

DIPHTHERIA ANTITOXIN

Schering

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A Guarantee from the German Government

OF THE PURITY
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Schering's (Aronson's)
Diphtheria Antitoxin.

Since April 1st, 1895, the Diphtheria Antitoxin made in Schering's Bacteriological Department, under the supervision of Dr. Hans Aronson, has been controlled by the German Government.

The official requirements are as follows:

1. That the serum be clear, containing at most only a slight sediment.
2. That the preservative be used in the proper proportion.
3. That the Antitoxin possess the specified degree of immunizing power.

The Berlin Institute for infectious diseases is charged with the official control. The weighing out, drawing of samples, and filling in the factory are all conducted in the presence of a sworn State official. Further, the State requirements include the control of the health of the animals; and the keeping of a record book in which entries are made of all the horses, the period of their treatment, the amount and the frequency of the blood drawing, etc.

When all the Government requirements have been fulfilled, the Imperial Double Eagle is stamped on each vial, and the label further bears the record of the immunizing units contained, the serial number of the specimen, and the date when the serum was tested.

Physicians will readily see the extreme importance of this measure. It gives a satisfactory guarantee that the preparation has been made, tested, and packed under the direct supervision of the German Government and its scientific experts.

Another important point is the keeping qualities of this preparation. Schering's Antitoxin is preserved with $\frac{1}{10}$ of 1% of Trikresol; it keeps for an unlimited time, and, according to the latest investigation, *its full efficacy is retained for at least one year.*

The constant variations in strength, the presence of noxious albuminous bodies, and the many other deficiencies in the various Antitoxins that have been recently put on the market, have led to the occurrence of harmful secondary effects and sequelæ, and possibly even of deaths. The use of such uncertain preparations tends to create confusion, and has

already given rise to unpleasant personal recriminations in the medical press. The investigations of Wernicke, Ehrlich, Behring and Aronson on the subject of acquired immunity from diphtheria, which were published in the various medical papers, have enabled some manufacturers to produce a serum which is more apt to prejudice the value of the original discovery than to supply the demand for an efficient remedial agent.

It may be pointed out here that Antitoxin is not made by merely inoculating an animal, drawing off the blood after a certain interval, and coagulating and separating the serum. *Aronson's Antitoxin, from which the best results have been obtained, and on which the first clinical reports were based, is a highly concentrated Antitoxin, from which the inert and noxious materials have been removed. Its preparation requires long periods of time, the greatest of care, the minutest scientific supervision, and elaborate and expensive paraphernalia.*

Schering's (Aronson's) Diphtheria Antitoxin is supplied by us only in the strength of 100 units to each cubic centimeter. Of this one 5 ccm. vial, representing 500 antitoxic normal units, is sufficient for one average curative injection. As the German Government uses comparatively delicate guinea pigs for their standard tests, which naturally resist the diphtheria poison much less than older and more vigorous animals, the value of their official requirement of 100 units per cubic centimeter as a minimum strength will be seen at once.

EXCERPTS FROM THE LATEST LITERATURE.

One of the weightiest pieces of testimony in favor of the Antitoxin treatment of diphtheria is the article by **Dr. Adolf Baginsky**, Professor of Pediatrics at the University of Berlin, which has appeared in the "Archiv für Kinderheilkunde," Vol. xviii. It is entitled: "The First Series of Cases of Diphtheria treated with Antitoxin (Aronson); from the Diphtheria division of Prof. Baginsky at the Kaiser-und Kaiserin-Friedrich-Kinderkrankenhaus at Berlin." The material contained therein is also embodied in Prof. Baginsky's book, "The Serum Treatment of Diphtheria." Hirschwald, Berlin, 1895.

With the assistance of Dr. Otto Katz a complete history is given of all the cases treated with Antitoxin from March 15th, 1894, to March 15th, 1895, exclusive of the months of August and September, during which time no Antitoxin could be obtained. It is the most voluminous, and in many respects the most important contribution that has yet been made on the question of the therapeutic value of the diphtherial antitoxic serum.

Professor Baginsky has had the opportunity to test the remedy in a long series of cases. The general results were reported at the Munich Congress in April last; and some of the cases have been used by Dr. Katz in his paper read before

the Berlin Medical Society, and by Dr. Aronson at the Hygienic Congress at Buda-Pesth and at the Meeting of German Naturalists and Physicians at Vienna. But the work under consideration contains many additional clinical observations of great interest and value.

The work is divided into two nearly equal parts, the one consisting of a discussion of the pathology of diphtheria, the results of the earlier methods of the treatment, those of the serum method, and the mode of applying it; and the second containing the particulars of the 525 cases treated with the serum.

Professor Baginsky commences by stating that he leaves to the profession the task of passing judgment on the results that he has obtained. But he cannot forbear to remark that, with an experience of many years with diphtheria, both in the city and in the country, in public as well as in private practice, *he has never met with any remedy that made anything like so favorable an impression upon him in regard to its action upon the patients.* The impression thus formed, while the earlier cases were under treatment, has remained; and the experience of every day has renewed and strengthened it. Of course much still remains to be desired: even to-day we see cases that in which the intensity of the disease threatens the lives of the patients. But such cases are much less frequent than they used to be; and they are certainly much less frequent in cases that have been early treated with the serum than in those treated by the older methods. It would seem that when a physician of long years of experience, who has never been found guilty of therapeutic chauvinism before, calmly expresses this as his firm conviction, a radical error can be excluded. There may be differences as to the more or the less; but the fact itself cannot be doubted. And now the same thing is affirmed from all sides, wherever experiments have been made—from London, Vienna, Buda-Pesth, Prague, Trieste, Graz, etc.

And if doubt has arisen in spite of these facts, it is manifestly due to two things. The first is the necessarily severe struggle with medical conservatism. The unusual method by which the remedy is obtained; its strange mode of application; and its large and somewhat uncertain dose; all these frightened the practitioner. The recent failure of the tuberculin therapy was still in our minds.

The second cause of doubt was based on theoretical considerations lying mostly outside the realm of the busy practical physician. The natural tendency was to believe just so much of this as to frighten them out of the use of the remedy.

Every radical innovation in practice, as in diagnosis, is unpleasant; yet the first objection was more easily combated than the second one. Perhaps from his too great modesty the practitioner respects theory entirely too much; though certainly practical experience at the sick-bed is the one and only criterion

—the court of last resort. All therapeutics are more or less empirical. We do not know the real causes of the efficacy of a single remedy! The life processes in the animal organism are so complicated and so obscure, that a scientific theoretical explanation of the action of drugs is not for a moment to be thought of. Of most drugs we do not even know the point at which they begin their attack on the organism. So do not let us deceive ourselves on this point. Theoretical considerations may lead us where they will; they are always more or less hypothetical. Medical observation alone decides finally whether the remedy is useful or not, whether it helps or does harm.

From this point of view theoretical considerations as to the value of the Antitoxin treatment in diphtheria hardly concern us very closely. It would not be worth our while to consider them at any length, if so many clinical observations had not been dragged into the debate, giving rise to a terrible confusion of statements and opinions. It seems to be our duty to restate the facts that are the results of clinical observation, and to demonstrate those errors that have been so loudly proclaimed as truths to the medical world.

The first clinical question is that of the recognition of the disease—the diagnosis.

Doubtless in many cases the diagnosis of diphtheria may be made by inspection alone. The diphtheritic pharyngitis, ranging from a simple exudation on the tonsils and uvula to severe gangrenous destruction of the tissues affected; the systemic affection, the facial expression, the fever, the prostration—all these need only to be seen to be recognized by one of practical experience. But there is no disease in which every case shows all the symptoms completely; and even where the physical methods are most perfectly developed, there will always be a number of uncertain cases. How often is the most practiced physician in doubt as regards a case of croupous pneumonia, of pleurisy, because typical physical signs are absent or imperfectly appreciated; not to speak of diseases like tuberculosis, typhoid, malaria, and a dozen others. These are the doubtful cases in which the practitioner continually seeks for new diagnostic methods and aids. And in diphtheria we encounter these diagnostic riddles with especial frequency. To cite one of the simplest: a scarlatinal necrosis of the pharynx looks as much like a diphtheria as one egg does to another, and yet the clinical course and the after effects of the two diseases are entirely different. But the diagnosis from the course and sequelæ comes too late to be of value; and the physician seeks for new differential points to aid him in deciding the diagnosis and the necessary treatment.

Hence the advent of the Loeffler bacillus was welcomed. The bacteriological examination is a part of the clinical diagnosis, just as much as the chemical examination of the urine is a part of the clinical diagnosis of Bright's disease of the kidneys. *A priori* we make the diagnosis in diphtheria

purely clinically, from the symptoms that the patient presents, but in the cases where the symptoms are insufficient we thankfully accept the aid of the bacteriological examination; just as we do the diazo-reaction in typhoid fever, the albumen reaction in nephritis, the blood and urine examinations in pneumonia, the blood examinations in malaria and recurrent fever.

When, mainly through the labors of Roux and Yersin, it seemed probable that the Loeffler bacillus was the cause of diphtheria, we went to work systematically to find out how constantly the organism in question was to be found in cases that presented the outward phenomena and symptoms of diphtheria. We examined, as far as possible, each single case that presented itself in the diphtheria wards of our hospital.

In the first 154 cases, the Loeffler bacillus was found in 118 cases, with a mortality of 38.19%. In 36 cases the bacillus was not found: of these four died, three of them of accidental complications in no way related to the disease. From this I concluded that those cases in which the Loeffler bacillus was present were more dangerous than those in which it was absent.

The further results of these observations have been detailed by Dr. Philip in these archives. We found that in 376 cases that we called cases of pronounced diphtheria the bacillus was demonstrable in 332; in 31 cases of angina it was absent; and 13 cases were of an entirely different nature. The mortality of the 332 cases was 39.3%; there were no deaths in the 31 cases of angina, which showed only cocci when examined. One single case of diphtheria remained, in which, in spite of typical diphtheritic symptoms, the micro-organism could not be demonstrated.

The marked difference in the results of cases in which the Loeffler bacillus was present and those in which it was not, led us to place the former cases in the diphtheria wards at once, whilst the others were placed in a quarantine division for observation. And soon the following remarkable fact was noticed. In the first division there were received during the last year 529 cases, in only ten of which do I find any note of failure to find the diphtheria bacillus. These ten cases were only examined once, and they entered mostly at a time when there was an immense influx of patients, and when the carefulness and exactitude of the examination could not be guaranteed. In the quarantine division 260 children were received as suspicious cases. In 104 of them bacteriological examination finally showed the presence of the Loeffler bacillus, whilst 156 of them showed only streptococci. Of the 104 cases 84 showed by their course that they were marked cases of diphtheria, and were removed to the diphtheria division; 20 were mild and ran a rapid course, so that they remained in the quarantine division until they were cured. In the 156 cases in which the Loeffler bacillus was not found there were two deaths, one from pneumonia and one from atrophy.

I am therefore in a position to state that in the cases that a

most careful consideration of the clinical symptoms caused us to classify as true diphtheria, the Loeffler bacillus was practically never absent; the small percentage of cases, 1.9% in which it was not found, I feel justified in ascribing to oversight. Only in those cases in which the external symptoms were essentially doubtful was the Loeffler bacillus absent in the majority of cases. And the Loeffler bacillus was present in practically all the cases that presented the appearance of pronounced diphtheria.

The diphtheria bacillus is not absent, as Hansemann incorrectly states, in 25% and over of all cases; it is absent only in larger proportions in suspicious and doubtful cases. (Virchow's Archiv, Vol. 139, p. 365).

Hence our conclusion is that the bacteriological examination is a new and valuable aid to the other clinical diagnostic appearances of the disease.

It follows also that the careful physician should employ the method of bacteriological examination in all doubtful cases of angina; and thus be able to separate those which, containing the Loeffler bacillus, are mostly cases of dangerous diphtheria, from those which, not showing its presence, are mostly cases of simple angina. The pathological anatomist has nothing to say here to the practical physician. These latter cases are not real diphtheria; they are an entirely different disease, which I have called diphtheroid.

Hansemann has further objected that in children of the same family, sick of diphtheria, the Loeffler bacillus is found in some and not in others. I have seen this but once, so far as my memory and records go. Two children in the same family had mild and indefinite pharyngitides, and both were received in our quarantine division and treated there. In both cases there were abundant cocci, and in one of them undoubted Loeffler bacilli. There is no other explanation of such an isolated case possible than that in the one case the bacilli disappeared more rapidly than is usually the case. It was much more frequently the case that children in the same family all harbored the Loeffler bacillus, and presented apparently different forms of pharyngeal inflammation; ranging from a simple angina to a phlegmonous pharyngitis and diphtheritic necrosis.

And now as to Hansemann's healthy people who have the Loeffler bacillus in their pharynges. The complete healthiness of a mucous membrane is a doubtful thing, but I have never seen the Loeffler bacillus in an entirely healthy pharynx. But granting that it may be found, the varying reactibility of the organism would be sufficient to explain it fully. To give an example from an entirely different field, I have seen children take large quantities of alcohol without any serious inconvenience, whilst I have known a boy to have a violent epileptic attack after a single glass of wine.

Hence we can draw no conclusions from the tolerance of an organism to diphtheria bacillus. But we must not forget

the fact that these tolerant persons may be very dangerous to others who do not possess such resisting powers. As we have unfortunately but too often seen in the hospital, a child with an angina, and harboring the diphtheria bacillus, may be a source of extreme danger to all its neighbors, so that the disease spreads from bed to bed. The isolation of all persons that have the Loeffler bacillus is an urgent necessity; they carry and spread the contagion.

My experience leads me to regard the fact as proven, so far as such a fact can possibly be proven, that the Loeffler bacillus is the cause of the acute diphtheritic disease. And hence one of the objections to the serum therapy is removed at once. With this, however, the practical physician at the sick bed has nothing whatever to do. We may differ entirely, as I do, from the humoral-pathological reasoning with which the Diphtheria Antitoxin has been defended, and yet value the remedy itself most highly.

Dialectics, as employed by Kassowitz, Gottstein and others have no place in the discussion of a question that bedside observation alone can decide.

Then follows the report of **Dr. Otto Katz**, Assistant Physician at the Kaiser und Kaiserin-Friedrich-Kinderkrankenhaus, on 167 cases of diphtheria treated with Aronson's Antitoxin. This is a completion and elaboration of the communication made by Dr. Katz on the 27th of June of last year to the Berlin Medical Society. The cases are grouped into: I. Mild cases. II. Medium cases. III. Severe cases. IV. Septic cases.

The temperature curves are given in a number of cases. In some cases there was a sharp decline immediately after the administration of the Antitoxin. In others again the injection seemed to have no effect at all on the body heat. In a very few cases the temperature increased markedly. As Katz has before stated, there seems to be no constant effect on the temperature from the Antitoxin. The urinary examinations were very complete; Eschbach's test, and that of acetic acid and boiling, being employed for the determination of the presence of albumen. The morphotic elements were obtained by simple sedimentation, or, when their quantity was very small, by the centrifuge. The daily quantity of the urine is not given, since, in the case of children, such figures are manifestly very liable to be wrong. The pulse also showed nothing of special note, and in children is so liable to vary from slight and unimportant causes that it is of very little value. In a general way it kept pace pretty regularly with the temperature.

The Loeffler bacillus was found in every case, practically. In a very few cases its presence was doubtful, and in case 24 no bacilli were found at all. The staining method was that described at length by Professor Baginsky in the "Berliner Klinische Wochenschrift," No. 52, 1894, and in the "Archiv für Kinderheilkunde," Vol. xiv. I cannot agree with Dr. Ritter (Berliner Klinische Wochenschrift, No. 45, 1894), in his

opinion that in severe cases it is not easy to demonstrate the presence of the diphtheria bacillus. In severe as in mild cases it can be found if properly sought for, and if there is any difference in this respect it is certainly in favor of the serious cases. In these they can always be found. Practice and experience makes a difference, of course; and hence in all probability arise the varying results. There are a number of points that one finds out in the course of numerous examinations. To give one example: where one suspects that there are many other microorganisms beside the Loeffler bacillus present, as is the fact more especially in the septic cases, the serum-culture should not be allowed to remain too long in the incubator; cover-glass preparations should be made after six or seven hours. Again, it is often better to take a fresh culture, which has been six or eight hours in the incubator, and shows a delicate grey membrane, and inoculate a fresh tube therefrom. In this way we are much more likely to obtain a pure culture of the Loeffler bacillus. The washing of the membrane obtained from the pharynx is of extreme importance, and most of the failures result from its neglect.

The other treatment, purely local, employed in some of the cases, was very trivial; iron-lanolin, according to the following formula:

R Ferrum sesquichloratum,	30.0 ($\frac{3}{4}$ i)
Aqua dest.,	5.0 ($\frac{3}{4}$ i)
Lanolin,	60.0 ($\frac{3}{4}$ ii)

was used in a certain number of cases as a local application several times daily. We learned in time to value this salve very highly, and especially in cases where the membrane was pasty and stinking.

As regards the Antitoxin that was used, Dr. Aronson has already published the results of his animal experiments, more especially in the paper read before the Congress of Naturalists at Vienna (Wiener Medicinische Wochenschrift, Nos. 46 to 48, 1894). We ourselves have made a number of experiments in the laboratory here, to ascertain its exact action on animals, and our results exactly agree with those of Dr. Aronson. As recently as last December we made a new series of experiments, which proved to our satisfaction that the preparation that we employed in the spring is preferable to the Behring's (Hoechst) Antitoxin No. II.

We worked with a diphtheria poison, of which 0.6 ccm. killed guinea pigs weighing over 300 grammes in about 36 hours. When this dose of the poison was injected into an animal of this weight, together with $\frac{1}{1200}$ ccm. Behring's No. II in one ccm. of water, the animal remained entirely well; there was no local infiltration, etc. When the dose of the serum was diminished to $\frac{1}{1200}$ ccm., the animal survived, but it became sick; more especially there occurred that unmistakable swelling at the site of the injection, which took a considerable time to disappear. Thus $\frac{1}{1200}$ ccm. Behring's No. II was not suffi-

cient to entirely neutralize 0.6 ccm. of our poison. With Aronson's Antitoxin, however, even ~~0.1~~ 0.1 ccm. completely neutralized 0.6 of the poison; and that without any disturbance in the general condition of the animal, and without any local changes or infiltrations.

Grouping our patients together, we find the following general results:

In 167 cases there were 24 deaths, being a mortality of 14.3%. Arranged according to age, we have the following:

Under 1 year of age there were 7 cases with 3 deaths.

At	1	"	"	"	14	"	"	1	"
"	2	"	"	"	21	"	"	5	"
"	3	"	"	"	20	"	"	3	"
"	4	"	"	"	25	"	"	3	"
"	5	"	"	"	16	"	"	2	"
"	6	"	"	"	18	"	"	3	"
"	7	"	"	"	15	"	"	1	"
"	8	"	"	"	7	"	"	1	"
"	9	"	"	"	9	"	"	1	"
"	10	"	"	and over	15	"	"	1	"

Our figures showed that the relatively most favorable periods was the second year, the eighth year, and the time after the tenth year. The most unfavorable was the first. Of course no conclusions are to be drawn from such small numbers.

As regards the period at which treatment was begun:

1st day of sickness treatment was begun in	27 cases with	1 death.
2d	"	"
3d	"	"
4th	"	"
5th	"	"
6th	"	"
7th	"	"
8th	"	"

Cases where the beginning of the disease was uncertain, 11 cases with 4 deaths.

These facts were obtained mostly from the relatives of the patients, and I do not lay too great stress on them. Those of us who have had experience with dispensary and hospital patients know how unreliable such statistics are.

As regards tracheotomies and intubations:

19 children were tracheotomized, of whom 12 died (2 were secondary tracheotomies); 10 children were intubated, of whom 1 died. Altogether, 29 children were operated upon, with 16 recoveries: 52.2% of recoveries.

A number of children with fairly seriously laryngeal stenoses recovered under the use of lime water sprays. The patients that were intubated were mostly such in which there was not much pharyngeal swelling, so that there was some chance of successfully performing the operation. Those in which the reverse was the case were tracheotomized, and we

always did the high operation. The intubation statistics are much more favorable than the tracheotomy ones; this is not quite correct, for the two secondary tracheotomies should be reckoned as deaths after intubation, that operation having been done first without success before tracheotomy was performed as a last resort. Changing the figures to correspond, we have 17 tracheotomies with 10 deaths, and 12 intubations with 3 deaths. As regards the course of the disease after these operations, I do not know that there was any essential difference from similar cases where no Antitoxin had been used. Those cases that turned out fatally, as well as those that recovered, showed the same course and symptoms as did similar cases in the pre-Antitoxin days.

We have not grouped the cases in accordance with the amount of Antitoxin that was administered. We gradually went from smaller to larger doses. Finally we would give to an apparently mild case about 10 ccm.; to severer ones 20 to 25 ccm., or more. It is to be remarked, however, that in some very severe cases we remained at the smaller dose, and the patients made good recoveries. The administration of these small doses was due to various causes, but most often to a failure in the supply of Antitoxin.

And now a glance at our fatal cases. We had, as above stated, 143 recoveries and 24 deaths, a mortality of 14.3%. Some of these 24 deaths deserve a little closer consideration. One case (137), was regarded as recovered from the diphtheria; it succumbed to septic scarlatina, which set in during convalescence. Another one (138) passed through the diphtheria nicely. Five days after his reception his condition was a good one; there was no membrane in the pharynx. Eight days after his reception the patient was doing well. Then a pneumonia set in, with meningitis and miliary tuberculosis, which destroyed the patient. Six septic cases (162, 163, 164, 165, 166, 167) were hopeless when they were brought to us.

Three further cases must be mentioned (108, 118, 120), which were brought to us in a stage already so far advanced in the disease that tracheotomy was done merely to give the patients a little relief. We shall not attempt to remove these patients from the statistics of our fatalities, but shall relegate them to the class of those that were hopeless before the treatment was begun. Every one of our patients that died of diphtheria was extremely sick when brought to us, and we should probably have given an immediate fatal prognosis in all of them save two (93 and 194) in the pre-Antitoxin days. In cases 93 and 124 it is our opinion that the Antitoxin failed.

In the first group there were several cases that were very mild. But even in them the clinical diagnosis was clearly diphtheria, and the bacteriological examination showed the presence of the Loeffler bacillus. We have always been in the habit of treating such apparently mild cases with great care, for experience has demonstrated to us in former days how very

readily they become severe. This has not happened, however, during the Antitoxin time. Not a single one of the mild cases has become severer as it progressed; not one of them had to be removed from its class, and put in the second, third or fourth class. As the patients were classified on entrance, so they remained. One favorable result was this, and it deserves to be especially mentioned, that all the patients transferred to us from the other divisions did well; that we lost no patients transferred to us for other disease from infection in the hospital itself. Unfortunately, in former times under similar conditions, the same could not be said. I need only remind the reader of Baginsky's "Communication on Diphtheria Infection" in the *Verhandlungen der Berliner Med. Gesellschaft*, Vol. 23, p. 277.

When first we began to use the new remedy, our main endeavor was to find out if perchance it did any harm. This might occur in two ways. It might influence the course of the diphtheritic process unfavorably; or it might cause new pathological phenomena not proper to the disease itself. As regards these points the following is to be noted:

Exanthems were noted 22 times; they either likened those of rubeola, measles, or scarlet fever, or they were like extensive erythemas or urticarias. They were all of harmless nature, and soon disappeared. In three cases (62, 97, 158) they were accompanied with more or less pains in the joints, and swellings. Never, however, were they serious enough to cause us any concern. I refer the reader desirous for information on this point to Professor Baginsky's article in the "*Berliner Klinische Wochenschrift*," No. 52, 1894. I may mention, however, that we do not consider every exanthem that occurs after an injection as due to the Antitoxin. Diphtheria itself is often accompanied by exanthemata, and I cite here the following passage from Baginsky's "*Lehrbuch der Kinderkrankheiten*," 3d edition, p. 222:

"Further there appears in some cases a pale, rose-colored exanthem (Erythema), forming larger or smaller irregular non-elevated blotches, which may be spread over the whole body; or there may be a darker red exanthem, extremely similar to the well known cholera exanthem, especially affecting the extremities, which appears as irregular notched spots, sometimes confluent."

This was written in the year 1889, long before the Antitoxin time.

Amongst all our cases there was not a single one in which the affection, primarily located on the pharynx, went down into the deeper air passages. In the pharynx itself the spread of the process was not always controlled with certainty. We have the records of some rare cases in which this took place after the injection. Nevertheless the cases all ended favorably. In by far the majority of the cases the process came to a standstill in the pharynx itself immediately after the injection.

Not a single one of our cases became septic.

The nephritides that we noted were of the ordinary well known type. They were not more frequent than usual, nor especially severe. They showed no new or unusual microscopic urinary sediment. A few even, that were received suffering already from severe nephritis, as No. 122, got well rapidly. In some cases, where there was scarlatina in addition to the Diphtheria, and where the kidneys were thus doubly exposed, as in cases 87, 116, 123, etc., nothing of the kind occurred. The nephritis, when it occurred, ran a course in no sense parallel to the size of the dose of the Antitoxin. It corresponded to the severity of the case. This is well seen in the histories, where the severe cases in the beginning of the series received smaller doses than the milder ones did later on.

All our nephritis cases recovered, when they did not speedily die of the diphtheria. And with the patients that died, the kidney symptoms were by no means the most prominent ones that they presented. One patient (No. 106) left us with some albumen still in her urine. She had taken a comparatively small dose of Antitoxin, and I do not believe that the long duration of the nephritis had anything to do with the drug. Protracted nephritis cases are well known after diphtheria, as after scarlatina; though rare, they do occur.

Of the other organs I will consider only the heart, from which a considerable number of mild pathological symptoms did indeed make their appearance during convalescence. Yet I believe that these "impure sounds, blowing, systolic murmurs," etc., were rather the last manifestations of the diphtheria poison in the organism than the effects of the Antitoxin remedy. We found it in all the stages in our patients, from the most unimportant roughness of the heart-sounds to the most pronounced rhythmic disturbances and interferences with the functional activity of the valves. We saw all these before, when Antitoxin was not used; but they used always to change, and become serious and fatal phenomena. I believe that these symptoms are caused by the diphtheria poison, and not by the Antitoxin.

And now as regards the results obtained. We will cite no special cases, but will point to groups III. and II., which speak plainly for the advantages of the Antitoxin treatment. Two points only need be discussed, and that briefly: the behavior of the pharyngeal exudation, and the general condition of the patient after the injection. As stated above, in no case did the Antitoxin appear to exercise any deleterious effect on the local process. Nor, on the other hand, can we point to any especially beneficial effect, though it must always be regarded as extremely favorable that the membrane did not advance. But the membrane, once there, did not appear to be especially influenced; it did not melt away or clear off with any special rapidity. I can see no difference in its action from that of the membrane in former cases.

As regards the general condition of the patient after the injection, we frequently find in our bedside histories on the day after the injection the note "much brighter," etc. Indeed, in a number of patients the general condition was distinctly better the next day; the children looked fresher, had better appetites, etc. Perhaps the care and the nursing had a share in this, but the general improvement was always noticeable.

Though our opinion in general is that the septic cases were not influenced by the Antitoxin, this is only true for the most fully developed and severest septic cases. Several of our patients (Nos. 107, 117, 123, 130, etc.) showed such a condition of the pharynx, etc., on admission, that we expected to have the regular picture of sepsis developed in a short time. And we can venture the opinion that the course of these cases was most favorably influenced by the Antitoxin. It is difficult to prove this, of course; I simply give it as our opinion.

A few short words about immunization. I deem our experience in that direction to be still insufficient. Some of our cases got sick in spite of it. The doses that we used for that purpose at the beginning were certainly insufficient. When we gave larger doses in the later cases we had better results. We refer the reader to Aronson's communications on the subject.

One thing more in conclusion. It was formerly our common and sad experience to see two or more children die in a single family from this dread disease. Not a single such case is to be found in our list. We received a large number of patients with very severe diphtherias; some of them died, and their brothers and sisters were afterwards brought to us suffering from the same disease. Of these second cases none died. It is not impossible that the earlier treatment of these other members of the family with the Antitoxin did great good. The parents, aroused by the first case, bring the second and third ones to us much sooner, and not at a stage where all therapy is hopeless. Before the Antitoxin time the conditions were of course the same, but the other members of the family, however early the treatment was begun, but too frequently died. (See P. Philip, "Zur Aetiologie und Statistik der Diphtherie. Arbeiten aus dem Kaiser-und Kaiserin-Friedrich Kinderkrankenhause," Vol. II., pp. 159 and 160).

When the Antitoxin was first employed it was received with the greatest scepticism on all sides by us. But when the good results accumulated; when we saw one severe case after another run a most favorable course, we began to see that scepticism, however proper, must not be driven too far; and we do not claim to-day that the Diphtheria Antitoxin is a cure-all, or that it will cure the most hopeless cases. But we are certainly of the opinion that it is a remedy that will influence the majority of the cases of the disease in the most favorable manner.

In his more extensive work, "The Antitoxin Therapeutics of Diphtheria," **Professor Baginsky** reviews all the ex-

periences that he has had in the matter of the new treatment at the Kaiser-und Kaiserin-Friedrich-Kinderkrankenhaus, including therein the 167 cases already reported on by his assistant, Dr. Katz. These form, however, but a small proportion of the number observed from March, 1894, to March, 1895, the total number being 525 cases treated with the Antitoxin.

At the **Thirteenth Congress of Internal Medicine**, held in Munich in April, 1895, the commencement of the sessions was marked by a very valuable debate on the merits of the serum therapy in diphtheria. It occupied the first three sittings; and during its course some of the most eminent continental authorities expressed their opinions at very considerable length.

The subject was introduced by **Dr. O. Heubner**, Professor of Pediatrics at the University of Berlin, who, after reviewing the development of the investigations, showed, by a series of statistical curves, that the general character of the diphtheria epidemic in Germany and North America at the commencement of the serum therapy was of about medium virulence. Comparing the statistics of the Berlin Hospitals during 1894, the mortality since the introduction of the serum therapy had been reduced to one-half of what it was prior to that date. About 1500 cases were included in his statistics for each period. Allowing that this favorable result had been partly brought about by the admission of less severe cases, Professor Heubner believed that this factor alone could not explain the great difference. Up to the present, reliable information had been obtained from all parts of the world of over 3,000 cases of diphtheria treated with Antitoxin serum, and the average of cures was 80%.

Referring to clinical analysis of 300 cases of Diphtheria that had come under his own supervision, Professor Heubner declared that the disease could only be diagnosed by the identification of the diphtheria bacilli. Of 207 cases so diagnosed and treated with serum in the Berlin Charité, the mortality in simple cases was 10%, and in complicated ones 13%. From his personal experience the speaker regarded, as the specific results of the serum treatment, the improvement in the febrile symptoms and the quickened cleansing of the air passages. All other exceptionally favorable appearances, he suggested, might arise from a milder character of the disease. Nevertheless, the fact that these favorable changes in the character of the epidemic should have been first noted since the introduction of the specific therapy, and should have presented themselves in all places where the serum treatment was adopted, was worthy of note.

That the employment of Antitoxin was devoid of any secondary effects of a serious character on the patients, more especially that it did not produce nephritis, Professor Heubner showed, was demonstrated both by his own results, and by the general literature of the subject. It never caused albuminuria, and the air passages were never threatened if the larynx was

free at the beginning of the treatment. In the course of his experience with the specific treatment it had only failed twice in five cases, ending fatally on the second or third day after admission. Paralyses were observed in 7.4% of the cases. Immunization injections were made to 64 infected children; of these only two sickened six weeks later, one dying of chronic pneumonia.

Professor A. Baginsky, of Berlin, then spoke officially as in charge of the Diphtheria Wards of the Kaiser-und Kaiserin-Friedrich-Kinderkrankenhaus for the last five years. Prior to the introduction of the serum therapy the most difficult and sorrowful portion of his life had been spent in this position, as he felt absolutely helpless against the disease, except as regards ameliorating the suffering. In spite of every effort the average mortality for the last four years had been 50, 33, 36 and 42% respectively, and at the time that Dr. Hans Aronson had proffered his supplies of the Antitoxin, the epidemic was severer in form than ever. Professor Baginsky spoke highly of the independent efforts of Dr. Aronson in developing the discoveries of Wernicke, by increasing the antitoxin value of animal serum to remedial degree, and said that from comparison with Behring's serum, he had found Dr. Aronson's superior. The mortality in 525 cases treated with Dr. Aronson's preparation up to March 15th, 1895, had been 15%.

With regard to the relation of age to mortality, naturally the largest proportion of fatal cases was in young children. Compared with the experience of the previous four years the mortality had fallen in children

under 2 years	from 63 to 23%;
of 2 to 4 "	" 52 " 17%;
" 4 " 6 "	" 37 " 17%;
" 6 " 8 "	" 27 " 11%;
" 8 " 10 "	" 19 " 5%;
" 10 " 12 "	" 19 " 4.1%.

Mere clinical statistics, however, Professor Baginsky valued but little. The above figures had an especial value to himself personally, as the expression of his own experience; but he laid far greater weight on the impression produced on the physician at the bedside. Almost without exception a very extraordinary improvement in the general condition is observed, not on the first, but on the second and third day after the injection. Children who are languid, exhausted, pale and miserable, lose all these appearances and become bright, sit up in bed, play, notice surroundings, and take more nourishment. The second point observed is the fall of temperature some time after the injection; as a rule any subsequent rise is due to an insufficient injection. Further, the limitation of the diphtheritic process is most interesting. From the moment of injection in the majority of cases the growth makes no further progress in the pharynx or larynx. As a consequence the frequency of the necessity for operations has been materially reduced;

intubation has largely supplanted tracheotomy, and a much higher percentage of favorable results has been obtained.

In relation to the effects of the diphtheritic process on the heart and kidneys, Professor Baginsky has given the serum treatment special attention. He found *that the cardiac changes became far less serious, while he was sure that nephritis was not caused by the injections.* The effect of the serum treatment on the nervous system he was not in a position to discuss; but he pointed out that paralysis appeared now where formerly death had precluded observation.

The advantage of injecting as early as possible, the same speaker demonstrated, from the fact that in children treated on the first day of the appearance of the symptoms the mortality was less than 2½%, and rose simultaneously with its deference. Seven abscesses and 13 cases of exanthemata were on record as the probable after-effects of the serum, but nothing of serious nature or permanent effect. Experience with Antitoxin as an immunizing agent had this year been very favorable, 124 children having been injected without any subsequent attack.

Professor Baginsky therefore summarizes his experience with Schering's Antitoxin as follows:

1. *It is the most active remedy, and the best that has hitherto been employed against diphtheria.*

2. *It works the better the quicker (after the first appearance of the disease) it is injected, being advantageously combined with a mild local antiseptic treatment.*

3. *It is not followed by any serious effects; the sequela observed being those customary after diphtheria, and if more frequent, they were less severe.*

4. *The uncertainty as to the mode of action of the Antitoxin should not in the slightest degree influence its therapeutical employment after the activity of the remedy has been empirically determined.*

Professor von Widerhofer, of Vienna, also expressed himself as a warm advocate of the new treatment. Confining himself to generalities, he stated that of 300 cases of diphtheria treated with serum, from October to February last, in the first hundred 24 died, in the second hundred 30, and in the third hundred 17, corresponding to a rise and fall in the severity of the disease, and making an average mortality of 23.7%. The large proportion of deaths in the Vienna Hospital, as compared with other quarters, the speaker considered sufficiently explained by two reasons. In the first place, owing to the scarcity of the remedy, only the severer cases were injected with the serum; and secondly, a large proportion of the children so treated were brought in at a very advanced stage of the disease, more than half of them after the third day, so that if we exclude those that died in the first 24 hours, the mortality falls to 14.3%. In confirmation of this view, he added that a number of children already had laryngeal stenosis; yet in 22 cases the injection of the serum overcame this. With the

exception of gargles in a few instances, no further treatment was resorted to; but the speaker laid emphasis on the importance of combating cardiac weakness, if it should appear, by means of hypodermic strychnine injections.

At the second sitting, the discussion of the diphtheria question was again taken up by **Professor von Ranke**, of Munich. His observations were of especial importance, because they related to experience in the Munich University Children's Hospital, where only the most severe cases are admitted. Consequently the speaker had nothing to say with regard to the action of the Antitoxin in the early stages of the disease, even cases three days old on admission being exceptional, but referred especially to the effects of the remedy after laryngeal stenosis had set in.

Corresponding to the severity of the cases, large doses were injected, the average amounting to 1,184 antitoxic normal units per child. Of 124 cases thus treated during the past six months, several of which were complicated with scarlet fever and measles, 26 children, or 22.4%, died; 102 cases presented the features of uncomplicated diphtheria, although in the majority of these, Professor H. Buchner discovered streptococci along with the diphtheria bacilli, and of these 18.6% died. Compared with the mortality during the preceding eight years the reduction is enormous, being less than half the minimum record for any time during that period.

Dealing with the cases in which laryngeal stenosis was already present on admission, Professor von Ranke stated that in one-third of their number this symptom disappeared after the injection. Intubation was performed on the remainder, of which nearly a third had a fatal termination. Intubation had hitherto been the principal means of amelioration adopted; and the speaker, seeing as he so frequently did the quieting effect of the operation on the patients, often lamented to his assistants and scholars the absence of a remedy to prevent the descent of the diphtheritic process into the bronchi, which nullified the therapeutic effects of the procedure. In the antitoxic serum, Professor von Ranke recognizes the missing remedy, which in a large number of cases prevents the diphtheritic process from extending from the larynx down into the bronchial tubes. Since the commencement of the serum treatment the diphtheria ward had acquired a most hopeful appearance, which it has maintained to the present day. Operations have been less frequently required, and have been more successfully done; the task of the assistants has been enormously lightened, and the night bell is seldom heard. *It is impossible that all these occurrences are mere coincidences; it must be due to the specific remedial action of the serum.*

Injurious effects from the serum injections on important organs like the heart and the kidneys have not been observed by Professor Ranke, and the few cases of exanthemata that have occurred have possessed no particular clinical importance.

Dr. C. Seitz, of Munich, continued the debate on the line of demonstrating that there was no valid reason for the reticence observed in many quarters respecting the serum therapy, to a great extent apparently from the fear of further injury to the system. In reviewing some 140 cases that had come under his own observation, he therefore passed over general and local improvement, and confined himself to the consideration of the effects of the treatment on the specific organisms.

Dr. Rehn, of Frankfort-on-Main, speaking as a private practitioner, who had first clung to local treatment, said that from his own small experience, and the more numerous clinical observations of his colleagues, he had come to the conclusion that Diphtheria Antitoxin was a powerful agent, which stayed the progress of the local process without danger to the organism, and without in general any need of further medication. The duration of the attack was, in his experience, shortened by about one-half by well-timed injections, and he had not observed either joint affections, paralyzes, or other ill effects. On the other hand, he had observed in a case treated without serum during this period, the joint pains that have been attributed to the injections.

Professor Rauchfuss, of St. Petersburg, also related his experience with 34 serum-treated cases in the Oldenburg Hospital, where, although a number of patients still died, there was a difference of 21% in the mortality in favor of the serum treatment. He had never yet seen anything to equal the general improvement and delimitation of the process that appeared subsequent to the serum injections.

The diphtheria discussion was brought to a close at the third sitting of Congress, when **Professor von Mehring**, of Halle, **Professor Vierordt**, of Heidelberg, and **Professor von Noorden**, of Frankfort-on-Main, took up the debate.

Professor von Mehring reported on 74 cases, all of which had been treated with serum on the first or second day. Only four died, giving a mortality of 5%. During the five years preceding, 30% of his diphtheria cases had died, and the mortality amongst his patients in 1894, up to the time that the serum treatment was commenced, was 28%. Injurious by-effects the speaker had not observed; the remedy employed was obtained from Schering, as well as some of Behring's preparation.

Professor Vierordt also regarded the new remedy as extremely effective, though he recognized the fact that the different character possessed by the epidemic in various places rendered the comparison of results difficult. Though the serum treatment still requires much investigation, its use should be encouraged for the following reasons:

1. It was inoffensive.
2. The results were sufficient to warrant trial, even if not convincing.

Professor von Noorden contributed the results of his experience in 81 cases treated with the serum at the Frankfort Hospital. Most of these cases, unfortunately, came in at a late stage of the disease, generally on the third or the fourth day, with the severest symptoms developed, and such favorable results as were before reported could not be expected. Nevertheless, in the place of the earlier mortality of 45%, only 23% had to be recorded. Albuminuria he considered from his own experience to be a regular symptom of diphtheria, and had nothing to do with the serum injections. The more frequent occurrence of paralysis, also, he recognized as entirely due to the larger proportion of severe cases saved. *In the Diphtheria Antitoxin he recognized a remedy, which, if used in time, reduced the danger of the malady to a minimum.*

At the conclusion of this most remarkable debate, noteworthy on account of its one-sided character, and which so brilliantly confirms in every particular the theories advanced by **Dr. Aronson** two years ago, **Professor Heubner** emphasized the following points in his reply:

1. During the whole debate not a single fact has been brought to light from which any deleterious character could be attributed to the remedy. This is a most important factor in determining its future.

2. Every medical man must now seriously consider the question whether he is not doing a great wrong by not employing the remedy.

3. All medical men who have had control of large clinical material have observed a very considerable reduction in mortality since the introduction of the serum treatment. The only speaker at the Congress who did not concur in this opinion had had but little experience with the remedy.

4. As the remedy is innocuous, it is advisable to treat also all doubtful cases with it, and at as early a date as possible.

Dr. G. Seiz, of Constance, contributes an article on the Serum Therapy of Diphtheria to the "Therapeutische Monatshefte," December, 1894. During the last 18 months an epidemic of diphtheria, with a considerable number of severe cases, had been present in Constance; and since June, 1894, Seiz had employed the serum. Out of 27 cases treated with the serum he lost only one.

He formulates the general impression that he had gotten of the serum-treated cases of diphtheria, as follows:

"1. A favorable influence of the Antitoxin on the course of the disease is undeniable.

"2. It is of extreme importance that the inoculation be done as early as possible.

"3. The effect of the Antitoxin is seen in from 24 to 36 hours, and is shown most markedly in the fever and the general condition.

"4. When the injection is done early, the local process runs its course without any threatening symptoms.

"5. Complications, especially from the kidneys, are absent, or, if present, disappear rapidly. Paralyses were not observed.

"6. Convalescence is remarkably rapid and good, in accordance with the very small degree of involvement of the general health.

"7. Both the Schering and the Behring lymph are efficacious, but the latter sometimes causes pain and the appearance of an exanthem.

"8. The remedy is entirely harmless.

"If I consider my small number of 27 cases as being worthy of publication, it is on account of the immense importance of the serum question, which requires for its elucidation the records of practice as well as those of clinics and hospitals. The practitioner sees most cases first, and is in a position to apply the remedy early; and this, as I have said before, is of vital importance. By the time the parents decide to send their child to the hospital the case has usually advanced so far that we cannot expect too much from the Antitoxin treatment."

Professor Sigel, in charge of the Olga Hospital at Stuttgart, reports on the Antitoxin treatment as employed in 100 cases there since October 4th last. His report shows that the general mortality in the five years previous to 1894 was 40.1%, whilst among those upon whom tracheotomy was performed it was 60.3%. In the first nine months of 1894, in fact until the day on which the Antitoxin treatment was commenced, the mortality rose higher than ever, averaging 50.3 and 70% respectively. During the three months of the Antitoxin treatment in 1894, there was an enormous reduction of the mortality; it fell to 12% in general, and to 20.3% in the tracheotomy cases. This difference is too precise and marked to be explained away as a chance coincidence. As Professor Sigel says in closing:

"My statistics speak, I consider, a distinct language. A final decision on the value of the remedy can only be given, of course, after indefinite experience, but at present there is no remedy for diphtheria which influences the natural process of recovery so quickly and favorably as Antitoxin."

A recent article by **Dr. O. Leichtenstern** and **Dr. H. Wendelstadt**, in the *Münchener Medicinische Wochenschrift*, discusses again the value of the Antitoxin, and brings further statistics to bear upon it. They are particularly valuable, because they have been collected and studied with special reference to excluding all possible sources of error. They treated 123 cases with the serum, and 1,353 without it. The cases treated without the serum occurred during the years 1892, 1893 and 1894, and may therefore be assumed to be free from any special epidemic influence. The mortality in the 1,353 cases treated without Antitoxin averaged 30.9%, while the mor-

tality among the cases treated with it was 20.3%; they also show that the class of cases treated with the Antitoxin was not of the milder kind, for the percentage in which tracheotomy was done was 30 in both series. In the cases where tracheotomy was performed, however, the mortality after the operation was 15% for those not treated with the serum, whilst it was only 10% for those thus treated.

Professor F. Massei, of Naples, assisted by **Professor Arena** and **Dr. A. Damieno**, says as the result of his experience with the serum (*Universal Medical Journal*, July, 1895):

The beneficial effects of the general treatment of these cases was undeniable, and in Italy the Antitoxin, especially combined with intubation, has become very popular. In some cases of malignant pharyngeal diphtheria the value of the Antitoxin was demonstrated in a striking manner. In some 40 of these cases were some in which treatment was instituted at a late period, when the clinical form of the disease was very severe; notwithstanding this, recovery took place. A certain degree of mortality in diphtheria does not lessen the value of the anti-diphtheritic serum, because:

1. There are cases in which the treatment is begun very late, when the kidneys, heart, or nervous system may be impaired, and it cannot be successful.

2. In other cases again there are complications, such as scarlet fever or measles, and we cannot ascertain whether some lesions, and more especially glomerular nephritis, are to be attributed to one or the other injection.

3. Death frequently occurs from suffocation, unless intubation or tracheotomy be promptly performed.

But, Massei concludes, if time will permit, the Antitoxin treatment will succeed.

Dr. Louis Fischer, Instructor in Diseases of Children at the New York Post-Graduate School and Hospital, Physician to the Messiah Home for Children, Attending Physician to the Children's Department, German Poliklinik, in an article on the Antitoxin treatment of Diphtheria (*American Journal of the Medical Sciences*, January, 1895), after discussing the theory of immunity, and describing the general methods employed, records some cases of his own treatment by injection.

In all he employed the treatment in 34 cases. Out of these 29 were malignant, in which a grave prognosis was given by the attendant or by himself in consultation. They were all cases that showed a distinct evidence of sepsis, low or very high temperatures, marked somnolence, considerable enlargement of the cervical glands, a cold, clammy or even icteric skin, a foul mouth, and a cadaveric breath. Some not only showed the pharynx, tonsils and uvula involved, but also had symptoms of stenosis of the larynx and occlusion of the nares.

Four were mild cases when first seen; the membranes

were limited to small areas of the pharynx, tonsils or uvula, and there were no laryngeal or nasal complications. Sometimes there were small quantities of albumen in the urine, but no distinct nephritis, and no pulmonary complications were noted.

One case was moribund, and was seen in consultation with Dr. Welch at the Municipal Hospital at Philadelphia; the child was pulseless, had cold extremities, and showed marked evidences of general septicæmia. Still it lingered a number of days, showing the influence of the strong Schering serum in neutralizing the toxic elements.

Out of these 34 cases there were 32 recoveries, a mortality of 5.8%.

These were not selected cases. Some were poorly nourished, whilst others were of excellent vitality, and had the advantages of careful hygiene and good nursing. The main point was to apply the Antitoxin as early as possible, so as to counteract the septic matter absorbed, and thereby avoid complications. The local treatment consisted only in swabbing the throat out with a 1:2000 bichloride of mercury solution, using a new swab at each application, and burning it immediately thereafter.

The technique of injection was simple. Having properly sterilized the syringe by boiling, and using a one-half per cent. Trikresol solution, 10 ccm. was used in mild, and 20 ccm. in malignant cases. The injection was made in the interscapular region, and slowly. A syringe of suitable size, and a large needle, was employed.

If on the second day no result was seen, the injection was repeated; and the same course was pursued on the third day. Dr. Fischer is emphatic in stating that it is a perfectly safe remedy, and that there is no risk at all from the injection. It differs from tuberculin and vaccine in that it causes no reaction. The temperature falls not by crisis, but by lysis. Massage after the serum injection should not be practised.

The author warns us not to lose sight of the other subsidiary treatment. All discharges should be rigidly disinfected by swabbing the visible membranes with the bichloride solution mentioned above. Naso-pharyngeal antiseptics must be attended to by injecting luke-warm normal salt solution through either nostril, using considerable force to make it come all the way round and out through the other nostril, if necessary. The recumbent posture must be insisted on; the child is to be douched lying flat on its back, with a rubber sheet wound round its arms and neck to prevent useless struggling.

The cases treated by Dr. Fischer at the Municipal Hospital of Philadelphia were examined bacteriologically by Dr. D. Braden Kyle, Bacteriologist to the Orthopædic Hospital and Infirmary for Nervous Diseases, and Assistant Demonstrator of Pathology at the Jefferson Medical College. The presence of the Klebs-Loeffler bacillus was proved in every case.

Dr. Louis Fischer also read a paper on May 8th, 1895, before the Pediatric Section at the Meeting of the American Medical Association in Baltimore, entitled "Clinical Experience with Antitoxin in private and hospital practice in the treatment of Diphtheria (all forms)." In the course of his article he says:

The proportion of deaths in his first list was 5.8%. In the 225 cases reported in the New York Medical Record, April 6th, 1895, the mortality was 15.19%. This is double the mortality reported by him in January. It is accounted for by the fact that most of the latter cases were consultation ones, moribund and hopeless, in which Antitoxin was used as a last resort, and that many of them were mixed infections, cases of scarlatina, measles and chickenpox, with diphtheria, and were septicæmic when first seen. As an instance in point, Dr. Fischer recounts a consultation case with Dr. Roberts of New York, in which he refused to inject the Antitoxin on account of the presence of scarlet fever as a complication, and in which the child died an hour or two afterwards. This case, had it been injected, would have been put down to the discredit of the Antitoxin. An immunizing injection, however, given at the same time to another child in the same family, fully protected it.

Dr. Fischer then calls attention to the complaint of inefficiency, the noxious secondary effects and sequelæ that have followed the use of the various Antitoxins that have recently been put on the market; and the extreme importance of the official control and stamp that the German Government places on the material produced at Schering's Laboratory. He also gives the history of three new and successful cases, one of which was a distinctly bad one, and another of which was also intubated.

The author refers enthusiastically to the value of combined intubation and Antitoxin injection, provided the Antitoxin is absolutely reliable. He claims that his general results, since he began the use of the injection treatment, have been 500% better than they were before, and points to the many eminent foreign pediatricists who have stopped all manner of other treatment since the introduction of the new method. There are, of course, some contra-indications to the use of the drug. Severe precedent kidney disease is one; but so it is to etherization. His record now amounts to over 260 cases, and some at least of the brilliant results obtained must have been due to the Antitoxin alone. He would be no more willing to attend a case of diphtheria to-day without being allowed to use Antitoxin, than he would be to treat intermittent fever without quinine, or syphilis without mercury.

Finally, Dr. Fischer recounts an unfortunate experience with the domestic Antitoxin, and makes a plea for the prescription of a specific kind, of whose purity and reliability there is some guarantee: in exactly the same way as we habitually prescribe drugs prepared by some special manufacturer in whose preparations we have confidence.

At the meeting of the Medical Society of the State of Pennsylvania, held in Chambersburg, in May, 1895, **Dr. Edwin Rosenthal**, of Philadelphia, read "a report of a series of cases of Laryngeal Diphtheria treated by Antitoxin, with and without intubation," of which the following is an abstract. (The Medical News, June 8th, 1895.)

He divides the cases into two groups, one upon whom the operation of intubation was performed, and the other where the operation was not a necessity.

Those cases, ten in number, treated without intubation, all recovered.

Of the twelve cases treated with intubation two died, and ten recovered, a mortality of 16%. Combined statistics before the advent of Antitoxin, in cases treated with intubation, showed a mortality of 72%—that is, 28 recoveries in 100. Dr. Rosenthal's own statistics, in a former paper, showed a mortality of 62%—38 recoveries in 100. In contrast to this the combined statistics of the Antitoxin treatment have shown a marvelous reduction in the death rates.

Dr. Rosenthal found that the German Antitoxin brought quicker reaction than the domestic, and for that reason was to be preferred. His conclusions are:

"Antitoxin is a specific for diphtheria. In early cases, those seen one or two days after infection, no death rate should be recorded. In laryngeal diphtheria, the so-called membranous croup, Antitoxin is especially indicated. It should be used in every stage and at any date of the disease, no matter how late we see the case. Its influence can be proven, for cases of laryngeal diphtheria perish from suffocation long before any toxic symptoms can be manifested. For that reason he strongly urges the necessity of prompt intubation when indicated, even if before the injection of the Antitoxin."

Regarding the use of the Antitoxin, he says:

"Do not delay or hesitate in this disease because the case is not so bad, or because it might get well without it, but use it at once; the earlier it is used, the more certain is its success."

Dr. Voemel (Zeitschrift für Aertzliche Landpraxis, 1895, No. 6) has published a short preliminary notice on the treatment of puerperal fever with Diphtheria Antitoxin. The hopelessness of treatment in severe cases of this kind led him to try it in three cases. The results were surprisingly favorable; the fever fell with remarkable rapidity; the pulse and the local phenomena improved; the author desires that this harmless remedy be further tried. 660 to 1,000 units were employed.

Careful tests carried out by **Dr. M. Charteris**, Professor of Materia Medica and Therapeutics, University of Glasgow, vide report of the 63d annual meeting of the British Medical Association (British Medical Journal, Aug. 17, 1895), show that Schering's (Aronson's) Antitoxin was found to be twice as strong as Behring's No. 2, and four times as powerful as that

of Burroughs & Wellcome, and that from the British Institute of Preventive Medicine.

Dr. G. C. Crandall, Professor of the Principles and Practice of Medicine, Marion-Sims College of Medicine, St. Louis, Mo., has published in the Journal of the American Medical Association, July 27th, 1895, an excellent resumé of the statistics of the Diphtheria Serum Therapy, compiled from the Library of the Royal College of Surgeons of England. There is not the remotest doubt, the author says, that the mortality is much lower than it was before the treatment was inaugurated. The following table embodies the results of his collected statistics.

		No. Cases treated with Serum	Mortality in per Cent.	Previous Mortality in per Cent.
Vierordt.....	Heidelberg	55	14.6	58.0
Ganghofner.....	Prague	110	12.7	50.0
Widerhofer.....	Vienna	100	25.3	42.8
Kossel.....	Berlin	350	16.7	34.7
Baginsky (quoted by Virchow).	Berlin	303	13.2	47.8
Sonnenburg.....	Berlin	107	20.6	27.6
Aronson.....	Berlin	190	14.0	37.0
Ranke.....	Munich	85	18.8	48.5
Soltmann.....	Leipsic	122	18.0
Risel.....	Halle	114	8.0
Roux, Martin, and Chaillou...	Paris	300	26.0	51.7
Lebreton.....	Paris	258	12.0
Moizard.....	Paris	231	14.7	50.0
Washbourn, Goodall, Card and others.....	London	195	18.6	31.1
White.....	New York	32	25.0	42.7
Withington.....	Boston	80	16.0	45.0
Total number of cases.....		2,632		
Average mortality, per cent.....			16.8	
Previous average mortality, per cent.....				42.0
Collective report of other observers in different countries.....		4,022	17.1	

In regard to the **immunizing effects** during epidemics of diphtheria in institutions, some very interesting papers have been read before the "American Pediatric Society," at its seventh annual meeting at the Virginia Hot Springs, May 27, 1895, by **Dr. L. Emmett Holt** and **Dr. A. Seibert** of New York, and **Dr. F. Gordon Morrill** of Boston.

These well-known specialists of children's diseases showed in their reports, which were published in the "Archives of Pediatrics," July, 1895, that injections of Antitoxin for immunizing purposes are of inestimable value. Dr. Morrill described the results obtained from 438 immunizing injections of Antitoxin at the Children's Hospital in Boston, of which 109 were of Gibier's serum; 104 of Behring's; 74 of Aronson's, and 151 of the Antitoxin prepared by the Massachusetts State Board of Health. As regards the urticaria, its frequency, severity, time of appearance, and duration varied greatly with the

brand of serum employed. That of Gibier (Pasteur Institute of New York) produced it in 22 per cent. of the cases on the (average) seventh day, and lasting (average) two and a half days. Behring's caused it in but one case, appearing on the eighth day and lasting three days. *Aronson's gave rise to no urticaria.* The serum of the Massachusetts State Board of Health produced in about 4½ per cent. of the cases, an eruption appearing on the (average) second day, and disappearing in a day and a half.

Official Report from the Imperial German Health Department.

From the "Kaiserliches Gesundheitsamt" in Berlin comes the report of the results of the Collective Investigation of Diphtheria Antitoxin for the first quarter (January to April) of the year 1895. Recognizing the fact that the statistics at the disposal of many of the individual investigators have been but small, and realizing the importance of obtaining figures sufficiently large to eliminate the various accidental and subsidiary factors, the Chancellor of the Empire and the Reichstag have arranged that the reports of the various hospitals should be sent to the Department of Health and there be collated and tabulated. In compliance therewith, there have been received for the first quarter of the year 1895, up to the date of June 20th, 2,228 replies from 232 physicians in 191 hospitals. In 1,148 of these cases the diagnosis was confirmed by bacteriological examination.

Of the 2,228 cases treated, 1805 or 81.0% recovered, and 386 or 17.3% died. In 37 cases, 1.7% the issue of the disease was not known at the time that the return was made. The mortality of 17.3% must be characterized as a very low one, since it includes all the complicated cases, and even those that were moribund on admission to the hospitals.

The ordinary diphtheria mortality, according to hospital statistics, is on the average 50%, and the results may fairly be called favorable ones. The previous statistics of cases treated with the serum gave similar figures. Heubner collected from a number of hospitals to the end of January, 1895, 3,036 cases, mortality 20.6%; Baginsky treated 525, mortality 15.6%, and Monti tabulated 3,888 cases, mortality 18.4%.

Grouped according to severity, the following is the result in the 2,228 cases reported on:

Of mild cases there were	749 (33.6%),	of which there recovered	743 (99.2%)
Of medium " " "	336 (15.1%),	" " "	322 (95.8%)
Of severe " " "	1076 (48.3%),	" " "	722 (67.1%)
Of indefinite cases	67 (3.0%),	" " "	53 (79.1%)

As regards the influence of the serum on the general clinical course of the disease the report agrees thoroughly with Professor Baginsky, and cites his words. The phenomena of the disease and its complications were of the usual nature; but they were favorably modified as regards their severity. The entire course of the disease under the serum treatment was a

quieter, and milder one; and the return to a normal condition was quicker than usual. The nature of the process was not changed; but its effect on the general organism was much milder.

The influence of the remedy on the local phenomena in the pharyngeal organs is an unmistakable one, as has been proven by earlier publications. According to Heubner the local malady, in cases not treated with the serum, most commonly gets well at the eighth day; in cases treated with the Antitoxin it occurs at the sixth day. The exfoliation of the membrane is frequently complete by the fourth or fifth day. The present statistics prove the same thing. In a large number of cases the following is noted: "Membranes began to come away on the third or fourth day;" "on the fourth or fifth day the pharynx was entirely clear." In connection with this disappearance of the membrane a rapid decrease in the size of the cervical lymphatic glands was frequently noticed.

Abscesses occurred at the site of the injection in 13 cases. With care and cleanliness they could probably be always avoided. As is well known, Trikresol is added to the serum for the purpose of not only destroying any germs that may have reached it through the air, but also of rendering innocuous any infectious material from the animal itself. And before the Antitoxin is put upon the market, it is subjected to a Government examination, *more especially as regards its innocuousness*. The danger of an accidental inflammation at the seat of the injection is therefore less, in spite of the large quantities of fluid employed, than is the case with the ordinary hypodermatic injections, such as those of morphine.

Finally, the report concludes, our statistics confirm the reports that have been received from all sides, that the Diphtheria Antitoxin is *harmless*. This fact, with the favorable mortality under its use, should encourage its further application.

Further German statistics (Journal of the American Medical Association, August 10th, 1895), read as follows:

The results of treatment in 10,240 cases of diphtheria in the German hospitals and in private practice were recently reported to the Society for Internal Medicine by **Professor Eulenburg**. Of this number 5,790 were treated with the antitoxic serum, with 552 deaths—a mortality of 9.5% for all ages; 4,450 were treated by other methods with 652 deaths—a mortality of 14.7%. By ages, the mortality was, for those under two years, 21.7% by the Antitoxin treatment, 39.7% without; between two and ten years of age, the mortality was 8.8 and 15.2% respectively; for all cases over ten years of age, the mortality was 4.1% under Antitoxin, and 8.8% under other methods. Professor Eulenburg again called attention to the importance of early recourse to the Antitoxin; used within the first forty-eight hours the mortality was only 4.2%; delayed

beyond this period the mortality was increased to 16.8%. These figures must certainly be regarded as a vigorous addition to what Virchow has called the "brute force" of the numerical argument.

CRITICISMS OF THE SERUM TREATMENT OF DIPHTHERIA ANSWERED BY AUTHORITIES.

An objection has recently been raised to the entire serum therapy based on the well known globulicidal action of horse serum. Dr. Joseph Winters and Dr. S. T. Armstrong, of New York, have both expressed their concern that so important and possibly deleterious an effect of the Antitoxin injections have been overlooked.

In an able letter to the editor of the New York Medical Journal, **Dr. S. J. Meltzer**, of New York, shows the baselessness of the objections, and emphasizes the following points:

1. All statements as to the detrimental effects of heterogenous blood, have reference only to the intra-venous transfusion of the blood of another species; as yet no one has ever raised the contention that the subcutaneous injection of foreign blood showed globulicidal effects. Even for the peritoneal cavity, from which absorption certainly occurs far more rapidly than from the subcutaneous tissue, Hayem, the authority cited by Dr. Armstrong, says that the infusion of alien blood into it is of no detriment to the blood of the recipient (*Compt. Rend. t. xxviii., No. 12*). Dr. Armstrong's quotations deal only with transfusion (or direct contact with the heterogenous blood); he is apparently not conscious of the fact that he is confounding intra-venous with hypodermic injections.

2. Even in intra-venous infusion the fatal effect depends largely upon the quantity of the injected heterogenous blood. According to Ponfick (*Virchow's Archiv, Vol. Lxii., p. 303*), dogs died from transfusion of sheep's blood after two hours, if the proportion was 32 grammes (500 grains) of the transfused blood to 1,000 grammes (15,000 grains) of the weight of the receiving animal; after 9 hours the proportion was 20 to 1,000; after 15 hours, 14 to the 1,000; but at 10 to 1,000 no dog died from the effects of the transfusion. Now let us assume that the weight of the seventeen-year-old Miss Valentine, of Brooklyn, who is claimed to have died from the injection of Behring's Antitoxin, was about 100 pounds, or 50,000 grammes; ten grammes of the injected antitoxic serum was only $\frac{1}{5}$ to 1,000. Is there in the entire literature on this subject (not alone since Landois, in 1875, but since Dumas and Prevost, *Annales de chimie, 1821*) a report of the death of an animal or a human being occurring after the transfusion of such a minimum quantity of foreign blood, and occurring a few minutes after the injection?

3. Since the introduction of the experimental study and the practical preparation and application of the Diphtheria Antitoxin, the horse serum has been injected subcutaneously into

rabbits and guinea pigs many thousands of times, certainly more often than in all the experiments on transfusion taken together. As is well known, the rabbit is the most sensitive of all animals to foreign blood; nevertheless, not even once was bloody urine observed after the injection.

Is not that proof enough that the globulicidal powers of the horse serum do not come at all into consideration in the subcutaneous injection of the Diphtheria Antitoxin? The harmlessness of the subcutaneous injection of heterogenous blood serum is probably due partly to the slow absorption from the subcutaneous tissue, and partly to the fact that the foreign blood, while passing the lymphatics, takes or gives up a quantity of certain salts, which, according to H. Buchner (*Centralblatt f. Physiologie*, 1893, No. 7) are essential for the globulicidal power of the alexines.

Finally Dr. Meltzer states that the facts concerning the globulicidal character of the heterogenous blood serum are stated in many text books of physiology, and it is expected of every student of medicine to know something about them. Is it then justifiable to assume, as Dr. Winters and Dr. Armstrong do, that the men, who for years have made a special study of the blood, as a carrier of germicidal properties and acquired immunity, will overlook such a factor of elementary knowledge, a knowledge which can be acquired in a few minutes from any text book? One of these men is Professor Ehrlich, of Berlin, a world-wide and acknowledged authority on the blood. And it so happens that the first publication of Ehrlich, in 1875, was a study of the effects of the subcutaneous injection of blood.

The following is taken from an editorial in the "American Medico-Surgical Bulletin" of April 1, 1895:

Dr. Kolisko, of Vienna, who has made over 1,000 autopsies upon children dying of diphtheria, before the days of Antitoxin, and during the last few months of serum treatment, has carefully studied the organs of 75 fatal cases. He states unhesitatingly that the serum injections exert an indisputably favorable effect upon the diphtheritic process, as shown at the autopsy. Especially is this true concerning its effect upon the diphtheritic membrane, producing a loosening and dissolution of the exudate, with a rapidity which was never seen with other lines of treatment. Concerning the lungs, the heart, and the kidneys, he speaks none the less authoritatively, and confirms the claim of Roux and other observers, that purulent bronchitis and pneumonia, and the degenerative changes in the heart muscle, are in no wise altered by the use of Antitoxin. The effect upon the kidneys was also carefully studied, and it was found that the condition of the kidneys differs in no respect from that found during previous years.

Parenchymatous degeneration of the kidneys is of the same degree, and appears at the same times as before. These conclusions, arrived at by so careful an observer as Kolisko, are

timely, and may well set at rest the recently aroused fears with respect to possible harmful after-effects of the new treatment.

Dr. Van Kahlden (Centralblatt für Allgemeine Pathologie und für Pathologische Anatomie, Feb. 23, 1895, Vol. vi., Nos. 3 and 4) experimented upon a series of rabbits and guinea pigs to determine whether the injection of the Diphtheria Antitoxic Serum in large amounts produced any untoward effects upon the kidneys and heart. The largest amounts used were 16 cubic centimetres given to a rabbit weighing 1,350 grammes, and 12 cubic centimetres to a guinea pig. The kidneys were preserved in alcohol and Flemming's solution. The microscopic examination of all the specimens led Van Kahlden to conclude that no pathological changes were present, and that the serum was absolutely harmless upon the kidneys. When doses of such size produce no alterations one can readily conclude that the ordinary doses, given in proportion to the body-weight and relatively much smaller, are without effect upon these organs. Van Kahlden points out that the kidneys of men may behave differently from those of animals, but calls attention to the fact, that this difference cannot be very great, as the action of the diphtheria toxin is the same upon both. He examined several kidneys from cases treated with the Antitoxin, but found nothing to suggest that they had been damaged by the treatment.

Inasmuch as cardiac paralysis had been several times mentioned as following the use of Antitoxin, Van Kahlden carefully examined the hearts of the animals experimented upon, without finding the slightest pathological change.

DISADVANTAGES OF SOLID DIPHTHERIA ANTITOXIN.

The London Therapist, June 15th, 1895, contains the following, of which we give an abstract: Attention has been called to the importance of appreciating the fact that inert and even dangerous preparations are sold as Antitoxin or serum remedies, as well as the genuine and active medicament. As the therapeutic value of the true remedy becomes more firmly established, so does this question press more to the front; it being evident that the most weighty reason that still keeps honest and fair-minded practitioners from its use, is their personal experience with inferior or bad preparations.

It should now be generally known in the interests of humanity that reliable and active preparations are put up in clear liquid form in small sealed vials, bearing an official guarantee of the antitoxic value, concentration, and aseptic condition of the preparation. The necessity and wisdom of this precaution in insuring the safety of the patient and the reputation of the physician becomes daily more apparent. The new remedy for diphtheria is not only the first representative of a completely new departure in therapeutics, but, because of its want of amenability to ordinary physical and chemical tests, novel and

extraordinary measures must be taken to make it certain that pure and strong preparations only are placed in the hands of the medical profession.

There has been some expectation in the profession that a solid and not a liquid preparation would be supplied. Dr. Aronson at first thought himself that this was possible, but he publicly renounced this idea in a paper read before the Berlin Medical Society long ago. Albuminous bodies of the class to which the Antitoxins belong are of such delicate nature, and are so prone to decomposition, that they suffer a very considerable and variable loss in physiological activity by any process of physical or chemical isolation at present known. Besides this, they *inevitably become contaminated with bacterial life*, and the solution of the solid material is *more liable to cause pain and produce infiltrations*. As Dr. A. P. Ohlmacher (Cincinnati Lancet-Clinic, May 25th, 1895) says: "Desiccated blood serum becomes an ill-smelling, bacteria-laden substance. With the present uncertain state of our knowledge of the chemistry of even the best known proteids, it is scarcely possible that we shall succeed in isolating a substance of whose exact nature comparatively nothing is known—the Antitoxin contained in the blood serum of an immune animal."

Directions for Use.—Schering's (Aronson's) Diphtheria Antitoxin is distinguished from other brands by its prompt and powerful therapeutic action, hence for the cure of diphtheria a comparatively small injection is required.

Dose.—For mild and medium cases: one vial of 5 ccm., representing 500 antitoxic normal units.

For severe or septic cases: the contents of two 5 ccm. vials, representing 1,000 units, should be injected at once.

Further instructions are printed on the wrapper that is around every vial.

Diphtheria Antitoxin (Schering's) is supplied by us in 5 cubic centimeter (80 minims) vials, at **\$1.00 per vial**. This includes packing, postage, or expressage, to all parts of the United States and Canada.

We furnish also the **imported hypodermic syringe of metal, with asbestos piston**, which is most suitable for these injections, and which Dr. Aronson described at the 66th Meeting of the Association of German Naturalists and Physicians at Vienna, at **\$3.00**; or the **Dr. Francis H. Williams' glass syringe with rubber tubing**, recommended by Dr. Louis Fischer, of New York, at **\$1.50**. Both including postage or express charges.

The attention of the medical profession is called to the fact, that, as a guarantee of genuineness, the box containing each vial of Schering's Antitoxin bears the name of

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