Auto-intoxication as a cause and complication of disease / by W. Louis Chapman.

AUTO-INTOXICATION

AS A

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W. LOUIS CHAPMAN, M.D.

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MOTTO:

"Asperges me Hyssopo et Mundabor."

BY

W. LOUIS CHAPMAN, M. D

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THE Trustees of the Fiske Fund, at the annual meeting of the Rhode Island Medical Society, held at Providence, June 4, 1903, announced that they had awarded a premium of two hundred and fifty dollars to an essay on "Auto-intoxication as a Cause and Complication of Disease," bearing the motto:

"Asperges me Hyssopo et Mundabor."

The author was found to be W. Louis Chapman, M. D., of Providence, R. I.

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PREFACE.

It will be the general plan of this paper to discuss the individual factors of auto-intoxication, their properties and the conditions under which they may be formed, and the diseases into whose etiology they enter, or which they may complicate.

Believing that recent advances in experimental medicine are of more importance, the more commonly known features of auto-intoxication will be but briefly discussed.

It would be interesting to make deductions and conclusions as to the rational treatment of diseases caused by auto-intoxication, but this is not properly within the scope of this paper which deals exclusively with the condition as an etiological factor, and treatment will be referred to only as argument for the validity of theoretical views.

It would also be interesting to discuss the poisons of the specific infectious diseases, but the writer will adhere to the view that they are not autogenetic, but the result of definite extraneous infection.

Auto-intoxication as a Cause and Complication of Disease.

PART I.

Although all the vital processes which take place in the body are in a great measure co-operative and interdependent, that of metabolism, with its indispensable function of elimination is conspicuous in its importance. The property of casting off unabsorbable materials and the chemical substances resulting from digestive processes is one which all living things possess. It is observed in the most primitive forms of animal and plant life, and the process becomes more and more complex as we ascend in the scale of creatures, attaining its greatest intricacy in the human body. Unicellular animals exhibit biological phenomena in their simplest form, but as yet we are unable to explain the features we may observe — the changes which take place in the cytoplasm, the chemical and dynamic forces which perpetuate cell life, the substances cast off as the result of food assimilation or the environmental changes which the organism induces by its existence. But although we cannot examine protoplasm chemically and thus interpret movements and process which may be seen, we are able to study the excreta from the tissues of higher animal forms, and determine by experiment their physical and physiological properties.

Wherever there are living things the process of appropriating food from the environment, assimilating a part of it and casting off the residue constantly goes on. Through the microscope we may see the slowly moving ameba surround food masses, retain them for a time, and then cast them off as containing no further nutriment. This residue contains more than indigestible refuse, there is also metamorphosed food material. If fish are confined in a limited space with no egress for their waste products they soon die, even if their food is yet unconsumed. If animals or human beings are likewise confined, and no provision is made for the admission of fresh air, they too die and with symptoms of narcotic poisoning. Air once breathed is poisonous and the organism is killed by that which is cast off from its own lungs. If bacteria are cultivated in nutrient media their multiplication continues until a time when their growth ceases, even if there remains a surplus of nutriment. The media are found to contain a substance which is unfavorable to the growth of germs which is clearly the result of the metamorphosis of the nutrient media by the bacteria. They too cast off a substance which is harmful to themselves. If the kidneys, through destructive processes in their substance or obstruction of their efferent ducts are unable to perform their eliminative functions, the animal soon dies, and with clinical phenomena which are fairly constant in different animals. If obstruction of the bowel lumen occurs and an organism is unable to eliminate fecal residues, poisonous symptoms soon ensue and unless the condition be relieved they terminate in death. In the tissues,—if waste materials are retained too long, cellular death and lesions result, for if a cell

is not separated from the products of its metabolism its life cannot continue. For example, if the ducts of the pancreas become occluded and its specific secretion finds no outlet, pancreatitis and necrosis is likely to occur. These facts are illustrative of a biological truth, that the end-products of metabolism are harmful to the organism from which they proceed, and to the resulting phenomena the appropriate name of auto-intoxication or self-poisoning has been given.

The variety of definitions given for this state is a testimony to the difficulty of obtaining one terse yet comprehensive. It is "the poisoning of an organism by matter produced within itself" to be sure, but this is too broad a conception since the toxins of all infectious diseases are produced within the organism, yet the toxemia of tuberculosis, diphtheria, or tetanus, cannot properly be classified as intrinsic. It is also "that form of self-poisoning in which neither wound nor gross pathological lesions exist, but poisons elaborated within the system are not excreted with proper activity, and the system at large is injured." This is open to the objection that it implies that these poisons are pathological products, while some of them are produced normally. One might coin a definition : — Auto-intoxication is the poisoning of an organism by the retention of its metabolism end-products which normally are excreted ; but this too is incomplete since it does not include, as it should, those poisons elaborated in deranged functions. Intestinal fermentation and putrefaction are not normal, constipation is not physiological, and the retention of bile from duct stenosis is distinctly pathological, so it is evident that other than normal excretions are concerned. For it is impossible

to conceive any perversion of function without variation in the specific product of such function, and the greater the departure from the normal, the more abnormal do the excreta become, and, as we shall see, the more poisonous. So we must add to our coined definition that these materials are of two kinds, those that are regularly formed in the system, and those formed in abnormal states where there is perverted or disordered function.

There is a tendency with many writers to include all the specific infectious diseases in the class of autogenetic disorders, a thing which, to the writer's mind, extends its scope far beyond its proper boundaries. The conception of the prefix "auto" should be that of inherent or intrinsic substances — those which originate in or are elaborated within the system. In diphtheria, for example, we have a poison elaborated within the body, but in no way related to it, as truly extrinsic as would be any poison administered by another individual. In death from this disease the toxin kills, as would a drug, through its effect upon vital nerves, the anatomical structures of which are visibly changed, and not through a true self-poisoning. The principals of auto-intoxication may apply in the case, affecting the course of the disease, and failure of the emunctories may be an important factor in dissolution, yet it is not within the scope of the subject according to our accepted definition. Non-pathogenic bacteria, upon whose action so many of the factors of auto-intoxication depend, are to be found normally in the alimentary tract, which is not true of pathogenic species. To more completely explain this important difference we may compare mussel poisoning with

intestinal putrefaction in which poisonous diamins are formed in the intestinal lumen. In the former, the mussel contains a preformed poison when ingested, and it will cause symptoms shortly after ingestion as would a drug. On the other hand, if a normal and innocuous food remains in the intestinal tract for any length of time, it is to be expected that it would be wrought upon by the intestinal bacteria, its nucleins become metamorphosed and harmful substances liberated from them. Thus protesting against too broad an application of the term we must add that this subject is often confused with auto-infection.

Here a person adds another focus of germ infection to those already existing. A patient with typhoid fever may inflict wounds upon himself while in delirium and these abrasions, being infected from his nails, may become abscesses or pustules. A convalescent typhoid may become reinfected through his urine which may contain the bacillus in pure culture, illustrating also the importance of urinary disinfection. Gonorrheal ophthalmia may be transplanted from the genital focus, or a patient with pulmonary tuberculosis may swallow the sputum and in this way infect the alimentary tract, producing tuberculosis of the intestine and peritoneum.

Whenever any function of the human organism fails in its specific action, organic equilibrium is disturbed in a measure proportionate to such failure; and this disturbance is transient if compensation is established by increased action of other organs, permanent if they fail to perform this added duty or if there is actual destruction of tissue. This is particularly true of those organs of the body concerned in the elimination of the excreta, the retention of which causes poisoning.

Intoxications manifest themselves in a great variety of ways, according to the toxic power of the substance itself, its degree of concentration, the part of the body with which it is brought in contact, and the susceptibility of the individual. This susceptibility may be some pre-existing lesion or anatomical anomaly, it may be mental instability from heredity, the precise philosophy of which we do not know, or it may be a group of factors into which enter the diet, habits and personality of the individual. Or the predisposition may itself be the result of a morbid process and it may only remain for the added influence of another force to precipitate or develop its activity. For a substance may require combination with another before its toxic powers may be developed, and materials may circulate in the system without injury, causing cellular damage only when brought into contact with some particular part or its emanations. For example, when normal bile comes in contact with the tissue of the pancreas marked necrotic changes result; and when peptones and albumoses are introduced into the blood stream they induce cytolysis and other hemic changes.

The investigation of a large number of cases of auto-intoxication shows that no clinical symptoms may result until the cells of a part have been under the influence of autogenous poisons for a long time, and in this we find a resemblance to disease in general, for it is a well-known truth that pathological conditions may progress for some time without pain or subjective symptoms unless there is irritation of some sensory nerve. And unless the toxic agencies at work are of the major grade of poisons there may be but few manifestations or perhaps none, until the degree of concen-

tration is great enough for cumulative action. The intrinsic poisons of the body spend their force chiefly upon the nervous and circulatory systems as will be shown in Part II.

A disease may both cause auto-intoxication and be caused by it. We know that nephritis may be caused by endogenous as well as exogenous poisons circulating in the blood stream, and with this nephritis comes decreased functional power and failure of elimination proportional to such loss. This necessarily produces intoxication whenever accumulation becomes great enough to produce toxemia. Gastric dilitation is increased by the fermentation which its original dependency occasions, and the effect of auto-toxins upon the mind predisposes to errors of judgment and dietary indiscretions which promote the continuance of the underlying cause. We have reason to believe that cirrhosis of the liver is caused by intrinsic systemic poisons and from the peculiarly important place this organ occupies in the animal economy any failure in its activity predisposes to the elaboration of intestinal auto-toxins.

The autogenous, like other poisons may cause marked and severe symptoms lasting for a short time and be acute, or they may be insidious in their action, endure for a longer time and become chronic. It is to be regretted that there are so few studies as to the experimental administration for extended periods of time, of substances known to cause self-poisoning, and until such investigations are made we shall not know to what extent they enter into the etiology of chronic conditions, a matter clinically of equal importance with the acute.

The most convincing arguments in the study of endogenous poisons are analagous to those which Koch formulated in his celebrated studies of the bacteria. The substance is first found associated with a diseased state, it is next administered to a healthy organism and produces a state similar to that from which it was derived, and lastly it is obtained from the individual experimented upon. Such cogent reasoning is almost direct proof, and in a great many cases of experiment with metabolic end-products all of these stipulations are satisfied. For example, indol, which is representative of a class of sub-oxidation bodies, has been found in the urine and feces of persons suffering with nervous disorders of a neurasthenic nature; experimental poisonings with indol produces similar symptoms and the material may be recovered from the individual experimented upon. In the same way it is found that the administration of uric acid will produce migrim, and that following an attack the alkalinity of the blood is lessened and the urine contains this acid in increased amount. And so the scientific aspect of this subject is built not upon conjecture but upon actual experiment and conclusions reasonably drawn from such investigations.

The Theoretical Biology of the Cyto-Lysins.

Besides the better known products of metabolism the properties of which are fairly well understood, there is a class of bodies the functions of which are not so well known, the study of which is now engrossing the ablest biologists of the present time.

The healthy organism has the power of producing substances which are antagonistic to foreign cellular

products and derivatives. These are for the most part of an albuminous nature and have the power of neutralizing poisons and ferments, of injuring or destroying cells, of causing the cessation of cellular motion, and of agglutination, precipitation and coagulation. These are called respectively anti-toxins or anti-enzymes, cyto-toxins or cyto-lysins, agglutinins, precipitins and coagulins. Of these the cyto-lysins are particularly concerned in auto-intoxication. The lysins are specific not only for the species but also for the cellular group from which they proceed, and they take their name from their origin. The toxin derived from the renal cells are termed nephro-toxins, those from the thyroid thyreo-toxins, and those from the placenta syncytio-toxins. A lysin contains two bodies: one, called the complement, actually injures or destroys foreign cells, but it is incapable of action without the assistance of the other component called the intermediary body or amboceptor. These two elements exist independently and one may be artificially removed without affecting the other. Now the intermediary body may be considered as having a single cyto-philic affinity and a number of complementophilic affinities, the former being specialized for association with bacterial or other cells, the latter for combination with the various complements of other anti-bodies. The side or lateral chains are the receptors or amboceptors and the ability of an organism to produce an auto-toxin depends upon the formation of a substance that will set free a side chain. The absence of suitable receptors explains immunity to corresponding poisons. If then in the life history of a cell there is brought to it in the blood stream any substance capable of doing

this, the intermediary body thus formed acts in conjunction with the complement and cytolysis takes place. The perfect organism may be considered as being in a continued condition of immunity from self-generated poisons, damage being done to the tissues only when immune bodies are not forthcoming to meet the invading poison, whether this be from within or from without.

This is in brief the principle upon which the cytolysins act and their operations are studied by experiments upon one animal with the elaborated serum of another. Now it seems reasonable to suppose that the emanations from a tissue may under certain conditions act upon the cells of another part, complementary bodies striving through their affinities to associate themselves with the receptors or specialized portions of the cells through the intervention of the intermediary bodies, without which such a union cannot take place.

The researches of Lindemann (1) show that iso-lysins are a reality and throw much light upon the probable origin of certain phases of disease. In his experiments the kidney of a rabbit was emulsified and introduced into the peritoneal cavity of a guinea pig. The serum of this animal when injected into rabbits caused albuminuria, anuria and death, and the histological examination showed disintegration and necrosis of the convoluted tubules of the kidneys, a state common in experiments with the better known renal poisons. He also found that the serum of dogs in which nephritis had been artificially induced by the injection of potassium chromate, caused nephritis terminating in death when injected into other dogs. It has furthermore

been found that the ligation of one of the ureters of a rabbit is followed by a change in the nephritis-producing power of its blood serum. Twenty-four days after ligation the serum caused distinct albuminuria which persisted for four days, and forty-one days after ligation the injection into a perfectly healthy rabbit, free from any evidence of nephritis, was followed by a large amount of albumen in the urine, and the examination of the kidneys showed necrosis, vacuolization of the convoluted tubules, disintegration of the epithelial nuclei, and, in the straight tubules epithelial casts, the cells of which were so disintegrated as to be almost structureless.

Of absolutely definite auto-lysins we know but little save that the trend of experiment and research points strongly towards them. We look for a more complete realization of these biologic truths, and as the Periodic Law of Mendeljeff predicted undiscovered chemical elements, so does the trend of research indicate that we shall soon know more of these mysterious bodies, the knowledge of which has already been of such inestimable value.

PART II.

The Individual Factors of Auto-intoxication — The Urine as Concerned in Auto-intoxication.

The idea that the urine is distinctly poisonous is not a new one. For a long time it has been known that it contained poisons cast off from the system, that toxic symptoms ensued if it was consumed by man in lieu of pure water, and that death followed if the kidneys failed to do their work, if both kidneys were removed, or if the ureters were obstructed. It has, however, remained for modern investigation to determine the nature of these toxic agents, the amounts in which they are harmful, and the causes which co-operate to retain them in the system. Although the kidney is very tolerant and permits surgical interference, it is subject to acute and chronic inflammations which cause those changes of structure which occasion auto-intoxication from non-excretion of the urine. Renal insufficiency comprises all those conditions in which the kidneys are for any reason unable to properly perform their work, the most common of these being loss of functionally active mass through the lesions of nephritis. The poisons of the body are not eliminated, they remain in the circulation and accumulate until present in sufficient concentration to produce the well known symptoms of uremia. The preponderance of experimental evidence shows that the toxemia is mixed, not

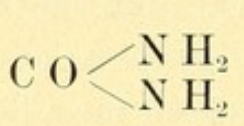
the result of any single urinary component, but the sum total of all of them. When it is shown that nephritis may be autogenous in its genesis, it becomes evident that a *circulus viciosus* is formed, they causing nephritis, and this in turn an intoxication from faulty elimination.

The Urine. The experimental study of the urine as a toxic factor consists in the administration to animals of the urine and the several substances which compose it. If injected subcutaneously we find that it acts as a poison, and if given in sufficient quantity will cause death. In the latter case a fairly constant chain of symptoms is observed. The first is an extreme degree of diuresis, — so great is the amount of urine passed and so frequent the urinations that Bouchard claims that the urine is the most powerful of all diuretics. Contraction of the pupil is almost invariably noticed, the animal becomes feeble, the respirations shorter and quicker, somnolence follows which may be interrupted by convulsions, the body temperature falls and death with muscular tremors follows, the heart being arrested in diastole. In this train of symptoms we are compelled to see the resemblance to the clinical picture of uremia, either from chronic renal disease or from ligature of the ureters. When the kidneys of rabbits are removed there are at first no noticeable effects, the animals moving freely and eating as usual. A state of great irritability then supervenes and slight stimuli evoke great uneasiness. Convulsions of groups of muscles increasing to general tonic and clonic spasms then occur which soon give place to a condition of stuporous anesthesia, followed in some eighty hours by death.

Normal urine is toxic when injected subcutaneously in amounts varying from 30 cc. to 60 cc. per K. weight; the urines of disease are toxic in greater or less amounts according to the variation in its components. The ability of the urinary poisons to produce structural changes has been shown by recent studies in which it is found that ulceration of the stomach and small intestine is an occasional result of nephritis and uremia. Some twenty-two cases have been collected (2) and the lesions seem to be due to toxic materials circulating in the blood rather than to infarction of the vessels supplying the ulcerated area.

The Urinary Components.

Urea is the amid of carbonic acid, best represented by the constitution formula:



It is neutral in its reaction, readily soluble in water, and when administered is excreted unchanged and as ammonium carbamate. It is formed from the numerous amido acids and basic substances which result from the disintegration of proteids: among the former we have leucin, tyrosin, aspartic and glutamic acids and glycocol, and of the latter diamidoacetic acid, lysatin, arganin, protamins and histons. Upon being heated with acids or alkalies, urea adds to itself two molecules of water and becomes ammonium carbonate, a change which is also accomplished by ferments and enzymes.

This suggests the possibility of urea being made synthetically from ammonium carbonate, by dehydration, a thing which probably takes place in the liver. Creatin is another important source of urea, breaking up into it and methyl-amido-acetic acid.

The pendulum of opinion as to the toxicity of urea and the part it plays in the causation of uremia, has swung from one extreme, in which it was thought that it did not participate in any material way in its production, to the other, in which it was considered as the sole cause of uremia. Bouchard has claimed that it has but little toxic action, but the more exhaustive researches of Herter (3) have shown that it is a very important toxic factor, symptoms of uremia invariably following whenever the percentage of urea in the blood of animals exceeds .4 per cent. or .5 per cent., death resulting when it reaches .6 per cent. or 1 per cent. of the body weight.

When injected into dogs in aqueous solution, fibrillary twitchings, clonic convulsions, intractable diarrhea and intense congestion of the intestinal mucous membrane were observed. The diuresis occasioned was enormous, the kidneys doing in an hour that which they would usually perform in a day. The excretion of urea was markedly increased, not from the elimination of the urea given, but from increased nitrogenous metabolism of the tissues. When the dosage was large, or the urea was rapidly administered, there was hemoglobinuria and hematuria, but these disappeared upon the advent of free diuresis; there was very little influence upon blood pressure.

In a ring-tailed monkey of about 2 K. weight, 5 grams produced fibrillary twitchings and internal strabismus in four and one-half minutes. The injection was continued and in four and one-half minutes 7.5 g. had been given, producing violent general clonic spasms. After seven and one-half minutes 11 g. had been given, the respirations were labored and deep,

there was vertical nystagmus and dilated pupils and grating of the teeth between the clonic seizures. After eight minutes, 13 g. had been given, the animal was comatose, the heart weak, there was fibrillation of the muscles of the throat and feeble clonic spasms, and in ten minutes the animal was dead, having received 15 g. of urea in 66 cc. of water. Fibrillary twitchings continued for several minutes after death.

The nervous symptoms in poisoning by urea very much resemble those from the injection of strong solutions of K Cl, $N H_4$ Cl, Na Cl, or creatinine.

Urea is normally present in the blood from .01 per cent. to .06 per cent., averaging .03 per cent. This proportion varies with the state of health and the functional activity of the kidneys. In pneumonia .1 per cent. and .28 per cent. are noted and in nephritis it may be increased to .449 per cent. with a corresponding reduction in the amount in the urine.

Uric Acid, $C_5H_4N_4O_3$. Haig more than any other observer has enriched our knowledge of this body, and has proved beyond cavil that its retention in the system is attended by a great variety of morbid symptoms, yet the injection of its solutions does not cause phenomena commensurate with those of the more active poisons. The purin bodies are the antecedents of uric acid, as is shown by their chemical symbols, are much more poisonous, and their toxicity decreases with their oxygenation.

Purin,	$C_5H_4N_4$
Hypoxanthin,	$C_5H_4N_4O$
Xanthin,	$C_5H_4N_4O_2$
Uric Acid,	$C_5H_4N_4O_3$

As yet we do not know the precise genesis of this important substance. That it is not formed primarily in the kidneys has been proved by Minkowski who found that it accumulated in the blood and tissues of snakes and fowls after the extirpation of the kidneys. He also showed that the total nitrogenous elimination was diminished by but one-third after the removal of the liver, and the nitrogen eliminated as uric acid, which is usually 60 per cent. to 70 per cent. of the total nitrogen, was reduced to 3 per cent. to 6 per cent. of it. He concludes that uric acid is formed by the synthesis of ammonia and lactic acid, both of which originate in proteid.

But in mammals the reverse is true, for it is found that uric acid output is increased rather than diminished in diseases where there is loss of functional liver mass, such as acute yellow atrophy, phosphorous poisoning, cirrhosis, and after experimental destruction of circumscribed areas. Uric acid is probably formed by the physiological breaking down of the nuclei of the leucocytes and tissue cells, and anything which increases destructive metabolism increases uric acid output.

Zoetber and Ibrahim (4) have studied the history of uric acid when introduced into the organism, and have shown that it acts as a poison to the tissues, not one of the major grade of active poisons, yet quite capable of producing intoxication, and that it is excreted unchanged and not as urea. It also causes increased production and consequently increased elimination of uric acid.

That uric acid is capable of causing migrim is proved by Hall who took half a gram, producing intense head-

ache with confusion of ideas which lasted for several hours.

The retention of uric acid must necessarily be considered a true auto-intoxication, and not only does it cause disturbance when circulating in solution, but it is also precipitated under certain conditions and crystals may cause trouble by their mechanical presence. Among the agencies which cause the precipitation of uric acid and its salts are poisoning by corrosive sublimate, bismuth, aloin, phosphorous, potassium chromate, and oxalic acid, and of the auto-intoxicants adenin and probably others.

Von Jaksch claims that uric acid does not take part in the acid intoxications of fevers, as elevation of temperature is unfavorable to its presence in the blood. Wright (5) has shown that the alkalinity of the blood, determined chemically, is an accurate index of the amount of acid intoxication in scorbutus and other diseases, and has proved by his experiments that the internal administration of the alkalies is shortly followed by a corresponding change in the hemic state.

Indol, $C_6H_4 \begin{cases} CH \\ CH \\ NH \end{cases}$, although it exists in small amount in normal urine is formed particularly by the bacterial decomposition of proteids in the intestine. Its chief source is tyrosin, one of the cleavage products of the proteid molecule. It is readily absorbed from the intestine and unites with sulphuric acid and potassium salts forming indoxyl-potassium-sulphate or indican, $C_8H_6N\,K\,S\,O_4$, which is colorless. Indigo blue is formed by the oxidation of this as in the following reaction:

$$2C_8H_6N\,K\,S\,O_4 + O_2 = C_{16}H_{10}N_2O_2 + 2H\,K\,S\,O_4$$

There are three other aromatic products of putrefaction — phenol-, cresol-, and skatol-potassium sulphate, of which the foregoing reaction is representative. All are caused by excessive proteid diet, catarrh of the digestive tract, constipation, alimentary fermentation or putrefaction, decrease of the normal digestive fluids, and the internal exhibition of salophen, creasote, salol and benzosol.

Experiment shows that indol is highly poisonous. Herter administered it to animals and observed cardiac and respiratory depression, marked contraction of the pupils, clonic spasms and increased reflex irritability. Small quantities taken daily for several weeks produced nutritive changes, frontal and occipital headache, colic, diarrhea, unnatural mental activity, and a tendency to the neurasthenic state.

Urinary Pigments contain a large proportion of the toxic matter of the urine, for it is found that if it is decolorized with charcoal a much larger dose is required to cause poisoning in animals. In decolorization the urine loses about a third of its toxicity, but in jaundice, where the coloring matters are enormously increased, we have a urine which is capable of causing death in the exceedingly small dose of 13 cc. per K. This urine is three times as poisonous as normal urine and nine times as poisonous as decolorized normal urine.

Urobilin is constant in normal urine and produces the well-known reddish-brown color which is particularly noticeable in febrile urines. It probably originates in the intestine from the action of nascent hydrogen on bilirubin, and may be made experimentally in this way or by the action of hydrogen on hematin.

Its reaction with hematin and bilirubin is apparent from the following symbols:

Hematin,	$C_{32}H_{32}N_4O_4Fe$
Bilirubin,	$C_{32}H_{36}N_4O_6$
Urobilin,	$C_{32}H_{40}N_4O_7$

The remaining pigments will be briefly described among the auto-toxins of intestinal origin.

In addition to these substances the urine contains sodium and potassium salts, the relative toxicity of which is seen from the accompanying table of Tapret and Bouchard:

SUBSTANCE.	LETHAL DOSE PER K.
Potassium bicarbonate,	0.05 g.
" chloride,	0.181 g.
" phosphate,	0.263 g.
" sulphate,	0.181 g.
Sodium chloride,	5.17 g.
" sulphate,	9.00 g.
" phosphate,	6.00 g.
Magnesium chloride,	0.463 g.
" sulphate,	0.542 g.
Calcium chloride,	1.011 g.

It is to the potassium salts that the convulsive properties of the urine are due.

Ammonia and its compounds are toxic in the dose of .15 g. of anhydrous ammonia per K. Although normal urine does not usually contain appreciable amounts of ammonia, it is markedly increased and the urine becomes alkaline after a vegetable diet containing potassium salts of combustible acids. The intestine is by far the more usual source of ammonia and

its salts. About one gram is excreted by the kidneys in twenty-four hours. Rachford has found that the salts of ammonia are much more toxic than the hydrate (6) and considers it a very important element in auto-intoxication.

Auto-toxins of Intestinal Origin.

The auto-toxins of intestinal origin comprise by far the greater number of factors which may act as causes and by far the most virulent of the intrinsic poisons. Endeavoring always to exclude poisons which enter the body as such, and which, therefore, do not properly contribute to autogenous disease, we find that the chief substances to be considsred are the bile, certain ptomaines and leucomaines, acids formed by intestinal changes and poisonous gases.

The Bile may not properly be termed an excretion as its constituents are largely resorbed from the intestine, and for this reason there is no equilibrium between the sulphur and nitrogen constituents of the bile and the amount of proteid decomposed in the body.

That the bile is toxic is readily demonstrated, for four to 6 cc. per K. causes death in convulsions. Of the biliary constituents the coloring matters are the chief poisons, for the bile loses two-thirds of its toxicity when decolorized.

Bilirubin is the chief pigment and it is derived from hemoglobin through hematin as shown by the following symbols:

Hematin,	$C_{32}H_{32}N_4O_4Fe$
Bilirubin,	$C_{32}H_{36}N_4O_6$
Biliverdin,	$C_{32}H_{36}N_4O_8$

When hemoglobin is infused into the blood, bile pigment appears in the urine. The bile salts also do this as they liberate hemoglobin by the destruction of the red blood corpuscles.

Uroerythrin is the essential pigment of red urines, is unstable, existing only in acid media, and has a characteristic spectrum. Although not a strictly normal constituent of urine it occurs when there are slight variations from health, in diseases of the liver, acute rheumatism, pneumonia and passive congestion of the lungs it is enormously increased. *Hematoporphyrin* also has a characteristic spectrum, but as yet there is but little positive knowledge as to its precise origin or the proportion in which it exists in the urine. If excreted in excess it indicates increased hemolysis and it may also be found in the urine of patients who have taken sulphonal.

The Bile Acids have a powerful cytolitic action and even in small amounts cause widespread disintegration of the red blood corpuscles with liberation of their hemoglobin, and also the disintegration of other cells of the body with which they may come in contact. (7) They also have a distinct cholagogue action, their effect on the hepatic function being comparable with that of urea on the renal. In small doses they aid and in large doses delay the coagulation period of the blood. In minute doses they act as vaso-dilators and in large amounts as vaso-constrictors, and they slow the heart-beat by direct action on the cardiac ganglia and the myocardium. When injected in large amount they reduce motor and sensory irritability and act on the higher cerebral centres causing coma, insensibility and death. It has been shown that the bile acids are

always present in the blood, but in minute quantities, causing these characteristic symptoms only when the amount is considerably increased in disease.

It has been found that the bile itself has but little germicidal power and outside of the body will itself putrefy. Its action in the body is twofold: by stimulating peristalsis it relieves the bowel of its burden and hastens on its contents before decomposition can take place, and, by the decomposition of the bile acids, which is probably accomplished by the intestinal fluids, a germicidal substance is set free which has a marked inhibitory influence over septic processes. (8).

Ptomaines.

Although many of the monamins and diamins are physiologically inactive, and although many of the poisonous ones are the result of the pathogenic bacteria of the specific infectious diseases, there are a number which are occasionally produced by other than pathogenic bacteria. Brieger has shown that diamins are absent from perfectly normal feces, but in disordered metabolism their formation is of frequent occurrence. The ptomaines cannot be said to originate in the bacterial cell, are not direct metabolic products of the bacterial cytoplasm, but are looked upon as secondary cleavage products, the result of bacterial activity upon ingested proteid. The following ptomaines and leucomaines are occasionally formed in the body, are toxic, and are to be classed as factors of autointoxication conforming with our accepted definition. There is no proof that mydatoxin and tetanin are autogenous, and they will not be described. Muscarin is briefly mentioned on account of its probable exist-

ence associated with cholin, and the fact that it occasionally appears in the decomposition of ordinary food stuffs.

It is of great clinical importance to note that the toxicity of these substances increases with their oxygenation, but a perfectly free supply of oxygen renders them harmless.

Isoamylamin, $C_5 H_{13} N$, occurs in cod-liver oil and putrefying yeast, and may be produced from leucin by heating. It is actively poisonous, producing spastic contractions, general convulsions and death. The lethal dose is about 0.040 g. per K.

Dihydrolutidin, $C_7 H_{11} N$, is found in decomposing oils, and produces diminished sensibility, tremblings, profound depression alternating with periods of extreme excitement, paralysis of the posterior limbs and death.

Hydrocollidin, $C_8 H_{13} N$, with its isomers, is frequently found in the bacterial decomposition of albuminoid substances, and is often accompanied by the base $C_{17} H_{38} N_4$; 0.0017 g. injected under the skin of a bird causes unsteadiness of gait, paralysis of the extremities and death. Larger doses cause vomiting and staggering, tetanic convulsions, and complete paralysis.

Ethylidenediamin, $C_2 H_8 N_2$, has been found by Kulneff in the liquids of the stomach in gastriectasis and also associated with cholin, trimethylamin and gadinin and in cultures of proteus vulgaris. Pohl has shown that this base in dose of 0.66 g. per K. subcutaneously in a rabbit produced parenchymatous nephritis, and a larger dose clonic convulsions, paralysis of the extremities and death. In mice and guinea pigs it occasioned exophthalmos, dilitation of the pupils, violent dyspnea,

blenorrhea of the conjunctiva, and, finally, stoppage of the heart in diastole.

Putrescin, $C_4 H_{12} N_2$, is intimately associated and usually found with cadaverin, and is obtained from putrefying meat and pancreas, the bacteria of human feces, and from herring, pickerel and haddock. It is a water-clear thin liquid which fumes in the air and has a peculiar and characteristic odor which is lost upon exposure to the air, from which it extracts carbonic acid. The tetra-methyl derivative of putrescin is enormously poisonous, the symptoms resembling those of neurin and muscarin — salivation, dyspnea, myosis, paralysis of the muscles of the trunk and limbs, increased intestinal peristalsis, relaxation of the sphincters, dribbling of urine and clonic convulsions.

Cadaverin, $C_5 H_{14} N_2$, is isomeric with saprin and neuridin, and is very commonly met with in decomposing animal tissues. It forms as early as the third day of putrefaction, preceding putrescin in this process. Since twelve isomers of this base are possible it is readily seen that more than one of them may be at work in a given case. It is produced by the decomposition of di-amido-caproic acid, and occurs in diarrheas, in putrefying fish and eggs. It can set up suppurative processes without the presence of bacteria, and also causes necrosis of the intestinal mucous membrane. Cadaverin is identical with the pentamethylenediamin of Ladenberg and is particularly active in intestinal obstruction.

Neuridin, $C_5 H_{14} N_2$, is one of the most common products of putrefaction, is not poisonous in a pure state, but when combined with other ptomaines resembles peptotoxin. It is almost invariably accompanied

by cholin, occurs in the decomposition of gelatine, and is found in putrefying beef, cheese, haddock and perch.

Methyl Guanidin, $C_2H_7N_3$, is the substance resulting from the oxidation of creatin and creatinin and its genesis illustrates how a comparatively non-poisonous substance may be readily changed into a violent poison by bacterial action. It may be prepared synthetically from creatin by oxidation, may be converted into methyl urea, and this in turn into ammonia and methylamine. Brieger injected 0.2 g. into a guinea pig and observed fibrillary twitchings, rapid respiration, extreme pupillary dilitation of the pupils, paralysis of the extremities, dyspnea and death in clonic convulsions. The heart is found to be arrested in diastole, the intestines filled with fluid, the bladder contracted, and the renal cortex hyperemic but the papillae pale and anemic.

Cholin, $C_5H_{15}NO_2$, $(CH_3)_3{\equiv}N\begin{matrix}\diagup OH\\ \diagdown CH_2CH_2OH\end{matrix}$

is one of the most important factors in auto-intoxication on account of its important relation to nervous disorders. It may be extracted from the brain by normal salt solution, is found in the bile, yolks of eggs, blood, lecithin, commercial muscarin sulphate, human placenta, and from various drugs, among others belladonna, ipecac and agaricus muscaris. Its commonest source is lecithin and its formation is illustrated by the following reaction:

$$\underset{\text{Lecithin.}}{C_{44}H_{90}NPO_4} + 3H_2O = \underset{\text{Stearic acid.}}{2C_{18}H_{36}O_2} + \underset{\text{Glycero-phosphoric acid.}}{C_3H_9PO_6} + \underset{\text{Cholin.}}{C_5H_{15}NO_2}$$

It is probable that it exists in the tissues in exceedingly minute amount as the result of cell metabolism, but in intestinal disorders its amount is increased and it may appear in the urine. In dilute watery solutions it may be transformed into the much more toxic neurin. The addition of platinum chloride to solutions of cholin produces characteristic octahedral crystals of the double salt cholin-platino-chloride.

0.59 g. of cholin cause almost instantaneous death in a cat and 0.1 g. of the chloride in a rabbit of one K. weight.

The symptoms produced in experimental poisoning are dilitation of the peripheral blood vessels, lowering of blood pressure, salivation, spastic contractions and stoppage of the heart in diastole.

Under the action of anaerobic bacteria, cholin is broken up into methylamin, carbon dioxid, and methane.

Neurin, $C_5 H_{13} N O$, $(CH_3)_3 \equiv N \begin{matrix} OH \\ \\ CH=CH_2 \end{matrix}$

is a highly toxic substance of obscure genesis. It may be prepared from cholin and is almost always accompanied by it, but the manner in which it is formed in the body is not yet clear. It is probably either derived from cholin by the removal of water or partly replacing cholin in the protagon molecule. In its physiological action it closely resembles curare. A few milligrams injected into a frog causes complete paralysis of the extremities, lessened reflex excitability, increasing failure of the respiration, which becomes superficial and finally ceases, the heart's beat continu-

ing and finally stopping in diastole. In mammalia, salivation, rhinorhea, mydriasis, dyspnea, increased intestinal peristalsis, irregular respiration and clonic convulsions are produced. Atropin has a marked antagonistic action to neurin, and its injection promptly causes a cessation of these toxic symptoms.

In order to prove that neurin was formed by the dehydration of cholin in lecithin, Nesbitt fed dogs upon the yolk of eggs for several days and then ligated the intestines. Upon examining the intestinal contents he found neurin and cholin, together with the base $C_{10} H_{15} N$. In the autopsies upon these animals it was found that the circulation of the entero-toxins had caused infiltration of Bowman's capsule, cloudy swelling of the convoluted tubules, tube casts, and necrosis of the renal epithelium. (9)

Muscarin, $C_5 H_{13} N O_2 + H_2O$, not only exists in poisonous mushrooms but also in decomposing fish, and it is interesting on account of its relation with cholin, from which it may be prepared by the oxidation of the platino-clorid with nitric acid, and with which it may exist in the body. In its toxic action, which is rapid, profuse salivation, lachrymation, myosis, diarrhea, and death in convulsions are observed. One drop of a one per cent. solution causes dilitation of the pupil of a bird in a very few minutes.

From these brief descriptions it is evident that more than one of these substances might act in a given case, and as many other ptomaines are non-poisonous when in a pure state, but are distinctly so when contaminated, the many possibilities of auto-intoxication are apparent. Since some of these poisons require some

time for their formation their presence in the intestines is not to be expected unless there is obstruction or some interference with the peristaltic wave.

Leucomaines.

These are basic substances which either exist preformed in the proteid molecule or are produced by tissue metabolism. The leucomaines are cleavage products while the ptomaines are formed by the splitting of the molecule through the action of bacteria. Their properties are determined more by the character of the parent substance than by that of the bacteria, as in the case of the ptomaines.

The sources of the leucomaines are the nucleins of cell nuclei and the proteids of cytoplasm. The great majority are not toxic, but their antecedents and nucleinic acid, histons and protamins and the amino derivatives purin and pyrimidin, are distinctly so.

They may be divided into five groups: 1. The Purin or uric acid. 2. The pyrimidin. 3. The hexon bases. 4. The creatinin. 5. Leucomaines of doubtful nature.

The *Purins*. The general action of these bodies resembles that of caffein, as they occasion increased irritability of muscle and the nervous system, marked diuresis, permanent muscular contraction with coagulation which resembles that produced by extreme heat or cold, and paralysis.

Hypoxanthin, $C_5H_4N_4O$, although it has no effect upon muscle, causes increased nervous irritability and tetanic convulsions. Gaucher and Kolisch found that it produced parenchymatous nephritis when injected into rabbits and guinea pigs for a period of a month or

over. Hall (10) injected $\frac{1}{25}$ grain daily for fifty days into rabbits and found that it produced degeneration of the renal convuluted tubules, and the liver cells showed evidences of the action of a cellular toxin. In a rabbit of three and one-half pounds weight, Hamilton produced great mental excitement and irritability, the reflexes being affected by the slightest tap, by the injection of 0.01 g. of hypoxanthin. This state of hyper-sensitiveness soon gave way to somnolence and torpor with insensibility to pain, the pupils being widely dilated and the pupillary reflexes lost.

Adenin, $C_5H_5N_5$, occurs together with guanin and hypoxanthin as a decomposition product of nuclein and may be obtained from all tissues rich in nucleated cells. In tea it exists preformed, the extract containing 6 g. per L. Sweetbreads which are rich in the antecedents of adenin may cause diarrhea, anorexia, nausea and vomiting, headache, malaise and abdominal pain if taken in excess, a chain of symptoms not unlike that of acute indigestion. Minkowski has shown that adenin is a violent poison, and that it causes rapid heart action and speedy death when injected subcutaneously. In small doses it causes intense inflammation of the duodenal mucous membrane which may lead to actual necrosis. In the kidneys true inflammation is occasioned with casts and albumin in the urine and sphereoliths of uric acid in the renal cortex as well as in the urine.

Paraxanthin, $C_7H_8N_4O_2$, sometimes called urotheobromin, is present in exceedingly minute quantities (0.0001 per cent.) in normal urine. Ratchford claims that it is excreted in excess during an attack of migrim and immediately following attacks of a certain

form of epilepsy, but his views are disputed by Pfaff who was unable to verify his results. The paraxanthin separated from one quart of urine passed after an epileptic attack, when injected into a guinea pig — increased reflex excitability followed by general clonic spasms, followed by tetanus, irregular and gasping respiration, trismus, involuntary urinations. Myosis and nystagmus frequently accompany the convulsions and death occurs, apparently from asphyxia, in from one to ten minutes. Schmiedeberg found that injections produced rigor of the muscles which became of wooden or waxy consistency. Dyspnea was an early symptom, the respirations dropping far below normal, even becoming suspended for a time, the heart's action continuing regular until just before death.

Paraxanthin is derived from caffein by the splitting off of the methyl group, and it is claimed that its toxicity is increased by its association with small quantities of ammonia.

Of the *Pyrimidin* bases the di- and tri-amino derivatives are toxic, and these yield insoluble compounds which may be deposited in the renal tubules.

Of the *Hexon* bases, *Gerontin*, $C_5H_{14}N_2$, only is poisonous, 0.5 mg. killing 10 g. of frogs. It is an isomer of cadaverin which it resembles somewhat, and is occasionally observed in crystalline form in the cell nuclei of the liver and kidneys. It exerts a paralyzing action upon the nerve centres and heart ganglia leaving the muscles unaffected.

The *Protamins* and *Histons* are primitive proteids yielding hexon bases on cleavage and exist in herring, sturgeon, shad, salmon, and in the substance of some of the bacteria. They are germicidal, and when in-

jected subcutaneously cause tissue necrosis at the point of injection, fall of blood temperature, decrease in the number of circulating leucocytes, delay in the coagulation of the blood and death from paralysis of respiration. In dogs death rapidly followed when the dose was 0.015 g. of culpein, and 0.02 g. of sturin per K.

Besides delaying the coagulation of the blood for many hours, these substances cause agglutination of the corpuscles as do albumose, ricin, venoms and agglutinating sera.

Histon is found in the thymus and thyroid glands and in dose of 0.1 g. in a rabbit caused irregular heart action, labored respiration, lachrymation, salivation, paralysis and death. That histon will neutralize bacterial toxins has been shown by Novy who found that its admixture with tetanus and diphtheria toxins rendered them harmless.

Of the Creatinin group, *Xantho-creatinin*, $C_5H_{10}N_4O$, alone has been shown to be distinctly poisonous. It is increased in muscular activity and when given to animals causes depression, somnolence, languor, frequent defecation and vomiting. The writer has been unable to find experimental evidence that the substances of this group are as poisonous as some writers state.

Other Substances acting as Auto-toxins.

Butyric Acid, $C_4H_8O_2$, is very commonly produced in gastro-intestinal fermentation, and is most commonly formed by the fermentation of cane sugar. It mixes with water in all proportions and its genesis is seen in the following symbols:

$$\underset{\text{Cane sugar.}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{Glucose.}}{2C_6H_{12}O_6}, \quad 2C_3H_6O_3 = \underset{\text{Lactic acid.}}{C_4H_8O_2} + 2CO_2 + 4H$$

This acid has a distinctly depressant effect on the central nervous system. Together with acetic and lactic acids its presence indicates gastric stagnation, destruction of glandular elements by malignant or other disease, putrefaction or fermentation.

On account of its depressant effect on the sensorium, butyric acid has been used as a hypnotic, but it has been found that it is capable of causing nephritis which prohibits its general use. The butyric acid occurring in diabetes is the *B*-oxy-butyric acid, which, by the loss of one molecule of water, becomes crotonic acid, also found in the urine and body fluids in this disease.

Hydrogen Sulphid, H_2S, is formed whenever there is residual nascent hydrogen after combination with all available oxygen, and from the splitting of the proteid molecule by bacteria. It is occasionally formed in the stomach, (11) and is over one hundred times as diffusible as oxygen. When inhaled it produces nausea, vomiting, dyspnea, tracheal irritation, extreme drowsiness and severe headache. When introduced into the rectum of a dog it is found that toxic symptoms occur within one minute.

In a patient suffering with acute intestinal catarrh, epigastric oppression and repeated attacks of vertigo, Senator found a gas in the urine which blackened lead acetate, and to this condition the name hydrothionuria has been given. Similar conditions are frequently seen in those who work in sewers and in the bilge of fishing vessels where large amounts of this gas are set free by decomposition. Kunkel, in the gases produced by the artificial digestion of fibrin by pancreatic juice, found nearly two per cent., but it is probably never

formed in a state of perfect digestion. With hydrogen sulphid there frequently exists the sulphur alcohol.

Methyl Mercaptan, C_2H_5S, whose physiological properties are as yet uninvestigated and which is undoubtedly a very important cause of many of the obscure symptoms of digestive diseases, exists associated with hydrogen sulphid and is formed in excessive carbohydrate diet and in gastrectasis.

Adrenalin or epinephrin, $C_{17}H_{15}NO_4$, is found together with adenin, epiguanin, hypoxanthin, and methyl xanthin, in the adrenal glands, and when injected into the circulation causes a marked rise of blood pressure, constriction of the peripheral blood vessels. When injected into mammals it produces excitement, tremors and vomiting. This is followed by paralysis of the hind limbs, dyspnea and rapid respiration, failure of the respiration and death. The urine is increased in quantity and hemorrhages occur from the mucous membrane and kidneys.

The importance of the ductless glands in auto-intoxication will be discussed in Part III.

The poison of *Expired Air*. It is well known that air once breathed is unfit for further respiration, and this change is due to the carbonic oxid it contains and to a peculiar poison caused by tissue waste and called by some "crowd poison." Without participating in the controversy regarding the importance of carbonic oxid as a toxic factor it may be stated that it is the most reliable index of air contamination and that Mosso found it occasioned unconsciousness and suspension of respiration if in excess of the proportion of 21 to 233. Angus Smith has shown that if the normal proportion of carbonic oxid in the air were increased

to 0.1 per cent. that systemic disturbances with increased respiration and decreased pulse rate were produced. But that this is not the chief poisonous agent in expired air has been shown by the researches of Brown-Sequard, d'Arsonval and Wurtz who experimented with the condensed vapors exhaled by dogs and man. These when injected into animals produced choleraic diarrhea, dilitation of the pupil, rapid lowering of the temperature, even as much as 5°, increase of the heart-beat to 240 or 280 and death from cardiac syncope. It has not yet been proven that carbon monoxid or nitrous acid exist in expired air in sufficient quantities to produce poisoning if inhaled.

That poisonous materials are expelled from the body in the perspiration is proved by the experiments of Arloing (12) who found that the sweat of a man who had been dancing, when injected into dogs caused drowsiness and violent diarrhea. That from the lower limbs injected into rabbits caused great nervous excitability, clonic spasms followed by paralysis and death. In the former case post mortem examination showed congestion of the entire alimentary canal, yellow patches on the liver surface and white clots in the heart cavities.

It was thought at one time that ochlosis or sweat poisoning was the cause of the serious and fatal symptoms which result from the varnishing of the body or from large burns. It is now believed that they are due to increased radiation of body heat and the formation of a body resembling peptotoxin.

The following table shows the toxicity of some of the Auto-toxins as compared with that of other poisons :

SUBSTANCE.	MINIMUM LETHAL DOSE PER K.		INVESTIGATOR.
Normal Urine	45.00	cc.	Bouchard.
Urine of Jaundice	13.00	cc.	Bouchard.
Aceton	8.00	g.	Albertoni.
Urea	6.60	g.	Herter.
Ethyl Alcohol	6.00	g.	Albertoni.
Normal Bile	4.00	g.	Vulpian.
Curin	0.63	g.	Bohm.
Gerontin	0.50	g.	Grandis.
Putrescin	0.50	g.	Pohl.
Cholin	0.50	g.	Brieger.
Paraxanthin	0.40	g.	Schmiedeberg.
Caffein	0.25	g.	Allen.
Invertin	0.20	g.	
Ammonia (anhydrous)	0.15	g.	Bouchard.
Methyl Guanidin	0.10	g.	Brieger.
Eel Serum	0,10	cc.	Mosso.
Morphin	0.0607	g.	Wood.
Emulsin	0.05	g.	
Sturin	0.02	g.	Thompson.
Arsenic	0.0153	g.	Lachese.
Culpein	0.015	g.	Thompson.
Phosphorous	0.0076	g.	Wood.
Strychnin	0.005	g.	Wood.
Hydrocyanic Acid	0,001	g.	Cushny.
Tetanotoxin	0.0006	g.	Brieger.
Ricin	0.0004	g.	Cushny.
Abrin	0.0001	g.	Ehrlich.

PART III.

The Particular Diseases which are caused by Auto-intoxication.

Although auto-intoxication may be concerned in any disease and any departure, however small, from normal physiological activity be followed by a corresponding change in the products of metabolism, it acts as a cause of disease particularly in diseases of the nervous and digestive systems, the kidneys, and in constitutional disorders. Having briefly reviewed the various substances which we know are causative factors in autogenous disease it now remains to see how they operate in the etiology of diseased states.

Diseases of the Digestive System.

Since the digestive tract is the most common source of intrinsic toxic materials it is natural to suppose that its disorders are very commonly due to these substances. As already stated disorders of the gastro-intestinal tract cause the formation of toxic materials, which in turn perpetuate the initial disorder and add new clinical features to it. For example, constipation may cause intestinal stasis; this allows the formation of some poisonous diamin from the absorption of which various symptoms result; this in turn aggravates the constipation until such a time arrives that some intestinal stimulant is formed, for many of the intestinal

auto-toxins cause diarrhea, and the noxious mass is expelled from the body. Art may interfere and curtail the process by the administration of some drug which anticipates the intestinal purge. From a review of the individual substances described in Part II, it seems very probable that many of the evanescent symptoms of ill-health, such as occasional diarrhea, neuralgic and rheumatic pains, somnolence and lethargy, disturbed vision, subjective symptoms of varied nature, and transient disorders of the urinary tract — all of which are frequently associated with digestive disturbances — are the direct result of the absorption of some of these materials. As yet we do not know the various combinations into which they enter, or the changes in toxicity which they undergo in different associations, and there are doubtless many substances of whose existence we are unaware and whose chemical formulæ have not yet been computed. As already noted, indol and other sub-oxidation products may be formed whenever there is lack of digestive fluids or faulty elimination of the excreta, and this may explain the remarkable clinical results which frequently follow the exhibition of sodium bicarbonate, diastase, malt, and other of the so-called "digestants." It would be interesting to dwell upon the philosophy of their actions, but we must be content with offering the view that this class of medicines shows the truth of the theories of auto-intoxication, for they attain results by stimulating the natural digestive functions, more completely oxidizing food materials, thereby preventing the formation of sub-oxids.

Constipation causes self-poisoning chiefly by retaining materials in the digestive tract long enough for

absorption to take place, or for poisonous bases to form. It was shown in Part II that putrescin, cadaverin and others required more than one day for their formation, so it is evident that unless there were stagnation of the intestinal current or crypts and diverticula in which food might lodge and putrefy, their formation would be impossible. For when the bowels move freely there is but little opportunity for the production of such poisons, many of whom fortunately cause diarrhea as part of their poisonous action. Constipation favors auto-intoxication not only by the mechanical retention and absorption of end-products, ptomaines and leucomaines, but also by the changes it induces in the digestive tract above. The automatic and co-operative mechanism of the system is altered by the presence of a burden in the colon and rectum, the stomach and higher bowel fail to properly digest and intestinal peristalsis is arrested or delayed.

To be constipated is not necessarily to be visited with fecal poisoning as is seen by the unusual case to be cited. In one person the failure of the bowels to move at the accustomed time invariably means malaise, severe headache, epigastric distress, lassitude, somnolence and nervous irritability ; in another no symptoms whatever are experienced until constipation exists for a long time. It is as yet impossible to explain this idiosyncrasy. The writer has carefully examined into the renal condition of many cases of this kind and fails to find any renal cause for the retention of poisonous materials or any reason why one person should be more susceptible to such agencies than another.

Auto-intoxication often takes place with but little disturbance to the rectum, the patient not appreciating

the cause until questioned by the attending physician, the symptoms of toxemia being the only ones which cause annoyance. The symptoms most commonly observed are: headache, usually of a dull, heavy character, frontal or temporal in character and increased by physical exertion or mental application, mental apathy, inability to concentrate the attention, failure of memory, general malaise and debility, slight exertion tires, somnolence and drowsiness, but the patient cannot sleep if opportunity offers. From slight ailments like these there are all grades of intoxication symptoms up to convulsions, mania and death. Of this extreme grade of auto-intoxication the following cases of Duprey are illustrative (13):

1. A woman of thirty-five suddenly became unconscious with rapid and shallow breathing, pulse 96, temperature normal. Examination of the urine showed no signs of nephritis. Attention to the bowels was followed by recovery.

2. A young man suddenly became unconscious, but could be roused from his stupor by shaking only to talk incoherently and relapse into the unconscious state. Heart, lungs, and kidneys normal. Recovery after free evacuations of the bowels.

3. A child of three years with a history of constipation suddenly expired while playing. Autopsy showed no condition which could account for death save that of fecal distension of the descending colon.

The following case is of interest as it shows the extreme possibilities of the human organism to eliminate through channels other than the bowels: (13) Mr. K., health good until the age of eleven when he became constipated and would have no movement for

three months at a time. At one time he took twenty drops of Croton oil within six hours, but without any result save pain. At the age of twenty-nine, five months and three days passed without a movement, and after a period of regularity his bowels did not move for six months and fourteen days. From June 18, 1900, to June 21, 1901, he had no movement whatever, a period of one year and three days. During these periods of costiveness the patient could eat full meals and do a good day's work, the respiration was always normal, the urine normal when he was free from pain, but high colored when he was in pain, and no convulsions or symptoms of intoxication save that of his sudden death.

The following arguments indicate that auto-intoxication may be the cause as well as the result of constipation:

We know that irritation of the vagus stimulates while that of the splanchnic nerves arrests intestinal movements. It is also true that moderate distension of the intestine with gas or feces increases peristalsis while extreme distension abolishes it, probably from the over-stretching of the muscular fibres. Now we know intestinal fermentation to be the cause of the production of intestinal gas in considerable quantity, as well as of proteid cleavage products, and these states co-operate to irritate the splanchnics, and to distend the bowels, thereby causing intestinal atony, accumulation of digestion residues, constipation, absorption, and the whole clinical sequence already described. It is fortunate that carbonic oxid, hydrogen sulphid, marsh gas, and many of the poisonous diamins are intestinal stimulants, for they tend to offset the retaining forces, and,

if present in sufficient potential, they serve to re-establish normal elimination.

Hepatic Disorders.

The claim that diseases of the liver and gall bladder produce toxemia is based upon four facts:

1. That bile itself, when absorbed into the system, acts as a poison and produces a definite toxemia.

2. That the liver is a destroyer of auto-toxins, therefore any diminution of the functional mass of the liver impairs this important property with resulting toxemia.

3. That the absence of bile from the intestinal tract favors putrefaction and consequently auto-intoxication.

4. That hepatic disease may be produced experimentally by substances allied to the auto-toxins.

The experiments of Croftan cited in Part II show the very close analogy between the phenomena obtained in experiments with the bile salts and those symptoms so commonly observed in cases of jaundice. The slowed heart, the lessened coagulability of the blood, the reduced motor and sensory irritability, and the constriction of the peripheral circulation, all are practically identical.

That the liver is a destroyer of certain poisons as well as auto-toxins appears in experiments in which nicotin, morphin, hyoscyamin, were shown to be retained, in part at least, by the liver, which also acts as a storage place for metals such as iron, manganese, lead, copper, silver, and antimony. The researches of Herter show that the liver is the chief organ for the removal of indol from the circulation. He showed,

too, that extracts of tetanus, pyocyaneus, and typhoid bacilli lost much of their toxicity in traversing the liver substance, and analysis of the resulting substances showed that these toxins were chemically changed.

The absence of the bile from the intestinal tract favors those conditions which result in intoxication chiefly by the obstinate constipation which it induces. In this connection one naturally recollects the success which so often attends the clinical use of ox gall in this affection. Bohm (15) not only observed that intestinal putrefaction very commonly occurred in cases of catarrhal icterus, but also found that the urine contained an excess of ethereal sulphates in the urine together with other evidences of auto-intoxication. The absence of bile with its consequent lack of normal intestinal antiseptic and peristaltic stimulant is quite enough to inaugurate all of the well-known symptoms of "bilious indigestion."

Jaundice is a disease in which the pathologic changes are unquestionably due to auto-intoxication. The bile, which in a state of health is cast off from the body in the feces, or is resorbed and eliminated as urinary pigments, is diffused through the body and produces toxic symptoms. The heart is usually slowed from the inhibitory action of the bile salts on the vagus and the pulse is soft, large and dicrotic from the paralytic condition of the blood vessels.

It has been found that poisons circulating in the blood cause a change in normal bile in which it increases in viscidity, causing agglutination of the walls of the bile ducts, obstruction of their lumen and consequent retention of the bile within the sac. Stadelman (16)

was able to produce jaundice experimentally in animals by poisoning them with arseniuretted hydrogen and toluenediamin, and found that there was an enormous increase in the biliary secretion and that it was very thick and tenacious. In none of his autopsies of the animals experimented upon was there catarrh of the duodenum or obstruction of the ductus communis. Even in the cystic duct the viscidity and occlusion is so slight that but little force is required to restore the patency of the canal. Jaundice is occasioned also in the experimental production of hemoglobinemia whether this be accomplished by the injection of free hemoglobin or of distilled water. It is then evident that the liver cannot produce normal bile from abnormal blood, and the fact that jaundice is caused by exposure to cold and by syphilis, typhoid fever, phosphorous, rattlesnake and other poisons, shows how readily the biliary secretion is altered and suggests that intrinsic poisons, which are often distinctly hemolytic in their action, may also act as causes. If this be true, auto-intoxication has a dual relation to the pathology of jaundice — toxic materials absorbed from the intestinal and urinary tracts may cause altered secretions, and the retention of bile from its own viscosity then completes the sequence. And so it seems that all jaundice is truly obstructive in its nature, whether it be from calculi or the result of poisons circulating in the blood.

The absorption of bile is a very important and serious complication when surgical operations are necessary. Such patients bear operation badly for two reasons. 1. The increased danger from hemorrhage on account of the lengthened coagulation period. 2. The condition of toxemia which causes them to

take anesthetics badly and renders them liable to unexpected shock and collapse. These patients have but little resisting power against septic invasions or the infectious diseases, and death sometimes occurs during or after an operation from shock, the system already enfeebled by cholemic toxemia, being unable to stand the additional tax of the operation. The effects of cholemia on the sensorium will be described in the pages devoted to Effects upon the Nervous System.

Hepatic Cirrhosis has been produced experimentally in animals by the administration of antipyrine, the bacillus coli communis, hyoscyamus, toxalbumins and an exclusive meat diet. (17) This suggests the possibility of cirrhosis of intrinsic origin. Following the reasoning of Garrod, Haig and others it might seem reasonable to infer that the sub-oxidation of the nitrogenous elements of an exclusive meat diet caused the formation of some poison, which, circulating in the blood, irritated the liver cells and caused proliferation of connective tissue.

One is compelled to see the similarity between this and the process of interstitial nephritis which is also the result of the circulation of poisons of both intrinsic and extrinsic origin. Cirrhosis is undoubtedly caused by nephritis and when there is chronic alcoholism often coexists with it.

The fact that children with congenital occlusion of the bile ducts develop cirrhosis before death, which almost invariably occurs before the eighth month, recalls the notable experiments of Charcot and Gombault (18) in which it was found that cirrhosis of the liver was caused when the common duct was experi-

mentally tied in animals. This would seem to prove that the bile itself must be reckoned among the specific irritants to the hepatic cytoplasm which cause increase of connective tissue, and is a realization of the general biologic truth that the cells, like the individual, must be separated from the products of their own metabolism.

Nephritis. Its intrinsic origin and its relation to auto-intoxication.

The great similarity of the numerous toxic agents described in Part II with the better known poisons warrants one in making analogies which suggest that they too are capable of causing tissue changes, inflammation, and, if the poisons are concentrated or their action persists for a long time, gross pathological lesions. It is in the kidneys that many poisons are separated and excreted. Strychnin, arsenic, lead, potassium chromate, phosphorous, cantharidin and the toxins of scarlet fever and diphtheria are all eliminated in the urine and all may produce true nephritis. Indeed the toxic origin of nephritis is so universally acknowledged that we need only discuss those arguments which show that it may be autogenetic. Applying the side-chain theory already described to nephritis, Vaughan would let the constitution symbol of the benzene ring with its six sides represent the kidney cell, and terms as a nephro-lysin any substance that will separate or split off a CH radicle.

Focal precipitations of uric acid and its salts are frequently found in the cells, interstitial tissue and tubules of the kidney, having been deposited there by precipitation from the cell secretion from the action of some precipitant acting as already described.

This recalls the crystalline deposits so frequently met with in the examination of vegetable tissues, the salts entering the cells in solution and becoming there precipitated by the specific secretion of the part or by some adventitious chemical substance. As will be shown in discussing acid intoxications, the auto-toxins cause such precipitations.

We must again refer to the experimental data given in Part II in arguing the intrinsic origin of nephritis, a disease which of itself is a primary cause of auto-intoxication. Adenin, one of the most poisonous of the purin bodies and one which is quite frequently formed, seems to have a peculiar selective affinity for renal tissue and in small doses causes nephritis with albumin, casts and spheroliths of uric acid in the urine, the latter occurring also in the renal cortex. Ethylene diamin, which we know is found in the liquids of the stomach in gastrectasis, is capable of producing nephritis even when given in very small doses. In order to show that hypoxanthin is capable of producing renal changes, Kolisch (20) administered it to rabbits and guinea pigs for periods of one and two months and found that parenchymatous degeneration was caused.

Butyric acid is known to cause nephritis, and for that reason it is not to be employed as a medicine.

In experiments upon animals in which intestinal obstruction was caused, it was observed that degenerative changes had begun in the kidneys as the result of the cholin and other poisonous bases elaborated.

Gerontin is occasionally observed in crystalline form in the cells and nuclei of the liver and kidneys. In

experimental poisonings with methyl guanidin the kidneys are found to be congested and the blood vessels injected, and as experimentation with this class of substances is continued, we may expect to find that other of these poisons, which we know cause degenerations of the neurons, cell metamorphoses, and the precipitation of acid salts, are quite capable of irritating the renal tissue and of producing nephritis.

From these few illustrations it is seen that we have positive evidence that nephritis may be of intrinsic origin. For clinical evidence shows these substances to be formed in various states, — experiment shows that they produce definite pathological changes which necessarily become a part of their toxicology.

Both nephritis and glycosuria may be dependent upon hepatic insufficiency. Ducamp (21) has shown the interdependence and co-operation of hepatic and renal functions, and that failure in one of them induces changes in the other. Suspension of the functional activity of the liver results in a diminution of urea with consequent lack of diuretic action on the renal epithelium. And in this way almost complete anuria may result, a thing which may be relieved by the administration of urea. In this way a *circulus viciosus* may be formed, the deficiency in liver action decreasing the urea, this in turn causing suppression of the urinary excretion, and thus a true intoxication with its poisoning of the entire system.

The importance of proper functional activity of the kidneys in the specific infectious diseases and where there are other extraneous poisons to be eliminated from the system, cannot be overestimated. In such cases the kidneys have added duties to perform and

must eliminate not only the normal poisons of the body but also the bacterial toxins of the specific affection. Many of these toxins are capable of producing nephritis, which would greatly increase the gravity of the case, adding to it the possibility of uremia and intoxication from the metabolic end-products. Examples of this are frequently seen during or after scarlet fever or diphtheria the toxins of which cause nephritis, and the organism, unable to eliminate both its own poisons and those of the pathogenic bacteria, soon succumbs if elimination is not re-established or the poisons neutralized.

A specific instance of the importance of permeable kidneys is reported by Brouardel (19) in which several persons who had partaken freely of turkey were made violently ill with pronounced gastro intestinal symptoms. Of these persons but one died, and the post-mortem examination showed a substance resembling coniine in the viscera, this also appearing in the fowl. Defective kidneys were also found, which would indicate that faulty elimination of the ingested poison was the cause of death. Haines (19) urges the importance of renal disease as a cause of sudden death, not only from causing uremia but also from failure to eliminate special poisons which might occur accidentally or in intercurrent digestive disorders.

Clinically it is frequently observed that renal disease is helped by measures which assist nutrition and digestion. The writer has observed a number of cases in which the use of strychnia in small doses has been followed by disappearance of myalgia, headache, swelling of the extremities, high tension pulse and many subjective symptoms, as well as disappearance

of casts and albumin from the urine. Brunton in 1877 found that cases of albuminuria were often helped by the use of arsenic, the albumin vanishing while the drug was employed and returning when it was discontinued, and the writer has observed the same thing in five cases. As these drugs have no specific influence over the renal epithelium, blood pressure or circulation, it may be assumed that they reach the underlying condition of incomplete oxidation and thus prevent the formation of renal irritants.

Lithemia and Allied States.

A large amount of clinical and experimental data combine in support of the view that the element of acid intoxication is a very important one in the etiology of lithemia, rheumatism, gout and the intoxication of diabetes. Most authorities are unanimous in the view that sodium bi-urate is the *materia peccans* of gout, its precipitation *en masse* the cause of gouty inflammations, and its irritation of nerve centres the cause of the characteristic nervous disorders. The kidneys undoubtedly play an important part in the causation of gout, for decreased elimination necessarily causes accumulation, and Roose considers that the precipitation of an attack or the acquirement of the gouty habit is quite dependent on the permeability of the kidneys. This is verified in clinical experience, for the alkaline diuretics, by stimulating renal activity, cause increased elimination, often with prompt amelioration of the symptoms.

The following arguments would seem to show improbability of a purely uric acid intoxication :

1. Experimental poisonings with uric acid fail to show the many symptoms so often observed clinically, and usually attributed to the uric acid diathesis.

2. The same causes which operate to produce uric acid in excess also furnish other purins and diamins.

3. Hepatic and renal insufficiency, the acknowledged causes of the retention of uric acid, would necessarily produce a mixed toxemia.

4. The investigation of individual cases of supposed uric acid intoxication shows the presence in the urine of other purins and in the feces of ptomaines and leucomaines.

5. As an immediate result of uric acid intoxication would come disordered metabolism with changed end-products and the formation of auto-toxins.

We may conclude that in this class of diseases there is a mixed toxemia with a preponderance of those auto-toxins which affect the muscles and joints, — the purins in particular, instead of the ptomaines and other leucomaines.

Although acid intoxications are not usually acknowledged as a cause of *arterio-sclerosis*, the writer has observed a number of cases in which syphilis and alcohol could be positively excluded, but in which the acid diathesis, as manifested by its well-known symptoms, was very much in evidence. Galen was the first to observe that an exclusive vegetable diet predisposed to atheroma. Raymond noted it in monastic orders where meat was forbidden, and Treille found a high percentage among the natives of Calcutta and Bombay, but these offer no arguments that the condition was not due to the use of alcohol. Although experimental proof is as yet lacking, it is reasonable

to suppose that the same poisons which will cause nerve degenerations, increase of connective tissue and even actual cell destruction in other parts of the body, may cause similar conditions in the intima of the channels through which they must necessarily flow to reach and affect parts of the body so remote from their original source.

Haig offers the interesting theory that uric acid or its salts may be precipitated from solution in the blood whenever the hemic alkalinity is materially lessened, — a thing that is sometimes brought about by nutritive disturbances and excessive muscular exercise ; and in Part II we have already stated the particular substances, some of them auto-toxins, which also cause such precipitation. If such precipitations occur in the tissues there may be an irritation due to their mechanical presence and necrosis of the parts immediately adjacent may occur, which will be macroscopic if the deposit is large, minute if it is very small ; if the mineral deposit be near a free surface, superficial degeneration may take place and the overlying tissue may slough leaving ulcerations. Illustrative of the former condition is the uric acid infarction of the new-born, in which the collecting tubules of the papillary zone of the medullary portion of the kidney, and even the renal cells, are filled with minute uric acid crystals and concretions, held in place by an albuminous stroma. And of the latter we may cite the ulcerations of endocarditis and endarteritis, in which focal precipitations have occurred in the vascular endothelium causing localized superficial necrosis.

According to Woods-Hutchinson (22) lithemic states are solely the result and consequence of gastric and

intestinal putrefaction, the only therapeutic agents of the slightest helpfulness being those which relieve this condition. Among his conclusions are the following: — 1. The uric acid produced in health comes from two sources, the larger moiety the exogenous, from the nucleins and purins of food; the smaller portion, the endogenous, from the destructive metabolism of the nucleins of the body tissues. 2. Gout and lithemia are mere symptom names for a group of chronic toxemic processes of widely varied origins. 3. The uric acid of gout, like the phosphoric acid which invariably accompanies it, is merely a result and measure of the destructive metabolism of the nucleins of tissue cells and leucocytes, in response to the invasions of poisons which may be organic or inorganic, intrinsic or extrinsic.

Acid intoxication may not only manifest itself as a diathesis, with chronic symptoms of a variable character, but it may also cause profound intoxication of the nervous system with coma, convulsions, and even death. Littin reports a series of five cases in which, after several days of digestive disturbance, the patients showed restlessness, nervous debility, headache and sleeplessness followed by increasing stupor and coma. There was a strong odor of acetone in the breath and perspiration, and the urine showed diacetic acid. Careful examination failed to show any cause other than the digestive disorder, and the symptoms disappeared upon improvement in the cause.

Krause reports a case of retro-bulbar neuritis with progressive coma and death, in which the autopsy failed to show any cause save gastro-intestinal catarrh with 2.5 per cent. oxy-butyric acid in the urine.

Cases like this, verified by post-mortem examination, are of great importance as they show the possibility of fatal acid intoxication in non-diabetic persons.

Edsall (23) reports a case of acid intoxication with cyanosis, unconsciousness, and muscular rigidity in which the urine showed acetone and diacetic acid but no nephritis. In these cases the similarity to uremia, diabetes, internal hydrocephalus. alcoholism and cerebral hemorrhage is very marked.

Diabetes.

Although many theories as to the cause of diabetes have been offered, the concensus of opinion is that it arises either from irritation of the diabetic centre in the floor of the fourth ventricle, or from disease of the Islands of Langerhans in the pancreas. In the former case the glycogenic function of the liver is disturbed, and in the latter it is probable that there is failure of a specific internal secretion, whose particular property is to oxidize the sugar molecule, from disease of the groups of cells in the pancreas which produce it.

That the glycosuria of pancreatic diabetes is due to the failure of a specific internal secretion is suggested by Tuckett (24) who found that if thoracic lymph from a digesting dog were injected into the portal circulation of a cat, a glycemia of 1 per cent. and a glycosuria of 9 per cent. resulted, but the lymph from a fasting dog occasioned no sugar.

It has furthermore been suggested that diabetes may originate from toxic substances absorbed from the intestinal tract, and Topfer and others induced diabetes in dogs by feeding them fecal material from diabetic

patients. These theories are as yet *sub judice* and we await more complete experimental evidence.

It has been found, however, that the coma of diabetes is due to a saturation of the alkalies of the blood by the products of incomplete combustion, and these are of an acid nature like oxy-butyric acid. Walter, (25) by the administration of acids to animals, has produced dyspnea, loss of motion, collapse and unconsciousness, — a state closely resembling diabetic coma. Upon examining the blood of animals thus poisoned he found that the amount of carbonic acid was only 2 per cent. to 3 per cent. *by volume*, which is the amount always dissolved in the blood, normal venous blood containing nearly 50 per cent. As the alkalies of the blood were saturated by acid, no carrier of carbonic acid remained, and this accumulated in the brain and caused its usual toxic symptoms. Minkowski (26) has shown that the amount of carbonic acid in the blood of a comatose diabetic patient was only 3.3 per cent. by volume, and the blood obtained post-mortem had a distinctly acid reaction and contained large quantities of oxy-butyric acid and sarcolactic acids.

Acetone resembles alcohol and ether in its toxic properties and can be given to dogs in dose of 1 g. per K. without any effect; 4 g. per K. cause symptoms of intoxication with motor disturbances like those of ethyl alcohol; 8 g. per K. is fatal, — hence to a person weighing 75 K., 600 g. of acetone would be necessary to cause death, an amount which could not be caused by the decomposition of proteid. We may then infer that acetone is not a prime cause of diabetic coma. Although ammonium is increased to five or ten times its usual amount in diabetes, it is probably neutralized

by acids so that it does not participate in causing coma or convulsions.

The relations of *B*-oxy-butyric acid in diabetes have been studied clinically by Herter (27) who formulates the following important conclusions: —

1. Crotonic acid can usually be obtained from the urine of persons in diabetic coma.

2. Diabetic coma is preceded by a period of days, weeks or months in which there is a large excretion of *B*-oxy-butyric acid.

3. The persistence of more than 25 g. per diem indicates impending coma.

4. A patient passing 30 g. of *B*-oxy-butyric acid *may* be able to be about all day and do considerable muscular work.

5. The acid intoxication is an important element in prognosis, and frequent chemical examinations are necessary to show the results of treatment.

Auto-intoxication as a Complication in Pregnancy and the Puerperium.

Puerperal Temperatures.

It is highly probable that many cases of puerperal temperature which have been reported as those of auto-intoxication are in reality unrecognized infections from germ invasion. In puerperal disorders one must bear in mind the very considerable traumatism which invariably accompanies the parturient process. The researches of His and of Winter have shown that the vagina and os uteri are always the seat of a great variety of bacteria, non-pathogenetic to be sure, but capable of causing inflammation if admitted to the circulation through wounds. And if an infection occurs

it is quite certain to cause elevation of temperature which is high and enduring if the virus is toxic, or if the bacteria are admitted in large numbers, — slight and evanescent if the battle between the bacteria and the leucocytes is a short one. A puerperal temperature which promptly disappears upon the administration of a laxative may very properly be attributed to constipation and consequent mild grade of auto-intoxication, but if this temperature with its concomitant symptoms continues there is frequently another cause. In five obscure cases of puerperal temperature of the writer's, further study showed the malarial plasmodium in one, internal laceration in two, a small pneumonic percussion area in one, and an ulcerating varicose vein in one.

Paralyses.

Aldrich (28) attributes cases of gestational and puerperal paralyses to neuritis, which may be the result of auto-intoxication from poisons formed by the disturbed ratio between production and elimination.

Eclampsia.

This disorder has long been considered as a form of auto-intoxication and the theories propounded have been many and varied. Its similarity with uremia has led to the opinion that renal insufficiency was the prime cause but this does not explain many of its clinical features. It has been shown by the experiments of Blumreich (29) in which the kidneys of gravid rabbits were removed, that the induced uremia did not cause eclampsia, and also that the brain of gravid animals is much more sensitive to irritation than that of the non-pregnant. In this latter conclusion we have

an experimental realization of the well known fact that pregnant women are sensitive to influences that usually would have no effect, the nervous organism being markedly changed by their condition. Thinking that pregnancy might induce some peculiar change in the urine, Stewart (30) studied the urine of women in the later months of pregnancy but found that it showed no toxicity beyond that of ordinary urine.

Wells (31) has had the opportunity of observing the effects of gastric and intestinal catarrh in pregnant women, and finds that the auto-toxemia is more likely to appear in plethoric than anemic patients. The symptoms noted are pain about the eyes, headache, photophobia, malaise, frequent urination but diminished urinary quantity, mental dullness and casts and albumin in the urine. These observations are of importance, not in showing that the pregnant are liable to auto-intoxication, for that is evident as is also the fact that they are particularly susceptible to it, but as showing that the intoxication did not cause eclampsia even if the kidneys were affected.

Strumpf considers that acetone or some similar body is the *materia peccans* of eclampsia, and claims that it is invariably present in the breath and in large quantities in the urine. He would class this disease with diabetes as an acid intoxication. Massen believes the convulsions to be the result of a true auto-intoxication caused by non-oxidized cellular substances, which through faulty liver action are not destroyed.

But by far the most light has been thrown on this disorder by the researches of Ascoli (32) in which eclampsia has been produced experimentally. He found that when placental extract was injected into an

organism, a reaction takes place with the formation of cyto-toxins, and when these are injected into other gravid animals a train of symptoms appear which closely resembles that of eclampsia. His serum was prepared by injecting into rabbits filtered emulsions of guinea pig placenta, and separating their blood serum. This when injected into the circulation of gravid guinea pigs caused no disturbance, but when injected under the dura the animals went into a state of coma which was interrupted by tetanic clonic and tonic convulsions which, without delivery, continued into profound coma and death. These experiments suggest that placental cells or soluble effluvium from them may be concerned in the etiology of eclampsia, and it is conceivable that immunity against these cyto-toxins might be developed. This is probably the case for we know that eclampsia occurs much more commonly in primipirae than in multipirae. In the case of puerperal eclampsia it matters not whether we consider that the poison proceeds from the fetal or the maternal organism, for they are made one through the circulation, each shares nutrition and tissue waste with the other, and we have a true auto-cyto-toxin, the advent of any heterogenous serum being impossible.

Diseases of the Skin.

In the auto-toxic etiology of diseases of the skin two elements are of importance, — the nervous and the vascular. The nervous because the peripheral nerves are everywhere present in the skin, and impulses generated centrally may elicit responses at the most remote parts of the body. The vascular, because toxic materials may be borne in the blood stream to

every part of the body visited by the circulation, and have a local effect anywhere in the vascular system, but particularly in the capillaries where the blood current is slowed. The cellular changes which take place in nerve paths in chemical poisonings indicate that similar changes probably take place in autogenous poisonings and these result in the impairment in the functional activity of the neurons which necessarily causes trophic and vaso-motor changes.

It is well known that disorders of the digestion are very frequently accompanied or followed by cutaneous eruptions, and these are due to auto-intoxication if the poison is formed within the body, but are extrinsic if it is ingested preformed. For this reason shell-fish and food poisoning will not be discussed.

We shall see that auto-intoxication causes a great variety of mental symptoms varying from slight indisposition to delirium and coma. It is well known that the insane and mentally depressed are particularly liable to skin diseases, and it is quite reasonable to suppose that the same cause may in many cases act as the cause of both disorders. The probability of these views is increased by the fact that the most helpful drugs in skin diseases are those which stimulate the nutritive processes, increasing oxidation and enhancing the action of the emunctories.

Constipation, the *bete noir* of modern strenuous life, is undoubtedly the cause of many cases of eczema, acne, erythema and dermatitis, for these frequently disappear when the lower bowel is regularly relieved by enemata or when the disorder is corrected by suitable diet. Degenerations, infectious granulomata, and neoplasms cannot be attributed to auto-intoxication

which produces erythemas and angio-neuroses of which urticaria is the type.

Of the neuroses, pruritus and anesthesia may be traced to intrinsic poisons.

In *urticaria*, through the action of intestinal poisons, the nerve cells of higher centres are irritated, efferent impulses are sent from the vaso-motor centres to the peripheral vascular nerves, momentary contraction is first caused and then paralytic dilitation ensues. This causes blood stasis with serous effusion and even corpuscular extravasation.

That *Eczema* is the direct result of auto-intoxication appears from its intimate relation with lithemia and gouty states, and from its dependency upon digestive disorders. The eczema and herpes which are such a source of discomfort to diabetics must be looked upon as the result of the acid intoxication of this disorder, and the eczema of children is usually only a part of the symptoms arising from disordered metabolism. True *Zoster* is probably not caused by intestinal poisons for the exhaustive researches of Head and Campbell (33) have shown it to be caused by lesions of the posterior ganglia of the cord and the Gasserian ganglia, and that in only a small percentage of cases do visceral disturbances accompany it. But the frequent occurrence of zosteroid with gastro-intestinal disorders and CO and CO_2 poisoning, suggests that it may be due to intrinsic poisons.

Gilchrist claims that *Acne* is not due to digestive disturbances but is purely a bacterial process, and states that a particular bacillus, which he has named the Bacillus Acnes was present in all smears taken from 240 lesions in 85 patients, and that pure cultures

were obtained from 62 lesions in 29 patients. He suggests that the constitutional disturbances which are so commonly observed in acne are due to the absorption of the toxins of these bacteria, for he finds that the bacilli acnes are agglutinated by the sera of patients suffering from the disease, (34). The writer has been unable to find the bacillus in the majority of his cases.

Akin to these skin diseases are several minor affections of modified skin and mucous membrane which are undoubtedly the result of intoxication caused by digestive disorders. Among these are the minute ulcerations which frequently appear in the buccal epithelium, the enlargement and occasionally the ulceration of the filiform papillæ of the tongue, and, in infants, a true stomatitis. These are usually accompanied by migrim, malaise, constipation, and urinary diminution followed by polyuria, and it is a significant fact that they yield promptly to measures directed towards the digestive system, rather than to antiseptics applied to the lesions themselves.

Talbot (35) urges that persons of sedentary habits do not require excessive nitrogenous or starchy diet, which is quite likely to cause inflammation of the gums and alveolar process with absorption. It is also claimed that interstitial gingyvitis is benefited by measures which improve the digestion.

Cases are occasionally seen in which temporary intestinal obstruction is followed by acceleration of the pulse, mydriasis and a scarlatinal redness of the skin resembling that of atropia or scarlet fever. When faucial angina, nausea and vomiting with a considerable rise of temperature accompanies these symptoms, the picture is even more convincing, but with a free

evacuation of the bowels all these symptoms promptly disappear and the temperature falls to normal. Lèpine reports a case of this kind and the writer recalls two.

Punctate ecchymoses and emphysema are occasional skin manifestations of uremia.

Diseases of the Nose and Throat.

That acute disorders of the nose and throat are often caused by digestive disturbances is almost universally acknowledged, for clinical experience frequently shows the correlation between these organs. The precise philosophy of this inter-dependence is in part explained by the supposition of an auto-intoxication, in which poisons derived from the alimentary tract are carried by the blood stream and have an irritating effect on the epithelium, cause vaso-motor disturbances through their actions on the neurons, or even cause minute structural changes through their cytolytic affinities. It is to be remembered too, that rhinorhea and congestion of mucous membranes are frequent symptoms in the experimental study of intestinal auto-toxins.

It cannot be denied that any chronic depressant predisposes to catarrhal inflammations and causes what is commonly termed the catarrhal constitution, and it is equally true that auto-intoxication causes an impairment of the general health and the lithemic state. But as a specific cause of nasal and pharyngeal disease we have no experimental evidence to warrant the sweeping assertions so often seen in literature. For a great many cases of chronic rhinitis are dependent upon anatomical imperfections as is seen by the countless instances in which relief and cure follow upon the removal of nasal obstructions, of hypertrophied turbina-

teds, the straightening of deflected septa and the removal of post-nasal adenoids. It affords but little satisfaction to attribute every departure from perfect health to a mysterious and unexplainable predisposition or dyscrasia, and frequently the careful examination of individual cases shows an underlying cause such as syphilis, tuberculosis, congenital malformation or unsuitable environment.

We have as yet but little definite knowledge of the specific properties of the faucial and pharyngeal tonsils or of lymphoid tissue generally, and it is certainly true that children of the *constitutio lymphatica* are subject to a variety of systemic disturbances and rises of temperature from slight causes, even if the growths are not large enough to interfere with respiration. The writer cannot agree with those who would attribute these states to the supposed toxic secretions of these masses, thinking instead that they serve as foci for the retention of bacterial masses thereby causing infection rather than intoxication. For examination of these lymphoid bodies frequently shows them to contain crypts filled with foul pultaceous nodules containing a variety of bacteria, which might easily account for systemic disturbances and furnish material for auto-infection.

Disorders of the Heart.

Of the various disorders of the heart, we must recognize palpitation, overaction, delirium cordis, peripheral hyperemia, variations in blood pressure, toxic angina and the manifestations of the rheumatic diathesis as due to auto-intoxication, for nearly all of these are features of experimental poisonings and all are relieved by measures helpful to the underlying alimentary

cause. Lead syphilis, gout and other intoxications may be considered causes of angina, and cases of neuralgia of the cardiac plexus are often undoubtedly due to purins and other bases, but the autogenous origin of these conditions cannot be put upon a scientific basis until the circulatory organs of animals poisoned by metabolism end-products have been studied in a large number of cases. In experimental poisonings death is usually due to stoppage of the heart through the acute action of poisons of the major grade directly upon the cardiac plexus.

Auto-Intoxication Affecting the Nervous System.

Since experimental poisonings with almost all the auto-toxins show their selective affinity for the nervous system it is necessary to discuss more fully these effects and see how they contribute to the production of disease. In common with other parts of the body the nervous system is attacked not only by poisons brought to it by the blood and lymph streams from remote parts of the body, but it may be also affected by the products of its own inherent metabolism. Auto-toxins affect the nervous system in two ways, the first as furnishing toxic stimuli which act as involuntary impulses causing muscular spasms, vaso-motor changes and the like; the second as causing actual change in nerve tissue and degeneration of neurons. The first of these actions is very evident from the experimental data given in Part II, the second is shown by analogies with well known poisons and by the association of auto-toxins with diseased nerve tissue.

Nissl (36) has studied the nervous system as influenced by poisonous doses of morphin, strychnin, lead,

mercury, alcohol and tetanin, and has shown that definite structural changes are caused in the large motor cells of the ventral horns of the cord in the rabbit. The tetanus toxin caused in two hours a swelling of the nucleolus and of the tigroid masses which were much paler than normal although their arrangement was not changed. Five days afterwards the nucleolus was very much swollen and there was observed a breaking up and intermingling of the tigroid bodies, and in extremely severe cases of poisoning the nucleolus becomes deformed and crenated. In experimental phosphorous poisoning there was complete obscuring of cell structure the process going as far as atrophy, disintegration or even disappearance of the neurons. Tetanin has a predilection for the motor cells of the fifth nerve nucleus, the toxin of diphtheria for the pneumogastric, and from the investigations assembled in Part II it is evident that auto-toxins too have selective affinities. That the integrity of nerve tissue is dependent upon free circulation has been shown by the experiments of Ehrlich and Brieger, in which compression of the aorta of a rabbit, produced in one hour, necrosis of the gray matter and cells of the spinal cord.

The power of alcohol to cause degeneration and inflammation in the brain has been indisputably demonstrated by recent investigations, and Kremiansky (37) has produced internal convexity pachymeningitis in dogs by the experimental induction of chronic alcohol poisoning.

As yet we have no experimental poisonings with known auto-toxins which compare with the researches of Nissl in thoroughness, for thus far there have been no microscopic examinations of nervous tissues of the animal subjects of experiment.

It has been shown that in any considerable degenerative process of the nervous system, cholin may be detected in the blood and cerebro-spinal fluid. This substance, the properties of which have been discussed in Part II, is constantly being given off from the brain in exceedingly minute amounts, being formed by the hydration of the lecithin in myelin, the reaction of which has already been given.

In a state of health no appreciable amounts of cholin can be found in the fresh brain, but in paresis, beri beri, and degenerations of the central and peripheral nerves it gradually accumulates and from lumbar puncture of the living or directly after death sufficient cholin may be obtained to give distinct chemical and physiological reactions. In this way we see that cholin can not only originate in the intestine but also in nervous tissue by its decomposition. If by future experiment it is proved that cholin is the cause and not the result of nerve degeneration, we have established the intrinsic origin of nervous disease, a thing already made to seem probable by analogy, but lacking experimental proof, without which no scientific truth may become accepted.

The probability of the intrinsic origin of nerve degenerations is materially strengthened by recent investigations (60) in which it is found that acute delirious mania is almost invariably associated with fatty degeneration of the liver, resulting in imperfect oxidization of end-products, retaining poisons within the system, inducing the processes which form diamins, — thereby causing the nerve cells to be bathed in a poison impregnated fluid, thus irritating and destroying their cytoplasm.

Migrim is caused by a number of the auto-toxins. Uric acid, paraxanthin and other of the purins, cholin, neurin, butyric acid, carbon monoxid and dioxid, hydrogen sulphid, and the bile salts have all been proven causes by actual experiment. Cholin commonly acts as a cause when eggs are eaten, from the hydration of lecithin, and cases are common in which the omission of eggs from the dietary is followed by relief of chronic neuralgia and headache. Migrim may be accompanied by a marked rise of temperature from the irritation of the fever centre by the poison, and it is very often preceded or followed by severe gastro-intestinal disturbances the underlying cause of the whole.

Convulsive States.

Epilepsy has long been classiffied as a neurosis without known anatomical basis and although its precise origin has not yet been proven, recent investigation has contributed much information as to the factors which predispose to it. Some thirty years ago Meynert attributed epilepsy to the accumulation of a toxic substance of a proteid nature and the work of passing years tends to confirm this view. The convulsive element is very prominent in the pathogenesis of nearly all the auto-toxins described in Part II and the clinical pictures described often very closely resemble that of epilepsy. The hyper-sensitiveness of hypoxanthin poisoning, in which slight stimuli caused muscular and nervous phenomena out of all proportion to the exciting cause, the fibrillary twitchings, rapid respirations, dilitation of the pupils, dyspnea, labored breathing and clonic convulsions with unconsciousness, of methyl guanidin; the dyspnea, salivation, mydriasis, irregular

and labored respirations, unconsciousness and clonic convulsions of neurin; — all furnish a closer analogue to the convulsive phenomena of epilepsy than can be found in any other class of poisons. Intoxication of this kind must then be reckoned as at least one of the causes of epileptic and epileptoid convulsions.

This might account for an occasional epileptiform convulsion, the result of an auto-toxin developed from time to time in the digestive tract, but in order that the epilepsy continue in regularly repeated attacks it is necessary that there be a predisposing cause, set in operation by a toxic exciting cause, or else the intoxication cause a permanent structural change. Medical literature abounds in case histories which show that instability of the nervous system may be dependent upon reflex influences such as ovarian or uterine enlargements, adherent prepuce, and upon toxic materials circulating in the blood. It may be contended that the auto-toxins furnish both of these elements, the toxic exciting cause and, by causing cellular changes in the cerebral cortex, the predisposing condition.

It has been found that the toxicity of the urine varies in attacks of epilepsy even more than it does in migrim. Rachford (6) has found that paraxanthin is excreted in excess during attacks of a certain form of epilepsy and he terms this form, paraxanthin epilepsy. This substance does not occur in the urine of other disorders and does not normally exist in the urine in any appreciable amounts.

Pellagrini (39) has found that the cerebro-spinal fluid taken from an epileptic directly after an attack, possesses markedly toxic properties, and when injected

into guinea pigs causes epileptoid convulsions and even the status epilepticus. The nearer to the time of the attack, the more toxic was the fluid. That these symptoms were not caused by any bacterial contamination was shown by the fact that the cultures from the fluid remained sterile.

Clark and Prout (40) show that the predisposition necessary for the production of epilepsy is an organic anomaly in the cerebral cortex. Toxins of autogenous or other origin cause actual lesions with swollen cell nuclei, destruction of the nuclear membrane and intranuclear reticulum, easy abstraction of the nucleolus by the knife, diffuse chromatolysis and protoplasmic changes in the cells, tending to their disappearance as living units and their replacement by a gliosis.

Ceni (41) has given to science the most rational explanation of the philosophy of this disease and the most practical application of such philosophy. His theoretical conclusion is that epileptic blood contains two active principles of different natures and origins. One of these circulates in a free state and becomes toxic only when injected into the blood of another epileptic: the other active principle circulates in a latent state and is endowed with properties which have a stimulating effect on those cells which are concerned in the elaboration of the epileptogenous toxins. These active principles, when injected in serum form, exert an influence upon nutrition and epileptic manifestations which may be restoring and therapeutic, or weakening and poisonous. In the former case the patient improves in physical condition and nervous disturbances become less frequent and milder in grade. In the latter, there is diminution in weight and

strength, and a retrograde change in organic life with its consequent aggravation of nervous manifestations. As a practical application of these investigations Ceni has elaborated a serum containing the epileptogenous bodies and by injection into patients has found that the cellular sensibility of the epileptogenous nerve centres is lessened by repeated and progressive doses of this serum. This treatment was markedly successful in eight out of ten cases experimented upon.

These studies show that the exciting irritant of epilepsy is undoubtedly of autogenous origin, and the fact that no immunity occurs from repeated attacks and that the serum has no inoculating power shows that the process is not bacterial in its nature.

As might be supposed from the pathogenesy of cholin, it has an important relation to the production of epileptic seizures which will be discussed in the researches of Donath, (42) shortly to be published.

Tremor. An interesting and unusual manifestation of urine intoxication is reported by Hock (43) in which intense tremor of the entire body, such as is occasionally observed in ether intoxication, was caused by partial retention of urine in the bladder, and this disappeared after complete emptying of the bladder. From his observations it seems that suppression or complete retention of the urine is not necessary to cause urine intoxication, and that severe diarrheas, rebellious vomiting and uncontrollable disturbances of the gastro-intestinal tract may be removed by treating the urinary condition. He also attributes the singultus accompanying cystitis to the absorption of urine and resulting systemic poisoning. In this connection the occurrence of uncontrollable diarrheas in the pathogenesis of urea may be cited.

Infantile Convulsions. Gastro-intestinal disorders are among the most common causes of infantile convulsions, and they act in the ways already explained. The intestinal walls of infants permit the passage of proteids while those of adults do not, which may account for the greater frequency of nervous manifestations in children. These may be dependent upon constipation and if so are relieved by laxatives. And they are not always caused by improper food but often by an atonic condition of the alimentary tract with the formation of auto-toxins in the ways already described. Violent vomiting followed or preceded by convulsions which are usually of brief duration, constipation followed by diarrhea, all accompanied by great nervous irritability alternating with somnolence, — are the symptoms most commonly observed. Such cases may be attended by rise of temperature and a cutaneous eruption closely resembling that of measles but differing from it in that it may vanish and reappear in successive crops and does not seem to bear any relation to the temperature. These attacks are very likely to be preceded by urinary suppression and followed by polyuria, and often the specific auto-toxin causing the disturbance may be obtained from the urine by appropriate methods.

The appearance in infantile constipation or diarrhea, of blood in the stools is of great importance, as it shows that there is abrasion of the mucous membrane by scybalous masses or that there is desquamation of epithelium. This would assist the absorption of poisonous materials and also allow infection from bacteria.

As the kidneys are at this time compelled to do additional eliminative work, the urine contains an

increased amount of poisonous materials, both normal to it and the intestinal auto-poisons, and the renal tubules and epithelium may become congested and inflamed by the irritation of these abnormal toxic constituents. Should there be a nephritis caused in this way, symptoms of toxemia would very soon develop and if the poisons formed are of a virulent nature death might result. Conditions such as these undoubtedly contribute in the high mortality of infants in diseases of the gastro-intestinal tract.

Gastric Tetany. In the experimental study of the factors which may act as auto-toxins their resemblance to the bacterial toxins is continually in evidence, and the ability of many of these materials to produce muscular spasm and convulsions leads one to think that atypical cases formerly supposed to be of bacterial origin may be autogenous. Smith (44) reports a case in which a patient with dyspepsia and much gastro-intestinal flatus failed rapidly in strength, and became troubled with insomnia. Occasionally tetanic attacks occurred in which the fingers were forced into the palms, there was trismus and the wrists were extended and rotated outwards to an extreme degree causing intense pain. There was much mental suffering and sleep was disturbed by spectral delusions. The stomach was found to be dilated and dependent, and the patient was exhausted almost to the point of death. These recurring attacks were entirely relieved by lavage and a non-nitrogenous diet, but when these measures were neglected, premonitory symptoms at once showed themselves.

Dujardin-Beaumetz reports a case of gastric dilitation with very similar symptoms, and Strong (45) reports

seven cases characterized by spontaneous intermittent muscular contractions, of which only one died, and remarks their similarity to epilepsy.

Simpson (46) finds tetany a very common accompaniment of gastrectasis and quotes Kussmaul who found it in 92 per cent. of such cases with a mortality of 75 per cent. Monyhan (47) does not believe this disease to be as rare or as serious as it is usually considered. He reports five cases in which gastro-enterostomy was performed with cure in each.

A case of gastric tetany observed by Amato (48) occurred in a man who had suffered with gastric dilitation and its many symptoms for five years, when he was suddenly attacked by tonic contractions of the upper limbs, trismus and coma which ended in death. By introducing fermenting materials into the stomachs of animals this observer was able to produce dyspnea, myosis, muscular contractions, anuria and trismus, a clinical picture closely resembling that of tetanus. Post-mortem the liver and pancreas showed lesions such as are usually found in poisonings and intoxications.

Thus it is made evident that substances other than the specific toxin of the bacillus tetani are capable of causing this much dreaded chain of symptoms, and that the dilated and dependent stomach is a source of real danger to the individual.

Delirium Tremens. It is very probable that the auto-toxins play an important part in the etiology of delirium tremens. This disease is primarily a toxic state due to alcoholic saturation, but when renal and hepatic functions are disturbed the autogenous poisons are added. The possibility of these insufficiences is two-fold. First, that the alcoholic poison has caused

interstitial nephritis and a loss of functional liver mass through fatty degeneration or cirrhosis; secondly, that alcohol has occasioned gastro-intestinal catarrh with general perversion of alimentary function which predisposes to the formation of auto-toxins. It is a clinical fact that cases of *mania a potu* which have good digestion and functionally active kidneys do well, while those in which the emunctories are faulty do not do as well and are likely to end fatally, (49).

Eichorst attributes the delirium which occasionally accompanies heart disease with edema, to toxic bodies derived from the edematous fluid, and the failure of the kidneys to eliminate the same, (50). In this condition there is at first somnolence which soon gives way to loss of consciousness interrupted by delirium and violent mania. The respirations are deep and frequent, the face flushed, and the clinical picture resembles that of delirium tremens.

Night Terrors of children with their numerous concomitant symptoms may be considered as the result of CO poisoning. In substantiation of this view it appears that pharyngeal obstruction prevents proper oxygenation of the blood, that the symptoms are identical with those of known CO poisoning, and that the disorder disappears after the obstacles to respiration and hematosis are removed.

Depressed States.

Mental depression is a very common accompaniment or symptom of the absorption of toxic materials of autogenous origin. It occurs in the pathogenesis of many of the substances described in Part II and varies in grade from slight bodily fatigue to total prostration

and depression insanity. Two classes of symptoms result from auto-intoxications, the subjective,— apathy, insomnia, somnolence, inability to concentrate the attention, headache, sense of oppression and many others of this character. The other class illustrates the more severe grade, — unconsciousness, convulsions, coma, choreiform movements, contraction of the pupils, vomiting and purging. The former class suggests the clinical features of neurasthenia, the latter those of organic disease of the nervous system, and acute poisoning. The sensations of suffocation and the dyspnea of auto-intoxication may be due to the direct irritation of the respiratory centre in the brain by the poison in the blood or lymph streams, or they may be reflex, due to the irritation of the gastric terminals of the pulmonary vagus.

The well known depression of *Jaundice* results from the disturbed intestinal function which necessarily ensues from hepatic insufficiency, as well as from the toxic action of the bile salts and pigments, and presents all grades from malaise and prostration to absolute insanity and melancholia. For these reasons the toxemia is not purely hepatic in character, and the more complete the suspension of liver function, the greater the probability of the addition of the intestinal element. The subjective mental symptoms of ordinarily severe cases of jaundice are those of generally depressed mentality, malaise, dull heavy frontal headache, rheumatoid pains in all parts of the body, somnolence and inability to concentrate the attention upon any subject or do any intellectual work. A patient is unable to remember that which he read or did a few minutes before, — all of which might be in-

terpreted as indicative of cerebral disease, did not clinical experience teach that these symptoms are but the effects of biliary insufficiency. If however the intoxication is more profound, the lassitude develops into coma which may be interrupted by convulsions, delirium, muscular twitchings and hiccough, all increasing in severity until death supervenes. This is very much the clinical picture in acute yellow atrophy. Or, the symptoms may develop into a true melancholia, which is not uncommon in hepatic disease.

In *Albuminuria* there is a marked tendency to depression and irritability. Worry and hypochondriasis are frequently due to renal disorders and these may increase to temporary mental abberration with suicidal tendency. In these states there is not only the element of toxemia, but also the general impoverishment of the tissues and blood serum from loss of albumin.

In acid intoxications the tendency to mental misery and suicide is very marked. Suicide may be from premeditation dependent upon long continued malaise, or it may be from mania in which the patient is insane and has no knowledge of his acts. Hypochondriacal melancholia may occur before an attack of gout and end promptly upon its appearance. The mania of the gouty is usually violent and dangerous and such patients chatter without ceasing, rapidly exhausting themselves.

It is hardly necessary to allude to the characteristic temperaments of the dyspeptic and gouty which are simply the result of the chronic depressant effects of these poisons upon the system and brain.

Insomnia. Auto-intoxication not only causes mental lassitude, malaise, languor and depression, but also the

opposite state, that of insomnia and mental exaltation. The philosophy of this is that the auto-toxins keep the cerebral cortex in a state of hyperemia. It will be remembered that renal, cerebral and peripheral hyperemia are very common phenomena in experiments with the purins, diamins and many other organic poisons, and that some of them act as vaso-dilators in small and as vaso-constrictors in large doses. It is also true that several of the auto-toxins resemble caffein in their stimulating action on the heart and its governing nerves, and not only increase the force and frequency of the heart's beat, but also raise blood pressure in the brain. A great variety of grades of toxic symptoms may be produced by different degrees of concentration of the same poison, and clinical insomnia may be reckoned as a mild manifestation of the same cerebral congestion which, if continued, goes on to irritation and even inflammation with its violent clinical symptoms. One observes in these actions of the auto-toxins the similarity with the peculiar wakefulness of those who are not accustomed to the use of tea, coffee and tobacco. Clinically it is found that with the restoration of the proper digestive functions, with consequent diminished elaboration of entero-toxins, we have a relief of the sleepless condition, a marked decrease in the number of subjective symptoms of the patient, and more normal heart action with lessened arterial pressure. It is easy to see the origin of congestive headaches in a more intense grade of intoxication than that which causes insomnia, for it is clinically found that this affection is very commonly due to constipation or intestinal fermentation, and the headache is relieved by appropriate therapeutic means directed to the intestinal cause.

In *Narcolepsy* we have the very opposite condition to insomnia, in which the patient is seized with a sudden and uncontrollable desire to sleep. Fisher claims that if hysteria, diabetes and nephritis can be excluded that the disease is almost pathognomonic of cerebral syphilis and that there is syphilitic endarteritis. Important in this connection are the researches of Barker (59) in which he shows the correlation between mental diseases and cerebral endarteritis, and the latter to be due to a variety of poisons. Stern (51) reports a case in which these may be excluded and which seems to be the result of intrinsic metabolic causes. His patient was mentally active, showed no evidences of hysteria, and the seizures occurred independently of the ingestion of food. The following arguments show the intrinsic origin of this case: — 1. The stomach was dilated and hyperchlorhydria was present. 2. There was high urinary density and acidity. 3. Urinary chlorids in great excess. 4. Diminished alkalinity of the blood. 5. The salts of oxalic, sulphuric and uric acids, carbamid, creatin and creatinin were in great excess. 6. There was a low degree of urinary toxicity before and after the attacks of somnolence. His explanation of the disease is that deficiency in the chlorids of the blood causes low osmotic pressure and as a result of this there is a temporary diminution in the nutrition and electrical conductivity of the nerves.

The records of experimental poisonings with autotoxins suggest an explanation of that class of cases which simulate typhoid fever, but which differ from it in that they do not give the serum reaction, do not show symptoms of perforation or result fatally, are

more prone to constipation than diarrhea, and do not have as high or as long a temperature. Bruce (52) reports cases of this kind in which there were nervous depression, languor, drowsiness, vertigo, cephalalgia, pyrexia, vomiting, diarrhea and abdominal tenderness. The writer has observed a number of these cases and finds them usually accompanied by a cutaneous eruption similar to that described under infantile convulsions. All of the writer's cases were in adults. It may be that research will soon show these cases to be of the para-typhoid type or discover a specific bacterium as the cause; their similarity with known intoxications however, is so marked that the possible auto-toxic origin should not be overlooked.

Insanity. All modern investigators acknowledge the importance of autogenous poisons in the etiology of insanity. Hamilton (53) has made a special study of the urine and digestion in the insane and offers the following important conclusions: —

1. Varying and fugaceous illusions and hallucinations, pallor, increasing exhaustion, verbigeration, confusion and unsystematized delirium are due to auto-intoxication.

2. Paranoia, chronic stuporous conditions and some forms of dementia have little to do with auto-intoxication.

3. Auto-intoxication is most common in post-febrile states, traumatisms, alcoholism and drug disorders.

4. The variation in the excretion of combined urinary sulphates, keeps pace with the changes in an established insanity. Epileptiform attacks are directly connected with putrefactive conditions in the intestine.

The Ductless Glands as concerned in Auto-intoxication.

At the present state of our knowledge it is difficult to assign to the ductless glands their proper place in the animal economy, or to tell what part they play in the elaboration or neutralization of auto-toxins. There can be no doubt but that they are intimately concerned in the bio-chemistry of the body, for changes in their functional powers are followed by profound tissue changes. Their internal exhibition as medicine and experimental poisonings show that they contain powerful active principles producing phenomena of a constant nature.

Blum (54) considers that the prime function of the thyroid is to destroy the poisons which circulate in the blood and which are derived chiefly from the intestinal canal. These entero-toxins are arrested in their passage through the gland, are deposited there as thyreo-toxalbumin and are gradually rendered harmless. Now if the activity of the thyroid is in any way impaired, and the entero-toxins circulate unhindered, accumulation and consequently intoxication take place.

In a series of important experiments Breisacher (55) has shown that the extirpation of the thyroid in animals is not necessarily fatal, and that in animals so treated a milk diet is much more favorable to life than meat. This not only throws light on the dietary treatment of myxedema, but also suggests that the thyroids are of great importance in the oxidation of purins, of which milk contains none and meat 15 to 20 grains per pound.

That the thyroid has special power in neutralizing toxics is shown by the experiments of Remedi (56)

who injected diphtheria toxin and bacteria nucleoproteids into the substance of the thyroid, and, although the secretion of the gland was temporarily increased, there was no inflammation or necrosis such as inevitably follows the injection of these substances into other tissues.

The chief diseases into which intoxication resulting from diminished or excessive secretion of the ductless glands enters are exopthalmic goitre, myxedema, including cretinism, and Addison's Disease. In myxedema and exopthalmic goitre we have two states due to opposite conditions of the thyroid; the former due to decrease and the latter to increase in its functional activity. Horsley, Kocher and Riverdin produced conditions closely analagous to myxedema by the removal of the thyroids of animals, and the symptoms of goitre may be produced at will by the experimental administration of thyroid substance or its extracts. That lack of functionally active thyroids and parathyroids is the prime cause of myxedema and cretinism is apparent from the abundant testimony of relief of the disease when thyroids are given as medicine. And the aggravation of many cases of exopthalmic goitre when thyroids are administered shows that they only increase the amount of poison already in the system.

Mosse offers the theory that the *Adrenals* have two functions, one, the production of a physiological substance of a stimulating nature, the other, the neutralization of poisons formed in various parts of the body.

In this disease both of these functions are impaired by the atrophy or calcification of the adrenals, and the auto-toxins are appropriated by the spleen, extracts of which are toxic to mice, (57).

This secretion which is supposed to control and govern blood oxidation is called by Sajous *adrenoxin* and the general symptoms of any poison circulating in the blood is to be considered as due to the disordered function of the ductless gland system.

Poehl claims that the ferment which regulates oxidation processes is spermin, a base found in the pancreas, thyroid, testicles and the adrenals.

The function of the pituitary body is still *sub judice*, and experiments seem to show that it is in some way concerned in the phenomena of nutrition and toxemia. Its obliteration in dogs and cats is promptly followed by slowing of the respiration, acceleration of the pulse, mental depression and motor disturbances, arching of the back and spasticity of the gait without contractions of the limbs: progressive cachexia then occurs, followed by death in coma. This is interpreted as showing that the hypothesis is concerned in destroying or neutralizing auto-toxins. Cyon has corroborated these experiments and considers that disease of the pituitary is the cause of acromegaly. Lomonaco and Rymberk do not agree in these findings and claim that the results obtained are due to surgical shock, and infection or injury to tissues adjacent to the body and necessary to the operation itself.

In a case where fracture of the inferior maxilla produced jaundice, high temperature and blood disintegration, Wasdin (58) found the pituitary to be gangrenous, and from an investigation of the subject he concludes that this body acts through the cervico-sympathetic system upon the secretion of the adrenals, the normal function of which is to prevent hemolysis.

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