Ptomaines.

Toxicological, Clinical, Chemical,

by

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A Thesis.

1891.

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Chapter I

On Alkaloids in General.

Termin-ology 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 "gali" signifying the ashes of plants from which soda was first obtained, and from the Greek we have "εἶδος," likeness. From the union of these two words, gali and εἶδος, we have the word "alkaloid", alkali like and indicating the supposed exclusively plant connection of these bodies.

Constitution 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 Phosphorus, Arsenic, antimony &c but it is not proposed to deal with these here. As to the constitution of natural alkaloids these are generally regarded as products derived from ammonia by process of substitution, - the hydrogen atoms of the ammonia being replaced by radicals as C_2H_5 C_3H_5 &c. To the compounds so derived the termination "Amine"

Constitution

is used to indicate them 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 a three molecules have been used. This is usually represented in the following formulae. Let R = radical employed.-

$$\left.\begin{matrix} R \\ H \\ H \end{matrix}\right\} N \quad \left.\begin{matrix} R \\ R \\ H \end{matrix}\right\} N \quad \left.\begin{matrix} R \\ R \\ R \end{matrix}\right\} N: \qquad \left.\begin{matrix} R_2 \\ H_2 \\ H_2 \end{matrix}\right\} N_2 \quad \left.\begin{matrix} R_2 \\ R_2 \\ H_2 \end{matrix}\right\} N_2 \quad \left.\begin{matrix} R_2 \\ R_2 \\ R_2 \end{matrix}\right\} N_2 \qquad \left.\begin{matrix} R_3 \\ H_3 \\ H_3 \end{matrix}\right\} N_3 \quad \left.\begin{matrix} R_3 \\ R_3 \\ H_3 \end{matrix}\right\} N_3 \quad \left.\begin{matrix} R_3 \\ R_3 \\ R_3 \end{matrix}\right\} N_3$$

Monamines. Diamines. Triamines.

It will be observed that one or more Hydrogen atoms may be substituted in <u>one</u> 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 vegetal kingdom was regarded as the only source from which alkaloids could be obtained, but it has now been shown that bodies which are in every way identical with the vegetal alkaloids are elaborated in animal tissues, excretions, secretionose and can be obtained

Chap I 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 removed from vital functions.

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

In "With regard to the origin of alkaloids in the plant, there can living "be little doubt that they are derived more or less from proteid. plants. "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

Chap. I "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 connexion 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 & 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 shew that the demand for comb- "ined 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 occuring in the plant.

* Vines. Physiology of plants. p 224.

Chap I 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 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 ab- "undance in their normal habitat produce only small quantities "when grown in hothouses in this country. On the other hand "it appears that too intense a light is unfavourable to the acc- "umulation of alkaloids for it has been observed that in certain "cases plants which have grown in the shade are richer in alk- "aloids than others which have been exposed to the full glare of "the tropical sun". * But while light may thus appear of import- ance as a factor in the formation of alkaloids it can only be 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 occur- ing in the plant and indirectly the elaboration of alkaloids.

* Vines Physiology of Plants p 268.

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

In dead vegetable matter Lombroso and Erba showed that decomposed maize contained alkaloidal bodies and that the products of this maize contained poisonous principles, extracts of which producing, when administered to animals tetanic and narcotic symptoms. Pohl 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. Pohl 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 purpurea

‡ Journ Chem Soc Lond 1883 p 1157.

Chap I (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 when merely exposed to damp evolved trimethylamine when heated with alkalies, in this agreeing 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 occuring in Rye, Rye meal, maize, oats we have fermentation of glucose formed from the starch, peptonisation of the albumins and finally formation of the putrefactive alkaloids. While it may be safe to aver that these phenomena undoubtedly

chap I 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 plant 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 & 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 metamorphosis 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, which in the case of urine is fixed, oxidizable and

Chap I forms a crystalline chloride and a double salt with platinic chloride and chloride of gold. Paterno and Spica* Bechamp + Gautier and Coppola ⊙ have all shown that chemical and physiological properties similar to those exhibited by ptomaines might be obtained from substances procured from normal blood, egg albumin, 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.

Alkaloids 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 (ɔc) 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 temperature of the blood x

* Journ Chem Soc Lond 1882, p 741. (ɔc) Repertoire de Pharmacie July 1885.
+ Compt Rendu tome XCIV p 973. x Ueber Ptomaine - Hirschwald Berlin 1885.
⊙ Journ Chem Soc Lond 1883. p 522
⊗ Lauder Brunton, Lancets for 10th Jan, 24th & Feb 7th 1885.

Chapt Gautier however in his researches extending from 1881 to 1886
has conclusively shown that they are neccessary products of
Leucomaines 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 manner 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 Haemoglobin or
diminished oxidation of the Haemoglobin.

It is very difficult to see however where this strictly physiolog-
-ical production of alkaloids becomes significant of pathol-
In -ogical conditions; and if the alkaloid found, be the effect
Pathological or the cause of the physiological deviation. There can be
conditions no doubt whatever that alkaloids are abundantly found in
the animal tissues & fluids in pathological states. The urines
of patients suffering from progressive paralysis, pneumonia

Chap I Typhus & Typhoid Fevers, tetanus, miliary and Scarlet Fevers have all yielded in greater & 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 a 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

Chap I in the course of certain disorders. With regard to this Murchison says in his Treatise on Continued Fevers p 114." — 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 bowel 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 most readily to persons in health and in many of "these cases where the symptoms of typhus have supervened "immediately on exposure to the source of contagion and where "we may suppose the poison to have been unusually concentrated "the affected persons have been conscious at the time of exposure "of a most disagreeable odour, pungent and ammoniacal."

The injurious effect of respired air is mainly due to organic matter, principally combinations of ammonia; sewer air owes its 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 as in plants, ammonia forms, in the animal economy 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 albumin, peptone, casein fibrin, myosin &c 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 during the first day, and probably the first two days after death any alkaloid found in the cadaver would be a leucomaine or vegetal alkaloid and this is a point which is of very considerable medico-legal importance. So strongly toxic bodies are developed as a rule until the disappearance

Chap I of Cholin which along with neuridin are the only toxic bodies which appear during the first few 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 other basic substances disappear. So that in the order of putrefaction basic & toxic bodies as Cholin, Neuridin, trimethylamine, Cadaverin, putrescin, Saprin, Mydalein &c 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.

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

1856 Panum — In 1856 the Danish Savant, Panum showed that the inflammatory changes which occured in the intestines of animals fed on putrid matter were produced by a chemical poison and that 2 or 3 Centigrammes of an extract of these given intervially

Chap II were sufficient to kill a dog.

AD 1856 to 1866 During the following ten years researches were made by Stick, Weber, Schweninger, Hennmer and Thiersch upon putrid animal tissues and fluids deducing the general fact that a poison was present in these substances, which was of a chemical nature but they seem to have made no attempt to isolate or determine the exact properties of this chemical poison. In 1866 Dupré + 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.

Dupré + Bence Jones

1868 In 1868 Bergmann + Schmiedeberg obtained from the yeast of putrefying beer a small quantity of a poisonous, nitrogenous crystallisable substance to which they gave the name of "Sepsin".

"Sepsin"

1869 In 1869 Zuelzer + Sonnenschein extracted from macerated muscle which had been kept at a temperature

Chap II of 25°C for 5 or 6 weeks small quantities of a crystallizable substance closely resembling atropine in its physiological and chemical reactions. When injected into rabbits or 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. (1) In the same year while examining dead bodies for medicolegal 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.

Schwanert About the same time Schwanert, while engaged on a similar investigation, discovered in the liver, Spleen of a child that had died suddenly, a volatile fluid with poisonous properties and having an odour like propylamine. Marquardt, Liebermann, Gautier & Hager during forensic investigations all noted the presence of poisonous substances possessing properties similar to bodies such as amylamine, propylamine Caprylamine and to one of these Hager gave the name "Septicin"

1870 Since 1870 However the subject has attained far greater importance than that merely attaching to it from a forensic

1. Berlin Klin Wochenschr No 12 1869.

Chap II point of view. Partially investigated phenomena begin to give place to accurate & exhaustive data and their relations are seen to be more significant than had hitherto been thought of. About this time the work of Selmi began to attract attention—and to him I think falls a large share of the honour of discovering the animal alkaloids—and a spirit of rivalry seems to have existed, for numerous papers were contributed by men such as, Brouardel, Boutmy, Bechamp Guareschi, Mosso, Graanetti, Corona, Coppola, Baldwin 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 platinic Chloride. Selmi's second attempt was made by extracting the liquid with aqueous alcohol, then making 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

A.D. 1870. Selmi

Chap II 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 till the liquid became colourless. The alkaloid thus extracted was so strongly poisonous as to destroy frogs with the greatest rapidity (1.) Both of these extracts were free from arsenic. In the year 1872 he announced in a memoir to the Academy of Sciences in Bologna

1872

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.

Selmi 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 as to closely resemble the vegetal alkaloid strychnia, and tried to show that under certain circumstances peculiar arsenical bases

1 Lancet. Nov 17 1883.

Chap II "arsines" are formed. The alkaline liquid yielded, on distillation in an atmosphere of hydrogen, an alkaline distillate which gave white crystals with hydr-ochloric acid. These when moistened with caustic soda exhaled an odour somewhat resembling that of trimeth-ylamine. The presence of arsenic was determined in the hydrochlorate of this volatile base. If Selmi be correct in his assertion that volatile arsines are thus produced by the contact of arsenious acid and albuminous matter of a highly poisonous nature it is of importance, in that it suggests a possible explanation of poisoning from arse-
Husemann nical wall papers. Husemann (1) thinks it likely that a similar product may be formed from the size emplo-yed 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 & 18th centuries, Toffa and other professionals, understood how to render arsenic more potent. In Italy the Acquetta di Perugia

1 Archiv der Pharm, No XVI, 1881 p 415-
& London Medical Recorder 1882, p 259.

Chap II 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 Aqua Toffana have been in view in preparing Aqua Toffanna with the addition of the juice of the ivy leaved broad flax (Linaria Cymbalaria). Selmi & Valla were of opinion that in the Acquetta di Perugia the concealment of the action of arsenic, on the one hand, and also of the tetanising portions of the other was accomplished; but this opinion which is based on an observation of Valla's in a case of poisoning with arsenic & strychnia, does not accord with observations made on warmblooded animals with a mixture of potassium arsenite and strychnine, the tetanising action of strychnia not being prevented.

Selmi devoted the last 10 years of his life to this subject and probably did more than any one had formerly done for its permanent advancement. He originally regarded Ptomaines as exclusively products of putrefaction of

Chap II 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. (1)

A.D. 1881 About this time, this subject attained considerable importance in Russia. (2) The Russians were threatened with an epidemic which had some similarity to epidemics which had overrun the country in 1814, 1832 & 1837. A commission was appointed to investigate the subject and of this commission Pochl of St Petersburg was a member. In 1884 he published, in conjunction with Anrep, a summary of his views on the subject. (3) They say:-

Pochl

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 is very great and their chemical & poisonous properties are very different.

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

(1) Annual Alkaloids p. 10.
(2). Vide Chap I.
(3). London Medical Recorder, p. 331. 1884.

Chap II 4. Almost all ptomaines change red litmus blue, and syrup of violets to green.

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

6. In regard to their solubility ptomaines behave very differently; some of them being soluble in water others in ether benzene, chloroform & amyl alcohol.

7. Some ptomaines are tasteless & colourless; others possess an intense bitter taste & aromatic sweetish odour; others again evolve a cadaveric odour or resembling coniine or nicotine. When heated with acids they emit sometimes a pleasant floral odour.

8. Ptomaines obtained from ryemeal (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

Chap II inquiry on this subject in Russia and appeared to bring home the fact that the epidemics were in a large measure simply universal ptomaine poisoning due to the use of tainted rye meal.

1881-82 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 & others asserting that a ptomaine was formed only to be changed into another one in course of putrefaction. Gautier & Etard[1] in opposition to this asserted that whatever be the source of the putrefying albumin the chief ptomaines formed are constant in properties & 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 & tissues. Paterno & Spicca (2) 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 before these showed any signs of putrefaction. The liquids experimented on were fresh blood, and fresh egg albumin. After treating with the usual

Paterno & Spica

1. Compt Rend Tome XCVII p 263.
2. Journ Chem Soc Lond 1882, p 741.

Chap II. 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[1] 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 analyzed the urine of patients affected with progressive paralysis, insanity & 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.

Gautier The investigations of Gautier, in France, now began to attract much attention having in 1881 announced that the excretions of animals contained ptomaines, & seeking to trace in them and

1. London Medical Recorder 1882, p 339.

Chap II their defective elimination a cause of disease. He extracted
A D from the muscular juices of large animals 5 definite crystallisable
1881— alkaloids exhibiting the reactions of ptomaines in a lesser degree.
—1886 Following up the mass of available data Gautier in his more
important investigations extending from 1881–6 86, confirmed
the idea of the development, normally of alkaloids in the system
and as has been said gave to these bodies the name of
Leucomaines. As an explanation of the development under
these conditions of such bodies he offers the following
ingenious explanation (1) "The transformation in the tissues
of the higher order of animals are, in a large proportion, of
the anaerobic order. Four fifths of the products of animal
combustion are positive aerobic formations comparable to
the oxydation of alcohol under the influence of mycoderma
vini or aceti: the fifth part of the combustion of the animal
economy takes 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 anaerobic or putrid
ferments. Most of these toxic alkaloids are easily oxidized
they enter into combustion and disappear entirely or in

(1) London Medical Records 1886. p103.

Chap II 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 haemoglobin be diminished as in chlorosis or anaemia, or if substances be introduced into the blood which prevent haematosis, 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 more poisonous.

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

A D 1885 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 & painstaking analyses on putrefaction products and in 1885 published one of the most valuable contributions to the literature of this subject(1)

(1) Weitere Untersuchungen über ptomaine. (Hirschwald Berlin)

Chap II 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 alkaloidal reactions but destitute of the characters of pure 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 ferric to ferro-cyanide 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 preceded him in giving a chemical formula to a putrefaction alkaloid, to Brieger falls the large share

Chapt II 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 and gives a complete description of the chemical relations & physiological reactions of these.

Besides the names mentioned as recent workers in
Luff this country may be added those of Dr. A. P. Luff and A. M. Brown. The latter deals with the subject more from a litterateur's point of view but the former from that of an investigator.
He has recently experimentally investigated the ptomaines in the urine of patients suffering from infective fevers and has so far brought out some very interesting facts. (1) His experiments strongly suggesting that there is increased formation and also elimination of these during pyrexial states and with diminution of the pyrexia

(1) British Med Journal. 27th July 1889.

Chap II we have the disappearance of the pathological alkaloid from the urine.

The whole subject however is but in its infancy and recent experimental investigations on proteid putrefactive products suggest that the great share of the toxicity is not due to the pure alkaloid but to some other albuminous body coexisting with the alkaloid. To this class of bodies may also be added the much vaunted "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

A. Methods of Extraction.

If the alkaloids be sought for in such organs as the heart, liver, spleen &c 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 & 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 or amyl alcohol the pure alkaloids are taken up by the ether or amyl alcohol (1)

The finely divided substance is heated

(1) Fresenius, Qualitative Analysis, p 445.

Chap III Stas Otto method

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 a 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 & evaporated down in a vacuum at a temperature of 35°C. This is filtered through filter paper moistened with water and so removing 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 24 hours and again evaporated at 35°C in vacuo. This second residue is dissolved in a small quantity of water and sodium or potassium bicarbonate is added till the mixture has an alkaline reaction; the solution is then shaken up

Chap III 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 24 hours: it is afterwards filtered and evaporated down. The residue which is thus obtained is shaken with benzine which is decanted off after settling for some time & 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

Chap III this is decomposed by ammonia, then dissolve up in suitable solvent and evaporate the solution thus obtained to dryness when the alkaloid will be obtained.

3. Gautier & 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 & 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 being taken to avoid the admission of air and the elevation of 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 set free.

Chap. III. 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 crystallisation, the mother liquors 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 are afterwards decomposed by an alkali and the ptomaines thus set free extracted with chloroform, ether or petroleum ether and obtained from these solutions by evaporation.

Chap III

5. Brieger's Method.

The flesh is finely cut up and left in contact with water for 5 or 6 days after which the mixture is boiled and filtered, to the filtrate is added sub-acetate 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, 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 acidified with sulphuric acid, repeatedly agitated with ether to extract the oxyaromatic, and then evaporated to a quarter of its original volume to drive off the volatile fatty acids. The sulphuric acid is got rid off by precipitating by means of 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

ased the filtrate concentrated by evaporation. The inorganic bodies which crystallise 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 chemically pure by repeated crystallisation 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 are 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 slightly 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

Chap III

Sonnenschein's Method

washed with water to which some phospho molybdic 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 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 heated 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.[17]

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 waterbath and connecting

Chap III Fischer's Method

the flask with a filter pump. The residue is thoroughly extracted with absolute alcohol and the alcoholic solution after filtering is again evaporated in the same manner. By this means all the fat &c 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. 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, intestine &c. The substance is acidified with hydrochloric acid and placed in the 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 be at once precipitated or they may be treated by any of the foregoing methods.

9. Luff's Method

This method be applied specially to the detection of ptomaines in urine. The urine in large quantity is rendered alkaline

Chap III by 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)

Chap III 5. Potassium Bismuth Iodide. (Dragendorff)

6. Phospho-molybdic acid. (Sonnenschein)

General 7. Phospho-antimonic acid. (Schulze)

Reagents 8. Phospho Tungstic acid (Scheibler)

9. Picric Acid (Hager)

They are not all precipitated by the above reagents, phospho-molybdic acid being the only reagent which does this, but as a test it is of little or no practical 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, generally crystalline bodies which are very 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

Chap III 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 Chloroplatinates with chloroplatinic acid and chloroaurates with chloroauric acid.

General Properties

D. Physiological Effects.

These although showing many analogies, differ too greatly to allow of generalizations and these 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, dilatation of the pupil of the eye, frequently accompanied by a copious flow of saliva.

Chap III 2. Motor paralysis, loss of cutaneous sensibility.

3. Tetanic Convulsions.

4. Diminution of cardiac impulses.

5. Lethargy, torpor and frequently death.

Physiological properties

Gautier examined the physiological properties of ptomaines according to their solubility in ether, chloroform & 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 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 paralyzed 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 & tetanic convulsions soon followed by muscular flaccidity, slowness of the hearts action, absolute loss of cutaneous sensibility and loss of

Chap III 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 characterised in the human being by vomiting, purging often alternating with diarrhoea, 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 " soluble in excess

Meyer's Reagent, oily precipitate soon becoming crystalline

Dragendorff's Reagent, " " " " "

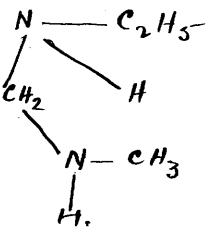
Marmé's Reagent, " " " " "

Picric acid, yellow needles.

Tannic Acid, dirty white precipitate.

Chap IV Putrescine forms crystalline salts with acids. The Chloro-
platinate and chloroaurate are difficultly soluble in water.
Putrescine 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, $CH_2-NH-CH_3$ / $CH_2-NH-CH_3$ or methyl-ethyl-methylenediamine,



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 the crystallisation out of Putrescine. Chloroplatinates & chloroaurates of the base was obtained. Free cadaverine is a colourless, viscous liquid readily absorbing carbonic acid from the 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 unde-

Chap IV - composed when its chloride is heated with caustic potash or soda lime. Its reactions are as follows:-

Cadaverine 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.

Marmés 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 & 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

Chap IV and Cadaverine. The free base, in its reactions is
Saprine closely analogous to cadaverine differing however in
giving an amorphous precipitate with Dragendorff's
reagent. It forms salts, its chloride crystallising 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 an easily chloroplatinate. It forms salts the investigation of which show that it is a diamine ptomaine much resembling the preceding ptomaine 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 4 weeks. Its chloride crystallises with difficulty even in vacuo as it effloresces easily in contact with air.

It gives the following reactions:-

Chloroplatinic acid: microscopic needles.

Chlorauric acid: oily drops.

Chap IV Phospho molybdic acid, amorphous yellow precipitate.
Mydaleine phosphotungstic acid: white precipitate soluble in excess.
Meyer's reagent, yellow oily drops.
Dragendorff's reagent, Wagner's reagent and Iodine in hydriodic acids all give 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 guineapig produce the following symptoms:- profuse flow of saliva, purging and very liquid motions, dilatation of the pupil & excessive lachrymation. The symptoms increase in severity as the poisonous action attains its maximum, the hind legs & subsequently the fore legs become paralysed and the animal lies prone on the ground. Tremor and spasms occur in the muscles of 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.

Chap IV

Neuridine $C_5H_{14}N_2$.

Discovered by Brieger in decomposing flesh, fish, cheese, glue and fresh human brains. Found in great quantity in horseflesh which had been kept at a temperature of 37°C for 5 or 6 days. It is a diamine and its chloride forms in long well defined needles somewhat resembling urea. The free base is obtained by treating the chloride with moist silver oxide, in the form of a gelatinous mass having a very disagreeable odour, easily decomposed and readily soluble in water. It is insoluble in ether, absolute alcohol and amylalcohol. In pure state it is non-poisonous.

It forms chloroplatinates, chloroaurates, and a curious insoluble compound with picric acid. Its chloride gives these reactions:-

Phospho molybdic acid: white crystalline precipitate.

Schulze's reagent, white flocculent precipitate;

Picric Acid: yellow needles formed on standing.

Dragendorff's reagent: red amorphous precipitate.

Chloraurie Acid: Crystalline precipitate.

Mercuric Chloride, Meyer's reagent, Marmé's reagent, Iodine in Iodide of potassium, tannic acid and Erdmann's reagent give no precipitate nor coloration.

Chap IV

Hydrocollidine $C_8 H_{13} N$.

Discovered by Gautier & Etard in decomposing mackerel and horse. 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. 1 milligrammes will kill a bird. It forms a chloride crystallising in fine needles and an unstable chloraurate.

Parvoline $C_9 H_{13} N$.

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

It forms a chloroplatinate and chloraurate.

Collidine $C_8 H_{11} N$.

This is one of the most abundant of ptomaines and was

Chap IV first discovered by Nencki in decomposing glue. The
Collidine 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 chloroplatinate crystallizes in flat
needles soluble in hot water, sparingly so in cold.

Besides these alkaloids several nonoxygenated
unnamed bases have been discovered by Gautier & Etard
Brouardel & de Coninck all giving certain alkaloid
-al reactions but not of sufficient importance nor
completeness of investigation to admit of detailed
description.

Chapter V
Oxygenated Ptomaines.

Choline, $C_5 H_{15} NO_2$

This base was first obtained from bile and has been found in human brains, hops, beer &c, Brieger prepared it from human lungs, heart, liver & 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 chloroplatinate, Chloraurate 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:- $\begin{matrix}(CH_3)_3 \\ C_2H_4OH\end{matrix} \rangle NOH$ 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 from the lees after separation of neuridin by Brieger. 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 chloroplatinates & chloraurates in crystalline yellow needles & lamellae and its chloride answers to the following reactions:-
Phosphomolybdic acid: white crystalline precipitate.
Phosphotungstic acid: No precipitate.

Chap I Schulze's reagent: white voluminous precipitate.

Newrine Meyer's reagent: voluminous, yellowish white precipitate

Dragendorff's reagent: amorphous red precipitate.

Marmes reagent: white precipitate.

Tannic Acid: voluminous dirty white precipitate.

Mercuric Chloride: granular white precipitate.

Iodine in Iodide of potassium: amorphous brown precipitate.

The chlorides of newrine and choline behave in a very similar manner with reagents, but distinctions may be made with Tannic and phosphotungstic acids.

Thus:	Chlorides of Newrine	and Choline
Tannic Acid gives	dirty white ppt^te	no precipitate
Phosphotungstic acid.	no precipitate	voluminous white crystalline ppt^te.

These two alkaloids are very similar in their physiological effects. A dose of about ·03 grammes 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 becomes irregular less frequent and of a sighing nature as death

Chap V approaches. The action of the heart is accelerated then
Neurine as the case of the lungs its movements become less & 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 is so contraction is observed.
Incontinence of urine & semen, increased bowel discharges
tetanic contractions, motor paralysis, and death.
'05 gr of chloride of choline produces similar effects.

Muscarine $C_5 H_{15} NO_3$

Schmiedeberg discovered this alkaloid in the fungus
Agaricus Muscarius, and afterwards Brieger isolated from
decomposing fish. It is a tasteless, syrupy liquid,
little soluble in chloroform & 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.
Chlorauric Acid: fine grained precipitate
Phosphomolybdic Acid: Flocculent precipitate.
Meyer's reagent: Yellow precipitate gradually becoming crystalline

Chap V Dragendorff's reagent: red precipitate becoming crystalline.

Muscarine Picric acid, Iodine in Iodide of potassium, potassium bichromate, and chloroplatinic 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 formula $(CH_3)_3 - N \begin{matrix} OH \\ \diagdown \\ \diagup \\ CH_2CH(OH)_2 \end{matrix}$ Its physiological effects are similar to those of neurine already described.

Gadinine. $C_7 H_{15} NO_2$

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 chloroplatinate but not a chloraurate. Phosphotungstic, phosphomolybdic and picric Acids all give precipitates

Chap V

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 sulphide and extracting with alcohol. It has a very nauseous, disagreeable odour but on exposure to air loses this and becomes harmless as a poison. Alkaloidal reagents give mostly oily precipitates with this base, but the Chloride & Chloraurate 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 & 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 impressions, 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.

Chap V 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, paralyses of lower limbs preceeded by a feeling of unbearable heaviness, vomiting unaccompanied by pain or purging, feeling of cold and collapse and entire retention of conscience and mental faculties to the last. Death is ushered in generally by a violent choking sensation or feeling of constriction as if a rope drawn tightly round the throat. Death may occur from 2 to 4 hours to several days from partaking of a few mussels in which mytilotoxine has formed.

Mytilotoxine.

Besides these ptomaines described above, several non-oxygenated bases have been discovered the most well defined being. - $C_{17}H_{38}N_4$: $C_{10}H_{16}N$: and $C_{32}H_{31}N$.

Unnamed Bases

$C_{17}H_{38}N_4$ was obtained from the lees after the removal of hydrocollidine and the analysis of its platinum

Chap V salt by Gautier and Etard gave the formula $C_{17} H_{38} N_4 2HCl Pt Cl_4$.

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

Typhoid Bacillus

Chap V not forms aromatic products, occasionally he obtained very small quantities of a base which in guineapigs produced profuse salivation, paralysis of limbs, dilatation of the pupils, slowing of the heart, stopping in systole & death in from 24 to 48 hours.

Streptococcus Pyogenes A Culture of Staphylococcus pyogenes on broth or extract of meat yielded a ptomaine which yielded a chloride but was otherwise indifferent

A culture of Friedländers pneumococcus upon carbohydrates yields formic and acetic acids and ethylic alcohol.

Chap VI

Clinical.

The phrase "ptomaine poisoning" has lately come much into prominence and the conditions under which it arises are so various that it appears difficult on all occasions to define and explain in scientific terms what is exactly meant by it. The physician is naturally tempted in many obscure cases of poisoning to seize upon and discover the existence of ptomaines as explaining everything unfortunately however in many instances also explaining nothing. So when one is asked to give a definition which will at once exclude all forms of poisoning not due to ptomaines, and includes only those arising therefrom, one is at once beset by the entirely fragmentary nature of the knowledge regarding ptomaines themselves, and the task becomes a difficult one. Without seeking therefore, to attempt any scientific definition of what is meant by "ptomaine poisoning", it is proposed to deal with it simply on its generally accepted grounds: strictly speaking the word "ptomaine" implies a body of cadaveric origin but there is a

Chap VI very general departure from this limited significance of the word in the usage of the phrase "ptomaine poisoning". It is not proposed to adhere, in what follows, to the exclusively cadaveric sense 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.

These bodies find their way into the human economy by various paths, but broadly speaking by one of two ways; 1) introduced from without as in articles of diet, inhalation or by wounds, or 2) generated within by physiological processes as in the tissues or alimentary canal.

It is proposed to consider these in the following order:-

1. Toxic substances generated in the tissues.
2. " " developed in alimentary canal.
3 " " introduced in articles of food.
4 " " " in respiration.

Chap VI 5) Toxic substances developed in course of disease.

6) " " introduced by wounds.

a) of a specific character

b) of a nonspecific character.

1. In the development and accumulation of ptomaines, or more properly leucomaines in the tissues we have a condition of Auto-intoxication and this doubtless produced in the first instance by an impairment of the relations of Constructive and destructive metabolism. Toxic substances are admittedly products, necessary products of vital processes in our tissues, constantly excreted in small quantities and partially destroyed in the organism itself, under the influence of respiration.

All disturbances in secretion and normal excretion, every arrest or diminution of the respiratory function or in the blood making process are necessarily followed by, or coincident with the retention of physiological debris of a poisonous nature.

Chap VI This retention excercises a threefold influence, it impairs nutrition, diminishes vitality and on the nerve centres exercises a pathological action which gives rise to the most remote symptoms.

The incessant formation of these bodies in the tissues is quite independent of oxygen and is due to what Gautier terms "anaërobic" changes or simply putrefactive phenomena. This he demonstrates 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 abundantly found and as a supposed derivative from it by processes of fermentation. 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

Chap VI intervention of external oxygen, that is to say by putrefactive or fermentive processes.

This condition of incessant putrefactive change in our tissues is quite consistent with a normal state of health, and is indicative simply of metabolic activity, but when the putrefactive products accumulate from deficient elimination the pass into the lymph channels and blood vessels and are borne along by their contents.

Sir William Aitken [1] makes a suggestion of great importance with regard to this auto-infecting of the system. In diseases such as Typhus, Typhoid and "fatigue" fevers, dysentery, Smallpox & Erysipelas he seeks to suggest that they are possibly progressive conditions or developments of an autoinfection; "a pathological series of ailments" depending on different degrees of self vitiation by the accumulation of products of physiological processes.

The vital mechanism at work in preventing

[1] Animal Alkaloids.

Chap VI the surcharging of the system with these toxic products is two fold a) Eliminative b) 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 in the circulating blood. The accumulation of these bodies in the blood is the result of deficient elimination and any circumstances which impedes circulation or diminish respiratory movements are favourable to the manifestation of their toxic effects.

2. Turning to poisons developed in the alimentary canal we find ample clinical evidence of their existence. It is very difficult to draw a distinction between the fermentive processes occuring in the tissues and in the intestine so far as the development of a toxic product is concerned. In the intestine the formation of an alkaloid is the result of putrefactive changes in the albuminous elements of its contents, the conditions for their development being exceedingly

favourable. There is ample experimental evidence of the origin of toxic bodies in imperfect digestive processes occurring in the stomach, in certain disorders, but even these are as a rule much less poisonous than those developed low down in the small intestine. To put it shortly, decomposing albuminous matter in a sewer differs only from decomposing albuminous matter in the intestine in the nature of the ferment and in situation.

Many papers have been written on the intestinal origin of toxic products and of the many evils attending their absorption into the blood. Dr Lauder Brunton on "Disorders of Digestion", "Indigestion a cause of nervous depression; Prof Bouchard on Self-Intoxication in Disease; Sir Andrew Clark on Chlorotic Anaemia and others attach great importance to these intestinal products as factors in the causation of disease and acting in many cases as the starting point of the most diverse disorders.

Since Nitrogen is an essential constituent of

Chap VI these alkaloids it follows that it is in the albuminous elements of the diet that we have the alkaloid yielding material and consequently a diet very rich in albuminous food stuffs will be favourable to their development. It is probably this fact which underlies the well known utility of farinaceous diet in many cases of indigestion &c. Lauder Brunton says "the cardinal fact is, that the proteid substances such as albumin, fibrin and gelatin 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." The effects of the absorption of these products are in general so much matter of every day experience that one is liable to attach little importance to them. Drowsiness, langnor, sensations of stiffness and soreness, inability and disinclination for mental effort, feelings of discomfort, perverted sensations partly referable to the nervous, partly to the digestive system are

Chap VI common symptoms observed during the absorption of digestive products. Some say that these symptoms are simply due to hyperaemia of bowels and anaemia of brain consequent upon the ingestion of food but there are many points which go to suggest that it is not so, but that we have mild and temporary manifestations of the toxicity of intestinal products.

In a simple anaemia of the brain such as here suggested there is an agreeable superinduction of slumber without many of the symptoms of poisoning as feelings of oppression, tinglings and perverted sensations. Again the nature of the diet is in favour of the poisoning theory, all these symptoms are at a minimum after the leanest meal of farinaceous food and probably at a maximum after a similar meal of albuminous food. The time at which these symptoms are most palpable also favours this idea. Dr Brunton says that "in many cases of nervous depression we find a feeling of weakness and prostration coming on during digestion and becoming so very marked

Chap VI about the second hour after a meal, and at the very time when its absorption is going on that we can hardly do otherwise than ascribe it to actual poisoning by digestive products absorbed into the circulation. The similarity of the symptoms to those produced by a paralysing narcotic, like curare is also very suggestive. In the couplet "Eat not to dulness, drink not to elevation" we have touched in brief the earlier symptoms of poisoning from two entirely different but toxic bodies. In "elevation" we have, in common with narcotic poisons the early stimulant stage of alcohol and in the "dulness" the premonitory symptom of poisoning by toxic products developed in the intestine. Possibly in the majority of instances these symptoms are significant of temporary effects and may from time to time be removed by the free use of purgatives, but unfortunately in many cases they form the starting point for greater deviations from normal conditions and a chain of varied evil effects may follow. The accumulation

Chap VI of partially digested matter in the bowels acts injuriously in several ways 1) It dilutes the digestive fluids 2) Impedes & interferes with the action of these on fresh ingesta 3) Obstructs the absorptive surface of the intestine and 4) Is a constant source of supply of toxic products. 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". Now the amount absorbed will depend on the amount formed and this will depend in turn upon the nature of the food, upon the accumulation of digestive products in the intestinal canal, upon the deficiency of intestinal action and lastly upon the period of time during which these conditions operate. It must also be remembered that the normal temperature and other physical conditions in the intestine are essentially favourable

to putrefactive processes.

It is a matter of everyday experience with most practitioners that in diseases associated with constipation a certain amount of relief (and very often fever abates) follows the free use of aperient medicines, the explanation being that masses of poison developing material are removed from the bowel. In many cases of Epilepsy and especially in the periodic attacks of excitement in recurrent mania it is most remarkable the beneficial effects following on free purgation but more than this, two cases are here quoted which suggest something more than a periodic or temporary relief in the treatment of certain forms of Insanity.

R. J.(*) aet 51 mar. Admitted 3rd Oct 1890. Suffered for past 2 months from Acute Melancholia, extremely dejected and very deluded. Been a temperate, steady man, abstained from stimulants but a slight neurotic taint in family history. The routine physical examination revealed nothing abnormal but there was a strong history of obstinate constipation & indigestion the nature of his employment (a Tailor) no doubt aggravating

* From Burntwood Asylum Medical Reports by permission of Dr Spence Medical Superintendent.

Chap VI this. The daily administration of an enema for the first week or 10 days removed large quantities of faeces: in addition, a tonic aperient mixture three times a day was given to him. Improvement was slow at first but every now and then one could catch a glimpse of a mental awakening to brighter things and before a month had elapsed he had so far recovered as to cheerfully resume his occupation in the tailoring department of this institution. If the treatment were withheld his condition seemed to change if he went a couple of days without an intestinal evacuation but when this was regularly and carefully seen to his improvement became more and more evident and permanent. With this treatment,- in addition of course the effect of environment and general routine treatment of the institution - he was at the end of 2 months discharged recovered.

Weight on Admission 12 Stones 4 lbs, on Discharge 11 Stones 4 lbs.

M. A. R: aet 56 years. Admitted 26th Nov 1890 in a condition of Active or Acute Stupor: very demented. Body fixed & rigid, muscles of face & expression compressed & as if tightly drawn.

Sept 87 Limbs in a condition not unlike the initial rigidity of cerebral lesions, eyes fixed & gazing, pupils normal

Mother of 15 children: been a steady, temperate wellbehaved woman and a good mother. No neurotic taint but had for the 3 weeks previous to admission manifested acutely maniacal symptoms. Physical examination revealed nothing abnormal but enquiry elicited the fact that she was known to suffer from obstinate constipation. The same treatment as in the previous case was here adopted and with similar results: in a month's time she had brightened up, began to take an interest in her surroundings, sewing, reading and revealing now and then a very pleasant motherly disposition. There was still, and for some time afterwards, a mental instability, especially tending towards mild excitement and manifesting itself in emphatic protestations of conscious recovery and mental perturbation. The treatment persevered in and this gradually subsided and she settled down into a state of rational & stable mental equilibrium. On 10th of March 1891 she was discharged recovered.

Chap VI. The same oscillatory mental phenomena ensued in this case also when free evacuations were not ensured. One must not forget however the great importance of environment and routine treatment in the success of these and other similar cases but still the facts are sufficiently clear as to render it very suggestive that the mental disorders of these patients had in their causation by no means an unimportant factor in the condition of the bowels. In one case there was a family taint and probably a predisposition to disease which an auto-infection called into existence but in the other case there was no remote history whatever. No timid suggestion is here offered that auto-infection from intestine or tissues is the gentle breeze that fans the smouldering embers of disease into existence, but to say that the chronic cumulative, long drawn out poisoning of the system as in these cases is the disease and the mental phenomena symptomatic or superinduced. In these cases & in others symptoms were ascertainable which had many points in common with the toxic action of ptomaines and considering the deductions from history, treatment and rationale of these cases the above is submitted as no fanciful dogma.

Chap VI 3 Ptomaines introduced in articles of diet.

Regarding the clinical aspects of Ptomaine poisoning following the ingestion of food in which some animal alkaloid or putrid product has developed much need not be said. In these cases we simply find the toxic bodies focussed in sufficient quantities to immediately produce their injurious effects upon the system and in this differing from the long drawn out phenomena following autochthonous poisoning.

Vomiting, purging and prostration are as a rule the main characteristics of the disease. The vomiting commences from 1 to 10 hours (rarely longer) after ingestion lasting generally throughout the whole course of the disease when ending fatally, and long after the contents of the stomach have been expelled. Purging is excessive, the stools generally of a very liquid, foetid, dark brown appearance with milky like substances floating in them in fact not unlike dirty water ~~mixed~~ with lymph flocculi suspended in it.

 Prostration is not complete from the onset but very soon becomes so and very often paralytic symptoms precede death though as a rule intelligence remains intact to the end. These are the symptoms common to nearly all cases of ptomaine poisoning but as this arises from many different articles of food it is safe to assume that we have not always one and the same ptomaine to deal with. Cheese, mussels, tinned meats, mushrooms, oysters, steak and pork pies are the most frequent sources of poisonous substances, and it has already been shown that some of these give rise to definite ptomaines which presumably on ingestion, manifest characteristic symptoms and this may explain the somewhat diverse symptoms on record, regarding ptomaine poisoning. It is not proposed to deal here with that diversity but to state shortly alleged symptoms. The temperature may be high, normal or subnormal; respiration may be natural, hurried, stertorous or slow and deliberate; pulse may be quick and feeble or

Chap VI slow and full. Pupils may be dilated or contracted. Acute pain in the abdomen may or may not be a leading symptom: unconsciousness, coma and stupor sometimes supervenes but very commonly the intellectual faculties are unimpaired throughout.
Sensations of cold or warmth, tingling sensations, salivation, skin rashes, involuntary discharges and intense thirst are symptoms not infrequently observed and need only be mentioned.

4. Ptomaines introduced by the respiratory tract.

The noxious effects arising from the inhalation of respired air have as a rule been attributed to the presence of carbonic acid gas, and a quantitative estimate of this taken as indicative of the degree of atmospheric vitiation, but this is true only to a certain extent. Pure CO_2 can be breathed in the air with impunity in much larger quantity than when this gas is added as a product of respiration, the explanation being that the CO_2 given off by

Chap VI human beings is invariably accompanied by an organic excretion which Du Bois Raymond terms "anthropotoxin", and to this substance it is alleged the noxiousness of respired air is almost entirely due. D'Arsonval in a paper to the "Societe de Biologie" pointed out the resemblance between the toxic action of the pulmonary poison and the ptomaine "neurin". In both cases one observes, movements of mastication and deglutition, an acceleration of cardiac beats, contraction of the pupils, diarrhoea, paresis of the lower extremities and an arrest of the heart in diastole. Professor Simpson in his Lectures on Public Health establishes a ratio between the respired CO_2 + this "organic impurity", and says that in certain diseases the odours peculiar to them are simply those of the impurity for the time being exhaled from the lungs. It is evident therefore that air unrenewed by fresh supplies gradually becomes charged with a toxic principle, the degree of discomfort experienced by its inhalation, and the estimation of

chap II Carbonic acid gas being simply quantitative physiological and chemical expressions of its presence.

The rationale of this is manifest when we bear in mind the anaerobic nature of part of the physiological processes in the human body, which by implication puts these organic emanations on precisely the same level as the organic effluvia arising from any decomposing matter whatever, the only difference being that in the human body the "decomposing matter" is associated with life and the lungs and respiratory passages a constant and ever open path of exit for them. Much might here be said in favour of vito-chemical agencies in the propogation of disease by the inhalation of effluvia from diseased persons as in typhus fever but this does not fall within the limits of this paper.

5 Ptomaines in Disease.

It has been abundantly shown that the excretions and secretions of diseased individuals contain

Chap VI ~ ptomaines in greater or lesser quantities and also that they are found in the fluids &c of the apparently healthy, the question therefore arising is:- What pathological significance, if any, may be attached to the presence of these substances in diseased tissues or fluids? Are they in other words the cause or the effect of pathological states? In auto infection they are clearly pointed to as causative but it is also possible to conceive a condition in which they are the result of pathological processes. When we remember that these processes are as a rule exaggerated normal functions; life struggling to exist under some baneful condition it becomes easy to imagine that in common with other exaggerated processes we have an increased production of ptomaines. Metabolic processes are at their height, the whole frame is working under high pressure so to speak, waste is excessive and paraffin alkaloids are developed in greater quantity than is normally the case. This is perhaps sufficient in theory to explain their presence

Chap VI but when looked at as an element of the disease itself the question assumes the form of a puzzle.
We are here speaking of diseases such as the Infective fevers, Paralysis, Pneumonia, Chlorosis &c and the note it is here aimed at striking is:- the any of the symptoms observed in these affections no part of the disease proper but the complications arising from the presence of ptomaines in the blood stream? This is especially hinted at with reference to many nervous symptoms appearing in the course of certain affections where the nervous system is at best but involved in a secondary degree, and the symptoms strongly suggestive of toxic action.
In Typhoid fever, Dr Dixon Mann attaches importance to "typhotoxin", which he isolated from cadavers dead of typhoid fever, and on injection into a guinea pig rapidly caused motor paralysis, coma & death.
Dr Luff only found ptomaines in the urine of scarlet & typhoid fever cases when the temperature was high and on the temperature reaching the normal the

Chap VI alkaloid disappeared. This rather suggests that when the fever is at its height we have an increased depletion of the system of these alkaloids and consequently a removal of their noxious effects, but it is also possible that this increased elimination is but an expression of the saturated condition of the system due to a rapid & extensive formation of alkaloids during active pyrexial conditions of the body. The development of alkaloids may, as has been shown, be accelerated & retarded in virtue of the physico-chemical agencies bearing on them and it is possible that the human body in diseased states offers a maximum of favourable conditions for their rapid development and hence increased formation is followed by an increased elimination. This notion perhaps gains weight when we remember that substances such as morphia and alcohol only appear in the urine when the body has attained a certain degree of saturation.

On the other hand, it is not safe to assume that ptomaines present in the blood in large

Chap VI quantities in diseased conditions, must neccessarily increase, supplement or aggravate symptoms peculiar to certain pathological states, on the contrary, it is quite conceivable that in certain cases their presence may be actively beneficial. In diseases due to the action of bacteridia, it is possible that ptomaines may assist in the extermination of microbes by rendering the soil uncongenial for these minute individuals. Some writers hold the view that the ptomaines are the result of the putrefactive action of the bacteria on the albuminous elements of the body: in other words they are effete products elaborated by the vital processes of the microbes vegetating for the time being in a congenial habitat. The accumulation of these products therefore, means an active consumption of their food supply and its admixture with a newly formed body which is presumably antagonistic to their existence. But shortly, they sterilize their soil by the products of their own vitality, they eat themselves out!
Here a conflict of ideas besets one, for what is true

chap VI of a physiological leucomaine may also be true for a bacterial ptomaine in that the ptomaine may actually aid the bacteria in their struggle for existence by destroying the baeillicide leucocyte and thus acquiring fresh supplies of nitrogenous matter to exist upon. In that case, the natural termination so far as the human body is concerned, is Death, the rapid putrefaction after death as in infectious diseases being presumably the expression of the activity of myriads of bacilli let loose on free and uncontested grounds. but in those cases tending to and terminating in recovery the ptomaines may, so long as the "physiological unit" is undestroyed, react and prove effective factors in the extermination of the bacilli.

The sterilization of the soil in relation to microbes hinted at above possibly underlies the principle of vaccination for Smallpox and injection of special fluids for Hydrophobia and Phthisis or Tuberculosis. However these are at best but theories, Science itself cannot say and with Science one must be content to wait

Chap VI 6. Ptomaines introduced by wounds of either a specific or non specific character.

It is not attempted here to deal in any way with the large subject of human Sepsis and the above subsection is introduced so as to complete the clinical picture sought to be drawn of the ways in which ptomaine poisoning may originate in human beings. It is possible however that the various affections known as Pyohaemia, Pyoseptheamia, Septhaemia, Septicaemia and Saprhaemia might be included under this heading especially so if we accept Gussenbauer's definition of these affections as "that general affection of the body which arises from the absorption of products of putrefaction into the circulation and is characterized by a definite alteration of the blood or typical series of inflammatory processes and a continued fever with peculiar nervous phenomena and critical secretions", but so far as the limits of this paper are concerned it is sufficient to note that

Chap XI cases of pure ptomaine poisoning by wounds are exceedingly rare. Several cases are on record where people working with materials such as rotten cheese & stinking fish have developed well marked symptoms of poisoning on rubbing mucous surfaces or wounds with their hands, but these cases are exceptional and on the whole the case is correctly stated by Rosenbach viz:-..."in general one may accept the occurrence of cases of pure sapraemia, i.e. pure ptomaine poisoning, but it does not follow that it is a frequent occurrence."

With regard to introduction of poisons by wounds having specific characteristics as Glanders, Erysipelas, Gonnorhoea & possibly Syphilis the development of ptomaines is secondary in importance to that of the specific microbes and of which presumably they are the products. What has already been said with regard to the relation of ptomaines to disease may be equally said here, but one word of criticism in conclusion.

Microbial Pathology has been very much the fashion for some years and while there is presumptive

Chap VI evidence that pathogenic bacteria are actively at work in many of the "ills that human flesh is heir to" still it must not be forgotten, that accepting Koch's Canons as rigidly criteria of specificity, then only in 2 and possibly 3 cases do we find that the microorganisms answer to these tests. In the case of the Anthrax bacillus the experiments of Bert & Brimus go to prove that the virulent principle is really to be found in a poison circulating in the blood and elaborated by this microbe, but in the other assumed instance viz the Spirillum Obermeiri of relapsing fever there is no evidence of this nature. So here we may say that subject is left in doubt. Of the presumptively microbial affections as Lupus, Tuberculosis, Leprosy, Erysipelas, Pneumonia, Gonnorhoea & puerperal fever it is quite probable that the symptom producing substance is a toxic principle elaborated by microorganisms but at most the really ascertained facts relating to this huge subject have not passed beyond a preliminary stage. Many fallacies are rampant in conclusions drawn

Chap VI from partially investigated phenomena. In no case has it been shown that a specific organism always produces the same poison, i.e. the question of a specific poison is untouched. Poisons extracted from affected individuals do not always manifest symptoms similar to those present in the individual from which they were taken. No ptomaine has been definitely associated with any one disease. Ptomaines are not constant in properties & composition when impure or mixed with foreign matter, they vary greatly with the conditions under which they are elaborated and they depend almost entirely on the media in which they are formed. A ptomaine does not always produce the same symptoms in different individuals or animals and lastly the most obvious fallacy of all to compare without reservation the results obtained from a culture in broth, gelatine or beef tea to that occurring in the human being & to make deductions therefrom.

The Subject is large, much has yet to be done and we can only look to the Past for Guidance from error, to the Present for Utility and to the Future with Hope.

Appendix.

The alkaloids which Dr Luff isolated from Typhoid & Scarlet fever patients urine gave respectively the following reactions:- [1]

Typhoid Fever: White crystalline substance converted into a chloride when treated with dilute HCl.

Phosphomolybdic acid: Gave White precipitate
Phosphotungstic acid: " nothing.
Mercuric & Potassium Iodide: " dense yellow precipitate
Iodine Solution: " brown precipitate
Tannic Acid: " Yellowish brown precipitate
Picric Acid: " dense yellow precipitate
Platinic Chloride: " Nothing
Gold Chloride: " dense yellow precipitate.

Scarlet Fever: White resinous crystalline substance soluble in water and faintly alkaline. It was also convertible into hydrochlorate.

Phosphomolybdic acid: Gave a pale yellow precipitate.
Phosphotungstic " " white precipitate
Mercuric & Potassium Iodide " pale yellowish white precipitate

[1] From Brit Med Journ for July 27th 1889.

Appendix.

Iodine Solution	Gave brown precipitate.
Tannic Acid	" Nothing
Picric Acid	" Yellow "
Platinic Chloride	" Nothing
Gold Chloride	Slight Yellow precipitate

My own experiences, which from circumstances have been only too few & limited have been of urines of patients suffering from diabetes, Scarlet Fever and at present I am engaged on the examination of the urine of patients in different forms of Insanity.

My first experiments, conducted in August 1889 at Peterhead in conjunction with Mr J. F. Tocher A.I.C. F.C.S., were on diabetic urine and from an ethereal extract we obtained reactions very similar to those of morphia. In the Spring of 1890 I experimented on Scarlet Fever urines, but the results were entirely negative one difficulty which one had to contend with in private practice being the withholding of

Alkaloidal remedies and when the fever was high and the dangers imminent one was loth to do this even in the interests of Science. The migratory condition of my habits for the last two years has also militated against repeated & confirmatory experiments, but latterly I have obtained good results with the urines of insane patients and have only succeeded in verifying some previous observations. My attempts in this thesis however have been directed less in the direction of airing out my own experiments but more in that of placing on record the facts, experiments & observations of all those of any note and in short presenting a entailed picture of how I have endeavoured during the last few years to approach this subject. In saying this I respectfully submit the above dissertation.

A. J. Farquharson