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Animal Alkaloids

SIR W. AITKEN

ON THE ANIMAL ALKALOIDS

ON THE

ANIMAL ALKALOIDS

THE PTOMAÏNES, LEUCOMAÏNES, AND EXTRACTIVES IN THEIR PATHOLOGICAL RELATIONS

BEING

A SHORT SUMMARY OF RECENT RESEARCHES AS TO THE ORIGIN OF SOME DISEASES BY OR THROUGH THE PHYSIOLOGICAL PROCESSES GOING ON DURING LIFE

BY

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PREFACE.

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 last. They are now published by request; and with the permission of the Secretary of State for War.

Speaking generally, it may be said 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

* "Glasgow Medical Journal," 1885-6.

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 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 physiological 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.
August 12*th*, 1887.

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ON THE ANIMAL ALKALOIDS.

THE recent researches and expositions of MM. Gautier and Peter (two eminent French physiological Chemists and Physicians), of Dr. A. M. Brown and of Dr. Lauder Brunton 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 mainly to the writings of Dr. A. M. Brown,* and those of Dr. T. Lauder Brunton,† that I am indebted for the facts and arguments contained in this short notice.

* "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).

† "Disorders of Digestion," comprising various papers from "The Practitioner," 1873 to 1885, collected and published 1886. "Pharmacology, Therapeutics, and Materia Medica," Third edition. London, Macmillan and Co., 1887.

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. 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 living animal tissues, 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 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.

* "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.*

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, that 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 has been pointed out to me by my friend 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 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. Selmi's investigations were unfortunately too soon brought to a close by his early death.

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.

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

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. (Dr. L. Brunton, *loc. cit.*, p. 282).

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."†

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.

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 putrifaction 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."‡

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 destinction 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.

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

† "Lancet," August, 1885, p. 60.

‡ 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.

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 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, while 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

* "Pharmacology and Therapeutics," p. 100.

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*" 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*," 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 upon; 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."

But Gautier has further shown by his researches extending from 1881 to 1886 that the animal alkaloids are also 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 $\frac{4}{5}$ of our disassimilations are the result of transformations within the body, comparable to the oxidation of alcohol; and that the

remaining $\frac{1}{5}$ 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 production is inconceivable apart from it? Do we not also spontaneously and normally fabricate bases such as urea—a most complex product which can 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

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

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

considerable production of alkaloids takes place in the intestines, 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 secretion 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 kidneys are impaired 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 ptomaines."*

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 Petenkofer 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

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

human urine; and so recently as 1880, Pouchet has recorded the presence of "*karnine*" and an alkaloid in well-defined chlorate 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 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.

He has recently also announced the discovery of two

new "*leucomaïnes*," namely, "*adenine*" from the pancreas, and one from the spleen.* The second body isolated from the spleen by Morell, has a paralyso-motor action, with a powerful effect on the medulla oblongata.†

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. But however important the distinction, 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.

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:—

I. The Uric Leucomaine Group.—Betaines.

Betaine is the representative of this group, having the chemical formula of $C^5H^{11}NO^2 = \begin{matrix}(CH^3)_3 \equiv N - O \\ \quad\quad\quad\quad\quad | \quad\quad | \\ \quad\quad\quad\quad CH^2 - CO.\end{matrix}$

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

† "The Lancet," April 24th, 1886.

‡ *Loc. cit.*, p. 5.

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

Karnine, $C^7 H^8 N^4 O^3$.—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, $C^5 H^5 N^5$.—Discovered by Kossel in 1885.

Guanine, $C^5 H^5 N^5 O$.—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*, $C^5 H^4 N^4 O$.—Found in certain plants, but for the most part in animal tissues.

Xanthine, $C^5 H^4 N^4 O^2$.—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, $C^4 H^5 N^5 O$.—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 ($C^5 H^4 N^4$) 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 which 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*, $C^4 H^7 N^3 O$ NH =

$$HN = C\begin{array}{l} NH \quad - \quad CO \\ | \qquad\qquad | \\ N \ (CH_3) - CH_2 \end{array}$$

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

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

Amphicreatine, $C^9 H^{19} N^7 O$.—Corresponds with two molecules of kreatine plus the C N H 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 $C^7 H^{14} N^4 O^2$.

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

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 *mytîloxin* and given its formula as $C^6 H^{15} N O^2$.

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

2. The clinical, pathological and practical aspects.

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 "ex-

tractive 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. In other words, the healthy living organism may become poisoned (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?"

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

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 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

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

"*scoria*" (Brown) or "*physiological ashes*" (Lauder Brunton) resulting from the processes of combustion of the elements of organic tissues.

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, it is 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 oxygenation; 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 accumu-

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

lation 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 manifestations 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 generally 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

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

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. 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," he writes (equal to a long march) "exceeding nine hours daily, 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.

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

* Page 13, note.

accumulative after their elaboration in the system. Let us suppose then in this given case that 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 cumulative store 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. 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 generates 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 Sonnenschein 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 together of men in large bodies, we may recognise how in this way the typhus of armies and camps may under special conditions originate and spread.

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.†

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, over crowding, and privation generally as antecedent factors in its causation; and they no more questioned its appearing spontaneously than its contagiousness. Observation

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

† Dr. A. M. Brown, *loc. cit.*

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.

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

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 all 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 onwards from the hands and feet and so pressing it 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 "barber's pole" when barbers did that then conventional operation. 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. These are further aided by the stimulus of mental activity, so that when the brain is *over* worked and the respiration and muscular movements are *under* worked cerebral nutrition comes to be diminished by the imperfect removal of waste products from its substance. Its

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

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; if in process of putrefaction it ceases to be so, and 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. 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 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

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

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

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, 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 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

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

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

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, Mr. 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.*

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 then 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

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

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

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 excreted 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 found, 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 poison, somewhat resembling hydrocyanic acid in its action. It is a powerful protoplasmic poison."† 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 ob-

* "Comptes Rendus," ix., p. 724.

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

serves, "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 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 re-

sults. 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

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

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 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

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

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 are 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).

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

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 continued for several days. With some eggs and milk when so continued in a monotony of diet, are thus apt 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

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

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; and 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 predominates. The existence of a muscarine-like poison is still

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

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 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 was 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 probable that the symptoms

* *Loc. cit.*, p. 286.

of poisoning by sausages, fish, cheese, and the like may be due to a mixture of the alkaloids.*

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, 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 peristaltic 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

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

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 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 when he says:—"No one 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

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

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 the poisonous effects of ptomaïnes in the body as productive of disease in the fact that he has shown that the poisonous activity of human fæces is very great even when they are quite healthy; and that a substance has been obtained from them by dialysis capable of producing violent convulsions when administered to rabbits. And Bouchard has come to the conclusion that the alkaloids formed in the intestine of a healthy man in twenty-four hours would be quite sufficient to kill him if they were all absorbed and excretion stopped. When the functions of the kidneys are impaired so that secretion is stopped, uræmia occurs; and when excretion is similarly in abeyance from the intestines, Bouchard would describe the condition by the name of *stercorœmia*, believing that it is due to alkaloids absorbed from the intestines; and he

* Dr. Lauder Brunton, *loc. cit.*, p. 288.

is further of opinion that the nervous disturbances which occur in cases of dyspepsia and in dilatation of the stomach are due to poisoning by the ptomaïnes.

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 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.

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.*

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; although some appear to belong also 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

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

shewn 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

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

† Bechamp, "Compt. Rendus," 1872.

and in the solid organs of patients dead of diabetic coma.* It has also been found in the urine; and is often developed in the urine after it has been passed.†

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 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 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, vomiting, 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 also predominates in such cases, precisely such as may be observed in poisoning by tartar-emetic or arsenic. In cholera similar pheno-

* Berti, "London Medical Record," 1874.

† Foster, *loc. cit.*, and Kussmaul.

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

mena are characteristic, diminished temperature and algidity accompanying 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 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 two 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 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."

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

† "Glasgow Medical Journal," 1885-1886.

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. And 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 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.

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, the doctrine of spontaneity is as true of health as of disease.

Thus it is that our old traditional Medicine still continues to light up our path by brilliant gleams of truth.

In recent years we have heard and read much as to the malignant and mysterious influence of "microbes," "bacteria," "bacilli," and germs "*of sorts*" as causes of diseases.

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

† Dr. A. M. Brown, *loc. cit.*

The pathological domain of these organisms has now become so far reaching in extent, that every form of 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, so that 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 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

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

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 may bacteria 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 develope 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 they may find within the body, and in proper combinations all the conditions necessary for 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 develope 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* as to their existence in relation to the antecedent factors of any particular disease.

Therefore it appears to me that we have no need to call any form of microbes out of the "vasty deep" of their putrefactive abodes, or to set them up as the sole cause of any disease; for "it is not less interesting than it is pathologically gratifying to learn that the beautiful bio-chemical researches of Gautier, Peter and others, may help to emancipate us from the tyranny of belief in any microbial creed as the sole cause of any disease."*

Their researches amply explain the formation of

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

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

"To my friend and colleague 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 has kindly allowed me to publish here.

* 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 printed by Messrs. Hazell, Watson and Viney, London, 1887.

† 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.

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.

4. **Phosphates.**—Similarly 50 cc. of this urine took 16 cc. of uræmic nitrate standard solution, equal 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 has 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 × ·3	= 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).

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 the result, 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

Ratio of solids to specific gravity $= \frac{53{\cdot}19}{23} = 2{\cdot}31$.

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

But, 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. 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.*

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

To hunt for new forms of "microbes" is a comparatively easy and perhaps an exciting form of "sport"; but to determine the presence, the nature, the physiological effects, and the place in Pathology of the "ptomaïnes," the "leucomaïnes," and the "extractives" is a far more difficult (if it is a less exciting) investigation, because of the tedious and prolonged chemical processes that are required, and the subsequent experiments on the products.

"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. They have all, however, 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 Koch has not yet discovered;* (2) the supposition merely of the secretion of a 'ptomaïne' by that bacillus which is just as far from being demonstrated."†

The attempt to reproduce the disease in animals by inoculation or otherwise by the supposed specific bacillus has failed; while the experiments and observations

* 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.

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; and a great number and variety of experiments of contrast are yet needed to satisfy a just scepticism."†

Another feature of these microbes which warrants continued scepticism is brought out very conspicuously in the attempts to photograph them, namely:—that they are all so much alike that no distinguishing features exist amongst them for differentiation; their family likenesses are so strikingly similar.

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

* "Special Pathological Anatomy," by Ziegler and Dr. D. Mac Alister, p. 290, Macmillan and Co.

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

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.

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

Time is therefore 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.

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.

[Since these pages were printed, I have received from my friend Dr. A. M. Brown an early copy of 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. Published by John Bale and Sons, Great Titchfield Street, W, 1887.]

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