the stomach wall near the pylorus. This had evidently become malignant, there being a large cancerous mass at the pylorus.

In this case, of course, the primary cause of all the symptoms was the pyloric tumour, but it is interesting to note the presence of some symptoms which I have pointed out are frequently associated with gastro-intestinal toxaemia including the state of the blood which approached that usually found in pernicious anaemia.

Case 8.

Which presents certain symptoms of gastro-intestinal toxaemia and suggestive of Pernicious Anaemia.

W.M., age 40, first came under observation in August 1909. He complained ofweakness, shortness of breath, sickness and vomiting, all of about eight months' duration. The vomiting occurred two or three times weekly and had no relation to the taking of food. On examination, the skin was seen to be of a lemon yellow tint and numerous small haemorrhages were present. The teeth were dirty, the tongue was denuded of its superficial epithelium, and on the right side there was a rough painful area which had been troublesome for eighteen months. Pulse was of low tension and numbered 100 per minute.

The urine showed a haze of albumen on boiling.

Blood. Hb. 35%, Red cells 1,200,000, White cells 5,000, Colour index 1·4.

Films showed variability in the size of the reds.

Many megalocytes were observed and poikilocytosis was marked. No nucleated reds were seen.

While under observation the temperature was noted to be irregular and frequently above 99° or 100°. The urine showed irregularity in the amount excreted daily but there were no definite attacks of polyuria or diarrhoea.

With treatment, part of which was the administration of arsenic, the patient improved rapidly. On 7th October 1909 the blood examination was as follows: Hb. 72%, Red cells 3,800,000 per c.m. Colour index ·95.

Case 9.

P.H., female, age 19, first seen in June 1911. Suffering from Lymphatic Leukaemia. On examination she was found to have a coated tongue, carious teeth, foul breath and albuminuria. While under observation the temperature was noted to be of the intermittent type, ranging between 98° and 102°.

Blood examination. Haemoglobin 50%, Red cells 2,600,000 per c.m., White cells 26,000 per c.m.

Films showed the reds pale, slight poikilocytosis, a few normoblasts and megaloblasts with polychromatophilia.

Whites . Polymorpho-nuclear neutrophils 34%.

Eosinophils. ·75%.

Non-granulars 64% (Small lymphocytes 55%.

(Large mononuclears 9%.

Case 10.

Mrs. B., age 38. Seen on 28th November 1911. Diagnosis made of Spleno-medullary leukaemia. Her chief complaints were of menorrhagia, constipation and swelling of the abdomen, the last was due to enlargement of the spleen. On examination she was found to have furred tongue, carious teeth and albuminuria. The blood was found to contain 130,000 leucocytes per c.m. With treatment the numbers were reduced to 20,000 in a month.

Case 11.

W.M.,male, age 19, was first seen on the 7th January 1912. He gave the following history: Seven months ago he had a severe attack of haematemesis which came on suddenly and without warning. Prior to this, he had been in good health and with the exception of slight constipation never had any gastro-intestinal symptoms. Another attack of haematemesis came on two months ago and a third three days ago. After the second attack he felt slight pain in the epigastrium. On examination he was found to be very anaemic, the tongue was pale and flabby and he complained of thirst. A haemic murmur was heard over the base of the heart. The spleen was enlarged and no albuminuria.

Blood: Haemoglobin 30%. Red cells 2,400,000 per c.m.

White cells 3600 per c.m. Colour index ·6. For a month after admission the blood showed striking evidences of a progressive haemolysis; no further haemorrhages occurred.

On 13/1/12. Hb. 25% - Reds 2,000,000, - Whites 2000

1/2/12. Hb. 21% - Reds 1,600,000, - Whites 3500

8/2/12. Hb. 21% - Reds 1,450000 , - Whites 1600.

After this he gradually improved.

18/2/12. Hb. 28% - Reds 2,050,000, - Whites 1600.

26/2/12. Hb. 30% - Reds 2,400,000, - Whites 3600.

The urine was free from albumen and the Diazo reaction was always negative except on one occasion when a positive reaction was obtained. No drugs were administered but iron and arsenic. The daily output of urine varied considerably though the patient was taking fluids regularly. During the first week the average daily amount was (34⅓) $34\frac{1}{3}$ ozs., during the second week it was (28½) $28\frac{1}{2}$ ozs. The amount gradually increased and during the eighth week the average daily amount was 64 ozs. At times the amount varied greatly from day to day, there being sometimes a marked polyuria, e.g. on 10 successive days the amounts were in ozs. 50 - 74 - 30 -44 - 70 - 46 - 86 - 32 - 92 - 68 - and on five other days - 60 - 103 - 68 - 56 - 80 ozs.

In this patient the blood examinations showed a

progressive destruction of red and white cells and of haemoglobin. Associated with this blood destruction there was a progressive enlargement of the spleen. The patient is now fairly well and has had no further haemorrhages, but the spleen remains very large. At first the case was regarded as one of ulceration, probably duodenal but with the absence of definite symptoms, other than haemorrhage, and with the definite evidences of blood destruction and increasing enlargement of the spleen it appears more probable that the case was one of toxic anaemia. It corresponded in many respects to the usual descriptions of splenic anaemia.

Case 12.

W.R., male, age 52, first came under observation on the 28th March 1911, complaining of weakness, and shortness of breath of eight months' duration. Since the illness began his appetite had been poor, and his bowels irregular - constipation alternating with attacks of diarrhoea. For a short time he had suffered from a soreness of the tongue.

On examination, the patient was seen to be very anaemic, the skin being of a lemon yellow tinge; the tongue was furred and the teeth very carious.

Blood. Hb. 35%, Red cells 1,300,000 per c.m., Whites 5,600 per c.m., colour index 1·3.

On 17/4/11 Hb. 50% - Reds, 2400,000, Whites 5,600 per c.m., Colour index 1·0.

Films showed megalocytes and poikilocytosis and a few nucleated reds, ~~were seen~~. The patient recovered sufficiently to be able to work, but he broke down again and was under treatment in bed from February till April of this year.

The urine was free from albumen. It showed variations in the amount excreted daily as in Case 11, though not so marked.

On several occasions a positive Diazo reaction was obtained.

Case 13.

L.B., female, age 19, was under observation for several weeks suffering from anaemia, constipation and convulsions.

The urine showed great variations in the specific gravity, 1012 to 1030. The quantity was often greatly reduced (20 ozs. in 24 hours). Sometimes there was a period of almost complete anuria followed by an excessive flow (polyuria). No local cause could be found for this irregularity. but the case presented features suggestive of an hysterical nature.

The temperature for the most part varied between 97° and 98° F. and frequently shewed the inverse type lasting for several days.

Case 14.

A.H., female, age 21. Epileptic for nine years.

Urine. Faint albuminuria.

Temperature. As a rule between 97° and 98° F. During two weeks' observation it was of the inverse type.

Pulse. Showed great variations in rate. Although the patient was confined to bed tachycardia was present most of the time, but sometimes the rate was as low as sixty-four per minute.

Conclusions.

In reviewing the subject briefly I would like to emphasise the following points with regard to gastro-intestinal toxaemia.

(1) That gastro-intestinal toxaemia as a pure clinical entity is not common.

(2) That gastro-intestinal toxaemia as an etiological factor in the production of certain diseases is common.

(3) That the symptoms dependent on gastro-intestinal toxins are fairly definite.

(4) That in most cases the production of a gastro-intestinal toxaemia is dependent upon a weakening of the defensive processes of the body.

(5) That, while the principal toxic substances are ptomaines produced by the bacterial disintegration of proteins, there is no definite evidence that the symptoms are always dependent upon specific toxins. We must rather regard the production of symptoms as dependent upon the special vulner ability of the organs or tissues affected.

Therapeutic Considerations.

I do not intend to enter into a detailed description of the treatment of gastro-intestinal toxaemia. Our investigations will naturally indicate the lines

upon which treatment should be carried out. Thus, the treatment may be considered under the following four heads:

(1) The elimination of poisons from the body.

(2) The prevention of the production of poisons in the gastro-intestinal tract.

(3) The stimulation of the defensive processes.

(4) The correction of the vulnerability of the organs or tissues affected.

(1) The elimination of poisons from the body.

From the intestines.

By purgatives and by gastric and intestinal lavage.

From the body generally.

(a) By the administration of large quantities of fluids, diuretic drugs, etc.

(b) By lavage of the blood by the hypodermic or intravenous injection of fluids.

(c) By stimulation of the functions of the skin.

(2) The prevention of the production of gastro-intestinal poisons.

(a) By the ordering of a suitable diet.

(b) By the administration of gastro-intestinal antiseptics.

(3) The stimulation of the defensive processes.

(a) By treating gastro-intestinal lesions or functional derangements.

(b) By treating hepatic insufficiency.

(c) By organotherapy.

(4) <u>The correction of the vulnerability of the organs or tissues affected</u>.

By rest, and the administration of tonics, stimulants or sedatives, as indicated.

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