Ptomaines and other animal alkaloids : their detection, separation, and clinical features / by A.C. Farquharson.

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AND OTHER ANIMAL ALKALOIDS

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ANIMAL ALKALOIDS:

Their DETECTION, SEPARATION, and CLINICAL FEATURES.

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PREFACE.

This little book lays no claim to originality. An attempt is made to bring together in an accurate and concise *résumé*, the main facts pertaining to a subject which does not receive the attention in this country that it deserves.

The statement made regarding metabolic and putrefactive products as causative agents in certain forms of acute mental disease may have the appearance of novelty, but it is in reality only an interpretation of old facts in the new light of modern research. If this book is of assistance to anyone who may be engaged on the same subject, it will not have been written in vain.

A. C. Farquharson.

The County Asylum, Lichfield,
May, 1892.

CONTENTS.

CHAPTER III.

CHAPTER IV.

CHAPTER V.

CHAPTER VI.

PTOMAINES,

And other Animal Alkaloids.

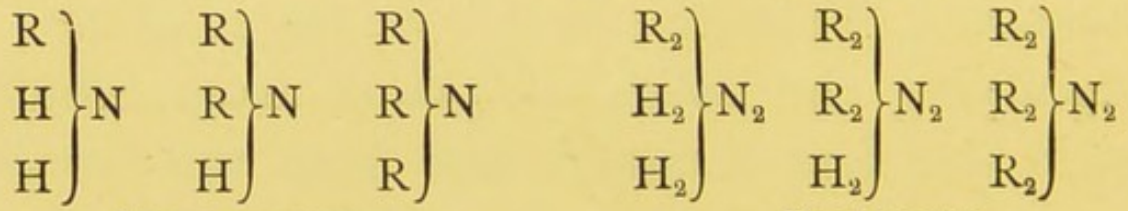
CHAPTER I.

ON ALKALOIDS IN GENERAL.

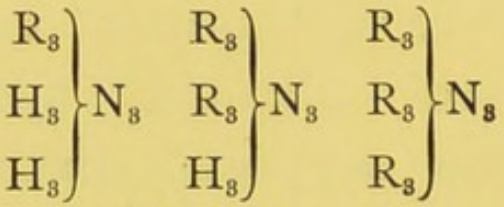
THE term "Alkaloids" is used in chemistry to denote a group of bodies possessing properties similar to those of the alkalies, soda, potash and ammonia. From the Arabic we have "al-qali" signifying the ashes of plants from which soda was first obtained, and from the Greek we have "ειδος," likeness. From the union of these two words "al-qali" and "ειδος" we have the word "alkaloid," alkali like, and indicating the supposed exclusively plant connection of these bodies. Terminology.

In all natural alkaloids, nitrogen is found to be present, and it may be regarded as THE essential constituent. In recent years many alkaloids have been artificially prepared, in which this nitrogen is substituted for phos- Constitution.

phorus, arsenic, antimony, etc., but it is not proposed to deal with these here. So far as regards their constitution, natural alkaloids are generally regarded as products derived from ammonia by a process of substitution, the hydrogen atoms of the ammonia being replaced by radicals as $(C_2 H_5)$ $(C_3 H_5)$, etc. To the compounds so derived, the termination "amine" is applied, and by substituting the hydrogen atoms in one or more molecules of ammonia we obtain mon-amines, di-amines, tri-amines, according as one, two, or three molecules have been used. This is usually represented in the following formulæ. Let R = radical employed :—



MONAMINES. DIAMINES.



TRIAMINES.

It will be observed that one or more hydrogen atoms may be substituted in *one* molecule of ammonia, and where the radical is say ethyl (C_2H_5), we have from the substitution of one hydrogen atom monethylamine; from

two atoms diethylamine ; and from three triethylamine. Thus an almost interminable series of bodies of the nature of "amines" may be obtained.

Source. Until recently the vegetable kingdom was regarded as the only source from which alkaloids could be obtained, but it is now known that bodies which are in every way identical with the vegetal alkaloids are elaborated in animal tissues, excretions, secretions, etc., and can be obtained therefrom by suitable methods of extraction. They are not necessarily products of the vital activity of the tissues, or of the protoplasmic elements of these, since they have been abundantly found in the bodies of organisms long after death, and in animal fluids long after the vital functions have ceased.

Origin Their development, however, both in plants and animals, and the successive steps in the re-arrangement of the atoms of either plant or animal substance, which result in the formation of any definite alkaloid are still subjects of investigation.

In living plants. "With regard to the origin of alkaloids in the plant, there can be little doubt that they are derived more or less from proteids. It is an almost necessary assumption that they are

built up from ammonia; we have therefore to enquire into the possibility of the formation of ammonia in the plant. It has been suggested that ammonia is formed in connection with the processes of destructive metabolism, and under abnormal conditions ammonia may be even excreted. The mode of the formation of ammonia in the plant is not difficult to imagine. It is well known that the 'amides' are readily decomposed into organic acids and ammonia. Thus, when asparagin is boiled with dilute acids or alkalies, aspartic acid is formed, and ammonia is evolved according to the equation:

$$C_4H_8N_2O_3 + H_2O = C_4H_7NO_4 + NH_3$$

"It is therefore quite possible that free ammonia may be formed in the plant, and that from this the alkaloids may be built up. It is interesting to note in connection with this that neither urea nor uric acid have ever been found in plants. According to a commonly accepted view it would appear that these bodies may be formed in the animal body from leucin and tyrosin; these substances apparently undergo decomposition into CO_2 and ammonia, and the carbon dioxide and ammonia combine to form urea and uric acid. We have every reason to believe that the

alkaloids are in reality waste products, that is, substances which cannot enter into the constructive metabolism of the plant, for the observations of Knop and Wolf show that the demand for combined nitrogen cannot be met by supplying the plant with it in the form of alkaloid." * The suggestion is here thrown out that in the formation of an alkaloid we have for a starting point the formation of ammonia, this being formed as the result of processes of destructive metabolism occurring in the plant. Then from ammonia by synthetic processes similar to those occurring in the human body, and resulting in the formation of urea, we have a building up of the more complex alkaloid. These changes in the plant are influenced by external agencies, and Vines mentions especially certain physical conditions necessary to their formation. Light is of great importance. " Tropical plants which produce these substances in abundance in their normal habitat produce only small quantities when grown in hot-houses in this country. On the other hand, it appears that too intense a light is unfavourable to the accumu-

Action of light.

* Vines' " Physiology of Plants," page 224.

lation of alkaloids, for it has been observed that in certain cases plants which have grown in the shade are richer in alkaloids than others which have been exposed to the full glare of the tropical sun." * But while light may thus appear of importance as a factor in the formation of alkaloids, it can only be considered of secondary importance in so far as it is only one of many factors which go to make up the environment or habitat of the plant, all of which, varying or modified, will, in a greater or lesser degree affect the vital processes occurring in the plant, and indirectly the elaboration of alkaloids.

In dead vegetable matter.

Alkaloids, however, are not exclusively the accompaniments of vital processes in organized structures, but are often vigorously developed in plants, plant tissues and fluids, long after all vital physiological processes have ceased to occur in them.

Lembrose and Erba showed that decomposed maize contained alkaloidal bodies, and that the products of this maize contained poisonous principles, extracts of which produced when administered to animals tetanic

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* Vines' "Physiology of Plants," page 268.

and narcotic symptoms. Poehl, of St. Petersburg, has endeavoured to establish a connection between the epidemics of *Ergotismus gangrenosus* which occurred in Russia in 1832 and 1837, and the development of an alkaloid in the meal used for making the bread eaten by the infected persons.* Eichwald, amongst other conclusions arrived at in relation to these epidemics, pointed out that the putrefaction of the grain is a necessary condition of the ergotism, and that toxic results are produced only in certain stages of the decomposition.

Poehl further elucidates the development of these bodies as follows:—(1,) The conversion of the starch of the grain into glucose, (2,) Fermentation of glucose with formation of lactic acid, (3,) Peptonisation of the albumins by the peptic action of the mycelium of *Claviceps purpura*, (4,) Conversion of the peptone into ptomo-peptone, and its decomposition with formation of putrefactive alkaloids. He further observed that rye grain, though not attacked by the claviceps, but merely exposed to damp, evolved trimethylamine when heated with alkalies, in this agreeing

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* Journ. Chem. Soc., Lond., 1883, page 1157.

with the fact that albumins generally evolve ammonia or amines under the action of alkalies, at the moment of putrefaction. Tainted rye-meal under similar conditions decomposed more readily with a greater elaboration of putrefactive alkaloids. These changes are brought about, he asserts, by the peptonising action of ergot and mould: ptomopeptones are formed, and these, when heated with sodium hypobromite yield nitrogen, which may be taken as a measure of the conversion, the degree of putrefaction being directly proportional to their peptonisation. It has also been observed in epidemics caused by maize, that a form of mildew appears in the grain, which has the power of peptonising albumins, so in changes occurring in rye, rye-meal, maize, oats, etc., we have fermentation of glucose formed from the starch, peptonisation of the albumins, and finally, formation of the putrefactive alkaloid. While it may be safe to aver that these phenomena undoubtedly do occur, it cannot be said that they reduce the formation of a putrefactive alkaloid to anything of the nature of a chemical equation. They may be products derived from ammonia formed early in these changes, or ammonia may appear simply as a by-product

or indirect measure of their formation, but there is no doubt that whether in living or dead plants they are always found associated closely in some way with ammonia and ammoniacal products.

In animals.

Until recently alkaloids were not looked for in any animal or animal product, unless putrefactive phenomena had ensued for some time; but it has been determined that these bodies can be obtained also from the excretions, secretions and tissues of animals in an apparently healthy condition, as well as in pathological conditions.

In normal tissues.

They occur as constituents of normal tissues or fluids, and in such conditions are regarded as products of tissue metamorphoses, just as in plants they are regarded as products of destructive metabolism. Fresh saliva and normal urine, according to several observers, contain poisonous substances of the nature of alkaloids; in the case of urine the poison is fixed, oxidizable, and forms a crystalline chloride, and a double salt with platinic chloride and chloride of gold. Paterno and Spicca,* Bechamp,† Gautier and Coppola,‡ have all shown

* Journ. Chem. Soc., Lond., 1882, page 741.

† Compt. Rendu. Tome. xciv., page 973.

‡ Journ. Chem. Soc., Lond., 1883, page 522.

that chemical and physiological properties similar to those exhibited by ptomaines might be obtained from substances procured from normal blood, egg-albumen, normal urine and other healthy fluids which have undergone no putrefactive change whatever, and there is every reason to believe that these alkaloids are formed during the performance of strictly physiological functions.

In normal functions.

Bouchard showed that alkaloids were formed in the body even in health. They appear in the intestines as the result of intestinal digestion, and may be excreted as in the urine, or, retained in the system, may give rise to very distant symptoms of their retention.*

Villiers subsequently challenged some of these conclusions, and contended that the appearance of an alkaloid was significant of deviation, however slight, from normal functions,† but Brieger demonstrated, on the other hand, the production of a poisonous alkaloid, pepto-toxine, during the gastric digestion of 200 grammes of moist fibrin for 24 hours, at a temperature equal to that of the normal tem-

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* Lauder Brunton, *Lancet* for Jan. 10th and 24th, and Feb. 7th, 1885.

† Repertoire de Pharmacie, July, 1885.

perature of the blood.* Gautier, however, in his researches extending from 1881 to 1886, has conclusively shown that they are necessary products of vital functions, and applying the term "leucomaines" to the alkaloids thus produced, he attributes great importance to their presence in the animal economy, and in the genesis of disease. These substances, he asserts, are called into existence during life just in the same way as carbonic acid or urea. Their defective elimination either by the skin, mucous membrane of intestines or kidneys, leads to their retention in the system, thus exercising a more or less energetic action on the nerve centres, the mechanism at work in the production of these being insufficient aeration of the blood, diminished hæmoglobin, or diminished oxidation of the hæmoglobin.

Leucomaines.

It is very difficult to see, however, where this strictly physiological production of alkaloids becomes significant of pathological conditions, and if the alkaloid found be the effect or the cause of the physiological deviation. There can be no doubt whatever, that alkaloids are abundantly found in the animal

* Ueber Ptomaine, Hirschwald, Berlin, 1885.

In pathological conditions.

tissues and fluids in pathological states. The urines of patients suffering from progressive paralysis, pneumonia, typhus or typhoid fever, tetanus, miliary and scarlet fevers, have all yielded in greater or lesser quantities toxic bodies of the nature of alkaloids. They may owe their origin to exaggerated physiological processes, fermentative states, or be the specific product or chemical principle elaborated in the body as the result of the existence of micro-organisms, but anything approaching a chemical formula descriptive of their development has not been discovered. Ammonia has been shown to play an important part in the production of vegetal alkaloids, and it is probable that it is equally important in the development of animal alkaloids. It is impossible to draw any line of demarcation between the two groups, they are both the products of albuminous decomposition and, as Dr. Lauder Brunton points out, it is immaterial whether the "albuminous precursor" be contained in plant or animal, or undergoing decomposition outside or inside the animal body, the result is one and the same, viz., the development of alkaloids. The odour of ammonia has been ascribed to several alkaloidal bases, and it is

well known that patients develop an ammoniacal odour in the course of certain disorders. With regard to this, Murchison says,* "In severe cases of typhus, not only is there reason to believe that the blood is ammoniacal, but the exhalations from the lungs and skin, and the discharges from the bowels contain a large amount of ammonia. It is a common observation that a pungent ammoniacal odour is given off by the skin and lungs in typhus, while the presence of a large quantity of it in the breath admits of actual demonstration. It has also been observed that the cases in which the odour is strongest, communicate typhus more readily to persons in health, and in many cases where the symptoms of typhus have supervened immediately on exposure to the source of contagion, and where we may suppose the poison to have been usually concentrated, the affected persons have been conscious at the time of exposure, of a most disagreeable odour, pungent and ammoniacal."

The injurious effect of respired air is mainly due to organic matter, principally combinations of ammonia; sewer air owes its

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* "Treatise on Continued Fevers," page 114.

injurious effect to carbo-ammoniacal compounds, and in the compound alcoholic ammonias we cannot fail to detect poisonous properties. So it is very probable that ammonia forms in animals, as well as in plants, the starting point for the development of alkaloids, and that with a more vigorous formation of ammonia we have a greater production of alkaloids, and a more evident deviation from normal conditions in the individual.

In cadavers.

To the alkaloids developed in dead bodies, Selmi applied the term "Ptomaines," and that these are abundantly formed in the cadaver has long been known. In putrefying animal tissues and fluids, decomposing albumen, peptone, casein, fibrin, myosin, etc., they can be obtained, ammonia being formed at some stage of their development, and they are only found in the ammoniacal products of the decomposing substances. It appears certain, however, that decomposition must have commenced before ptomaines make their appearance; for the first day, and probably the first two days after death any alkaloid found in the cadaver would be leucomaine or vegetal alkaloid, and this is a point which is of very considerable medico-legal importance.

No strongly toxic bodies are developed, as a rule, until the disappearance of cholin, which along with neuridin, are the only toxic bodies which appear during the first two days, and do not possess any marked toxicity. Brieger asserts and attaches much importance to the following propositions: That in the different stages of decomposition in the human body different basic products are formed, that many ptomaines disappear, their place being taken by others, and that certain bases, though present in spare quantities at the beginning of decomposition, gradually acquire a greater prominence as the other basic substances disappear. So that in the order of putrefaction, basic and toxic bodies as cholin, neuridin, trimethylamine, cadaverin, putrescin, saprin, mydalein, etc., appear for a time only, to be replaced by other and more poisonous bodies.

CHAPTER II.

HISTORICAL.

ALKALOIDS in their relation to disease, apart from their pharmacological and forensic interest, have grown steadily in importance, and no apology need be offered for introducing here a short narrative of the work of the most important of the scientists who have devoted themselves to this subject. The countries of France, Germany, Italy, Russia and Britain have all had workers in this branch of science, and although the names of two or three scientists stand out in relief, yet each has a particular importance from the particular nature of his observations.

Kerner, A.D. 1820.

As far back as 1820, Kerner, and in 1822, Gaspard and Stick, pointed out that symptoms of poisoning would be manifested by introducing into an animal products of decomposing and putrefying organic matter.

Panum, A.D. 1856.

In 1856, the Danish savant, Panum, showed that the inflammatory changes which occurred in the intestines of animals fed on putrid matter were produced by a chemical

poison, and that two or three centigrammes of an extract of these given internally were sufficient to kill a dog.

During the following ten years, researches were made by Stick, Weber, Schweninger, Hemmer and Thiersch upon putrid animal tissues and fluids, deducing therefrom the general fact that a poison was present in these substances and was of a chemical nature ; but they seem to have made no attempt to isolate or determine the exact properties of this chemical substance. In 1866, Duprè and Bence Jones noted the presence of alkaloid-like bodies in the organs, tissues and fluids of human and other animal bodies, and by treating these with dilute sulphuric acid they obtained a solution of the alkaloid which, from its bluish fluorescence, resembled sulphate of quinine, so much so that they gave it the name "quinodin." They were, however, unable to obtain a sufficient quantity in a pure state for ultimate organic analysis.

Duprè and Bence Jones, A.D. 1866.

Quinodin.

In 1868, Bergmann and Schmiedeberg obtained from the yeast of putrefying beer a small quantity of a poisonous nitrogenous and crystallizable substance, to which they gave the name of "sepsin." In 1869, Zuelzer and

Sepsin.

Sonnenschein extracted from macerated muscle which had been kept at a temperature of 25° C. for five or six weeks, small quantities of a crystallizable substance closely resembling atropine in its physiological and chemical reaction. When injected into rabbits and dogs, it dilated the pupils, increased the number of the beats of the heart and, in two animals, completely stopped the peristaltic action of the intestines.* In the same year, while examining dead bodies for medico-legal purposes, Rorsch and Fasbender discovered a tasteless, amorphous substance, on shaking up acid and alkaline extracts of the liver, spleen and kidneys with ether. It closely resembled digitalin.

About the same time Schwanert, while engaged in a similar investigation, discovered in the spleen and liver of a child that had died suddenly, a volatile fluid with poisonous properties, and having an odour like propylamine. Marquardt, Liebermann, Gautier and Hager, during forensic investigations, all noted the presence of poisonous substances, possessing properties similar to bodies as amylamine, propylamine, capryl-

* "Berlin. klin. Woch." No. 12, 1869.

amine, and to one of these Hager gave the name "septicin." Septicin.

Since 1870, however, the subject has attained far greater importance than that merely attaching to it from a forensic point of view. Partially investigated phenomena then began to give place to accurate and exhaustive data, and their relations were seen to be more significant than had hitherto been thought of. About this time the work of Selmi began to attract attention—to him I think falls a large share of the honour of discovering the animal alkaloids—and a spirit of rivalry seems to have sprung up, for numerous papers were contributed by men such as Brouardel, Boutmy, Bechamp, Mosso Guareschi, Grannetti, Corona, Coppola, Balduino and others. Selmi's first observations were made on corpses dead of arsenical poisoning, and it is interesting to observe his methods. The liquid under observation was made alkaline with baryta water, and then extracted with ether; acicular crystals were produced, which precipitated the principal reagents that alkaloids answered to, with the exception of platanic chloride. Selmi's second attempt was made by extracting the liquid with aqueous alcohol, then making

A.D. 1870.

Selmi.

Selmi's early observations.

alkaline with baryta, shaking with ether, and ridding of the ether by spontaneous evaporation and distillation, treating the turbid liquid thus left by water acidulated with acetic acid, filtering and evaporating to dryness, then taking up the residue with water, again rendering alkaline with baryta and extracting with ether, and repeating the process until the liquid became colourless. The alkaloid thus extracted was so strongly poisonous as to destroy frogs with the greatest rapidity.* Both of these extracts were free from arsenic. In the year 1872 he announced in a memoir to the Academy of Sciences in Bologna :—

1.—That the stomachs of persons who have succumbed to a natural death contain substances which behave to reagents like certain vegetable alkaloids.

2.—That these products are neither creatin, creatinin, or tyrosin.

3.—That analogous products are found in alcohol in which flesh has been macerated.

Subsequently, Selmi extracted from the stomach of a hog which had been kept in arsenious acid, a compound of an alkaloid and arsenic of such an intensely poisonous nature

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* "Lancet," Nov. 17th, 1883

as to closely resemble the vegetal alkaloid strychnia, and he tried to show that, under certain circumstances, peculiar arsenical bases, "arsines," are formed. The alkaline liquid yielded on distillation in an atmosphere of hydrogen an alkaline distillate which gave white crystals with hydrochloric acid. These, when moistened with caustic soda, exhaled an odour somewhat resembling that of trimethylamine. The presence of arsenic was determined in the hydrochlorate of this volatile base. If Selmi be correct in his assertion that volatile arsines of a highly poisonous nature are thus produced by the contact of arsenious acid and albuminous matter, it is of importance, in that it may suggest a possible explanation of poisoning from arsenical wall papers Hausemann* thinks it likely that a similar product may be formed from the size employed in affixing the arsenical paper of a room, the moisture of the air playing a part in the formation of the arsine. He thinks also that Selmi's researches throw light upon an obscure page in the history of toxicology. It is asserted that the poisoners of the 17th and

Arsines.

* "Archiv. der Pharm.," No. XVI., 1881, p. 415, and "London Medical Recorder," 1882, p. 259

18th centuries, Toffa and other professionals, understood how to render arsenic more potent. In Italy, the Acquetta di Perugia was, according to tradition, a secret compound prepared by rubbing white arsenic into the flesh of a pig and collecting the liquid which dripped from the flesh. The liquid thus prepared was thought more poisonous than a simple arsenical solution. The same object may have been in view in preparing Aqua Toffanna with the addition of the juice of the ivy leaved broad flax (*Linaria cymbalaria*). Selmi and Valla were of opinion that in Acquetta di Perugia the concealment of the action of arsenic on the one hand, and also of the tetanising portions on the other, were accomplished; but this opinion, which is based on an observation of Valla's in a case of poisoning with arsenic and strychnia, does not accord with observations made on warm blooded animals with a mixture of potassium arsenite and strychnine, the tetanising action of strychnia not being prevented.

Acquetta di Perugia.

Aqua Toffanna.

Selmi devoted the last ten years of his life to this subject, and probably did more than anyone had formerly done for its permanent advancement. He originally regarded

ptomaines as exclusively products of the putrefaction of dead bodies, but subsequently modified his views, and even went so far as to acknowledge their existence in normal structures, and in this he appears to have anticipated what Sir William Aitken refers to as "the crowning discovery" of Gautier, in 1885.* Ptomaines.

About this time this subject attained to considerable importance in Russia.† The Russians were threatened with an epidemic which had some similarity to those which had overrun the country in 1824, 1832 and 1837. A commission was appointed to investigate the subject, and of this commission Poehl, of St. Petersburg, was a member. In 1884 he published, in conjunction with Anrep, a summary of his views on the subject.‡ They said :— Russian commission. Poehl.

1.—Putrefaction, fermentation and other as yet indefinable alterations of albuminous substances, are accompanied by the generation of alkaloid-like bodies—ptomaines.

2.—The number of ptomaines are very

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* "Animal Alkaloids," p. 10.

† *Vide* Chap. I.

‡ "London Medical Recorder," p. 331, 1884.

great, and their chemical and poisonous properties are very different.

3.—There are known fixed and volatile, fluid and solid, amorphous and crystalline ptomaines.

4.—Almost all ptomaines change red litmus, blue; and syrup of violets, green.

5.—In regard to their solubility, ptomaines behave very differently, some of them being soluble in water, others in ether, benzine, chloroform and amyl-alcohol.

6.—Like alkaloids, they form salts with acids, the formation proceeding without giving off water.

7.—Some ptomaines are tasteless or colourless, others possess an intense bitter taste, or aromatic, sweetish odour. Others again, evolve a cadaveric odour, or resemble coniine or nicotine. When treated with acids they emit sometimes a pleasant, floral odour.

8.—Ptomaines obtained from rye meal (and it was to these that the investigation was mainly directed) which has been subjected to fermentation, give the same reactions as the ptomaines of any other extractions.

9.—Ptomaines are optically inactive bodies.

10.—The colour reactions of ptomaines are as various as those of the vegetal alkaloids.

This is a brief resumé of probably the most important inquiry on this subject in Russia, and it seemed to press home the fact that the epidemics were in a large measure simply universal ptomaine poisoning, due to the use of tainted rye meal.

A.D. 1882. Conflicting opinions.

A conflict of opinion seems to have existed about this time as to the permanency of ptomaines produced in putrefying albuminous matter, Brieger, Poehl, Selmi, and others, asserting that one ptomaine was formed only to be changed into another in the course of putrefaction. Gautier and Etard,* in opposition to this, asserted, that whatever be the source of the putrefying albumen, the chief ptomaines formed are constant in properties and composition. But soon after this controversy the idea seems slowly to have gained on scientists that ptomaines were not exclusively putrefaction products, but may be present in healthy fluids and tissues. Paterno and Spicca† recorded experiments made with a view of ascertaining whether substances identical with, or similar to, ptomaines could be extracted from animal fluids in their normal state, and before they had shown any

Paterno and Spicca.

* "Compt. Rend.," tome xcvii., p. 263.

† "Journ. Chem. Soc. Lond.," 1882, p. 741.

signs of putrefaction. The liquids experimented on were fresh blood and fresh egg albumen. After treating with the usual reagents, they showed that reactions could be obtained exactly similar to those produced by the same reagents in solutions of the so-called ptomaines extracted from the dead animal body. Selmi* also suspected that in various diseases there are found in the tissues substances of a poisonous nature which, together with the alteration of the tissues, or by their sole action, determine the death of a patient. He analysed the urine of patients affected with progressive paralysis, insanity and various other diseases, and found that in all these cases, as in the animal body after death, poisonous bases resembling alkaloids were found. The urine of a patient suffering from progressive paralysis, with increasing imbecility, yielded: (1,) A base very like nicotine, but not identical therewith, having a specific poisonous action, especially on the spinal cord, destroying its activity and diminishing the general sensibility, the respirations and the cardiac pulsations; (2,) Another base, but in much smaller quantity, having the odour of coniine.

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* "London Medical Recorder," 1882, p. 339.

The investigations of Gautier, in France, now began to attract much attention; he had announced in 1881 that the excretions of animals contained ptomaines, and he sought to trace in them and their defective elimination a cause of disease. He extracted from the muscular juices of large animals five definite crystallizable alkaloids exhibiting the reactions of ptomaines in a lesser degree. Following up the mass of available data, Gautier, in his more important investigations, extending from 1881 to 1886, confirmed the idea of the normal development of alkaloids in the system and, as has been said, gave to those bodies the name of "leucomaines." As an explanation of the development, under these conditions, of such bodies, he offers the following ingenious explanation:—* Gautier.

"The transformation in the tissues of the higher order of animals is, in a large proportion, of the anærobic order. Four-fifths of the products of animal combustion are positive ærobic formations, comparable to the oxidation of alcohol under the influence of *Mycoderma vini* or *aceti*; the remaining part of the combustion of the animal economy takes

* "London Medical Recorder," 1886, p. 103.

Fermentation in normal tissues.

place at the expense of the tissues, without oxygen playing any part in the process; or, in other words, that portion of the tissue behaves like the anærobic or putrid ferments. Most of the toxic alkaloids are easily oxidized; they enter into combustion and disappear, entirely or in part. In a normal condition a very small proportion of muscular leucomaines is found in urine. But if the air that reaches the blood be diminished in quantity, or if the proportion of hæmoglobin be diminished, as in chlorosis or anæmia, or if substances be introduced into the blood which prevent hæmatosis, substances of the character of leucomaines or ptomaines accumulate in the blood." He further states that, with these toxic alkaloids, there exist nitrogenous substances, not alkaloids, which are still poisonous.

During the last few years Mr. Hankin and Dr. Sidney Martin, in this country, have shown what these more poisonous bodies are, and place them in front of ptomaines as disease-producing agencies, viz., toxalbumens or albumoses.

Brieger.

No name stands out more conspicuously in this field of research than that of Brieger. Contemporaneously with Gautier, Professor

Brieger, of Berlin, was conducting exhaustive and painstaking analyses on putrefaction products and, in 1885, published one of the most valuable contributions to the literature of this subject.* Commencing with the history of the cadaveric alkaloids, he freely criticises the results obtained by his predecessors in this field of research, and points out defects which have been fully appreciated by experts in this country, viz., that the products which they describe generally appear to have been syrupy extracts, solutions in glycerine, and the like—alkaline in reaction and giving some alkaloids or their salts. One common description runs through most writers on the subject—they were brown substances, and underwent spontaneous decomposition with great facility. Brieger also showed the fallacy of supposing the reduction of ferri to ferrocyanide of potassium in the presence of a ferric salt to be distinctive of ptomaines as a class, and discriminating them from vegetal alkaloids. The success of this test seems to depend upon the presence of impurities. In his book he gives 78 analyses of these bodies and their salts, and although Nencki did

* "Weitere Untersuchungen über Ptomaine" (Hirschwald, Berlin).

precede him in giving a chemical formula to a putrefaction alkaloid, to Brieger falls the large share of success in this method of investigation. He has investigated :—

1.—The ptomaines of the gastric digestion of fibrin.

2.—Those derived from the putrefaction of mammalian flesh.

3.—The ptomaines of the putrefaction of fish.

4.—Those of putrid cheese.

5.—The ptomaines of putrid yeast. He gives a complete description of the chemical relations and physiological reactions of these.

Besides the names mentioned as recent workers in this country, may be added those of Drs. A. P. Luff and A. M. Brown. The latter deals with the subject purely from a litterateur's point of view, but the former from that of an investigator.

Ptomaines in fevers.

Dr. Luff has recently investigated the ptomaines in the urine of patients suffering from infective fevers, and has so far brought out some very interesting facts ;* his experiments strongly suggest that there is an increased formation and also elimination of

* "British Med. Journal," 27th July, 1889.

these during the pyrexial state, and with diminution of the pyrexia we have the disappearance of the pathological alkaloid from the urine.

The whole subject, however, is but in its infancy, and recent experimental investigation on proteid putrefactive products suggests that a great share of the toxicity is not due to the pure alkaloid, but to some other albuminous body co-existing with the alkaloid. To this class of bodies may also be added the "tuberculin" of Koch and, in fact, the production of a ptomaine seems to have been the problem he set before himself. There are many workers on this subject at present, and hope for the future may certainly be indulged in.

CHAPTER III.

THE GENERAL PROPERTIES AND DETECTION OF PTOMAINES.

(A.)—Methods of Extraction.

If the alkaloids be sought for in such organs as the heart, liver, spleen, etc., the flesh is finely divided and cut up before operating on them. In pappy substances, or in the contents of the stomach or bowels, the fluids may be tested at once.

1.—Otto's method as modified by Stas.

This depends on the following facts :—

(a) The acid salts of the alkaloids are soluble in water and alcohol.

(b) The neutral and acid salts of the alkaloids are mostly insoluble in ether.

(c) If an aqueous solution containing neutral or acid salts of alkaloids is mixed with caustic, carbonated or bicarbonated alkalies, the alkaloids are liberated and, on shaking the alkaline solution with ether

Stas-Otto's method.

or amyl-alcohol, the pure alkaloids are taken up by the ether or amyl-alcohol.*

The finely divided substance is heated to 90° C. and mixed with alcohol; tartaric acid is added sufficient to produce a decidedly acid reaction, and left to macerate for a sufficient time at the temperature of 70°–75° C. It is then allowed to cool, the liquid filtered, and the residue well pressed out. This operation is repeated several times. The alcoholic solutions obtained from the repeated digest are then united, filtered and evaporated down in a vacuum at a temperature of 35° C. This is filtered through filter paper moistened with water, so as to remove part of the fatty bodies in solution; any fat in the filtrate may be removed by vigorously shaking it with ether in a separating funnel. The liquid is now drawn off from the ethereal solution, powdered glass is added, and the mixture evaporated almost to dryness over sulphuric acid in a vacuum. The residuum thus obtained is treated with absolute alcohol, allowed to macerate for twenty-four hours, and again evaporated at 35° C. *in vacuo*. This second residue is dissolved in a small

* Fresenius' "Qualitative Analysis," p. 445.

quantity of water and sodium, or potassium bicarbonate is added till the mixture has an alkaline reaction ; the solution is then shaken up with four volumes of pure ether, the ethereal solution decanted off, evaporated to dryness at a low temperature, and the alkaloid is left behind as a residue.

2.—*Dragendorff's Method.*

The finely cut up matter, to which water is first added, is acidulated with H_2SO_4, and left to digest for a few hours at 50° C. ; the mixture is filtered, the residue pressed, and the operation repeated. The liquids are united, evaporated to the consistence of a syrup, and allowed to remain in contact with alcohol at a temperature of 95° C. for twenty-four hours ; they are afterwards filtered and evaporated down. The residue which is thus obtained is shaken with benzine, which is decanted off after settling for some hours, and this operation is twice repeated. After having decanted off the second portion of the benzine, the residue is made alkaline with ammonia heated to 40°–50° C., and again treated with benzine. This treatment, which is several times repeated, gives a certain quantity of benzine containing the impure

alkaloid in solution. The alkaloid is then converted into the sulphate by addition of sulphuric acid ; this is decomposed by ammonia, then dissolved up in suitable solvent, and the solution thus obtained evaporated to dryness, when the alkaloid will be obtained. Dragendorff's method.

3.—Gautier and Etard's Method.

The decomposing mixtures are acidified with very dilute sulphuric acid and shaken up ; the oils which float on the surface are separated from the rest of the liquid, and the latter finally distilled in a vacuum. The syrupy residue, after removal of the crystals, is rendered alkaline with baryta, filtered and treated with chloroform, which dissolves out the bases. The excess of chloroform is now evaporated away *in vacuo* or in a current of carbonic acid gas. Care should be taken to avoid the admission of air, and the elevation of the temperature, which would destroy the bodies to be isolated. The liquid which remains after separation from the chloroform is treated with water and tartaric acid, by which treatment a brown resinous mass and a liquid are obtained. When the potash is added to this liquid a strong smell of carbylamines is given off, while the ptomaines are

Gautier and Etard's method.

set free. The liquid is now treated with ether, the ethereal solution is drawn off and evaporated under reduced pressure over caustic potash.

4.—Gautier's Method.

The liquids or finely divided substances are acidulated with oxalic acid, filtered and distilled as long as the liquid which passes over is turbid. The residue is then freed from the fatty acids by the addition of lime, and afterwards distilled in a vacuum. The alkaline liquid which distils over is collected in very dilute sulphuric acid, which retains the ammonia and very volatile bases. The sulphate of ammonia is separated out by repeated crystallization, the mother liquids are evaporated nearly to dryness, and treated with strong alcohol, which dissolves the sulphates of the alkaloids, leaving the sulphate of ammonia behind. The sulphates of the ptomaines thus set free are extracted with chloroform, ether, or petroleum ether, and obtained from these solutions by evaporation.

5.—Brieger's Method.

The flesh is finely cut up and left in contact with water for five or six days, after

Brieger's method.

which the mixture is boiled and filtered; to the filtrate is added subacetate of lead, the precipitate is filtered off, and sulphuretted hydrogen is passed through the filtrate to remove the excess of lead. This is again filtered, and the filtrate is evaporated to the consistency of a syrup, and this is then extracted with amyl-alcohol. The extract is several times treated with water and evaporated, after which it is strongly acidulated with sulphuric acid, repeatedly agitated with ether to extract the oxyaromatic acids, and then evaporated to a quarter of its original volume to drive off the volatile fatty acids. The sulphuric acid is got rid of by precipitating with baryta, the excess of the latter is removed by carbonic acid gas, and the solution is filtered and heated on a water bath for some time. After cooling, mercuric chloride is added to the liquid, the precipitate filtered off, well washed with water, then decomposed by sulphuretted hydrogen, again filtered, and the filtrate concentrated by evaporation. The inorganic bodies which crystallize out first are removed and well washed with absolute alcohol. Shortly afterwards long needles of substances of an organic nature make their appearance. These bodies are obtained

Brieger's method.

chemically pure by repeated crystallization from hot dilute alcohol. Brieger, however, subsequently modified his process. The putrefying liquids are first heated to boiling and, after filtration, mercuric chloride is added; this is then filtered, and the precipitate as well as the filtrate is separately treated with sulphuretted hydrogen, giving products which are separated out in the manner described.

6.—Sonnenschein's Method.

The substance is extracted with water rendered strongly acid with hydrochloric acid, the extract evaporated at 30° C. to the consistence of a thin syrup, diluted with water, allowed to cool and remain for some time, then filtered and the filtrate precipitated with phosphomolybdic acid. After a considerable time the precipitate is collected and washed with water to which some phosphomolbydic and nitric acids have been added, and then rinsed into a flask. Baryta water is then added to alkaline reaction, and the flask connected by means of a condenser with a receiver containing hydrochloric acid, to which a Peligot's tube is fitted. On boiling the contents of the flask for some time the

Sonnenschien's method.

ammonia and volatile bases pass over and combine with the hydrochloric acid in the receiver. The excess of baryta is thrown down from the residue in the distillation flask by means of carbonic acid, the liquid evaporated to dryness, the residue treated with strong alcohol, filtered, and the filtrate allowed to evaporate, when the alkaloid will be obtained. If it is not sufficiently pure, treat it after the methods of Stas, Otto, or Dragendorff.

7.—*Fischer's Method.*

The substance or fluid under investigation is acidified with hydrochloric acid and evaporated on a water bath *in vacuo*. This may be effected by placing the liquid in a flask on a water bath, and connecting the flask with a filter pump. The residue is thoroughly extracted with absolute alcohol, and the alcoholic solution, after being filtered, is again evaporated in the same manner. By this means all the fat, etc., is eliminated; then dissolve the residue in water, add alkali, shake up with ether, and from the ethereal solution the base is obtained sufficiently pure for physiological tests.

Fischer's method.

This is a very simple process, but is not entirely reliable.

8.—Graham's Method.

This method is very useful in separating alkaloids from the contents of the stomach, intestines, etc. The substance is acidified with hydrochloric acid and placed in a dialyser. The alkaloids pass through the membrane and, after twenty-four hours, are found for the greater part in the outer liquid. This solution is concentrated by evaporation, and the alkaloids may at once be precipitated or they may be treated by any of the foregoing methods.

9.—Luff's Method.

This method he applied specially to the detection of ptomaines in urine. The urine in large quantity is rendered alkaline by a solution of sodium carbonate. The urine thus treated is then thoroughly shaken up with half its bulk of ether. The whole is left to stand for several hours, the ethereal solution is filtered and agitated with solution of tartaric acid, which, settling to the bottom of the vessel, carries in solution any animal alkaloids in the form of soluble tartrates. The tartaric

acid solution is separated from the ether, rendered alkaline by solution of sodium carbonate, and is again agitated with half its bulk of ether. After standing, the ethereal solution is removed and the ether allowed to evaporate spontaneously, the residue being dried over strong sulphuric acid. The residue thus obtained is then examined for alkaloids. Luff's method.

(B.)—General Reagents.

The ptomaines are in general precipitated by the group reagents for alkaloids. These reagents are as follows :—

1.—Chloride of Platinum.

2.—Solution of Iodine in Iodide of Potassium (Wagner).

3.—Potassium Mercury Iodide (Planta).

4.—Potassium Cadmium Iodide (Marmé).

5.—Potassium Bismuth Iodide (Dragendorff).

6.—Phosphomolybdic acid (Sonnenschein).

7.—Phosphoantimonic acid (Schulze).

8.—Phosphotungstic acid (Scheibler).

9.—Picric acid (Hager).

They are not all precipitated by the above reagents, phosphomolybdic acid being the only reagent which reacts thus with all, and as a test it is of little or no practical

General reagents.

value, since it shows a like behaviour with ammonia.

(C.)—General Properties.

Ptomaines are of two kinds, liquid and solid, volatile and non-volatile. They are strongly alkaline, unstable bases, which unite readily with acids to form salts, a few of them combining with the carbonic acid of the air. The former are peculiar smelling, oily liquids, soluble in ether-alcohol, and the latter are white, crystalline bodies which are soluble in water and insoluble in liquids such as alcohol, benzine and chloroform. The degree of solubility is greatly influenced by the presence of impurities, as solvents which leave the pure substance unacted upon, often dissolve it when contaminated with other extractives. Thus amyl-alcohol, which possesses in a high degree the property of dissolving the ptomaines as well as other animal substances when in an impure state, dissolves pure neuridin only very sparingly, while the impure alkaloid is taken into solution in considerable quantity. Ptomaines, on account of their easy oxidizability, play the part of energetic reducing agents in a number of reactions, and reduce, among other compounds, chromic and

iodic acids, nitrate and bromide of silver. They form chloro-platinates with chloro-platinic acid, and chloro-aurates with chloro-auric acid. General Properties.

(D.)—Physiological Effects.

These, although showing many analogies, differ too greatly to allow of generalization, and they are best dealt with under each ptomaine. The following symptoms, however, have been observed by different experimenters in animals to which these alkaloids have been administered :—

1.—Rapid contraction and dilatation of the pupil of the eye, frequently accompanied by a copious flow of saliva.

2.—Motor paralysis, loss of cutaneous sensibility.

3.—Tetanic convulsions.

4.—Diminution of cardiac impulses.

5.—Lethargy, torpor and, frequently, death.

Gautier examined the physiological properties of ptomaines according to their solubility in ether, chloroform and amylic alcohol. The alkaloids obtained by digesting with ether caused convulsive movements, rapid action of the heart, injection of the ears, stupefaction and contraction of the pupils in dogs. The chloroform extractives accelerated

Physiological effects.

markedly the respiration and, slightly, the action of the heart, and also injected the concha ; the symptoms disappeared in a dog of medium size in fifty minutes. The amylic alcohol alkaloids paralysed the movements of frogs, dilated the pupil and killed with general relaxation of the muscles. Free ptomaines are more dangerous than their salts, and especially those soluble in ether.

Dilatation of the pupil and tetanic convulsions, soon followed by muscular flaccidity, slowness of the heart's action, absolute loss of cutaneous sensibility and loss of muscular contraction, were the chief phenomena observed in frogs. Irregularity ending in contraction of the pupil, remarkable injection of the concha of the ears, due to vaso-motor paralysis, slow respiration, somnolence, succeeded by convulsions, and death, with loss of muscular contractility, were the main effects in dogs.

Poisoning by ptomaines is characterized in the human being by vomiting, purging, often alternating with diarrhœa, temperature may be increased or diminished, salivation, rapid pulse, paralysis, and death. Each individual ptomaine has physiological effects peculiar to itself, and only by a combination of these with its individual chemical reactions can it be discriminated from all others.

CHAPTER IV.

NON-OXYGENATED PTOMAINES

Putrescine, $C_4H_{12}N_2$.

First obtained by Brieger from the extract of human liver and spleen, which had been allowed to decay for three weeks; the mass was acidified with hydrochloric acid, boiled, repeatedly exhausted with alcohol, and filtered. From the filtrate there were obtained long hard transparent crystals, non-deliquescent in contact with air, and giving the formula $C_4H_{12}N_2 2HCl$. Free putrescine is a colourless non-poisonous liquid, having an odour somewhat like that of pyridin. Boiling point, 156° C.

Reactions :—

Phosphomolybdic acid	Yellow precipitate.
Phosphotungstic acid	White precipitate, soluble in excess.
Meyer's reagent	Oily precipitate, soon becoming crystalline.
Dragendorff's reagent	Oily precipitate, soon becoming crystalline.
Marme's reagent	Oily precipitate, soon becoming crystalline.
Picric acid	Yellow needles.
Tannic acid	Dirty white precipitate.

Putrescine.

Putrescine forms crystalline salts with acids. The chloro-platinate and chloro-aurate are soluble in water with difficulty. The chloride of the base has peculiar reactions.

Brieger had some difficulty in determining the constitution of putrescine, but after repeated investigation came to the conclusion that it was either dimethylethylene diamine,

$$\begin{array}{l} CH_2—NH—CH_3 \\ | \\ CH_2—NH—CH_3 \end{array}$$

or methyl-ethyl-methylene diamine,

$$\begin{array}{l} \qquad\qquad N—C_2H_5 \\ \qquad\qquad\quad / \quad \backslash \\ CH_2 \quad H \\ \qquad\quad \backslash \\ \qquad\quad N—CH_3 \\ \qquad\quad | \\ \qquad\quad H. \end{array}$$

It appears about the 11th day of putrefaction, and does not possess any appreciable toxic properties.

Cadaverine, $C_6H_{14}N_2$.

This was obtained by Brieger in the mother liquor remaining after crystallization out of putrescine. Chloro-platinates and chloro-aurates of the base obtained. Free cadaverine is a colourless, viscous liquid, readily absorbing carbonic acid from the

Cadaverine.

air, and forming a crystalline mass. Pure cadaverine dried over caustic potash boils at 175° C. and has a very disagreeable odour, resembling coniine. It volatilizes with the vapour of water, and distils undecomposed when its chloride is heated with caustic potash, or soda lime.

Reactions:—

Phosphotungstic acid	White precipitate, easily soluble in excess.
Phosphomolybdic acid	White crystalline precipitate, soluble in excess.
Schulze's reagent	White crystalline precipitate.
Meyer's reagent	Resiny precipitate.
Marme's reagent	Resiny precipitate, afterwards curdy.
Dragendorff's reagent	Brown precipitate.
Iodine in iodide of potassium	Brown precipitate.
Iodine in hydriodic acid	Brown needles.
Picric acid	Yellow needles.
Tannic acid	White amorphous precipitate.

It forms salts, chlorides, and sulphates in beautiful crystalline needles. Its chloride has special reactions. Its constitution is considered identical with pentamethylenediamine, $NH_2—CH_2—CH_2—CH_2—CH_2—CH_2—NH_2$. Appears on 3rd day of putrefaction, and is non-poisonous.

Saprine, $C_5H_{16}N_2$.

This base was, along with the next mentioned ptomaine, found in the liquid after the removal of putrescine and cadaverine. The free base in its reactions is closely analagous to cadaverine, differing, however, in giving an amorphous precipitate with Dragendorff's reagent. It forms salts, the chloride crystallizing in flat needles, greatly resembles the corresponding salt of cadaverine, but, unlike the latter, gives no reddish brown colouration when treated with concentrated sulphuric acid and bichromate of potash. It has little or no toxicity.

Mydaleine.

This ptomaine was found, as stated above, in the form of small needles, as an easily soluble chloro-platinate. It forms salts, the investigation of which show that it is a diamine ptomaine, much resembling the preceding one, but no definite formula has been discovered. It forms as early as the 7th day of putrefaction, but sufficient quantity for examination can only be obtained after four weeks. Its chloride crystallizes with difficulty even *in vacuo*, as it effloresces easily in contact with air.

Mydaleine.

Reactions:—

Chloro-platinic acid	Microscopic needles.
Chloro-auric acid	Oily drops.
Phosphomolybdic acid	Amorphous yellow precipitate.
Phosphotungstic acid	White precipitate, soluble in excess.
Meyer's reagent	Wagner's reagent and iodine in hydriodic acid, dirty brown oils.
Picric acid	Yellow oil.

Physiological effects are as follows:—

Its action is very energetic; 5 milligrammes injected under the skin of a guinea-pig produce the following symptoms:—profuse flow of saliva, purging and very liquid motions, dilatation of the pupil, and excessive lachrymation. The symptoms increase in severity as the poisonous action attains its maximum; the hind legs and, subsequently, the fore legs become paralysed, and the animal lies prone on the ground. Tremor and spasms occur in the muscles of the limbs, breathing becomes irregular and hurried, temperature gradually falls, movement becomes weaker and weaker, and the animal dies with the heart in a condition of diastole, and generally ushered in by a rapid diminution of temperature.

Neuridine, $C_5H_{14}N_2$.

Discovered by Brieger in decomposing flesh, fish, cheese, glue, and fresh human brains. Found in great quantity in horse-flesh which had been kept at a temperature of 37°C. for five or six days. It is a diamine, and its chloride forms in long well defined needles, somewhat resembling urea. The free base is obtained in the form of a gelatinous mass, by treating the chloride with moist silver oxide. It has a very disagreeable odour, is easily decomposed, and readily soluble in water. In a pure state it is non-poisonous. It is insoluble in ether, absolute alcohol, and amyl-alcohol. It forms chloro-platinates, chloro-aurates, and a curious insoluble compound with picric acid.

Its chloride gives these reactions :—

Phosphomolybdic acid	White crystalline precipitate.
Schulze's reagent	White flocculent precipitate.
Picric acid	Yellow needles formed on standing.
Dragendorff's reagent	Red amorphous precipitate.
Chloro-auric acid	Crystalline precipitate.

Mercuric chloride, Meyer's reagent, Marme's reagent, iodine in iodide of potassium, tannic acid and Fröhde's reagent give no precipitate nor coloration.

Hydrocollidine, $C_{11}H_{13}N$.

Discovered by Gautier and Etard in decomposing mackerel and horse-flesh. Almost colourless oily liquid, boiling at 210°C., oxidizing in contact with air, darkening in colour, having an odour of lilac, and combining with carbonic acid of the air. It is very poisonous; tremor, spasms and convulsions usher in death, which occurs with the heart in diastole and full of blood; 7 milligrammes will kill a bird. It forms a chloride crystallizing in fine needles, and an unstable chloro-aurate.

Parvoline, $C_9H_{13}N$.

Discovered along with hydrocollidine, by Gautier and Etard, in putrefying mackerel and horse-flesh. It is an oily base of an amber colour, smelling like hawthorn, boiling slightly below 200°C. and becoming dark and resinous on exposure to air. It dissolves sparingly in water, but is readily soluble in alcohol, ether and chloroform. It forms a chloro-platinate and chloro-aurate.

Collidine, $C_8H_{11}N$.

This is one of the most abundant of ptomaines, and was first discovered by Nencki in

Collidine.

decomposing glue. The free base can be obtained by decomposing the chloride with caustic soda, shaking with ether, and allowing the ethereal solution to evaporate. It is an oily liquid, having a strong smell of syringa, absorbs CO_2 from the air, forms a carbonate, and appears as a foliated crystalline mass. Its chloro-platinate crystallizes in flat needles, soluble in hot water, sparingly so in cold.

Besides these alkaloids, several non-oxygenated un-named bases have been discovered by Gautier and Etard, Brouardel and de Coninck, all giving a certain alkaloidal reaction, but not of sufficient importance nor completeness of investigation to admit of detailed description.

Peptotoxine.

Obtained from fibrin, peptonised by the gastric juice, without decomposition having taken place. It is a very permanent substance, and gives with strong reagents the same reactions as vegetable alkaloids. It dissolves in amylic alcohol and very readily in water, but is insoluble in ether, benzine, and chloroform. Millons' reagent (nitrate of mercury) forms with the base a white precipitate, which, by boiling, turns into a deep red. This base is extremely poisonous.

CHAPTER V.

OXYGENATED PTOMAINES.

Choline, $C_5H_{15}NO_2$.

This base was first obtained from bile, and has been found in human brains, hops, beer, etc. Brieger prepared it from human lungs, heart, liver and spleen.

It is a syrupy liquid, alkaline in reaction, soluble in water, and forming characteristic salts with acids, of which the best marked are the chloro-platinate, chloro-aurate and chloride. The latter gives the following reactions :—

Phosphotungstic acid	White precipitate, insoluble in water.
Phosphomolybdic acid	Voluminous precipitate.
Schulze's reagent	White curdy precipitate.
Meyer's reagent	Yellow crystalline precipitate.
Dragendorff's reagent	Red amorphous precipitate.
Iodine in iodide of potassium	Granular brown precipitate.
Mercuric chloride	Granular white precipitate.

Its constitution may be represented thus:—

$$\begin{matrix}(CH_3)_3\\ C_2H_4OH\end{matrix}\Big\rangle NOH,$$

or trimethyloxyethyloxyammonium hydrate.

Choline.

By treating it with hydriodic acid and oxide of silver, one molecule of water is abstracted and "neurin" is formed, possessing the same properties as the "neurin" obtained from putrid meat. Choline can also be obtained from trimethylamine and oxyethyl. In its physiological actions it closely resembles those of neurin, and is intensely poisonous.

Neurine, $C_5H_{13}NO$.

Putrefactive neurine was extracted by Brieger from the lees after separation of neuridin. It appears as very deliquescent needles when treated with hydrochloric acid. The free base is a syrupy, very alkaline liquid, readily soluble in water, a concentrated solution decomposing when boiled, giving off trimethylamine.

It forms chloro-platinates and chloro-aurates in crystalline yellow needles and lamellæ, and its chloride answers to the following tests :—

Phosphomolybdic acid	White crystalline precipitate.
Phosphotungstic acid	No precipitate.
Schulze's reagent	White voluminous precipitate.
Meyer's reagent	Voluminous yellowish-white precipitate.
Dragendorff's reagent	Amorphous red precipitate.
Marme's reagent	White precipitate.

Tannic acid	Voluminous dirty white precipitate.	Neurine.
Iodine in iodide of potassium	Amorphous brown precipitate.	

The chlorides of neurine and choline behave in a very similar manner with reagents, but distinctions may be made with tannic and phosphotungstic acids. Thus:—

Chlorides of Neurine and Choline.

Neurine:
- Tannic acids give dirty white precipitate.
- Phosphotungstic acid gives no precipitate.

Choline:
- No precipitate
- Voluminous white crystalline precipitate.

These two alkaloids are very similar in their physiological effects. A dose of about 3 centigrammes of the chloride given to a rabbit produces the following symptoms:—salivation and excessive lachrymation (the latter is of temporary duration, while the flow of saliva continues). Quickened respiration at first, then gradually becoming irregular, less frequent, and of a sighing nature as death approaches. The action of the heart is accelerated, then, as in the case of the lungs, its movements become less and less frequent, loss of tone and energy, and pulse gradually becomes so feeble that it can scarcely be felt. The pupil is not always affected, but when it

Neurine.

is so, contraction is observed. Incontinence of urine and semen, increased bowel discharges, tetanic contractions, motor-paralysis and death. 5 centigrammes of chloride of choline produce similar effects.

Muscarine, $C_5H_{10}NO_3$.

Schmiedeberg discovered this alkaloid in the fungus *Agaricus Muscarius*, and afterwards Brieger isolated it from decomposing flesh. It is a tasteless, syrupy liquid, little soluble in chloroform and insoluble in ether; deposits crystals after a time *in vacuo* over sulphuric acid, but on exposure to the air these rapidly deliquesce.

Its reactions are as follows :—

Mercuric chloride	Large glittering crystals on standing.
Chloro-auric acid	Fine grained precipitate.
Phosphomolybdic acid	Flocculent precipitate.
Meyer's reagent	Yellow precipitate, gradually becoming crystalline.
Dragendorff's reagent	Red precipitate, becoming crystalline.

Picric acid, iodine in iodide of potassium, potassium bichromate and chloro-platinic acid do not precipitate salts of muscarine in solution. The sulphate, chloride and nitrate are deliquescent and readily soluble in water.

Muscarine contains one atom more of oxygen than choline, and can be prepared from it by oxidation with nitric acid. Schmiedeberg gives it the following formulæ :— Muscarine.

$$(CH_3)_3 - N\begin{matrix}OH \\ CH_2CH(OH)_2.\end{matrix}$$

Its physiological effects are similar to those of neurine, already described.

Gadinine, $C_7H_{16}NO_2$.

Discovered by Brieger in putrid fish, while investigating the forementioned ptomaine. It is non-poisonous, and in the form of its chloride occurs as thick, white or colourless crystals, soluble in water.

It forms a chloro-platinate, but not a chloro-aurate. Phosphotungstic, phosphomolybdic and picric acids all give precipitates.

Mytilotoxine, $C_6H_{15}NO_2$.

Brieger isolated this ptomaine from poisonous mussels in the form of a double salt with mercury, decomposing this with hydrogen sulphate, and extracting with alcohol. It has a very nauseous, disagreeable odour, but on exposure to the air loses this and becomes harmless as a poison. Alkaloidal reagents generally yield oily precipitates with

Mytilotoxine.

this base, but the chloride and chloro-aurate have both definite crystalline forms, the former tetrahedra and the latter cubes. The physiological effects which follow the eating of poisonous mussels, ingestion of mytilotoxine, are as follows :—

General feeling of excitement, like the stimulant stage of narcotic or alcoholic poisoning; everything feels light and airy, patient experiences a sensation as if he would take wings and fly, giddiness, prickling sensation in hands and feet, perverted mental impression, objects grasped seem to rise to the hand, feeling of tightness about the throat and mouth, restlessness, inclination to be very busy and energetic, running about aimlessly. Gradually these minor symptoms give place to those of a more serious type. Feeling of dread comes over patient, pulse becomes quick and feeble, there is no increase of temperature, pupils dilate, paralysis of lower limbs, preceded by a feeling of unbearable heaviness, vomiting unaccompanied by pain, or purging, feeling of cold and collapse, and entire retention of consciousness and mental faculties to the last. Death is generally ushered in by a violent choking sensation or feeling of constriction, as of a rope drawn

tightly round the throat, and it may occur in from two to four hours, or not until several days have elapsed, from partaking of a few mussels in which mytilotoxine has formed. Mytilotoxine.

Besides the ptomaines described above, several non-oxygenated bases have been discovered, the best defined being $C_{17}H_{38}N_4$; $C_{10}H_{15}N$, and $C_{32}H_{31}N$.

$C_{17}H_{38}N_4$ was obtained from the lees after the removal of hydrocollidine, and the analysis of its platinum salt by Gautier and Etard gave the formula:—

$$C_{17}H_{38}N_4, HClHCl_4.$$

The base $C_{10}H_{15}N$ was extracted by Guareschi and Mosso from decomposing flesh, and by de Coninck from putrid fish. It forms precipitates with chloro-platinic and auric acids, corrosive sublimate and tannin.

The base $C_{32}H_{31}N$ was discovered by Brouardel and, in contact with air, closely resembles veratrine in its reactions. It appears to be an amine.

Brieger and others have for some time hoped to show that specific products could be obtained by the culture of individual pathogenic organisms in nutritive media. He demonstrated the disintegrating action of pathogenic bacteria on organic tissues, and

from a culture of the typhoid bacillus on grape sugar and starch in presence of nutritive salts he only obtained alcohol, volatile, fatty and lactic acids. On albuminous matter it grows and neither evolves sulphuretted hydrogen nor forms aromatic products. Occasionally he obtained very small quantities of a base which in guinea-pigs produced profuse salivation, paralysis of limbs, dilatation of the pupils, slowing of the heart, arrest in systole, and death in from twenty-four to forty-eight hours. Culture of *Staphylococcus pyogeneus* on broth or extract of meat yielded a ptomaine from which a chloride was obtained, but was otherwise indifferent.

A culture of Friedlander's *pneumococcus* upon carbohydrates yields formic and acetic acids and ethylic alcohol.

Dr. A. P. Luff* describes two ptomaines which he has isolated from the urines of cases of scarlet and typhoid fevers. The methods he employed are described in Chapter III. He made several experiments on normal urines with this process, and in no case was anything alkaloidal extracted. He infers therefore that if an alkaloid is detected

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* "Brit. Med. Journ.," July 27th, 1889.

by this process in the urine of a patient suffering from an infectious fever, it has been produced in the body during the course of the fever, providing that the patient is not treated by alkaloidal or antipyretic remedies.

Typhoid fever.

Ptomaine from urine of patient suffering from typhoid fever.—Patient, female adult. Temperature, during collection of urine, 102·5° to 104° F. Urine passed during four days, while the fever was at its height, was collected and extracted by the ether process. A small quantity of a white crystalline substance was obtained, which exhibited all the properties, and gave the reactions of an animal alkaloid; it was converted into the hydrochlorate by dissolving in very dilute hydrochloric acid, and gave the following reactions: —

Phosphomolybdic acid	White precipitate.
Phosphotungstic acid	Nil.
Mercuric and potassium iodide	Dense yellow precipitate.
Iodine solution	Yellowish brown precipitate.
Picric acid	Dense yellow precipitate.
Platinic chloride	Nil.
Gold chloride	Dense yellow precipitate.

These reactions are not given by any other animal alkaloid, and this ptomaine has

not previously been found in urine of typhoid fever cases.

Scarlet fever.

Ptomaine from urine of patients suffering from scarlet fever.—The urine was collected from patients at the London Fever Hospital, during the height of the fever. Four gallons of urine were extracted by the ether process, and a small but appreciable quantity of an animal alkaloid was obtained. It was white, semi-crystalline, soluble in water, and faintly alkaline. It was converted into the hydrochlorate by dissolving in very dilute hydrochloric acid, and gave the following reactions :—

Phosphomolybdic acid	Pale yellowish white precipitate.
Phosphotungstic acid	White precipitate.
Mercuric and potassium iodide	Pale yellowish white precipitate.
Iodine solution	Brown precipitate.
Tannic acid	Nil.
Picric acid	Yellow precipitate.
Platinic chloride	Nil.
Gold chloride	Slight yellow precipitate.

These reactions are unlike those given by any other alkaloid. Sufficient quantities of these substances for organic analysis were not obtained, and their exact chemical composition and constitution are yet undetermined.

Pernicious anæmia.

Ptomaines in urine of patient suffering from pernicious anæmia.—Dr. Hunter describes ptomaines extracted from urine in a case of pernicious anæmia.* He obtained the alkaloids in combination with benzoyl chloride, which he used in the process. From a number of different portions of urine treated during the last two months of patient's illness, he obtained a very small quantity of a benzoyl compound, possessing "very definite crystalline characters and equally definite physical properties." Extremely soluble in alcohol, insoluble in water. It crystallized out of alcohol in form of long fine needles, arranged in rosette-like bunches. After repeated purification and crystallization its melting point remained constant at 175° C. to 176° C. It was in all respects identical with putrescine. Along with it was found another ptomaine which formed a double benzoyl compound, crystallizing in characteristic, long, elongated, rectangular prisms. This, Dr. Hunter identified as cadaverine, which is usually found in association with putrescine. From one of the specimens of urine a compound was

* "Brit. Med. Journ.," July 12th, 1890.

Pernicious anæmia.

isolated in a perfectly crystalline form. Its double benzoyl compound crystallized in long rectangular prisms, resembling those of the cadaverine compound. Melting point lay between 70° and 80° C.—the wide margin suggesting the presence of more than one body. From its behaviour in other respects it also differed from cadaverine, and is probably a special diamine body.

CHAPTER VI.

CLINICAL.

Ptomaine poisoning.

THE phrase "ptomaine poisoning" has been in general use during recent years, and no attempts appear to have been made to correct the vague and rather misleading impressions which its use may give rise to. The conditions under which ptomaine poisoning may arise are so various, and at times so inexplainable, that it appears difficult on all occasions to define in scientific terms what is exactly meant, and the physician not unnaturally seeks in many obscure cases of disease to discover and seize upon the existence of ptomaines as powerful causative agents, attempting thereby to explain everything, unfortunately in many cases explaining nothing. On the other hand, when one is asked to give a definition of the phrase which will at the same time exclude all forms of poisoning not due to these alkaloids, and include only those arising from the presence of these substances in the body, one is at once beset by the fragmentary

nature of the knowledge of ptomaines, and in the present state of our knowledge the task becomes a necessarily hazardous one. Strictly speaking, the word "ptomaine," as shown in the text, was originally applied and confined to alkaloids developed in dead bodies, but in the usage of the above phrase at present, there is a very general departure from this limited significance, and the most varied symptoms following the ingestion of diverse articles of diet are promptly diagnosed and described as "ptomaine poisoning." That this scientific vagueness is to be deplored cannot be doubted, but definitions are at all times difficult, and it is not sought in what follows to adhere to any exclusive sense of the word "ptomaine," but on the contrary to include under it all active, inanimate, septic or toxic substances, resulting from processes of decomposition and disintegration in albuminous materials.

Definition.

The presence of these substances in the human body can be generally accounted for in one of two ways. (1) Introduced from without, as in articles of diet, by wounds and by inhalation, or (2) Developed within, as in the tissues, fluids, organs and alimentary

canal, both in physiological and pathological conditions. These may be subdivided and considered in the following order :—

1.—Toxic substances developed in the body in physiological conditions.
2.— „ „ „ „ pathological conditions.
3.— „ „ „ „ the alimentary canal.
4.— „ „ introduced into the body by inhalation.
5.— „ „ „ „ „ ingestion.

There might be included as a sixth group : Toxic substances introduced by wounds of a specific or non-specific character, but it is not proposed to deal with these in this little work.

1.—*Toxic substances developed in the tissues of the normal body.*

Reference has already been made in Chap. I. to the fact that normal blood, urine, and egg albumen, contain toxic substances. The details of some of the experiments demonstrating these facts are very interesting. Bouchard injected normal urine into the veins of a rabbit, and observed the following phenomena : contraction of the pupils, slow respiration, muscular weakness, lowered temperature, abolition of the reflexes and torpor, followed by death from respiratory paralysis. Bouchard.

These symptoms were not due to the urea, for he found that to produce a fatal result much more urea was required than was contained in a fatal dose of urine. Uric acid and extractive matters proved to be harmless, or nearly so. The small quantity of the potash salts contained in the fatal dose of urine was insufficient to cause the effects. Decolorisation of the urine by animal charcoal also deprived it of half its toxic power. That the poison is not volatile is shown by the circumstance that boiling does not destroy its power. An extract of urine also contained the poison which possessed sialagogue properties. This alkaloidal sialagogue has also been extracted from muscle, liver and blood. From brains in a normal condition, Mosso and Guareschi extracted small quantities of ammonia, trimethylamine, and substances giving the reactions of alkaloids.

Urinary poisons.

Poisons in blood, liver, muscle, brain.

Coppola made a series of experiments on the physiological action of bases extracted from the blood of a healthy dog, and concluded that healthy animal fluids which had undergone no putrefactive change outside the animal body, may exhibit highly poisonous properties. If from 20 to 30 cubic centi-

metres of fresh saliva be taken and evaporated over a water bath to dryness, and the residue extracted with boiling water and finally filtered, a toxic substance is obtained, which is strongly reducing, and converts ferrocyanide of potassium in presence of one or two drops of perchloride of iron into prussian blue. Saliva.

Gautier extracted from normal urine a poisonous alkaloid, which, when injected into rabbits, arrests the heart in systole, paralysis and death following. He also extracted from muscular juice of large animals, alkaloids which acted with varying energy, causing sleep, fatigue, and in some instances, vomiting and excessive action of the bowels; in a lesser degree, however, than alkaloids from putrid flesh. Thus it appears possible always to obtain from normal secretions and excretions of the higher animals, substances with physiological and chemical properties, closely resembling those which were believed only to be produced by the action of bacteria on putrefying matter. Their formation is the result of normal processes, but their presence in the animal economy is not required, and like other waste products they are expelled by the various paths of exit. Circumstances may, Formation.

Auto-infection.

however, arise in which their expulsion is retarded, and their toxic effects are then manifested on the individual retaining them.

In the development and accumulation of ptomaines or leucomaines in the tissues and fluids, we have produced a condition of auto-infection, a simple self-poisoning from the *débris* of the functional activity of the cell units of our bodies.

Some writers assert that the presence of ptomaines denotes a deviation, however slight and transitory, from the strictly normal condition of health; and this is, so far, true, if the health of the individual be defined in terms of the normal conditions of its component units. Doubtless, auto-infection is produced in the first instance by some impairment in the functional relations of the cell, leading to an increased formation of toxic substances, these reacting and disturbing nutrition of the cell; and it is as difficult to say when the processes occurring in the cell cease to be physiological and become pathological, as in the case of the multicellular organism, depending for its healthy condition upon the normal discharge of the functions of its units. Let us glance at the physiology of cell nutrition.

Cell nutrition

"By assimilation the cell receives from the medium which surrounds it, certain materials which it converts into its own proper substance, or which it may utilize in various ways. There appear to be two phases of the assimilative process: (1) One in which the cell transforms the matter which it receives, and (2) The other in which the substances transformed become an integral part of the cell. The first phase is well marked in the life of a vegetable cell, but is not so distinct in an animal; the second phase, on the contrary, exists to an equal extent both in the animal and vegetable cell. The assimilating process in the living portion of the cell has received the name of metabolism, while the chemical change by which matters taken up by the cell may be converted into other matters, is called metastasis. Thus a cell may, by metabolic processes, convert dead matter into living matter like itself, or it may, by metastatic processes, convert dead matter into another form. The disassimilative processes occurring in the living cell, consist of chemical changes in the substance of the cell itself, or of materials in contact with the cell. Certain materials are separated from cells by a process which may be termed

cellular excretion, and other cells may store up certain materials in their interior, a process called cellular secretion." *

It is probable that, as in the case of plants, alkaloids play no part in the constructive metabolism of the animal cell, and they appear as a bye product of disassimilative processes occurring in the cell, and separated from it by a process of excretion, or from changes in the material in contact with the cell. There is, however, something more than this purely physiological mechanism at work in the production of animal alkaloids in the tissues, and Gautier has shown this to be simply putrefactive or fermentative changes. Nutritional changes in the cell are, up to a certain point, independent of the presence of free oxygen, and the formation of toxic bodies in the tissues is quite independent of this gas: in other words, the cells of our bodies, among other properties, possess that of ferments. To the animal cell may in part be applied that which Pasteur said regarding the yeast plant, "that in the presence of abundance of oxygen, it ceases to exhibit the

Putrefactive phenomena.

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* McKendrick: "Text Book of Physiology," Vol. I, p. 294.

properties of a ferment, and in the absence of free oxygen it acquires these properties." His view of fermentative decomposition is this, that it is the expression of the effort of the cell or organism to obtain oxygen from substances which contain this gas in combination. Cells as ferments.

Another possible view is, that the organism obtains by fermentative decomposition of other substances that necessary supply of energy, which in the presence of free oxygen it obtains by the decomposition of its own protoplasm. This applies equally to animal cells, and whether the cell is struggling to liberate and obtain combined oxygen from the nutritive medium surrounding it, or to gain a supply of energy, it is still the case that it is by a fermentative change. Thus the physiology of the animal cell is, in a measure, on precisely the same level as that of the anaerobiotic groups of *Thallophytes*, the *Saccharomyces* and *Schizomyces*.

Gautier demonstrates the anaerobiotic changes in our tissues in two ways. In the first place, he says, our secretions contain all the substances which have hitherto been met with in proteid matter submitted to putrefaction. In putrid products urea is wanting, but in its place carbonate of ammonia is Anaerobiotic changes.

Fermentation.

abundantly found, and as a supposed derivative from it by fermentation processes. Again, according to the experiments of Pettenkofer and Voit, if the quantity of oxygen respired and rejected under all forms by one of the higher animals be calculated, it is found that a part of the food, and of the tissues, has become destroyed without the intervention of external oxygen, a destruction probably of the nature of fermentation. The formation of alkaloids and other waste products in the tissues follows as a natural result of these fermentative or putrefactive changes: changes which are in no way incompatible with the normal discharge of the functions of the cell, but are, in fact, part of these functions. In life, therefore, we live in a condition of incessant putrefaction, and, as Sir William Aitken says, "our organism is constantly dying; and strange as the paradox may seem, we cannot live unless it does die. How precarious, therefore, is the condition we call health; and how, by the simple accumulation of cadaveric material, disease may manifest itself! How scientifically and literally do the truths stand out that 'in the midst of life we are in death;' and that 'as we begin to live, so we begin to die.'"

Causes of auto-infection.

Toxic substances are, therefore, necessary products of the normal discharge of cell functions, constantly formed in the cell and excreted in small quantities, or developed in the materials in contact with the cell. Accumulation of these products in the body may arise in various ways, and when it does occur, constitutes the condition of auto-infection. All disturbances in secretion and normal excretion, every arrest or diminution of the respiratory functions, or in the blood-making processes, are necessarily followed by the retention of this toxic physiological *débris* in the body. This impairs nutrition, diminishes vitality, and exercises a pathological action on the nerve centres, giving rise to the most remote symptoms. It is possible that impairment of nutrition may be the result of something more than simple dilution of the materials in contact with the cell by a substance which cannot enter into constructive metabolism; not a mere adulteration of nutritive materials, but that these substances react on the cells, and we have an arrest of the functions of the cell similar to that observed in cases of *Saccharomyces Cerevisiæ*, *Mucor racemosus* and *Mucor otolonifer*, when the fermenting liquids contain respectively

Effects of auto-infection.

14, 5 and 1·5 per cent. of alcohol. In a similar manner, butyric and lactic acid fermentations are arrested when the acids reach a certain proportion. Diminished vitality follows as a result of impaired nutrition, and the toxic action on nerve centres arises from accumulation in the blood as the result of deficient elimination, impeded circulation, or diminished respiratory movements.

Influences operating against auto-infection.

The vital mechanism at work in preventing the surcharging of the system with these substances, is two-fold: (1) Eliminative; (2) Oxidative. Elimination takes place by the lungs, skin, kidneys, liver, and intestinal canal; alkaloids having been found in the secretions and excretions of all these. Oxidation is effected under the influence of respiration in the circulating blood, and is probably an aid to elimination by converting the waste products in the blood into substances easy of elimination, and rendering them less likely to be retained in the blood, or deposited in the tissues. Destruction and elimination of these substances are as necessary for the normal condition of the fluid media in which the cells of multicellular organisms live, as the supplies of fresh oxygen and nutritive materials.

Auto-infection.

Other conditions in which auto-infection arises, are those under which individuals undergo privation, fatigue, great physical exertion, especially when co-existing with bad hygiene of the individual and surroundings. Charrin and Roger showed that white rats, which generally are immune against anthrax, developed the disease readily when suffering from muscular fatigue. Bouchard showed that the micro-organisms in the alimentary canal and lungs readily passed into the blood when a healthy animal was exposed to cold for a considerable time. Aitken quotes Mosso's experiments on the soldiers of the Italian army, and finds "that when fatigue is carried beyond the moderate stage, at which it is decidely beneficial, the blood is subjected to a decomposing process, through the infiltration into it of substances which act as poisons—substances which, when injected into the circulation of healthy animals, induce malaise and all the signs of excessive exhaustion."

From a consideration of various ailments, their clinical features and treatment, he seeks in the case of diseases, as typhus and typhoid fevers, the fevers of prostration, fatigue and over-exertion, dysentery, small pox, and

erysipelas, to suggest that we may have presented a pathological series of ailments, each depending on, and representing a certain degree of self vitiation, passing gradually from a mild to a serious condition of self-developed disease.

Self vitiation in disease.

No better example of a self-propagated disease could be found than gout, and the same relations which nitrogenous waste products bear to this affection may be assumed by the alkaloids developed in the tissues to other diseases. So long as the elimination of urea and uric acid is effective and adequate, the uric acid diathesis remains in abeyance; in a similar way, the efficient elimination of ptomaines or leucomaines may prevent the establishing of any of those diseases which Aitken would place in a pathological series.

The conclusions, therefore, emerge that toxic substances are developed in the tissues in virtue of their metabolic activity; that they are normal products of chemical change in the cells and fluid media; that up to a certain point their development and presence in the animal economy are compatible with a normal condition, but, beyond this imaginary point, their development and relations may

cease to be physiological, and assume a pathological form; that micro-organisms, pathogenic or non-pathogenic, take no part in their formation; and, lastly, that they are important agents in the causation of many diseases.

2.—*Toxic Substances developed in the Body in Pathological Conditions.*

Apart from the clinical features which characterise disease, pathology teaches us that morbid conditions are the result of the modifications of normal processes; that symptoms and signs are tangible expressions of the struggle under which normal functions are discharged, and that pathology itself is simply advanced or exaggerated physiology. If, therefore, a pathological state be recognised as a condition of exaggerated function, and since normal functions are attended by the development of ptomaines, it follows that in disease we may look for an increased production of these alkaloids. In this we may discover both a qualitative and quantitative expression of the operation of pathological agencies. But this increased production can only be inferred from the presence of these substances in larger quantities than the normal,

Toxic substances in pathological conditions.

in the fluids, excretions and secretions of diseased individuals. Mere quantity is insufficient to establish in all cases the relation of ptomaines to the genesis of disease, and when it does fail, recourse must be had to the characteristic chemical and physiological reactions of the substance under observation. Lépine and Guérin have shown that various acute diseases, as typhoid fever and pneumonia, are attended with an increased urinary discharge of alkaloids. Bouchard detected alkaloids which yielded characteristic reactions in the urine of patients suffering from typhoid and scarlet fevers. The ptomaines detected in the same fevers by Luff have been described, and a point of importance which he noticed was, that the quantity excreted was greatest when fever symptoms were at their height, and that the alkaloids in the urine disappeared with a reduction in temperature. Villiers, by means of the Stas-Otto process, found a peculiar alkaloid in the viscera of two children who died of broncho-pneumonia following on measles, identical with one he found in a child dead of diphtheria and broncho-pneumonia. In the urine of patients suffering from measles, diphtheria, phthisis.

Ptomaines in pathological conditions.

pneumonia and cephalic abscess, he detected alkaloids in increased quantities. Spicca separated four ptomaines from the fluid taken during life from a patient suffering from peritonitis; all were poisonous, one in very minute doses, and resembling curare in its action. Selmi's observations on the urine of progressive paralysis have been referred to (Chap. II.); he also noticed in the urine passed in a case of interstitial pneumonia two bases, one having the odour of stinking fish, the other of ammonia. Similar bases were found in typhoid fever, and in tetanus a base tetanine was detected, which gave reactions similar to coniine. The alkaloids detected by Dr. Hunter in a case of pernicious anæmia have been noted. Dr. Mann obtained a ptomaine similar to choline in a case of typhoid fever, and also one with special characters differing slightly from the "typho-toxin" described by Brieger. The toxic effects of this ptomaine, when a few drops of an aqueous solution were injected under the skin of a guinea pig, were motor paralysis and general insensibility, death supervening rapidly with heart in diastole. Charrin has recently demonstrated the toxicity of serum taken from cases of

Ptomaines in pathological conditions.

uræmia, and in the same journal* two writers assert that normal blood freed from proteid loses all toxicity. Bourget isolated several toxic bases from the viscera of a woman who died of puerperal fever, and from the urine of patients suffering from this disease he obtained similar bases, which killed frogs and guinea pigs when injected under the skin. The amount of poison in the urine was greatest when the symptoms were most severe, and gradually disappeared as the patients recovered.

From pure cultivations of the bacillus of tetanus, Brieger separated four ptomaines. The first one, tetanine, produced, in minute quantity, tetanus in mice; the second also caused tetanus, in addition to salivation and lachrymation; the third, tetano-toxine, caused tremor, paralysis and violent convulsions; the fourth, spasmo-toxine, gave rise to severe clonic and tonic convulsions. Anrep isolated a ptomaine from the medulla oblongata of rabbits suffering from rabies. It is very poisonous, and when given in small doses reproduces some of the symptoms of hydrophobia.

Thus, it appears, in disease we have a

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* "Compt. Rend. Soc. Biol.," 1890.

condition of active disintegration of the nitrogenous elements of the body followed by increased elimination of alkaloids. But neither of these circumstances, taken together or singly, can establish a relation between the existing disease as effect, and the toxic alkaloids as cause; they are simply the expression of an increased production of physical and chemical agencies operating more actively in common with increased physiological changes. The development of alkaloids has been shown, especially in plant physiology, to be directly influenced by various physical and chemical factors, and it is possible that the tissues of the human body in disease offer a maximum of conditions favourable to the formation of ptomaines. As a necessary result increased production is followed by increased elimination. How far the balance of these two processes goes towards the saturation of the body and accumulation in sufficient quantity to place disease in the relation of effect can only be conjectured, but it is significant that many poisons only appear in the urine when given in lethal doses, and that substances as morphia and alcohol can only be detected in the urine when the

Causes of increase in discharge of ptomaines.

Ptomaines and disease as cause and effect.

body has attained a certain degree of saturation. Such a hypothetical condition appears necessary when we remember that these bodies are normal products, and it simply remains to admit the difficulty of drawing any line of demarcation between physiological and pathological quantities. They will vary in different individuals, but in all, such a condition as suggested may be reached by the gradual retention and progressive action of these substances. Increased production and elimination, saturation of the body and coexistence of disease do not in themselves establish relations of cause and effect; neither, in addition to this, do the physiological and chemical reactions of the isolated alkaloids afford us anything beyond presumptive evidence. It has been demonstrated experimentally that some of these bodies are intensely poisonous, and if not in themselves the primary cause of disease, it is not unsafe to assume that their presence in large quantities in the blood supplement and aggravate recognised symptoms, predispose to sequelæ, and militate against the normal course of an otherwise uncomplicated case. This assumption accords with observations made in various diseases,

Complication in disease due to ptomaines.

and the following remarks by Dr. Hunter on a case of pernicious anæmia serve to elucidate it. "If we now consider whether any of the symptoms observed in the foregoing case pointed to the action of such poisons (cadaverine, putrescine, and an unrecognised diamine), we come upon certain very interesting facts pointing very directly to such a conclusion. The exacerbations from which the patient suffered from time to time presented all the phenomena of toxic poisoning, whether regard be had to the more nervous phenomena, the sudden onset of drowsiness, the contracted pupils, the slight fever and the sweating; or to the more local manifestations of the action of such poisons, the intestinal disturbance, and the obviously increased destruction of blood which always attended such attacks. The latter was manifested by (1) The high colour of the urine, and the appearance of urinary pigments and chromogens other than those of health; (2) By the excretion of hæmoglobin through the kidneys, and its appearance in the urine in the form of granules of blood pigment; (3) By increase in the pigments of the fæces; and (4) By the more marked lemon tint, from the

Ptomaines in pernicious anæmia.

presence of a special pigment in the subcutaneous fat. All these phenomena were so closely related to one another in their occurrence and their degree, and were always marked by such an increase in the patient's weakness, as to point, in my opinion, to the closest possible connection between them—the weakness being due to an excessive destruction of blood caused by the absorption of specific poisons from the alimentary tract, the more stable and less toxic of these being excreted at the same time in the urine. So closely did certain of the phenomena, more especially those connected with the nervous system—the drowsiness, sudden in onset and of short duration, in a person intellectually very bright and of a disposition naturally keen and active, the contraction of pupils and the perspirations—resemble those of a poison of the nature of muscarine, that even at the time, and before I was aware of the presence of certain ptomaines in the urine, I regarded them as toxic, and began the administration of atropine with the view of antagonising, if possible, their action."* It must be ob-

* "Brit. Med. Journ.," July 12th, 1890.

served, however, that the alkaloids cadaverine and putrescine never occur as the products of the metabolism of the tissues, and in this case they were derived from the action of bacteria on the nitrogenous contents of the bowel.

Ptomaines in cystinuria.

Udransky and Baumann detected their presence in a case of cystinuria, but failed to find a trace of them in cases of scarlet fever, diphtheria, typhoid fever, pneumonia, tuberculous peritonitis, and intestinal obstruction. The diamine cadaverine has a strong odour characteristic of cholera stools, and when injected along with putrescine into the circulation, produces hæmorrhages and ulcerations similar to those of cholera, the muscular cramps and other symptoms of that disease being produced by toxines which have not been isolated.

Udransky and Baumann, from chemical experiments, concluded that these diamines are never produced by the bacteria which cause the usual putrefactive changes in the alimentary canal. They are readily formed in large quantities in cultivations of the cholera bacillus, and of the Finkler prior vibrio. Cultivations of pathogenic bacteria also yield carbonic acid gas, sulphuretted hydrogen and ammonia, nitrates, water,

Bacterial products.

volatile bodies as trimethylamine; alcohols, formic, acetic, propionic and butyric acids; fixed acids, as lactic, malic, succinic, oxalic and tartaric; amides of fatty acids, as leucin; aromatic bodies, as phenol, carbohydrates, peptones, and poisonous alkaloids which, when isolated and injected, reproduce some of the features of the disease characteristic of the cultivated organism. Injections of cadaverine produce suppuration. Leber extracted from culture of *Staphylococcus aureus* a crystalline body which produced intense inflammation and suppuration in animals, and from a similar source Christmas obtained another toxine differing from the former in physical characters, but with the same physiological reactions. Suppurations accompanying tuberculosis are partly due to poisons developed by tubercle bacilli, and as in diphtheria, to the presence of other micro-organisms complicating the primary affection. There is abundant proof that the growth of pathogenic bacteria in the human body is accompanied by the development of powerful poisons. These are of two kinds: (1) Toxines, diffusible alkaloidal substances analogous in their action to that of vegetable alkaloids; and

(2) Toxalbumins, proteid substances resembling ferments more than poisons. The relations of bacteria to disease are however not sufficiently well defined to exclude the probability that even pathogenic microbes are not the primary cause of certain affections, but that antecedent changes have been in operation in the organism, and that these constitute the first step towards disease, developing conditions necessary to the growth of bacteria. Bacterial products.

As Sir Wm. Aitken puts it, "They are entirely *post hoc* in relation to antecedent factors of any particular disease." The detection of microbes is but the first step towards the discovery of the cause of the disease, and the mode of its operation.* A suitable and nutrient medium has to be prepared, certain physico-chemical changes are necessary, and molecular disintegration or death precedes the evidences of the growth of pathogenic bacteria. What these antecedent changes are, still remain to be determined, but it appears probable that there is destruction or disappearance of products injurious to the vitality of micro- Changes antecedent to bacterial invasion.

* Ziegler, "General Pathological Anatomy," p. 2.

Antecedent changes in disease.

organisms, and a development of decomposition products in which are the materials required for their growth and nutrition.

The metabiotic relations of bacteria support the latter suggestion, and Liebrich's experiments on cholesterin fats lend some weight to the former; but admitting that these hypothetical changes are partly physical, partly chemical in their nature, and that substances disappear and new substances are formed, it does not follow that they are the results of bacterial agency.

Besides the toxines and toxalbumins, one other class of substances, products of bacterial agency, remains to be mentioned, viz., the "proteins." They were first discovered by Nencki, and worked out by Buchner. The former two groups are found in largest quantity when the bacteria are most active and disease at its maximum, the latter only in the later stages of the disease, and when the bacteria are dying. "Proteins" are said to be derived from the bodies of the bacteria themselves, and possess the remarkable property of causing a leucocytosis wherever they are present. This "chemio-tactic power" really provides the invaded organisms with a weapon of defence. By it there

Chemiotaxis.

is a determination of leucocytes to the part, and these, acting as scavengers, clean up and sweep away the *débris* of dying bacteria. Metschnikoff first showed how the leucocytes of the blood take into their substance everything animate and inaminate possessing a less power of resistance than themselves, and upon this property, together with the chemio-tactic reaction of the bacterial products, the theory of phagocytosis in immunity to disease has been constructed. The doctrine of phagocytosis asserts the priority of leucocytic function as an immune producing agency, the opponents of this view maintaining that these cells fulfil simply a scavenging function, and that the bacillicide properties reside not in the cells but in the serum. From the chemical point of view, whichever theory is adopted, the questions of most interest are, What are those substances which, formed in the blood or tissues, attract amæboid cells, or, normally present there, possess bactericidal properties, and how are they identified?

Metschnikoff.

Phagocytosis.

When pathogenic bacteria are established in the tissues or fluids of the body, the poisons they elaborate may exercise a fourfold influence: (1) By developing disease;

Action of bacterial products.

(2) By arresting the growth and development of the bacteria, and consequent cessation of the disease; (3) By conferring immunity from further attack of the same microbe; and (4) By creating a greater degree of susceptibility for reception of other micro-organisms.

The symptoms of some diseases are undoubtedly referable to the presence in the blood, and diffusion throughout the body, of poisons formed by microbes. These substances show a rise and fall in quantity in the urine at a time when there is an apparent correlation with increasing and diminishing gravity in the symptoms. In diseases where there is a primary infective agent—bacilli—it is found located at the site of inoculation, but the chemical products of the bacterial agents pass into the lymph and blood circulatory systems, and in this way the "constitutional symptoms" originate. Some writers assert that specific poisons are associated with, and formed by, specific microbes, and that different poisons are formed by one and the same microbe, which, by their supplemental actions, may even determine the sequence of symptoms. In this way the albumose of anthrax, when

injected into mice, causes fever, and the alkaloid of the same disease produces coma; and recently Dr. Martin* has shown that the albumose of diphtheria produces paralysis in guinea-pigs and rabbits, and is probably associated with the paretic symptoms which complicate this disease.

Control of disease.

Control of the disease, arrest in the growth and propagation of bacteria, and conference of immunity on the invaded organism, are all intimately connected with the properties and reactions of the poisons formed by the invading microbes; and the conflict between the organism and the microbe, whether it is anti-toxic or anti-biotic in its nature, is reducible at certain stages of the disease to a kind of chemical warfare. On the one hand we have chemical substances, such as alexin and the "defensive proteids" of Hankin, the fibrinogen of Wooldridge, and the nuclein of Horbaczewski, arranged in defence of the organism; and on the other, albumoses and peptones doing battle for the microbe. The albumoses and ptomaines destroy the cells of the body, but it does not appear certain that the chemically

Defensive proteids.

* "Goulstonian Lectures for 1892."

Chemical reaction in vital action.

protective substances of the latter exercise a similar effect on the microbe; on the contrary, their mode of operation seems to be, that they react on the leucocytes, attract these to the area of infection, and, by their stimulating action, transform the mimic battle into one of leucocyte *versus* bacterium. It has been said that this remarkable property of attracting leucocytes is also possessed by the "proteins" derived from the bacteria, and a definite relation appears to exist between the chemical action of the substances so formed, and the movements of the cells. It can hardly be supposed that the wandering cell has the power of guiding its own movements; still less are they, as according to the Metschnikovian theories, "actuated by an almost conscious discrimination between what is advantageous and what is detrimental to the organism as a whole."* In any case it is to this reaction, essentially protective in its results, that phagocytic doctrinarians attribute the essence of immunity. By immunity is meant a relative insusceptibility to disease, or put in another way and as Professor Sanderson defines it, that "power

* "Brit. Med. Journ.," 1889, p. 1034.

Theories regarding immunity to disease.

which the human or animal organism possesses of so resenting the presence of a disease producing microphyte, as to protect itself from the disease." Before the theory of phagocytosis was applied to immunity, destruction of the microbe was attributed to chemical substances derived from the metabolic activity of living protoplasm in the infected organism, and immunity conferred by the creation of a chemical unfitness of the human tissues to act as nutritive media for pathogenic bacteria. Two opinions existed as to the manner in which this so called sterilization of the soil was produced. One was, that the bacteria deprived the nutrient materials in the body of chemical substances necessary to the life of the specific microbes, and in virtue of the anti-bacterial effect of this exhaustion, the organism acquired immunity; the other theory asserted that, in virtue of bacterial vito-chemical processes, changes occurred in the nutrient media of the body, and chemical substances were formed which were found to be inimical to microbial life, and remaining in the tissues after death of the micro-organism, perpetuated for a time, in virtue of this acquired uncongeniality of soil, a degree

Theories regarding immunity.

of resistance and antagonism to the same microbes. The essence of the former theory consists in the removal of bacterial life-supporting substances; of the latter, in the introduction of bacterial life-destroying substances. Out of the retention theory there has sprung up the practice of conferring immunity by injection of sterilized cultures, and to the chemical products of a germ free filtrate Professor Sanderson* attributes properties within the body—when used as vaccines—which they do not possess outside it, and he remarks that, "the only view which we can take of the matter is, that when used as vaccines, they so act on the organism as either to awaken in it an inhibitory or destructive power, which was before latent or too feeble." He attaches no importance to the facts of phagocytosis, excepting first, "that the emigration of leucocytes is an essential part of the process of inflammation, and that there is an antagonism between this process and the process of general infection." But surely, that theory which interprets the phenomena of disease in terms of the units of the organism, and not

* "Croonian Lectures for 1891."

of systems, or the organism as a whole, is a scientific advance worthy of acceptation.

Increased susceptibility to disease.

The converse problem of increased susceptibility for other micro-organisms presents itself. Viewed in the light of experiments on animals, and analagous processes in cultures and fermentations, the same principle underlies both increased and diminished susceptibility. There may be removal of antagonistic chemical ingredients by pre-existing microbes, or these may simply elaborate nutrient material suitable for subsequent microbial invasions, or both these conditions may co-exist, and be supplemental the one to the other. If, for instance, sterilized cultures of the tetanus bacillus be introduced into the subcutaneous tissues of a guinea-pig, no evil effects follow, but if along with these there be introduced any of the microbes of putrefaction, the animal soon dies, with well-marked tetanic symptoms. It cannot be said at present what those antecedent changes are upon which the metabiotic and antibiotic relationships of bacteria depend. Recent experiments minimise the probability that the production of chemical substances adapted to the use of one species of microbe, and

Chemistry in pathology.

chemically unfit for the use of others, is the only explanation. However this may be there is no doubt that the chemical agents existing or produced in the human body are its strongest defensive agents in protecting it from specific infections.

Disease is a gigantic chemical problem, and the importance of chemical pathology has been emphasized by the bacteriological discoveries of recent years.

"The processes of chemistry are now far in advance of microscopical revelations, so that henceforth the results of microscopic work, especially as regards micro-organisms, must be more controlled or checked by the chemist than they have hitherto been. Hence it is by chemical, combined with biological and bacteriological methods, that we must look for the discovery of the many factors in the causation of diseases, and for the power of preventing or removing diseases. The physiological symptoms of the infective diseases appear to be traceable to definite chemical compounds, to animal alkaloids; and that to the action of such poisonous compounds during life the special characteristics of the disease are to be traced. For it has been shown that disease can be

communicated by such poisons in the entire absence of living micro-organisms." *

3.—*Toxic Substances developed in the Alimentary Canal.*

No structure or organ in the human body exercises a more important influence upon the condition we call health, than the alimentary canal. This is a fact of as old standing as the practice of medicine itself, but only of recent years has it been demonstrated that alkaloids developed in the intestinal contents are important factors in the processes wherein this influence originates. Clinicians were well aware of the diversity of subjective and objective phenomena attributable to the condition of the stomach and bowels, and in diseases differing widely, purgation was regarded as an essential feature of treatment. Writers of fifty years ago ascribed the most anomalous mental and physical symptoms to "functional disorders of the digestive apparatus," or to the "agency of a poisonous secretion upon the intestinal nerves." Chemical changes in the contents of the stomach and bowels; the products of these changes;

Chemical changes in bowels.

* Sir Wm. Aitken, *loc. cit.* pp. 98, 99.

absorption into the blood of decomposition products so formed, and their subsequent action on the tissues and organs were overlooked, and their importance has only been established by observations of recent date.

Toxic substances formed in digestion.

In the food we eat there are, given the necessary conditions, all the materials required for the formation of toxic substances, and there is ample clinical and experimental evidence to show that these are formed in large quantities during digestive processes.

It has been said that nitrogen is an essential constituent of the alkaloids; hence a diet formed largely of nitrogenous food-stuffs will be attended by a greater development of alkaloids than one in which they do not predominate. Lauder Brunton says that the proteid substances "become split up so as to yield the poisonous leucomaines or ptomaines, and that these poisonous products may be brought about by the digestive ferments of the healthy body;" in other words, the decomposition and disintegration of albuminous material in the stomach and intestines are attended with the formation of alkaloids in the same manner as if the material were decomposing outside the animal body.

Substances such as albumen, fibrin and

gelatine are readily decomposed by the secretions of the digestive organs, and the peptic digestion of fibrin has been shown to yield the alkaloid "pepto-toxine," and the same body is always formed in the putrefaction of albuminoids. The physical and chemical conditions under which digestion occurs are also favourable to the development of alkaloids, and the presence of micro-organisms greatly increase those.

Albuminous substances are of a very complex composition, and contain a huge number of atoms. In the process of decomposition by heat, as in burning or dry distillation, by putrefaction, or by the action of enzymes, such as pepsin or trypsin, the large molecule of albumen becomes decomposed, yielding simpler and simpler substances. The huge albuminous molecule will not diffuse through vegetable parchment. The final products of its decomposition, such as compound ammonias and organic acids, diffuse readily. Between these two stages we find intermediate substances—albumoses and peptones.

Absorption of albumen.

Albumoses and peptones are amongst the products of normal digestion, but they are now acquiring a special interest from the

discovery that, when introduced into the blood without passing through the liver, these digestive products may act as powerful poisons.

It seems strange that food and poison should be so nearly allied, and that, while albuminous substances are indispensable for the maintenance of life, the substance into which they must be broken up before they can be assimilated, will kill an animal if they are applied in a wrong way, and are injected into the jugular vein instead of being absorbed from the intestine in passing through the liver.* Certain poisons are rendered harmless by heating, but the poisonous properties of the products of the more complete decomposition of albuminous materials are not so destroyed, and the alkaloidal substances so formed have simply to escape the synthetic action to which they are submitted in the portal circulation, and pass through the liver into the general blood system. The compound ammonias and organic acids are absorbed into the blood direct from the intestine.

Absorption of decomposition products.

A fair approximation of the amount of putre-

* Dr. Lauder Brunton, "Croonian Lectures for 1889."

Estimation of putrefaction occurring in intestine.

factive change occurring in the intestine may be obtained from quantitative estimation of ethereal hydrogen sulphate in the urine,* and a relative increase of putrefaction may be estimated by comparative examination of the output of aromatic and free sulphuric acid in the urine.† This is based on the fact that the former are derived from the sulphur present in the decomposed proteids, and the latter from the free acid present in the salts of the food. In health, whatever quantity of food is taken, the amount of putrefaction which occurs in the proteid constituents bears a certain more or less constant relation to the amount ingested. The relation may be expressed in terms of the excretion in urine thus :—

$$\text{Aromatic } H_2SO_4 \; : \; \text{Free } H_2SO_4 \; :: \; 1 : 10.$$

The last number may vary, in conditions compatible with health and a normal amount of putrefaction, between 8 and 12.

In conditions associated with excessive putrefaction the ratio is greatly increased, and the aromatic sulphuric acid in some cases may even exceed that of the free

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* A. Rovighi ("Zeit. Physiol. Chem.," 16, 20-46).

† Hunter, "Brit. Med. Journ.," July 12th, 1890.

sulphuric acid. In such cases there is also increased urinary discharge of ptomaines, the less stable and more toxic of these being absorbed into the blood. Sir Andrew Clark says, "It is impossible to doubt that poisonous alkaloids are formed in the alimentary canal; that when excretion is seriously diminished they must be in some degree absorbed, and that, mixing with the blood and entering the tissues, they must produce some sort of injurious effects determined by the rate of absorption and the amount absorbed." Diminished excretion indicates accumulation of decomposing albuminous materials, and these act injuriously both by their presence, and by the absorption of the products of chemical change. They dilute digestive fluids, impede the action of the gastric and intestinal juices on fresh ingesta, and provide a fertile source of poisonous substances, the injurious effects of which become more manifest when these agencies operate over lengthened periods of time. In the production of alkaloids in the intestine, micro-organisms play an active part; they find all the materials and conditions necessary for their luxuriant growth and multiplication, and although the resistive

Poisonous alkaloids formed in alimentary canal.

Resistive action of mucous membrane.

action of the healthy intestine prevents their passage into the blood, their products are constantly absorbed. The different mucous membranes of the animal body secrete fluids in which micro-organisms find suitable media for their development, and while epithelial membranes present an effective barrier to the inroads of the bacteria themselves, it affords no protection from the passage into the blood of the chemical products they elaborate. This is eminently true of the intestinal tract, which teems with living germs from beginning to end, and so long as morbid influences do not destroy the epithelial barrier, the evil effects of their presence is confined to the absorption of their putrid products.

The symptoms referable to the absorption of poisonous alkaloids developed in the intestine vary both in occurrence and degree, and will depend upon the nature of the alkaloid, the amount absorbed, and the time during which it operates. "In many cases of nervous depression we find a feeling of weakness and prostration coming on during digestion, and becoming so very marked about the second hour after a meal, and at the very time that its absorption is going on, that we

can hardly do otherwise than ascribe it to actual poisoning by digestive products absorbed into the circulation." *

Symptoms due to putrefaction products.

Drowsiness, languor, inaptitude for mental and physical effort, sensations of stiffness and prostration, feelings of discomfort and uneasiness, perverted sensations partly referable to the nervous, partly to the digestive system; slumber followed by no sense of refreshment, but by an increase in some of these symptoms, and usually with a feeling of intense depression; these are symptoms commonly observed two to three hours after a full meal, and are probably due, as Dr. Brunton suggests, to "actual poisoning by digestive products." These symptoms, which in many cases resemble the action of a paralysing narcotic, as curare, are not entirely referable to the direct soporific action of certain digestive products, but are in some way connected with the dilatation of the gastro-intestinal blood vessels, and consequent anæmia of the brain. But it is possible that the determination of blood to the intestine during digestion is the result of something more than a reflex dilatation of the

* Lauder Brunton: "Indigestion a Cause of Nervous Depression."

blood vessels; it may be a definite hæmic reaction possessed by digestive products, and in effect comparable to the chemio-tactic phenomena observed in inflammatory changes. In fact, many of the processes in digestion and absorption are very similar to those observed in inflammatory conditions associated with local production and absorption of poisons. The nature of the diet influences these symptoms, greatest after a meal rich in albuminous materials, and at a minimum, or entirely absent, in an exclusively farinaceous diet. In the healthy individual this condition of temporary poisoning soon passes off, active discharge of excretory functions preventing anything like permanent effect; but in persons weakened from any cause whatever, toleration of these products is lost, debilitated function is aggravated, and organic disease actually established. Bouchard has shown experimentally that certain forms of suppuration in man, *e.g.*, boils, may be immediately arrested by rendering the alimentary canal aseptic. Evacuation of the bowels is known to have a marked effect in diminishing certain pyrexial states, and Clark, Brunton and others attach great importance to formation of alkaloids in the intestine in

Leucocytosis in digestion.

Ptomaines in mental disease.

cases of chlorosis, anæmia, and nervous disorders. Amongst alien physicians the good results which follow free and regular evacuation of the bowels is a matter of every-day experience. In epilepsy, mania and melancholia, exacerbations of excitement and mental distress are found closely associated with putrid accumulations in the bowels; physical symptoms are sometimes present, strongly suggestive of the action of toxic substances in the circulating blood, and, taken together, the clinical features are so marked as to almost point to a definite relation between potentiality of disease and intensity of poisoning. A few cases may not inaptly illustrate this.

1.—R. T.,* æt. 51. Admitted 3rd October, 1890. History of gradually increasing mental aberration during previous three months. Had been a steady, temperate man, led a careful life, a very slight neurotic taint in the family history, but well marked symptoms of intestinal derangement, extending over a year previous to admission. His mental condition was that of acute melancholia, with one well-marked delusion. There was no disease of

* From Burntwood Asylum Medical Reports. By permission of Dr. Spence, Med. Superintendent.

Ptomaines in mental disease.

the heart or lungs beyond feeble action of the former, and the most apparent physical condition was that of muscular weakness. He could scarcely stand upright, legs trembled, gait unsteady and uncertain, grasp of hand feeble, and general physical debility quite disproportionate to the state of nutrition or the relation of weight to his height. He had all the appearances of a patient suffering from incipient paralysis, and was so manifestly debilitated that he was at once put to bed. Active treatment was adopted. The daily administration of an enema during the first week of treatment removed large quantities of fæces, and subsequently ʒss doses of liq. ext. of cascara sagrada were given to produce at least one free motion daily. Diet was simple and equivalent to two pints of milk, twelve ounces of bread and six ounces of meat, in twenty-four hours. In two weeks the condition of physical debility had almost disappeared, and he was able to be out of bed during the greater part of the day. Elimination was maintained, in addition to baths, by continuous use of cascara sagrada in diminishing doses, and during the first four weeks the mental state of extreme dejection gradually dispelled, a more cheerful view of

things presented itself to his mind, and lastly the one delusion—that the devil was on his back—disappeared soon after. One noticeable feature was the mild exacerbations of all the symptoms if a couple of days elapsed without his having obtained a free intestinal evacuation. At the end of two months he was discharged recovered, having during that time gained two stones in weight.

Putrefaction products in mental disease.

2.—M. A. R., æt. 52 years. Admitted 26th November, 1890. Previous history similar to preceding case. No neurotic family history. Mental condition that of acute melancholia. Physical examination of heart and lungs revealed nothing abnormal. Instead of the weak paralytic condition observed in the last patient, she appeared convulsed, body held firm and rigid, arms and legs flexed or pronated with difficulty, muscles of face and expression tightly drawn, jaws clenched, eyes fixed and staring, pupils normal, and a generalised muscular tension, reminding one of the condition observed in the initial rigidity of cerebral lesions.

The same treatment was adopted in this case, with similar results. In three weeks the physical symptoms had entirely disappeared, and she was able to leave the

infirmary ward, her mental condition having much improved. Putrefaction products in mental disease.

Exacerbations were even more marked in this case, and the apparent relation of these to the condition of the alimentary canal was too suggestive to be overlooked. After three months' treatment she was, on the 10th March, 1891, discharged recovered.

3.—F. W., æt. 26 years. Admitted 30th June, 1891. Good personal and family history, no neurotic taint, steady, temperate, well-behaved individual, and no apparent social, moral, or hereditary cause for insanity. Her mental condition was that of acute mania. Routine physical examination revealed nothing abnormal in the great organs. Paralytic symptoms were well marked, and although it must be admitted that the patient was in an indifferent state of nutrition, still the muscular debility was quite disproportionate to this, and unlike that arising from simple emaciation. She appeared without muscular control, unable to stand or grasp with any degree of firmness, and had all the physical symptoms of the first mentioned case, but in a more pronounced form.

History of obstinate constipation, as in previous cases, and during the first two months

Putrefaction products in mental disease.

of treatment aperients had to be given regularly to obtain free motion of the bowels. Mental instability persisted rather longer in this case than in Cases 1 and 2, but after six months' treatment she was discharged recovered, having gained four stones in weight.

4.—E. M., æt. 25 years. Admitted 22nd October, 1891. Personal and family history as in previous cases, good, and no obvious cause for insanity. Similar history of gradual increase in symptoms of mental aberration, of increasing physical weakness or oppression, and of marked intestinal derangement. Her mental condition was one of acute melancholia. Physical condition similar to Case 3, and a month's treatment in bed was required before she was sufficiently improved to leave the infirmary wards. The same treatment was adopted as in the other cases, and in the course of eight months she was discharged recovered, having gained in weight two stones eight pounds.

The subsequent history of this case is interesting. She was readmitted six months after discharge, and had done well during this time until about twelve days before admission, when she felt all her "queer feelings," as she describes them, coming back

Melancholia in typhoid fever.

again; these gained in intensity, and she was admitted, suffering from acute melancholia. Mental aberration was very marked, and physical symptoms equally so. In addition to these, which were essentially of the paralytic type, she had symptoms of a convulsive character, in their mode of onset like an attack of *petit mal*, but of longer duration. The peculiar nature of these paroxysmal convulsions was observed before a diagnosis as to her physical condition had been arrived at. On the second day after admission, in consultation, typhoid fever was diagnosed, and this disease ran a fairly normal course. Symptoms of mental disease were manifest throughout, but with convalescence, which was somewhat protracted, they steadily disappeared, and three months after admission she had regained a condition of sanity.

The suggestive side of this case, so far as the present purpose is concerned, is, that in it we have a repetition of an acutely melancholic condition beginning, coexisting and ending soon after a recognisable physical affection. A bodily disease in which toxic products are largely formed in the alimentary canal, and circulating in increased quantities in the blood, determines to some extent its characteristic

Ptomaines in mental disease.

symptoms, exercising a tangible influence on the body and, *ergo*, on the mind.

It is beyond the scope of this work to attempt to enter into detail as to the possibility of animal alkaloids and other putrid or metabolic products being active agents in the causation of *certain forms* of insanity, and in the absence of evidence which may be derived from quantitative analytical examination of the urine, the following clinical features of these and other observed cases may be summarised without comment.

1.—*Age of the Patient.* Common in middle life; observed cases from twenty-five to fifty-two years of age.

2.—*Family History.* Good, no hereditary taint of insanity.

3.—*Causation.* The generally recognised causes of insanity were absent.

4.—*Personal History.* Usually good; a slight neurotic taint may have been manifested at some time of patient's life, but commonly there is nothing in mode of life, condition, or habits to suggest predisposition to insanity.

5.—*Temperament.* Anxious minded, sensitive and restless. Ever concerned in doing the right, fearful of the commission of wrong,

Ptomaines in mental disease.

and undue apprehension of erroneous interpretations of their conduct.

6.—*Premonitory Symptoms.* These are characteristic. The patient becomes aware of a change in his condition, is conscious of perverted sensations, "queer feelings," uncontrollable emotions, ridiculous and exaggerated ideas of the simplest incidents; these gradually become intensified, and in the struggle which goes on in the attempts to out-reason those mental aberrations, the governing or control faculty of will is worsted, and a state of apparent delusional insanity is established. *Pari passu* with this gradual increase in mental aberration—of which the patient is all the while painfully conscious—there are unmistakeable signs of intestinal derangement, and of the absorption of poisonous substances.

7.—*Psychical Condition.* When disease is fully established, depression occurs more frequently than exaltation. In either case the mental state is intense. The melancholy is characteristic, the mind is wrapped in gloom, impenetrable and deep; no ray of hope can possibly enter into it; all is utterly lost; the sufferer is unfit to live, and all his acts are wicked and he deserves to die. The

Psychical condition.

surprising and significant result is the extraordinary rapidity with which this condition is ameliorated by appropriate treatment. Whether the condition is acutely maniacal or melancholic, symptoms of mental instability manifest themselves for a time after removal of the cause, and disappearance of physical symptoms. The same remark may be applied to these cases that Sir James Simpson made regarding puerperal insanity: "The fire of the disease goes on burning in these cases of insanity after the lighted match is merely applied, and the strange morbid clockwork runs on, as it were, after the key that wound it is withdrawn."

8.—*Nature of Delusions.* There is usually one fixed delusion; self-impeachment, unmeaning and irrelevant self-criticism, exaggerated consciousness, morbid dread of death or disaster, all partake of the "ego," and the delusions conform to this type. It may be the devil is on the patient's back; that his (the patient's) arm is the handle of a pump; that there is something working inside; that there are parts of his body made of glass and so on. All are morbid developments of the "ego."

9.—*Physical Condition.* Attenuation and

loss of flesh apparent, but not marked; loss of sensation; tinglings and twitchings of the limbs and facial muscles; occasionally muscular rigidity or spasmodic contractions; loss of muscular control, not attributable to simple inanition and quite disproportionate to emaciation when this is present; physical debility and muscular spasms are comparable to the paralytic and convulsive reactions of known animal alkaloids; hypothermia usually present, and feeble action of the heart; lastly, a constant history of intestinal derangement. The physical and mental symptoms develop concurrently, but the latter persist for some time after the former have disappeared. Physical condition.

10.—*Duration.* Under appropriate treatment this varies from two to seven months.

11.—*Treatment.* This is of the simplest; rest, appropriate diet and active elimination. Rest in bed during first few weeks, and diet principally farinaceous.

12.—*Recovery.* If proper attention be paid to the hygiene of the body, and especially that of the alimentary canal, this is permanent. Recovery is accompanied by an increase in weight, the average in cases observed being two stones for an average period of four months.

13.—*Relapse.* When this occurs it is a repetition of all the same mental and physical symptoms as before, and the patient is quite as amenable to treatment.

Evidences of auto-infection in mental disease.

In suggesting that mental disorder may in some cases be a result of autochthonous poisoning, greatest importance is attached (*a*) to following negative evidence: the absence, of ordinary mental or physical predisposing or exciting causes; of organic disease as deduced from a consideration of the duration, treatment and recovery; and of disease of the intellectual faculties as manifested by the consciousness of the patient that his ideas are aberrant; (*b*) to following positive evidence: concurrent development of mental and physical symptoms, subsidence under appropriate treatment, the existence of a certain source of poison in the putrefying accumulations in the intestine, and lastly, peculiar physical symptoms suggestive of the toxic action of an absorbed poison.

Since some of these observations were made,* Professor Wagner read a paper on "The Physical Basis of Acute Mental Disorders," before the Austrian Association for

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* "Graduation Thesis," July, 1891.

Physical basis of acute mental disorders.

the study of Psychiatry and Forensic Psychology,* in which he said that in the light of recent researches it appeared probable that in the causation of these disorders an important part was played by toxic substances not only introduced from without, but produced within the organism by metabolic processes. Professor Meynert, of Vienna, expressed his agreement with this view, and supported it with facts furnished by the study of tabes in its relation to progressive paralysis. Professor Laufenauer, of Buda Pesth, instanced in confirmation of the same theory, certain acute psychoses which he had observed in chorea and hydrophobia.

If it be admitted, that animal alkaloids and other toxic substances produce characteristic symptoms in certain bodily disorders; that they may be active causative agents in establishing or creating such conditions as favour the development of bodily disease; that in certain bodily disorders the gravity of mental and physical symptoms is correlated with the degree of toxæmia; that in certain aberrant states of the mind all the conditions favour-

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* "Brit. Med. Journ.," Nov. 7, 1891.

able to the assumption of such a hypothesis are present, and remembering the relation of body to mind, the conclusions arrived at do not apear illogical.

4.—*Ptomaines introduced into the Body by Inhalation.*

The noxious effects following upon the inhalation of respired air are well known, and have generally been attributed to two circumstances; (1) A diminution in the quantity of oxygen; and (2) An increase in the carbonic acid gas. A quantitative estimate of the latter is taken as indicating the degree of atmospheric vitiation, and for practical purposes this is a useful and reliable method. Impure air, however, owes its injurious effects to something more than the coexistence of these two conditions. The inhalation of air, diluted with CO_2 in excess of the "admissible limit of respiratory impurity" of sanitarians, would vary in its physiological effects, according to the purity of the gas. Thus, air charged with pure CO_2 much beyond ·7 per 1000 vols. can be breathed with impunity, and when present in sufficient quantity to affect a healthy individual, the symptoms produced

Injurious effects of impure air.

would be those of asphyxia, whereas a similar amount of vitiation from respiratory impurities would produce characteristic symptoms, other than those of simple asphyxia.

Organic matter in respired air.

In respired air several substances coexist, and temperature is increased, but the injurious matter is an organic poison, probably of an alkaloidal nature. Gavarret and Hammond separated the carbonic acid gas and watery vapour, and on allowing a mouse to inhale the air containing the residuum of organic matter, they found that it died in forty-five minutes. Several instances have been recorded in which, on the inhalation of a similar atmosphere, adults have developed, in from three to four hours, well marked febrile symptoms (increased temperature, quickened pulse, furred tongue, loss of appetite and thirst), which remained for even twenty-four or forty-eight hours subsequently.* When the poison accumulates in the air to a sufficient extent, as in the cases of the Black Hole of Calcutta, and of the prison in which three hundred Austrian prisoners were put after the battle

* Parkes, "Manual of Hygiene," 7th Edit., p. 160.

of Austerlitz, the symptoms preceding death are not those of asphyxia, but of acute poisoning, resembling in many of their features the toxic effects of animal alkaloids.

Anthropotoxin.

Du Bois Raymond terms the organic poison excreted by the lungs of human beings "anthropotoxin," and certain observers have endeavoured to establish a quantitative relationship between the respired poison and the carbonic acid gas so eliminated. Nitrogen is present in the blood in very small quantities, and from seven to eight grammes are eliminated daily by the lungs, more nitrogen being excreted by herbivorous than carnivorous animals; the characteristic odours of certain diseases are closely associated with nitrogenous waste products; the injurious effects of sewer gas are due to volatile carbo-ammoniacal compounds, and the peculiar "stuffiness" imparted to the air of a room which has been breathed for some time is probably due to volatile combinations of nitrogen derived from the anaerobiotic changes in the tissues and fluids of the body, and excreted by the lungs. Animal alkaloids are both volatile and non-volatile, the less stable being generally more noxious in their effects; and peculiar sensations of

drowsiness, languor, mental depression and inertness have been experienced by analysts in the early stages of investigations on the organs of persons dead of infectious fevers. D'Arsonval read a paper* at the Société de Biologie, Paris, on the resemblance between the toxic action of certain ptomaines, and that of the pulmonary poison. The mode of action of the poison of expired air, remarked the author, is similar to that of the toxic agent which was studied by Brieger under the name of putrefactive neurin. In these two kinds of poisoning, one observes movements of mastication and of deglutition, an acceleration of the cardiac beats, an arrest of the heart in diastole, a contraction of the pupils, diarrhœa, and a paresis of the lower extremities. In concluding, the author states that there is no doubt, after this comparative examination of the phenomena produced by the putrefactive neurin and the pulmonary poison, that these two substances have a great analogy of action. This is another reason why the toxic agent of expired air should be looked on as an animal alkaloid.

Identity of pulmonary poison and neurin.

If this be true of the respired air of

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* "Lancet," Feb. 25th, 1888.

healthy individuals, it is also true for the vitiation caused by exhalations from the sick. Differential experiments have shown that the smell of organic impurities, emanating from the healthy, was still imperceptible when the air contained 0·208 per 1,000 of respiratory impurity as CO_2; whereas, in hospitals containing ordinary cases, it was quite distinct when the CO_2 reached 0·166, and in some diseases the organic matters thrown off are so great that scarcely any ventilation is sufficient to remove the odour.

Respired air in diseased conditions.

After mentioning many places in which phthisis had prevailed from time to time, Parkes* says: "In addition to a general impaired state of health, arising, probably, from faulty aeration of the blood, and to phthisis and other lung affections, which may reasonably be believed to have their origin in the constant breathing of air vitiated by the organic vapours and particles arising from the person, it has long been considered, and apparently quite correctly, that such an atmosphere causes a more rapid spread of several specific diseases, especially typhus exanthematicus,† plague,

Effects of volatile contagia.

* "Loc. cit.," p. 163. † See Chap. I.

small-pox, scarlet fever, and measles. This may arise in several ways: the specific poison may simply accumulate in the air so imperfectly changed, or it may grow in it, or the vitiated atmosphere may simply render the body less resisting or more predisposed." The introduction of the poison of cholera by inhalation has long been admitted, and it is a knowledge of this fact which prompts the Indians to march at right angles to the wind, and never against it. The wind is supposed to contain the poison given off by the cholera evacuations deposited on the ground. Volatile poisons introduced by inhalation also give rise to non-specific diseases; air from water closets, putrefying animal substances, sewage farms, sewage matter on lands, foul and stagnant water containing decaying animal and vegetable matter, have all given rise to dysentery and diarrhœa. It has also been said that typhus fever is communicated most readily when the characteristic odour is strongest, *i.e.*, when the volatile poison is most concentrated; and the most effective means of preventing the spread of this disease is by rapid and extensive dilution of the poison by efficient ventilation.

The conclusions, therefore, which may be urged, are (1) That volatile poisons are excreted by the lungs; (2) When they accumulate in the air to a sufficient extent, symptoms are developed, on inhalation, which resemble the toxic action of certain animal alkaloids — the more vitiated the atmosphere, the greater severity and acuteness of symptoms; (3) Experimental evidence points to a close resemblance between the ptomaine, neurin, and the expired poison; (4) Clinical history of various specific and non-specific diseases, by analogy, lend support to these statements, and point to the probability that the exhaled poisons are the volatile products of putrefactive change occurring within our bodies, just as putrefying animal matter, in ordinary circumstances, evolves noxious gases.

5.—*Ptomaines introduced into the Body in Articles of Food.*

The ingestion of food stuffs which have undergone putrefaction is usually followed by the development of well-marked symptoms, and when ptomaines and other toxic bodies have been formed in sufficient

quantity, the acutely toxic symptoms may run a rapid and fatal course.

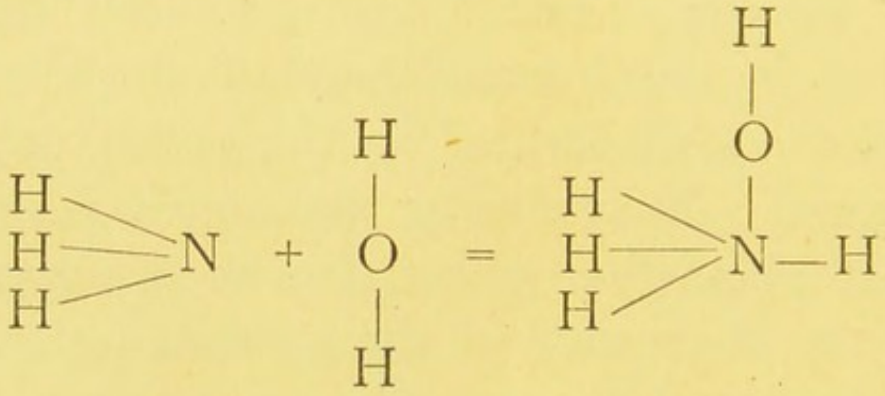
The formation of alkaloids in albuminous food stuffs is the result of processes similar to those referred to as occurring in the stomach and bowels, in certain conditions. In either case, no matter what the active agent may be, the chemical disintegration of albuminous matter is the essential step towards production of the poison. The presence of putrefactive bacteria in tainted or decomposing food does not determine the nature of the symptoms, or the character of the disease. These are produced by the action in the human body of the chemical substances elaborated in the putrefying food material. In a similar manner, it is not the yeast plant that gives rise to intoxication, but the absorption of the product—alcohol—of its growth and development. It is probable, however, that in acute cases of poisoning by meat, specific poisons are correlated on the one hand with a specific microbe, and on the other with characteristic symptoms. What makes this more likely is the fact that on comparing the chemical constitution of some of these bodies with their physiological action, we find dissimilarity of

Formation of ptomaines.

Formation of ptomaines.

the former existing with a certain community of the latter.

The relation of ammonia to the production of alkaloids in plants and animals has frequently been referred to, and the properties of this gas bear a close resemblance to those of some of the ptomaines. Nitrogen, which is generally regarded as trivalent, is found in certain hypothetical combinations to be pentavelent, as in the formation of ammonium hydroxide from ammonia gas and water, thus :—

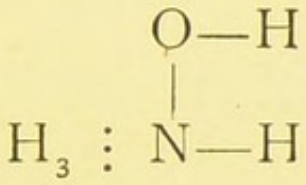


Ammonia gas. Water. Ammonium hydroxide.

This appears to be the plan upon which some of these alkaloids are formed, the nitrogen being pentavelent, and hydroxyl group retained in combination.

The following table shows how three of the commonest ptomaines (neurine, choline, and muscarine) are formed from trimethylamine and alkyl radicals, in a manner similar to the formation of liquor ammonia from ammoniacal gas and water.* Formation of ptomaines.

Ammonium hydroxide



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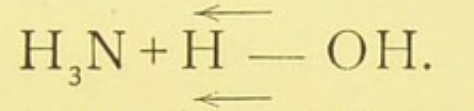
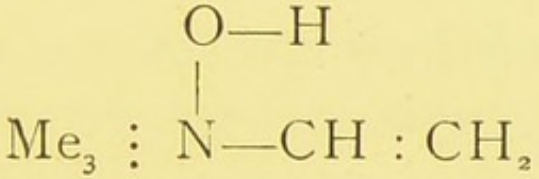


Ammonia. Water.

Neurine



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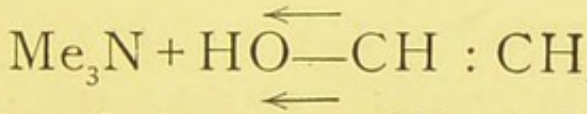

Trimethylamine. Vinyl alcohol.

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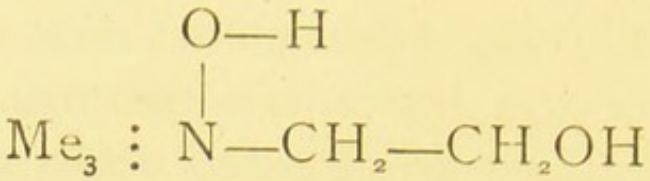
* Armstrong, "Journal of Chemical Industry," July 30th, 1887.

Choline



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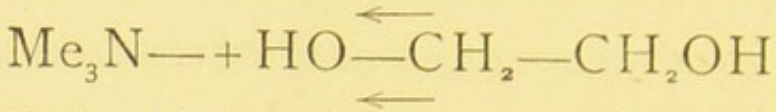
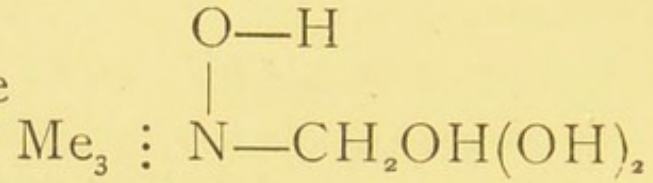


Trimethylamine. Glycol.

Muscarine



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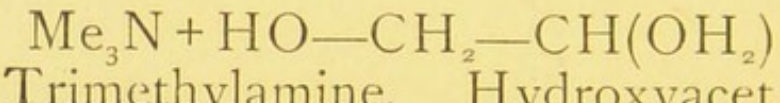

Trimethylamine. Hydroxyacet aldehydrol.

An atom of hydroxyl passes from the alkyl to the nitrogen of the trimethylamine, and the residue also becomes attached to the nitrogen. Certain ptomaines, as collidine and tyrotoxicon, seem, however, to be associated with the aromatic series of organic compounds.

Poisonous food.

Many articles of diet have given rise to poisonous symptoms, and among those of common occurrence are tinned meats, cheese,

Acute ptomaine poisoning.

pork, salt fish, mussels, mackerel, oysters, preserved turkey, pigeon pie, roes of the herring, sturgeon, pike, barbel and perch, tainted beef and mutton. The injurious effects attributable to certain substances taken as food have long been known, and Dr. George Johnson, in his "Medical Lectures and Essays," mentions the fact of some Irish peasants who, in 1826, having made a stew of the flesh of a dead calf which they found on the sea-shore, soon developed choleraic symptoms, and death was ushered in by a comatose condition resembling opium poisoning. During the last ten years, however, many of the toxic substances developed in food materials have been isolated, their chemical and physiological characteristics defined, and this form of ptomaine poisoning is seen to be a well-defined disease.

Gautier studied the action of ptomaines extracted from putrefying meat, according to their solubility in ether, chloroform and amylic alcohol, and the results he obtained have already been referred to (Chap. III, p. 43). It is not necessary to fall back on the physiological characteristics to show the existence of a ptomaine in tainted and

Acute ptomaine poisoning.

decomposing foods, the symptoms following ingestion are in themselves sufficient to establish the presence of an actively toxic animal poison.

Period of incubation.

In most cases there is a period of incubation, varying from four to thirty-six hours, during which feelings of malaise, loss of appetite, languor, nausea, fœtid eructations, and griping pains in the belly are experienced, but not uncommonly acute symptoms are developed within the first two hours after ingestion of the poison.

The first definite symptoms are sudden in their onset, not unlike those of an attack of acute gastero-enteritis, and at times so severe as to suggest strangulated hernia, ruptured intestine, and even acute maniacal delirium.

Abdominal pain.

Abdominal pain is intense, and generally is the first symptom to which the patient's attention is directed; then follow diarrhœa,

Diarrhœa.

vomiting and prostration. The diarrhœal discharge is accompanied with frightful colic, is quite unrestrainable, and the stools are liquid, offensive, dark in colour, and in some cases resemble dirty water, with lymph

Vomiting.

flocculi suspended in it. Vomiting is of less frequent occurrence than diarrhœa, but

when present is violent, and expulsive efforts continue long after the contents of the stomach have been expelled. Vomiting persists in some cases till the fatal termination of the disease. Prostration is marked and early of appearance, and seems to be caused, in the first instance, by the excessive pain ; sensations of extreme muscular weakness, faintness, cold clammy skin, lead up to the collapse, which is not unlike that of cholera, and invariably precedes death. Prostration.

Temperature in the earliest stage is subnormal, but, especially in cases tending towards recovery; this is followed by an increase, and it may even reach 104° F. A combination or succession of hyperthermic and hypothermic phenomena points to the presence of more than one toxic substance. The pulse is quickened, varying from 100 to 132 per minute, and not uncommonly an acceleration of the pulse is found associated with a subnormal temperature, a pulse of 120 coexisting with a temperature of 96° F. Pyrexia. Pulse.

In most cases there are peculiar symptoms referred to the throat. It feels dry, sore and parched. The patient feels thirsty, and there are also burning sensations, at times intense and depressing ; a sense of tightness and Peculiar symptoms.

Acute ptomaine poisoning.

constriction as if being strangulated; the articulation is difficult, and the voice a hoarse whisper. The tongue is dry, brown and coated, and often red at the tip. In some cases the pupils are dilated, but when at all affected they are more commonly contracted.

Atropine an antidote.

Hence atropine is given in certain cases of ptomaine poisoning as an antidote, from the fact that some of the symptoms are the reverse of those of atropine poisoning, and atropine is supposed to paralyse the identical nervous structures which are irritated by the ptomaine. The eyes are sunken, and the face assumes the appearance noticed in the stage of collapse in cholera, with headache and mental depression. Convalescence is often slow and protracted, extending over several weeks, with feelings of weakness, languor, and low spirits. In a very few

Cardiac symptoms.

cases heart symptoms have been observed, *e.g.*, sensations of pressure in the region of the heart, with pain and discomfort; first sound weakened, and the second quite inaudible at the base, with an intermittent, very compressible, and scarcely perceptible pulse. In one case of poisoning by decayed American cheese, amongst other symptoms,

Epileptic fits.

epileptiform fits were developed, the patient

never having suffered from these before ; and in a case of mackerel poisoning, in which the symptoms did not appear until twenty-four hours after eating, acute peritonitis supervened, whereas two individuals who partook of the same meal were taken ill within a few hours of eating, and made rapid recoveries. There are many kinds of food fishes, however—a list of over forty is given by Pappenheim—which give rise to poisonous symptoms when eaten by man. The little herring (*Clupea harengo minor*), the silver fish, the pilchard, and several others, when eaten before the flesh is apparently decomposed, set up severe gastro-intestinal irritation, ataxic nervous symptoms, great depression and algidity, but some writers assert that these effects are really due to putrefactive products rapidly formed after death of the fish.

Acute peritonitis.

Poisonous fishes.

The blood and lymph of fishes teem with bacteria ; and especially in fishes caught in large shoals decomposition sets in very soon after death, so that many of the so-called poisonous fishes may simply be those which undergo a more rapid putrefaction than others. The alkaloid which Anrep isolated from poisonous fish produced the same

symptoms as those when the fish itself was eaten. These resembled atropine poisoning, and were probably due to muscarine in presence of one or more poisons, different classes of symptoms being referable to the action of several ptomaines, or toxic substances. Tyrotoxicon, the alkaloid which is developed in milk during hot weather, gives rise to nausea, vomiting, headache, quick pulse, laboured breathing, constipation and great prostration, with stupor. The pupils may be slightly dilated, and there may be also a scarlatina-like rash on the skin. This alkaloid,—which is really di-azobenzene butyrate—Dr. Lauder Brunton* thinks may form along with other poisonous products in the intestines of children from the decomposition of the milk. "One of the most fruitful sources of diarrhœa in children is certainly the use of feeding bottles with long tubes, which are generally imperfectly cleaned, so that even when the milk is put quite fresh into the bottle, it becomes inoculated with bacteria before it reaches the child's stomach, where the temperature is just right for their rapid

Tyrotoxicon.

Decomposition of milk.

* "Croonian Lectures for 1889."

multiplication and the decomposition of the milk. The difference between the chances of a child fed at the breast, and in this way, is enormous, for in the former case the milk flows free from germs directly into the child's mouth, and the risk of bacterial inoculation is greatly diminished. Indeed, Andeer finds that in cows there is an antiseptic substance, resorcin, present in the udder, as if for the purpose of rendering the milk not only aseptic, but antiseptic." Sausages, pork pies, and beefsteak pies are not infrequent sources of poisoning, and it is a point of some importance that meat, or pies, which are eaten with safety soon after cooking, may develop poisons in process of cooling, and when eaten cold produce serious symptoms. This is the result of action of the microbial ferment; while the heat in cooking may be sufficient to destroy the microbes themselves, it does not affect the ferment they have formed, and in the cooling of the food this ferment exercises a decomposing action. In this way the disintegration of the albuminous substances takes place in a manner similar to that of the intestinal ferments, pepsin and trypsin, and yields albumoses, peptones, organic acids, compound ammonias

Ptomaines formed by microbial ferments.

and alkaloids. The only difference is that in the one case albuminous decomposition takes place outside the animal body, and in the other within it. The adage, "What is one man's food is another man's poison," becomes very intelligible in the light of these facts, and one feels tempted even to go farther, and bring it up to date by saying that "What is one's own food *may* also be one's poison."

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