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Animal Alkaloids

Sir W. Aitken

ON THE ANIMAL ALKALOIDS

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THE PTOMAÏNES, LEUCOMAÏNES, AND EXTRACTIVES IN THEIR PATHOLOGICAL RELATIONS

BY

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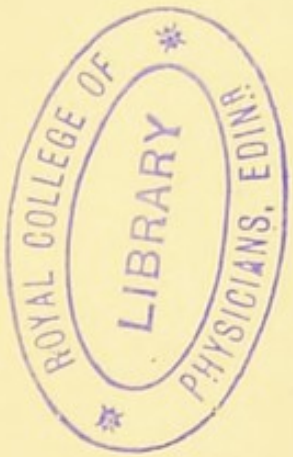

SECOND EDITION

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PREFACE TO THE SECOND EDITION.

The first edition of this little volume having been disposed of by the publishers in a comparatively short time, I gladly avail myself of the opportunity which the call for a second edition presents, to express my acknowledgments for the reception which the first has met with.

This new edition has not only undergone a careful revision, so as to remove some inaccuracies and other blemishes, but it has been my aim in it to bring the subject up to the present state of knowledge regarding the Animal Alkaloids, and generally to make the work more complete without altering its original character—namely, that of giving a concise account in small compass of recent discoveries regarding the Animal Alkaloids, and their relation to diseases.

The discovery of these substances is so comparatively recent that the important problems of their relations to diseases as causative factors have not yet been sufficiently appreciated by the profession. While, therefore the subject is of much interest, it is comparatively new,

and it deals with phenomena and researches of a very practical character.

But while the direction of modern thought tends to assign an important place to the part played by Animal Alkaloids in the production of diseases, any conclusions drawn in the present state of our knowledge must be considered merely as suggestions. Many more facts must come to light before the *rôle* played by the Animal Alkaloids in *living* pathological processes can be adequately or even reasonably discussed. The researches of the last 17 years (of which a resumé is given in this volume) can only be regarded as a basis for future work, and be suggestive as to its scope and method.

Nevertheless from a practical point of view some important considerations at once arise out of this study of the Animal Alkaloids in their relation to disease, especially as regards treatment, inasmuch as a great deal may be done, alike in the prevention and cure of disease by attention to the personal Physiological Pathology of the patient.

From this practical view of the subject the cardinal idea embodied in this volume points :—(1) to the evolution of diseased states from retention in the body of its own "excretions," and of the products of their decomposition; (2) to the consequences and direct issues of inadequacies of function, as regards especially the cutaneous, intestinal, hepatic, pulmonary, and renal functions.

These considerations are of wide application, and of

extreme importance in medical practice, and in this view of the subject I am pleased to find myself borne out by the authority of the present distinguished President of the Royal College of Physicians of London—Sir Andrew Clark.

We have now also arrived at that stage in our knowledge when we can appreciate the ideas of autogenetic and of bacterial infection, as so closely related, and so curiously interwoven in their actions and results, "that the true place of Bacteriology in Scientific Medicine cannot be finally determined until the chemistry of the functional processes of living protoplasm (including the living blood and the living bacteria) have been further advanced, and until the relation of the Animal Alkaloids and 'Extractives' to the genesis of pathological processes have been experimentally investigated anew."

And even if the bacterial origin of all infective diseases were to be fully established, the main teachings of this little book would still hold good, namely:—the great importance of soundness of tissue, and "adequacy of function"—not only of the larger organs, but still more so as regards the soundness of protoplasm and of the vitality and functional activity of each individual component cell of the living body, seeing that it is in the soundness and vitality of the blood and tissues, and the presence in them of those normally characteristic chemical substances which are the result of their *healthful* life, that our safety lies, and in which the power exists of checking the ingress and progress of all micro-organisms (whether pathogenic or non-pathogenic) by the

direct adequacy of the vital reactions of those tissue elements themselves. Undamaged tissues of standard vitality (*i.e.*, standard adequacy of function) perfectly resist the entrance of invading organisms; on the other hand, damaged tissues with lowered vitality or impaired adequacy of function favour the entrance of pathogenic organisms whence the body may become an easy prey to their influences.

WILLIAM AITKEN.

Army Medical School, Netley.
October, 1889.

PREFACE TO THE FIRST EDITION.

The following pages owe their existence to the necessity of finding a subject suitable for a lecture introductory to the course of instruction at the Army Medical School at Netley, on the 1st of April, 1887. They are now published by request; and with the permission of the Secretary of State for War.

Speaking generally, it may be stated that the investigations which underlie the most important practical work of the Military Medical Officer, alike on land and sea, relate especially to the causation of diseases with a view to their prevention; and in carrying out such investigations, the time appears to me to have come when it is desirable to open up new lines of thought and of practical departure in Pathology, which may lead us to entertain broader, or at any rate less narrow views, than those we have been accustomed to entertain as to the origin of some diseases.

By the selection of a topic such as the following pages concern, I hoped that I might awaken in young, ardent, ingenuous and impressionable minds, a desire to work out various philosophical problems in Pathology; while the nature of the Military Services the young medical officers were about to join would give

them leisure not only to study and to work out, but would give them also opportunities in many climates and in many lands to add to our knowledge regarding the causation of disease.

When I had the honour of discharging a similar duty two years ago, I endeavoured to show how far "The Doctrine of Evolution" was competent to explain the *origin* of some diseases;* and now I once more try to open up to view another new and fresh territory in Pathology only just beginning to be explored, which is calculated to render obvious certain modes of origin of many forms of disease. I do so in the hope that the glimpse I am able to give of this fresh field, however hazy its vista may be; yet as Time (with increasing knowledge) clears away the mists of our ignorance, lines of thought and inquiry may suggest themselves in many fruitful directions for investigation.

While much remains to be done in the direction indicated in the following pages, yet so much has been already done by experiment and research in the past twelve or fifteen years, that such a concise summary as I have here attempted to give may show the bearing of the results and their value, as illustrating the Pathology and the origin of some diseases.

It is further desirable, if possible, to get rid of the term "cause" altogether as applicable to any particular disease. Our textbooks, as yet, have been unable to specify and establish any *single* thing as

* "Glasgow Medical Journal"

the final cause of any disease. There is no disease I know of which acknowledges a *single* cause.

It ought rather to be our business to find out the many and ever varying factors or conditions which, as antecedents, combine to produce disease; and while we must acknowledge the influence of many physical agents in aiding and abetting these factors, we must mainly look to the physiological agencies within our own bodies during life as competent to bring about many forms of disease.

WILLIAM AITKEN.

Army Medical School, Netley.

CONTENTS.

PAGE

ON THE ANIMAL ALKALOIDS.

The word "alkaloid" is used in chemistry to denote a class of substances having alkaline properties, that is to say, having in some degree the qualities which alkalies (such as soda and ammonia) possess of being soluble in water, and of combining with acids to form salts. Their generic name (derived from the Arab "qali," signifying the ashes of the plant or the plant itself from which soda was first obtained) denotes a plant connection. Until recently, the vegetable was believed to be the only source whence these substances were obtained; and they were regarded as natural alkaloids, the organic basis existing already formed in plants. But it has now been conclusively shown that the living animal cells are capable of elaborating alkaloids, so that henceforth it may be convenient to classify alkaloids into two classes, namely:—the vegetable and the animal alkaloids, and to sub-divide the animal alkaloids (as Gautier has done) into (1) those due to the action of bacteria (or ferments which may be fluid or solid) on the albuminoid substance of the dead tissues (ptomaïnes), and (2) those elaborated by the vital energy of the cells themselves (leucomaïnes). Moreover, the recent researches and expositions of MM. Gautier and Peter (two eminent French physiological Chemists and Physicians), of Drs.

A. M. Brown and Lauder Brunton and others in this country, have furnished numerous facts, which (apart from their chemical and medico-legal value) have the important merit of confirming our belief in "the poisoning or intoxication of the animal economy with its own products." In this direction they have added to our previous knowledge; and to pathological investigation they have imparted a greater degree of method and precision than heretofore. But it is to the writings of Dr. A. M. Brown,* and those of Dr. T. Lauder Brunton,† that I am mainly indebted for the facts and arguments contained in the following short notice of the animal alkaloids.

What then are the questions involved in the subject matter of the researches of these eminent physicians?

They may be considered under two aspects:—1.

* "Contributions to the Study of the Cadaveric Alkaloids, the Ptomaïnes and Leucomaïnes; their Physiological and Pathological Significance in Relation to Scientific Medicine," 1886. "MM. Gautier and Peter on the Ptomaïnes, Leucomaïnes, and Microbes, a New Departure in Pathology." "Contributions to the Study of the Animal Alkaloids; Leucomaïnes, their Antecedents and Discovery, their Classification and Chemical Definitions," 1887. "The Animal Alkaloids, Ptomaïnes, and Leucomaïnes; their Common Origin, a fresh page in Bio-Chemics," 1886. (Published by John Bale and Sons, 89 Great Titchfield Street, London). Also by same author and publisher, 1887, a very exhaustive "Treatise on Cadaveric Alkaloids and Ptomaïnes," in which he gives full details as to the methods devised and practised for extracting the cadaveric alkaloids; and as to the chemical properties of them, their physiological action, and place in scientific medicine; concluding with a very complete Bibliographical list of the works which deal with this very interesting subject.

† "Disorders of Digestion," comprising various papers from "The Practitioner," 1873 to 1885, collected aud published 1886. "Pharmacology, Therapeutics, and Materia Medica." Third Edition. London, Macmillan and Co., 1887; also Croonian Lectures, 1889.

Chemical and physiological or bio-chemical. 2. Clinical or pathological.

1. As to the chemical and physiological aspect, Gautier has shown that in dead animal tissues, processes of putrefactive decomposition set in by which certain alkaloids are elaborated from the proteid substances, which by the late Selmi, of Bologna, have been called "ptomaïnes."* But Gautier has further shown that in the animal tissues during normal life, and that by virtue of their vitality, certain other alkaloids are elaborated which are analogous to the "ptomaïnes," and these he has named "leucomaïnes."† Still further in addition to these facts, he has demonstrated that in the living animal economy there are elaborated certain azotised uncrystallisable substances, which are as yet undetermined, which we call "extractives" or "extractive matters," and which are quite as unknown as the *x*, *y*, *z*'s of an algebraical formula (Dr. H. L. Veale). The nature of these "extractives" has therefore still to be found out; but this much we know of them: that

* "Ptomaïnes from Πτῶμα, *a carcase, a dead body*, and *ine*, denoting *material*; or *In*, from Latin *inus, belonging to*. A common termination in chemical terms, but varying much in significance, as *hæmatin*, *hæmatine*, *stearin*, *stearine*, *innulin*, etc. *Ine* or *in* has been usually applied to the alkaloids produced from vegetable substances, and the compounds possessing the closest analogies to them, *e.g.*, *quinine*, *atropine*, *aniline*.

† Λεύκωμα, *anything whitened—albumen*, or *white of egg*.

The nomenclature is not quite satisfactory. The selection of the word "ptomaïne" indicative merely of the conditions under which animal alkaloids were first discovered, as a root whence to derive a name for these bodies is too restrictive, since it is only appropriate for alkaloids of *post-mortem* origin. A name is still wanted for animal alkaloids formed by *morbid* processes during life—the ptomaïnes of *disease* formed during life.

while we are assured that the "ptomaïnes" are toxic, and that the "leucomaïnes" are also toxic, these unknown "extractives" are more toxic or poisonous to the system than either.

Take for example the urine; we know that by or through it we eliminate chlorides, phosphates, urea, glucose, albumen, and "extractives," in variable amounts, and that these go to make up the total solids of the urine. We know further, the chemical composition and the dangers of all of these, when found in over abundance or when not eliminated, except as regards the unknown and mysterious "extractives." We know further, that in proportion as the cypher of albumen increases in the urine, those of the urea and extractive matters diminish, and a series of accidents supervene which we name "uræmic," as the non-eliminated extractive matters (which are retained) increase in the blood. It may also be noted, as was pointed out to me by my friend the late Dr. F. de Chaumont, that when the glucose is in excess, some inhibitory influence seems to be exercised over the elimination of the extractives, so that they seem less in quantity; but whether their actual formation is prevented, or merely their elimination, is not known.

The alkaloids of animal origin were first discovered by Armand Gautier in 1872. He discovered them in the ammoniacal products of putrefaction of albuminoid material, a discovery which excited much interest; especially when sometime afterwards Selmi, of Bologna, published his researches (from 1878 to 1882) confirming the observations of the Chemist of the College of France in their medico-legal applications. These researches and their results were worked out by those

eminent toxicologists independently of each other. Selmi's investigations were unfortunately too soon brought to a close by his early death. In 1877 he extracted two new alkaloids from pure albumen which he had caused to undergo putrefaction free from atmospheric contact.

But so long ago as 1820, Kerner pointed out the resemblance between the symptoms of poisoning by sausages and by atropine. He was thus the first to raise the suspicion that alkaloids were formed through the decomposition of albumen; and by the experiments on animals which he made, he appears to have come to the conclusion that an alkaloid was present in poisonous sausages; although he afterwards came to regard fatty acids as the really poisonous agent in them.

In 1856 Panum showed that the inflammatory change which occurs in the intestinal mucous membrane of animals poisoned by putrid matter, is due to a chemical poison which remained unaltered when its aqueous solution was boiled for a long time; and his conclusion that the poison contained in putrid matter was of a chemical nature, was confirmed by C. O. Weber, Hemmer, Schweninger, Stich and Thiersch.

Fourteen years ago Dr. W. B. Richardson showed that sero-sanguineous fluid from the peritoneal cavity of a person suffering from pyæmia could communicate fatal disease from one animal to another in a direct series. To this poison he gave the name of "septine." He also found that it could be made to combine with acids so as to form salts, and that these retained the poisonous qualities of the original substance.*

* "Lancet," April 3rd, 1875. "British Medical Journal," May 27th, 1876. Aitken's "Science and Practice of Medicine," 7th edition, vol. i., p. 376, 1880.

Bergmann and Schmiedeberg isolated a crystalline poison from decomposing yeast, to which they gave the name of "sepsin."

Bence Jones and Dupré found a substance resembling quinine in the liver.*

Zuelzer and Sonnenschein obtained both from macerated dead bodies and from putrid meat infusions, small quantities of a crystallisable substance which exhibited the reactions of an alkaloid, and had a physiological action like atropine, dilating the pupil, paralysing the muscular fibres of the intestine, and increasing the rapidity of the pulse.†

Rörsch and Fasbender obtained from dead bodies a substance which had properties like digitaline, but which was not crystalline.

Pellicani has found a poison in the supra-renal capsule, and sometimes ptomaïnes may be obtained from the flesh of healthy animals.‡

An alkaloid has been separated by V. Anrep from poisonous fish,§ so also Vaughan has obtained an alkaloid from poisonous cheese, which he has named "tyro-toxican."‖ The development of this substance in milk is a frequent cause of diarrhœa in infants. It has also been found in ice-cream and oysters.¶

But while the question in Italy was confined to researches in toxicology, in France first and afterwards in Germany it took a position more important and wider in its range.

* Zeitschr. f. Chem. u. Pharm., 1886.

† Berlin Klin. Wochenschr., 1869.

‡ Dr. Lauder Brunton, *loc. cit.* p. 282.

§ "London Medical Record," 1885, p. 271.

‖ "Lancet," August, 1885, p. 60.

¶ Victor C. Vaughan, University of Michigan, 1886.

Gautier, Etard, Brieger, and others gave precision to the data previously acquired; and adding largely to the varied and careful examination of cadaveric tissues, "they forced the conclusion that during the putrefaction of nitrogenous animal material there are formed organic bases, fixed or volatile, presenting by their chemical and physiological properties, the closest similitude to the vegetable alkaloids."* They have succeeded in isolating a number of these ptomaïnes in the crystalline form and have submitted them to ultimate analysis.

It was at first supposed that these animal alkaloids differed in their nature from the organic alkaloids formed by vegetables, and various reactions had been given to distinguish between them. More recent researches, however, especially those of Brieger appear to show that this distinction can be maintained no longer; but that the animal and vegetable alkaloids are similar in their chemical constitution, and that they are both products of albuminous or proteid decomposition; and that some at least of the so-called ptomaïnes are identical with vegetable alkaloids.†

"We may now indeed regard alkaloids," writes Dr. Brunton in the third edition of his valuable work on Pharmacology, "as products of albuminous decomposition, whether their albuminous precursor be contained in the cells of plants and altered during the process of growth, or whether the albuminous substances undergo decomposition outside or inside the animal body, or

* Dr. A. M. Brown, *loc. cit.*

† Dr. Lauder Brunton in "Practitioner," vol. xxxv., 1885, "Poisons formed from food," also "Disorders of Digestion," p. 222, 1886.

by processes of digestion as by unorganised ferments."*

It has been also shown that the alkaloid products formed by the putrefaction of albuminous substances vary according to the stage of decay at which they are produced. At first the poisonous action of the ptomaïnes may be slight; but as decomposition advances the poisons become more virulent, while after a still longer period they become more broken up and lose to a greater extent their poisonous power (Brunton).

The poison *muscarine* which had only been known as obtainable from a plant, (the *Agaricus muscarius*, "fly-fungus") has been discovered by Brieger to be a product of the decomposition of fish; and it has also been made synthetically by Schmiedeberg and Harnack from choline.

It is further to be noted that some of the products of decomposition thus obtained are found to be poisonous, and that others are not so; that among the poisonous ones various degrees of activity prevail, some being but slightly poisonous, whilst others are most virulent;—also that while many retain their properties for a length of time, yet when mixed or in combinations (still uncertain) they further decompose or neuralize each other, appearing to have an antagonistic action the one to the other, and so become inert. Brieger, for example, has obtained from decomposing albuminous substances several well-defined chemical bodies.† From flesh he has got a substance which he calls "*neuridine*" which is innocuous, and another substance "*neurine*" which, however, is poisonous, while the "*muscarine*"

* "Pharmacology and Therapeutics," p. 100.

† Brieger, "Ueber Ptomaïnes," Berlin Klin. Wochenschr, 1887.

from fish is more poisonous still. Two other substances, one "*ethylenediamine*" is poisonous, while "*gadenine*" is not poisonous. He has also obtained from human corpses a different set of bodies, one of which he calls "*cadaverine,*" and the other "*putrescine:*" which are but feeble poisons; while two others "*madeleïne*" and "*sepsine*" which are produced later on in the decomposition are much more powerful poisons—causing paralysis and death. From decomposing albuminous substances he has obtained many other well-defined chemical bodies; as well as some substances to which no names have yet been given.

In addition to these alkaloids obtained by Brieger, a number of poisons have been got by other workers from decomposing articles of food or from dead bodies, and even from portions of healthy animal bodies. And although these may not have been obtained in the same state of purity, nor have had their chemical constitutions so well-defined as Brieger's, they are still, as unknown "extractives" (*x*, *y*, *z*'*s*), of great interest and importance.

The physiological action of these alkaline bases of animal origin do not present the diversity of action which has given to the study of vegetable alkaloids so much interest.

Nevertheless the physiological effects of the ptomaïnes and the leucomaïnes are powerful enough to compare with those of "*muscarine,*" "*curare,*" "*nicotine,*" and other very active and virulent vegetable poisons. In support of this view a series of investigations and experiments have shown that the primary products of albuminous decomposition of digestive ferments, such as peptones are poisonous. Brieger has recently shown

that pepsine will split up albuminous substances still further, so that by digesting fibrine with artificial gastric juice, he obtained an alkaloid to which he has given the name of "*peptotoxine.*"

The bitter taste which sometimes appears during the digestion of meat, or of milk artificially, as Dr. L. Brunton has pointed out, is suggestive of the formation of some alkaloid, although it has not yet been determined what this bitterness really depends on; and Dr. Lauder Brunton further gives the timely and much needed caution against the extreme and indiscriminate use of the various digestive ferments, and of the many varied artificially digested foods which have now become so common. From this point of view a study of the products of albuminous decomposition has become of much practical importance, not only as regards pathology, but as regards therapeutics, for "it is possible that digestive ferments like other powerful agents may be edged tools, and capable of doing harm as well as good."

Ever since 1877, one ptomaïne after another has been discovered, each fresh observation making the course of their origin more clear, until at last in 1885, Gautier made the crowning discovery regarding the formation of leucomaïnes in the vital cells of the body. His researches extending from 1881 to 1886, show that the animal alkaloids are a necessary product of *vital physiological processes*, he having obtained from the secretions of living beings alkaloid bodies having poisonous properties—results which have been confirmed by M. Peter.

They have shown that about four-fifths of our disassimilations are the result of transformations

within the body, comparable to the oxidation of alcohol; and that the remaining fifth of the disassimilations are formed at the expense of the living tissues themselves "free of all demands on foreign oxygen." In other words a fifth part of our tissues live after the manner of ferments; that is, they are anaerobious or putrefactive as to their life. Hence the possibility of alkaloids being thus formed within the living organism, independent of bacterial fermentation is quite within our conception.

"Every instant of our lives, do we not elaborate normally and in the physiological processes of our existence, acids and bases, not merely carbonic acid, but uric acid—the latter a product of animal life whose normal production is inconceivable apart from it, although it may have been formed synthetically? "The yearly increasing number of so-called organic bodies, which until recently were regarded as the outcome solely of life-processes, but which chemists have succeeded in building up synthetically, compel us to admit that the line between organic and inorganic matter is an arbitrary limit interposed by defective knowledge. If certain organic bodies can be built up synthetically, without the aid of vital forces, it is not unreasonable to believe that variations in the character of life-processes may be effected by the purely physical action of basic products formed within the organism. This is all the more easy of acceptance, since it is admitted that these by-products are the result of that form of chemical action at present inseparable from 'life.'"* Do we not also spontaneously and normally fabricate bases such as urea—a most complex product—which can

* Dr. J. Dixon Mann, "Medical Chronicle," March, 1888.

combine with azotic (or nitric) and oxalic acid; and which by splitting up chemically may go to the formation of carbonate of ammonia? In the face of such potentialities may we not admit that the living organism is capable of fabricating various alkaloids.*

Bio-chemically, such a capacity has been proved to demonstration, and therefore it is probable that poisonous alkaloids are continuously being formed in healthy men and animals by the decomposition of albumen in the intestinal canal, during the process of digestion or in the blood and tissues generally by the metabolism which occurs during the functional activities of life. A considerable portion of these alkaloids is in all probability destroyed in the body, and some are excreted in the urine and fæces, from both of which powerful poisons have been extracted.† Moreover, "a considerable production of alkaloids takes place in the intestine, both when the digestive processes are normal and more especially when they are disordered; at the same time alkaloids are being formed in the muscles, and possibly also in other tissues. Were all the alkaloids to be retained in the body, poisoning would undoubtedly ensue, and Bouchard considers that the alkaloids formed in the intestine of a healthy man in twenty-four hours would be sufficient to kill him if they were all absorbed and excretion stopped. He finds that the poisonous activity of even healthy human fæces is very great, and a substance obtained from them by dialysis produced violent convulsions in rabbits. When the functions of the kidney are im-

* Dr. A. M. Brown, *loc. cit.*

† Dr. Lauder Brunton, "On Disorders of Digestion," p. 283.

paired so that excretion is stopped, uræmia occurs, and Bouchard would give the name of stercoræmia to this condition, because he believes it to be due to alkaloids absorbed from the intestines. He also thinks that the nervous disturbance which occurs in cases of dyspepsia is due to poisoning by ptomaïnes."*

But long before Armand Gautier's *Mémoire* was published in the "Archives of the Academy of Sciences of Paris," evidences of the existence of a physiological function in the animal economy were not wanting as to its power of elaborating alkaloids during life.

Liebig and Pettenkofer had long made known the existence of "*kreatinine*" in urines—a product of animal origin possessing properties clearly alkaloid. "*Kreatine*" was soon after detected in the animal tissues resulting from kreatinine. Twenty years later, Liebreich detected the vegetable alkaloid "*betaine*" in human urine; and so recently as 1880, Pouchet has recorded the presence of "*karnine*" and an alkaloid in well-defined crystals, concerning which Gautier has not only confirmed the fact, but also that the alkaloid possesses the properties of a ptomaïne. In 1880, by carefully operating with glands of snakes, he was enabled to eliminate material from them of an alkaloid nature; and from the cobra he obtained two new substances, each of the nature of a ptomaïne.

From this time onwards, the study of a new class of alkaloids, the products physiologically of animals during life, has steadily progressed, and this preliminary advance was further strengthened when in 1882 Bouchard disclosed the fact that not only were alkaloids present

* Dr. Lauder Brunton, "Pharmacology and Therapeutics," 3rd edition, p. 101.

in appreciable quantities in normal urine, but that they augmented notably in the course of certain maladies—in typhoid fever for example. And this applies to a still wider pathological area, so that, generalising the facts we already know, we venture to conclude that in the course of certain maladies these poisonous products of the urinary secretion notably increase in quantity, until a crisis is reached when they again diminish and finally disappear (Lepine, Guerin, Aubert, A. M. Brown, Lauder Brunton).

Thus, the incessant elaboration of alkaloid products formed at the expense of proteid elements, precisely as urea and carbonic acid are similarly and simultaneously formed, is now fully confirmed; and to distinguish this class of products from that of the cadaveric alkaloids or "*ptomaïnes*," Gautier has named them "*leucomaïnes*," or alkaloids derived during the processes of life from the decomposition of albuminoid substances.

Gautier has further shown that there is a distinction to be appreciated between alkaloids formed during the *bacterial* destruction of albuminoids, and alkaloids which owe their formation to the bio-chemical and physiological activities of the normal tissues. He asserts that oxygen is not the only cause of these transformative processes, but that nearly one-fifth part of the life of the larger animals is what Pasteur has termed "anaerobic"—that is to say—deriving its force-vitality from internal modifications brought about independently of the help of oxygen, and with the resulting formation of the "leucomaïnes." Pasteur's researches, as well as those of other scientific observers, have shown that anaerobic life is a characteristic of the lower orders of bacterial ferments; and that oxygen is not essential to

their existence. And just as the vital cells elaborate "leucomaïnes," so these bacterial ferments, feeding on the albuminoid substances of the body and causing what is known as putrefaction, develop "ptomaïnes" as their waste products. But however important this distinction may be, it does not support the view that the ptomaïnes and leucomaïnes are distinct or opposed to each other. On the contrary, it is impossible to trace the limits where the one series of alkaloids begins or the other ends; and there are a certain number of known alkaloids which are common to both series.

Gautier has recently also announced the discovery of five new "*leucomaïnes*," namely, "*adenine*" from the pancreas, and one from the spleen,* the other three resulting from experiments on the muscular juices of the higher animals. The second body isolated from the spleen by Morell, has a paralyso-motor action, with a powerful effect on the medulla oblongata.†

The late Dr. L. C. Wooldridge (whose early death is so much to be deplored) found that a remarkable intoxicant proteid could be prepared from the thymus or testicle; and that when this was injected into the veins it produced widespread clotting in the vessels.‡

They all exhibit simpler chemical formulæ than vegetable alkaloids for the most part do; and a number of the leucomaïnes have been manufactured synthetically.

Dr. A. M. Brown§ gives us a classification of these "new physiological alkaloids" with their sources, based on that of Dr. Hugounenq, of Lyons, in the following groups:—

* Hoppe-Seyler's "Zeitschrift," March 11th, 1886.

† "The Lancet," April 24th, 1886.

‡ "Proceed. Royal Society," 1886.

§ *Loc. cit.*, p. 5.

I. The Uric Leucomaine Group.—Betaines.

Betaine is the representative of this group, having the chemical formula of $C^5 H^{11} NO^2 = \begin{matrix}(CH^3)=N-O \\ | \\ CH^2—CO.\end{matrix}$

The base was originally discovered in beetroot in 1866 by Scheifler, and in 1869 Liebreich detected its presence in human urine.

Karnine, $C^7H^8N^4O^3$.—Commences the natural series of alkaloids of the uric groups. The base was isolated from imported meat by Weidel, and afterwards in yeast waters by Schutzenberger.

Adenine, $C^5H^5N^5$.—Discovered by Kossel in 1885.

Guanine, $C^5H^5N^5O$.—Discovered in 1884 by Unger, and since met with in a great number of products of animal nature in the flesh, the organs, and the excremental matters of certain mammifera, in fowls and fish, and also in certain plants.

Sarkine or *hypo-xanthine*, $C^5H^4N^4O$.—Found in certain plants, but for the most part in animal tissues.

Xanthine, $C^5H^4N^4O^2$.—Is widely distributed in the organism, in almost all the liquids and tissues of the animal economy from the splitting up of *nucleine*. The base was first isolated by Marcet in 1819.

Pseudo-exanthine, $C^4H^5N^5O$.—Discovered by Gautier in the muscular tissue of the higher animals.

These last four leucomaïnes form a distinct group as to community of origin, with analogous chemical properties:—(1) They all possess a combination ($C^5H^4N^4$) of a remarkable stability, analogous in certain respects to the stability of the pyridic compounds. (2)

They can all give up cyanhydric acid, and two of them, xanthine and hypo-exanthine, may be obtained synthetically in operating with the same cyanhydric acid. (3) All of them are derived from albuminoid substances by reactions which are identical in origin. (4) Three of them present in a high degree that insolubility in water the pyridic compounds exhibit.

Dr. Brown further notes the startling fact "that the most terrible poison, cyanhydric acid, forms the chemical skeleton of that cellular nucleus which is the most active phenomenon of vitality."

II. The Kreatinine Leucomaine Group.

That well known base *kreatinine*, $C^4H^7N^3O^5$ NH=

$$C< \begin{matrix} NH & - & CO \\ | & & | \\ N & (CH_3) - & CN_2 \end{matrix}$$

heads the list of the other new alkaloids discovered by Gautier since 1881. They are all of fresh meat origin. Kreatinine was discovered by Liebig in the action of chlorohydric acid on kreatine, and Pettenkofer afterwards found it in human urine.

Xantho-creatinine, $C^5H^{10}N^4O$.—The most abundant of these bases is of cadaveric odour, soluble in cold water, and with a strongly alkaline reaction.

Crusocreatinine, $C^5H^8N^4O$.—Possessing the general properties of kreatinine which it strongly resembles in chemical elements and alkalinity.

Amphicreatine, $C^9H^{19}N^7O$.—Corresponds with two molecules of kreatine plus CNH groupment, thus having the closest analogy to kreatine, although the formula seems widely to differ from it.

III. An Unclassified Group—According to their Sources.

From the urine.—A uride—allantoine—and a base—karnine—already known, a second alkaloid has been discovered with the formula $C^7H^{14}N^4O^2$.

From the blood and important viscera.—Alkaloids have been met with in appreciable quantities.

From the breath.—Du Bois-Raymond has obtained a poisonous alkaloid which he has named "Anthropotoxine."*

From thymus or testicle.—A proteid intoxicant by Dr. Wooldridge.

From the spleen.—M. Morel, of Lille, has obtained an alkaloid isolated in deliquescent crystals.

From the intestines.—A base which seems to belong to the pyridic group isolated from choleraic dejections.

From the saliva.—Gautier has determined the existence of an alkaloid in human saliva.

The venoms of certain snakes and batrachians as well as from certain *mollusca* and *fishes*. From this latter class Breiger has identified an active principle in the *mytiloxin* and given its formula as $C^6H^{15}NO^2$.

So much for the purely bio-chemical aspect of these researches; let us now consider:—

2. The clinical, pathological and practical aspects.

As to the poisonous character of both ptomaïnes and leucomaïnes there is no doubt; for when injected into birds and other animals even an extremely minute dose has been sufficient to cause death. Moreover, the symptoms, which preceded death in these experiments were thoroughly characteristic of poisoning by putrid

* "Lancet," April 6th, 1889, p. 710.

animal matter; namely diarrhœa, intestinal inflammation, dilatation of the pupil, loss of muscular power and convulsions.

According to the different sources of poisoning or intoxication (as it is technically called), there are correspondingly different indications, signs, or symptoms capable of classification as below:—(1) Poisoning by the "Extractives" is attended by hyperthermia. (2) Poisoning by the "Animal alkaloids" is accompanied by hypothermia. (3) A combination or succession of hyperthermic and hypothermic phenomena may become manifest, according to the combination or alternation of poisoning by the deleterious physiological products, or their antagonistic action. (Dr. A. M. Brown).

Some of the clinical facts may thus appear to be contradictory or inconsistent; for in certain cases (so-called uræmia for example) there is to be observed an elevation of temperature; while in certain other cases the temperature may be normal; and in others it may fall. But once it has been determined that when "extractive matters" accumulate in the blood we detect hyperthermia; on the other hand if "alkaloids" accumulate we have hypothermia; while if the two factors co-exist they may neutralise each other, or become antagonistic in their action, so that temperature may remain stationary or normal. But should one or other of the factors predominate, immediately the scale is turned, so that some variation may be noted. Thus, the balance of metabolic changes gives unmistakable evidence of a nitrogenous residuum which is morbid.

There is in these researches still further disclosed the fact that in this auto-infection, this spontaneous or self-infection of the living organism by the "alkaloids" and

"extractives" of its own formation there is no question of quality, but simply one of quantity to be considered, by reason of the essential physiological source and action of the poison. Many of the phenomena which manifest themselves in disease seem best capable of explanation on the supposition of the presence of some autogenic toxic agent circulating in the blood, and thus producing a specific effect on the tissues. In other words, the healthy living organism may become poisoned (gradually and more or less slowly), by the accumulation within itself of deleterious substances normally elaborated, but imperfectly or defectively eliminated. Hence the slow and insidious onset of much ill-health; and from which recovery is correspondingly slow. I might here instance all the "constitutional" diseases of which rheumatism and gout are typical representatives. "They are such diseases as become developed under the influence of agents generated within the body itself through the continuous exercise of its functions in the daily course of nutrition, development and growth."*

An important aspect of the question now presents itself for solution; namely:—"in what way does this auto-infection or spontaneous poisoning of the system take place?"

This is a very complex question, and as Dr. A. M. Brown observes, it can only be understood and explained by the mode in which we regard the phenomena of life. Life is undoubtedly an active state, the result of the combination of many physiological processes, in the concurrent exercise of the bodily functions which are essentially relative and contingent on one

* "Science and Practice of Medicine," 7th edit., vol. i., p. 829.

another, implying at the same time a series of partial and local deaths. Thus, it is that our organism lives on conditions of incessant elementary disintegrations, so that "we constantly bear about within us the effete debris of our living selves."

Health must therefore always, and can only be a phenomenal phase of life which is relative and contingent; life's equilibrium between the rough and the smooth; the ease and unease; the good and the evil; when the vital functions are performed in a united and harmonious manner which experience has taught us to regard as normal; and as the "wholesome unity which constitutes health."*

Hence normal health comes to be conditional on an incessant formation, transformation and elimination of the effete or old organic materials which must give place to the new. It is this effete material in (whatsoever form it is found) which, therefore, represents a series of partial deaths; and which as the result of organic functional operations, constitutes life, during which the tissues and organs in the processes of their metabolic changes, perform a constant function of disintegration—fabricating during these processes those "alkaloids" and "extractives"—"those *x*, *y*, *z*'s of pathology" which must be regarded as veritable "*scoria*" (Brown) or "*physiological ashes*" (Lauder Brunton) resulting from the processes of combustion in the elements of organic tissues. For the processes of life have been likened to a slow continuous burning; so that fresh fuel in the form of food, must be frequently added to supply the place of the waste material which the burning process entails. In every living cell which

* "Medical Pathology," by H. G. Sutton, 1886, p. 2.

makes up the animal body, there thus goes on a constant transformation of energy, thereby inducing certain modifications of the material substance of the cells—the prime mover in the process being oxygen, which by acting on the material of the cell burns it up, at the same time giving off material which if not cast out of the system would poison it and ultimately destroy its life.

And it will further appear in the following pages that "the vital processes are much more readily arrested by the accumulation of waste products within the organs of the body than by any want of nutriment of the organs themselves."*

Thus is it, that our organism is constantly dying; and strange as the paradox may sound, we cannot live unless it does die. How precarious therefore is the condition we call health; and how by the simple accumulation of cadaveric material disease may manifest itself! How scientifically and also prosaically literal do the truths stand out that "in the midst of life we are in death;" and that "as we begin to live, so we begin to die!"

Then comes another important question; namely, "how do we resist the constant auto-infection to which we are thus constantly exposed?

In reply to this we may say that there are two physiological modes or vital mechanisms as constantly at work in our bodies for our protection. These are—(1) the elimination of the toxic products as excretions by the various emunctories, the liver, the kidneys, the skin, the lungs and the intestinal mucous membranes; (2) the destruction of the toxic products by oxygena-

* Dr. Lauder Brunton, *loc. cit.*, p. 237.

tion; which consists in a continuous combustion of the leucomaïnes by the oxygen of the blood, in which they are burned or consumed in its current, or partially in the tissues and organs.

On the other hand also we know that their accumulation may take place under two widely different conditions: as when there is an excess of "extractive matters" and "alkaloids," with normal but inadequate elimination by the emunctories: or, the production of the deleterious materials being normal, their elimination is inadequate from disease or derangement of the emunctories.

Hence auto-infection may result from excessive production, and inefficient (*i.e.*, inadequate) elimination, the emunctories remaining sound, a condition which is constantly seen in all forms of physical over-taxation or over-exertion, as in a prolonged march, or by excessive drill, especially in young and adolescent soldiers. Of such examples Army Medical Officers acquire considerable experience.

In a paper recently submitted to the *Accademia dei Lincei* (to be printed in its Transactions) the physiology of fatigue has been carefully worked out by Professor Angelo Mosso of Turin, with a view to the determination of the pathological manifestions which accompany that physical condition. He has found that when fatigue is carried beyond the moderate stage, at which it is decidedly beneficial, the blood is subjected to a decomposing process through the infiltration into it of substances which act as poisons—substances which when injected into the circulation of healthy animals, induce malaise, and all the signs of excessive exhaustion. It was on the soldiers of the Italian Army that

Mosso's experiments were made; and he has convinced himself that he has arrived at practical results, which might be formulated in regulations, as to the amount of exertion to be put forth on the march, as to the best distribution of the halts and of sleep, and as to the lightening of the weight which each soldier has to carry.*

Meanwhile M. Peter gives us the following illustration of this auto-infection as observed by him in the wards of the illustrious French physician M. Chomel, his teacher. Under the Professor's charge there came a young man apparently suffering from great prostration, muscular pain and spine-ache. Chomel made his examination with great care and attention; and in the presence of his patient, he gave his diagnosis in Latin, which was "*Aut febris Peyerica, aut variola incipiens*"—typhoid fever or incipient smallpox—a diagnosis which seemed so little precise, pronounced by one so eminent in his art, that it surprised somewhat and dissatisfied his inexperienced pupil. But Chomel was not then aware of certain antecedent factors which had brought about the ailments of his patient. The young fellow, in a state of destitution, had walked from Compiègne to Paris in two days, sleeping by the wayside at night, and nourishing himself with such refuse food as chance supplied. Under these circumstances the patient developed febrile symptoms, from the excretory products of his metabolism having accumulated in his system and disturbed it. But the day after his admission (and simply from rest in bed) he felt better; and the day following he was altogether well. Simple rest had enabled the muscular system and the constitution gene-

* "Lancet," June 25, 1887, p. 1295.

rally to rid itself of the proteid embarrassment resulting from the functional destruction of the tissues. His ailment was entirely due to "the fever of over-taxation" or "of over-exertion," brought on by accumulation in his system of material elaborated in excess and inefficiently (or inadequately) eliminated. Thus, a temporary poisoning of the system had lit up "the fever of prostration;" and hence the hesitating diagnosis of the illustrious physician which length of time cleared up.

This "fever of prostration" engendered by over-exertion is a very characteristic one, due to the proteid embarrassment which results from the functional disturbance of the tissues. In the process of fatigue, the weak link is at the junction of nerve with muscle, where we have an effect similar to that brought about by the action of curare and the result of degeneration.* The changes which take place (chemical and functional) although they cannot be actually seen, yet to some extent they can be measured, judged of and made out, or realised from their effects. The extent of the metabolism may perhaps be best appreciated from such records of experience as Mr. Maclaren, of Oxford, has given in his very interesting work on "*Training*."† "During a long pedestrian tour, exceeding nine hours daily (equal to a long march) with a knapsack of twelve pounds, the chest measurement fell from 41 inches to 39½ inches; the upper arm from 14½ inches girth to 13¾; the lower arm remaining unchanged at 12½. The lower limbs on the contrary, were vastly increased; the calf of the leg passing from 16 inches to 17¼, and the thigh from 23½ to 25 inches."

* Waller in "British Medical Journal," July 25th, 1885.

† Page 13, note.

Let us now analyse the conditions of M. Chomel's patient a little further in the light of more recent knowledge regarding the metabolism of the body. We know that certain medicinal agents are cumulative in their action, *e.g.*, *digitaline* and *strychnine;* so also do we know that "extractives" are similarly accumulative in the system after their elaboration. Let us suppose that in this given case the elaboration of the "extractives" and "alkaloids" in this young lad's body is represented by 10, and that their elimination is represented by 8; we have then a storing up or accumulation of these "extractives" to the extent of 2 per day of auto-infective elements. But suppose his walk had been much longer, and that it had extended over 20 days instead of 2; then instead of storing up twice 2, he would have stored up twice 20; and instead of a comparatively simple or mild attack of the toxic "fever of prostration" or of "febrile symptoms from over-exertion"—an auto-infective fever of short duration—he would have suffered from a febrile intoxication more complete, more persistent, and more serious. He would in all probability have developed a form of typhus, such as has been known to occur in soldiers on a long and harassing march, of which there are many instances in the European campaigns of the latter half of the last and beginning of the present century.

But in the typhus of armies another important factor (besides over-exertion) intervenes which must also be reckoned with, and that is the massing together of large bodies of troops, and all that must result from this. The noxious effects of air in places where many persons have been breathing, have been attributed hitherto to carbonic acid; but recent experiments con-

ducted by capable observers show that this is an error, or at any rate, an insufficient explanation. It has been found that air copiously impregnated with *pure* carbonic acid can be breathed with absolute impunity; but that air spoiled by the breathing of human beings contains small quantities of one or more extremely poisonous substances, which Du Bois-Raymond has named "anthropotoxine," and to which alone the noxiousness of air in unventilated rooms is due. The most recent experiments show that these poisons came from the lungs.* Hence the typhusation of one man by the many comes into play; and this having taken place, there is no reason why the subject in whom a fever is generated, may not communicate it to his neighbour. In this connection it is further worthy of note that an alkaloid resembling *atropine* in its action has been separated by Sonnenschien and Zuelzer from decomposing animal matter; and that this alkaloid has also been found in the bodies of persons dying from typhus fever.†

And further in relation to tissue waste it is not to be forgotten that the products of the functional activity of an organ are not only poisonous to itself, but may be poisonous to other organs. Thus the waste products of muscular activity gradually poison the muscle and prevent its contractions. *Lactic acid* which is a product of muscular waste is poisonous not only to muscle, but to some extent to nerves, while it also lessens the functional activity of the brain and produces sleep.

Making all due allowance, therefore, for the massing

* "Lancet," April 6th, 1889, p. 710.

† "Pharmacology and Therapeutics," by Dr. Lauder Brunton, p. 81.

together of men in large bodies, we may recognise how in this way the typhus of armies and camps may under special conditions originate *de novo* and spread, so that the men become poisoned by their own exhalations. "No less an authority than Virchow has endorsed the opinion that the poison of typhus can be brought into existence by the concurrence of such conditions as are here described. The late Dr. Murchison, of London, and Dr. Hudson, of Dublin, have maintained similar views."*

It is therefore scarcely possible to escape the conviction that there exists a morbid or pathological series of ailments which naturally lead from the simple form of "fatigue fever' or "fever of prostration" (such as after a long march) up to that of the more deadly typhus, which is thus the highest expression of the poisoning of the organism by itself or by contact with others under conditions such as are now referred to.† War and typhus fever have thus always gone together, and the military medical officers of former days were wont to recognise this form of typhus spontaneously developing itself in the continental campaigns. Its origin, they did not doubt, recognised prolonged fatigue, overcrowding, and privation generally as antecedent factors in its causation ; and they no more questioned its appearing spontaneously then its contagiousness. Observation and experience alike forced them to admit the view (once recognised as inconsistent) that such fevers might be at once spontaneous in origin and contagious as to propagation. The history of all typhus epidemics shows that it is essentially associated with overcrowding

* See Fagge's "Principles and Practice of Medicine," vol. i., p. 144.

† Dr. A. M. Brown, *loc. cit.*

and destitution, with the fouling of the air by the concentrated emanations of living bodies, so that the atmosphere became unfit for respiration from its closeness and pollution by aerial filth and overcrowding. These are the combination of factors under which typhus fever is generated. Its origin *de novo* thus reads as a progressive development especially in association with the putrefying products of animal exhalations and the excrementitious matters of diarrhœal and dysenteric cases, an origin strongly substantiated by more recent experience as well as by the records of campaigns and war pestilences long gone by, but which we can now read in a different way from heretofore, and interpret by the light of knowledge more recently acquired.

The idea that "the source of all typhus matter is to be looked for solely in concentrated human effluvia"—the idea that overcrowding in filthy and unventilated rooms affords the essential condition for the development of typhus foci and for the spread of the disease therefrom, has been completely borne out by the experience of all time.* The mode of origin of sporadic cases in the absence of any epidemic, and of outbreaks in public institutions and amongst isolated bodies of men, furnishes the more conclusive evidence of typhus arising *de novo*. The fever known as jail fever was undoubtedly typhus, and many observations show that it originated in the prisons from overcrowding and deficient ventilation. The prisons then became the principal foci whence the disease spread, and the story of the various "black assizes" (six in number), in which prisoners brought up for trial gave typhus to the

* Cheyne, "Dublin Hosp. Reports," 1818, vol. ii., p. 53.

judges, counsel, and jurymen, is full of pathological interest, especially, as Lord Bacon observed, "that the prisoners were not suffering from typhus themselves." The circumstances under which the fever appeared in jails and prisons in this country and on the continent were always the same, and to the exclusion of every conceivable source of importation.* On shipboard its origin *de novo* has a similar history; and with regard to war pestilences, its origin has invariably been due to overcrowding, with bodily and mental depression. It has also been especially noted that in many parts of the continent of Europe, where typhus never occurs in time of peace, it became epidemic in time of war. Similarly, it has originated in overcrowded and badly ventilated hospitals, and then it was originally described as "hospital fever" by Sir John Pringle, who published "Observations on Diseases of the Army," 1768.†

Down to the commencement of the present century no doubt existed as to the spontaneous origin *de novo* of typhus fever. Lord Bacon thus expressed his belief: "The most pernicious infection, next to the plague, is the smell of the jail, where the prisoners have been long and close and nastily kept, wherein we have had experience twice or thrice, when both the judges that sat upon the bench, and numbers who attended the business, sickened upon it and died." And the opinions of the great physicians of the past were to the effect that vapours were constantly being exhaled from the

* Murchison, "Treatise on Continued Fevers," 1st Edition, p. 106.

† A contagious fever similar to typhus has been known to occur amongst animals on board ships in which they were crowded in transit from England to America during the American War (Murchison, *loc. cit.*, p. 111).

human body—that such vapours were subtle, acrid, and offensive to the smell; when retained in the body it became morbid, and if re-absorbed by the body they were highly deleterious. If a number of persons, therefore, are long confined in a close place, not properly ventilated, so that they inspire and swallow with their spittle the vapours of each other, they soon feel its bad effects. Bad food, nervous depression, add to the misery, and soon the seeds of a pestilential fever arise, dangerous to themselves and to others; and once produced, the fever easily spreads by contagion.*

The connection between yellow fever and the dysenteric, and other discharges of the negro body, is only a part of that general connection between dysentery and typhus, which has so pronounced a history in famines and war pestilences. The subject is full of pathological interest, and requires more investigation, especially as to the connection between dysentery and other diseases such as typhus fever, and in relation to animal alkaloids. There is evidence to show that these diseases are sometimes vicarious—dysentery in the dark races, taking the place of typhus in the white man. The disease which carried off the miserable negroes in the crowded holds of the slave ships was dysentery and not typhus; but out of the dysenteric corruption and putrefaction typhus fever sprung: and there is much evidence to show that the active generating cause is some highly ammoniacal compound. The existence of ammonia in the blood has long been believed to account for the phenomena of typhus. Dr. Richardson has shown that ammonia introduced artificially into the blood "produces typhoid (or typhus-like) symptoms;"

* Grant (1775), quoted by Murchison, *loc. cit.*

and the late Dr. Murchison* sums up the argument, from his own personal extensive experience in the London Fever Hospital, in the following words :—

"In severe cases of typhus, not only is there reason to believe that the blood is ammoniacal, but the exhalations from the lungs and skin, and the discharges from the bowels, contain a large amount of ammonia. It is a common observation that a pungent ammoniacal odour is given off by the skin and lungs in typhus, while the presence of a large quantity of ammonia in the breath admits of actual demonstration. It has also been ascertained that the cases in which the odour is strongest, communicate typhus most readily to persons in health; and in many of these cases where the symptoms of typhus have supervened immediately on exposure to the source of contagion, and where we may suppose the poison to have been unusually concentrated, the affected persons have been conscious, at the time of exposure, of a most disagreeable odour, pungent, and ammoniacal."

Hence, we may expect to find the origin of typhus in some physiological disorder of the ammonia-producing function—some relation between the common aberration of the functions producing ammonia in health and the self-existent specific infective disease known as typhus. Its spontaneous origin may be in this way physiologically explained. The experiments of chemists show that ammonia is contained in the cutaneous exhalations in health, and minute traces of ammonia are constantly being exhaled in healthy respiration. And although the quantity may be much smaller than in typhus, it is probable that, when a large number of human beings

* *Loc. cit.* p. 114.

are crowded into a small unventilated place, the ammoniacal exhalations are much increased and concentrated, and that by this putrefaction typhus fever is generated. Here we have another example as to how the living tissue elements of the body itself play an important part in the elaboration of disease.* The first effect of over-crowding with no ventilation is to cause the respiration to go on in an atmosphere charged with impure carbonic acid; and it has been shown by experiment that even a small percentage of carbonic acid in the respired air is sufficient to leave a serious diminution in the amount of carbonic acid thrown off, and of oxygen absorbed, with the result "that those oxidating processes which minister to the elimination of effete matter from the system must be imperfectly performed, and that an accumulation of substances tending to putrescence must take place in the blood. Hence, there will be probably a considerable increase in the amount of such matters in the pulmonary and cutaneous exhalation."† The unrenewed air thus becomes charged, not only with carbonic acid, (which *per se* and pure has been shown by Du Bois-Raymond to be harmless), but also with organic matters in a state of decomposition, of which the chief product is ammonia. When we consider also the existence of compound alcoholic ammonias, and with their powers as poisons, we cannot fail to see how such or allied bodies may arise within the system, though we may not yet be able to trace the processes. These ammonias have a near co-relation to

* Surgeon-Major Dr. T. R. Lewis, *loc. cit.*

† Dr. W. B. Carpenter, "Human Physiology." Fifth edition, p. 301.

the cyanogen compounds—themselves derivatives of ammonia.*

The nominal quantity of ammonia contained in the breath is exceeded in other diseases besides typhus, a circumstance which may account for the spontaneous progressive evolution of typhus fever in unventilated hospitals under circumstances of crowding insufficient to generate it elsewhere; and also for the observation that a deteriorated state of the constitution predisposes to the development of typhus.

"From the present state of our knowledge, therefore, it seems not unreasonable to conclude that the disagreeable odour of the cutaneous and pulmonary exhalations of typhus patients, as well as the offensive smell generated by over-crowding are due to one and the same source, namely, some unknown compound of ammonia."†

It appears to me, therefore, that like erysipelas and diphtheria, the weight of evidence and of argument is in favour of the occasional *de novo* origin of typhus fever by "progressive developments," through as yet unknown and undetermined concurrent factors in the surroundings of the patient; his environment in the widest sense of the term, and that such *de novo* origin of these diseases does not exclude the possibility of their subsequent spread by contagion."‡

What is true of "fatigue fever" and of "typhus fever," is equally true as regards typhoid. Military

* "A Sketch of an hypothesis towards vito-chemical methods in Pathology and Therapeutics," by W. H. Pearse, Esq., M.D., in "Prov. Med. Journal," 1888.

† Murchison, *loc. cit.*, 116.

‡ "The Doctrine of Evolution in its application to Pathology," by W. Aitken, M.D., F.R.S., in "Glasgow Medical Journal" for 1886.

medical officers alike in India, in Egypt, and in the Soudan, have of late been convinced of its occasional spontaneous origin, as physicians in civil life have been not less convinced in this country. And we all know that under certain circumstances it *too* is contagious. Brieger obtained a small quantity of a poisonous base that he calls "typhotoxin" from cultivations of the typhoid bacillus, which yielded reactions different from the bases he had previously isolated from putrefying animal matter, and Dr. Dixon Mann has obtained a somewhat similar alkaloid from an enteric fever case.

Hence the existence of a typhoid, (as well as of a typhus) morbid or pathological series of ailments must be recognised—a series in which ordinary typhoid fever stands between the simple fever of over-taxation and orthodox typhus—and this vitiation of the system may be from without or from within. Auto-infection may start the epidemic or the inhalation of morbific organic emanations, of either of which we as yet know nothing, beyond the fact that whatever may be the source or combination of the etiological factors, the concurrence of their action is recognised in the stupor or τῦφος which is so characteristic of the clinical aspect of the patient, and which gives the name to this condition.

In connection with the formation and elimination of waste products, we may also notice (before leaving this part of the subject) that even here throughout the body there are most elaborate arrangements for removing waste products. In the muscles the fascia which surrounds them forms a pumping arrangement, because of the two layers of which it consists being separated from each other at each muscular relaxation and pressed

together at each contraction.* The lymph and the waste products which it contains are thus actually pumped out of the muscles at each contraction and sent onwards into the large lymph spaces and lymph channels, so that muscular action of itself alone removes waste products. At the same time the movements of the muscles of the arm and leg will also pump out blood from the veins sending it from the hands and feet and so pressing it onwards to the trunk. This was a well-understood physiological phenomenon in the days when bleeding from the arm was a usual practice in the spring and fall of the year; when the apprentice of those days requested the patient to manipulate the lancet case in his hand, or when he was made to twist about the pole or staff when barbers did the then conventional operation of blood-letting. The movements of the muscles, thereby secured, caused the blood to flow upwards through the veins, so that a full and satisfactory outflow into the basin† was obtained. The movements of the abdomen and thorax in the acts of respiration secure a similar pumping arrangement, by which any excess of serous fluid, which bathes the intestines and lungs, is pumped out of the peritoneal and pleural cavities by the action of respiration. These movements also indirectly influence the removal of waste products from the brain and spinal cord. They are further aided by the stimulus of mental activity, so that when the brain is *over* worked and the re-

* Ludwig's "Genersich," p. 53, Ludwig's "Arbeiten," 1870, in Brunton, *loc. cit.* pp. 250 and 332.

† The basin with its scooped out edge, and the pole or long staff with its painted bandage now remains as the barber's sign, reminding us that he was the phlebotomist of days long gone by.

spiration and muscular movements are *under* worked cerebral nutrition comes to be diminished by the imperfect removal of waste products from its substance. Its cells and fibres may be still further poisoned by the circulation within the vessels which supply them with blood full of noxious substances due to imperfect digestion and assimilation.

For all these conditions abstinence from food is the best remedy, and especially abstinence from alcoholic liquors. It is in the well fed who have little exercise and in whom inadequacy of the function of liver, kidney and other organs, generally prevail, that the symptoms of lassitude and sinking after meals are mostly seen, and which Dr. Lauder Brunton justly regards as a condition of poisoning, "both on account of the time of its occurrence during the absorption of the digestive products, and by reason of the peculiar symptoms, namely, of a sense of weight in the arms and legs," as if they were lumps of lead. These are symptoms which resemble the effect produced by a poison like "curare," the action of a paralyser or depressant of motor nerves or centres. The recent researches just referred to render it very probable that peptones are the poisonous agents in these cases—a conclusion confirmed by Dr. Lauder Brunton's observation that "the weakness and languor are apparently less after meals consisting of farinaceous food only."

So much for the clinical phenomena associated with the cumulative action of the unknown "*extractives*," the result of physiological metabolism.

Let us now consider the phenomena in relation to "*animal alkaloid poisoning*," that is to cases in which hypothermia predominates.

In Germany the typical condition is known by the name of "*botulism*," a form of poisoning which results from the ingestion of putrefying meats.

Such ailments of flesh or meat origin are in reality the products of dead animal matter. So long as the meat is fresh it may be wholesome; but if in process of putrefaction it ceases to be so, both Selmi and Gautier have shown that it is by reason of such putrefying meats containing cadaveric alkaloids—the "ptomaïnes"—that it becomes deleterious. Further, when a solution of peptone is treated with potash and ether, it yields a body which appears to be a volatile alkaloid, and if putrid peptone is treated in the same way a solid non-volatile alkaloid is obtained.*

But "ptomaïnes" are not only found in dead bodies, they are also found in the intestines by the decomposition of parts of its contents. They have been found in large quantities by Bouchard, both in the stools of persons suffering from diarrhœa or typhoid fever, and in normal fæces. They appeared to be absorbed by the intestine into the blood, and excreted by the urine, (see p. 54). Thus, they have been found by Bouchard in the urine, both in health and disease, and Bocci has shown that the human urine has a paralysing action on frogs like that of *curare* or of the "ptomaïnes," which Mosso and Guareschi have obtained from putrefied fibrine or brain.† Some time ago Dr. L. Brunton pointed out the resemblance between the languor and weakness which occur in many cases of indigestion, and the symptoms of poisoning by curare, and drew

* Tanret, "Comptes Rendus," xcii., 1163, quoted by Brunton, *loc. cit.*, p. 351.

† Dr. L. Brunton, *loc. cit.*, p. 351.

attention to the probability that the languor was due to the effect of poisonous substances absorbed from the intestine. These he considered to be probably peptones, but they may be "ptomaïnes," and whichsoever they may be, the function of the liver is of importance in preventing them from reaching the circulation. This large gland prevents the passage of injurious substances from the intestinal canal into the blood.*

Thus, the albuminoids seem to undergo the same changes in the intestine as they do in artificial putrefaction brought about outside the body, so that if the chyme is retained overlong in the small intestine, the aromatic products of albuminoid putrefaction will gather in excessive quantity; and these various aromatic products of the putrefaction of albumen are equally well obtained, whether it is set up by the addition of sewer-mud or of pancreas ferment.† The same series of changes may also be set up in putrid pleurisy, stagnating secretions of the bronchi, in pulmonary gangrene, and in balanitis. (Brieger). Thus also the system generally may come to suffer by absorption into the blood of such soluble products of decomposition as the "ptomaïnes" may supply, unorganised chemical substances poisoning the system. But, as it has been shown that the liver has a most important function, namely, that (amongst others) of destroying the poisonous properties of peptones and perhaps of "ptomaïnes," and other substances produced during digestion, and possibly also of the poisonous

* "Indigestion as a Cause of Nervous Depression," *Practitioner*, vol. xxv., Oct. and Nov., 1880.

† "General Pathological Anatomy," Ziegler, translated by Dr. D. MacAlister, vol. i., p. 276—281.

products of waste tissue, any combination of factors which interferes for any length of time with such normal functions as are exercised by this (the largest gland in the body) may prove rapidly fatal, or at any rate induce very serious ailments.

Tracing the origin of an epidemic of purging and vomiting among soldiers in the Punjaub, Surgeon Frith obtained from some suspected milk a crystalline substance of unpleasant odour and taste, which communicated similar symptoms to men and dogs. Pure milk after standing for two months yielded the same substance. So also C. Gram obtained from lactates of the bases of the ptomaïnes—from putrid meats when exposed to heat—poisonous results. These facts seem to illustrate the ready formation of poisonous ptomaïnes from milk.* "From partial decay cheese similarly sometimes acquires irritant properties, and will give rise to vomiting and purging, more or less violent, in those who have eaten of it. Pickled or tinned salmon, salted herrings, and even fresh mussels, are examples of articles of diet which have caused poisonous symptoms in those who have partaken of them. In 1856 Panum (the eminent professor of physiology at Copenhagen) showed that these effects were the result of some chemical poison (an animal alkaloid) developed in putrefying material. He subjected the fluid to prolonged boiling so as to destroy any living organisms, and on injecting it into animals the poisonous effects were still produced, though in a slighter form than from the unboiled fluid. Further, after filtering the fluid and boiling it for an hour, he evaporated it to dryness, then digested it with absolute alcohol, and

* The "Lancet," 1887, vol. i., p. 213.

treated the residue with boiling water. This watery extract also was poisonous."*

In looking therefore at the clinical evidence and symptoms of the action of the ptomaïnes and leucomaïnes, we must recognise in them the results of "Indigestion as a cause of nervous depression.† Sleeplessness, drowsiness, and languor, are the symptoms which are associated with such indigestion. It would therefore seem "that the vital processes are more readily arrested by the accumulation of waste products within the organs of the body, than by any want of nutriment to the organs themselves. We are now also completely alive to the important results produced by the absorption from the intestinal canal of poisonous matters introduced from without; but we are not yet sufficiently alive to the important results produced from absorption by the intestinal canal of substances generated in it by fermentation or imperfect digestion. We recognise the danger of breathing gas from a sewer, but probably we do not sufficiently realise that noxious gases may be produced in the intestine; and, being absorbed from it into the circulation, may produce symptoms of poisoning. And yet we know from recorded observation that such is the case, and that one at least of the chief components of sewer gas, namely, sulphuretted hydrogen, may be produced in the intestine. This gas, which is so readily recognised by its smell resembling rotten eggs, was found by Dumarquay‡ to be very quickly absorbed indeed from the intestine when injected into the rectum, and to be quickly ex-

* Dr. Latham's "Harveian Orations," 1888, p. 18.

† Dr. L. Brunton in "Practitioner," vol. xx., Oct. and Nov., 1880.

‡ "Comptes Rendus," ix., p. 724.

creted from the lungs, sometimes appearing to produce, during its elimination, an inflammation of the trachea and bronchi. This was especially the case when small quantities were injected, and it seems not improbable that the production of this gas in the intestines may have something to do with the bronchitis which is not unfrequently observed in connection with digestive disturbances. In cases of indigestion this gas seems to be not unfrequently formed, because persons often complain of the taste of rotten eggs in the mouth or in the eructations. Even in small quantities it is not improbable that it may exert a deleterious influence both upon the nervous system and upon the blood; for it is a powerful protoplasmic poison, somewhat resembling hydrocyanic acid in its action."* Butyric acid which is also formed in the stomach in some cases of indigestion, has been shown by O. Weber to be a powerful poison, acting chiefly on the nervous system.

"It seems probable, however," as Dr. Brunton observes, "that the substances, both gaseous and solid, formed in the stomach and absorbed from it, are upon the whole less poisonous in cases of indigestion than those which are produced lower down in the intestinal canal. We often find that patients are affected with severe gastric disorder without any affection of the nerve-centres, beyond the weakness produced by the inability to digest food; while in many persons the mere omission to evacuate the contents of the bowels at the usual time will lead to a headache in the course of the day . . . . . which it is quite possible may be due to the absorption of some of the elements of the fæcal matter itself." Nor do we know at present what may

* Dr. T. Lauder Brunton, "Disorders of Digestion," p. 240.

be the effects of the absorption of the various digestive juices themselves and the ferments they contain, of the bile, of the gastric juice and pepsine, of the pancreatic juice and pancreatine, and of the "succus entericus." That absorption of these juices takes place there can be little doubt. It has been demonstrated with regard to the bile that it is absorbed with great rapidity from the intestine, and re-excreted by the liver, so that it may not pass into the general circulation at all. Pepsine on the other hand finds its way in minute quantities through the liver, and has been discovered in various tissues of the body and in the urine. So also with the pancreatic fluid; but with regard to mere absorbed digestive fluids, Dr. Lauder Brunton has pointed out that "it seems not unlikely that the liver has got another function (besides those usually assigned to it) namely, that of preventing the digestive ferments from reaching the general circulation so as to act upon the tissues." If therefore this function should ever be in abeyance, then we may expect to have deleterious results. There is no doubt also that the products of intestinal digestion undergo very remarkable changes in the liver, as shown by the formation from them of very large quantities of "glycogen," a substance which does not exist in the products of the gastric and intestinal digestion which reach the liver. Under ordinary circumstances in health, nearly the whole of the sugar formed in the intestine and absorbed from it, is arrested in the liver, so that very little ought to pass into the general circulation to be excreted by the kidneys.

But albuminous substances, the products of intestinal digestion, and peptones also, occasionally make their

appearance in the urine, and the products of nitrogenous waste frequently occur in the form of lithates in the urine, any excess of which indicates some pathological condition, however trivial it may seem to be. These may also appear in the urine after excessive or violent muscular exertion, accompanied by profuse sweating, so that they may possibly represent some of the products of muscular waste. On the other hand they also may occur in the urine in large quantities after slight indiscretions in diet, although no muscular exertion has been gone through. They can then only represent the products of the imperfect assimilation of nitrogenous matters which ought to have been eliminated not in the form of urates but of urea. But as physiological experiment and observation indicate that the liver is the chief, if not the only part, of the body in the healthy state in which urea is formed, the old notion which connects the appearance of lithates in the urine with disordered function of the liver, is probably in a great measure a correct notion still. Their presence indicates defective assimilation, so that they may be accompanied by the formation of other substances which have a much more pernicious action. "Hence, the importance of the functions of the liver in reference to assimilation is now generally recognised; although for a long time this, the largest gland in the body, was considered to have no other function than simply to secrete bile." The greatest care appears to have been taken in the construction of the liver to prevent the bile coming in contact with the blood, or entering the general circulation; and the effect of bile acids circulating in the blood (as shown by physiological experiments) is to depress the functions of the spinal

cord, to impair and lessen the functions of the brain, producing drowsiness, ending in coma; and to weaken the circulation by paralysing the cardiac ganglia.*

Dr. Lauder Brunton has further shown that certain albuminous products of intestinal digestion and peptones occasionally make their appearance in the urine. Amongst the former is an albuminous substance not precipitated by boiling, but by *nitric acid in the cold.* This substance Dr. Brunton observed in the urine of a healthy man after he had drunk a large quantity of strong beef-tea at a draught on an empty stomach; and in examining the beef-tea a similar albuminous substance was found in it. In this case the albumen seemed to be so rapidly absorbed from the stomach or intestines, that it passed without change through the portal system into the general circulation, and thus reached the kidneys where it was excreted in much the same way as sugar would have been under similar circumstances.† Under certain conditions therefore, of impaired functions of the liver especially, beef-tea and such like products may be actually injurious, so that the products of muscular waste (which really constitute the chief portion of beef-tea or beef-essence), may under certain circumstances be actually poisonous, and to this poisonous property the stimulant action of beef-tea may be due in the first instance, and its administration, like that of alcohol, may in some cases be overdone, and the patient weakened instead of strengthened. "In many cases of nervous depression we find a feeling of weakness and prostration coming

* Wickham Legg, "Bile, Jaundice, and Bilious Diseases," p. 207-216, 217.

† Dr. Lauder Brunton, "Disorders of Digestion," p. 247.

on during digestion, and becoming so very marked about the second hour after a meal, and at the very time when its absorption is going on, that we can hardly do otherwise than ascribe it to actual poisoning by digestive products absorbed into the circulation." And from observation of a number of cases, Dr. Brunton came to the conclusion that the languor and faintness of which many patients complained, and which occurred about eleven and four o'clock, was due to the actual poisoning by the products of digestion of breakfast and lunch.

Since these observations of Dr. Brunton, experimental data have shown that the products of digestion were actually poisonous in themselves, so that Dr. Brunton's conclusions from clinical observation have been confirmed by experiments made in the physiological and pathological laboratories of Albertoni, of Genoa, and by Dr. Schmidt-Mühlheim, in Professor Ludwig's laboratory at Leipsic. By these observers it has been shown that peptones have the power of completely destroying the coagulability of the blood in dogs; and but little power in this respect over the blood of rabbits and sheep; and so far as experiments go, it would seem that peptones prevent the coagulability of the blood in carnivora and not in herbivora. Under Professor Ludwig's direction of experiments it has been found that when peptones are injected into the circulation by a vein, they greatly depress the circulation, so that the blood pressure falls very considerably; and when the quantity injected is large they produce a condition of sleepiness, complete arrest of the secretion by the kidneys, convulsions and death.

From these experiments it is evident that the normal

products of digestion may become poisons of no inconsiderable power; and that if, through inadequacy of organic functions they reach the general circulation in large quantities, they may produce very alarming, if not dangerous, symptoms.

Practically the nature of peptones has still to be investigated. It has been usual to consider them all as one and the same, out of whatever digestive ferment they may have come. But it is quite possible that the peptones differ as much from each other as different kinds of sugar differ.* Usually they disappear from the blood before it reaches the general circulation, and even in the portal blood before it reaches the liver, very little, if any, peptone is found; but it is not yet known where peptones undergo changes. Some regard the liver as the seat of their transformation, which may to some extent prevent any peptones from getting into the general circulation, which may have escaped transformation in the portal blood before reaching it (Brunton, Schmidt-Mühlheim, Albertoni).

Another phase of the clinical evidence and symptoms of the action of the ptomaïnes and leucomaïnes must be recognised in "the poisons formed from food, and their relation to biliousness and diarrhœa."†

The poisonous alkaloids formed from various sorts of proteid elements in food decomposition, produce symptoms and sensation of discomfort which are referable partly to the digestion and partly to the nervous system, and at periods varying from a few hours after the food which disagrees, or after it has been in use and con-

* Dr. Lauder Brunton, *loc. cit.*, p. 248.

† Dr. Lauder Brunton, "The Practitioner," vol. xxxv., August, September, October, 1885, also "Disorders of Digestion," p. 275.

tinued for several days. Eggs and milk when so continued in a monotony of diet, are thus apt with some to cause an unpleasant taste in the mouth, general discomfort and frontal headache; or after persevering in such diet for some two or three days, the appetite becomes impaired, the intellect becomes less clear, the conjunctivæ slightly yellow, headache sets in, and the discomfort may culminate in an attack of vomiting or diarrhœa—preceded or not by constipation, on account of which eggs and milk are popularly believed to be "binding" as to the function of defæcation. But although we do not yet know the bearing of these well known observations and popular beliefs on the pathology of disease, Dr. Lauder Brunton has shown that "the cardinal fact which results from all these researches is that the "proteid substances," such as albumen, fibrine and gelatine, which are themselves foods, become split up so as to yield the poisonous "*ptomaïnes*" or "*leucomaïnes*," and that such poisonous products may be brought about by the digestive ferments of the healthy body, or by the metabolism which goes on during the normal physiological processes of life. It also appears that these self-generated poisons vary not only according to the particular body which is decomposed, but to the particular ferment which sets up decomposition, to the temperature at which it occurs, and to the length of time it continues. The process may also be much modified by other factors, such as the quantity of moisture in the albuminous substance itself, or in the atmosphere generally; also by electrical atmospheric conditions, such as those which occur during or after a thunderstorm, when meat as well as milk often becomes "tainted" during the electrical

conditions, when "thunder" is said to be "in the air."*

Vomiting and purging are among the most characteristic symptoms of poisoning by the putrefactive alkaloids; but the most marked symptoms which the poisonous ptomaïnes and leucomaïnes produce (such as neurine, muscarine and choline) are salivation, diarrhœa and vomiting, dyspnœa, paralysis and death. They seem to stimulate the secretion of glandular organs, for along with salivation there comes a flow of tears, and the secretion of the bronchial mucus becomes more abundant and fluid as shown by the occurrence of moist râles within the chest. They also render the heart's beats slow and weak; and one of the most marked characteristics in the action of these poisons, is the effect of "atropine" as an antidote to them. Dr. Lauder Brunton regards paleness of the face as a symptom which indicates the presence of a muscarine-like poison—in addition to one like atropine, in which the skin is scarlet—the muscarine-like poison predominating. The existence of a muscarine-like poison is still further indicated by the presence of diarrhœa, alternating with constipation and colic; the pulse slow, small and almost imperceptible—a condition which Brunton considers typical of muscarine poisoning; while in atropine poisoning "the pulse is rapid from the complete paralysis of the inhibitory fibres in the vagus, which the poison produces.† "It is possible" therefore "that instead of there being two or more poisons having a partly antagonistic action, there may be only one having an action resembling atropine in some respects

* Dr. Lauder Brunton, *loc. cit.*, p. 279.

† *Loc. cit.*, p. 286.

and muscarine in others. In some cases of poisoning by fish, the symptoms have resembled those of poisoning by atropine; namely, dryness of the mouth, difficulty of swallowing, weight of the limbs, paralysis of the superior and inferior recti and of the oblique muscles of the eyes, as well as ptosis and paralysis of accommodation, dilatation of the pupil and double vision; but the pulse not quickened as in poisoning by pure atropine. The alkaloid obtained by V. Anrep from poisonous fish produces similar symptoms to those caused by the fish itself; and in like manner the alkaloid obtained from poisonous cheese (tyrotoxican) produces symptoms similar to those caused by the cheese. If these alkaloids were obtainable in a state of perfect purity we should be obliged to regard them as having an action similar to atropine in many respects, but differing from it in respect to their action on the pulse. But there are many vegetable alkaloids hitherto supposed to be pure, which have been shown recently to be mixed with others having a perfectly opposite action; hence we may regard it as propable that the symptoms of poisoning by sausages, fish,* cheese, and the like may be due to a mixture of the alkaloids.†

* Mackerel Poisoning.—*To the Editors of the Lancet.*

Sirs.—Referring to your note on mackerel poisoning, it may possibly interest some of your readers to know that fishermen have a saying that white mackerel is the best, then green, but that the red variety is poisonous. In Guadaloupe there is a red boned mackerel used as a rat poison. There are known and noted already upwards of seventy different kinds of food fishes, which within a few hours after their death are reported to undergo such decomposition in their bodies or flesh as to give rise to poisonous symptoms after being eaten by man. So convinced is the Russian Government of the importance of this question that it offers in 1894 a prize of 5000

In cases of poisoning by the ptomaïnes having a purely atropine-like action, the administration of physostigma either by application to the eye, or by subcutaneous injection is that which is indicated and which has been adopted in one case at least (Brunton).

The presence of choline, neurine, or muscarine, may be made manifest by the production of diarrhœa, alternating with constipation, in the presence of an antagonistic atropine-like poison. If, however, they are present alone, or singly, the symptoms most likely to be produced are salivation, vomiting, purging and collapse, according to the amount of the poison.

Atropine as a remedy has been found to do good in a case of muscarine-like poisoning from unwholesome food (Brunton).

Of the alkaloids isolated by Brieger from human cadavers in certain stages of decomposition two of them have been proven to possess a powerful physiological action. One of these when injected into the veins of guinea-pigs, or rabbits, appeared to affect the intestine alone; and to have no action on any of the other organs. It caused an enormous increase in the peri-

roubles (say, £500) for the best essay on the nature and cure of fish poisoning. None of the fish found in the Norwegian waters are poisonous. It has been stated that all living healthy fish swarm with bacteria in their blood and lymph, which bears out my own observations regarding the early and rapid rate of decomposition of even freshly caught fish. Hence I have long advocated that fish on capture should be immediately bled and gutted. The bleeding must, of course, take place before clotting; but British fishermen and fishmongers only gut their fish after clotting has taken place.

I am, Sirs, your obedient servant,

J. Lawrence-Hamilton, M.R.C.S.

Folkestone, June 8th, 1889.

† Dr. Lauder Brunton, *loc. cit.*, p. 287.

staltic action of the bowels, which lasted for several days and the continuous diarrhœa led to extreme weakness of the animals. The other alkaloid, which Brieger has named "mydaleïn," has a still more marked physiological action of much clinical interest, inasmuch as we find hyperthermia is amongst its symptoms. Its physiological action is specific. When a very minute quantity is injected into guinea-pigs or rabbits, salivation sets in, nasal secretion is increased, and a copious flow of tears occurs. The pupils become dilated, the vessels of the ear much injected, and the rectal temperature rises from 1° to 2° per cent. The pupils gradually dilate to the maximum and cease to react to light The coat of the animal becomes staring; and sometimes they tremble. Gradually the salivation diminishes, the respiration and pulse become slower, temperature falls and the animal recovers. Larger doses to the extent of $\frac{1}{13}$ of a grain (under half a centigramme)—are always fatal, and their action exceedingly violent.

Many, but not all of these symptoms occur in men in consequence of poisoning from decomposing food, or from disease; and it is possible that the occurrence of some symptoms and not of others may be due to the occurrence in disease of alkaloids allied to mydaleïn, although not identical with it, or to the presence of two or more alkaloids which partially neutralise each other's effects.*

Although, however, positive evidence may be as yet wanting as to the formation of alkaloids within the body; it is highly probable that a formation of alkaloids, such as has been described, does occur in the

* Dr. Lauder Brunton, *loc. cit.*, p. 289.

intestine, because it has been found that such alkaloids are formed in the freshly voided fæces. On this point we have further clinical evidence furnished by Dr. Lauder Brunton. "No one" he writes, "who has watched cases of acute disease, such as pneumonia, can have failed to see how a rise of temperature sometimes coincides with the occurrence of constipation, and is removed by opening the bowels. In the case of such an acute disease as pneumonia, one has hitherto been unable to say definitely why constipation should produce this rise of temperature, but it seems not improbable that it may be due to the absorption from the intestine of some ptomaïnes (or to the retention of some of the unknown extractives which ought to have been eliminated). In his work on "Purgative Medicines" also, Hamilton says that "in cases of typhus fever the administration of an antimonial remedy was beneficial only when it moved the belly. In this case the fæces were black and fœtid, and generally copious. On the discharge of these, the low delirium, tremor, floccitatio, and subsultus tendinum which had prevailed were abated; the tongue which had been dry and furred, became moist and cleaner; and a feeble creeping pulse acquired a firmer beat."

Bouchard has still further shown in his lectures on "Self-intoxication in Disease" that the poisonous activity of human fæces is very great even when they are quite healthy (see p. 10, *ante*). Since the first edition of this book was published, Sir Andrew Clark read a paper before the Medical Society of London, Nov. 14th, 1887, on "Chlorotic Anæmia" in which I am pleased to see that so distinguised an authority adopts and confirms the conclusions of Bouchard. In that paper he says

that it is "impossible to doubt that poisonous alkaloids are formed in the alimentary canal; that when excretion is seriously diminished, they must be in some degree absorbed; and that mixing with the blood, and entering the tissues, they must produce some sort of injurious effects determined by the rate of absorption and the amount absorbed."*

He further goes on to show that the treatment which most speedily and effectually cures chlorotic anæmia, is a treatment which by the use of tonic aperients produces full and regularly recurring action of the bowels. With the suspension of this treatment the disease recurs; with its resumption the disease again subsides, and no treatment appears to be permanently successful which does not provide means for securing daily relief to the intestinal canal. He then gives details of this treatment,† and records as the result of his extensive experience that were he limited to the employment of one sort of drug in the treatment of chlorotic anæmia, the drug he should choose for use would be an aperient.

That alkaloids are present in the circulating blood, is shown by the fact that they are separated from it by the kidneys, and are found in the urine; and according to Lépine and Guerin the poisons contained in the urine in different diseases differ in their physiological action. The extract obtained from the urine in cases of typhoid fever produced in frogs increased reflex action and death after three hours, the heart being usually found in a state of diastole. In cases of pneumonia the urine had a similar action, except that the

* "Lancet," Nov. 19th, 1887, p. 1005, also "Med. Soc. Proceedings," vol. xi., p. 55.

† *Loc. cit.*, "Lancet," p. 1005, and "Proceedings," p. 63.

heart was found in a more or less contracted state, varying with the severity of the case from which the urine and its poison had been obtained.

It has been stated that thrombosis in the puerperium takes place independently of septic influence. But it has been abundantly shown that the constitutional condition of the female after delivery is an exceptional one physiologically; and that there are sources of septic matter which arise in the patient's own system, from repressed secretion and other causes. An enormous quantity of effete matter is thrown into the circulation during the involution of the womb, and if this is not rapidly discharged, uræmia and fever result. Thus, thrombosis, as well as broncho-pneumonia, may set in. The puerperal blood highly charged with fibrine, and a noxious stuff capable of producing coagulation in the living vessels, are the factors necessary for the production of thrombosis.

Arrest of secretion thus plays a most important part in the induction of puerperal fever, so that meterological influences and conditions should in future be registered, together with the usual factors in the clinical records of puerperal diseases.*

Hence there appears to be little doubt that the amount of ptomaïnes formed in the body in disease is greater than it is in health; and very probably they are of a different character, possibly varying with the disease.† Their existence in disease can only be proved by searching in the cadaver for them, and by

* Dr. Robert Barnes in Meeting of Obstetrical Society, "Lancet," May 18th, 1889. See also "Science and Practice of Medicine," vol. i., p. 315, 7th edition, by William Aitken, M.D., F.R.S., 1880.

† Dr. Lauder Brunton, *loc. cit.*, p. 290.

the chemical examination of the excretions during life. "Although it may be admitted that the chances are against the isolation of a ptomaïne formed during life (*i.e.*, a morbid leucomaïne) and which has been the cause of death,* still until the attempt has been repeatedly made, the question can by no means be regarded as conclusively settled. Improved methods of investigation may accomplish what at present seems impossible."

Dr. Dixon Mann has for some time past investigated this part of the subject practically in the Toxicological Laboratory of Owens College; and has placed on record the results he obtained in a case of enteric fever, in which death occurred suddenly from perforation of the bowels during the third week of the fever. Following the process devised by Brieger, and which so far as his experience goes, yields the best results. Dr. Dixon Mann obtained fine needle-shaped and highly deliquescent crystals, whose forms and reactions established the identity of the body with *choline*—a ptomaïne common to all cadavers, and the first that appears in the usual sequence of post-mortem changes. So far he obtained no specific result. But he still further examined the residue to see if any ptomaïne of a special character, in relation to enteric fever, was present in it. He then obtained a quantity of fine colourless needle-shaped crystals, which gave certain reactions, which he describes, and which differed from those obtained by Brieger, with the substance he named "typhotoxin." Dr. Mann further experimented with a solution of needle-shaped crystals in water, by injecting a few drops under the skin of a guinea pig. The chief

* Dr. J. Dixon Mann, "Medical Chronicle," March, 1888.

toxic effects of this ptomaïne were motor paralysis and general insensibility, both of which supervened very rapidly. Examination after death showed the heart in dyastole, the bladder empty and contracted, and the bowels containing some mucus similar to that which was discharged after the reception of the ptomaïne. In a second case of the same disease the result was negative. (See also Luff in "Brit. Med. Jour.," July, 1889, p. 193).

Most of the alkaloids which have been obtained by the decomposition of albumen appear to belong to the leucomaïnes of the "muscarine" type; and to have a tendency to cause diarrhœa; but some appear to belong to the "atropine" type, which to a certain extent counteracts the effects due to "muscarine."

In the peculiar condition called "Kussmaul's coma," or "diabetic coma," we have another example of the self-infection of the system, or autochthonous evolution of disease by the formation of poisonous compounds within the body. It is an evolution, however, which is shown to be *not* peculiar to diabetes, but occurs in pernicious anæmia and in the typhoid states, presumably through some (as yet unknown) chemical decomposition occurring within the body, and affecting the blood or other fluids. It has been described under the name of "*acetonæmia*," in the belief that it is due to "*acetone*" in the blood. The condition certainly betokens a suddenly spontaneous self-infection process and usually a rapid death. The blood is pale and cream-like, or like grumous pus. It does not clot, but on exposure to the air it becomes pink and brighter in colour—of a magenta-like tinge. The microscope shows the creamy condition to be due, not to fat, but to the presence of

a large quantity of molecular matter, which does not dissolve in ether. The action of acetone on healthy blood is found to be similar.* The blood corpuscles break down into granular debris; and such destructive effects of acetone on the blood accounts for such symptoms as great dyspnœa and cyanosis; for the blood cells are so destroyed that they are no longer able to absorb and fix oxygen. In 1857 Fetters and Kaulich showed that acetone was developed in the blood of diabetics, as well as in chronic affections of the stomach and digestive organs, such as chronic gastric catarrh. The state of acetonæmia of various forms brings about great depression of the whole nervous system; and the source of the acetone is probably from the alcoholic and acetous fermentation of the grape sugar, and possibly of other organic matters in the stomach in catarrhal conditions.† Acetone has also been found in the blood and in the solid organs of patients dead of diabetic coma.‡ It has been found in the urine; and is often developed in the urine after it has been passed.§ Von Jaksch Penzoldt, and others, have shown that acetonuria is not peculiar to the diabetic condition but may occur in a variety of febrile states; and that there are grounds for believing that even the healthy organism may not be altogether free from *acetone*. It would appear from the researches of Baginsky, that amongst children a physiological acetonuria of slight degree and inconstant nature, does exist; that a pathological acetonuria is common

* "British Medical Journal" for 1878, p. 79, Foster and Saundby.

† Bechamp, "Compt. Rendus," 1872.

‡ Berti, "London Medical Record," 1874.

§ Foster, *loc. cit.*, and Kussmaul.

among children suffering from febrile disorders; and further, that the presence of acetone in the urine appears to be related directly to the intensity of the febrile process. But, as yet, we neither know for certain the place at which acetone originates, the materials out of which it is constructed, the precise effects on different tissues, nor its ultimate fate in the metabolism of the tissues. It appears probable, however, that nitrogenous disintegrations may be the source of this chemical body.*

In such blood poisoning there is great muscular feebleness; the pulse is quickened; and deep slow breathing is induced like that of alcoholic poisoning, followed by coma and anæsthesia. Suddenly the chronic poisoning takes on an acute form like *delirium tremens*,† when death speedily ensues.

In view of the extraordinary activity of some of these alkaloids—the ptomaïnes and leucomaïnes—we cannot wonder at the violent symptoms which sometimes occur after the use of tainted meat, nor even at the extraordinary poisonous action of eggs in some persons; and it is probable that the diarrhœa and vomiting which are characteristic symptoms of such poisoning may be due to the decomposition of the proteid elements of such kinds of food in the intestinal canal itself.

Thus it comes to pass that a typically morbid or pathological series of phenomena have been seen to follow the ingestion of various "animal alkaloids;" characterised especially by choleraic diarrhœa, vomit-

* "Lancet," vol. ii., 1885, p. 392, and vol. ii., 1887, p. 492.

† Ziemssen's "Cyclopædia of Practical Medicine," vol. xvi., *Art.* "Diabetes."

ing, cramps, algidity and the like, presumably induced by the "ptomaïnes" which have been elaborated from the articles of animal diet in progressive stages of decomposition. Hypothermia predominates in such cases, precisely such as may be observed in poisoning by tartar-emetic or arsenic. In cholera similar phenomena are characteristic, diminished temperature and algidity accompany the digestive troubles.

May we not therefore recognise in these affections the evidence of poisoning by a toxic alkaloid, or alkaloid of purifaction; and that certain nutritive ingesta may give rise to the formation of such toxic alkaloids? "Hence it is no great stretch of scientific license for us to recognise or trace in pathology a very natural series of morbid phenomena or ailments starting from the '*botulism*' of the Germans up to Asiatic Cholera."*

We are also justified in holding that there are in pathology a morbid series of ailments as legitimate as those natural series of things with which we are familiar in Chemistry, Geology, Palæontology, or Botany. Variation and gradation are the rule in Nature, alike in Pathology, as in other departments of Natural Science; and in recognising the fact that the "animal alkaloids" can be elaborated by the spontaneous physiological processes of life, I am once more brought to the conclusion I attempted to expound four years ago, namely:—that in facts such as I have detailed in these pages we have additional evidence that "The Doctrine of Evolution is capable of explaining the origin of some diseases."†

We must also ever keep in view the circumstance

* Dr. A. M. Brown, *loc. cit.*

† "Glasgow Medical Journal," 1885-1886.

that diseases are not "entities," but morbid processes which are more or less slowly developed in the course of physiological life; and to study them with success we must take that broad view of Pathology which fully recognises in its investigations "the never old, and the ever new." "It is not the fact that the human body is ever taken possession of by some seed-like principle, destined in the future infallibly to evolve the phenomena which receive certain names. Rather by these names we recognise the fully developed results of a complex chain of causes. The order of events which has in any given case ended in the production of such a malady, was one which might have failed at any point, or might have been broken by art. The right study of rare diseases will induce us to forego the search for *entities*, to disuse such terms as "*sui generis*," and find pleasure in the discovery of laws of relationship rather than divergence."*

But really there is nothing new under the sun. In this field of recent research which I have tried to open up to view in the preceding pages, and which I may have rashly described as new territory, I have only turned over a new leaf and opened up a new chapter in the Humoral Pathology of ancient days. In so doing we once more bring to the aid of the Medicine of the present day the Pathology of the past, as has been so often done before.† Humoralism we know is of very ancient date—old as the Grand Old Man of Cos; but it is still a fundamental principle in our healing art, which we are sometimes not only apt to forget, but to ignore.

* Jonathan Hutchinson, "Clinical Uses of Rare Diseases," "Lancet," May 18th, 1889, p. 974.

† Aitken, "Science and Practice of Medicine," 7th edit., vol. i., p. 40.

In the view I have endeavoured to expound as to the antecedent factors which may combine to produce disease we cannot fail to recognise a partial return to Humoralism, seeing that poisoning or auto-infection by soluble animal alkaloids is in reality poisoning by an organic liquid which has undergone deterioration;* and that from the chemical demonstrations of Gautier, the clinical observations of Peter, and the critical expositions of Drs. A. M. Brown and Lauder Brunton, Dixon Mann, and others, the doctrine of spontaneity is as true of health as of disease. Thus it is that our old traditional records of Medicine still continue to light up our path by brilliant gleams of truth. Many factors in the causation of diseases, and as influencing their course, have now to be reckoned with, which before were unknown; and even if they were known to exist, they were but little regarded; and now looking to the future we know not in what direction the next advance in practical and scientific pathology may be made.

Prior to the time of Haller, our masters in medical science, from mere observation, evolved a "Humoral" Pathology, which to them explained not only the cause of diseases, but also the cure of them, or the resulting death of the body.

In due course of time (great improvements having taken place in instruments of precision) clinical examinations came to be made more carefully and with greater accuracy. Hence the comparison of such carefully made clinical records gave rise eventually to those experimental methods which have so largely contributed to our knowledge of pathology, especially by continental pathologists; while legislation in this country has been

* Dr. A. M. Brown, *loc. cit.*

not less influential in hindering the progress of experimental pathology, and thereby obstructing the advance of medical science. Under these influences the cellular doctrines of Virchow came to be developed. The physiology of cell-growth by Schleiden and Schwan led up to this, and many a word battle has been fought over the cell-theory of disease. Bigger microscopes, with more powerful lenses, afterwards enabled John Hughes Bennett, of Edinburgh, to appreciate the importance of molecules, and a "molecular" pathology swept, for a time, the cellular pathology out of the field. The explanations of the processes of disease based on these theories appeared for the time to be conclusive.

But subsequent investigations with still more powerful lenses, fostered mainly by experiments on animals, and by micro-chemical tests, have recently led to the study of minute micro-organisms in the form of bacilli, bacteria and spores, so that a "bacillary" pathology at present holds the field, almost to the exclusion of all else. It recognises the causation of some diseases as of the nature of a parasitical influence. Professor Koch, of Berlin, is the leader of this new school, with Pasteur in France, Lister, Watson-Cheyne, Woodhead, Ogston, Crookshank, and many others in this country and abroad.

These observers teach that many diseases are now ranked as infective, through the agency of these micro-organisms, which were not so considered formerly; and also that each such disease has its etiological peculiarities demanding a prophylaxis, so special to itself, that the general prophylactic principles based on present knowledge as to the nature of infection, have come to require many far-reaching and comprehensive inquiries to be

made in directions altogether new, before we can arrive at a definite solution of the many sanitary and pathological problems involved.

The micro-organisms as causes of diseases seem to be as numerous and varied as the sands on the sea-shore; while their pathological domain has become so far-reaching in extent, that every form of infective disease seems bound to acknowledge some one or other form of microbe as the author of its being. But the only difference between these parasitic existences and those of former times (then believed to be equally potent) is that they are more minute, and require higher powers of the microscope to see them. This belief has given a great impetus to the improvement of optical instruments. Consequently also we have become aware of a greater number of minute and hitherto unperceived forms of parasitic organisms, some of which are set down as causes of certain forms of grave diseases. Hence these "bacterial" affections are very widely diffused. But, as yet, no one has succeeded in making out the manner in which such microbes act, or the causal relation which exists between them and disease. "The mere presence of such 'microbes' in the system cannot be described as disease. Disease only begins when, owing to the presence of 'the microbe,' changes take place in the tissues of the organism which induce disturbances in their functions; and the detection of 'microbes' in the diseased organism is but the first step towards the discovery of the cause of the disease and its mode of operation.* In other words the presence of a microbe can but suggest an inquiry into these antecedent factors which have combined to bring

* Ziegler, *loc. cit.*, pp. 1 and 2.

about the disease or the morbid conditions favourable to the development of the "microbe." There is a great gap still to be filled up in the interval between the concurrent factors in the physiology of life which bring about disease, and the stamps which are left by diseases as evidence of their having existed, whether these be of a microbial character or in the cruder forms of well-known morbid anatomical changes. It may even lie beyond the powers of the anatomist to follow the processes of morphological change or of molecular transformations recognisable only by the chemist, to whom a region lies exposed to his peculiar means of research, which is as yet unexplored.

Certain it is that molecular death precedes all evidence of the existence of the bacterial microbes; and hence their diffusion is enormously wide. Matters on which they grow and thrive are found everywhere; and therefore whenever dead organic substances are found, either in solution or with a certain amount of water, there also bacteria may be found. They are found in all waters, whether flowing or stagnant, in all liquids that can ferment or putrefy, and in all vegetable and animal tissues that are sufficiently moist. Organic matters, moisture and warmth go to favour their multiplication; and we cannot avoid swallowing numbers of them with our food, and inhaling them with our breath. Bacterial invasion of the system may thus start from the mucous membrane "*in special circumstances;*" and it is "*in these special circumstances*" that we must recognise the antecedent unknown factors which combine to bring about the disease, and contribute to the conditions favourable to the existence of bacteria. "They are unable to settle in a perfectly healthy body; they can

only develop when the physico-chemical constitution of the tissues is morbidly altered so as to correspond with their requirements."

On the one hand therefore the "microbes" must be endowed with certain vital properties of a special kind; and on the other there must be a predisposition of the system in a certain physico-chemical constitution of the tissues, so that the micro-organisms may find within the body, and in proper combinations, all the conditions necessary for their growth and development.

It has also been determined by experiment that very slight chemical changes in the constitution of a tissue are enough to determine whether a given "microbe" can develop in it or not. A local lesion yielding the poisonous products of tissue necrosis or of wounds is one of the commonest and most obvious alterations, but there are many other instances in which the antecedent factors are as yet beyond our ken, either from their apparent slightness, or because they are not such as our tests can yet discover. All that is necessary is that the "microbe" should reach a spot that affords the conditions for its development.

We are thus driven to the conclusion that at present the evidence regarding "microbes" tends to show that they are entirely *post hoc* in relation to the antecedent factors of any particular disease.

Nevertheless it has been accepted as proven, that the "virus" or "infecting stuff" of (at least) two infective diseases is a micro-organism; and that in cases in which this has not yet been accepted as absolutely proven, the rise and progress of them are so similar to those in which micro-organisms have been shown to be the virus, it is assumed that all the infectious diseases

are entitled to rank amongst these parasitic affections.

But accepting this position, the facts are not such as to exclude the possibility of some infective diseases being the result of a combination of factors in which micro-organisms have no special influence. Even with regard to anthrax—the disease of all others which has been absolutely proved to have a specific bacillus as its cause, there are some experiments which would seem to invalidate that conclusion. For example, it has been shown by Mons. P. Bert that compressed oxygen kills all living things, but that infective material in solution, such as scorpion venom, vaccine matter, whether liquid, or dried and re-dissolved, resist the action of compressed oxygen; and from further experiments he was led to infer that the active agent in vaccine and in glanders is not a living micro-organism. He also exposed anthracic splenic blood to the action of compressed oxygen; the blood retained its virulent properties intact, as proved by inoculation; but in no instance did the blood contain *bacilli*.

MM. Jaillard and Laplat likewise came to the following conclusions, namely:—(1) That anthrax is not a parasitic disease; (2) that the presence of *bacteridia* is to be considered as an epiphenomenon and not as a cause; and (3) that the fewer bacteridia the blood of anthrax contains, the more virulent it is. Hence cases of anthrax are described, some with and some without bacilli. While experiments abundantly prove that anthrax or splenic fever is an inoculable disease, those of Brauell, Bouley and Bollinger, prove that the micro-organisms found in the blood cannot be the carriers of the virus (nor the virus itself), seeing that the blood

not containing bacilli had been found to propagate the disease; that the disease may exist without the presence of *bacilli* in the blood; that such *non-bacillary* blood will induce the disease in other animals; and that even in such circumstances, organisms may develop in the blood of the inoculated animal, and be detected during life as well as after death. Bert subsequently concluded that the blood in splenic fever contains a toxic and virulent principle which resists the action of compressed oxygen.*

Generally it appears to me that the isolation of such a toxic principle as that first suggested by P. Bert, points to the generation of a contagion, which is the result of a living morbific process, and which may be explained by the presence of some autogenetic toxic agent circulating in the blood, and thus producing its specific effect on the tissues and blood.

The experiments of Onimus with dialysed blood also confirm this view; and that the really poisonous material is an albuminoid product not dialysable. As regards the propagation of disease by bacteria as the active agent, the so-called bacillary tuberculosis, typhoid of the pig, and recurrent fever, are all in the same category as anthrax from this point of view. It has therefore been inferred from such experiments that the virulence of septinous substances is not dependent on micro-organisms, but that septinous fluids, after filtration through porous porcelain, were still virulent. It has thus been concluded that a fluid which can retain its specific property after being filtered, boiled, evaporated

* "Comptes Rendus," lxxxiv., p. 1130, May, 1877. Also Lewis's "Memorial Volume," and Aitken, "Science and Practice of Medicine," 7th edit., p. 375, vol. i.

to dryness, and the residue digested in cold and in boiling alcohol, then redissolved, and again filtered, cannot owe its toxic property to living *organisms* of any kind.*

But more recent bacteriological methods, combined with micro-chemical investigations, have furnished evidence that various products of a poisonous nature are produced as the result of the growth of bacteria. From this point of view it may still be possible to reconcile the present conflicting theories as to the influence and relations of micro-organisms to disease. But the fallacies which beset bacterial methods of investigations are such that trustworthy conclusions are difficult to be arrived at.

The influences of life, of putrefactive processes after life has ceased, of the results of growing germs in living tissue, and in sterilised media, have all been used in drawing conclusions and in comparing results which are not comparable. To apply and compare conclusions derived from beef-tea, gelatine, and other dead organic infusions in the chemist's flask or test-tube, to the phenomena in living beings, is an obvious fallacy. The things have nothing in common, the factors are not the same, and the phenomena of decomposition or chemical change can never explain the phenomena of disease. This is one great fallacy which runs through much of the pathology which pertains to micro-organisms in relation to disease. It is only when the concurrent exercise of the functions which maintain life, ceases, that a chemical change at once begins; and until that change sets in (either locally or generally)

* Aitken, "Science and Practice of Medicine," 7th edit., p. 376, 1880.

the phenomena of putrefaction by the invasion of micro-organisms are impossible. Here another fallacy introduces itself, namely, the elevation of the germ facts concerned with putrefaction into a germ-theory of disease.

Pure cultivations of specific micro-organisms have been made with a view to ascertain the nature of resulting chemical products ; but whether the products thus obtained have or have not a chemical constitution identical with those formed by the agency of the same micro-organism when acting on living tissue is not known. Brieger obtained a small quantity of a poisonous base (typhotoxin) from cultivations of the typhoid bacillus, which yielded reactions different from the bases he had previously isolated from putrefying animal matter. He found that in some cultivations the quantity of typhotoxin was very minute compared with previous yields, and that in others it was altogether wanting. The temperature and the composition of the material in which the cultivations are made, exercise an influence on the results. When the cultivation of a micro-organism is considered to be successful, it must be at the expense of the organic matter used as soil, so that the pabulum on which it lives and is nourished, undergoes chemical changes. If then a certain product is yielded on one occasion and not at another, the inference is that its place is occupied by a different product. Hence the result is, to a certain extent, determined by the character of the material in which the micro-organism is cultivated; and so it remains doubtful whether identical chemical products are formed by the same micro-organisms in the living body and in artificial cultivations; and the

difference in physiological action between the actively toxic ptomaïnes obtained from recent cadavers, in which death had been caused by an infective disease, and the actively toxic ptomaïnes obtained from the putrifying cadavers of those who had died from non-infective diseases, points to a dissimilarity between some of the products yielded by pathogenic micro-organisms, as compared with those yielded by putrefactive bacteria; and that the actual toxic products obtained were not the result of mere post-mortem changes, but were the outcome of the disease from which the patient died.*

Dr. Mann further gives an instance in which Koch's comma-bacillus yielded on cultivation six distinct ptomaïnes, three of which were actively poisonous; and while two were probably specifically related to the micro-organisms, four were common to them and to the bacteria of putrefaction. Moreover, some highly important experiments made by Bocklisch† show that a certain bacillus may under altered conditions produce ptomaïnes of dissimilar chemical constitution and physiological action; and his experiments establish the possibility of the formation of highly toxic ptomaïnes by the combined action of disease and putrefaction, possibly through the micro-organisms.

In the first edition of this book I too strongly expressed myself as an unbeliever in any micro-organism being the sole cause of any disease. But there are exceptions; and I have had the advantage of practically studying and appreciating the evidence now at our disposal; and of coming to certain definite

* Dr. Dixon Mann, *loc. cit.*

† "Berichte der deutsch," "Chem. Gesellch.," 1887.

conclusions from personal observation, and to the exclusion of mere theory. I had long since ceased to believe in the powers of the microscope being able alone to differentiate the minutest micro-organisms of a like kind from each other. Microscopical differentiation is indeed oftentimes absolutely impossible; and I have seen that it is only by cultivation of the micro-organisms out of the body, by their careful isolation from tissues, and from other organisms, and by being able to demonstrate the same typical appearances through a long series of cultivations, carried on under certain definite conditions, that the differentiation of micro-organisms becomes possible. Artificially cultivated growths are thus capable of being compared directly, one with another, side by side; and it is only by such individual comparison that one is able finally to appreciate differences in form and general appearance of one growth as compared with another; to know that they are pure as to cultivation; to be able to place them in one or other class to which they may belong; and to broadly describe the physiological and pathogenic functions with which the micro-organism is likely to be endowed.

We are indebted to the distinguished bacteriologist, Dr. Koch, of Berlin, for thus pointing out the great importance and value of observing the general appearances, the modes and conditions of growth of micro-organisms, and that these points are of much greater value than mere microscopical and chemical characters. Then we have the very important canons laid down by Koch, by which we are able to determine whether any definite micro-organism is the sole cause of any disease. These canons are embraced in the

following conditions, which justify our regarding a given organism as the material cause—the *contagium vivum* of a given malady.*

(1) The malady must have such distinct and constant features, whether clinical or anatomical, as shall enable it to be identified.

(2) The microphyte (or micro-organism) must be itself distinguishable from all others by its size and shape, its staining properties, but above all by its mode of propagation in "a pure cultivation" (*i.e.*, artificial separation from other organisms) and by the form, colour and general appearance of the colonies it produces, and its mode of growth, both in plate cultivations, in tubes, and in drop cultures.

(3) The organism thus identified must occur in the blood or tissues, not merely on the surface (cutaneous or intestinal) but below the epithelium, in the lymph spaces or blood vessels, in every case of the disease in question.

(4) It must not occur in the human body except in cases of the particular disease in question. It may, however, conceivably occur in other animals, without giving rise to the same pathological symptoms, or in air or water, as of course it does occur in the test-tubes and plates of "pure cultivations," and in whatever media convey the contagion from one person to another.

(5) When a pure cultivation of the organism is introduced into the blood and tissues of an animal, the phenomena (clinical and anatomical) of the disease in question must be reproduced.

* Dr. Pye-Smith in 2nd edition of Fagge's "Principles and Practice of Medicine," vol. i., p. 22.

(6) From that animal a "pure cultivation" must be again capable of reproduction, from which another animal may be again infected, and so on.

These conditions in all their rigor I have seen satisfied in the case of anthrax; and with scarcely less abundant proof I believe they have been satisfied as regards relapsing fever, and in Malta fever.*

Under these canons it is now held to be indisputable that in certain forms of disease, definite micro-organisms do play the part of the exciting cause. It is therefore of importance to note the means which have been employed to arrive at this conclusion, so that the same principles may be employed in working out the investigation of other diseases with which micro-organisms are associated, but in which they are not yet proven to be the sole cause of the disease. The mere presence of a micro-organism in the body or in any of its cavities, is of no value whatever from an etiological point of view. Proof must be experimental in accordance with the above canons.

"But of late evidence has been accumulating from many various quarters, which almost, if not quite, amounts to proof that the contagia of certain infective diseases are *living* micro-organisms of extremely minute size. There is in the first place the fact that in at least two infective diseases—relapsing fever and anthrax—*the constant presence* of definite and characteristic organisms has been positively demonstrated. To these may be added tuberculosis, lupus, leprosy, Malta fever, and perhaps also glanders, erysipelas, gonorrhœa, and several forms of septicæmia in the lower animals and

* See account of Malta fever by Surgeon David Bruce, in "Practitioner" for 1888.

in man. But constancy of occurrence and experimental proof are not yet established, except as regards anthrax, relapsing fever, and Malta fever."

A micrococcus has been established on good evidence as the *contagium vivum* of *erysipelas*.

In *variola* and *vaccinia*, micrococci are present, but they have not been proved pathogenic by experiment. The same is true as regards *diphtheria*. In *pneumonia* several micro-organisms occur, but not constantly; and which, if any, is the true pathogenic organism, is still uncertain. The micrococci of gonorrhœa and of ulcerative endocarditis are probably pathogenic, but they are as yet less clearly identified, and the proof is incomplete.

The bacilli which have been found in enteric fever, measles, cow-pox, sheep-pox, ague and cholera, are still the subjects of controversy as to identity, constancy, and pathology. That of tubercle is believed to be constant, specific and pathogenic, but its relation to much of what is clinically and anatomically called tubercle in man is not fully established. Here the first of the above conditions is wanting.*

It is obvious, therefore, that we have not yet succeeded in tracing *all* infective diseases to micro-organisms; and it is possible that further researches may even modify the views now held by some with regard to the relations of the micro-organisms to diseases in which they are regarded as the cause. This is especially so in regard to the views now beginning to be entertained as to the relation of microbes to the generation of poisons by them.

Hitherto the microbe has been looked upon as directly

* Dr. Pye-Smith, *loc. cit.*

causing disease by its effects upon the tissue of the patient; but since chemical investigation has been applied to the processes of disease, and to the products of putrefaction and fermentation, and to the products resulting from the artificial cultivation of microbes in nutrient media, we must now look upon many of the symptoms which occur in consequence of the action of microbes as due, not to their direct action on the tissues, but to their indirect action in generating poisons; that they are, in fact, the active agents in the formation of ptomaïnes.

Thus, the researches of Koch, Brieger, and others, in bacteriology, have put the chemistry of putrefaction and zymotic diseases on an entirely new basis.*

Dr. L. Brunton, in co-operation with Dr. Alan Macfadyen, obtained important and interesting results, which show that bacteria liquefy gelatine by means of an *enzyme*, which can be isolated, and which will continue to act after the microbes have been destroyed; and like the ferments of the pancreas, this *enzyme* acts most readily in alkaline solutions. Bacteria seem to have the power of adapting themselves to the soil on which they grow, and of manufacturing a ferment suited to their needs; for the same bacilli when grown in starch paste instead of in gelatine or in beef-tea, produced a different ferment, which would convert starch into sugar, but would not act upon gelatine.

Similar results had been obtained by Bitter, who found that Koch's cholera bacillus produces in meat peptone, a peptonising ferment which is quite distinct from the bacillus itself, and which continues active after the bacillus itself is destroyed. Similar results

* Dr. Lauder Brunton in "Gulstonian Lectures" for 1889.

have also been obtained by Steinberg. Moreover, the microbes themselves may be destroyed by a temperature which does not destroy the activity of the ferment which they have formed—as shown by experiments of Bert and others (p. 67).

Dr. Brunton then proceeded to show the practical application of these results, as regards the relation of the ferments formed by microbes, to poisoning by meat, and to the prevention of disease from that source. It is shown that meat which has become tainted by the presence of putrefactive microbes, may possibly be cooked sufficiently to destroy the microbes themselves, while the ferments they have formed continue to decompose the meat and give rise to poisonous substances. "We can thus see how a cold beefsteak pie, or other cold meat, may become poisonous and produce serious symptoms, although the same food may have been eaten with impunity immediately after being cooked; for during the process of slowly cooling poisons may have been formed in the meat, although there may have been none in it immediately after it had been removed from the oven, and any microbes present were likely to have been killed by the cooking. The frequency with which meat, very slightly tainted, must be eaten in summer, and the common rule of not eating game at all until it is somewhat "high," as it is termed, makes one rather wonder why poisoning by ptomaïnes formed in such meat and game does not occur more frequently, although I believe that it occurs, in a slight degree, more frequently than people are generally willing to allow."*

In further explanation of the danger of diseased

* "Brit. Med. Journal," June 15th, 1889, p. 1336.

meat, Dr. Brunton refers to some interesting experiments by Bocklisch, which may explain the rarity of ptomaïne poisoning from this source. In experimenting with pure cultivation of *vibrio proteus*, better known as "Finkler's bacillus," he found that it did not seem to produce any poisonous substances, although it occurs in the dejecta of patients who have been suffering from sporadic cholera (*cholera nostras* or *cholera Europæa*), and is supposed to cause the disease. It occurred to him, however, that it is never present in the human intestine as a pure cultivation, and that possibly the presence of another bacillus along with it might cause the formation of the poisonous products in sporadic cholera. He therefore mixed some other putrefactive bacteria with it, and found that the mixed bacilli formed the highly poisonous *methyl-quanidine.*

In the same way it seemed not unlikely that cases of acute poisoning by meat or game may be due to the accidental presence of more than one kind of bacillus, leading to the formation of specially poisonous products. More especially is this likely to be the case if one of them is a pathogenic microbe which has already produced disease in the beast or bird yielding the meat, and a certain amount of decomposition of its tissues before its death.

The belief is now entertained by many that choleraic diarrhœa, Asiatic cholera, and typhoid fever, are all due to microbes, although bacteriologists may not have definitely settled the nature of the microbe in each case. In choleraic diarrhœa and cholera it is probable that a definite combination of more than one kind of

* Dr. L. Brunton, "British Medical Journal," June 22nd, 1889, p. 1389.

microbe acts to a great extent indirectly upon the organism by producing chemical poisons in the intestine.

With regard to cholera, it was pointed out by Dr. L. Brunton, in 1873, that the symptoms of cholera "are exactly those of muscarine poisoning, and most of the recent researches on the subject have tended to show that these symptoms are due to the action of a chemical poison which may act independently of the microbes which produce it. Lewis and Cunningham showed in 1874 that boiled cholera dejecta would still cause diarrhœa, although any microbe present in them must have been destroyed in boiling. Cantani and Klebs have also obtained symptoms of poisoning from sterilised cultivations of the cholera bacillus. Pouchet obtained an oily base belonging to the pyridine series from cholera stools, and Brieger got from pure cultivations of the comma bacillus in beef broth, in addition to the common ptomaïnes of putrefaction, two poisons which he regarded as specific products of the comma bacillus. But none of the poisons which have been isolated produce exactly the symptoms of cholera. In Cantani's experiments, tremor, prostration, spasms, and repeated vomiting were observed, while Klebs noticed muscular contractions and alterations of the kidney. The poison obtained by Pouchet irritated the stomach and slowed the heart, while one of Brieger's produced muscular tremor and cramps; the other lethargy, and feebleness of the circulation, with occasional bloody diarrhœa. These facts render it probable that the symptoms in cholera are not caused by a poison formed by the action of the comma bacillus alone, and it is evident that much more extended

investigation is required before the pathology of cholera is accurately understood."

"In all such investigations, too, one must bear in mind the possibility of the poison being formed not in the intestines merely but in the blood or tissues."*

So also with regard to typhoid fever, Dr. Brunton observes that "the symptoms do not point so much to the formation of a poison affecting the body generally, as to the local action of the microbes upon the intestine, although in some epidemics of typhoid the intestinal symptoms are but slightly marked, while bronchial irritation is very prominent. Whether this bronchial irritation is due to the action of a microbe or to a ptomaïne produced by it on the bronchial mucous membrane I cannot say."

With regard to other infective diseases, Dr. Lauder Brunton gives the following account of them, from the bacteriological point of view and in relation to animal alkaloids:—

With regard to *anthrax*, "various theories have been proposed as to the mode in which the anthrax bacillus causes death. One idea is that the bacilli, by aggregating together, block the capillaries and cause embolism; a second that they produce a ferment which decomposes the tissues; a third is that they give rise to one or more definite poisons. It is quite possible that all these theories may be, to a certain extent, correct, and that each of them may represent one factor in the production of the symptoms. The third of them is probably the most important, however, and the symptoms probably depend chiefly upon the

* See also Fagge's "Principles and Practice of Medicine," vol. i., p. 292.

formation of a poison. Indeed, Hoffa has obtained from pure cultures of the *bacillus anthracis* a ptomaïne which subcutaneously injected produces the symptoms of anthrax, and death; but it is not unlikely that the presence of a ferment may aid the anthrax bacillus in the production of a poison. Pasteur showed that the anthrax bacillus did not produce a ferment which was capable of causing the disease when injected, for by filtering the blood of animals suffering from anthrax through porous cylinders, and thus keeping back the bacilli, he obtained a filtrate which was inactive. In all probability, any ferment which the bacilli had formed would have passed through in the filtrate, and would have produced the ordinary symptoms after injection; but Nencki proved this in a way still more free from objection, for he inoculated gelatine jelly with anthrax bacilli. These liquefied the gelatine and fell to the bottom, and the clear liquid which remained above produced no effect on animals. Wooldridge, indeed, claims to have transmitted the toxic power of anthrax to vegetable albumen, organisms being absent.

"These experiments appear to prove that if the anthrax bacilli produce a ferment at all, that ferment is incapable of producing the disease. At the same time one must remember that after the injection either of the vegetable ferment, papain, or of sterilised septic blood into animals, Rossbach and Rosenberger found their blood swarming with bacilli. This observation seems to show that the ferment had rendered the blood more suitable for the rapid growth and multiplication of the bacilli."

The late Dr. Wooldridge found that when anthrax bacilli were cultivated in beef-broth, and the bacilli

themselves removed by filtration, the filtrate (containing as it did the products which they had formed during their growth) rendered an animal into which it was injected proof against anthrax inoculated afterwards.

Pasteur and Perdrix found that the blood of animals suffering from anthrax, when sterilised and injected into rabbits, appeared to protect them against subsequent inoculation.

In *puerperal fever* it is probable that the production of ptomaïnes in the tissues plays an important part, for Bourget isolated several toxic bases from the viscera of a woman who had died of this disease. This would not by itself prove that these poisons had been formed during life, and were not simply the products of putrefaction, but he also obtained from the urine of patients similar bases which were highly toxic, and killed frogs and guinea-pigs when administered by injection. The amount of poison in the urine was greatest when the symptoms were most severe, and diminished when the patients recovered. This fact appears to indicate a connection not only between the poison and the disease but between the gravity of the disease and the amount of poison.

With regard to *tetanus*, when animals are inoculated with matter taken from suppurating points or with the medulla of animals which have died of tetanus, the disease is reproduced, and on microscopic examination a bacillus has been found to be present. From pure cultivations of this bacillus Brieger obtained four poisons. The first, *tetanine*, produces tetanus in mice when injected in minute quantity. Another, which he has not named, also causes tetanus, along with a free flow of saliva and tears. Another, *tetanatoxine*, first

produces tremor, then paralysis, and lastly violent convulsions. A fourth, *spasmotoxine*, causes severe convulsions both clonic and tonic. This discovery of Brieger renders it probable that the convulsions in tetanus are due to the action of a poison, but we cannot at once assume that this poison necessarily circulates in quantities with the blood, especially as the flesh of animals which have died of the disease may be eaten with impunity. It is quite possible that it may be formed either entirely or chiefly in the nerve centres, and that only very small quantities of it pass into the general circulation.

From cultivations of *diphtheria* Roux and Yersin have obtained a soluble poison which may cause the symptoms of diphtheria in various degrees of intensity according to the dose. A large dose may cause rapid death, a smaller one may produce paralysis, ending fatally, while a still smaller one may cause only temporary paralysis.*

"This poison, however, is not a ptomaïne, that is, it is not of an alkaloidal nature. It appears to be rather allied to ferments, and is destroyed by boiling for ten minutes. The results of experiments already made render it hopeful that it may be possible by its means to confer immunity from the disease, but this is not yet certain."†

With regard to *hydrophobia* or *rabies* its virus is still unknown.‡ It is only presumed by analogy to be a

* Roux and Yersin, "Annales de l'Institute," Pasteur, 1888, Nos. 11 and 12.

† Dr. L. Brunton, *loc. cit.*, p. 1395.

‡ "Croonian Lecture delivered before Royal Society," by M. Roux on behalf of M. Pasteur, June 8th, 1889, "British Medical Journal," p. 1269.

microbe, which no one yet has been able to isolate. Nevertheless, the poison is daily being "attenuated" and made to pass through various stages of virulence. This is done through the inoculation of living rabbits, the virus being unable to be cultivated artificially in flasks or tubes. Thus, Pasteur has arrived at this conclusion, namely—that the active agent in preventing hydrophobia is a chemical substance (possibly formed by an unknown microbe) and upon this idea his plan of preventing hydrophobia is based.

Anrep says that he has isolated a ptomaïne from the brain and medulla oblongata of rabbits suffering from a severe form of rabies. This ptomaïne is very poisonous, and minute doses cause the earlier symptoms of rabies, while larger doses cause the phenomena usually observed in the later period of the disease. A gradual habituation of the animal to small doses of the ptomaïne produced a certain degree of immunity.*

The greatest source of danger from microbes is now believed to exist in the poisonous products which they manufacture; and it is in the artificial cultivations in flasks and tubes that the poisonous products of the pathogenic activity of the microbes are to be sought for.

It has been shown that many pathogenic microbes manufacture poisonous products. The microbes of typhoid fever, of Asiatic cholera, of blue pus, acute experimental septicæmia, and of diphtheria, all belong to this class.

It is therefore argued that in infectious maladies the cause of death is poisoning, and that the microbe is not merely the means of spreading infection, but it is also

* "British Medical Journal," Feb. 9th, 1889, p. 319.

the maker of the poison. On such facts the principle of protective inoculation by chemical substances rests.

"By introducing little by little into the bodies of animals these chemical substances produced by pathogenic microbes, such, for instance, as that of acute septicæmia, in such a manner as to avoid causing speedy poisoning, but so as to gradually accustom the animal to its presence, it becomes refractory not only to toxic doses, which would have originally caused death, but also even to the microbe itself; and the immunity which hitherto we could only give by the introduction of a living virus into the body we can now effect by the introduction of a chemical substance into the tissues, and these inoculable substances are exactly those which we have observed in infectious diseases as being the cause of death. In large quantities they kill, in small they confer immunity. These experiments on protective inoculation by means of soluble substances without microbes have been successful in various maladies, and we may be allowed to hope that their field of utility will become much wider."

The question now arises—has the animal, the recipient of a sufficient dose of these products, become refractory in consequence of their being present in the tissues, and thus preventing the growth of the microbe? Upon this point, while we do know that in cultivation the growth of certain microbes is arrested by the accumulation of the products which they form, we must carefully avoid forming a definite opinion as to what happens in the living body upon the basis of phenomena which have been observed to take place in culture tubes. For example, if we take a little blood from a sheep which has been rendered refractory to anthrax, and

place in it anthrax bacilli, they will grow there rapidly and abundantly, thus showing that there is in the blood of this protected animal no substance capable of destroying the life of the bacteria. This experiment is, of course, an extremely crude one, since from a chemical point of view there is an enormous difference between (living) blood while still retained in the living vessels, and the same blood drawn from the body and placed in a culture flask. If any positive result were obtained, it could only be from an absolutely enormous chemical change in the composition of the tissues.

But in addition to the chemical there is the physiological question to be dealt with, and M. Roux shows how by artificial necrosis of the tissue the virus of anthrax is able to gain a footing in a rabbit—an animal which by nature is refractory to this disease *if its tissues are sound.*

A distinction must now therefore be made as to (1) diseases which acknowledge as a cause agents devoid of life, which are essentially chemical—as are the *animal alkaloids* (ptomaïnes and leucomaïnes)—alkaloids found during the decomposition of animal matter, and also during the process of life—healthy and morbid—agents producing acute septic intoxication without the presence of a single micro-organism in the tissues, sufficient toxic material being developed on a large exposed surface, whence being absorbed, may give rise to the death of the patient, as occurs in cases of what used to be called hospital gangrene, where a large surface of suppurating tissue being established numbers of putrefactive organisms grow and induce septic poisoning. (2) Diseases which are also essentially chemical, but the agents of which act catalytically after the manner

of *ferments*, and which are therefore really *zymotic*. Such are associated with the presence of minute organisms, which in some cases are shown to be the cause of the fermentation—just as the *bacterium lactis* has been shown by Lister to be the active agent in determining the lactic acid fermentation on souring milk.*

Pasteur has shown that alcoholic and butyric fermentation acknowledge a similar agency. Other examples are the *micrococcus urinæ*, causing the ammoniacal fermentations of urine, and the micrococcus in putrid meat and fish to which phosphorescence-like appearance is due, and forming aërobic zoogloœa. That putrefaction is set up by organisms, is demonstrated by Lister's method of treating wounds, seeing that the discharges from them remain sweet so long as the organisms which induce decomposition and fermentation can be excluded by the appropriate dressings and antiseptics. Septicæmia is an example of a zymotic disease from this point of view.

The *chromogenic micro-organisms* are characterised by their power of producing colours of various hues. They are all aërobic, and only produce pigments when in free access of air. Transplanted specimens always produce the same pigments.

The *pathogenic micro-organisms* are those associated with disease.

The physiological effects of the micro-organisms have been classified by Flügge as (1) *septic* or putrefactive, (2) *zymogenic* or fermentive, *chromogenic* or pigment-forming, and *pathogenic* or those productive of specific infective diseases.†

* "Pathological Society Transactions," 1877.

† "Fermenti und Micro-parisiten," Leipzig, 1883.

Whatever may be proved to be the relation of these micro-organisms to the production of chemical and poisonous products, as the result of their life in artificial cultivations, or in the living body—the researches of Selmi, Gautier, Peter, Brieger and others, amply explain the formation of poisonous animal alkaloids, and of still more poisonous extractive compounds —the *x*, *y*, *z*'s of morbid anatomy and pathology— by means alone of the physiological processes of life within our bodies which are continually at work, as explained in the previous pages. They show us that the living being is constantly manufacturing in his own tissues, agents which can produce disease and even death. Hence it must be admitted that "the living tissue elements of the body itself play a much more important part in the elaboration of septinous and allied poisons than what has been of late ordinarily ascribed to them;* and neither have we "yet grasped the infinite potentialities of molecular energy, which must play so great a part in pyrexia, in living function and in growth.† How very interesting then becomes the study of the "animal alkaloids" and the "extractives" in their chemical, toxical, and pathological relations; and particularly of the "leucomaïnes" and the "extractives" as they are found in the urine. Their variations in quantity and quality in that excretion as indications of varying conditions of

* T. R. Lewis, M.B., "Microscopic Organisms found in the Blood," Calcutta, 1879, p. 57, also, "Memorial Volume of his Collected Works," published by subscription and sold by Mr. H. K. Lewis, London.

† "A sketch of an hypothesis towards vito-chemical methods in Pathology and Therapeutics," by W. H. Pearse, M.D., Prov. Med. Journal, 1888.

health and disease call for the most searching methods of investigation with all the modern appliances of the day.*

To my friend and colleague, the late Professor de Chaumont, I am indebted for the following method of determining (approximatively and by exclusion) the specific gravity of the "extractives" and other solid constituents of the urine, which he kindly allowed me to publish in the first edition of this work.

The results are interesting and instructive, inasmuch as when the calculations from the daily amount of urine are regularly worked out and compared day by day, the method of thus estimating the constituents that go to make up the total solids and specific gravity furnishes an excellent check upon the chemical analysis.

Professor de Chaumont's method of procedure is as follows:—

1. Collect measure and record the total quantity in cubic centimetres of the urine passed during twenty-four hours. Let it be 1850 cc.

2. Note its specific gravity. Let it be 1023.

3. **Chlorides.**—Determine their amount by noting how many cubic centimetres of standard nitrate of silver solution are required to precipitate the *chlorine* in 1 cc. of urine. The result multiplied by 1·65 (chloride of sodium) gives the amount of chlorides, seeing that each cc. gives one of chlorine.

If, for example, 1 cc. of this urine took 5·4 cc. of standard nitrate of silver solution, that multiplied by 1·65 gives 8·91 of chlorides per 1000 cc.

* See also Parkes "On the Urine"—a book which ought to be republished by the New Sydenham Society. No other book on the urine surpasses it in the scope, accuracy, and care with which the observations have been made.

4. **Phosphates.**—Similarly 50 cc. of this urine took 16 cc. of uranic nitrate standard solution, equal to 1·6 of phosphoric acid per 1000, which multiplied by 2 gives 3·20 as the amount of phosphates.

5. **Urea.**—Similarly 10 cc. of this urine took 20 cc. of mercurial solution which is equal to 20 of urea per 1000.

6. **Glucose.**—10 cc. of Fehling's solution took 4·2 of urine, equal 11·9 per 1000.

Dr. de Chaumont further calculated that the *chlorides* in solution give (by experiment) 8 degrees specific gravity for every 10 parts per 1000; that *phosphates* give about 4 degrees for every 10 parts per 1000; that *urea* gives 3 degrees specific gravity for every 10 parts per 1000; that *glucose* gives 4 degrees specific gravity for every 10 parts per 1000; the sulphates give about 5 degrees; and the sulphates may be assumed to be about half the amount of the phosphates.

Therefore make all these several multiplications; add up the results and find the difference between the total and the excess of the specific gravity over 1000.

Amount of Chlorides	8·91 × ·8	= 7·13
,, ,, Phosphates	3·20 × ·4	= 1·28
,, ,, Sulphates	1·60 × ·5	= 0·80
,, ,, Urea	20·00 × ·3	= 6·00
,, ,, Glucose	11·90 × ·4	= 4·76
	Total 19·97	=

specific gravity due to solids less extractives.

The specific gravity of the total urine was found to be 1023, then 23·00—19·97 = 3·03 = the residue of the

specific gravity which may be taken as representing the *x*, *y*, *z's* (the unknown extractives). In these extractive matters recent investigations have discovered powerful poisons.

Assuming these to be at least equal to the weight of the *glucose* or other extractiform material, namely, 4 degrees specific gravity for 10 parts per 1000 of weight, dividing that residue, therefore, by ·4 will give the weight of the *x*, *y*, *z's* (the unknown extractives) approximately. Therefore 3·03 = residual specific gravity divided by ·4 = 7·58 per 1000 to be added on to the weight of the other things per 1000, thus giving 53·19 as the total solids per 1000.

The daily products would then appear in the following tabular form :—

Urine (June, 1887) = 1850 cc., specific gravity, 1023.

	Per 1000	Sp. Gr.	Total in 1850 cc.
Chlorides	8·91	7·13	16·48
Phosphates	3·20	1·28	5·92
Sulphates	1·60	0·80	2·96
Urea	20·00	6·00	37·00
Glucose	11·90	4·76	22·01
Extractives	7·58	3·03	14·02
Total Solids* . .	53·19	23·00	98·39

* There is a source of error (not material) namely, that no allowance has been made for precipitated uric acid, as urates.

$$\text{Ratio of solids to specific gravity} = \frac{53{\cdot}19}{23} = 231.$$

The recognition of toxic urine in relation to surgical operations "on the urinary organs," is of great practical importance.*

Mr. Harrison, of Liverpool, has shown that the rigors and fever which sometimes attend catheterism and internal urethrotomy, are symptomatic of poisoning rather than of shock—of poisoning by material furnished directly from the urine. Free-flowing healthy urine may be regarded as absolutely innocuous; so that when it makes its way over a fresh cut surface, or out of a cavity, just as fast and uninterruptedly as it flows over or in it, it need cause no apprehension. On the other hand, when pent up in a wound or cavity, it is apt to be speedily converted into a most destructive poisonous agent. Urine-fever is thus easily set up by catheterism and by the operation of internal urethrotomy. The decomposing urine, or otherwise morbid urine, provides septic material of a kind sufficient to cause the urinary fever; and in illustration of this point the researches of Dr. Bouchard, at the Hospital Lariboisière, on "Toxic Urine," are of much interest; and at p. 256 of the Review, Mr. Harrison gives the following digest of Dr. Bouchard's papers, which were presented to the "Société de Biologie" in 1882.

In these papers Bouchard showed that alkaloidal substances were constantly present in the urine in certain infective disorders, and that these alkaloids

* Reginald Harrison, F.R.C.S., Surgeon to Liverpool Royal Infirmary, and Lecturer on Clinical Surgery in Victoria University, in "Liverpool Medico-Chirurgical Journal," vol. vi., p. 251.

were of intestinal origin.* That is to say, they were substances produced in the intestinal canal, and were analogous to the ptomaïnes. Subsequently these alkaloids were found to be present in normal urine. Dr. L. Brunton looks upon much *indican* in urine as an indication for a mercurial purgative. It shows that bacteria are active in the small intestines, and that albuminous matters are undergoing rapid decomposition there.† Bouchard found the same alkaloids present in the fæces; and he divided them into two groups:—(*a*) Those soluble in ether, and (*b*) those soluble in chloroform. He found that when present in large quantities in the fæces, they were also present in proportionally large amount in the urine. The following are his conclusions:—

(1) In health alkaloids exist in the living subject. (2) These alkaloids arise in the intestinal canal, through the action of putrefactive intestinal organisms. (3) The alkaloids of normal urine represent a practical part of these intestinal alkaloids, absorbed by the intestinal mucous membrane, and excreted by the kidneys. (4) Diseases augmenting intestinal alkaloids, augment *par consequence* the urinary.

In his next paper‡ he determined experimentally the effects of normal urine on rabbits, and found that the same doses produced different effects according as the individual furnishing the urine was in health or not; also that the *toxicity* varied in different individuals,

* "De l'origine intestinale de certains alkaloides normaux ou pathologiques," par Ch. Bouchard. "Rev. de Med.," 1882, tome ii., p. 825.

† "Gulstonian Lectures," 1889, *loc. cit.*

‡ Recherches experimentales sur la toxicité des urines normales, "Comptes Rendus," 6 Dec., 1884.

that the symptoms depended on several distinct substances. He proved that the symptoms were not due to the water of the urine, nor to the urea, uric acid, creatin, salts or volatile matters. Further, he showed that the alkaloids soluble in alcohol differed in their effects from those insoluble in alcohol; and that although there might be five or six different substances present, they could symptomatically be arranged in two groups—a convulsive and a narcotic; and he concluded that the symptoms in different cases of uræmia might be explained by these groups being present in the blood in varying proportions.

More recently Bouchard has brought forward some further facts with regard to the urinary alkaloids and their properties.* He defines a *toxic* or a unit of poison as that amount of poison required to kill one kilogram of living matter, *e.g.*, of rabbit. The *urotoxic* is that quantity of urinary alkaloids capable of killing a rabbit weighing one kilogram.

The symptoms of urinary toxæmia produced by introducing urine into the veins of a rabbit, are in the order of their occurrence:—(1) Contraction of pupils. (2) Acceleration and diminished amplitude of the respiratory movements. (3) Increase of urine. (4) Fall of temperature. (5) Diminution and final abolition of reflexes. (6) Convulsions usually with coma; and (7) death. The action of the heart and the electro-contractility of the muscles persisting for a time after death.

* Sur les poisons qui existent normalment dans l'organisme et en particuliere sur la toxicité urinaire, "Gazette Hebdomadaire," Avril, 1886; "Sur la variations de la toxicité urinaire pendent la veille et pendent la sommeil."

The fall in the temperature is due not to increase in the loss of heat, but to diminution of heat production. The urotoxic co-efficient in man is ·465; in other words, for each kilogram of body weight enough poison is excreted in twenty-four hours to kill ·465 grammes of living matter; or in two days and four hours a man excretes enough to kill himself.

During eight hours, if asleep, only from one-quarter to one-half as much poison is excreted as during the same period when awake. If the day be divided into three periods of eight hours each, the proportional quantities of poison excreted are:—Asleep, 3; early waking period, 7; late waking period, 5. The urine after sleeping and waking hours also differs qualitatively as well as quantitatively.

The alkaloid of the urine of sleep is *convulsive*, that of the waking urine *narcotic*.

The urinary poisons of the sleeping and waking hours are not only different, they are physiologically antagonistic. Fasting increases the toxicity of the urine, probably because then the individual lives on his own tissues; and these are relatively more difficult of oxidation than the ordinary food, and are less completely oxidised. Labour greatly diminishes the toxicity of the urine, so does also the breathing of compressed air.*

When we consider how many conditions influence the nature of the products of albuminous decomposition, we cannot be astonished to find that very different substances have been obtained by different experimenters.

* Influence de l'abstinence dutravail musculaire, et de l'air compriné sur la toxicité urinaire, "Gazette Hebdomadaire," le 19 Mai, 1886.

The chemical operations required to isolate the different products are so complicated and laborious that most experimenters have been satisfied with obtaining "extractiform bodies," and have not as yet attempted to crystallise them.*

A question has also arisen with respect to the actively toxic products obtained from the bodies of patients dying from specific diseases, namely:—What relation have the toxic alkaloids so obtained, to the diseases from which the respective patients have died? Physiological experiments have shown that actively poisonous cadaveric alkaloids (ptomaïnes) have not been found in *recent* animal tissues, so as to be isolated in the crystalline form as definite chemical products. The physiological product *choline* is the only basic product found within 24 to 48 hours after death (Brieger and Dixon Mann). No actively toxic base has been obtained in this early post-mortem period—a fact of great importance in a medico-legal point of view. No basic product occurs at this early period, which can be confounded with any vegetable alkaloid administered criminally. *Choline*, which is but feebly toxic, is not found after putrefactive changes have been in progress for about a week; and with its disappearance the actively poisonous ptomaïnes begin to form—the outcome of advanced putrefaction, for the formation of which the access of oxygen is necessary.

Alcoholic extracts, prepared from recent animal tissues, contain many physiological products, some of which have more or less toxic properties. Many ptomaïnes are toxic when impure (extractives), but lose their poisonous properties when freed from other pro-

† Dr. Lauder Brunton, *loc. cit.*, p. 281.

ducts; so that comparatively few of the *pure* crystalline cadaveric alkaloids are actively toxic (Dixon Mann). These facts point to the existence of other substances which as yet have not been identified; and Dr. Dixon Mann is inclined to believe that some of these products are volatile; because, in the early stage of the operations, when working at the isolation of the ptomaïnes from the organs of patients who had died from infective diseases, he experienced the peculiar effects of drowsiness, lassitude and mental depression, characteristic of such poisoning.

The key to the question of identification of the pathogenic ptomaïnes is to be found in (1) chemical constitution; (2) physiological experiments. In the latter investigations it is necessary to recognise the obvious difference between the introduction of a lethal dose of a ptomaïne into the circulation of a healthy animal; and the gradual accumulation and progressive action of morbid leucomaïnes developed in the course of disease. Another difficulty complicates the judgment arising from the unequal susceptibility to the action of ptomaïnes that has been proved to exist amongst various kinds of animals; and a still greater difference probably exists betwixt animals and human beings.

The physiological experiments, however, demonstrate on the one hand, the strong lethal potency of animal alkaloids obtained from bodies dead from infective diseases; and on the other a distinct difference in physiological action between these products and the actively toxic ptomaïnes obtained from putrefying animal tissues—differences which are not the result of post-mortem changes.

To determine the presence, the nature, the physio-

logical effects, and the place in Pathology of the "ptomaïnes," the "leucomaïnes," and the "extractives," is a difficult investigation, because of the tedious and prolonged chemical processes that are required, and the subsequent experiments on the products.

The main difficulties are these:—(1) It is obvious that the newly formed substances being antagonistic to life, as soon as a lethal amount has been formed, death results. If the substance is very active, the quantity necessary to cause death will be small, and being distributed throughout the organism, will be difficult to isolate. (2) These alkaloidal bodies are very unstable, and the means taken for their identification, unless great care is exercised, may hasten their transformation into other combinations of a totally different nature. (3) The post-mortem changes which intervene ere the investigation can be commenced, tend to complicate matters by introducing other chemical changes, and possibly destroying the identity of the combinations previously formed. In the face of these difficulties it has hitherto been deemed futile to attempt to demonstrate, in the dead body, the presence of pathological animal alkaloids (*i.e.*, morbid leucomaïnes) supposed to have been formed before death.*

Nevertheless the influence which chemistry has exerted on the Science of Pathology during the past 50 years, cannot be overrated, and points to the conclusion that the microscopist must give way, and share or divide his work with the chemist. The processes of chemistry are now far in advance of microscopical revelations, so that henceforth the results of microscopic work, especially as regards micro-organisms, must be more

* Dr. Dixon Mann, *loc. cit.*

controlled or checked by the chemist than they have hitherto been. Hence it is by chemical, combined with biological and bacteriological methods, that we must look for the discovery of the many factors in the causation of diseases, and for the power of preventing or removing diseases. The physiological symptoms of the infective diseases appear to be thus far traceable to definite chemical compounds, to animal alkaloids; and that to the action of such poisonous compounds during life, the special characteristics of the disease are to be traced. For it has been shown that disease can be communicated by such poisons in the entire absence of living micro-organisms.

"Scientific missions inspired in the interests of 'germ pathology' have visited India, Egypt, and Southern Europe, in the quest of a specific microbe for cholera; but they have all signally failed. Dr. Koch, the chief of one of them, thought he had found the pathogermic entity of cholera; but, confronted and constrained by facts, this eminent bacteriologist has felt himself obliged to admit that his 'comma bacillus' does not directly engender the disease; but that it may do so indirectly by the intervention of a 'ptomaïne' which it is supposed to secrete. But this implies two suppositions, namely:—(1) The existence of a specific bacillus which has not yet been discovered;* (2) the supposition merely of the secretion of a 'ptomaïne' by that bacillus which is just as far from being demonstrated, as already explained."†

* Dr. A. M. Brown, *loc. cit.*

† Transactions of a "Committee convened by the Secretary of State for India" to consider a Report by Drs. Klein and Gibbes entitled "An inquiry into the etiology of Asiatic Cholera," July, 1885. Also Dr. Lewis in "Lancet" of Sep. 20th, 1884, p. 513.

The attempt to reproduce the disease in animals by inoculation or otherwise by the supposed specific bacillus has failed; while the experiments and observations hitherto made leave the question of the genesis of the disease quite unsettled.* At the same time "while some of the points of contention regarding microbes appear to be proved, others are only probable, and they are neither universally nor unconditionally accepted. The exclusively causal agency of bacilli in the diseases with which they have been associated, although extremely plausible, is not conclusively proved (except as regards anthrax and relapsing fever and Malta fever); and a great number and variety of experiments of contrast are yet needed to satisfy a just scepticism, surrounded as the investigations are by the many fallacies, to some of which I have referred."†

Another feature of these microbes which warrants continued scepticism as to the powers of the microscope to differentiate them is brought out very conspicuously by the attempts to photograph them, namely:—That they are all so much alike that no sufficient distinguishing features exist amongst them for differentiation. Their family likenesses are strikingly similar; "and the results of photography are so unsatisfactory, that even Koch has abandoned it in lieu of accurate drawings made in the usual way."‡

The direct advantage of the scientific missions avowedly sent to discover "something" is very much

* "Special Pathological Anatomy," by Ziegler and Dr. D. Mac Alister, p. 290, Macmillan and Co.; also Klein's "Micro-organisms and Disease."

† Sir Andrew Clark, Bart., M.D., Lumleian Lectures, "Lancet," April 4th, 1885.

‡ Klein, *loc. cit.*, p. 14.

open to question, and to doubt, as to their usefulness. If one is sent to seek for some specific thing, there may be many and varied inducements to find it, or something which may meet the requirements of the mission. Discoveries are not made in this way. No single man has yet accomplished *by himself* any notable discovery—not even when he sat himself down more or less comfortably to seek for one. Discoveries have usually been the outcome of "many thoughts of many minds," working through many cycles of time. Thus it is that discoveries are very slowly and as it were quite unconsciously elaborated—one man's work preparing the way for advances towards ultimate discovery by another. It in no way detracts from the great discovery of Harvey that the way had been paved for it by the discovery of the valves in the veins by Sylvius and Fabricius, and by that of the lesser circulation by Servetus. Neither is the merit of the subsequent discovery of the lesser circulation by the great anatomist Malpighi, in any way lessened by the fact that the existence of the channels first seen by him, was as clearly pointed to by Harvey's reasoning, as the existence of Neptune by the calculations of Le Verrier and of Adams. So also there can be no doubt that Kepler's elaborate series of measurements, and subsequently the measurements of Picard, as well as the discussions of Wren, Halley and Hooke, led up to and enabled Newton (by calculating from Kepler's laws), to arrive at the great discovery of the law of gravity, which up to that time had been merely a conjecture.*

But there is still another point to be noted as regards discoveries, namely:—That when discoveries are made

* "Encyclopædia Britannica," art. Newton.

it is not always easy to appreciate their value, or even to comprehend their significance, and far less to forecast the numerous and important results to which, in the future, they may lead, or the place they will finally hold in the circle of the Sciences. Time is an important element in their evolution, their development, their influence and their powers of usefulness.

Therefore it is that we may look forward with confidence to the future for much thoughtful work to help onwards those discoveries which have yet to come, alike in bacteriological and in micro-chemical methods. I have elsewhere pointed out* the very great differences of opinion entertained regarding the identity and causation of enteric fever in India and Egypt and even in this country; and especially in India do we require some one like Sir William Jenner who will teach us to differentiate the fevers prevailing there. The methods of Jenner combined with bacteriological and chemical methods may help to do this.

Could we but climb some pathological Pisgah and be allowed to stand as Moses stood, when he was permitted to view the promised land, we too might rejoice in the bright and certain prospect that there lays before us a great and glorious future for Pathology and for the Science and Practice of our Art.

* "Science and Practice of Medicine," 7th edit.

APPENDIX.*

Ptomaïnes in Infective Fevers.†

Arthur P. Luff, M.B., B.Sc., F.C.S., Lecturer on Medical Jurisprudence and Toxicology at St. Mary's Hospital School, has experimentally investigated the relation of ptomaïnes or animal alkaloids to some of the infective fevers. He has examined the urine in typhoid and in scarlet fever, so as to determine the presence of animal alkaloids or the formation of ptomaïnes in that secretion in these diseases; and he describes the following method for their extraction—a method which presupposes that the animal alkaloids are soluble in ether—and that no heat is employed in the process.

The details of the method are:—

1. A large quantity of urine is to be rendered alkaline by solution of sodium carbonate.

2. The alkalinised urine is to be thoroughly agitated with half its bulk of ether.

3. After standing, the etherial solution is to be filtered and agitated with solution of tartaric acid, which settles to the bottom of the vessel, and carries in solution any animal alkaloids in the form of soluble tartrates.

* See pages 55, 57, 91 to 96 of text.

† British Medical Journal, July 27th, 1889, p. 193.

4. The tartaric acid solution is separated from the ether; is also rendered alkaline by solution of sodium carbonate; and is again agitated by half its bulk of ether.

5. After standing the ethereal solution is removed, and the ether allowed to evaporate spontaneously.

6. The residue is to be dried over strong sulphuric acid, and then examined for animal alkaloids.

Normal urines yield no animal alkaloids. Therefore if animal alkaloids are extracted by this process from urines of patients suffering from any infective fever, such an alkaloid has been produced within the system during the course of the fever—a morbid leucomaïne. The patient must not be at the time taking any alkaloid or antipyretic remedy.

In typhoid fever and in scarlet fever Mr. Luff has in each discovered a new animal alkaloid. In typhoid he obtained a white crystalline substance which exhibited all the properties, and gave all the reactions of an animal alkaloid; and was converted into a hydrochlorate by dissolving in very dilute hydrochloric acid.

The reactions were as follows:—

Phosphomolybdic acid	Gave a white precipitate.	
Phosphotungstic acid	nil.	
Mercuric and potassium iodide ...	,,	dense yellow precipitate.
Iodine solution	,,	brown precipitate.
Tannic acid	,,	yellowish-brown precipitate.
Picric acid	,,	dense yellow precipitate.
Platinic chloride	nil.	
Gold chloride	,,	dense yellow precipitate.

No known animal alkaloid gives such reactions.

In scarlet fever the animal alkaloid was in the form

of a white semi-crystalline substance, soluble in water and faintly alkaline. It was also converted into a hydrochlorate. It gave the following reactions :—

Phosphomolybdic acid		Gave a pale yellow white precipitate.
Phosphotungstic ,, ...	,,	white precipitate.
Mercuric and potassium iodide ...	,,	pale yellowish-white precipitate.
Iodine solution	,,	brown precipitate.
Tannic acid		nil.
Picric acid	,,	yellow.
Platinic chloride		nil.
Gold chloride	,,	slight yellow.

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