THE RÔLE OF PTOMAINES IN INFECTIOUS DISEASES.

THE trustees of the Fiske Fund, — Albert Potter, M.D., Chepachet; John W. Mitchell, M.D., Providence; William H. Palmer, M.D., Providence, — with George L. Collins, M.D., Providence, as secretary, at the annual meeting of the Rhode Island Medical Society, held June 13, 1889, announced that they had awarded a premium of two hundred and fifty dollars for the best essay on "The Rôle of Ptomaïnes in Infectious Diseases," to an essay bearing the motto, "Their poison is like the poison of a serpent." The author was found to be Charles V. Chapin, M.D., of Providence, R.I.

From Dr. Chapin's historical sketch we learn that the word "ptomaïne" (from πτῶμα, "a corpse") was first applied by Selmi to basic substances derived from the putrefaction of organic nitrogenous material. The ptomaïnes are of the same general chemical composition as the vegetable alkaloids of pharmacy, and they are not to be distinguished from them by chemical tests. Individual alkaloids can, of course, be distinguished one from another, but there is no sharp line of demarcation, and no general tests, which seem to distinguish the ptomaïnes from the alkaloids.

The former term is applied to those alkaloidal substances which are produced by putrefactive decomposition; that is, by the action of micro-organisms. The alkaloids proper are produced by changes going on within the living organism of plants. But they have this in common, that they are both produced by a retrograde metamorphosis of highly organized albuminoid material.

The ptomaïnes are divided into two classes, according to their chemical composition; the first containing no oxygen and volatile, the second containing oxygen and corresponding to the fixed alkaloids. The internal chemical composition, and the methods by which they are isolated, belong rather to the domain of chemistry than pathology. It is sufficient to say that they are separated from their aqueous extracts by means of ether, chloroform, benzine, or other non-miscible solvents, which are then evaporated, the residue extracted, and the process repeated, and finally the different ptomaïnes separated and isolated by precipitation with various re-agents suitable for the purpose.

A history of the various experiments and observations which gradually led up to a correct understanding of the chemistry and pathology of these compounds is most important in this connection.

Haller, in the middle of the last century, was the first to experiment in regard to the nature of putrefactive poisons, determining that the aqueous solutions of putrid substances would cause death when injected into the veins of animals. Gaspard, in an article published in 1822, related similar experiments, and noted among the symptoms, vomiting, twitching and convulsions, hiccough, and great thirst. He found the intensity of these symptoms increased with the amount of the dose: in the majority of cases, death occurred within twenty-four hours. He determined by experiment that neither CO_2, nor H_2S, nor NH_3 could produce such symptoms, but believed that it must be some other chemical substance. Gaspard showed that the blood from an animal thus infected could infect another, and he referred to the similarity of the nature of this infection to that of the specific infectious fevers. Somewhat similar results, which he obtained by the intra-venous injection of pus, he attributed to the products of septic processes, which had begun in the pus.

Magendie found that putrid materials introduced into the alimentary canal were not productive of any such marked symptoms as when introduced into the veins, and he therefore concluded that the mucous membrane acted as a sort of filter to separate the poisonous elements; and he believed that the respiratory mucous membrane had the same function, for he exposed pigs, fowls, rabbits, and dogs to putrid exhalations, and only the latter succumbed, and they only gradually, giving no evidences of acute poisoning.

Leuret repeated the injection experiments of Gaspard and Magendie, and accepted their views of the chemical nature of the septic poison; but he did not succeed in isolating it, or determining its nature.

Virchow also showed that septic infection quickly caused vomiting, diarrhœa, muscular weakness, and convulsive symptoms, with great heart weakness, and death in a few hours. Beck repeated these experiments, and determined the presence of sulphide of ammonia in the putrid material, and showed that it would also produce a fatal result.

Stich performed similar experiments, and came to the same conclusions as to the chemical nature of the poison. Then followed the experiments of Panum in 1850. He was the first to actually determine the chemical nature of the septic poison by separating it from septic solutions.

Weber v. Hemmer repeated Panum's experiments with substantially the same results, and Thiersch, Stich, and Schwenninger followed in the same path; but none of their work was as thorough and satisfactory as Panum's.

In 1866 Bence Jones and Dupré separated from the decomposing organs of men and animals, especially from the liver, an amorphous substance to which they gave the name "animal chinoidin," from its presenting a fluorescence like quinia when dissolved in dilute sulphuric acid.

In 1868 Bergmann succeeded in isolating a putrid poison, and, in company with Schmedeberg, he separated a poisonous substance from putrid yeast. This substance they obtained by a circuitous process, in the shape of minute crystals of the sulphate. Its watery solution produced in dogs the symptoms of septic poisoning, such as vomiting, diarrhœa with bloody stools, and, on autopsy, there was ecchymosis of the stomach and intestines. In frogs, also, severe symptoms were produced. This poisonous substance was called "sepsin," but was not obtained in sufficient quantity to admit of a determination of its chemical structure.

In 1869 Zuelzer and Sonnenschein separated from macerated bodies a crystalline substance which exhibited all the alkaloidal re-actions. Physiologically it seemed to be a narcotic, somewhat like atropine, and resembled the so-called "sausage poison." It produced dilatation of the pupil, muscular paralysis, and acceleration of the cardiac pulsations. The authors obtained this substance by the ether and alcohol process for separating alkaloids, called Otto-Stas's method, and also by diffusion and extraction with glycerine.

Rörsch and Fassbender obtained from a cadaver a non-crystallizable substance resembling digitaline in its properties, but not having its bitter taste.

Schwanert, at about the same time, obtained from a dead body an oil with strong basic properties, and which smelled like propylamine.

Marquardt, and later Hager, obtained a substance to which was given the name "septicin," and which Hager believed was a mixture of amylamine and caprylamine. Lieberman also obtained a similar substance from the stomach of a person who had been poisoned by arsenic. The physiological action of none of these was determined.

Krebs-Brandes obtained a coniine-like substance, and found that .007 of a gram injected into a frog killed it instantly, and .044 of a gram had the same effect on a pigeon in a few minutes.

Brouardel and Boutmy found in a decomposed goose a substance which gave re-actions, like coniine, and which produced toxic symptoms.

According to Husemann, there are a large number of cadaveric alkaloids which resemble coniine.

Wolckenhaar separated an amorphous base, which resembled nicotine, but had no toxic properties.

Moriggia and Battistini found in the watery extract of dead bodies a poison somewhat like curara; which, however, gradually lost its toxic properties the more it was purified.

Selmi, in Italy, while engaged as a medico-legal expert, became convinced that alkaloidal substances were formed in the human body after death by the putrefactive processes there taking place. From 1870 till the day of his death, Selmi devoted himself to the study of these substances; and he determined the occurrence of several alkaloids similar to morphine, coniine, atropine, and delphine, and other vegetable alkaloids, but he did not succeed in separating any of them with sufficient purity to permit of chemical determination. Selmi, however, did much to encourage and advance the study of these substances, and definitely determined that they were produced by the action of microbes on proteid tissue. Among the other Italians who were encouraged to pursue this line of study by Selmi's work may be mentioned Brugnatelli, Zenoni, and Cortez, who found an alkaloid resembling strychnine in decaying corn-meal. At the same time, Gautier, in France, was attacking the problem, and independently arrived at the same results, — that alkaloids are produced by the decomposition of albuminous substances.

The first to actually separate and determine the chemical composition of an animal alkaloid was Nencki, in 1876. He obtained from decomposing gelatine needle-shaped crystals of a salt to which he gave the name "collidin," and which he determined had the formula $C_8H_{11}N$.

During the last five or six years the study of ptomaïnes has received much attention on both sides of the Atlantic; but no one has done so much to develop methods of procedure, and put our chemical knowledge of these substances on a firm scientific basis, as Brieger. Of the ptomaïnes whose composition has been determined, Brieger analyzed nineteen, while Gautier and Etard come next with three.

The infectious diseases, at least those which are caused by micro-organisms (and those are the only ones we are now considering), may be classed in two divisions.

First, we have those in which the organism invades the blood and propagates there, and by so doing produces profound alterations in that medium. Among such diseases may be mentioned anthrax, malaria, relapsing fever, and certain forms of septicæmia.

The second class includes those diseases in which the micro-organism does not develop in the blood, but only reproduces itself in limited foci. Thus in typhoid-fever the specific organism grows only in glandular structures in the walls of the intestines, and in the mesenteric glands and the spleen; in cholera the growth is confined chiefly to the lumen of the intestines, though the walls of the gut are sometimes invaded; in abscesses and suppurating wounds the pus-forming organisms are confined to the abscess, or the tissues of the wound, and are not found in the blood; and in sapræmia the organisms of putrefaction in most cases do not involve the living tissue at all, but find their pabulum in blood-clots, exudations, and spots of necrosis.

It has been an interesting and important problem to discover how micro-organisms actually produce the symptoms in these different affections. It has been variously attributed to the "mechanical irritation" of the microbes, to their occlusion of minute vessels, to their consumption of certain elements in the blood or tissues necessary to the physiological integrity of the host, and, lastly, to the production of poisonous materials which re-act upon the tissues.

While there are some theoretical and experimental reasons for believing that micro-organisms may occasionally act in all of these ways, the evidence has of late been accumulating, as Dr. Chapin has attempted to show, that the last-named method is by far the most common and important. Even if there were no experimental evidence, we should hardly be able to explain the constitutional symptoms of the second class of infectious diseases in which the organisms are strictly localized, except on the hypothesis of the production of soluble substances which are taken up in the circulation.

But we know that there is much besides mere hypothesis which would lead us to attach great importance to the *rôle* of the chemical products of bacterial life in the production of the symptoms of the infectious diseases. In certain forms of septic disease the demonstration is complete that the entire circle of symptoms is immediately caused by the action of such substances. The experiments of Bergmann, Hemmer, Weber, and, first and most important of all, Panum, show that chemical substances, which can be isolated, produce precisely the same set of symptoms that are caused by the injection of untreated putrid material containing living organisms; and recently, since the perfection of bacteriological methods, Roux, Chamberland, and Arloing have shown that cultures of septic organisms produce substantially the same results, whether the organisms are present or have been removed by heating or filtration. And not only this, but Roux and Chamberland have obtained the same substances from the tissues of animals suffering with the diseases concerning which the experiments were made.

In the formation of pus it has been demonstrated, that, in some cases at least, it is the ptomaïne produced by the organism which induces the migration of the leucocytes.

It is in regard to tetanus, however, that we have the most accurate knowledge in regard to the mechanism of the production of the symptoms. That this disease is caused by a bacillus, which develops in wounds, and does not migrate into the blood-vessels, is beyond question. From artificial cultures of this organism, and also from the tissues of a human subject suffering from the disease, a ptomaïne has been obtained which produces in animals the identical symptoms of the disease; and, furthermore, it has been obtained in such purity that its chemical formula has been accurately determined.

Typhoid-fever and cholera do not normally occur in the lower animals, though the administration of their specific organisms under certain conditions is followed by a set of symptoms called "experimental typhoid fever," and "experimental cholera." The experiments of Sirotinin, and Beumer and Peiper, for typhoid-fever, and of Gamaleïa and Löwenthal for cholera, have shown that all the essential features of these diseases are dependent upon the soluble substances contained in cultures of the organisms.

The experiments that have been made with anthrax, hog-cholera, fowl-cholera, and erysipelas, while indicating to some degree the importance of the *rôle* played by soluble substances in these diseases, have not given very complete or satisfactory results.

As the subject of the essay is "The Rôle of Ptomaïnes in Infectious Diseases," the action of other substances has only been briefly alluded to; but it must be remembered that a very large number of substances besides those belonging to this particular chemical group are elaborated by the growth of micro-organisms. We have every reason to believe that the most important are, indeed, of an alkaloidal nature: for the sepsin of Panum, and the tetanine of Brieger, produce all the symptoms of septic poisoning and of tetanus; and cadaverine is, in and of itself, capable of producing true suppuration.

Nevertheless it is probable that such substances as sulphuretted hydrogen, ammonic sulphide, phenol, etc., all elaborated by bacterial life, have some influence upon the body. Moreover, the experiments of De Christmas, Arloing, Rietsch, and Wooldridge, afford very strong evidence that ferments of a proteid nature play a very important part in the production of infectious diseases. The ptomaïnes, like the vegetable alkaloids and the leucomaïnes, all chemical allies, have a markedly selective action on the nervous system; and we may assume with a fair degree of probability that many of the nervous phenomena, the delirium, stupor, tremblings, and paralysis of the infectious diseases are due to these substances. The action of typhotoxine, found in the cultures of the typhoid bacillus by Brieger, and the ptomaïne isolated by Hoffa from anthrax cultures, are indications of this.

One of the most common and important phenomena of the infectious diseases is fever. That fever may be produced by ptomaïnes is shown by Panum's experiments with sepsin, and Hoffa's with the anthrax ptomaïne.

That the fever of the infectious diseases is frequently due to these substances is very probable; but that it may be due to other materials or causes is also probable, and, in fact, quite certain. Angerer and Edelberg have shown that fever can be caused by the injection of blood and of fibrine ferment; and Schmiedeberg obtained like results with another proteid substance.

Wood, Reichert, and Hare, Otto, Bergmann, and others have shown that pepsin, trypsin, and pancreatin are all capable of producing a rise in temperature; so that it is highly probable that proteid substances, as well as those of an alkaloidal nature, have much to do with the production of febrile symptoms in the infectious fevers.

The experiments of Arloing and De Christmas would also show that some pyretic substances are not readily diffusible, and are probably of the nature of ferments.

Another *rôle* of the ptomaïnes and other soluble substances is the preparation of tissues and fluids for the growth of microbes. There is in the living body a constant tendency towards the destruction of all micro-organisms. This tendency varies greatly from time to time, and can doubtless be greatly affected by the action of ptomaïnes. Thus, in the case of the pus-forming organisms, it has been shown that they can much more readily attack the living tissues when the latter are inflamed; and it has also been shown that the ptomaïnes, some of them at least, do thus prepare the tissues for the microbes by exciting inflammation. In a broad area of suppuration the ptomaïnes diffuse into the tissues out beyond the sphere of direct bacterial action, and the organisms follow closely in the wake of the inflammatory area thus formed. This was observed to be the course of events, in the keratitis excited by Leber with cadaverine.

Typhoid, cholera, and many other organisms, are destroyed when injected directly into the blood; but in later stages of these, as of most infectious diseases, the organisms are found often in large numbers in the circulating fluid. It is very possible that the changes in the blood which permit of the growth of the organisms are due in part to the action of ptomaïnes on the blood itself; but it is also probable that they are due to changes in general nutrition, affecting the organs by means of which the blood is formed. This, however, is a branch of the subject on which we have only just begun to speculate, and on which little work has been done.

On the other hand, we have considerable positive knowledge in regard to an opposite action of ptomaïnes; namely, the rendering of tissues refractory to the action of microbes. It has long been known that the growth of micro-organisms in artificial culture-media, in very many instances, soon produces such changes that the media are no longer capable of supporting baterial life. Various explanations have been offered of this phenomenon; but it is now definitely settled, particularly by the experiments of Garré and Freudenreich, that it is in most instances due to the production of substances which exert a hostile influence upon the vegetation of the organisms. This explanation is of very great importance, both practical and theoretical, in relation to immunity, particularly acquired immunity, in animals. Various theories have from time to time been advanced to account for this phenomenon.

1. The theory was advanced by Pasteur and Klebs that the immunity was due to the consumption by the organisms of certain ingredients of the tissues which were necessary for the growth of the organisms, and which were not afterwards replaced. This "exhaustion hypothesis" has now been generally abandoned as not in accord with observed facts.

2. The theory of Metchnikoff is, that the invading organisms are devoured by the leucocytes, which, by this exercise of their functions, acquire an increased power in this direction which can be effectually exercised on a subsequent occasion.

3. Lastly, it has been suspected, that, during the first attack of an infectious disease, soluble substances are elaborated which exert such a physiological action on the tissues that the latter are enabled to resist the inroads of the organisms; and that this refractory condition remains a longer or shorter time, until it is lost through the regular metabolic changes of the animal body. This is the "retention hypothesis," and is favored by most of the evidence which has been accumulating during the last few years.

The immunity which is thus produced has varying degrees of permanency. In malarial and relapsing fevers where there is a distinct remission, it is probable that the organisms produce a substance which is a poison to themselves as well as their host, and that its presence in the blood destroys or drives out the organisms in that fluid, while those that are in the spleen and other lymphatic glands remain unaffected. This constitutes the remission, which only lasts a short time, until the objectionable substances disappear or until the corpuscular elements which have been made refractory have been replaced by others newly formed. In such instances the refractory condition is very brief. In other cases, as in anthrax, studied by Roux and Chamberland, or the experimental cholera of Löwenthal, the immunity may last a few days or weeks. In still other cases it may continue indefinitely, as in measles and small-pox.

The success of so many experimenters in obtaining immunity in animals by the administration of chemical substances opens up the most hopeful field of therapeutic research.

Much was expected from prophylactic inoculations with attenuated but living virus; but the difficulty of keeping the virus of the proper degree of virulence, and the danger that arises from the fact that every inoculation establishes a focus from which the disease may spread in severe form, have prevented these expectations from being fully realized. But if immunity can be secured by the use of chemical substances, the action of which can be measured and regulated, and which can be prepared outside of the body, we shall obtain an invaluable means of controlling the infectious diseases.

Every experiment which throws any light on this important subject is worthy of close attention, and, if verified, is a step towards the solution of the great problem of the prevention of disease.

RUSSIAN LITERATURE.

IN *The Publishers' Weekly* for Oct. 12 is printed a statistical report, compiled from official sources, of the number of books published and printed in the Russian Empire (excepting Finland) during 1888. The number of titles recorded amounted to 7,427; the total number of copies printed, 21,103,272. Of these, 5,318 books were in the Russian language, 716 in Polish, 343 in Hebrew, 311 in German, 217 in Lettic, and 178 in Esthonian. The following is a classified list, in tabulated form, showing the number of titles and the editions printed of books in the Russian language: —

	Works.	Copies printed.
Works of reference	629	3,877,092
Educational:		
Religious	521	3.691,838
General	720	3.334,182
General	848	1,953,818
Medical	445	446,985
History	256	288,023
Jurisprudence	176	248,206
Agriculture	173	214,819
Military science	159	211,944
Literature	155	178,623
Juveniles	150	545,662
Geography and travels	144	141,062
Popular literature	142	821,800
Political economy	115	65,341
Technology	101	84,088
Natural history	93	109,240
Pedagogics	60	64,818
Art	52	43,417
Philosophy	46	62,960
Mathematics	{ 45	{ 32,150
Mathematics	{ 43	{ 34,417
Politics, etc	33	31,070
Miscellaneous	312	913,495
	5,318	17,395,050

Among the books of reference there are catalogued 155 Russian almanacs, of which 1,537,649 copies were printed. Besides these, there were also 205 almanacs in other than the Russian language. St. Petersburg and Moscow, of course, lead in the production of literature. Then follow Warsaw, Odessa, Riga, Kasan, Kiew, Tiflis, Wilna, Dorpat, Charkow, Reval, Mitau, etc. The total number of periodicals was 667, of which 493 were printed in the Russian language, 76 in Polish, 49 in German, 13 in Esthonian, 8 in Lettic, 7 in French, etc. The most of these are printed in St. Petersburg. The statistics showing the proportion of inhabitants to the daily journals issued are most remarkable. It appears, that, taking European and Asiatic Russia together, there is but one journal to 484,590 inhabitants. The proportions taken in the cities, for instance, show, in Reval, one daily journal to 8,550 inhabitants; in Riga, one to 13,490; in Tiflis, one to 14,860; in St. Petersburg, one to 28,970; and in Moscow, one to 75,350. This gives one a tolerably clear idea of the intellectual development of the masses.

M. Pawlenkow gives the following facts concerning the prices some of the prominent Russian authors realized for their work. Shortly before his death, Turguenieff sold the rights in all his published works, "for all time," to Glasunow, for 90,000 rubles (over $69,300). The publishing-house of Ssalajewy offered to the novelist Shtshedrin for his writings 60,000 rubles, but the transaction was not consummated. Gogol received 60,000 rubles; Pushkin, 35,000 rubles; Schukowskij, 5,000 rubles; Krylow (for his fables), 14,000 rubles; Nekrassow, 15,000 rubles; Gontsharow, 35,000 rubles; Ostrowskij, 10,000 rubles (for one edition); Grigorowitsh, 5,000 rubles; Aksakow, 3,000 rubles (for one edition); Mey, 1,000 rubles. The popular author, Gleb Uspenskij, sold his works to Pawlenkow and Ssibirjakow for 25,000 rubles. Pawlenkow printed