No. 2.

Menthol.	10 grms.
Toluol, q. s.	36 c.c.
Creolin.	2 c.c.
Alcohol absol.	65 c.c.

They are used by applying locally to the throat or nose by a mop or spray. Löffler's No. 1 is a painful application and is very much objected to for that reason, and can not be frequently used. The No. 2 is less painful and is applicable to a wider range of use.

The chlorin-iron mixture is administered in teaspoonful doses to a child 5 years of age once in two or three hours, during the day time only.

The formula is:

Potassii chloridi	
Ac. hydrochloric, C. P.	āā 1 00
Tinct. ferric chlor.	5 00
Syr. simplicis or glycerini	120,00

The bacilli disappeared under either of these medicaments in two weeks.

Guaiacol has been used by Dr. Martin W. Barr and Dr. Solomon Solis Cohen as a local application. The application is as painful as Löffler's, though Dr. Cohen has obviated this somewhat by the addition of menthol. Their results have been good, though systematic bacteriologic examinations have not demonstrated any superiority over my methods.

As an immunizing agent. That antitoxin produces immunity against an attack of diphtheria has been abundantly verified by a vast number of observers both in hospital experience and in private practice.

The quarantine system in vogue in Philadelphia has given me frequent opportunities to verify the assertion of Behring, Roux and others. This immunity is not lasting. Biggs of New York places it (from careful observation) at thirty days, Behring places it from six to eight weeks. I have seen no case immunized show clinical traces of the disease, though frequently Löffler's bacilli were found in the throat; where such cases existed, they were carefully watched and cultures made from time to time (once in three days). No other treatment except the immunizing dose was used, and cultures made and examined by Dr. B. Meade Bolton or Dr. H. D. Pease evinced the presence of the bacilli even to three weeks, though no visual traces were ever seen.

Antitoxin does not confer permanent or lasting immunity from diphtheria even to those who suffered from an attack of diphtheria and were treated with a curative quantity of the serum. For the susceptibility to a reinfection on exposure still remains with the patient, and therefore it should always be proper to immunize the patient whenever exposed.

The influence of antitoxin on the mortality records. There is no city in the world whose records have been carefully kept that has not shown a marked reduction in the death rates by the antitoxin treatment. I might except Philadelphia, which seems to be behindhand in the method of presenting her records as compared with other cities.

There is no hospital in the world where antitoxin has been used that has not shown a reduction in the death rate. Again I must note exception to this by the records of the Philadelphia Municipal Hospital, where it appears only hopeless or the most serious cases are sent, for this hospital holds the most unique position of recording an increased mortality from this method of treatment.

There is hardly an exception to be noted in the

statistics of private practitioners, which also show a reduction in the death rate.

Still, despite these positive proofs of the utility of the serum treatment; there seems to be a passive antagonism by some to this form of treatment. I can only explain it in the words of Dr. Charles L. Dana, New York (Diphtheritic Palsies and the Use of Antitoxin, *Medical Record*, April 11, 1896), from whose excellent monograph I quote: "While the treatment of diphtheria by antitoxin is a method that has been approved in all parts of the world and is upheld by a volume of statistics whose brute force is almost overwhelming, yet there is still some degree of skepticism about its real value. Most of the skepticism is the result of profound and banal ignorance, coupled, perhaps, with some hysterical obsession in the lines of zoöphilism and antivivisection. There are, however, some conservative physicians whose character and attainments we respect, who still hold a position of reserve, if not of disbelief, as to the value of the method, and they advance some very ingenious explanations of the way in which the statistics that so apparently favor antitoxin are gotten up."

These statistics are supposed to contain in a majority of instances cases whose recognition is simply bacteriologic and where the clinical diagnosis is secondary. Even if this be so, and I for my part have not counted as cases treated those immunized in whom the specific bacilli were found. I think the statistics are superior to the former for this reason: Given a case of diphtheria as formerly treated prognosis was out of the question; a mild case might suddenly become a serious one. A laryngeal case may become tracheal. With antitoxin the disease is aborted and the serious lesions now so commonly noted by different observers as broncho-pneumonia, multiple neuritis, post-diphtheritic palsies, etc., were not noted before because the patients perished long before these complications were noted. Therefore, given a case as now treated with antitoxin, if the serum is used early enough and in a judicious manner, mortality records should be simply to prove exceptions to the rule, and the death rate noted show a lack of careful observance of the earliest symptoms of diphtheria.

AN INTRODUCTION TO THE DISCUSSION UPON "BLOOD-SERUM THERAPEUTICS."

Read in the Section on Materia Medica, Pharmacy and Therapeutics at the Forty-seventh Annual Meeting of the American Medical Association at Atlanta, Georgia, May 5-8, 1896.

BY HAROLD C. ERNST, A.M., M.D.

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Probably the most radical change in the ideas of the causation of disease that has ever occurred has taken place during the last thirty years, its final outcome being the subject of the discussion before this meeting to-day. The steps leading up to the position at present occupied have been taken only after many wanderings and painful experiences, but as a result we seem to have reached a rational standpoint from which further progress may be made. The basis of blood-serum therapeutics is the idea of *immunity*, and the procedure is the result of the investigations made to determine how immunity occurs. It had been known for a long time that after attacks of certain

¹ In the preparation of this paper I have received much assistance from the little work of Lachalme, "Blood-Serum Therapeutics, Paris, 1896."

diseases, there was a period during which a second attack of this same disease did not occur. This was, and is, known as *acquired immunity* to the disease in question. Certain races of animals are known to be immune to certain diseases, and this is a *natural immunity*, for which there must be some explanation if only it could be found. This explanation would give a basis for work directed toward the solving of the problem of how this immunity could be produced intentionally, and if this could only be done, we should have made a long step toward the actual and proper treatment of disease.

The securing of artificial immunity has been attempted in several ways; the best known and longest employed is that of vaccination. This method consists in the employment of the virus of a milder disease of the same type, thus, after the attack of the milder disease, and because of it, securing an immunity against the malignant form of disease. Since the introduction of bacteriologic methods, other means have been sought to attain the same end. The protective inoculations against rabies illustrate the use of the actual virus of the disease in an attenuated form, but of gradually increasing strength, to produce an immunity against the full strength of the same virus. Another method makes use of the living cultures of the bacteria producing the disease, as in the protective inoculations against anthrax, and still another of the products of the growth of the bacteria in the test tube, as in the employment of tuberculin. The theory of the action of these various methods is not the same, but their results, so far as they have been explained at all, have been supposed to rest upon some changes produced in the tissue cells or those of the blood, and it is to explain these results that much of the recent work has been carried on.

As to priority in the suggestion of the method under discussion, the position of the *British Medical Journal* seems to be a reasonable one: "The question of who was the originator of the serum treatment is one of interest. It is always difficult to speak with certainty on a point of priority of this kind, for new ideas seldom spring from one man, but we believe that the method had its origin from the observation made in 1887 by Von Fodor, that blood, when drawn from the body, had a distinct bactericidal action. Nuttall and others then pointed out that although this bactericidal action might be connected with the corpuscles of the blood, it was not confined to them, as the serum of freshly coagulated blood was found to contain some proteid substance which undoubtedly exerted a powerful bactericidal effect. In July, 1889, Babes and Lepp recorded a number of experiments in which they had found that the blood of dogs which had been vaccinated against rabies exerted a distinctly protective action when injected into susceptible animals either previous to or along with the virus procured from a rabid animal. Ferran appears to have been the next observer to accentuate this point. He was followed by Bouchard in France, whilst Behring and Kitasato in Germany, and then Roux in Paris, and others in rapid succession pointed out that there was in the serum of the blood of animals vaccinated against diphtheria and tetanus a distinct prophylactic and curative agent which, however, it was difficult to separate from the serum. In 1891 patients were treated in Berlin by the serum prepared by Behring," and the endeavors in this direction are more numerous and widespread to-day than in any other line of medical activity.

So far as the bactericidal properties of an immune body are concerned, all experiments tended to show that they lay especially in the blood, and the main portion of modern endeavor is in the study of the properties of this portion of the body.

The results put it beyond question that the serum of certain animals is so much opposed to some bacteria as not only to hinder their development but actually to destroy them. But this is very far from establishing a general rule as regards immunity, for the refractory condition of an animal and the bactericidal property of its blood are not by any means always, or even most often, present in proportional degree. As for example the bactericidal property of the rabbit's serum, an animal extremely receptive to anthrax, and the absence of bactericidal properties in a dog's blood, who is especially refractory himself to anthrax. So that while the bactericidal property of the serum is a very important matter, it can not be considered as being a factor in the production of immunity. Its existence, however, has served to show that the serum is not an inert material and has been the basis of other important investigations upon the properties of this tissue.

The attenuating power is one to which much attention has been paid by Bouchard, Roger and others, and is probably only a part of its preventive power. This latter factor seems to have been neglected by these observers, and it would seem that the mixtures of serum and bacteria they injected were harmless, not because the bacteria were attenuated but because the serum preserved the tissues from the pathogenic action of the bacteria which accompanied it. From the latest work on this question it appears that the bacteria increase their virulence in the blood of refractory animals, whether in the living body or in the test tube, and that this increase of virulence is the result of a new adaptation, or of a selection among the most resistant bacteria. So that even the existence of an *attenuating* power of the serum seems to be doubtful at present.

The possibility of the *antitoxic* action of the serum first suggested itself to Behring as an explanation of the constantly observed fact of the persistence and development of bacteria at the point of inoculation in refractory animals. The immunity in such cases could not be due to any effect upon the vitality of the bacteria, and the only explanation remaining was that of a neutralizing or destructive action upon their toxic products, this action being carried out by the blood-serum, in preference to the other tissues of the body. Taking up the study of diphtheria and tetanus, two diseases in which the results appeared to be especially due to the action of the products of the bacteria and not of the bacteria themselves, Behring and Kitasato showed that a mixture of the toxins of these bacteria with a small amount of the serum of immune animals could be injected without any results in animals extremely susceptible to the toxin alone. The results were found to be the same whether the mixture was made in the living animal after injection or in the test tube before injection; and also that the injection of the serum in another part of the body, and a little before or a little after that of the toxin could protect the animal from many times the fatal dose of the toxin so far that no effect would be produced by the latter. These observations were of the utmost importance and were asserted to destroy any ground for belief in the theory of phagocytosis. They

were and are believed by many to represent a direct chemical action of the antitoxin upon the toxin, which it either destroys entirely or turns into an harmless product. This antitoxic property is something wholly distinct from a bactericidal power, and is much less easily destroyed, for it resists a temperature of 65 degrees C., the addition of small percentages of antiseptics, and dilution of the serum with water. The antitoxic property has been ascribed to a definite substance contained in the serum, and this substance has been compared to a globulin or a diastase, without as yet ever having been separated, although many efforts to that end have been made. Whatever it may be, its power is enormous, as is shown by the experimental results obtained with serum containing it.

The idea of Behring and Kitasato, of the destruction of the toxin by the serum containing the antitoxin, although simple and easy of comprehension, does not appear to be applicable as a general theory, the more particularly if the observations of Metschnikoff and his followers be correct and taken into account. Metschnikoff has shown in his researches upon the blood of rabbits immunized against hog cholera, that their serum exercised a manifestly curative and preventive effect in fresh animals and without of itself possessing any attenuating or antitoxic property. In other words, that the effect was not merely due to a direct action upon the toxin or bacteria, but that a most important factor was the vitality of the tissues themselves in which the action took place. So that according to Metschnikoff, the action of the serum is especially a stimulation of the tissue resistance, exercised more particularly upon the phagocytes, making them better able to carry out their defensive action. The globucidal power of the serum is another factor that has to be reckoned with. It is closely allied to the bactericidal, and has been studied more especially by Buchner and Daremberg. It is shown upon introducing blood corpuscles of one animal into the serum of another. In such an experiment, the corpuscles are very rapidly disintegrated, and disappear in a very few moments.

This phenomenon occurs in the circulating blood or in the test tube, and Buchner especially has attempted to identify it with the bactericidal property of the blood-serum. They do in fact have characteristics in common, for they are both destroyed at a temperature of about 55 degrees C., upon exposure to light, or upon a modification of the saline constituents of the serum, but the existence of a special albuminoid substance, an alexin, as supposed by Buchner, is not by any means an accepted fact. The coagulating power of the serum is shown by its introduction by intravenous injection in another species of animal. Coagulation very quickly follows because of the precipitation of fibrin, but Richet and Hericourt demonstrated that this was to be avoided by making the injection in the cellular tissue, *not* directly into the blood vessels, so that the injected serum could only enter the blood current after passing through the lymphatics; and it has been recently shown by Hayem that this coagulating power is destroyed by raising to a temperature of 55 degrees C., while Mairot and Bosc found that only 52 degrees C. was necessary to accomplish the same purpose. The same authors have demonstrated the toxic properties of serum injected into animals of another species, as manifested by muscular pains, febrile disturbances, respiratory affec-

tions and even fatal convulsions. These properties are somewhat more resistant to heat than those already spoken of and are supposed to be due to certain albuminoid materials. They are extremely variable in different animals and in the same animal toward different species, and they also vary very much in accordance with the condition of health of the animal from which the serum comes. The existence of such properties as these in the serum is of the utmost importance, and that they may exist is unquestionable. At the same time it must be remembered that their effects are only markedly present in intravenous injection and that a wholly different picture is presented as the result of introduction into the subcutaneous cellular tissue. In this situation these toxic effects are so slight as to be inappreciable and may therefore be practically disregarded.

These powers of the serum are apparently closely allied to the physiological characteristics like the "glycolitic" of Lepine and others, and the "peptosaccharizing" of Lepine and Barral.

This paper being merely introductory, the foregoing portion has been devoted to a brief and incomplete summary of the present knowledge of the properties of the serum in general, so far as they are concerned with the present subject.

The production of the antitoxic power has been attempted in the effort to secure immunity or the cure of many diseases, and these efforts are carried out in the same general way. The steps include the production of a toxin immunity first and then an antitoxin immunity. The differences between the two conditions are, that the former is slow in coming, is dangerous during the process, but is lasting and complete when obtained. It is, however, wholly inapplicable to general use. The second is very easy to obtain, is very rapidly reached, is not dangerous, but is not lasting, and sometimes, owing to the uncertainty as to how far it is necessary to go, is not complete. The process of obtaining the first is by the injection into the selected animals of gradually increasing doses of the toxin, either filtered free of the bacteria, or else with them still present, these injections being kept up until they have reached such a point that the animal is not affected by a dose of the toxin or culture sufficiently large to be fatal to untreated controls. This animal has then reached the condition of toxin immunity, and this immunity is a very lasting one. The condition is due to the presence of the antitoxic principle in the blood-serum. This antitoxic property may be used to secure an antitoxic immunity in other animals, and these not necessarily of the same species, provided the serum containing it be injected subcutaneously.

These are the simple bases of the method, the details are of the most varying and, as yet, indefinite character. The remarkable thing is, not that we know so little in regard to these details, but that so much has been accomplished in the time over which the investigations have extended.

A simple list of the diseases in which it has been sought to apply these principles for the production of the antitoxin is a long one, without any attempt being made to give an account of the methods pursued in each. Such a list—and incomplete perhaps—would include the investigations of Richet and Hericourt upon their *staphylococcus pyosepticus*, and the work upon *anthrax*, *hog cholera*, *avian septicemia* and *symptomatic anthrax*. *Rabies*, *typhoid fever*, *pneu-*

monia and *tuberculosis* have also been studied, without great success so far as is generally known. In *diphtheria* certainly, probably in *cholera*, and possibly in *tetanus* are to be found the main results that justify us in hoping for further advances in this direction so far as the application to man is concerned. Very possibly, too, results that may be immediately forthcoming will show that we are much nearer to a solution of the problem of the streptococcus antitoxin than at present seems to me to be the case.

THE FALLACY OF ANTITOXIN TREATMENT AS A CURE FOR DIPHTHERIA.

Read in the Section on Diseases of Children, at the Forty-seventh Annual Meeting of the American Medical Association, at Atlanta, Ga., May 5-8, 1896.

BY ELMER LEE, A.M., M.D., PH.B.

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Early in my medical career, and at the time that Pasteur declared he had discovered a certain remedy for hydrophobia, it seemed a pity to me that the profound effort could not have been directed to the cure of diphtheria. Hydrophobia is such a rare disease, occurring not oftener than one to the million per annum, whereas diphtheria is universally prevalent, is the reason why regret was felt at the time of his publication. What it was hoped he might have done, is alleged to have been done by other investigators. Pasteur claimed in 1884, that a product made from the culture of the brain of an animal which had been inoculated with the disease of hydrophobia, was able, when injected beneath the skin of the human being, to cure rabies. This prophetic utterance emanated from a man who seemed to me, during this period of medical adolescence, to be utterly irrefutable. The scientific position which was accorded him, made his declaration appear to the world at that time, and to me with almost the same awe inspiring force, as if it had been an inspiration which had directed his mind and his hand. Hundreds and thousands of human beings have turned their faces toward the Pasteur Laboratory since 1884, supposing that they were mortally wounded by the teeth and the virus of mad dogs. There have been many who have presented themselves at his gate who were bitten, but not by a mad dog; hundreds of others who were bitten through the protecting folds of the clothing; many, indeed, who were simply licked by the tongue of a dog, not bitten at all. Still others have submitted to the inoculation through curiosity, having had no injury whatsoever. So great is the influence of the modern press that a scientific proposition, while still in the germinative state, is heralded throughout the civilized world, and is quickly transformed into a perfected science by writers of the press. There were a few who were able to doubt the truth of the allegation as to the curative influence of the Pasteur lymph. Long before cool and scientific inquiry could be made by physicians away from this center of discovery, the die had been cast that hydrophobia was curable by Pasteur lymph. At this present moment there are unmistakable proofs that error in judgment and in practice is the largest element in the hydrophobia cure. During the first few years of the experimental inoculations for rabies, many deaths occurred among the patients; so many, in fact, that Pasteur himself became alarmed at his own work. During a later period the death rate from

hydrophobia, as stated at the Pasteur institute, became less. The lowered death rate was proclaimed to be the result of the natural improvement in the process, and at the time, was accepted by nearly all. In the last few years of the hydrophobia cure the death rate has been materially lessened and is attributed to still further advancement in the understanding of the treatment. Right here is where the point, which is to be drawn from the foregoing statements, appears.

Whatever may be the view of persons who have not personally investigated the treatment of hydrophobia by Pasteur lymph, the real explanation of the reduced mortality since the declaration of the treatment in 1884, is directly due to the dilution of the curative lymph. In so far as the reduction of the virility of the laboratory product is concerned, just so far has there been advancement in the progress; perhaps, if the lymph was indefinitely attenuated, the mortality would be still less. This recital is introduced to show the error which may exist in one of the greatest therapeutic faiths close to the end of the nineteenth century.

Bacteriologic investigators, in Berlin and Paris, sent word to the United States recently, that diphtheria is curable by a specific medicine. This specific cure is produced as follows: A culture of the germs of diphtheria is injected, day after day, in increasing doses for a long time, into a horse, until it is able to withstand the poison of 250 cubic centimeters of the diphtheria virus, whereas one-tenth of a cubic centimeter of the same virus would be fatal to a guinea pig. After a certain period has elapsed a quantity of blood is drawn from the jugular vein of the horse, and the serum, after being further treated in the laboratory, is ready to be injected beneath the skin as a cure for diphtheria.

Ever since the discovery by Tyndall that the atmosphere, as well as the soil and the water, is inhabited by life in invisible form, there has been a prolific series of theories concerning germ organisms. It is generally accepted that a constant state of antagonism exists between minute organic life, and it is supposed that preservation as well as destruction of life, is attributable to these germs which are warring with each other. First came the discovery of germ life in nature, followed in due time by the declaration that all diseases are due to the influence of pathogenic germs. The next step consisted of a conception that pathogenic germs must be antagonized by other germs in the preservation of life and the treatment of disease. The next step in the process is that pathogenic germs, or their ptomaines, are able to be counteracted in their influence upon the life of the human body, by either the same germ or its own ptomaine. It is believed that during the period of inoculation of a horse with the diphtheria culture, a process is going on which is generating a fluid in the animal, that is antagonistic to the disease which it is assumed is caused by the original germ, namely, diphtheria.

Let us now consider diphtheria from a clinical standpoint. There are two varieties of diphtheria which exist to-day, but, one of which did not exist yesterday. One is true clinical diphtheria, the gross symptoms of which are entirely sufficient for practical diagnosis. The other form is the diphtheria of the bacteriologic laboratory. One is diagnosed by the clinician, while the other is discovered by the bacteriologist. These two varieties are made necessary by reason of the claims of bacteriology, by which