WHAT ARE ANTITOXINS?*

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In a lecture delivered by Dr. T. Clifford Allbutt, regius professor of physics in Cambridge University, England, before the Johns Hopkins University in October, 1898, occur these words¹: "The study of origins, then, is not only the new method of modern criticism, of modern history, of modern anthropology, of our reading of the evolution of the universe itself from elements which even themselves are falling under the same analytic inquiry, but the study of origins is leading to a revolution in our conceptions of therapeutics, as all of these other studies; a revolution which as yet we have not fully understood."

Never were truer or more profound words uttered than these. The revolution to which Prof. Allbutt refers is one so momentous that but few have scanned the horizon of modern therapeutics closely enough to duly appreciate its far-reaching consequences and importance. That this fact be made clear to those present at this Section meeting, and to as many members of the AMERICAN MEDICAL ASSOCIATION as do me the honor of reading this essay when it appears in the JOURNAL, permit me to ask how much and what does the name "Antitoxin" stand for when seen in print by the average medical man? To some, perhaps to most, progressive physicians, it means a new kind of remedy that may or may not be better than the old and well-tried ones of the past. How many, do you suppose, can see more than this it is as related to the destiny of our race? To the skeptic it is but the shibboleth of a new therapeutic fad. He doubts its value, and quietly to himself mutters, "what fools these mortals be." To the hosts of the sectarian pathies and their antivivisection allies it is nothing more than a filthy and diabolic lying invention of the vivisector, concocted as a piece of spurious evidence to prop up his wicked designs against dumb brutes.

How large a proportion of mankind see any more than one or the other of these claims in it? Have you watched the steps by which we have come to believe that such things as antitoxins really exist? Have you followed the logic of the men who have claimed to discover them? Have you seen how, step by step, the belief in their existence came to these men? If you have not, then you are not prepared to fully appreciate but the smallest fraction of what their discovery means. The antitoxins themselves are of far less importance to the race than are the solutions of the problems that cluster around them. They are but stepping-stones leading back into the mystic origins to which Prof. Allbutt refers. To fully and correctly understand what they are and how they are produced is to be able to solve some of the deepest riddles of life, health and happiness. They are leading us toward a true science of therapeutics and a true conception of how we have accidentally in the past cured diseases, and how we shall in the future prevent death "by the subtle strategy which consists in knowing all the moves of the game," as Prof. Allbutt put it. What little we have discovered concerning the antitoxins has come to us from a pursuit of the same methods of thought, the same style of research, the same processes

of verification, and through the same class of minds as gave us the whole fabric of modern civilization. They have come to us as a part of the grand mental movement that built up the doctrines of the conservation of energy, the unity of natural phenomena and the universality of evolution. Have you noticed the methods of the men who are at work on the subject? Have you seen how they turn the light of counter-experiment and counter-criticism on each other in scorching concentration? Have you noticed that every question is put to Nature for final reply, and every answer verified or condemned by a competent peer? Have you observed how every mistake in logic is pounced on by a whole army of coworkers, and every mistake in experiment is mercilessly gibbeted in the same manner? Every idea and every fact must run the gauntlet and survive or perish in the struggle. The system only needs to be understood to be respected. When serums, toxins and antitoxins reached the general profession they had already been tried and found worthy of consideration by experts. They were given to us for further trial with human beings, where we have a right to experiment, but they may not. Whatever our verdict may be concerning them, it can not alter theirs, and will only prove that we had new and altered conditions to deal with, if it is adverse. To decry them without trial, or with unfair or imperfect trial, is dishonest, sinful, and unjust to the whole of animated nature, now and through all future time. We, as medical men, owe it as a sacred duty to give them a fair trial. Whether we do or not, however, workers in this field of pathology and physiology will go on making their discoveries along the same line of investigation. The laws of their action will be found, their chemical composition discovered, and their bearings on the greater questions of life as a totality worked out.

What are some of the questions now before them in which we as physicians are interested? It is only necessary to name them for all to see their importance. Here are a few. How come we to gain tolerance of poisons? What is the nature of immunity? How do neurotic poisons poison? How are toxins produced? How are they related to antitoxins? How do they act on each other? Is the action chemical or vital? To what class, or classes, of organic bodies do they belong? Is either, or are both, enzymes, albumins, globulins, or are they even proteids?

As a sample of the way the work is being prosecuted in the endeavor to get replies from Nature to these and kindred questions, let us take the late experiments of Besredka with orpiment or yellow sulphid of arsenic². He found that injections of this almost insoluble substance, if very finely powdered, killed quicker than when injected in a suspension composed of coarser particles. When a membranous sac containing a quantity of the orpiment is placed in the abdominal cavity of a guinea-pig it will die almost as quickly as when the same quantity is injected directly into the same place. In the one instance the arsenic sulphid had to dialyze through the membrane, a thing it could only do by being dissolved; in the other it was brought into direct contact with the tissues. As this pigment is among the most insoluble of known poisons, it is here made manifest that it does not poison by mere contact. It evidently kills by chemical means. It can be stopped from killing by a proper chemical antidote. Besredka further found that if the quantity of orpiment injected is not too large the leucocytes take up the yellow particles into their structure, and for as long as ten days can be seen carrying them

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around. Constant examination shows that the poisonous material is being slowly dissolved and a less poisonous substance produced that can be eliminated by the kidneys. That the leucocytes take up and dispose of many other poisons than orpiment in this way has been shown by Metchnikoff and Kober³. The salts of silver, mercury and iron have been found to be carried throughout the system in this same manner. This work is done by the same leucocytes as are known to englobe and destroy microbes. It is evident that they have the power of secreting something that can unite with the poisons which they take up. What this something is happens to be one of the issues of the hour. That the leucocytes are not the only producers of this something that antagonizes poisons was shown by Widal and Nobecourt with strychnin and morphin⁴. They injected these hypodermically into animals with a small amount of fresh, sterile, brain substance, and found that the animals would live after double or treble the dose that would kill them without the brain substance. It appears as if the brain substance contained something that neutralized the poisons. Thoniot and G. Brouardel also found that when nerve-substance was used the results were the same. They kept their animals alive by injecting nerve substance in an emulsion before injecting the fatal dose of strychnin⁵.

In 1896 Van Ermengen discovered an anaerobic bacillus in ham which had caused some serious cases of illness at Elzelles, Belgium. He produced the same train of symptoms with sterilized cultures of his bacillus⁶. Kempner and Pollock have isolated the poisonous toxin of cultures of Van Ermengen's bacillus and studied its effects on the cells of the bodies of animals. Injections of this toxin were found to cause degeneration of the cells of the spinal cord. A finely granular disintegration or "partial pulverization" of the corpuscular elements occurs. The physical changes revealed by the microscope correspond with the symptoms observed both in time and volume. They immunized animals to this toxin, and securing a serum from the immune animals, studied the same degenerative changes under its administration. If the antitoxic serum was injected soon after the toxin, the degeneration was but slight. When the antitoxin was mixed with the toxin before injection no degeneration occurred⁷. What Thoniot and Brouardel found true regarding the action of nerve tissue injections with poisonous doses of strychnin, Wasserman found held good for nerve tissue and the virus of tetanus⁸. A. Marie found that what was shown by Widal and Nobecourt to be true regarding the action of brain substance on strychnin and morphin was equally true with brain substance and tetanus toxin. He declares that he found it necessary to have a previous direct contact of the toxin and the brain tissue to have it act⁹.

Metchnikoff has probably studied the subject of antitoxic action more than any other single individual. It was forced on him because it was at first supposed to be antagonistic to his belief regarding phagocytosis. He finds that while the brain tissue of the guinea-pig protects mice as well as guinea-pigs from the toxin of tetanus, neither the brain nor the spinal cord of tortoises or fowls has any protective effect on tetanus injected into guinea-pigs or mice. He believes that his many experiments have established it as a general principle that the more susceptible an animal is to tetanus the more efficacious its nerve substance or its brain substance is to tetanus. To this rule there are exceptions, and among them is the frog. Its brain seems to have no antitoxic power, although it is quite susceptible to the poison. In

a former communication he showed that low cryptogams, like bacteria and fungi, destroy toxins but do not produce from them antitoxins, that invertebrates can not produce the antitoxin of tetanus in amounts that are appreciable, that only in animals as high as and higher than the crocodile are antitoxins produced; that in fowls the antitoxic power resides in the blood, and not in the nerve tissue, and that phagocytic power is older than antitoxic in the life history of our planet¹⁰. He thinks that mixtures of brain substance and nerve substance with poisons do not destroy them by any kind of chemical union, but that such mixtures produce an inflamed condition of the tissues, when and where injected, that attracts leucocytes and encourages phagocytosis. Their activity is the agent of destruction, and not the nerve substance. W. W. Stephens and W. Meyers have found in their experimenting with serums that the same quantity of serum always neutralizes the same amount of toxin, whether in the test-tube or in the body of the animal. They hold that this strongly indicates an adhesion to the chemical law of definite proportions, and, therefore, to chemical and not vital action¹¹. Cantazene comes to the support of Metchnikoff, and shows that anything that suspends phagocytic activity in the presence of a powerful toxin causes the animal to die. This he holds indicates vital activity and not chemical¹².

Ehrlich finds that toxins and antitoxins affect each other more promptly in concentrated than in weak solution, in hot than cold solutions, and, with Stephens and Meyers, that they bear quantitative relations to each other. He claims that in the case of ricin he has proof of union in definite proportions¹³. He advances the theory that antitoxins are the tissue elements with which the toxins combine in the body to poison it. The irritation of partial poisoning causes the system to produce an increased amount of such tissue substance, this enters the circulation and acts as a means of neutralization before the toxin can get at the tissues for which it has an affinity. He thinks that there could be no poisoning of the cells if they did not contain elements having an affinity for the poison, and when the poison is fixed on such elements its power for further harm is gone. Just as a poisonous alkali unites with a poisonous acid to form a non-poisonous salt, so do the poisonous toxins unite with the tissue elements to form non-poisonous products. But as the tissue has thus been robbed of its necessary elements by the poison, a demand is made on the system to produce a surplus of such material, and this surplus constitutes the antitoxins. This ingenious theory has a number of able supporters in Europe. A number of the experiments which are here referred to seem to give support to it.

R. Pfeiffer and Marx accept this theory as a partial explanation of the phenomena of acquired immunity, but they do not believe it can explain the presence in the body of substances having bactericidal power. They find that the spleen shows this bactericidal power. They the blood, and that the spleen, bone-marrow, lymph-glands, and possibly lungs, contain larger amounts of it than the blood. Here they hold that they have evidence that the leucocytes are neither the only nor the most important agents in the destruction of disease germs and disease poisons¹⁴. A. Wasserman thinks that the toxins and some of the organs react with each other to produce by a chemical union new bodies having bactericidal power¹⁵. The fatal objection to this theory is that it violates the law of parsimony by introducing new substances that we know nothing about, with properties that are unusual. Such lawless theories are the kind that

bring all theorizing into disrepute among men not accustomed to scientific methods of thought.

Three legitimate theories now hold the field, and as they are each guiding distinct sets of exceedingly able men in their work as experimenters, it is pretty certain that the question will soon be settled by the consensus of the competent. It is not at all unlikely that all three have elements of truth within them, and that no one of them is entirely able to explain all the facts. The chief weakness of Ehrlich's theory is its inability to explain the fact pointed out by Metschnikoff, that frogs are very susceptible to tetanus, and yet their brain substance does not act as an antitoxin. It likewise fails to embrace a large number of facts that one might naturally expect it to. This last objection is equally powerful against the phagocyte theory, when pressed forward as a complete explanation of the phenomena of immunity. The experiments of Pfeiffer and Marx, already referred to, are as damaging to the phagocyte theory as to that of Ehrlich, in that they positively limit the sphere of action of each. If the spleen, bone-marrow, lymph-glands and lungs have greater bactericidal power than the blood, this throws the phagocytes into an inferior position as microbe killers. There may be a number of ways in which such destruction occurs and by which immunity can be maintained. E. de Cyon, of the Physiologic Institute of Berne, Switzerland, has shown that iodothyron from the thyroid gland, instantly destroys the toxic effects of atropin and nicotin¹⁶. If it also destroys the toxins it would be a very useful ally to the phagocytes, as well as the bacteria-destroying organs in their work. Salkowski¹⁷, Brieger¹⁸, and Ehrlich¹⁹, have shown that sulphuretted hydrogen and some antiseptics can destroy tetanus toxin²⁰.

The theory which seems at present to permit of the generalization of the largest number of facts is the one that assumes that the antitoxic and bactericidal power of serum is lodged in substances that are of the nature of enzymes. The fact that they have been precipitated by Brieger and Boer by numerous agents in a way that pepsin, trypsin and other enzymes are thrown out of solution, indicates a possibility of their being enzymes²¹. For over a year Emmerich and Loew have been at work in Munich studying how enzymes are related to immunity²². Nencki and Pfeiffer made the suggestion of some sort of relationship between them in a way that led Emmerich and Loew to take up such work. Prof. T. Lauder Brunton, in his address at the International Medical Congress at Moscow, said: "Perhaps the hypothesis I mentioned eight years ago to my pupil and friend, Mr. Hankin, that the germicidal power of organisms is proportioned to their power to produce enzymes, may not be altogether unfounded, and possibly we may discover also that immunity, natural or acquired, is nothing more than an extension to the cells of the tissues generally of a power which is constantly exercised during digestion by those of the intestine and liver²³. It appears then that the credit of first enunciating the theory belongs to Brunton. He, however, acknowledges his indebtedness to Dr. Johan Baptista van Helmont, a celebrated iatrochemist and disciple of Paracelsus, of the early part of the seventeenth century. Emmerich and Loew claim to have found that a number of different kinds of bacteria produce enzymes fatal to themselves and other germs. When combined with animal protein the enzyme is transformed into an immunizing product. Both substances have been isolated in tangible form so that it is a fully substantiated fact. DeSchweinitz has also isolated an enzyme from hog cholera germs, that

immunizes guinea-pigs. Kondratieff declares that such evidence as he has been able to collect experimentally and otherwise compels him to believe that the antitoxins are related to the enzymes²⁴.

Enzymes are substances that have the power of causing other organic substances to alter their chemical composition by their presence while they themselves remain unchanged. Like parsons who marry two people, while the act of marrying them does not alter their own state in the slightest, these enzymes cause chemical unions to occur while they retain their condition of singleness. Those we know best, such as pepsin, ptialin, trypsin and invertin, all force water into the chemical composition of various food stuffs, and enable them to dialyze through the walls of the stomach or intestines. They probably split all the substances they act on into smaller molecules²⁵. There are other ferments that instead of aiding solution and dialysis hinder the same by coagulating or fixing substances. It is evident that all living forms, depending as they do on foods for existence, must have the power of dissolving, coagulating, and fixing such foods as an essential condition of life. As all such changes, so far as we have ever been able to discover, are brought about by enzymes, we have no logical right to assume that any other form of agency is at this kind of work until one is found. Step by step the so-called vital force has been driven by the enzymes out of this department of life. They have been found in every form of life from the bacteria and molds up to monkeys and men. As the processes of life are unthinkable without the accomplishment of their kind of work, and as they only are known to do such work, we can not avoid the conclusion that they must have existed as long as life has existed on the planet. They have ever co-existed with protoplasm, and must have been subject to its experience. As the ameba has gone upward in development toward the brain cell, every change must have brought a corresponding change in the enzymes that made its food soluble within its structure, and that fixed that food as solid tissue again. The enzyme is the door-keeper of the cell. It is also, in its opposite form as a coagulant, the host within the cell. The first kind aids the substance in getting in, or if in and converted into waste makes it soluble so that it can get out. The second kind has a function that is just the reverse. It can keep out what is not wanted in or keep in what is not wanted out by rendering it insoluble.

Ehrlich has lately discussed this subject in connection with the administration of drugs²⁶. He uses Witt's hypothesis of "stiff solutions" to explain the processes of staining tissues and of the passage of drugs through the cell. Every chemist who has worked in commercial organic chemistry knows how by the aid of acid and alkaline radicals he can make alkaloids and the like miscible or immiscible as he chooses in different solvents. In a similar way the enzymes may render various substances soluble or insoluble in the substance of the cell. By adding the sulphonic acid radical to aniline it is at once rendered unable to stain tissues and to poison them. Its inability to enter the tissue cells in the new form renders it unable to poison such cells. If it could get in to stain them it could get in to poison them. Being excluded it can do neither. By acting on toxins and other organic poisons with the special enzymes of the different kinds of tissues so as to alter their structures and make them unable to penetrate such tissues, they would at once be rendered harmless. Not a single new enzyme needs to be formed. No violence has to be done to Nature to make such a

hypothesis true. The whole material is now and always has been ready formed in the body to meet every emergency. All that is needed is an alteration in the proportions of the fixing and of the solving enzymes that constantly are at work in behalf of the special tissue to which the poison has an affinity. Natural selection must during all past time have been picking out to live, such animals as were able under the irritation of selective poisons to increase their stock of the fixing enzyme for that tissue and killing off every animal that could not make such an adjustment. Organic poisons and foods merge into each other in their chemical structures. The processes of digesting the one are not greatly different from those of digesting the other. To split up a poison and make it immiscible in the cell matter can not be much harder than to do the same thing for a food. It may only require an increase in force. Increased volume of output of one kind of enzyme and diminished output of the other and opposite kind could easily come from a change of demand, if this function follows the laws of all other known bodily functions. According to this hypothesis, then, immunity is due to an increase in the production of the fixing enzyme of that tissue which happens to be the special point of attack of the poison, this increase being due to the irritation of the tissue elements that the poison seeks to damage. As food turned into the stomach brings hydrochloric acid and pepsin, so poison turned into a cell brings its digesting enzymes in continuously increasing proportions as the irritation persists. After the cell has been irritated for a considerable time, it gets into a habit of producing an excess, thus establishing continuous immunity. As an overproduction of gastric juice will cause intense hunger, so an overproduction of other enzymes would be expected to produce their form of hunger, i. e., a desire for the poison that caused them to be produced in excess. We find that this is actually the case. The morphin fiend has morphin hunger, and the tobacco user has nicotin hunger. The enzymes that keep these poisons from reaching the tissues for which they have a special affinity, in doses that are dangerous, when not having the poisons to act upon may produce this special form of poison hunger.

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CONDENSATION AND PRESERVATION OF MILK BY REFRIGERATION.*

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In an article contributed to the AMERICAN MEDICAL ASSOCIATION last year¹, entitled "The Milk-Supply of Cities; Can It Be Improved?" I described somewhat at length a process devised by Mr. B. F. McIntyre of New York by which 80 per cent. of the water is abstracted from milk by freezing it, when in moderate agitation. The water, as ice, is taken from the milk in comparatively stainless crystals, almost without loss of solid product. It has been shown that the expense of condensation is very much less than by evaporation in vacuo, and that the resultant product is of much greater value. A considerable series of experiments was undertaken during the summer, under the supervision of Prof. W. T. Sedgewick of the Institute of Technology, in order to ascertain the effect of refrigeration on the bacteria ever present in milk.

It was found, although the resultant was not perfectly sterile, that the bacteria were in large measure destroyed, and that the concentrate put up in glass jars, such as are commonly used in the distribution of milk, has a keeping quality of weeks rather than days. Encouraged by these results, Mr. Edward Burnett of Boston, well known for his practical studies in furnishing a better milk-supply, has established a plant¹ of sufficient capacity to demonstrate the commercial advantages of the process. It is believed that the process offers a practical solution of the difficult and expensive problem of milk distribution in cities; that the family supply will be furnished in a concentrate one-fifth the bulk of ordinary milk, and that distribution of it from house to house made once a week will be ample for practical purposes. By this process the fat globules are uninjured, and, as a result the cream is unimpaired for table use. Pathologic bacteria are destroyed by the process, and the milk-supply will be rendered safe for use.

The economic advantages are obvious. In the first place the milk will be furnished the consumer at a material reduction in cost, and the waste in its daily use will be very greatly lessened. A far more satisfactory product in every respect will be furnished, and with a little care the pantry will be in constant supply. Mr. McIntyre is by no means satisfied with furnishing a product which contains even so little as 7 per cent. of water, and he looks forward to the practical demonstration of furnishing milk in a solid form, with keeping qualities equal to that of butter or cheese. I have in my possession a sample of solid milk prepared by him, by this process, now some months old. I make this brief report of progress, since the milk-supply of the country is of the first importance to every individual, and we indulge the hope that the work thus begun will prove so satisfactory that it will revolutionize the distribution of the milk-supply of the world.

ACCORDING to the statements made by members of the crew of the *Sequoia*, which recently arrived at San Francisco, a large number of persons on the Clipperton Islands are afflicted with scurvy and already five deaths have been reported. It is said that this was the first vessel which had visited the port for a period of four months.

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¹ Journal, Dec. 10, 1898, p. 1386.

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