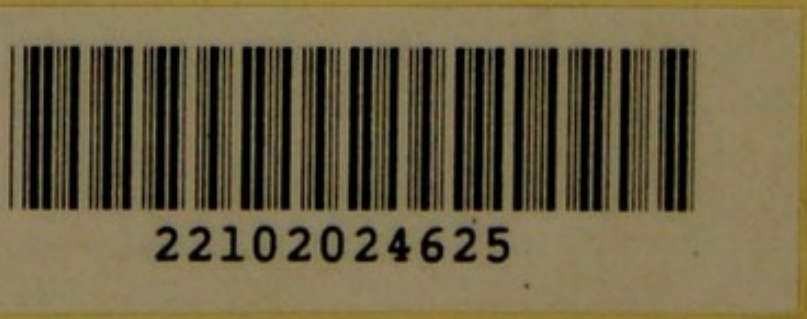
Elements of alkaloidal ætiology : introductory to the study of auto-intoxication in disease / A. M. Brown.

ELEMENTS OF ALKALOIDAL ÆTIOLOGY OR AUTO-INTOXICATION IN DISEASE



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INTRODUCTORY

TO THE STUDY OF

AUTO-INTOXICATION IN DISEASE

BY

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PREFACE

As my larger treatise entitled "The Animal Alkaloids in Relation to Scientific Medicine" is too technical in character to be of serviceable interest apart from teaching bodies, I venture in the present work to summarise such of its contents as relate directly to pathology, thus bringing within the range of the practitioner and student the elements of what the subject thus far, has to offer. Professing to be merely introductory to the study of the Alkaloidal *rôle* in constitutional disturbance and disease, the reader desirous of further knowledge on the subject will do well to consult the larger work referred to.

A. M. B.

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The essential phenomena of cellular life are still too little known in their mechanism, and even in their effects, to permit of our determining the intimate causes of their evolution, normal or abnormal, on which health and disease depend. What may, however, be positively affirmed is, that these phenomena are entirely physico-chemical in their nature, and that, if the reason of their succession still escapes detection, they are necessarily subject to the general law which requires that force in all its forms—heat, muscular activity, chemical or nervous action, etc.—is the result of a transformation of mechanical energy, potential or actual, present in the material substance of the cell itself.

It is now well known that in the case of living things, as in that of inert substances, the modifications which render force or energy appreciable and utilisable, are of two kinds. In the first case it results from molecular modifications brought about in matter without the intervention of oxygen. In the second it results from the chemical combination of substances, and particularly in the case of those which are combustible, in their union with oxygen.

In both cases the vital products become unsuitable for the maintenance of the vital functions of the cell which formed them; they must be got rid of. The animal would very soon succumb were the carbonic acid, urea, water, and even the heat, which it incessantly produces, to accumulate within its organism. Normally they undergo destruction and excretion by economic processes, which are constantly in operation. But if from any cause the functional play is interrupted; should there be emotional disturbance of the nervous centres; should sudden chills suppress the action of the skin, or insufficient aeration of the blood

take place; or, finally, if from any less obvious cause, alkaloid products are more abundantly formed within the cells, or be so defectively absorbed, excreted, or oxydised as that the blood becomes charged with them, they are carried to the nervous centres which regulate the central life and function as a whole; immediately disorder becomes general, complete, and necessarily assumes progressive forms—in a word, disease declares itself and undergoes development.

This admitted, facts must not, however, be too exclusively regarded. We must not too hastily assume that the succession of morbid phenomena are thus to be explained in every case. Without doubt, many pathological conditions arise from disarrangement of nutrition, assimilation, disassimilation, secretion and hæmatose—are, in a word, veritable auto-infections. Still, there are cases in which we cannot possibly ignore the presence of causes, which the organism would seem incapable of exciting spontaneously, as, for instance, in the generality of maladies known as contagious and specific and which do not appear sponta-

neously without previous contact, direct or indirect, with infected subjects.

Now as ever, it is erroneous to deny that maladies result from the invasion of specific infections. There are causes of disease which are resident within ourselves, that remain inoffensive whilst elimination and oxydation of detritus is normally operative, that give rise to disease if from some cause or other the detritus accumulates in the economy and acts upon the nervous centres. But to those morbific agents, which our living tissues incessantly dispose of, must be added the operation, though in rarer instances, of those held to accompany the generality of contagious or virulent diseases.

Ptomaines and leucomaines, like the extractive matters, urea, urides, carbonic acid, the oxalates and ammoniacal salts, are the vital reliquæ or residue material, effete and pernicious, which may become the cause of disease, no matter how they originate, that is, arise in the normal cells of the organism from within, or in *materies morbi* from without. Of all the extractive composite resi-

dua the alkaloids of animal origin, which the present work treats of, are worthy of the deepest interest. It is only lately that they have become familiar to us. They claim our special study from the fact of their constant presence in normal secretions, and must be classed with the most active agents known.

Now comes the important questions: What is the origin of these singular products? What is their mode of elimination? What is the mode or mechanism by which the cellular stroma disposes of them in health and disease? The solution of the problems involved, form the most interesting chapter of normal physiology and pathology of cellular life. If a completely satisfactory reply to them may be hoped for, it must be admitted the time has not yet arrived. The genesis and *rôle*,—the complete history of the leucomaines, in fact,—is too closely bound up with the essentially vital to permit of it. Following on the present lines of investigation where so much has been accomplished, it remains to indicate what that amounts to.

I

It is sometimes less difficult to make a discovery than it is to comprehend its significance or what it naturally leads on to. Before the publication of Gautier's researches, evidences as to the existence of an alkaloidal element in animal physiology were not wanting had they been read aright. Singularly enough, no attempt was made to read them. Though alkaline bases had been detected in animal tissues, no one had summarized the discoveries, or thought of generalizing results. But this could not continue, and to Gautier is mainly due the merit of overthrowing the artificial barriers, which theoretic preconceptions had hitherto recognised as separating the physiological phenomena of the animal and vegetable kingdoms, and in attributing exclusively to the tissues of the latter, the power of elaborating alkaloids.

This capacity of the economy in this function was not even suspected. Liebig and Pettenkoffer had long made known the existence of kreatinine in urines; this was the first body of animal origin acknowledged as possessing properties clearly alkaloidal. It was known that kreatine detected in animal tissues along with kreatinine resulted from that latter substance dishydrating in contact with salts, acids, or heat; but its presence and production was thought to be explicable by the processes involved. As for the kreatine itself, Liebig declared that it did not possess any of the properties which characterised organic bases. Such was the influence of false theory on minds the least prejudiced. Then, as largely still, it was taken for granted that animal organisms supplied no other nitrogenous substances than those of the nature of amides, unless it were methylamine and trimethylamine.

It was not till twenty years later Liebreich detected the presence of the already known vegetable alkaloid betaine in normal urine. And it is only so recently as 1880 that Pouchet, as the result of long-continued and care-

ful examination of the human urine announced, besides the presence of allantoine, since regarded by Meyer as a uride, karnine and an alkaloid in well-defined chlorate crystals. Analyses were incomplete, but the following year Gautier confirmed the fact, that Pouchet's alkaloid possessed the general properties of a ptomaine, and indirectly led to the study of this new class of alkaloids, the product physiologically of animals during life. This preliminary advance was strengthened by Bouchard in 1882, when he disclosed the fact, that not only were alkaloids present in appreciable quantity in normal urines, but that they augmented notably in the course of certain maladies, in typhoid fever for instance. Lepine and Guérin have since found that this applies to a still wider pathological area. Again, Lepine and Aubert, generalising facts acquired, concluded that in the course of certain maladies these poisonous products of the urinary secretion notably increase in quantity until the crisis is reached, when they finally diminish.

To return to 1880, Gautier having satisfied himself that the urinary alkaloid obtained by

Pouchet really belonged to the order of ptomaines, directed his investigations with a view to ascertain whether the normal secretions, of certain animals, notoriously toxic, might not owe their activity to substances of a similar nature and origin. By carefully operating on the glands of snakes, he was enabled to eliminate materials unquestionably of the alkaloidal order. From the *naja tripudians*—cobra di capello—in particular, two new substances were obtained by him, and evidently of the nature of ptomaines. From the salivas of the reptilia to that of man was but a step. In the same year others, subjecting this human secretion to examination, succeeded in isolating various toxic elements in sufficient quantity to note its action. Though the products in both instances responded to the reagents of Meyer and Nessler, and induced characteristic physiological effects on the nervous and digestive systems of smaller animals and birds, it is more than doubtful if they constitute the direful element of salivary venoms.

Facts such as these ought to have impressed inquiring minds, but prevailing views did not

permit it. The presence of alkaloids in the secretions was either doubted or allowed to pass unheeded. Gautier, as we have seen, was not disposed to halt. Feeling convinced of the pharmaceutic powers of the animal organism in the elaboration of alkaloids, he clearly set forth his views in 1881, whilst later investigations enabled him to give definite confirmation to these preliminary observations. But, before examining his results, the labours of others who had been similarly engaged require some notice.

A little before the death of Selmi, about 1879, two other Italian investigators—Paterno and Spica, advanced an objection to the effect, that all or a part of the alkaloids derivable from putrefactive materials might possibly have existed during life. In order to decide the point, blood, white of egg, and bread were severally examined, but by inefficient methods; though alkaloidal traces were detected, no analyses were given. Their labours were taken up by the Italian Ptomaine Commission, and with more success. The conclusion arrived at was, that alkaloid substance, ob-

tainable from animal tissues, was neurine resulting from the decomposition of lecithine; that it increased in amount according as either body is more abundant. "Is neurine always accompanied with another alkaloid which reagents separate with difficulty?" was a question which they left unsolved; the small quantity, however, deprived it of any toxological importance.

It ought to be noted that the preceding authors had neglected the extractive matters of normal muscular flesh formerly examined by Liebig. Professors Guareschi and Mosso resumed the study from the special point of view which now engages our attention. In their interesting work, these last authors state they had obtained a body apparently of the uride family, and intermediary between the kreatinine, sarkine, and urea.

But Gautier, as we have seen, having raised the question, the similarity of putrefactive phenomena to fermentation of proteid materials, led him to that series of investigations which were so brilliant in results. He not only confirmed his theoretical conceptions, but esta-

blished demonstratively the formation of leucomaines by the normal cellular activities of all living things, animal and vegetable.

In working out this problem be occupied himself with the study of the alkaloid products of muscular tissues, because they were abundant, and the nature of the material homogeneous. The new alkaloids discovered by him are consequently of fresh meat origin. His researches were conducted with great difficulty and with the greatest care, so as to avoid all suspicion that the alkaloid basic products could have been formed artificially in the course of operation.

Such was the purport of the *mémoires* of 1885, published with a view to the elucidation of this question. It now remains to note the course of continuous examination and study since that date. The results are most important, as they enable us to affirm to-day positively, that the important chemical function of all the animal tissues, however much it may have been ignored, is the incessant elaboration of alkaloidal products formed at the expense of proteid materials, precisely as urea and

carbonic acid are similarly and simultaneously formed. Seeing their albumenoid origin—and in order to distinguish this new class from that of the cadaveric alkaloids or ptomaines (πτῶμα)—Gautier has conferred on those vital alkaloids, the name of *leucomaines* (λεύκωμα), a term he limits to all those alkaloids derivable from albumenoid substances which appear in the animal tissues during life.

II

In previous works and in connection with the discovery and investigation of the vital alkaloids, some problems of physiology and pathology, abstruse and complex in their nature, have been approached. The most recent, which abounds in startling inductions, opens up a wide territory that has hitherto escaped investigation. If the indications submitted meet with the attention they deserve, a sweeping reformation may be looked for in our modern medicine. The method of dealing with the questions they involve reminds us little of pangermic and bacterial theorisings; it is based

on data which are positive, precise, and easy of verification. Organic chemistry being eminently exact, investigating minds may very profitably bestow on it a share of the attention they have hitherto directed so exclusively to bacterial and bacillar biologies.

To bring to the aid of the medicine of the present the medicine of the past is a duty. Though the grand time-honoured doctrine has of late lain somewhat in eclipse, we know full well that, from him of ancient Cos till now, traditional medicine supplies the only glimpse of truth to be met with in Hygeia's dimly-lighted corridors. No one should blink the fact that antiquated humoralism is still a fundamental principle of the healing art, though some have not been told so, and others have forgotten it. Those who are aware of this, and feel ashamed to own it, are to be pitied. As for the judicious who have been dreading recent doctrinal caprices, they may feel perfectly assured that when the prevailing bacterial mania loses its intensity or subsides, it will be found to have been much less revolutionary than was generally supposed.

Besides the fact that animal tissues in process of putrefaction invariably elaborate certain alkaloids of powerful toxic properties, there is every reason to suspect that substances of a poisonous nature are variably elaborated in animal tissues, even during life; and that through the medium of tissue-transformations, or independently and alone, their action is sufficient to determine specified maladies and death. Thus the exciting and proximate cause of the conditions of those under clinical observation promises to become more accessible and available to the practitioner in a numerous class of cases. These suspicions they have to some extent verified. In their hands, analysis of the various secretions and excretions of patients representing a variety of morbid conditions, has led to the detection of substances closely resembling, if not identical with, the alkaloids of putrefaction. Subjects suffering from rheumatic tetanus, progressive paralysis, and progressive imbecility, for example, yielded bases allied to aconitine and conia; the first, experimentally observed, showed a specific action on the nervous centres, destroying

their activity, diminishing general sensibility, the respiration, and the action of the heart.

But such suggestive data demand closer sifting and more reliable adjustment, in order to make clear their scientific purport. It is abundantly confirmed that not only after death, but even during life, the animal organism, in accordance with physiological chemical processes easy to determine, has the power of elaborating a numerous class of alkaloids; that these alkaloids or leucomaines are essentially toxic in their properties and actions on the economy that gives rise to them; that an auto-intoxication characterised by hyperthermia, hypothermia and allied morbid phenomena indicate the process of their physiological action. Some, with all the force of preconceived ideas, may naturally exclaim, "Admitting this to be true, what is to become of the bacterial impedimenta with which we have been harnessed? These alkaloids we have never heard of!" To this we can only reply, that the circumstance is much to be regretted; that their existence is by no means

a thing of yesterday; some workers have been familiar both with them and with their probable action for years. But in any case, it is never too late to learn; and to begin with, all must know that we are busy chemically manufacturing alkaloids every instant of our lives. As the organism can form alkalies, ammonia for example—seeing how marvellous are its pharmaceutical potentialities—why should it surprise us to find it forming alkaloids? It is only a question of chemical degree. And this most certainly it does, whether the fact we are contending for be accepted or rejected.

This function may certainly be a dangerous one, and might oftener prove fatal than it will be found to do, were it not that the action of its products are ingeniously frustrated and they themselves got rid of in one way or another. Their deleterious manufacture is, in reality, an essential element of life itself. Life is a contingent phenomenon, consisting of a series of partial deaths. It has been said, and truly said, "In the midst of life we are in death;" for, scientifically speaking, it must be admitted that the living body always bears

with it the components of the dead one. If the organism is to survive, the organic and the inorganic must march hand-in-hand till death severs them.

It is principles such as these, whether understood or not, that sound traditional medicine has always recognised. What is now endeavoured to be shown, is simply that the school of the past and the school of the future will be found to mutually support each other, and further, that humoralism, if you will, so far from being vanquished, has been only stolidly refurbishing its arms and reinspecting its resources; whilst pangermism has been exhausting its energies in sensational demonstrations of bacterial surprises and bacillar blunderings.

A recent *mémoire* of the late Michel Peter ought to make this evident to those who are unshackled and capable of thinking for themselves. In a passage remarkable for sound scientific force, he treats us to retrospective glimpses from personal experience, and admirably illustrates the type of mind of those who profit by the current of the day while swimming with it.

The import of authoritative teachings such as these has neither escaped the attention of the germ theorists on the one hand, nor of the advocates of the unity of poisons on the other. In Germany the intoxication of the system by substances which are the product of abnormal physiological processes has received the name of Botulism. The classes of cases towards which the observation of clinicists has chiefly been directed hitherto are those exhibiting the symptoms and conditions which Asiatic cholera presents. The patients so affected have all the appearance of toxication, and by the poisonous alkaloids—that is, the vital alkaloids or leucomaines. The symptoms which usher in the seizure indicate a form of poisoning so obviously that the chiefs of the bacillar theory of cholera—Koch to begin with—have been compelled to hesitate and ask themselves whether, after all, some ptomaine or other may not be the specific cause of the choleraic mischief, while claiming for it a bacillar origin. Klein, it would appear, is clearly of this view.

In pointing out more fully the method by

which Peter deals with the problem, which for medicine is of such etiological importance, Gautier, it is well to note, has clearly shown that four-fifths of our disassimilations are the result of internal economic combustion, and that the remaining fifth is produced at the expense of the tissues themselves. This, in a certain sense, leads us back in the direction of would-be discarded humoralism, because poisoning by a soluble alkaloid is poisoning by blood which has already undergone decided deterioration.

We instance cholera as the aptest illustration of this view. Monopolising, as it does, so much scientific interest, it supplies the freest field for airing the respective claims of two pathological theories which for the moment are apparently in mutual opposition. The one bacillar, organic and strictly biological; the other toxic, inorganic, and strictly bio-chemical. The first, so high in favour, and with the entire field to itself, has failed egregiously in its assumed solution. The various expeditions—Indian, African, and European—undertaken in bacterio-bacillar interests, have proved as prac-

tically hopeless and unprofitable as the discovery of a north-east passage to Cathay. By such missions Koch has only added to his hypothetical perplexities, while Klein, with modified appreciations, preserves his germ proclivities, and hopes by veiled, but truly humoralistic concessions, to solve the cholera problem among others.

Let us take our stand on the natural history of disease and physiological chemistry. The first observes the course of maladies and the nature of their products. The second demonstrates the bio-chemical data with which they are intimately associated, and only with a prudent caution looks beyond them. The recently discovered ptomaine alkaloids have given us the measure of nature's pharmaceutical potentialities in death. Directing our attention to the more recently discovered leucomaine alkaloids, has given us the measure of the same potentialities during life; it demonstrates their toxic properties and the means by which the living organism escapes their deleterious action, and shows that they constitute *materies morbi* as various as the con-

ditions with which they are associated, and that they are the cause of some of the most serious accidents to health that medicine has to fight against or man is liable to suffer from.

The objects of these comments must now be evident. It is merely to advance those claims which the newer views, with reference to the causes and nature of disease, have on our acceptance. Our contrasting such claims with those of the advocates of the bacterial theories now dominant, may, as a natural result, cause alarm, if not amusement, in many quarters. But those who know that diseases are not entities but processes, concern themselves but little with time-serving theories; they are well aware that even where they do perhaps contain a grain of truth, they still form but a part and not a whole in that broad conception of pathology which is at the same moment ever old and ever new.

Seeing the interest such work is likely to give rise to, and how much it is calculated to correct and mitigate the excesses, both in

the theory and practice of germ pathology, still in the ascendant, we will now proceed to briefly summarise results.

III

Generalising what has been elsewhere shown, viz., that with the excretions of healthy living animals there are substances of the nature of ptomaines almost uniformly present; that besides the alkaloids of the urine of Leibrecht and Pouchet similar alkaloids are detected in the muscular tissues and saliva. To these are given the name of leucomaines, in order to distinguish them from ptomaines or cadaveric alkaloids. We now proceed to point out the important relation which these products bear to the genesis of maladies, when their elimination by the kidneys, liver, skin, and intestinal mucous membrane was defective or suppressed.

With a view to confirming these preliminary observations, Gautier took up the study of the subject, carefully examining the muscular juices of the larger animals. He succeeded

in adding to the list five new alkaloids, all perfectly defined, crystallised, and having a specific action on the nervous centres, more or less marked; inducing somnolence, lassitude, some of them even exciting vomiting and purgation—effects similar to those of poisonous alkaloids, but less active than the cadaveric alkaloids. He satisfied himself of the fact that these bases originate during life as naturally and legitimately as carbonic acid and urea. It only now remained for him to ascertain by what mechanism, or process, those alkaloids originate and assume their definite forms and characters; how they comport themselves in the physiological, pathological, or putrefactive, correlations; what follows from their incessant formation in the economy; what becomes of them, and finally, how the organism itself escapes their deleterious effects. In common with previous and contemporary scientists, he found the lines of the enquiry vague and disconnected. Here want of space forbids our following him; we push on to his conclusions, and nothing in induction can be clearer.

While profiting by physiological facts ac-

quired, and the knowledge that the oxigen of the atmosphere, by means of the respiration and the circulation of the blood, finds everywhere its way throughout the animal organism, he cannot admit, as is generally assumed, that animal life—in other words, the successive phenomena of assimilation and disassimilation of the tissues—consists entirely in this fact. Gautier holds that if the tissue-transformations in inferior animals are in Pasteurean phraseology almost wholly *aërobic*, the tissue-transformations of the superior animals are, on the contrary, *anaërobic* in a notable proportion. According to conclusions hitherto accepted, this looks something like assumption, and seems paradoxical besides, but he carefully attacks the problem, and we think successfully; the force of his conclusions, whether we regard them practically or theoretically, amount to demonstration.

Tissue-Transformations in the Superior Animals.—Investigating on the lines here indicated, he has been enabled to show experimentally, that while four-fifths of our internal combustions are the result of a veritable *aërobic*

process analogous to, if not identical with, the oxydation of alcohol under the influence of *mycoderma vini* or *aceti*, the combustions, secretive and excretive that remain—to the extent of one-fifth—are produced at the cost of the tissues themselves, independently and exclusively of foreign oxygenous intervention; in other words, that a portion of our living tissues comport themselves precisely as ferments *anaërobic* or putrescent do. This point attained, he was naturally led to infer that, if the intimate organic life of such portion of animal tissue of cellular aggregates is independent of oxygenous supply from atmospheric sources, it resembles the bacterial ferments in the mode and manner of assimilating and disassimilating organised material, and we ought to find in the products of secretion and excretion those substances that are to be met with in an *aërobic* albumenoid fermentation—that is, the putrefactive fermentations; and he shows, as a matter of fact, that this is so. In the normal secreta and excreta are to be found the whole of the products of putrefactive processes properly so called—such as

carbonic acid and ammonia—in part free, in part in the form of urea, salts, phenol, endol, scatol, of our fæcal and urinary excrementa; the butyric, acetic, and other superior adipose acids; the lactic, succinic phenylactic acids of our muscular tissues, and in the glandular and renal secretions. In the processes of putrefaction, nitrogen, sulphuretted and phosphuretted gases, together with the hydrogen of the intestinal canal, are also to be met with. The identity is consequently complete, or nearly so, and he very logically asks, why ought we not to suspect and be able to detect the presence in the urine, glandular secretions, muscular fibres, etc., of these toxic alkaloids, whose history forms the subject of the remarkable *mémoire* he has recently submitted for the benefit of scientific workers?

He has here unmistakably ascertained their existence in operating in a wide area of animated nature; venoms, salivas, various glandular secretions, those even of the silkworm receiving close examination. Devoting special attention to study of these in relation to the muscular tissues in the blood of man and the

mammalia generally, he draws attention to the fact of the perceptible increase and accumulation of these alkaloids in the circulation, when from any cause the bowels, kidneys, liver, skin, etc., flag, or become defective in their functional activity. He has further insisted that it is under these circumstances that they are permitted to exert their toxic action on the nervous centres, and so give rise to a great variety of morbid phenomena whose determinate successive development and combination, when considered as a whole, make up the portraiture of particular cases or classes of cases of disease.

For those who give attention to the conservative character of our economic physiological processes, but know little of the organism's liability to perversion and deterioration by its own inherent forces, it will be pleasing to see in what way in health a normal balance is preserved, how the body escapes disturbance and disintegration by processes purely auto-infective which are ever ready to declare themselves.

THE PROCESSES BY WHICH AUTO-INTOXICATION

IS RESISTED.—Gautier goes on to show that the organism is enabled to resist the incessant dangers from auto-intoxication by two distinct methods: first by the separation of the effete toxic elements, and their destruction by oxygenation more or less efficiently. Elimination by the kidneys more particularly betrays this fact, and this he strongly urges, for he has almost invariably found slight traces of ptomaines in the normal urine; very slight, it is true, some would even deny their presence, but it is attested by others besides himself, as also by the fact that they increase and become considerable in quantity in many pathological conditions. Creatinine, for example, has been extracted in cases of uræmia. Their elimination by the bowels seems to him just as certain; though here, by reason of the difficulties of examination, it is less capable of demonstration.

The process which enables the economy to resist auto-intoxication from the alkaloids, and which he holds to be more powerful than elimination, is their incessant combustion in contact with the oxygen of the blood. For the

most part, those deleterious compounds are markedly oxydizable, and it is under the vivifying influence of the incessantly maintained supply of oxygen that they consume themselves and disappear, at least in part, facts which sufficiently explain why—under normal conditions—only traces of the muscular leucomaines are detected in the urines; in large proportion they having undergone combustion in the current of the circulation, if not in the tissues themselves.

In any case, if from any cause whatever the free and normal aeration of the blood is interfered with, or materially diminished, Gautier has always found the quantity of hæmoglobine decreased, as in anæmia and chlorosis, and should there be introduced into the blood, substances which interfere with the *hæmatose* or blood formation, immediately materials of the ptomaine and leucomaine order are generally found accompanying them. The appearance of the allantoine in the urine of dogs, whose means of respiration has been gradually reduced—according to Frerichs and Stadeler—and the reality of asphyxic glyce-

mia—according to Daster—is evidence of the fact.

THE PRACTICAL BEARINGS OF THE SUBJECT ON MEDICINE.—The physiological researches of Gautier as a chemist—fortunately for us—have taken a most important direction. Both as regards their special application to pathology and practical medicine, it is impossible to ignore the great value of his work to medical science. Labours in this direction have been considerable, but far from exact. Contributions of this class will do much to remedy our position, and afford an explanation of the morbid phenomena we are daily called upon to deal with, and yet know but little of essentially. As examples of this, take the nervous disturbances associated with anæmia, chlorosis, pregnancy, and the beneficial effects derived in such cases from the inhalation of pure air. Oxygen, for instance, is often the sole means known for combating effectually the persistent vomiting which arises from the retention of imperfectly burnt, or imperfectly eliminated, materials in the tissues or the blood. Again, is it not admissible for us to ask whether

fever itself—which is coincident with the smallest alimentary consumption, and an inverse proportional increase of carbonic acid eliminated and of oxigen consumed, with acceleration of the circulation to boot—may not have for its physiological aim and object the destruction of these deleterious substances which, under certain conditions are formed, or form themselves so abundantly in the economy?

Thus far it has been no small pleasure to follow the authority in his lucid inductions. And much averse as he is to venturing beyond the limits justified by a judicious scientific spirit of inquiry, based on data that are positively reliable, it only remains for us to acknowledge that to him belongs the largest share of merit in having indicated those beneficent agencies which excite the functions of the kidneys, skin, and intestinal mucous membrane, and what is still more important, the necessity of the constant disinfection of the economy by all that promotes the processes of respiration and *hæmatose*, in other words, renewal of the healthy blood.

It only remains to be added that the work

in this direction is not yet completed. It is evident that however actively poisonous to the animal economy the alkaloids we have been dealing with may be, there exist azotised substances non-alkaloidal which accompany them, and are endowed with activities still more remarkable. We know that Panum's septic poison contains little or no alkaloid; that the extractive and crystallisable matters are extremely toxic; furthermore, the essentially active principle of the venom of snakes is nitrogenous, but not alkaloidal. These substances are in other respects more important quantitatively than the ptomaines and the leucomaines oxydisable and azotised like them, and require that they should be studied still more closely than they have yet been. There is a growing conviction that their investigation will prove one of the most instructive sources reserved for the medicine of the future.

IV

These researches, apart from their chemical and medico-legal value, have the important

merit of confirming what we already know of the intoxication of the animal economy with its own products; whilst, at the same time, they add to our previous knowledge, and to pathological investigation a greater degree of method and precision.

But what are really the terms of the questions involved?

We know that in dead animal tissues undergoing the process of putrefactive decomposition, there are elaborated the alkaloid ptomaines. We further know that in the living animal tissues, and by virtue of their vitality, there are elaborated alkaloids which are analogous to these. Some of these we name leucomaines. This is not all, it is ascertained that in the living animal economy there are also elaborated azotised uncrystallisable substances which are still undetermined, and which are the extractive matters.

So much for the chemical aspect of the question. Now comes the clinical one. If the ptomaines are toxic, the leucomaines are also toxic, and that the extractive matters are more toxic than either.

According to the different sources of intoxication, there is a corresponding indication. Intoxication by the extractive matters is accompanied by hyperthermia, whilst intoxication by the animal alkaloids is accompanied by hypothermia; that in the living organism a variation or succession of extremes in temperature may manifest itself, according to the combination or alternation of poisonings by these deleterious physiological products. But what is of additional interest, and must be gratifying to many to learn in connection with recent researches, is the fact of their emancipating us from the tyranny of micro-germism. They explain the formation of poisonous alkaloids and still more poisonous extractive matters, by means alone of the physiological processes continually at work, thus disclosing the fact that in auto-intoxication, the spontaneous or self infection of the living organism by the alkaloids and extractive matters, there is, by reason of their essentially normal physiological origin, no question of quality, but simply one of quantity to be considered; that, in other words, the healthy living or-

ganism may become poisoned by the accumulation within itself of deleterious substances normally elaborated, but imperfectly or defectively eliminated.

The important question then presents itself —in what way does auto-intoxication or spontaneous infection of the economy take place? And here a word or two regarding life may not be superfluous or out of place. Life must be regarded as a phenomenon essentially relative and contingent; it is a series of partial deaths; the organism only lives on conditon of incessant elementary disintegration; we bear about with us, within us, the effete *débris* of our living selves. That phase of it called health is a phenomenon quite as relative and contingent, and may be regarded as life's equilibrium between organic good and evil. Normal health is conditional on an incessant transformation and elimination of the effete or old organic material which has to give place to renewal by the new. Nervous phenomena, central or peripheral, may modify the phenomena and so complicate the fact, but nothing can do away with it.

The series of partial deaths which constitute life is the result of organic functional operations. When thought is evolved the brain generates heat, and the material product of the cerebral action is neurine, an alkaloid prejudicial to normal life; when movement is exerted heat is evolved, and the material result of muscular action is the creatine, creatinine, and still other alkaloid congeners, which are proved to be equally prejudicial to the health of life. The tissues and organs perform a function of disintegration, and in the process they fabricate those alkaloids and extractive matters which must be regarded as veritable scoria, resulting in the processes of physiological combustion of the elements of the organic tissues. The organism is always dying, and strange, as the paradox may sound, could not live unless it died. We thus perceive how precarious a condition is that which we call health, and why, by the modifications of the organism in vital activity, disorder or disease may manifest itself in consequence of the simple accumulation of cadaveric materials.

It has been clearly shown, and must now

be freely accepted, that the animal alkaloids are a necessary product of vital physiological processes; this is both synthetically and analytically proved by numerous authorities, who press the important fact with all its consequences on our attention. The fact is further shown that about four-fifths of our disassimilations are the result of veritable internal combustions *aërobic* transformations comparable to the oxydation of alcohol under the influence of *mycoderma vini* or *aceti*, and that the remaining fifth of the disassimilations are formed at the expense of the living tissues themselves, free of all demands on foreign oxygen; in a word, that a fifth part of our tissues live after the manner of ferments *anaërobic* or putrefactive. Confronted with these facts, and studying their organo-chemical bearings, we are naturally forced to infer that if the essential life of that portion of the animal cells grouped in tissues and living without oxygen derivable from atmospheric sources, is analogous to the bacterial ferments in the mode by which it assimilates and disassimilates the organic elementary material, we ought

to be able to detect in the animal secretions the substances themselves which characterise and constantly accompany *anaërobic* fermenta tion of the albumenoids, and this we are enabled to demonstrate to be really the case.

All this should not surprise us. If the animal economy is not purely a chemical apparatus, it is far less a fermentating vat. It therefore requires no imaginative license to conceive of alkaloids being formed within the living organism and independent of bacterial fermentation, though somewhat resembling it. Do we not every instant of our lives, and quite normally, elaborate acids and bases, not merely carbonic acid, but uric acid? Uric acid is a product of animal life, and one which is inconceivable apart from it. Do we not spontaneously and normally fabricate bases such as urea, which can combine with azotic and oxalic acid, and which, by simply splitting up chemically, may go to the formation of carbonate of ammonia? Such being the case, why then should we not admit that the living organism—which by virtue of vital activities, by means of the living and acting cells, and

in the absence of all bacterial intervention, is capable of fabricating urea—is also capable of fabricating various alkaloids? That which might seem *a priori* evident, is now bio-chemically proved to demonstration. Undoubtedly it is in consequence of the splitting up of disassimilations, brought about at the expense of the tissues themselves, and in contact with oxygen, that all the disintegrative phenomena are accomplished in the animal economy, and by the physiological activities of animal cellules grouped in tissues.

We resist auto-intoxication by two modes or mechanisms—by the elimination of the toxic products, and by their destruction by oxygenation. Elimination is accomplished by the kidneys and the liver. As to their destruction, this consists in a continuous combustion of the leucomaines by the oxygen of the blood; the leucomaines are there burnt, consumed in the circulatory current, and, it may be, partially in the tissues.

Accumulation may take place under two widely different conditions; as when there is excess of extractive matters and alkaloids,

with normal but inadequate emunction, or when the production of deleterious materials is normal, but emunction insufficient, the emunctories being diseased or deranged.

It is in this way, in the massing of men in large bodies, that the typhus of armies originates and spreads. In this case there is a co-operation of auto-typhusation with hetero-typhusation. For those who are in the position of observing and appreciating such facts, it is scarcely possible to escape the conviction that there exists a morbid series, which is as natural as it is evident, leading from the simple form of fatigue fever to that of typhus, which is the highest expression of the poisoning of the organism by itself, or by contact with others under conditions such as now referred to. It is consequently something like an absurdity to introduce micro-germs into the question.

For those who have seen this form of typhusation develop itself, its origin is not to be doubted; it accompanies prolonged fatigue, over-crowding, and privation generally. They would no more question it appearing spontaneously than he would its being contagious. What is true

of fatigue fever and typhus fever is equally true of typhoid fever, whether it may have as an agent of transmission the bacillus of Eberth, displaced by that of Gofiky and Artaud, and this in turn to be displaced by other future bacteride, matters little.

What Peter insists on chiefly is the existence of a natural typhoid morbid series, in which ordinary tyhoid fever stands between the simple fever of over-taxation and typhus properly so-called. He tells us that when occupying the chair of medicine for Gresolle at the Faculty of Medicine, in 1869, he taught the doctrine of auto-typhusation, using this term to clearly define the nature of the accidents, the principal of which are in all cases hyperthermia, innervation and hæmorrhages. In his *Clinique Médicale* he points out that typhus may arise in various ways, and illustrates the question by its appearance in the navy, army, prison, and hospital establishments. Under such conditions there is unquestionably inhalation of morbific matter, organic emanations, productive of typhoid vitiations. But what does it matter, he asks, whether morbific matter finds its way,

into the organism from without, or whether it is elaborated from within? The individual suffering from attack is none the less contaminated because he is self-contaminated, and this is what Peter calls auto-typhusation, no matter what the form may be. Should functional disturbance cause difference in some respects from typhus of a given type, difference in morbid phenomena will depend largely on the various toxic elements in the blood, and here must be sought the explanation of the modifications of the distinctive forms, putrescent, cerebro-spinal, biliary, atheramic, or uræmic. The etiological factor extends to all the typhoid morbid series in all such maladies; he insists on the presence of an animal poison of cadaveric nature in the living organism, either communicated from without or orginating from within, but not eliminated—an organic product so highly prejudicial to life that it disturbs the vital activities of the living organisms with which it comes in contact, and this quality is what constitutes infection.

Inefficient elimination while the emunctories are sound is only one aspect of the question;

but supposing the emunctories are diseased, supposing the kidney in particular permits of percolation of the serum of the blood, its albumen, then we observe another series of accidents embraced under the term uræmia, and which to Peter constitutes typhusation, for in proportion as the cypher of albumen increases in the urine, that of urea and extracted matters diminish; that is to say, the non-eliminated extractive material retained increases in the blood. This has been abundantly demonstrated. Replying on the data which explain the clinical facts in appearance contradictory—that is, that in certain cases of uræmia there is to be observed an elevation of temperature, and that in certain other cases the temperature is sometimes stationary, at others it falls—if there is an accumulation of extractive matter in the blood we detect hyperthermia; if there is accumulation of the alkaloids, there is, on the other hand, hypothermia; but should the two factors co-exist they neutralise each other, and the temperature remains stationary. Let one or other turn the scale, and immediately a thermometric

variation may be noted. Add to this the typhoid accompaniments, perturbation of the nervous system and hæmorrhagic accidents. If, again, it is the liver which is the seat of the functional disturbance, or is so structurally affected that elimination is incomplete, and that there is cholemic typhusation, then we shall have also elevation of temperature, innervation, hæmorrhage, and disorders the most varied and serious.

It is very apparent that we have in this view a partial return to humoralism, poisoning by soluble alkaloids being in reality nothing short of poisoning by an organic liquid which has undergone change, in a word, deterioration, and, that this spontaneity goes on in health as it does in disease is equally established by the chemical demonstrations of Gautier, and the chemical observations of Peter.

A few words in conclusion. Scientific missions inspired in the interests of germ pathology have visited Egypt, India, and Southern Europe, in the quest of a specific microbe; they have signally failed. Dr. Koch, the leader of one

of them, thought he had found the pathogermic entity, but confronted and constrained by facts, the learned bacteriologist has felt himself obliged to admit that the said bacillus does not directly engender cholera, that it can only do so indirectly and by the intervention of a ptomaine which it secretes. But this implies two suppositions: firstly, the existence of the specific bacillus which Koch has not discovered; secondly, the supposition of the secretion of the ptomaine by that bacillus which Koch is just as far from discovering.

Hypothetical assumptions may easily be carried too far. Something simpler and more evident is needed to justify the theorising mania. Koch, assumes; Gautier, demonstrates; he shows the spontaneous elaboration of the ptomaine-leucomaines in the living organism, —demonstrates the formation of these by the splitting up of disassimilations—demonstrates that these chemical divisions are accomplished by the vital processes of the living cells; that these processes are peculiar to the living organism and altogether independent of the intervention of vegeto-micro-organisms; Gautier

also demonstrates their toxicity and the mechanism chemico-dynamical by which the healthy organism escapes intoxication and disease. Can the medical mind henceforth hesitate between pangermic doctrines bolstered up by hazy, vague hypotheses, and the doctrines we are maintaining, which are clear and precise, and which explain the phenomena of life, normal and abnormal, by life itself in action? Obviously not. Let us now proceed a little farther, that what is here evident, may become self-evident.

V

The new departure in pathology finds an able exponent in Bouchard. This eminent teacher must now be regarded as heading the movement. Medical investigation, if it has not undergone complete transformation, has, it must be frankly admitted, changed its objective; having been successively directed to the study of symptoms, anatomic lesions, and anatomical pathology, it has now as its chief aim physiological pathogeny. If this new direction of research has its speculative dan-

gers, it nevertheless promises a future brilliant in positive results. As I have elsewhere shown, it conducts analysis of morbid phenomena with a view to ascertain how far they may be productive of or dependent on the action of material obnoxious to nutrition and nervous reaction, and to demonstrate that, whether introduced into the system from without or resulting from perversion of metabolism, secretion, and elimination from within, these poisonous principles explain the origin and mechanism of much of what is called disorder and disease.

As the reality of auto-intoxication and auto-infection of the organism abounds in novelty and interest, and is every day receiving more and more the attention of the practical pathologist, a notice of the subject in relation to the lessons of Bouchard may be welcome to the studious practitioner, who may have little opportunity of sifting his well-stored page for himself. The pathological field which the survey covers is sufficiently comprehensive.

It may not always be an easy matter to distinguish the *ens mali* from the *agens mali*

in disease, but this teacher while subscribing to the theoretical import of a microbic *rôle* in etiology, unquestionably shows that as yet its range is very limited, and leaves things pretty much as they were. Of the vast variety of ailments man is heir to, some, we know, are contagious or infectious, or are liable to assume that character. His method of investigation, however, clearly discloses the fact that whatever the essential nature of contaminating elements may be, the more their operation on the organism is observed, the more evident it becomes that the vito-chemical processes involved, and their modes of manifestation are in no wise exceptional. Organic reaction is the law of disease, whether its processes are destructive or conservative in their issues. It is always with the nutritive and sensible nervous reactions that pathological inquiry properly commences.

Intoxication may act primarily, that is, directly, but the process of disordered nutrition, as well as those of nervous reaction and contagion or infection, may also cause intoxication; if in a secondary mode, that is, indirectly,

as instanced in those of flabby habit, accompanied with listlessness, depression, indisposition to exertion, and the like. In the renal, cutaneous and pulmonary secretions of such are detected incompletely oxidised products of disassimilations, such as oxalates, volatile fatty acid, etc. Substances which it may be reasonably assumed in some way set up the nervous symptoms, and thus supply a tracing sufficiently indicative of intoxication due to antecedent nutritive disorder. Again, in subjects ordinarily healthy, the same deleterious substances, by excessive accumulation or imperfect destruction, in consequence of loss of sleep, mental anxiety, bodily fatigue or defective hygiene, may induce the same result, and are quite as clearly outlined. Again, in the case of the more pernicious maladies, whether arising infectiously or not, among substances elaborated, some are powerfully toxic even in small quantity, and are analogous to those which are the product of the putrefactive processes, and may become pathogenic agents of systemic poisonings. Bouchard cites in illustration, septicæmia. If in such case, says he,

the malady is accompanied with no important organic lesions, if lesion is confined to the cellular tissues of the region affected, we naturally attribute the general accident to the absorption of toxic materials, alkaloidal or otherwise, elaborated in the course of morbid action. We can hardly understand their having any other origin. To all appearance, then, there are certain classes of disease in which infection leads to secondary intoxication. But, even in normal physiological conditions, and in the best of health, the animal organism is a laboratory and receptacle of what is poisonous. It develops them in disassimilation and secretion. The animal economy is thus the theatre of toxic evolution and elimination—phenomena which are even brought about by putrefactive processes, and which are always, normally present in the fæcal contents of the intestines. Fæcal putrid products defectively eliminated in the course of health, as in disease, may be absorbed and induce intoxication. It is in this way Bouchard accounts for many accidents which accompany dyspepsia and intestinal inaction.

Seeing the importance of the part played by disordered nutrition, nervous reaction and the putrefactive infectious processes continually at work in the economy, we are brought face to face with the luminous conceptions with which Gautier more particularly has enriched modern medical science. We are confronted with physico- and bio-chemical processes of animal organic growth and decay, their chemical products, particularly those now known as leucomaines, and finally with the grand facts that in life as in death, apart from and irrespective of microbic interventional activities, the so-called ærobic and anærobic processes co-exist; that in the higher animals, man included, cellular life, to a very notable extent, is independent of inspired oxygen; that the anatomical elements undergo their transformations and other phenomena of oxidation, but that it is in the organised substance they find it. This is evident from the fact that if we note the amount of oxygen derived from respiration, food and liquids on the one hand, and that returned in carbonic acid by the lungs, skin, and intestinal excreta on the other,

they are found equal. But what of the difference in excess of oxygen by water and carbonic acid? It is obviously derived from the reserve in tissue and cellular elementary combinations. Thus, it is now estimated that at least one-fifth of the vital processes is maintained by oxygen, which is not directly derivable from without, but from within; that the processes of metabolism and disassimilation are in a notable part carried on by the processes analogous to those of putrefaction or fermentation. In the removed excreta and ingesta are to be found the products of the putrefactive processes properly so-called. The comparative study of these processes in the physiology of health, as in disease, is consequently necessary from the pathological point of view. The constituent material of organic substances, that is, the cellular elements having served their purpose, break up, and then their effete noxious material products are set free. Passing into the extra cellular liquids, the resulting products of disintegrative activities are taken up by the lymphatics and thrown into the blood, in whose circulating

current all effete transformed material—that found in the intestines, in part at least, included—finds its way. Elimination being completed in the process of emunction where the skin, lungs, kidneys, and bowels, perform their respective *rôles*.

Thus, all poisons come through the blood. As we have seen, the blood necessarily disposes of its poisonous accessories through the various organs of elimination, and consumes them in the circulatory current in contact with the red globules. This being the case, can the blood be regarded as otherwise than toxic? Constantly traversed by noxious impurities it must necessarily and invariably contain toxic elements. Bouchard has shown that it is really toxic, and has succeeded in very closely defining the limits within which it is so; and this has enabled him to conclude that man would die from poisoning if the blood contained ten times more toxic material than it normally contains. But it is to the plasma that this applies. Its cells, like all other cells of the organism, contain elements potentially deleterious. The constituents, how-

ever, can only be set free by disassimilation or destruction of the cells themselves. Some are remarkably toxic and form two orders: the organic, largely alkaloidal; the other inorganic, mineral matter.

In co-operative combustion and elimination, then, lies the safeguard of the economy. This physiological conception admitted, its experimental verification has to be considered, say in the kidneys and their functions to begin with. The urine gives the key to the problems of intoxication, and forms the necessary introduction to the subject as a whole. This secretion has always been held as toxic, but of experimental proof of it there was little until Feltz's and Ritter's study of the point. But even their work left much to do, at least in detail. It remained for Bouchard to accomplish it. He found the urine toxic, and set himself to a systematic course of venous injection, conducted on the lower animal; he ascertained the intensity and variation of toxicity in a given weight of animal substance furnished in a given time, and in this way arrived at the comparative unity of urinary toxicity present.

Proceeding on these lines he has been enabled to give numerical expression to these, and in doing so has endowed pathology with yet another term—*urotoxy;* that is, the standard of toxicity of urine necessary to kill a kilogramme of living substance. It is very singular to read these values, in terms, of living animal matter that may be killed by given quantities of urine under examination; but it is not an easy matter to detect a fallacy in the procedure, one which promises a ready method of estimating specific actions of multiple poisonous constituents. By examining the normal urine passed in twenty-four hours he forms his urotoxic standard, and studies carefully the variations of toxicity in physiological conditions, and in various pathological states. In this way he establishes the fact that urine per kilogramme fabricates in twenty-four hours sufficient toxic matter to kill 464 grammes of living substance, or nearly the half of what would kill himself in forty-eight hours, all things equal. Variations are significant, and are dependent, in normal urine, on vital conditions, muscular and cerebral activity, ali-

mentation, sleep, etc., etc. Whilst dealing with familiar phases of investigation, Bouchard presents us with others which are altogether new and startling. He finds, for example, that night-urine is denser and richer in solid material, and always less toxic than day-urine; that during the hours of sleep man eliminates from two to four times less poisonous material than he does during an equal time of wakefulness or cerebral activity; further, that the toxicity of night and day urine not only differs in quantity and quality, they are also antagonistic in their action, and neutralise each other. The urines of the sleeping hours are always distinctly convulsivant—stimulant—while those of the working hours are soporific—narcotic—the organism by this mechanism thus eliminating during wakefulness material, which, if accumulated in the system, would induce sleep, and during the hours of sleep eliminating that which would induce wakefulness, thus opening up fresh lines of physiological speculation and research of the most vital and interesting kind.

VI

In continuation of Bouchard's investigations the elimination of toxic substances rendering the urine toxic, explains why the system escapes their deleterious action. The method and mechanism of their formation now claims a closer examination, especially the co-operative *rôle* of the liver and intestines. The bile which periodically flows into the alimentary canal contains poisonous elements, particularly in its colouring matters; less toxic are the biliary salts. Normally, however, secreted bile is little dangerous to the economy, and this by reason of the colouring matter and the salts in a great measure finding their way into the bowels. The intestinal ingesta undergoing putrefaction gives rise to the formation of toxic substances, but in the slow and intermittent passage of the fæces, a part, at least, of the toxic elements is liable to absorption through the mucous surfaces, and finds its way into the *vena porta* where it is arrested, when what is not rejected again into the intestines passes into the general circulation.

The alimentary canal is in this way a cause of poisoning to the system, and the question of intoxication from this source has consequently received much attention from observers such as Gautier, Brieger, Mosso and others. But it is to Bouchard we are chiefly indebted for our information. He has taken up the subject, extending it in its physiological and pathological applications more particularly. He has investigated the subject, and shown that alkaloids exist in the fæcal materials; these alkaloids are of several kinds, and that when markedly present in the intestines they are found to be markedly present in the urine also. After Stick, he has confirmed the fact of the toxicity of the fæcal matters. He has examined the toxicity and shown that it is due in great part to potash and ammonia; but that, even when relieved of these elements, they still retain a certain degree of toxicity which must not be disregarded. He shows that intestinal antisepsis, which disposes of the alkaloids of the fæcal and urinary matters at the same time, diminishes the toxicity of both. Thus, knowing the urinary poisons and

their various sources, he has been enabled to study that form of intoxication which is due to their retention, and known as uræmia, whilst carefully keeping clear of the urotoxic accidents liable to intrude themselves and complicate matters in disease of the kidneys, such as albuminuria, arterial œdemas, including, for example, that of the brain. By this means he has obtained decided proofs of the fact of the reality of toxic uræmia, while showing that the urine is not toxic. He shows that the uræmic urines are not toxic, for the reason that all the toxic substances which the urine normally eliminates are found to be retained in the organisms of those affected. To the question: "Is all that is retained toxic, or is only a portion of it, and, if so, which portion?" he finds it is neither the urea nor the potash exclusively. Neither of these of itself explains the intoxication. Each of them contributes in part, though differently, to that condition as a whole; the colouring matters three-tenths, the extractive matter one to two-tenths, potass and mineral matters four to five-tenths. A knowledge of the multiplicity of the toxic

agents enables us to understand, according as one or other of these eliminates, the various clinical forms uræmic poisonings may assume, the convulsive or comatose in particular. The presence of certain special symptoms, such as hypothermia, contraction of the pupil, and pathological intoxications, which he endeavours to show, not only satisfy scientific curiosity, but are suggestive of practical application and have a therapeutic value.

Next he proceeds to examine the morbid conditions which are caused by gastric embarrassments, of which excessive accumulations, constipation, and intestinal obstructions are examples. He traces the history of a variety of intoxications of intestinal origin, citing that of Senator, in which the offending element was sulphohydric acid. Poisoning from fish, which he personally observed, and in which the presence of an excess of alkaloidal substances, to which the same might be charged, was present, and refers to the instance of over-kept stuffed goose, in which Brouardel and Boutmy succeeded in isolating toxic alkaloids, showing that all these cases had actually passed through

infection to intoxication. There was detected between the ingestion of the putrid aliments and the setting in of toxic symptoms a period of incubation. It appeared to him that the poison, elaborated by microbic action of the goose meat, was too small in quantity to induce poisoning, but the microbic putrefaction acquiring a greater intensity in the intestinal canal became much increased, and then the toxic products were sufficiently abundant to produce intoxication. Here, again, incubation compels us to admit infection; but that the infectious agents manufacture a poison, and infection results in intoxication. Bouchard holds that the usual circumstances under which such accidents of toxicity take place, in consequence of the formation of poisonous elements in the digestive tube, is in the singular condition he recognises as dilatation of the stomach, and which—apart from dyspeptic troubles as nervous derangements always acknowledged in the *cortége* of dyspeptic disorders—seems to him to be capable of setting up many other disorders, such as albuminuria, a condition usually chronic, and liable to become per-

manent, but amenable to treatment, and that successfully when the real cause has been discerned. It is by setting up anomalous gastric fermentations, which extending to the intestinal canal, give rise to the formation of poisons, particularly acetic acid, that dilatation of the stomach vitiates nutrition of various structural tissues, even of the bones and cartilages, and may not be a stranger to ostiomalacia, nodular rheumatism, perhaps including rickets. Of other maladies dependent on matured intoxications caused by dilatation of the stomach, he thinks the most manifest are chlorosis and pulmonary phthisis.

This may take some by surprise. It is, however, dealt with in a most exhaustive manner by the learned experimentalist, who, if he does not convince, at least makes it very probable that dyspeptic and gastric affections must henceforth be given a wider range in pathological research. It may be difficult to accept the lengthened list of maladies dilatation of the stomach is parented with. Still it must be owned that it is precisely with respect to this question of etiology that we are most

ignorant, and any rational examinations of it based on demonstrated fact ought not to be lightly estimated, thus indicating the *rôle* which secondary or indirect poisoning plays, even in infectious maladies. Bouchard proceeds to lay down his views regarding the treatment of typhoid fever, in which he sees chiefly indicated intestinal antisepsis, and general balnear anti-thermics, and a particular line of dietary, thus laying down, *à propos* of enteric fever, general rules which might be found applicable to other acute maladies.

He next goes on to show that part intoxication holds in jaundice, pointing out that here intoxication is twofold. The bile, contrary to to what has been hitherto supposed, is toxic, particularly in its colouring matter, and that which protects the organism from the action of this element is the urine, which eliminates incessantly one part of it; there is also the cellular tissue, the white fibres of the fibrous tissues of which, fix or take up colouring matter not eliminated, and which, should it remain in the circulation, would seriously affect the functional play of the nerve cells. As for

the other part, the biliary salts, they go to augment disassimilations, to destroy the muscular cells and blood globules, thus liberating the poisons, organic and mineral, particularly potash.

In maladies that give rise to jaundice, the liver, which is normally charged with the protection of the organism from intestinal poisoning, is deranged or obstructed in its functional action. It ceases to fulfil its part; it ceases to manufacture urea—the diuretic *par excellence*. It is the urea, which, by forcing the renal barriers, conveys with it the other toxic materials. By its means a complex process takes place of intoxication, whose successive phases are cholæmia, acholia, and uræmia. There consequently can be but little question that the safeguard of the organism from intoxication lies chiefly in the kidneys. So long as this organ is functionally active, the urines of jaundiced subjects are very toxic, not from the bile which they contain, but from the material resulting from the unusual and increased disassimilation. When the kidneys cease to discharge their function of depuration, the urine of the jaun-

diced patient ceases to be toxic; and the patient becomes poisoned from the retention in the system of the poisons that failed of a normal discharge.

But the normal poisons are not alone in question in all intoxications. Bouchard points out in the acute atrophy of the liver the presence of a singular substance produced by the organism, which elaborates vitiated material; and further points out unusual albumen, unusual transformation of medical agents, such as naphthalin, which ceases, in the case of hypatic atrophy, to be eliminated in the state of naphthy-salphite of soda; some of these are toxic. Again, we are reminded that in glycosuric patients, besides accidents resulting from the complete destruction of sugar formed by the organism, this body may give rise to substances which, in the urines of subjects suffering from diabetic coma, take a wine-red colour in contact with perchlorate of iron. These substances, however, are not alone met with in the diabetic, for they have been detected in the cases of dyspeptic coma, in certain cases of cancer of the stomach, and

permanent anuræia, leucocythæmia, and more recently Bouchard has met with them in typhoid fever. These substances, as experimentally proved, are toxic. Contrary for the most part to the auto-intoxication hitherto exposed, that called acetonæmia is an intoxication by an anomalous poison, a morbid poison.

In cholera, also, there is sometimes the formation of anomalous material, and some of these are obviously alkaloidal; this is detected by the violet colour given by the urines of cholera patients, even on emission, while under naphtalin medication. But cholera is an example of multiple intoxication, and Bouchard has shown that in choleraics there is present a special poison, practically unknown, elaborated by the organisms. This substance appeared to Bouchard to be clearly evidenced from the specific toxicity of the urines of choleraic subjects when injected into the veins of rabbits; they determined in definite symptoms characteristic of cholera, though not the malady itself. He has also pointed out that, besides the accidents which choleraic intoxication exhibits the persons attacked are subject

to secondary intoxication consequent upon suppression of urine. This is from the retention of the normal poisons. Myosis—pupilar contraction—is present as the clinical criterion of uræmic intoxication having taken place.

Bouchard's admirable course on auto-intoxication closes with therapeutical applications deduced from the pathological conception which the study imposes. The treatment of auto-intoxication draws largely on the antiseptic method; and we naturally wish to know what may legitimately be expected of antisepsis in general. We know that the mastery of the mechanism of maladies does not bear with it the mastery of the remedy, but from the lucid exposition on this head, good results, if limited, may be reasonably looked for.

VII

If the student interested in pathology, and more particularly pathogenesis, may well exclaim—Where are we now?—the practitioner of thirty years' experience may safely assure himself that we are pretty much where we

were before. The speculative gropings of pangermists in general may have added some brilliant pages to the romance of medicine, but very little to our knowledge of disease and still less to its alleviation or cure. It must now be evident to many thinking minds that the so-called scientific method in medicine is no substitute for judicious observation, seeing that mathematical accuracy is out of the question. Precision in medicine is possible only in the direction of the fact realised—that is to say, in the evidence of physical alterations of living substance, as seen in lesion and its signs. As to the morbid act, that is to say, disease in the evolution, it escapes all efforts at precision, for the simple reason that the act which is the *to be* is always subordinate to the vitality of the organism affected, and so necessarily dependent on the forces of that organism and infinitely variable as these forces themselves.

Chiefly due to Lœnnec, instrumentation has gradually usurped the place of observation and the unaided senses. The stethoscope has suggested the still increasing list of scopes, and

the microscope has long been thought essential in the autopsy of the living as well as of the dead body wherever morbid results, processes, or even causes are in question. The examination of all that is physical in the phenomena of life is doubtless of much importance in pathology; mathematical precision may even be desirable, but only, be it observed, where precision is possible, that is, in the domain of the physio-chemical phenomena of life, in the domain of accomplished facts. In the order of dynamical processes it cannot be reckoned on. In medicine the danger which it threatens is a disregard of clinical observation. The undue study of lesion is liable to lead us to lose sight of the patient, and to indulge in estimates, illusory and incomplete, and of the malady as a whole from which the patient may be suffering. It is the living organism as a whole reacting on itself that we chiefly have to deal with in disease.

This great guiding principle has been lost sight of. The change of method has led to change of doctrines, and wondrous is the history thereof. The generalisers of disease be-

came localisers of disease, and now we witness another transformation, wherein ardent supporters of localisation are becoming equally ardent for generalisation. Having confined a given malady to a given organ, then to some parts of its parenchyma and later to its elementary cells, they have finally displaced it altogether and find in the alien microbe the cause and essence of the morbid evil. For example, pneumonia which used to be regarded as a general affection with a local pulmonary manifestation, became in the hands of the precisian pure inflammation of the lungs, a disease of plastic exudation. Histology, triumphant for a time, cellular caprices monopolised the attention; finally, the morbid microgerm found favour and the pneumono-coccus was discovered. But anatomical pathology, anatomical histology and bacillography do not exhaust the phases of the study of this illustrative malady. For some reason or other the pneumo-coccus is not permanent, nor pathognomonic of pneumonia. It would appear that the pneumono-coccus may become an endocardo-coccus in endo-carditis, or a me-

ningo-coccus in meningitis; thus it loses all claim to specificity, and now we are in the presence of another transformation; from humoralism we have passed to solidism, from solidism we return again to humoralism, and the microbe is only the connecting link. The first authorities, Pasteur, Koch and Brieger are convinced that the cocci, as we have already pointed out, are not dangerous in themselves, but only through certain deleterious matters which they give rise to in the animal economy.

Investigation is now in the direction of the animal alkaloids and their effects. The researches of Brieger have most important bearings on the subject. His recent work abounds in views and facts, which to some extent were utilised in our first edition. The author endeavours to demonstrate the great importance of the relations that exist between the three orders of study, microbes, ptomaines and maladies, supporting them by a series of investigations rigorously carried out according to methods of his own, and exposes the fact that microbes have the property in the course of

action of forming nitrogenous bases of chemical species perfectly defined, and he then proceeds to show that these alkaloids, even in the minutest quantities, are capable of giving rise to disorders more or less serious, and even to death itself—disturbances which frequently present relations analogous to those observed in the course of well-known infectious and other maladies. Researches on these lines Brieger has applied to septicæmia, where the tendency is in our day to award the preponderant *rôle* to chemical phenomena accompanying bacterial invasion.

Leading theorists loudly attribute to microbes the power, very enigmatical, of engendering maladies, but until now imperfect clinical attention has been employed with a view to clearing up the mystery that envelops these pathological properties. The subject is, however, of the highest importance to the clinicist, as indicated by the morbid phenomena which present themselves in the course of experiment. Abnormal temperatures, functional arrest, weakening of the mental faculties, disturbance of the most important acts of nutrition and

digestion—all force us to admit that in morbid conditions the organism is profoundly affected by abnormal chemical activities. Brieger points out, for instance, that the organism attacked with septicæmia is the theatre of chemical phenomena of an order very different from that which exists in the healthy state. He finds very striking evidence of this in the increase of phenol eliminated in the case of certain infectious maladies, such as diphtheria, erysipelas, pyæmia, and scarlatina, but at the same time repudiates the hypothesis based on intestinal putrefaction, which was admitted in cases of such maladies; and he confirms the fact that typhoid maladies, whether abdominal or recurrent, develop themselves without increase of phenol in the urines, irrespective of relaxation or constipation of the bowels. He further shows that in the greater number of cases of scarlatina observed by him this product increased during the period of the eruption, whilst, on the contrary, it decreased in the corresponding period in the case of measles. Yet we know the close resemblance of these maladies. He observed

the same in erysipelas and pneumonia, and thinks it to be therefore erroneous to suppose that intestinal fermentation plays a part in, or has anything to do with the matter. Thus it follows that the marked augmentation of the normal products of elimination which accompany infectious maladies justifies the conclusion that there are parallel gradations of consecutive chemical phenomena going on —processes of infection—and which are certainly not putrefactive.

It follows that the figured species of the cocci, bacilli and the rest are now of little consequence; it is the physio-chemical processes which they initiate that is all-important in the problem. The microbes are now discovered to be merely the porters, the carriers of disease, in infection. But how they act under the new conditions is the question. Formerly they were supposed to act mechanically on the mass, by emboli, etc., or traumatically by destruction of the living cells or organs by some more delicate physio-chemical action, as depriving the hæmoglobine of its oxygen and thus causing asphyxia; but, according to each hypothesis, the

microbes acted *per se*. Now all is changed. Leading bacillographers admit that it is not the bacilli, but the animal alkaloids which their action gives rise to, or genders, and these in turn become the object of research. The cultivation liquids of the particular form of bacilli associated with all these particular maladies specified now undergo chemical investigation with a view to the direction of the alkaloidal poisons, and apparently with much success.

But leaving germ-pathologists to exploit their new position, we must insist that the phenomena of disease, even to the most essential processes, are possible without the intervention of micro-organisms, bacillar or otherwise. And why not? Seeing there are so many diseases without them, such as hydrophobia, to begin with? The term animal alkaloid has been sufficiently explained. Those vital, or leucomaines, having been discovered to be true poisons which are formed during the transformations of the living cells, are liable at all times to lead to auto-intoxication, if we had not the power of getting rid of them by physiological combustion and excretion. Gau-

tier has succeeded, as we have seen, in isolating some of the agents which the healthiest of them are ever producing, as xantho-creatinine and cruso-creatinine, for example. Some of the maladies attributed to this cause we have already indicated: uræmo-typhus,—uræmia, cholo-typhus,—fatal jaundice, athero-typhus,—ulcerative endo-carditis, puerpero-typhus,—puerperal fever, and the like.

It is surprising that such poisons should result from healthy cell life, but the venom of the cobra is analogous. Their presence has been demonstrated in the breath even by Brown-Sequard and Arsonval, and also in the perspiration and the urine without any accompanying trace of microbes. The clinical observer ought then to turn attention seriously in this direction, and while trying to get rid of the new errors, add to the store of old truths. The clinical teaching in vogue for some years past has become altogether speculative, is incapable of affording a correct or adequate conception of the nature and mechanism of disease. This is not denying some indebtedness to the efforts of eminent experimentalists in

hazy regions of germ-pathology. But we must not forget bio-chemical elements which occupy the most important part in our analyses of disease. Neither in the teacher, far less in the practitioner, should theory usurp the place of careful clinical observation. Here it is above all where the claims of nature and art in the cure of disease can be made evident with satisfaction to ourselves and also to the patients.

VIII

The discovery of the leucomaine alkaloids is too recent to admit of tabulation as regards their physiological action. It may, however, be safely affirmed, that where they have been obtained in sufficient quantity for experimental purposes, they have in general been found to be deleterious to the animal economy, and this irrespective of the group to which they belong; that in variety and toxic intensity they are comparable with those of the ptomaine or cadaveric alkaloids, as these latter are with those of vegetable origin which supply us with the most active known as yet.

The kreatinic leucomaines, Gautier assures us, are deleterious,—xanthine, for example,—in very small traces. They exert a powerful influence on the nervous centres, producing sleepiness, lassitude, or occasionally vomiting and purgation; they operate, in fact, in the manner of the alkaloids derived from venoms, though less actively.

The spleen alkaloid of Morelle, as reported by Labord, may be taken as typical of the toxic bases of the structures, special or general. This observer noted its action as embracing stupor, paralysis of reflexes, convulsions and death. Injected into the cellular tissues of the guinea-pig, frog, etc., there is immediate toxic action, followed by collapse, gradual functional subsidence, with death in a few hours. The post-mortem appearances may also be regarded as of general application. There is marked and rapid visceral ecchymosis and œdematous infiltration, with cardiac systolic arrest.

Interest obviously increases as we approach the excremental products. The study of the intestinal and urinary excreta to begin with,

notwithstanding all that has been done, shows new and yet more complex aspects of the chemical problem to be dealt with.

The probable double origin of the intestinal leucomaines, for example, does not materially affect that of toxic action. The alkaline base that Pouchet isolated in the form of chlorohydrate, is unquestionably poisonous, a fact of which this eminent investigator had serious personal experience. It is found sufficiently energetic to control the heart's action, and to induce death, followed rapidly with cadaveric rigidity. This authority has also met with traces of alkaline substances in the cultivation liquid of the comma bacillus of Koch, and which would appear to be identical with the preceding. The more recent examination by Villiers of dejections of choleraic subjects, goes to strengthen this impression.

Whether defined or undefined, as has already been remarked, the urinary leucomaines stand first, in interest and importance, in a physiological sense. It was through the urines that their discovery and investigation was first entered on; it is through them that the pre-

sence of the alkaloid in varying traces is being recognised as a valuable index of the state of the animal economy, so variable in the conditions of health and disease. Clinically, this must soon come to be admitted. Facts such as these explain the value some would attach to them, and encourage the study rather of their pathological significance than of their chemical definitions, a field where much more caution is requisite.

Though scarcely traceable at times in normal, healthy urine, the alkaloids show, as Gautier has clearly established, their amount to be relatively increased in disease. Lépine and Guérin find that in the course of certain fevers, for instance, their poisonous quality increases in due proportion until the crisis is attained. But their presence is not perceptible in all maladies indiscriminately, nor always in a like degree in those where they are perceptible. The above-named investigators, for example, have detected the presence of alkaloids in the urines of typhoid and pneumonic patients, but not in those diabetic. Again, it has been ascertained experimentally that the basic

products vary according to the morbid conditions, not only in their toxic activity but also as regards their chemical characters. On this point we are indebted to Bouchard for his extensive and delicate examination of urines. He has, for instance, given the average of the alkaline products of his typhoid fever patients during a space of twenty-four hours, and shown that the leucomaines in certain forms of this fever, and under certain morbid conditions, are not so potent as might be supposed; experimentally, they need not even pass beyond simple dilatation of the pupil and acceleration of the heart's action.

Supposing that we turn from human urines to human salivas. In these, as we have seen, Gautier has also found extractive matters which respond to alkaloid reagents, and which further investigation will show to be not without analogies with the preceding, should their toxic properties be verified. The extract obtained from about twenty grammes of pure saliva secreted during the day, when injected into the subcellular tissue of a small bird, produced intense stupor

and drowsiness, which lasted for some hours. Bouchard's day urine alkaloid induced the same effects, while that of the night was exciting even to convulsions. It is not impossible, as Hougenenq suggests, that the night salivas of man might exhibit a similar action, and be also convulsive. The observation is worthy of the attention of the physiological experimentalist, as there is a possibility that the toxic principles of the human saliva, if not identical with that of human urine, at least obey the same laws, though widely differing in their elementary natures.

From man to the inferior animal is but a step. Passing from the salivas of man to those of the poisonous reptiles, the difficulties of the subject increase, and the greater caution is required in dealing with them. If the venoms of certain snakes, for instance, have long excited scientific interest and attention, it has been more with a view to the controlling of their terrible effects, and the discovery of specific antidotes, than to their chemical nature and constitution.

Researches are by no means exhaustive,

but there is little doubt that the toxic action of the snake-venoms is not simple, but multiple, due to the presence of various nitrogenous principles, of which the most energetic is not of an alkaloidal nature. Brieger has, however, as already stated, been enabled to isolate two leucomaines,—precipitable with Nessler's reagent and the iodide of potassium,—which give salts and metallic chlorides in well-defined crystals, and induce in smaller animals well-marked physiological effects.

The fact is well attested that certain classes of fish possess the power of secreting a toxic principle somewhat similar in physiological properties to the venoms of the ophidians. Those known, are met with chiefly on the Chinese and Australian coasts. Carri and Gautier have given attention to this fact, and the latter is of opinion that the venomous glands secrete alkaloid material as a normal function. The active principle has not yet received sufficient experimental examination—either chemical or physiological—to warrant conclusions on this point.

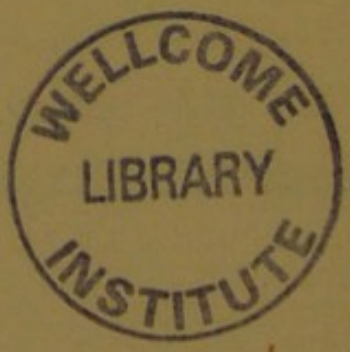
Poisoning with shell-fish too frequently

occurs to escape notice. Here, again, it is only very recently that the probable nature of the poisonous principle has been suspected. That of the common mussel is an example. Brieger has succeeded in isolating from that mollusc its active principle—mytilotoxine. He has even studied and defined its chemical and physiological properties; its effects curaraizing or convulsivant on animals, inducing death by accumulation of carbonic acid in the blood, and paralysis of the motor nerves. It thus resembles the impure extracts in its effects. This base is, however, not the only one; Brieger has detected several others, which are less active, or altogether inoffensive.

The same authority also confirms the observation made by Salkowski, relative to the removal of its toxic properties by distillation with carbonate of soda. This supplies a fact in physiology and hygiene, of important practical application, which has not been lost sight of by consumers.

In taking leave of this subject, it is but proper to repeat that, though the presence of

poisonous alkaloids in the foregoing secretions is not to be questioned, they do not alone explain the whole of the toxic phenomena, and leave us still in doubt as to their import in those cases where other azotized principles preponderate.



THE

ANIMAL ALKALOIDS,

CADAVERIC AND VITAL;

OR,

THE PTOMAINES AND LEUCOMAINES

Chemically, Physiologically and Pathologically considered in relation to Scientific Medicine.

BY

A. M. BROWN, M.D.

With an Introduction by

PROFESSOR ARMAND GAUTIER,

Of the Faculté de Médecine of Paris, and Member of the Académie de Médecine and of the Académie des Sciences.

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