Diphtheria Antitoxine "BEHRING."

GUARANTEED

UNDER OFFICIAL SEAL

BY THE

Imperial German Government.

Sole Agents and Licensees for the
UNITED STATES,

SCHULZE-BERGE & KOECHL,

79 MURRAY STREET,

NEW YORK.

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INTRODUCTION.

While there at present exists in the professional mind but little doubt concerning the wonderfully potent curative effect of the Diphtheria Antitoxic Serum presented to the world through the original scientific labors of Prof. Emil Behring, there still seems to be considerable misapprehension in regard to the composition, mode of manufacture, true nature and keeping qualities of this unique biological product. With a view, therefore, of correcting erroneous impressions, and for the purpose, at the same time, of placing before the profession in a comprehensive form all of the available and important facts in regard to the Serum Therapy of Diphtheria we have prepared this brochure. It is, of course, within the limits of such a publication, impossible to reproduce or even consider all of the already voluminous literature concerning the remedy with which the medical press has been teeming for the past year. We have therefore endeavored to collate and compile only such facts, statistics, reports and arguments as seem to have an important bearing upon the subject. We hope that this compilation may prove both of interest and benefit to the medical profession to whom it is respectfully submitted by

SCHULZE-BERGE & KOECHL,

Sole Licensees in the U. S. for

DIPHTHERIA ANTITOXINE-"BEHRING,"

79 Murray Street, New York.

DIPHTHERIA ANTITOXINE-"BEHRING."

The original and genuine Diphtheria Antitoxine-" Behring " is prepared only at the FARBWERKE vorm. MEISTER, LUCIUS & BRÜNING, Hoechst-on-Main, Germany, under the direct supervision of Professors BEHRING and EHRLICH, each of whom guarantees the innocuousness and antitoxic efficiency of every vial before it is given out. *In April, 1895, the* IMPERIAL GERMAN GOVERNMENT *instituted a system of state supervision and control of the serum. Since that time each vial of the "Behring" Antitoxine has been, and will hereafter, continue to be officially guaranteed by the Government, through its specially appointed experts, who witness the entire process of testing the serum, as well as the filling, sealing and labelling of the vials. Each vial bears as a guarantee upon its cap the official governmental control number, as well as the date of the official test of the serum.* The cap is fastened with a lead plummet bearing upon one side the Prussian double eagle, and on the reverse, the number of Antitoxine normal units contained in the flask (for instance, 200-600-1000-1500). The labels upon the vials are printed in different colors in order to distinguish the respective strengths of the serum, as expressed in Antitoxine units (for instance, Yellow-200, Green-600, White-1000, Red-1500). The current operation number and the number of Antitoxine units in the vial are also indicated thereon, together with the name and trade-mark of the Farbwerke and the firm name of SCHULZE-BERGE & KOECHL, New York, Sole Agents for the United States of America. *In order to be certain of obtaining the genuine "Behring" serum, it is advisable to specify Diphtheria Remedy,* "BEHRING," *or Diphtheria Antitoxine,* " BEHRING," and to *observe that each vial bears the above described label, which we herewith reproduce in facsimile :*

Each box containing a vial bears a similar label, as well as the current operation number, the official control number and the date of official test.

Also the number of Antitoxine normal units contained in each cubic centimetre and the number of cubic centimetres in each vial.

Wrapped around each vial is a printed circular giving full and complete directions concerning dosage, method of administration, &c.

STABILITY, KEEPING QUALITIES, ETC.

As Diphtheria Antitoxine-" Behring " has now been on the market for over 1½ years, a sufficient time has elapsed to enable the formulation of definite conclusions in regard to its stability, keeping qualities, &c. It has been satisfactorily demonstrated by bacteriological tests, trials upon animals and clinical experience that the serum, as prepared at the Farbwerke retains under favorable conditions both its sterility and antitoxic efficiency for a period of one year at least. It should always be protected from the influence of light and extreme heat; in other words it should be kept in a cool and dark place.

Freezing, while it tends to render the serum turbid or milky by precipitating its albuminoid constituents, does not affect its therapeutic virtue. This being the case, the druggist or physician can procure a stock in advance, in order to be prepared for emergencies, without fear of having the serum deteriorate or become unfit for use within the limit of time above mentioned.

THE PREPARATION OF DIPHTHERIA ANTITOXINE-"BEHRING"

At the Farbwerke vorm. Meister, Lucius & Brüning, Hoechst-on-the-Main, Germany.

As early as August, 1893, the Hoechst Farbwerke began to take marked interest in Behring's studies and to prepare, on a small scale, his Diphtheria-Antitoxine. After Kossel published his valuable article in May, 1894, they immediately commenced to devote themselves to the preparation of Antitoxine-" Behring " on a large scale and erected for the purpose a number of large buildings, which were dedicated in the presence of Robert Koch, Behring himself, Dr. Weigert and others.

Dr. Libbertz is the head of the sero-therapeutic department and Dr. Laubenheimer, director of the laboratory.

There are two main buildings in red brick not far from the main factory; the front one, one story high, is situated on the street, and contains all the laboratories; the rear one is fitted up as a stable for the horses; these two buildings are connected by a covered passage-way about 35 feet long. All parts of both buildings are heated by steam and lighted by electricity. Plenty of air and daylight can be admitted.

In the front building is First: The *Rinsing-room*, which is provided with running cold and hot water, basins, and large frames for the vessels which are cleansed immediately before and after use in the operating-room.

Second. The *Sterilizing-room*, which contains a dry sterilizer of very large dimensions (7 feet by 5) used for sterilizing the glass vessels. A steam sterilizer of the same size is used for sterilizing in live steam. Sterilizers of such size are necessary on account of the large quantities of culture media required, vessels containing 5-10 quarts being in general use.

Third. The *Incubating-room* (17 by 35 feet). Along the entire length of the walls are rows of incubators of ordinary size, and in the centre another double row, back to back, in all 36 in number. In these incubators the toxine is cultivated in large quantities. The great number of small incubators were selected in preference to a single large one, such as are used in other laboratories, because, on account of the great sensitiveness of the Diphtheria bacilli, the temperature of every single incubator must be carefully regulated; in order to regulate the temperature accurately every incubator has a separate gas supply.

Fourth. The *Laboratories*, consisting of two rooms fitted up with the most recent inventions and up-to-date in every respect. In one of these rooms a careful record is kept of all the animals as hereinafter described.

The walls are fitted up with closets for the storage of the toxines used for the inoculations which are carefully secluded from the air and light in large sealed jars. As large quantities of these toxines are frequently injected into an animal at one sitting an ample supply in various degrees of toxicity is always kept on hand.

Fifth. The *Cooling-room* in which the antitoxine is prepared. The blood taken from the horses is caught in sterilized pint or quart graduates; small vessels are used in order to facilitate the separation of the serum from the blood-cells. After twenty-four hours when the separation is complete the serum is filtered into large sterilized vessels and centrifuged, and thus thoroughly purified; it is then tested carefully as to its sterility. The antitoxic power of the serum is then determined by inoculating guinea-pigs. In order to better preserve the serum, 0.5 per cent. carbolic acid is added.

Sixth. *Stable for guinea pigs* and small animals used in experiments.

In the rear building is

First. The *Operating-room* (30x22 ft.) well lighted, provided with running water and fitted up in all its details (plastering, floors, etc.) with especial regard to the attainment of perfect asepsis. The horse to be operated upon

is fastened in a special stall; the hair is carefully removed and the skin thoroughly cleansed and disinfected. When blood is to be taken from an immunized animal the jugular vein is first compressed, causing it to swell, a slightly curved trocar about two inches long and 3-25 of an inch wide is thrust into the vein and the escaping blood is caught in sterilized vessels as described above. The operation causes but little pain. As soon as the trocar is withdrawn the small wound closes spontaneously.

Second. The *Stables*, which are divided into two parallel wings, each 113 ft. long, and 35 ft. wide. Light, heat and ventilation are obtained by means of the most modern appliances. All new purchases are watched for three or four weeks in a temporary stable until they prove to be free from all disease, after which they are transferred to the regular stable. A history of each horse is carefully kept. This history contains a record of the animal's temperature (taken twice a day) its weight, (determined once a week), the time, quantity and toxicity of every inoculation, and amount of the serum obtained at each operation.

With such care the horses keep in fine condition, and even after an inoculation with a large quantity of toxine or after being bled to the amount of three or four quarts at a sitting, appear out of sorts but for a day or two. Over eighty horses are at present in service, some of them continuously for two and a half years, and the number is constantly being augmented.

Third. The *Shipping Department* is in a new and isolated building which is a half mile distant from the laboratory in order to render it impossible to accidentally mix toxines or other substances with the antitoxic serum. Here the vials are filled, sealed, labeled and stamped. Every part of the work is done in such a manner as to absolutely insure the sterility of the serum. Each strength (I, II, III) is handled in a separate room, in order to avoid any error in the preparation of a given vial.

The graduates employed in filling, the vials, corks, etc., are thoroughly sterilized. Not a hand comes into direct contact with the serum during all of these manipulations. The work is divided among ten persons in such a way, that one tends to the filling, another to the corking, and still another to the labeling of the vials, etc., etc.

Every vial is numbered and recorded; the animal from which it was taken, and the date of the same being entered opposite its number in the record-book.

As a last precaution on the part of the Farbwerke, one vial of the serum obtained at each operation is kept for examination in case undesirable effects from an injection are complained of. In such a case the number of the vial containing the serum should be reported to the factory. Before the serum is put upon the market it is subjected to tests as to its sterility, antitoxic efficacy and relative strength, not only by Profs. Behring and Ehrlich, but also by the experts officially appointed by the Imperial German Government who guarantee the product in every respect as before described on Page —.

In the course of a paper on Diphtheria, Dr. I. N. Love, of St. Louis, said: Behring undoubtedly originated and developed the antitoxine treatment of diphtheria. Roux, who is a skilled bacteriologist, and presented remarkable results in a definite manner at the International Congress of Hygiene at Buda-Pesth last summer, freely accords the credit of this discovery to Behring. The literature that has been presented during the past few months in favor of the blood serum therapy as applied to diphtheria, is enormous, and no candid careful observer can ignore the fact that the great bulk of it is favorable.

Portion of Editorial A. M.-S. Bull., Jan. 15, 1895.—To Professor Behring, of Berlin, is due the honor of making these discoveries and putting them to a successful test. The honor is the greater for the reason that it was no chance discovery, but the legitimate result of logical reasoning. Suf-

fice it to say, in this connection, that he established a complete system for procuring and administering the attenuated virus, the modus operandi of which and the theory of whose efficacy are already pretty generally understood.

Dr. H. W. Berg, of N. Y. City, in a paper before N. Y. Academy of Medicine said: Behring should have the credit of first discovering the fact that animals rendered immune to diphtheria contained a substance which would neutralize the toxine of diphtheria. Upon the application of this discovery to the human being depends the recently advocated serum therapy for diphtheria.

BLOOD-SERUM THERAPY IN DIPHTHERIA.

Read before the Chicago Medical Society, December 3d, 1894, by G. E. Krieger, M.D., Surgeon to the Chicago Hospital.

The blood-serum therapy of Behring, Roux and others is based upon the fundamental fact, that the blood of an animal which has been rendered immune against a certain disease has the power, when injected into another individual of the same or other species, to immunize the latter also against that disease. Suppose, for instance, we have a guinea-pig immunized against tetanus or diphtheria bacilli and injected some of its blood into a rabbit, the latter would be protected for a certain length of time against infection of the germs or their poisonous products. Such products are especially dangerous and deleterious to the organism in diphtheria. If one intends to immunize an animal against the effect of diphtheria bacilli it will be necessary to increase its resistance against the toxic products of the germs, the toxins.

An increased resistance and finally an immunity is obtained by applying systematically such doses of the poison to the animal as are sufficient to make the latter ill without causing its death. As the tolerance of the animal increases, so does the immunizing power of the blood-serum increase, which has been proven by Ehrlich in reference to the vegetable poisons, and by Behring with bacterial toxins. The way of proceeding for the purpose of immunizing animals against diphtheria as advised by Behring, Ehrlich and Wasserman is by hypodermic injections of at first very small, and later, gradually increasing doses of diphtheria cultures and diphtheria toxins.

The latter is prepared by inoculation of beef-tea in large flasks with diphtheria bacilli. After the flasks have remained in an incubator for three to four weeks 0.5 per cent. carbolic acid or 0.33 per cent. trikresol is added, by which the germs are killed and precipitated to the bottom of the flasks. The liquid then contains the toxine in solution. From this solution the toxine can be prepared as a dry substance or it can be used while dissolved in the fluid. The effect of injections of the toxine, is fever, local swelling and the production of antitoxine. The latter is found in the blood of the animal after each injection and increases in quantity with the number of injections. This treatment is continued until the animal possesses a sufficient quantity of antitoxine. In order to estimate its efficacy, it is necessary to tap the animal, from time to time, for a small amount of blood with which experiments are made on others. Behring and Kitasato were the first who observed that such antitoxine is able to neutralize the effect of toxine, when mixed in a tube.

The mode of valuation of the diphtheria antitoxine, as advised by Ehrlich is this; of a toxine, the efficacy of which upon a guinea-pig is known, a certain quantity ten times the minimum fatal dose, which may be 1 gramme is mixed with a number of different quantities of the blood to be examined, for instance 0.5, 0.25, 0.15, 0.10 gr., and with these four mixtures four guinea-pigs are inoculated. The result will be that the one which received the largest dose of the blood together with the toxine shows no reaction; the one that

received the second largest dose will suffer from an acute local inflammation, followed by necrosis, but otherwise be not much affected. The third will probably become quite sick and the one which got the smallest quantity of blood will die in forty-eight hours, from the same dose of toxine as the other received. Hereby we can find out which amount of blood of the first animal is sufficient to neutralize a certain quantity of toxine, and so the value of serum can be established. This is simplified if one has a material of a standard strength with which to compare others. Behring and Ehrlich therefore prepared a serum of which 0.1 gr. is sufficient to neutralize ten times the fatal dose of toxine (for guinea-pigs) and this they called " normal therapeutic serum."

When the value of the serum has once been established by a series of experiments as stated above, the animal is tapped for a larger quantity of blood which, being received in sterilized vessels, is placed on ice until coagulation has been completed and the serum been separated as a clean yellowish fluid. This with 0.5 per cent. carbolic acid now presents the material to be used for therapeutic purposes. The most suitable animals for which the serum may be prepared are horses and goats on acount of their susceptibility, as well as because of the large quantity they are able to furnish.

Starting from the fact that the antitoxine must be given in certain proportions to the toxins present and that it works effectually only if the organism has not too long been preoccupied by the toxine it is evident that a curative effect can only be expected in an early stage or in a milder form of the disease. If the diphtheritic process already affects the bronchi and lungs, so that even tracheotomy is of no avail, the serum-therapy will do no better. Neither can recovery be secured if complications possibly due to infection with other germs have set in.

Equally doubtful is the prognosis if the toxins have circulated for a longer period, say three to four days because their paralyzing effect upon the nerves and ganglia of the heart can no more be eliminated. As, however, the application of the serum is an entirely harmless procedure it seems to be advisable to use it even in advanced cases, provided they are not perfectly hopeless. This has been made a principle in the antitoxine treatment in several hospitals of Berlin, with the effect that according to the latest report, the mortality of all cases has been reduced more than 20 per cent.

In regard to the effect of the injections it may emphasized that they are absolutely innocuous. After 5,000 injections but three abscesses have been observed. The temperature does not increase nor are other general disturbances noticed. Locally a tenderness or a harmless skin eruption is sometimes observed which, however, disappears after a day or two. Concerning the effect upon the tonsils and throat, the white plaques at first seem to spread after the injections; on the second day, however, the mucous membranes discharge the infective material and the swelling of the glands is also reduced. Besides this local effect, a change in the general feeling takes place soon after the injection. Pulse and temperature return to normal condition in early cases within the first forty-eight hours, dizziness and general weakness disappear, and the children soon become convalescents

The preferable place for the injections is on the lateral part of the chest, below the axilla, where on account of the soft subcutaneous tissue even large quantities are absorbed. The application is made with the usual aseptic precautions.

The antitoxine prepared as advised by Behring in the chemic works in Höchst-am-Main is put in different flasks, hermetically sealed, which bear on the label a mark as to the efficacy of their contents.

No. 1 contains a serum with 600 immunizing units, to be applied only in fresh cases on the first or second day.

No. 2 possesses 1,000 immunizing units to be used in more serious cases on the first or second day or in less serious cases of longer standing.

No. 3 possesses 1,500 units, and is meant for adults or very severe cases of children. As a rule but one injection is given. If this, however is found ineffective, another one should be applied the next day. It is usually unnecessary to give an additional treatment, either locally or internally.

RECENT STATISTICS.

An Official Report of the Imperial German Government Board of Health has lately been issued, which is of considerable value at the present time as facilitating a clearer judgment on the value of antitoxine in the treatment of diphtheria.

In England there is great difficulty in forming an opinion from the individual observations published in the medical papers, for it is to be remembered how widely different in quality and antitoxic value are the serums employed.

In Germany, however, the Imperial Board of Health has taken the control of all serum into its own hands, and all admitted for therapeutic use is required to contain at least 100 units of immunization in each cubic centimetre, and all of inferior strength is destroyed. The approved serum is filled into vials by the examining official, who attaches to each bottle his lead seal.

The antitoxine thus issued to medical men is uniform in strength and composition, and the official report quotes 2,228 cases under observation, which were treated in 191 hospitals, by 232 medical men during the months of January, February and March of this year.

Grouping the cases reported according to the severity of the attacks, the following brief summary is obtained:

Mild cases, 749 (33.6 per cent.) of which 743 or 99.2 per cent. recovered.

Medium cases, 336 (15.1 per cent.), of which 322 or 95.8 per cent. recovered.

Severe cases, 1,076 (48.3 per cent.), of which 722 or 67.1 per cent. recovered.

Unclassified, 67 (3 per cent.), of which 53 or 79.1 per cent. recovered.

In the above classification :

MILD includes such cases as exhibit on the first or second day a moderate extent and thickness of membranous growth, while the mucous membrane is not attacked in more than one place, the swelling of the glands is slight, and the general symptoms are only of a feverish nature, without any complications of debility of the cardiac or nervous systems—moreover, the child must be above four years of age.

MEDIUM includes cases where the membranous growth has developed on several places, or where the affection has commenced in the nose, and progressed downward, the glands are swollen and painful, the pulse is small and frequent, besides fever, the countenance is pale, and the facial expression anxious—moreover in all cases where the child is between the ages of two and four years.

SEVERE includes cases where the membrane has extended over palate and uvula, and the glandular swelling to the angle of the lower jaw, while there is a loss of strength, a very rapid pulse, and weak heart sounds; also all suckling children.

Tables are given which present an analysis of all of the cases according to the age of the patients, which is important for a correct appreciation of the results.

In the following table the cases are arranged in the order of the stage of the disease at which the first injection was made:

	Total.	Recovered.	Died.	Mortality. Per Cent.	
Injection on 1st day of attack	189	173	13	6.9	10.3 per cent.
" 2d "	632	570	47	7.4	
" 3d "	472	393	73	15.5	
" 4th "	254	205	46	18.1	
" 5th "	164	102	58	35.4	
" 6th "	97	63	32		
" 7th "	41	28	13		
" 8th "	38	28	10	30.0	
" 9th "	43	31	11		
" 10th "	8	6	2		
" 11th "	8	7	—		
" 12th "	5	3	2		
" 13th "	1	1	—		
" 14th "	2	1	1	18.8	
" 15th "	12	11	1		
" 16th "	1	—	1		
" 19th "	2	1	1		
" 29th "	1	1	—		
Unknown	258	181	75	29.1	
Total	2,228	1,805	386	17.3	

Naturally only the statements of the parents or guardians of the children are available for determining the date of the commencement of the attack, and it can generally be assumed that the actual commencement is earlier. In the majority of cases besides the antitoxine injections other more or less indifferent treatment was also employed; e. g., painting, gargling, etc.

A third table shows that the cases bacteriologically examined are fairly proportional to the total mortality, but the mortality among pure diphtheria cases was smaller than such where a mixed infection was determined.

There is strongly shown the necessity of having a fully-developed antitoxine having a capacity of 100 immunization units in every cubic centimeter as giving the maximum of remedial substance with a minimum of objectionable ballast. Of such an antitoxine a single dose of 5cc. once injected will satisfy all requirements of the ordinary medium type of attack.

Borger (*Deutsche medicin. Wochenschr.*, 1894, No. 48, p. 902) has reported the results obtained from the employment of Behring's serum at the medical clinic of the University of Greifswald. Thirty cases were treated between August 6 and November 3, 1894, in all but two of which diphtheria-bacilli were found. Two cases died, a mortality of seven per cent.; 28 recovered, 93 per cent. Tracheotomy was necessary in 5, one of which died. Among 313 cases of diphtheria treated from October, 1893, to September, 1894, 46 died, a mortality of 14.5 per cent. Deducting 20 cases treated with the antitoxine and 70 others in which either bacteriologic examination was not made or the diagnosis was not indubitable, there remain 223 cases, among which there took place 46 deaths, a mortality of 20 per cent. The employment of the antitoxine was as a rule, followed by improvement in the appearance of the diphtheritic process and by reduction of temperature, but the albuminuria was not prevented, and no direct influence upon the heart was observed.

Behring—In support of the utility of the antitoxine in the treatment of diphtheria (*Deutsche medicinische Wochenschrift*, 1895, No. 38, p. 623), has collected from official sources the following statistics, showing the reduction in the mortality from diphtheria in Berlin, both in and out of hospitals, since the introduction of the antitoxine:

	1891	1892	1893	1894	1895 7 mos.
Number of cases of diphtheria treated in the city of Berlin	3502	3772	4296	5240	3111
" deaths	1144	1376	1577	1496	495
Per cent	(32.6)	(36.5)	(36.7)	(28.5)	(15.9)
" cases of diphtheria treated in Berlin hospitals	1727	2120	2403	2900	1666
" deaths	613	867	931	611	250
Per cent	(35.5)	(40.9)	(38.7)	(21.1)	(15.5

Extended investigation shows that the mortality from diphtheria in Berlin

in the year 1895 was two-thirds less than in the previous seventeen years, during which careful official statistics have been collected.

The following figures show the results obtained in the surgical clinic of Prof. Bose at Giessen in the treatment of 112 cases of diphtheria with the antitoxine:

	All cases. Died.	Tracheotomized. Died.	Not Tracheotomized Died.
Jan. 1, 1890, to Jan. 1, 1893	93 48	84 45	9 3
Per cent	(51.6)	(53.5)	(33.3)
Jan. 1, 1893, to Jan. 1, 1894	186 82	148 78	38 4
Per cent	(44.0)	(52.7)	(10.5)
Jan. 1, 1894, to Oct. 26, 1894	144 54	91 49	53 5
Per cent	(37.5)	(53.8)	(9.4)
Oct. 27, 1894, to July 31, 1895	112 9	52 8	61 1
Per cent	(8.03)	(15.2)	(1.6)

Statistics in Berlin.—Dr. Behring has recently published a comparison of the results of the treatment of diphtheria in two of the Berlin hospitals. In the Charité, where antitoxine was employed, there were 299 patients with 53 deaths, or 17.7 per cent., in the Bethania Hospital, where antitoxine was excluded, there were 249 patients with 112 deaths, or forty-five per cent.

Korte (*Berliner klinische Wochenschrift*, 1894, 46 p. 1039) reports the results obtained in the treatment of 121 cases of diphtheria with the antitoxine. He divided the cases into three groups: (*a*) severe cases; (*b*) cases of moderate severity; (*c*) mild cases. Of the whole number recovery ensued in 81 (66.9 per cent.), and death in 40 (33.1 per cent.); while from June, 1890, to December 31, 1893, among 1160 cases of diphtheria the proportion of recoveries was 54.9 per cent., and that of deaths 45.1 per cent. In the intervals between the periods of treatment with the antitoxine, at a time when none of the remedy was to be had, among 106 cases there occurred 49 recoveries (46.2 per cent.), and 57 deaths (53.8 per cent.) Considering 121 cases treated with antitoxine according to their severity, there occurred among (*a*) 43 severe cases, 41.8 per cent. of recoveries, and 58.2 per cent. of deaths, among (*b*) 47 cases of moderate severity, 70.2 per cent. of recoveries, and 29.8 per cent. of deaths; and among (*c*) 31 mild cases, 96.7 per cent. of recoveries and 3.3 per cent of deaths. Fifteen of the cases occurred in children under 2 years of age, with 8 recoveries and 7 deaths. Tracheotomy became necessary in 42 cases on account of threatening dyspnea, of this number 20 (47.6 per cent.) recovered and 22 (52.4 per cent.)died, as compared with 22.5 per cent. of recoveries and 77.5 per cent. of deaths in previous years. Of 108 children under 2 years of age in whom tracheotomy became necessary between June, 1890, and March 31, 1893, 10 (9.2 per cent) recovered; while of 8 within the same age-limits treated with the antitoxine, 3 (57.5 per cent.) recovered. Fourteen severe cases came under treatment within the first three days of the disease. Of these 11 recovered, while 3 died. In 29 others the treatment could not be instituted earlier than on the fourth day. Of these but 7 recovered, while 22 died. Twenty-three cases of moderate severity came under treatment within the first three days of the attack. Of these 18 recovered and 5 died. Twenty-two others did not come under observation until after the fourth day. Of these 14 recovered and 8 died. In the one mild case that terminated fatally diphtheria-bacilli were not found in the exudate.

It appeared that in some cases general intoxication took place so rapidly as to render useless the employment of the antitoxine when the cases came under observation. It also appeared as if the results were better when the initial small dose (200 immunity units) was increased. In the fatal cases death was due to causes over which antitoxine was capable of exerting no influence. Nephritis was the most common complication. It was not observed that the treatment had any influence upon the temperature or upon the local condition, although the injections were soon followed by distinct improvement in the general condition.

Soltmann (*Deutsche medicinische Wochenschrift*, 1895, No. 4, p. 53) reports that from April 1 to December 31, 193 cases of diphtheria were treated in the Children's Hospital in Leipsic, with 50 deaths, a mortality of 27½ per cent. During the last five months of this period, when most of the children were treated with the antitoxic serum, there were 22 deaths among 122, a mortality of 18 per cent. Among those treated with the serum the mortality was 14.6 per cent., while among those treated with other measures the mortality was 27.2 per cent. In the first four months there were 28 deaths among 71 cases, a mortality of 39.8 per cent.

Ten Thousand Cases.—The New York *Herald's* European edition publishes deductions drawn from statistics collected by a Berlin physician, Dr. A. Eulenburg, of diphtheria cases treated with antidiphtheritic serum between October 1, 1894, and March 31, 1895, in private practice. "Out of 10,240 cases of diphtheria reported to him, 5,790 were treated by the antitoxic serum, and 4,450 by other methods. The report says that of the 5,790 that formed the first group 552 died—that is to say, 9.5 per cent.; of the 4,450 patients of the second group 652 died—that is to say 14.6 per cent. The compiler is of opinion, however, that the cases treated by serum were mostly bad cases of diphtheria, while those treated by the other methods were not so serious. This inference is rather confirmed by the report of Dr. Kurth, of Bremen, who had only 6.8 per cent. of deaths among patients treated by serum, but 24 per cent. of deaths among the others." Dr. Eulenburg's statistics show also that the efficacy of the serum treatment is greater when it is begun in the very early stage of the diphtheritic attack. Thus the total death rate among the patients with whom the serum treatment was begun on the first or second day of the attack was only 4.2 per cent., whereas among patients who did not receive an injection of serum until the third day of the complaint, or even later, the death rate was four times as large (16.8)per cent.). In cases of children less than 2 years old, the relative difference in the figures is still marked.

Huebner (*Deutsche medicin. Wochenschr.*, 1895, No. 42, p. 687) reports the treatment of 117 cases of diphtheria with the antitoxine in addition to those previously reported, making a total of more than 300 cases. Among the 117 there were 12 deaths—10.2 per cent. There were 97 cases of pure diphtheria, with 10 deaths (10.3 per cent.); and 20 cases of complicated diphtheria, with 2 deaths (10 per cent.). Among 220 cases treated from May, 1894, there were 25 deaths—11.4 per cent. There were 174 cases of pure diphtheria, with 15 deaths (8.6 per cent.); and 46 cases of complicated diphtheria, with 10 deaths (21.7 per cent.). Among the 110 uncomplicated cases treated between the first and third days there were but 6 deaths (5.4 per cent.).

Official statistics show that the mortality from diphtheria in the cities of Berlin, Dresden, Leipsic, Munich, and Hamburg during the first half of 1895, *was conspicuously lower, both absolutely and relatively, than during any year covered by the records, although the whole number of cases of the disease, in the city of Berlin, for instance, was larger and the proportion of cases received into the hospitals was smaller.*

Diphtheria-Serum Treatment.—It was natural that this subject should be discussed once more at the great meeting of German scientists and physicians, and that its introducer should be Dr. Behring himself. Without following either the introductory address or the subsequent papers and discussion too closely, it is sufficient to say that, on the whole, there was an air of satisfaction in dealing with the subject. Speaking of the report of the Collective Investigation Committee, Dr. Behring claimed that the mortality reported was 9.6 per cent. higher than it would have been if the cases in which the prognosis was bad had not been specially selected for the serum treatment. The most convincing reports had been received from Giessen and Amsterdam. The former showed that the mortality in cases where

tracheotomy had been performed had been reduced by serum treatment from 53 to 15 per cent., and, further, that the proportion of cases requiring tracheotomy had been considerably reduced, as by timely use of large doses of serum the spread of the disease to the larynx had been prevented.

The expression in regard to the use of the material as an immunizing agent had been of a somewhat Utopian character; he had reckoned that the requirements for this purpose in Europe and America would be from one to two million curative doses. Thanks to Ehrlich, the Höchst factory would be able to turn out over a million such doses. The most important and most recently noted point was the qualitative improvement. Whilst the curative dose had been hitherto contained in 5 cubic centimetres (1¼ drachms) of serum, the Höchst factory now manufactured one in which the dose was contained in only 1 cubic centimetre (15½ minims); ½ cubic centimetre (7¾ minims) was, therefore, sufficient for immunization. From this serum no unpleasant accompaniments need any longer be feared.

Dr. Soetman said that the efficacy of antitoxic serum can no longer be denied. The statistics in Leipzig had been strikingly favorable, in spite of the serious character of the disease.

Behring, in reply, said that he found carbolic acid the only reliable disinfectant in all cases. It was the only one he made use of, especially as, since a concentrated serum was used, not much was required in the shape of antiseptics.—*Medical Press and Circular*, October 16, 1895.

Witthauer (*Therapeutische Monatshefte*, 1895, Heft 2, p. 67) has reported the employment of the antitoxine in the treatment of thirty-six cases of diphtheria, with five deaths.

Dr. Louis Fischer, of New York, who has probably used antitoxine as extensively as any other physician in this country, says that before the introduction of this remedy his mortality in diphtheria was about 55 per cent. Since his use of antitoxine, his mortality has been reduced to 15 per cent., and he now declares that he would as soon think of treating intermittent fever without quinine, as to treat diphtheria without antitoxine.

Schroeder's experience has been quite favorable. In the city hospital of Altona, from September, 1894, to March 1, 1895, he injected 63 cases of diphtheria, 8 of which died (12.69 per cent. mortality). The Klebs-Löffler bacillus was found to be present in all but 7 cases, the diagnosis in the latter being clinical. Two of these died, so that, excluding all 7, the mortality of the true diphtheria cases was 10.71 per cent., as opposed to 29.41 per cent. for 1889, the lowest of the seven preceding years.

In 31 of the 63 cases tracheotomy was done, with a mortality of 3, or 9.67 per cent. These 3 were under two years of age, and in 1 no bacilli were found. Excluding this 1 and 1 recovery where there were no bacilli, the mortality of the tracheotomies was 6.55 per cent.

The prognosis, based on the usual clinical manifestations, was fixed as good in 15, doubtful in 20, and grave in 28 cases. Involvement of the larynx did not occur in any case after the injection.

Behring's serum was injected in all of the cases, solution No. 2 (1,000 units) being used for the most part. A sudden fall of temperature was rarely observed. The average duration of membrane after the injection was 4.9 days; the shortest being 2, the longest 10 days. In the tracheotomies the tube was worn, on an average, 6.4 days, as contrasted with 10.7 days for the same period of the preceding year.

The local treatment consisted in the application of carbolic acid and glycerin, equal parts, where the membrane was thick. In other cases a solution of chlorinated lime was used as a gargle.

In 44 cases, 69.8 per cent. albuminuria was present, 6 cases alone showing a true nephritis. In the corresponding period of the preceding year 58 per cent. of cases showed albuminuria; the increase being possibly due to

more careful study, as all cases were counted where even a trace of albumen was found.

Erythema multiforme was observed in 2 cases, and an urticaria in 5, usually seven or eight days after the injection.

ONE HUNDRED CASES TREATED WITH BEHRING'S SERUM.

Widerhofer gives the ages of these one hundred cases, which varied from one year to fourteen years; the larger number being less than five years old. He states the mortality, which was 24 per cent., and then analyzes the 24 deaths very carefully. A probable prognosis was made on the day of the first injection; and the writer divides the prognosis into four classes, Nos. 1, 2, 3 and 4, the latter class of cases having an absolutely unfavorable prognosis.

Prognosis No. 1	22 cases, mortality 3
Prognosis No. 2	36 cases, mortality 5
Prognosis No. 3	26 cases, mortality 6
Prognosis No. 4	16 cases, mortality 10

In the cases which appeared to be very light the antitoxine was not used, so they do not fall into this scale. In all the cases which come under prognosis Nos. 1 or 2, the writer injected a bottle of Behring's serum No. 1, and usually repeated the injection twelve or twenty-four hours later. If the course of the disease on the next day did not appear sufficiently favorable as regarded the removal of the membrane or the quality of the pulse, a third bottle was used. In very rare cases the writer obtained or thought he obtained his end with only one injection. In those cases where the symptoms of poisoning were marked and the local condition bad, Professor Widerhofer used Behring's serum No. 2, and followed it according to circumstances with the same number or with No. 1, once or twice.

In the severest cases where the prognosis fell under Class 4, Behring's solution No. 3 was used, and, according to the needs, was followed by a second and third injection of solution No. 2, or No. 1. In very rare cases a fourth bottle of No. 1 was administered.

The writer found Koch's syringe not easily managed. When an injection was made, the syringe as well as the skin were carefully disinfected with ether, then absolute alcohol, and finally with a two per cent. solution of carbolic acid.

The writer sums up as follows:

(1) He thinks there is not the slightest doubt that Behring's serum influences so favorably certain groups of cases of diphtheria, and those not of the mildest forms, that his serum-therapy deserves to be called a curative method for diphtheria.

(2) Severe cases of diphtheria, even those which present the most severe symptoms of poisoning, such as were described earlier in the article, if the antitoxine has been used within the first three days of the disease, are precisely those in which the favorable and even surprising effect of the serum is best shown. The writer saw many cases of this group recover, which before serum-therapy very rarely happened. But it should be remembered that the cases spoken of were those in which the Klebs-Löffler bacillus was found alone, not associated with other organisms, especially not with streptococci.

(3) There is no doubt that Behring is perfectly right in saying that if the antitoxine is not used until after the third or fourth day of illness its effect is doubtful. Still it must not be imagined that any later use of the serum is perfectly useless.

(4) In cases where the larynx was already attacked, the writer not infrequently saw favorable results in the beginning of the stenosis or very soon after, but if the disease had spread farther into the larynx such results were

only seen in individual cases. If the smaller bronchi were affected or if there was catarrhal pneumonia, no good results were seen.

(5) It follows from what has been said that Behring's serum-therapy will significantly reduce the mortality from diphtheria.

(6) The writer cannot yet say decidedly that the serum has any injurious effect on the child. The serious and frequent degeneration of the internal organs, particularly the kidneys, took place before the use of serum-therapy.

(7) Among the after-effects of diphtheria, paralysis occurs as before the use of serum; but the writer thinks it is not so severe, nor so frequent, but has not had sufficient experience to give an opinion on the matter.

(8) The local injuries arising from the injection of antitoxine were almost nothing, a little redness, urticaria, two abscesses about the place of injection that are not worth mentioning, comprises them all.

Vierordt (*Deut. med. Woch.*, March 14, 1895) has treated 75 cases with Behring's serum. In 61 cases Löffler's bacillus was found, and to this number two other cases must be added, as other children in the same house suffered from diphtheria, bacteriologically proved. From these 63 cases 8 are deducted, either as being moribund on admission or owing to some additional lesion being found after death. The mortality was then found to be fourteen per cent., as against sixty-seven to thirty-seven per cent. in the preceding six years. If the moribund cases were added the mortality would be twenty-five per cent. Among those not tracheotomized the mortality was 2.7 per cent., and among the tracheotomized forty-six per cent., the latter number not being more favorable than hitherto. Of the 24 cases admitted with the larynx intact, only one died, and, indeed, only one of these cases developed the barking cough. Of 5 admitted with a croupy cough and hoarseness, 1 died. Of 23 cases admitted with stridor and retraction of the soft parts, 13 were tracheotomized, in 9 of these 23 cases the symptoms of obstruction passed off without tracheotomy in eighteen to forty-eight hours, a fact hitherto not within the author's experience. Early treatment did not always prevent a fatal issue. The cases did not appear slighter, but even, perhaps, more serious than usual (37 belonged to the severe or very severe group). No noticeable changes were seen in the membrane after the injection. The absence of spread to the larynx was remarkable. In short, a number of severe, even desperate, cases recovered. A favorable action on the heart's action was noted. Albuminuria seemed to play a smaller part than hitherto. Paralysis of the palate was noted frequently, but no extension occurred. The author has never seen a rapid fall of temperature after the injection. A rash was noted fifteen times. A relapse occurred five times. The author concludes that no remote harmful effect was produced by the serum. Although these cases provide no absolute scientific proof, Vierordt is more and more inclined to believe in the specific action of the serum. Its use is imperative. Cases should be treated without waiting for bacteriological proof. Less than 1,000 units should be rarely used in slight cases in the young, and should be repeated in severer cases within twenty-four to forty-eight hours. The author draws attention to the rigid character of the observations which should be made upon cases treated with the serum. It must be some time before the value of the method can be absolutely proved.

Leichtenstern and Wendelstadt (*Munchener medicinische Wochenschrift*, 1895, No. 24, p. 553), presents the results of a careful analytic study of cases of diphtheria coming under observation during a series of years at the Augusta Hospital at Cologne.

The study embraces a series of 123 cases treated with the antitoxine during 1894-95. With this they compare eleven series of similar numbers seen consecutively before, from 1892 to 1894. During the period preceding the use of the antitoxine the average mortality of all cases was 30.9 per cent. (with a

minimum of 25 and a maximum of 39) while during the antitoxine-period it fell to 20.3 per cent—a considerable reduction in the mortality.

During the antitoxine-period tracheotomy was required in 30 per cent. of the cases, with a mortality of 43.2 per cent., while in the previous periods operative interference was required in 32 per cent. of the cases (from 21 to 38.3 per cent.), with a mortality of 64 per cent. (from 56 to 76 per cent.). It is thus clear that while the use of the antitoxine exercised but little influence upon the proportion of cases in which tracheotomy was required, it caused a material reduction in the mortality among cases operated upon.

Bokai (*Deutsche medicinische Wochenschrift*, 1895, No. 15, p. 233) reports the employment of Behring's antitoxine in the treatment of more than one hundred and fifty cases of diphtheria, and analyzes the results observed in one hundred and twenty followed to their termination. Diphtheria bacilli were found in all but five of these. Sixty-nine were in children less than three years old and forty-five in children less than two years. In forty-nine intubation was required. Of the one hundred and twenty, thirty-one died (25.5 per cent.). The mortality among the intubated cases was 43 per cent.; among the non-operative cases, 14 per cent. As compared with previous years, it appeared that in 1891 during a corresponding period the mortality among non-operative cases was 40 per cent., and among intubated cases 70 per cent.; in 1892, respectively 45.5 and 57.7 per cent.; in 1893, 45.7 and 77.5 per cent. Eighteen of the deaths occurred in children less than two years old, and twelve within forty hours after admission to the hospital.

Heim reported that of twenty-seven cases of diphtheria similarly treated from October 6 to November 4, 1894, six died (22 per cent.), while among 236 cases treated during the year previously by other methods the mortality was 52.4 per cent. The average mortality for ten years ending with 1894 was 51.1 per cent.; the lowest rate was 25.9 per cent. in 1886, and the highest 58.7 per cent. in 1892.

Monti, of Vienna (*British Medical Journal*, No. 1781, p. 385) reports that he has treated 25 cases of diphtheria with the antitoxine with but a single death.

Unterholzner stated that he had treated 37 cases between October 11, 1894, and January 10, 1895, with the serum, with eight deaths, five of which occurred within twenty-four hours of admission. He presented a table showing that among 31 cases treated with the serum there were eight deaths (25.8 per cent.), while among 36 cases treated without serum there were twenty-four deaths (66.6 per cent.). The second group included many mild cases.

Seiz (*Therapeutische Monatshefte*, 1894, H. xii, p. 605) reports that from July 1, 1893, to the middle of October, 1894, there were admitted to the hospital at Constance 159 cases of diphtheria, mostly of severe grade, 66 of which terminated fatally (41.5 per cent.). Tracheotomy was necessary in 54 cases, intubation in 8. In addition, 134 cases occurred in the city, with 24 deaths (17.9 per cent.). Included in these statistics are 27 cases treated with antitoxine, with a single death. Of these 20 received injections on the first day; 4, on the second; 1, each, on the first and second, and on the first and tenth days. The fatal case came under observation on the third day, with stenosis of the larynx, and died within a short time.

Ganghofner (*Prager medicin. Wochenschrift*, 1895, Nos. 1, 2, 3,) has reported 110 cases of diphtheria treated in the Kaiser Franz Josef Children's Hospital at Prague with the antitoxine, with 14 deaths, a mortality of 12.7 per cent. Of the whole number 44 required operative relief of laryngeal stenosis, with six deaths (13.6 per cent.). Among 144 cases treated in the intervals of antitoxine treatment and immediately preceding, there occurred 62 deaths (43 per cent.); 67 required intubation, and of these 41 died (61 per cent.). The mortality in previous years with other methods of treatment had ranged from 43.6 to 63.6 per cent.

Siegel (*Münchener medicinische Wochenschrift*, 1895, No. 21, p. 507) relates that between 1889 and 1893 the mortality from diphtheria in the Olga Hospital, in Stuttgart, averaged 40.1 per cent., and among cases requiring tracheotomy 63.3 per cent. During the year 1894, up to October 4, when the antitoxine was first employed, the mortality reached 50.3 per cent. and 70 per cent. respectively. In one hundred cases treated from October 4, 1894, to January 1, 1895, with the antitoxine the mortality was 12 per cent. and 20.3 per cent., respectively.

Furth (*Münchener medicinische Wochenschrift*, 1895, No. 30, p. 689) reports the results obtained at the medical and surgical clinics at Freiburg in the treatment of 100 cases of diphtheria with the antitoxine between October 1, 1894 and June 5, 1895. During this period 115 cases came under observation. Of this number, fifteen were not treated with the antitoxine, two being received in a moribund condition, and the remaining thirteen from economic reasons. In all of the latter recovery ensued. Of the 100, bacteriologic examination was made in fifty-five, and diphtheria bacilli found in fifty, rarely in pure culture but often associated with staphylococci and mostly with streptococci. In five cases diphtheria bacilli were not found upon a single examination. In conjunction with the injection of the antitoxine other measures in usual employ at the clinics were not omitted. Thus, the air of the wards containing the severe cases was kept constantly moist by means of the steam-spray; local applications or insufflations of precipitated sulphur or of chinolin-benzyl rhodanate were made three or four times a day; children able to do so used potassium chlorate or potassium permanganate as a gargle, and inhaled frequently a solution of carbolic acid; an ice-collar was applied; bits of ice were swallowed when pain was present; and in cases of involvement of the nose, irrigation of the nares with antiseptic solutions was practised. Among the 100 cases thus treated there were twelve deaths. The mortality from 1889 to 1894, with ordinary treatment, fluctuated between 31 and 49 per cent., averaging 39 per cent. The same average existed during the seven months of the year corresponding to the period during which the antitoxine was used. Forty-three of the 100 cases presented laryngeal involvement, and thirty-one required tracheotomy. Among the last number there were eleven deaths, 35.4 per cent. In previous years tracheotomy had been required in 46.2 per cent. of the cases, with a mortality of 70.4 per cent. The opinion is expressed that the antitoxine is a specific in the treatment of diphtheria with which no other therapeutic measure is to be compared.

Hager (*Centralblatt für innerne Medicin*, 1894, No. 48, p. 1121) reports the results obtained from the employment of the antitoxine in the treatment of 25 cases of diphtheria between August 20, and November 1, 1894, and in the prophylaxis of 35 children in the infected families. The children attacked were between eight months and sixteen years of age. Recovery took place in all but one. This occurred in an infant, eight months old, that was almost moribund when the treatment was undertaken. Of the 25 cases 8 were mild, 6 of moderate severity, and 10 severe and grave. In some cases an urticaria-like erythema appeared at the site of injection, but other complications were not noted. Of the 35 cases treated prophylactically one was subsequently attacked, but reacted favorably to 500 antitoxine units and recovered. Two other children had light attacks, but recovered without treatment. In the majority of cases the diagnosis was established by bacteriologic examination.

Rumpf (*Münchener medicin. Wochenschr.*, 1894, No. 47, p. 938) reported the results obtained in the new General Hospital of Hamburg from the employment of Behring's antitoxine in the treatment of diphtheria. Twenty-six cases were thus treated, the clinical diagnosis being confirmed by the results of bacteriologic examination in all of the cases but one. Eighteen of the cases came under observation on the second day of the disease, 3 on the third day, and 5 later. All were in children between the ages of ten months and

12 years. Among the whole number there were 2 deaths (8 per cent.): 1 among the group of 18 cases, the other among the group of five. Four of the cases were mild, 8 moderately severe, and 13 severe. Tracheotomy was performed in 7 cases; among this number were 2 fatal cases. The injections were made into the abdominal wall. In not a single instance was there any local reaction. In 11 cases the temperature appeared to be influenced by the injections; in 3 it rose, while in 8 it declined. In several cases the false membrane continued to spread. Albuminuria was found in 8 cases, in 1 of which it had not been present before the injection. The complete statistics for several months showed that there had been 91 cases of diphtheria in the hospital, with 11 deaths (12 per cent.). On bacteriologic examination of the kidneys and spleen from all fatal cases of diphtheria for a given period it was possible to isolate streptococci in 27 of 42 cases.

Escherich (*Münchener medicin. Wochenschr.*, 1895, No. 7, p. 155) has treated 51 cases of diphtheria with the antitoxine, with five deaths (9.5 per cent.). Three of the fatal cases were in a hopeless condition when they came under observation.

Gouguenheim (*Annales des Maladies de l'Oreille, du Larynx, du Nez et du Pharynx*, 1895, No. 5, p. 440) reports the results of the use of the antitoxine in the treatment of diphtheria at the Hospital Lariboisière. Prior to the institution of the new treatment, in October, 1894, there had been observed 135 cases of diphtheria in adults with 14 deaths (10.37 per cent.), and 40 in children, with 23 deaths (57.5 per cent.). Of 77 adults treated with the antitoxine 3 died (3.9 per cent.), and of 48 children 9 died (18.75 per cent). In 12 of the children, despite characteristic appearances, the bacillus of diphtheria was not found, but only streptococci. One of these children died after tracheotomy. In 10 cases only diphtheria bacilli were found; 2 of these died. In 16 cases diphtheria bacilli and streptococci were found in association; 1 of these died. In 1 case diphtheria bacilli and colon bacilli were found together. Five cases presented multiple associations. Of the whole number tracheotomy was performed in 4 cases, and of these 2 died. Among the cases of adults 12 presented only streptococci; 1 of these died after tracheotomy. Thirty presented diphtheria bacilli, and only one of these died. In 33 diphtheria bacilli and streptococci were associated; 1 of these died.

Dreyfus (*Lyon Médical*, 1895, No. 5, p. 146) relates that from October 15, 1894, to January 21, 1895, 78 cases of diphtheria were treated with the antitoxine at the Charité Hospital of Lyons. Among this number there were 15 deaths, a mortality of 19.29 per cent. Five of the deaths were due to conditions of which the diphtheria was a complication, 1 to typhoid fever, 1 to pneumonia, 1 to diarrhea, and 2 to broncho-pneumonia. In previous years the mortality of diphtheria has been 50 per cent.

Le Gendre (*Médicine Moderne*, 1894, No. 100, p. 1678) related that he had employed the antitoxine in the treatment of 16 cases of diphtheria, with 2 deaths.

Lebreton (*Ibidem*) reported that during October and November there had been treated at the Hôpital des Enfants 242 cases of diphtheria, with 28 deaths (11.66 per cent.). Deducting cases in which death followed within twenty-four hours of coming under observation, the mortality did not exceed 8 per cent.

Moisard (*Le Mercredi Médical*, 1894, No. 50, p. 613) reported the employment of the antitoxine during the months of October and November, 1894, in 248 cases of diphtheria, with 34 deaths (14.71 per cent.).

Washburn, Goodall and Card, in the *Lancet* for December 22, report the results of 72 cases of diphtheria treated with antitoxine in London between October 23 and November 27. In 61 of the cases the Klebs-Löffler bacillus was found in the fauces. In 45 cases streptococci were associated in large numbers. There were 14 deaths, or 19.4 per cent. The average mortality

in the same hospital during 1893, and up to October 22, 1894, was 38.8 per cent. The mortality of the 72 cases immediately preceding the beginning of the antitoxine treatment was 38.8 per cent In the opinion of the writers the cases treated with antitoxine were of more than average severity. From October 23 to November 27, the mortality from diphtheria at three other London hospitals where antitoxine was not employed was 33.3, 32.2, and 23.3 per cent. Tracheotomy was performed in nine of the cases treated with antitoxine, three of which died and six recovered. In 13 previous series of nine tracheotomies, the recoveries had varied from zero to four, the average of the recoveries per series being 1.75. According to the observations of the writers, and contrary to most previous statements, the association of the streptococcus did not appear to affect unfavorably the course of the disease, or the results of the antitoxine treatment.

Zabolotnui has furnished the following figures of the results of the antitoxine treatment of diphtheria in the district of Podolia, Russia, which have been reprinted from a local journal of the district in the *Meditzinskoe Obozrienie:* In 109 cases proved bacteriologically to be true diphtheria, injections of anti-diphtheritic serum were employed. The number of deaths was 14; the percentage death rate was therefore 12.8. Previously, under the old forms of treatment, the death rate had been 48 per cent. Prophylactic injections were given to 228 healthy children, stated to be members of families in which cases of diphtheria had occurred. None of these persons contracted the disease. Dr. Zabolotnui himself underwent the treatment for an attack of diphtheria, and describes graphically the rapid subjective improvement after the first injection, the disappearance of headache and of the apathetic state into which he had fallen, with corresponding rise in spirits and improvement in all the specific symptoms. The temperature fell from 39.6 C. to normal after the first injection.

DIPHTHERIA TREATED WITH AND WITHOUT THE ANTITOXINE.

By Romulus A. Foster, M.D., of Washington, D. C.

From the tabulated statements appended it appears:

1. That of 2740 cases of diphtheria—selected and unselected (and which included those that required tracheotomy and intubation)—treated with the antitoxine, only 509 died, or a mortality of 18.54 per cent.

2. That of 4445 cases, which also included those that required tracheotomy and intubation, not treated with the antitoxine, 2017 died, or a mortality of 45.36 per cent.

DIPHTHERIA TREATED WITH THE ANTITOXINE.

(*Medical News.*)

Reported by	Cases.	Recovered.	Died.	Mortality.	Reported in
Catlin,	1	1	....	....	Medical News, No. 1139.
Brewer,	6	6	....	....	" " No. 1149.
Maclachlan,	1	1	....	....	Brit. Med. Journ., No. 1765.
Mendel,	1	1	....	....	Berl. klin. Woch., 1894, No. 48.
Gleason,	1	1	....	....	Medical Record, No. 1253
Treymann,	1	1	....	....	Deut. med. Woch., 1894, No. 51.
Rembolt,	1	1			
Walker,	1	1	....	....	Lancet, No. 3710.
Macgregor,	1	1	....	....	" No. 3714.
Roué,	1	1	....	....	" No. 3715.
Rice,	2	2	....	....	Brit. Med. Journ., No. 1764.
Frith,	1	1	....	....	" " " No. 1766.
Fowler,	1	1			
Schippers,	1	1			
Simpson,	1	1	....	....	" " " No. 1767
Lees,	1	1			
Phillips,	1	1			
Pérignon,	1	1	....	....	Journ. des Sci. Méd. de Lille, 1894, No. 45.
Hilbert,	11	11	....	....	Deut. med. Woch., 1894, No. 48.
Seitz,	27	26	1	3.70	Therap. Monats., 1894, H. xii.
Hager,	25	24	1	4.00	Centralblatt für innere Med., 1894, No. 48.
Fischer,	34	32	2	5.88	Amer. Journ., Med. Sciences, No. 273.
Borger,	30	28	2	6.66	Deut. med. Woch., 1894, No. 48
MacCombie,	30	27	3	10.00	Brit. Med Journ., No. 1774.
Lebreton,	242	214	28	11.57	Méd. Moderne, 1894, No. 109.
Rumpf,	91	80	11	12.08	Münchener medicin. Woch., 1894, No. 47.
Legendre,	16	14	2	12.50	La Méd. Mod., 1894, No. 100.
Kuntzen,	24	21	3	12.50	Deut. med. Woch., 1894, No. 49.
Aronson,	192	167	25	13.02	La Méd. Mod., 1894, No. 85.
Virchow,	303	263	40	13.20	Münchener medicin. Woch., 1894, No. 50.
Katz,	128	111	17	13.28	La Méd. Mod., 1894, No. 85.
Moisard,	231	197	34	14.71	Le Merc. Med., 1894, No. 50.
Rokai,	35	30	5	14.30	Lancet, No. 3714.
Herringham,	18	15	3	16.66	Brit. Med. Journ., No. 1773.
Saw,	6	5	1	16.66	Lancet, 1894, No. 3711.
Caiger,	30	22	8	16.66	Brit. Med. Journ., No. 1774.
Sonnenburg	95	79	16	16.84	Deut. med. Woch., 1894, No. 50.
Washbourne, Goodall, and Card,	72	58	14	19.44	Brit. Med. Journ., No. 1773.
Welch,	5	4	1	20.00	Med. News, Nos. 1140, 1142.
Behring and Kossel,	30	24	6	20.00	La Médecine Moderne, 1894, No. 85.
Caillé,	9	7	2	22.22	Amer. Medico-Surgical Bull., 1894, No. 23.
Roux,	448	339	109	24.30	Wien. med. Presse, No. 38.
Wilderhofer,	100	75	24	24.00	" " " No. 52.
White,	32	24	8	25.00	Medical News, No. 1140.
Weilger,	63	46	17	27.14	La Méd. Mod., 1894, No. 85.
Wassermann, Ehrlich, and Kossel,	220	154	66	30.00	Deutsche medicin. Wosch., No. 16, xciv
Von Ranke,	36	25	11	30.55	Münchener medicin. Woch., 1894, No. 45.
Körte,	121	81	40	33.05	Berl. klin. Woch., 1894, No. 46.
Maurice,	2	1	1	50.00	Lancet, No. 3713.
Romer,	1	....	1	100.00	" No. 3715.
Browne,	8	2	6	75.00	Med. Press & Circ., No. 2005.
Wakeling,	1	....	1	100.00	Brit. Med. Journ., No. 1766.
Totals,	2740	2230	509		

Reduction of Diphtheria Mortality.—At the recent meeting of the British Medical Association, during the discussion on the antitoxine treatment of diphtheria, statistics were presented from the hospitals of England, Scotland,

Munich, Berlin and New York, showing a striking reduction of the mortality from diphtheria under the use of the antitoxine. Dr. E. W. Goodall, Medical Superintendent of the Eastern Hospital, Homerton, presented the following results of 241 cases under his own care or observation between January 1 and June 30 of this year:

Treated with antitoxine:

Under 5	57 cases, of whom	17 died	29.8 per cent.
5 to 10	36 cases, of whom	6 died	16.6 per cent.
10 to 15	12 cases, of whom	1 died	8.3 per cent.
	105	24	22.8

Treated without antitoxine:

Under 5	67 cases, of whom	30 died	44.7 per cent.
5 to 10	46 cases, of whom	14 died	30.4 per cent.
10 to 15	21 cases, of whom	1 died	4.3 per cent.
	136	45	33.6

Prof. Dr. Von Ranke, of the University of Munich, between September 24, 1895, and July 1, 1895, had 163 cases of primary diphtheria, with a mortality of 29=17.7 per cent. Of these there were 154 cases bacterially diagnosed as undoubted diphtheria, with a mortality of 18.8 per cent. The necessity of a prompt resort to the serum is shown in the following figures:

Of 19 cases treated on the first day	1 died	5.2 per cent.
Of 47 cases treated on the second day	4 died	8.5 per cent.
Of 39 cases treated on the third day	7 died	17.9 per cent.
Of 19 cases treated on the fourth day	3 died	15.8 per cent.
Of 9 cases treated on the fifth day	1 died	11.1 per cent.
Of 10 cases treated on the sixth day	4 died	40.0 per cent.
Of 15 cases treated on the seventh and later	7 died	46.6 per cent.

Mortality of patients according to age:

Under 12 months	5, all of whom died	100.0 per cent.
Under 2 years	24, of whom 9 died	37.5 per cent.
Under 3 years	25, of whom 3 died	12.0 per cent.
Under 4 years	32, of whom 4 died	12.5 per cent.
Under 5 years	17, of whom 2 died	11.8 per cent.
Under 6 years	20, of whom 2 died	10 0 per cent.
7 and over	39, of whom 3 died	7.7 per cent.

Mortality of primary diphtheria in former years:

1887	42.2 per cent.	1891	46.0 per cent.
1888	48 9 per cent	1892	36.2 per cent.
1889	46 5 per cent	1893	46.0 per cent.
1890	47.9 per cent.	1894	57.0 per cent.

Since beginning s rum treatment 17.7 per cent

The mortality has, therefore, been reduced considerably more than one-half from that of the best anti-serum year, and more than two-thirds from that of the worst. Prof. Dr. A. Baginsky, of the University of Berlin, reported that during the past year he had treated 525 cases of diphtheria with serum. Previous to the introduction of this form of treatment the mortality had, during four years, averaged 41 per cent. When the cases come to be examined in detail the improvement is even more striking.

Of cases	Previous Mortality. Per cent.	Present Mortality Per cent.
Under 2	63.30	25.20
2 to 4	52.85	17.12
4 to 6	37.90	17.24
6 to 8	27.41	11.39
8 to 10	19.35	5.11
10 to 12	15.07	10.00
12 to 13	13.00	0.13

As to the general condition of the patients, Dr. Baginsky considered that the serum treatment not only reduced the mortality, but that the general condition of the children was improved; that there was very much less danger from heart disease; that there were fewer cases of nephritis; that there was less danger of laryngeal stenosis—no cases in his experience ever having had laryngeal obstruction unless this condition had already begun, and that intubation was always possible, whereas under the older treatment tracheotomy

was very often necessary. Finally Dr. Herman Biggs, bacteriologist to the New York City Board of Health, stated that he had had under his charge between 400 and 500 cases of diphtheria which had been treated with antitoxine in their own homes. These had all been severe cases and the mortality had been slightly over 16 per cent. The mortality for the whole of New York, he added, had been reduced over 40 per cent.

Dr. Biggs then dwelt upon the importance of the antitoxine in preventing the spread of the disease by rendering those who were exposed to the infection immune. In one hospital there had been 107 cases of diphtheria in 108 days; immunizing injections of the serum were then resorted to with all the inmates—200 units of Behring's preparation being used in each case. During the next thirty days only one very mild case occurred; in the following thirty days another mild case occurred and then five more. Injections of 225 units were then used and there were no more cases. The same result was obtained in three other institutions and the value of the immunizing power of the antitoxine was conclusively demonstrated. The speaker concluded by saying that in over eight hundred subjects treated for the purpose of rendering them immune he had in no case observed any unfavorable symptom; in a few cases rashes, apparently urticarial in nature, had occurred on the eighth day, and in some there had been a temporary rise in temperature which, however, had in no case resisted treatment more than twelve hours.

Behring's Diphtheria Antitoxine.—Having recently had access to the Library of the Royal College of Surgeons of England, I gathered as fully as possible, statistics upon the use of the anti-diphtheritic serum.

The following table includes most of the serum treated cases which have been reported. The results of some of the most extensive observations are given separately:

		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
Wiederhofer	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
Saltmann	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
Washbourne, 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	

The above table shows a much lower mortality than has ever been generally attainable under former methods of treatment. Those who have used the remedy most extensively, report that the incidental action of the serum seems to be due to avoidable impurities and to the idiosyncrasy of the patient; also that paralysis, albuminuria, lung complications and necessities for operative procedures occur less frequently than under previous methods.

Dr. G. C. Crandall, St. Louis (*Journal Amer. Med. Assoc., July 27, 1895.*

W. H. Welch contributes an important article on the treatment of diphtheria by antitoxic serum (*Bulletin Johns Hopkins Hosp., July-Aug., 1895.*) and studies carefully the statistics of the results already reported.

Having considered the experimental basis and the theories of action of antitoxic treatment, the importance of early use in sufficient doses and some of the pathologic relations of human diphtheria, Welch turns his attention to the evidence at hand concerning the efficacy of the new treatment. He finds that the general impression of clinicians who have had good opportunities to

observe the effects of antitoxine is overwhelmingly in its favor and cites the observations of Baginsky, Huebner, Ganghofner and others, who all express favorable general opinions. But general clinical impressions do not furnish any strict scientific proof of the value of a therapeutic agent; here statistics are necessary. Welch has collected 7,166 cases from eighty different sources and it is not necessary to state these have been gathered with all possible accuracy and that they are considered from various points of view, in order to eliminate all the possible sources of error with which statistical results nearly always are vitiated.

Of these 7,166 patients with diphtheria treated with antitoxine, 1,239, or 17.3 per cent. died. The previous or simultaneous mortality of cases not treated with antitoxine is stated in forty-six of the reports, which contain 5,406 cases treated with antitoxine, with 1,008 deaths, a fatality of 18.6 cases. Estimating the number of deaths in these cases upon the basis of the previous or simultaneous fatality for each group, there would have been 2,279 deaths, or 42.1 per cent. *There was, therefore, an apparent reduction of case mortality by the use of antitoxine of 55.8 per cent.* Separating the hospital cases from those occurring in private practice, the unusually low death rate of 18.7 per cent. is obtained for hospital cases. Welch finds no reason to believe that the low percentage of fatality of diphtheria treated with antitoxine can be referred in any large measure to the prevalence of an unusually mild type of the disease. He does think, however, that a large number of cases are received for treatment in the earlier stages of disease now than formerly, and that for this reason the antitoxine statistics can not always be suitable for comparison with statistics based upon the former treatment of diphtheria, inasmuch as it is universally admitted that any good treatment of this disease gives better results the earlier it is begun. This factor just alluded to is not adequate, however, to explain the great reduction in fatality obtained with the antitoxine.

The reports from private practice collected by Welch, give a fatality percentage of only 6.9.

In a second table is shown the fatality in operated and non-operated cases of diphtheria treated with antitoxine. Of the 4,294 cases of this table, 27.2 per cent. required tracheotomy or intubation, the fatality in the tracheotomy cases being 39.8 per cent., in the cases of intubation 28.9 per cent., and in the cases of intubation followed by tracheotomy 53.8 per cent. Compared with previous statistics from the same hospitals, this means a reduction in fatality of tracheotomized cases of 34.1 per cent. since the introduction of the serum treatment—results that are strikingly favorable to the serum treatment. In the same way it is readily shown that the fatality of intubated cases is reduced 49.5 per cent. as the result of the antitoxic treatment. In connection with this, it is to be remembered that the great majority of observers bring testimony of the fact that the stenotic symptoms of laryngotracheal diphtheria are relieved without operation in a much larger proportion of the cases treated by antitoxine than by any other method. Von Ranke says that formerly 5 per cent. of his stenotic cases escaped operation, whereas now 33 per cent. escape; of Ganghofner's stenotic cases, formerly 12 per cent. escaped operation, whereas now 21 per cent. escape.

In his third table Welch considers the ages of patients treated with antitoxine, and several striking contrasts are presented. Thus the fatality percentage for cases of diphtheria under 2 years of age, treated with serum is 33.3, while it varies 60 to over 80 per cent. for cases of the same age not so treated. Table IV sets forth the fatality according to the day of the disease upon which antitoxine is injected. Of 232 cases supposed to have been treated the first day, 5 died; the assumed duration of the disease is, of course, doubtful and in some of the fatal cases in this group the statements of friends and parents were apparently contradicted by the clinical signs and symptoms.

It is very noteworthy that the percentage of deaths in 814 cases, in which treatment was begun before the third day of the disease is only 5.5. According to this table the percentage of deaths in cases in which the serum treatment is begun on the third or fourth day of the disease is nearly three times greater than that in cases treated on the first and second day.

The essential harmlessness of the serum has been demonstrated by over a hundred thousand injections, and Welch concludes that should the future show that through some idiosyncrasy on the part of the patient, death might be attributable to the serum, this would probably count for as much as the rare deaths from the use of ether or chloroform. The occasional untoward effects of the healing serum, such as erythema or urticaria, are annoying, but, being unattended with danger to life and without serious consequences, they do not contra-indicate the use of the serum.

The principal conclusion to be drawn from this able and timely article of Welch's is this; that the results of the treatment of over 7,000 cases of diphtheria by antitoxine demonstrated beyond all reasonable doubt that anti-diphtheric serum is a specific curative agent for diphtheria, surpassing in its efficacy all older methods. It is therefore the positive duty of the physician to use it. *Portion of Editorial Review Journal Amer. Med. Assoc.*

During the **DISCUSSION** which followed Dr. Welch's paper before the Assoc. of American Physicians, May, 1895, **DR. MASON** of Boston, said:

Dr. Welch has stated so clearly and fully the arguments for and against the antitoxine treatment that I will not dwell upon those points. I will simply present facts in relation to the series of cases which we have had under treatment in the diphtheria department of the Boston City Hospital, where we began to use serum December last. This department is a large one. It receives annually one-third to one-fourth of the diphtheria cases which are reported to the Board of Health in Boston. The material is large, and includes a large proportion of the worst cases, cases which are sent to us, often as a last resort, for tracheotomy, intubation or other treatment. The series of cases we have had to judge from the past year have been severe cases. About one-third of all these have come for intubation or tracheotomy. Each of the hospital staff takes his turn of a period of one or two months as it may be. The cases I mention have been under the care of several physicians. I speak therefore for my colleagues.

The mortality for a series of years was from 40 to 50 per cent. or thereabout, one year amounting to 52 per cent. From December 12, 1894, to May 14, of the current year, 306 patients were admitted. There were 81 deaths, or a mortality of 26.4 per cent., which is a reduction of one-half in the mortality. The operative cases numbered 31, with a mortality of 19, or 61 per cent., which was a reduction of about one-third in the mortality of previous years from tracheotomy and intubation. Comparing that series of cases with the cases for a like period in the year previous, from December 12, 1893, to May 12, 1894, the mortality for this series was 44 per cent. This gives a reduction of about 20 per cent. in the mortality between this year and last year.

There is another way in which, perhaps, the efficacy of this serum may be approximately tested, and that is the results upon the death-rate of the city at large. Of course, that could perhaps be open to more fallacies than the hospital figures; but in the city of Boston, the mortality during the last four months (January 1 to May 1,) has been 14 per cent. of diphtheria as against 41 per cent. in the previous year. Still, allowing for these sources of fallacy, I think the showing appears to be very favorable.

Dr. George A. Muehleck, in the *Philadelphia Polyclinic*, September 21, 1895, reports his experience with antitoxine in the treatment of diphtheria, and draws the following conclusions which are based on the study of twenty-six cases:

Of these cases 6 were laryngeal purely; 3 were laryngeal and faucial; 3

were laryngeal, faucial and nasal. Of the remaining 14, 8 were faucial, and 6 nasal and faucial. In these 26 cases there were 3 deaths, a mortality of about 12 per cent.

1. Antitoxic serum of diphtheria exerts a very marked influence upon the local manifestations of the disease, inasmuch as the membranes disappear sooner than under other forms of treatment. Intubated cases can, therefore be extubated sooner than heretofore.

2. Depression is markedly lessened.

3. Temperature is favorably influenced where mixed infection is not too marked.

4. The earlier in the attack the serum is injected, the more favorable is the prognosis.

5. When the disease has lasted a number of days, and the toxins have already exerted their deleterious effect on the organs and upon the nervous system, antitoxine is as powerless to restore these parts as any other plan of treatment.

6. Deleterious influence of the serum, in the vast majority of cases, is not observed; the most frequent manifestations being erythematous eruptions, which were, however, always temporary, and disappeared without serious results.

7. It is possible to temporarily immunize healthy individuals by injecting the serum.

8. The serum does not destroy the Klebs-Loeffler bacilli in the throat. They persist as long after convalescence as under other forms of treatment.

At a meeting of the Philadelphia County Medical Society, also, Dr. Edwin Rosenthal presented a paper embodying his experience with antitoxine in private practice and reported a series of seventy-eight cases treated with the serum, with only two deaths, and probably five times that number of persons, of the families of the patients immunized by serum injections, under the most unfavorable circumstances. At the same meeting the number of cases reported aggregated over an hundred with a mortality of less than 5 per cent., and conclusions were reached very similar to those of Dr. Muehleck, above quoted.

Decreased Mortality in New York City.—Mayor Strong has received from President Charles G. Wilson, of the Board of Health, a table of vital statistics, showing a large decrease in the number of deaths from diphtheria and croup since the Health Board began the use of antitoxine. The figures showing the number of cases, the deaths, and the percentage of deaths to cases in the first, second and third quarters of the years from 1891 to 1895, inclusive, are as follows:

Year.	Cases.	Deaths.	Per Cent.
1891	3686	1349	36.59
1892	4156	1540	37.04
1893	4721	1763	37.34
1894	7446	2264	30.67
Totals 1891-1894	20,011	6936	34.66
Totals 1895	7921	1643	19.43

President Wilson says "The reduction in the mortality-rate in the first, second and third quarters of 1895, as compared with the average death-rate for the corresponding periods of the previous four years, has been 43.94 per cent. This large reduction in the mortality-rate from diphtheria and croup for the first three quarters of 1895, is attributed mainly by the medical officers of this department to the introduction and use of diphtheria-antitoxine, and, if this remedy had been generally or universally employed, the reduction in the mortality-rate would, doubtless, have been larger."

During the course of a paper on "Recent Studies on Diphtheria and

Pseudo-Diphtheria," read before the N. Y. State Med. Assoc. Oct. 16, 1895, **DR. W. H. PARK** of New York said:

" In New York City the mortality statistics were very interesting. The average mortality for the past four years for all cases reported had been over thirty-four per cent. During the past nine months the mortality had been only seventeen per cent."

Dr. Park believed that if antitoxine had been used in all cases the mortality would not have been more than ten per cent. In Willard Parker Hospital the mortality had been reduced one-third, and, lately, one-half. Regarding the ill-effects, in some the injection caused a slight temporary rise in temperature. In about ten per cent. a local or general urticaria or other form of rash made its appearance between the fifth and twentieth days, and lasted twelve to forty-eight hours. In a few this was accompanied by a rise of temperature. In about one per cent. of the cases with this rash one or more joints became tender; the temperature might be considerably elevated. As a rule these symptoms subsided within forty-eight hours, but in a few there was swelling of the joints some weeks or even for months, as in one case. In a small per cent. albumin appeared in the urine, but with this there were no other symptoms showing any deleterious effects on the kidneys. He had seen at the hospital during the past nine months no serious effects upon the heart, kidney, or nervous system which seemed attributable to the antitoxine.

Denver.—According to the monthly report of the Bureau of Health of Denver, Col., it appears that in the eight months since December 1, when the antitoxic serum became available for use, there have occurred 112 cases of diphtheria, and of the total number 25 died. Of these cases 37 (all but three being identified by bacteriologic examination) were treated with the antitoxic serum, and of these but three died—a mortality of 8 per cent.; 75 cases (of which not more than 30 were determined bacteriologically) were treated without the antitoxine, and 22 died—a death-rate of 30 per cent.

Boston.—During a society discussion on the subject of Antitoxine Therapy, in Boston, May 9, 1895, **DR. WITHINGTON** said:

Possibly the most useful contribution which I can make to this subject is to speak of the results as I saw them in my own service at the City Hospital during the months of December and January. The cases in which the remedy was used were 91 in number, but 11 of these cases were rejected from the count from failure of the bacteriologist to report the specific germs of the disease in those cases, therefore leaving 80 cases in which the remedy was used. Of those 80 cases, 13 died; and of those 13, two died from scarlet fever which they contracted in the wards of the hospital, and both of them died with clear throats so far as diphtheria was concerned. Therefore these two are not properly to be included among the number of deaths in cases of antitoxine treatment; but as they died after antitoxine injection, I have left them in the list. That gives a mortality of 16 per cent. During the same period of time there were 40 cases of diphtheria in the wards, as shown by bacteriological tests, which were not treated by antitoxine; and they were not treated for various reasons, partly because of the lack of material, partly because of the patients entering moribund in four or five cases; in a few cases because the patients entered very late in the disease, beyond the fifth day from the onset of the disease. As the material was scarce, it seemed proper to withhold it where it did not promise to give good results; but the majority of those 40 cases were those in which the remedy was withheld because the cases were mild. Therefore, the group of 40 cases was a group of selected mild cases, as a whole, and yet the number of deaths among those was 12 or 30 per cent. The group of antitoxine cases, as a whole, were a severer type than those not treated in that way, and the mortality was 16 per cent.

Adding all together and including the entire series of cases of diphtheria which appeared in those six weeks, of which two-thirds were treated with antitoxine and one-third without, we had a mortality of a little less than 21 per cent. As Dr. McCollom said, the average hospital mortality has been about 50 per cent. in the City Hospital for a number of years. Assuming that it is from 40 per cent. to 50 per cent., as it is in most large hospitals, we have here a very manifest and striking reduction in the mortality under this method of treatment. In two cases there were autopsies, and the infection of the system was shown to a marked and surprising degree. Contrary to what we used to be taught as to the migration of the Klebs-Löffler bacilli from the site of the original infection, they were found in the lungs; both patients had broncho-pneumonia, and in the patches of broncho-pneumonia were found streptococci and the Klebs-Löffler bacillus. The same diphtheria bacillus was found in other organs of the body. One of the patients had streptococci in the blood of the left ventricle, and the general toxic infection was very great in both cases. In six of the fatal cases death occurred within forty-eight hours of the first injection, and in four within twenty-four hours. These were cases in which the remedy was used after it was more plentiful than at first and where it was deemed wise to give it in the cases practically hopeless.

Therefore, the numerical results are certainly very promising. The results apart from the question of figures seemed to me very striking. The gentlemen who went into the wards at that time, I think, will admit that the wards bore a very different appearance when that treatment was in force from what they have generally done in years past. Usually in going into those wards one would see a lot of steam being used for the purpose of relieving stenosis of the larynx, and the amount of steam was very much less in patients put early under this treatment. In the second place, the general septic appearance of children with advanced disease, lying in a stupid, comatose way, had very generally given way to a very much brighter aspect of the children, many of them sitting up in their cribs, sometimes sitting up within twenty-four hours of the time of receiving an injection; so that the type of the disease was alleviated as well as the death-rate reduced.

Connecticut.—Statistics of diphtheria in Connecticut show that in eighty-seven per cent. of the cases where antitoxine has been used the patients have recovered.

ANTITOXINE IN DIPHTHERIA.

By J. C. Davies, M.D., Emmetsburg, Ia.

The reports thus far appearing in the *Medical Record* on the antitoxine treatment of diphtheria are chiefly from the city hospitals. Having seen few cases reported in general practice, I have ventured to submit the subjoined report embracing the results of 21 cases treated with Behring's antitoxine, without a single death. Of this number 7 were under five years of age, 4 between five and eight years, 2 between eight and twelve years, 4 between twelve and sixteen years, and 4 were adults. Nine were affected in a severe form; of this number 4 were under five years of age, 2 under six years, and 3 under twelve years of age. In the remaining 12 cases the disease never reached a severe type, though their ages ranged from infants two years old to fifty-two years. Six cases were completely immunized after direct exposure, and no diphtheritic symptoms developed.

In 6 cases the antitoxine was given with the earliest manifestation of the disease, or within twenty-four hours after the appearance of the membrane, and in each instance the disease was either aborted or so modified that its course was comparatively light.

Of the 9 severe cases none were seen till the disease had progressed from the third to the seventh day. The disappearance of the membrane and subsidence of all active symptoms were complete in from two to three days. In 9 cases a mild rash, unaccompanied by any irritation of the skin, appeared over the face, neck, and some portions of the body, and, with one exception, disappearing the same day. In one case the rash persisted for about eight weeks without any noted result. In 3 cases there were marked renal complications with sharp albuminuria, and in 1 case, a boy four years of age, paralysis of the velum with bronchial inflammation and tedious convalescence.

The maximum amount of antitoxine used in any one case was 10 c.c. of No. 2, with 8 c.c. of No. 3 in a boy fourteen years of age. The minimum amount used was 4 c.c. in the smallest children, for immunizing purposes; number of doses in any single case, 3. The place selected for injecting was the interscapular region, the instrument used a large hypodermic syringe. No abscess or induration followed the introduction of the needle, which was always carefully cleaned in absolute alcohol after first washing with warm solution of boracic acid. *The contents of a vial from which there had been used about 4 c. c. two months before, and which had twice been frozen solid subsequently to its having been opened, was used successfully in the case of a boy, four years of age, on the fourth day of the disease, and while it did not suffice entirely to remove all the membrane it arrested the progress of the disease until the arrival of a fresh supply a few days later, thereby saving the little patient's life. I mention this simply to show that neither two months' time nor the freezing to which it was twice subjected destroyed its therapeutic value.* This was a severe case and the only one followed by paralysis. In one case of laryngeal diphtheria, in a girl twelve years of age, the symptoms promptly disappeared, although the case had reached an alarming stage before the administration of the antitoxine.

In all cases where the disease had made any considerable progress before the administration of antitoxine, alcoholic stimulants, together with iron and quinine, were given in connection with it; with the exception of the case of paralysis mentioned in the small boy, all recoveries were complete and uneventful. No cultures were made, as in two of the families there were several deaths before the administration of antitoxine. And, furthermore, exposures to these earlier cases resulted in at least seven other fatal cases in the adjoining country.—*Medical Record.*

Abstract of "A REPORT OF A SERIES OF LARYNGEAL DIPHTHERIA TREATED WITH ANTITOXINE WITH AND WITHOUT INTUBATION."

By Edwin Rosenthal, M.D., Philadelphia, Pa.

I report to-day twenty-two cases of laryngeal diphtheria, some of them complicated. Of this number, fourteen were females and eight males. Two died, a mortality of 9 per cent.

For analysis I divide these cases into two groups, those intubated and those not intubated. Of those not intubated, ten in number, I have no mortality to record, all recovered. Of this group, seven were females and three were males. There were three between one and two years old, three between two and three years old, one between three and four years old, one between four and five years old, one between five and six years old, one between six and seven years old.

The average time required for the relief of stenosis in this group was three days. These cases responded more quickly to the antitoxine, though the fall in the temperature and pulse-rate was different from that cited in recorded

cases, never under from thirty-six to forty-eight hours, and in other infections (pneumonia) it continued for a week or more.

Of those intubated—twelve in number—two died, a mortality of 16 per cent. Taking into consideration the average mortality of cases intubated without this method of treatment, 72 per cent., we can very well appreciate the difference.

As to the antitoxine used, most of my work was done with Behring's antitoxine, of which I always had a constant supply, through the kindness of a relative, Geheim Sanitäts rath, Dr. A. Baer, of Berlin, though I have treated cases with the antitoxines of Aronson, Gibier, and McFarland, all cases recovering. I must acknowledge equal value to each, although *that of Behring seemed to act more quickly and more decidedly, and has thus received more confidence from me.*

As to the method of using, if the child was very young and weighed little, one bottle of Behring's No. 1 was injected in one dose. If any complications existed, as infection of the pharynx, tonsils or lymphatics, a bottle of No. 2 was used in one injection. If, after twelve or twenty-four hours, improvement was noticed, no more antitoxine was used. But if the disease seemed to progress, or the symptoms became more urgent, another injection of No. 2 was given. Two injections sufficed to cure in the worst of my cases. My injections were all made in the back, to the one side or other of the spine, under the scapula. The parts were previously washed with alcohol, soaked upon sublimate cotton, and after injection the parts were sealed with iodoform-collodion.

The indications for intubation are the same as in cases without the use of the antitoxine, with this exception: the earlier the antitoxine is used, the less need is there of intubation. However, urgent necessity, by reason of the membrane becoming loosened and thus causing suffocation, may require intubation at any moment; for the first twenty-four hours, therefore, constant visits, say, once in two hours may be required. When, however, the treatment is begun late, say on the fifth day of the disease, my rule or practice would be to intubate first, even before injection.

My conclusions drawn from the use of antitoxine are these:

The antitoxine is a specific in diphtheria. In early cases, those seen one or two days after infection, no death-rate should be recorded.

In laryngeal diphtheria the antitoxine is specially indicated. It should be used in every stage or date of the disease, no matter how late we see the case; its influence can be proved, for cases of laryngeal diphtheria perish from suffocation long before any toxic symptoms could be manifested; for that reason I would strongly urge the necessity of prompt intubation when indicated, even before the injection of the antitoxine is made.

In conclusion I would emphatically reiterate that in early cases no death-rate should be recorded, and for that reason would say: do not delay or hesitate because the patient's condition is not so bad, or because he might get well anyhow, but use the antitoxine at once. The earlier its use the more certain its success.—*Medical News, June* 8, 1895.

The Value of Diphtheria Antitoxine Serum.—At the recent meeting of the American Pædiatric Society, held at Hot Springs, Va., it was resolved that in the opinion of the society the evidence thus far produced regarding the effects of diphtheria antitoxine serum justified its further and extensive trial.

IMMUNIZATION STATISTICS.

REPORT OF AN EXPERIENCE WITH ANTITOXINE AT THE NURSERY AND CHILD'S HOSPITAL.*

By Allen M. Thomas, M.D., Attending Physician, Nursery and Child's Hospital, New York.

The following report is limited to an account of the antitoxine immunization in regard to which the facts at hand came under my personal observation, are uncomplicated, and surely simple enough to be beyond the likelihood of misstatement or misconstruction. I present them without further comment as follows:

Total number of cases in the hospital from January 18, the time of outbreak, to April 18, the date of immunizing, 46. In all these cases cultures of the Klebs-Löffler bacilli were obtained, and observations of them doubly verified in most cases by the separate examinations of the Board of Health and Dr. Mapes. In 30 of these 46 cases abundant local clinical aspects existed, there being well-marked pseudo-membrane in the throat, nose, or larynx; the remaining 16 cases had only sero-purulent or serio-sanious nasal discharges as a local manifestation. Of the entire number of 46 cases 15 occurred between April 1, and April 18, and 7 between April 11, and April 18, plainly showing the epidemic to be gradually on the increase in the hospital up to the day of immunizing. On April 18, 30,000 units of antitoxine were obtained and 110 children immunized. On April 20, 26 more children were immunized, and the 32 remaining children in the hospital that had previously had throat or nose lesions containing Klebs-Löffler bacilli were not immunized. Of these cases immunized the following table shows the age, number and antitoxine units:

Age	Number.	Antitoxine Units.
3 to 4 weeks	7	50
2 months	12	50 to 75
3 to 6 months	36	100
7 months to 1 year	22	150
2 to 4 years	59	200

Careful examinations were made individually for albumin, variations of temperature, and skin lesions, in connection with the general observation of the children as a whole. A few (4) showed faint traces of albumin in the urine, but this in no cases (where the urine could be regularly obtained), persisted more than three to four days, nor was there in any case any rational symptoms pointing to any special disturbance of the kidneys. Three cases, eight days after the injections, and 4 cases, nine days after the injections, had an eruption, more or less profuse, of erythematous patches of the size of a silver dollar, in some isolated, in others running together about the head, trunk, and extremities; but in no case were they associated with any appreciable fever; in this respect markedly differing from cases that have been reported of erythematous eruptions occurring with rather startling elevations of temperature. Red, pea-sized, shotty papules appeared rather profusely on the face, in one case on the eighth day, and in another on the ninth, and the same kind of papules appeared on the face and both arms in a third case, also on the ninth day; these likewise were associated with no rise of temperature.

The only temperature which occurred following the injections that could be accredited to antitoxine (one case with persistent high fever proved to

*Read at a meeting of the New York Clinical Society.

be measles) happened within the twelve hours immediately succeeding the injections, and stood as follows:

In from six to twelve hours after the giving of the antitoxine the temperature rose, in the cases of children who had been previously normal, to

100°	plus	in	17	cases
101°	"	"	32	"
102°	"	"	16	"
103°	"	"	4	"

That is, in 69 cases out of a total of 136 children immunized the temperature rose within twelve hours from 100 to 103° F., but within the next twenty-four hours it had in all these cases virtually fallen to the normal. The amount of reaction, as manifested by rise of temperature, crying, restlessness and sleeplessness, seemed to be directly proportionate to the youth of the infants, and to their general debilitated condition; while the stronger and older ones showed little reaction, scarcely being disturbed at all, many of the younger infants, especially the marasmic ones, cried all night, going almost entirely without food or sleep for twelve to fifteen hours.

No new cases had broken out in the hospital since April 18, the day of immunizing, with the exception of the assistant physician on the resident staff, who about three weeks after the children were immunized, and one of the ward nurses, who five weeks after, developed well-marked cases of tonsillar and pharyngeal pseudo-membrane, with both clinical and bacteriological evidences of true diphtheria. Neither had been previously immunized. This would seem to show very conclusively the continued presence of diphtheria bacilli in the hospital, and will make subsequent observation of the children still more interesting and instructive.

The conclusions, which seem not only justifiable but fairly inevitable, to be drawn from this report are as follows: 1. The evident value of antitoxine in affording a certain period of immunity against the infection of diphtheria. 2. The apparent harmlesness of its use in this way with children even of tender age and condition.

May 28, 1895.

NOTE.—During the epidemic four nursing babies went to the diphtheria ward with their mothers who were suffering with diphtheria. These babies were all injected and then stayed from two to three weeks constantly exposed to diphtheria without contracting it.

Herman M. Biggs, M. D., of New York (*British Medical Journal, Aug. 31*) said: Remarkable results have attended the use in New York of diphtheria antitoxine for immunizing purposes. The conditions under which it has been employed have been peculiarly favorable for demonstrating its exact value. From May, 1892, to February 18, 1894, no cases of diphtheria occurred in the New York Infant Asylum, which ordinarily has about 400 inmates. From February 18 to September 1, 1894, there were 22 cases of diphtheria and 15 deaths. In September there were 16 cases, and from this time to February 10 (108 days) 107 cases of diphtheria occurred. These were very evenly distributed over this time, about 30 cases developing in each month. In the latter part of October systematic bacteriological examinations of the throats of the healthy children showed that diphtheria bacilli were present in so large a number that in order to isolate these, nearly one-half the inmates were quarantined. All efforts directed to checking the epidemic were unattended with success up to the time that antitoxine was employed for immunization. By the use of antitoxine it has been possible to completely stamp out diphtheria in four great institutions for children in which it was prevailing in epidemic form. In no instance have there been, so far as can be determined, any serious results from the administration of the remedy for this purpose. The duration of immunity is apparently not more than 30 days in many cases.

Dr. W. H. Park, *of New York, before N. Y. State Med. Assoc. Oct. 16,* 1895. *Some Recent Studies on Diphtheria and Pseudo-Diphtheria.* Regarding

the use of diphtheria antitoxine in preventing, by immunization, the development of diphtheria, he referred to its use in four asylums in the city, where outbreaks of diphtheria had occurred, the entire number of inmates being over 600. In every instance after commencing the injections no further cases of diphtheria developed. The following is an example: At the Reception House of the Juvenile Asylum four cases of diphtheria developed during the week ending April 11. On the 12th, the children (about 70) were injected with from 200 to 400 units. No cases occurred afterward except that an attendant and an engineer who handled the clothes from the diphtheria children, and who had not received immunizing injections, developed diphtheria.

Dr. Park said to him these results seemed conclusive as to the immunizing power of injections of from 100 to 400 units of antitoxine.

Abstract of "THE IMMUNIZING EFFECTS OF ANTITOXINE."

By F. Gordon Morrill, M.D., Visiting Physician to the Children's Hospital, Boston.

An analysis of all the cases shows a total of 438 immunizing injections given between January 13 and May 13. The largest number administered to one child was seven. Many of these patients were under treatment for acute diseases at the time of injection: croupous and broncho-pneumonia, grippe, tubercular peritonitis, empyema, typhoid, or such surgical troubles as naturally find their way to a children's hospital. No special symptoms were noted as produced by the serum with regard to the existent diseases at the time of injection excepting in one or two suppurative hip cases, in which there was a temporary improvement in the appetite and general condition. In a few cases of desperate illness the antitoxine was omitted, or postponed until the patient's condition improved; but as a rule, all fared alike. I have failed to observe any dangerous symptoms arise from immunization excepting one case, a boy, aged two, with leucocytosis and a large spleen, upon whom two preceding doses had produced no ill effect, had a temperature of 105.4° F. and considerable edema about the point of injection (given in the abdominal wall in this instance), and certainly appeared very sick. Cold baths and brandy soon made him better, however, much to my relief. Of course the results of an analysis of our cases are by no means claimed to be conclusive. They are, however, sufficiently well-based to permit their being regarded as suggestive. As a rule the temperature goes up less than a degree a few hours after immunization, and in 75 per cent. of all cases this is all there is to be seen. Erythema around the point of injection occurred in 23 cases. In four it was very extensive, and closely resembled erysipelas, in one instance the child was isolated. The average duration of this symptom is three days; in some cases it lasts only a few hours. It usually appears on the first day after antitoxine, and never later than the eighth. Urticaria occurred 28 times. In three instances the erythema was papular, and very closely resembled measles. In two instances an eruption like scarlet fever was present. Pain (at times intense) was noticed about the point of injection in 16; edema in 7; axillary or inguinal glands enlarged in three; general malaise (in one instance a mild delirium) in three. Pain in the articulations in less than 1 per cent. Nausea, with or without vomiting, in two per cent. Diarrhea (ephemeral) in less than three per cent. Increased frequency of micturition was noted in rare instances. The urine of 82 children was very carefully examined with reference to the effects of antitoxine on the kidneys, and the result of 540 examinations may be briefly stated as follows: In 20 per cent. no change whatever was detected. Of the remaining 80 per cent., those

which had been free from albumin previous to immunization, showed a slight trace, in most instances the slightest possible amount, which could be detected only when placed in front of a dark back-ground. This within twenty-four or forty-eight hours after injection. In cases where albumin had been present before the use of antitoxine, there was a very slight increase of the amount. In no case was there any diminution in the amount passed, or any evidence of failure to eliminate properly. Repeated microscopic examinations revealed nothing more than an insignificant amount of renal irritation in any case; and when the albuminuria was produced by antitoxine, it disappeared in a period varying from two or three days to a fortnight.

With regard to the protection afforded by antitoxine, our experience has tended to show that the serum, when fresh, can be relied upon to immunize against anything resembling clinical diphtheria thirteen days, and very probably for a longer space of time. Moreover, in no instance was the bacillus detected in the nose or throat of any child who started with a clear record, in a shorter space of time than that just mentioned. This last point (if eventually established) is of practical importance as showing that an immunized child is not only safe from diphtheria but is also safe as concerns others for a definite length of time.—*Boston Med. and Surg. Jour.*

EDITORIAL OPINIONS.

THE PRESENT STATUS OF THE ANTITOXINE TREATMENT OF DIPHTHERIA.

Nearly a year has elapsed since the antitoxine treatment of diphtheria has been at the service of more than a few favored investigators, and by this time a sufficient number of cases has accumulated upon which a fair estimate of the value of the healing serum can be based. Diphtheria is a disease so varied in the severity of its manifestations and so liable to be mistaken for less serious affections that it is only after a very careful analysis of many thousands of cases, in the hands of competent observers, that the true value of a given remedy can be determined. During the last year there have appeared in the various medical journals reports of the results obtained with the serum treatment in more than 15,000 cases, representing all ages and all degrees of severity, and after a careful consideration of this great mass of testimony, it must be admitted that we have in antitoxine a remedy for diphtheria far superior to any known heretofore, and one which should be employed at the earliest possible moment after the recognition of the disease.

At the recent meeting of the British Medical Association, Dr. Sydney Martin opened the discussion of the antitoxine treatment of diphtheria, by presenting a paper embodying the results obtained by him in a series of experiments with antitoxine. His investigations showed that when administered in sufficient dose antitoxine had the power of counteracting the effects not only of the diphtheritic toxine or ferment found in the false membrane, but also the effects of the albuminoses which are found in the tissues of patients dead of diphtheria, probably through the action of ferment on the cells. The testimony of the other members of the association who took part in the general discussion which followed the reading of Dr. Martin's paper, was with one exception uniformly favorable to the new treatment.

A collective investigation recently undertaken by the *Deutsche medicinische*

Wochenschrift, for the purpose of determining the status of the antitoxine treatment in Germany, yielded the following results: The report deals with 10,312 cases of diphtheria, all of which were treated between October 1, 1894, and April 1, 1895. Of this number 5,883 were treated with antitoxine, and 4,479 without it; the mortality in the former group was 9.6 per cent., while in the latter it was 14.7 per cent. Of 2,556 children, between 2 and 10 years of age, the fatality under the serum treatment was 4.0 per cent., while the death rate among the others not so treated was 15.2 per cent. Of 696 patients over 10 years of age treated with serum only 1 per cent. died, the mortality among the others between these years not so treated being 3.7 per cent.

A careful weighing of all the evidence submitted upon the subject up to the present time seems to establish the following facts: That antitoxine is a curative agent far more efficacious in diphtheria than any remedy heretofore employed; that its injection is very rarely followed by serious local disturbances, such as abscess, and, perhaps, never when the preparation is pure and employed under antiseptic precautions; that a marked improvement in both the local and general symptoms of diphtheria is noticeable within twenty-four to forty-eight hours after the injection of the serum; that the antitoxine has a decided influence in preventing the spread of the false membrane into the larynx and trachea; that the earlier in course of the disease the serum is employed the more favorable are the results; that it is distinctly more efficient in the fibrinous types of the disease than in the septic ones; that the liability to paralysis and albuminuria is not lessened by the use of serum, but probably somewhat enhanced thereby; that genuine nephritis, on the other hand, is less frequently observed in cases of diphtheria treated with antitoxine than with other remedies; that antitoxine may produce certain untoward symptoms, such as various cutaneous rashes, but that these are not serious in their nature and are unattended with danger to life; and that improvements in the methods of preparing the serum and more definite knowledge as to the manner of its employment have rendered the later reports even more favorable to its use than the earlier ones.—*University Med. Magazine, Nov.*, 1895.

Editorial Jour. Amer. Med. Assoc. April 20, 1895.—When Professor Virchow, repudiating the attack of his assistant, Dr. Hansemann, on Behring's theory of the serum treatment of diphtheria, said: "all theoretical considerations must give way to the brute force of these figures," referring to the statistics of the treatment in the Kaiser and Kaiserin Friedrich Hospital of Berlin, the question seemed to be settled as to the general merits of sero-therapy. During a given period 533 cases of diphtheria were treated in this hospital; of these 303 were treated with the serum, with a mortality rate of 13.2 per cent.; 230 were treated without serum, with a mortality rate of 47.8 per cent. A still more striking exhibit was afforded during June and July, when nearly all cases were treated with the serum and the mortality rate was 12.7 per cent. "Suddenly," says Virchow, "the supply of serum ceased, as, unfortunately, the very horses from which the serum was taken died. The old methods of treatment had again to be resorted to and the results were," 109 cases, 55 deaths in seven weeks, a mortality rate of 50.46 per cent. A supply of serum was then obtained from another source, and during the next six weeks 81 cases were treated with 12 deaths, a mortality rate of 14.81 per cent. It was the "brute force of these figures" which Virchow said compelled him to recommend the serum, *to* attribute to it "a brilliant therapeutic virtue;" to contend that, even if disagreeable by-effects were proved to occur occasionally, they were not sufficient to deter him from continuing the treatment.

Editorial Brit. Med. Jour., Aug. 24, 1895.—" Dr. Martin gave the result of his own investigations, showing that extensive nerve and heart muscle degeneration—the pathological characteristic of diphtheria, was produced by injection of pure diphtheria toxine, from which it is evident that the Klebs-Löffler bacillus is the cause of diphtheria. His experiments on the effect of the diphtheria antitoxine showed that when administered in sufficiently strong doses it counteracted all the effects of the toxine or the diphtheritic ferment. It has only a slight effect on the febrile temperature produced by the albuminose, but it completely counteracts the fatty degeneration of the heart, and to a very great extent also the nerve degeneration, which was insignificant in extent. It was found, also, that the injection of large doses of the anti-toxic serum into the venous circulation of the rabbit produced but little affect on the body temperature and no loss of weight, appearing to be, as far as could be judged, a perfectly innocuous substance.

It is evident from these experiments, carried out under such exactly observed and controlled conditions that the actions of the antitoxic serum may be followed with the greatest nicety. The actions are, first, that antitoxine serum, when given injected in considerable quantities, produces no appreciable injurious effect even on very susceptible animals. Secondly, that this serum, when given in sufficient doses, appears to neutralize completely the action of the active ferment which plays so important a part in the production of symptoms of diphtheria; whilst thirdly, it also neutralizes in a very marked degree the effect of those albuminoses which are formed in the later stages of the disease, apparently through the action of the ferment on the albuminoid substances with which it comes in contact, and which appeared to be stored up in the body for some considerable time after the ferments have ceased to act. Most of the speakers who followed were in full accord with Dr. Martin on most points, and brought forward strong clinical evidence in support of the position they assumed.

Medical Summary, Nov., 1895.—The British Medical Press and British Medical Association continue to assert the claims of antitoxine as an anti-diphtheritic of unequalled excellence.

On the Continent and in the States it has taken firm hold on professional confidence.

From all sources the testimony is so unequivocal, one is compelled to acknowledge that more than ordinary value and importance attach to the remedy.

That it is capable of causing immunization in a great majority of cases, is proven by Dr. Herman Bigg's statistics, who shows, too, that of eight hundred healthy children who had received injection, not one exhibited even the least ill effects.

The same gentleman also demonstrated that immunity lasted thirty days.

Results obtained by Drs. Goodall and Johnston and Prof. Von Ranke of Munich strongly attest its superior value.

Equally conclusive is the experience of Prof. Baginsky, of Berlin, who in the Empress Fredrica Hospital, found that it lowered the mortality per cent. from forty-one to fifteen.

Though a few eminent observers, like Dr. Lennox Browne, have not reached exactly the same estimate, the balance is so decidedly in favor of the remedy, we must admit we have a means, perhaps, as effectual against diphtheria as vaccine virus is against smallpox.

As a conclusion from foregoing considerations we state it as a conviction that antitoxine is probably the only true protective agent against the disease, and that with proper care, almost entirely safe, in other words, that its use will afford immunity from attacks of disease, and that too without engendering concurrent or after ill effects.

MISCELLANEOUS.

Morax: Diphtheritic Conjunctivitis; its Treatment with Antitoxine Serum. (*Annales D'Oculistique*, Vol. cxiii., No. 3).

Four cases are given in detail, two of which, in children aged respectively thirteen and ten months, were complicated by diphtheria of the nose or throat. Ten cubic centimetres of serum were injected at one dose, and the following day the false membranes were easily detached and the firmly closed lids could be opened. Recovery was complete on the fourth day, no other treatment being employed except a boracic acid wash. Another case, in a boy of six years, was accompanied by nasal and laryngeal diphtheria, following measles. The conjunctival diphtheria disappeared in three days; but the general condition necessitated a further injection of serum of which sixty-five c.c. were given, in three doses. A collyrium of silver nitrate was used twice. The fourth case involved the nose and both eyes of a child thirteen months old. An injection of ten c.c. of serum produced an improvement for twenty-four hours, followed by a relapse. Cure resulted in forty-eight hours after a second injection.

In all these cases the diagnosis was confirmed bacteriologically.

The writer concludes that in cases where there are false membranes and a purulent secretion, and where the diagnosis of diphtheria is not firmly established, it will be well to use silver nitrate in addition to the serum injection. If, however, bacteriological examination establishes the diagnosis of ocular diphtheria, injection of serum without local treatment is sufficient to bring about recovery.

Jessop (*British Medical Journal*, No. 1780, p. 304) reported two cases of diphtheritic conjunctivitis successfully treated with the antitoxine. The first was in a boy, nineteen months old, who presented membrane upon the upper and lower palpebral conjunctiva of the left eye, and a patch of membrane on the left side of the uvula; a lymphatic gland over the parotid was enlarged, and the urine contained albumin. Three injections of antitoxine were given, one-and-one-half drams in all. The membrane disappeared in five days, and left no conjunctivitis or other conjunctival change. In the second case, in a male child, eight months old, there was membrane on the palpebral conjunctiva of both eyes; the parotid lymphatic glands were enlarged, and there was a muco-purulent discharge from the nose. Two injections of antitoxine, one dram in all, were given, and the membrane disappeared in four days. Examination of the membrane in both cases disclosed the presence of diphtheria-bacilli.

PHYSIOLOGICAL ACTION OF ANTIDIPHTHERITIC SERUM.

Mya (*Lo Sperimentale*, April 11, 1895) has investigated the physiological action of the serum in children not suffering from diphtheria. They were cases of slight measles, malarial cachexia, mild rickets, and slight laryngeal catarrh. The ages were six years, eighteen months, two years, and twenty-nine months respectively. In these four cases there was no noteworthy action on the circulatory apparatus or kidneys. In the case of mild measles, slight arhythmia, noted before injection, was not aggravated by it. The author says that this arhythmia is sometimes seen in children after infectious diseases. No changes were produced in the temperature, except in one case, in which a scarlatinaform rash appeared. A slight increase in the quantity of urine was observed and also in the amount of urea. The most obvious change was noted in the blood, and consisted in an increase of the white cells and a diminution of the red cells immediately after the injection; it was transitory, not lasting more than twenty-four to forty-eight hours, and was not accompanied by any alteration in the coloring-matters of the urine. The

author's results correspond with those of Zagari and Calabrese, but he does not agree that there was any hæmolytic action exercised by the serum. He thinks that the injection of a heterogeneous serum causes a dilution of the blood, which is brought about by the absorption of lymph. Sevestre has lately shown that the injection of horse's serum produces fever and urticaria in children. Mya is of opinion that the anti-diphtheritic serum exercises no noxious action such as can be appreciated by present methods of examination, and that disturbances hitherto noted have been due to the lymphagogue action of the horse's serum introduced subcutaneously.—*British Medical Journal*, May 18, 1895.

THE EFFECT OF SERUM INJECTIONS ON THE BLOOD.

Meltzer, of New York, who is so well known for his good physiological work in this country and abroad, writes to the *New York Medical Journal* for April 27, 1895, in reply to an article offering objections to serum treatment of diphtheria, on the ground of the possibility of its globulicidal action. Dr. Winters claimed that "horse serum dissolved human blood-corpuscles," and Dr. Armstrong states that those who heard Dr. Winters's criticism "cannot but feel that an important factor has been overlooked in the consideration of the treatment of diphtheria with this substance (antitoxine serum), and that the factor is the globulicidal power of alien serum on the blood of an animal into which it is injected." Meltzer is quite sure that the gentlemen err on this point. Here are his reasons:

1. All statements as to the detrimental effect of heterogeneous blood have reference only to the intravenous transfusion with 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 not detrimental to the blood of the recipient (*Compt.-Rend.*, t. xcviii., No. 12). As Dr. Armstrong deals only with transfusion (or direct contact of the heterogeneous blood), he is apparently not conscious of the fact that he is confounding intravenous with hypodermic injections.

2. Even in intravenous transfusions the fatal effect depends largely upon the quantity of the injected heterogeneous 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 thirty-two grammes of the transfused blood to one thousand grammes of the weight of the receiving animal; after nine hours, if the proportion was twenty to one thousand; after fifteen hours, if fourteen to one thousand; if ten to one thousand was taken, no dog died from the effects of transfusion.

3. Since the introduction of the experimental study and the practical preparation and application of the diphtheria antitoxine, the horse serum has been injected subcutaneously into rabbits and guinea-pigs many thousand times, certainly more often than in all the experiments upon 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 antitoxine? The harmlessness of the subcutaneous injections of heterogeneous 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. Büchner (*Centralbl. f. Physiologie*, 1893, No. 7), are essential for the globulicidal power of the alexines.

And now one question. The facts concerning the globulicidal character of the heterogeneous blood serum are stated in many text books of physiology, and it is expected of every student of medicine to know something about them. Now, is it justifiable to assume, as Dr. Winters and Dr. Armstrong do, that the men who for years 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 could be acquired in a few minutes from any text book? One of the men is P. Ehrlich, a world-wide 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!—*Therapeutic Gazette.*

Effects of Serum Therapy on the Urinary Secretion.—As the result of his recent investigations M. Mongour announces that: 1, hyperazoturia is constant after injections of anti-diphtheritic serum; the amount of urea is generally double that found before the treatment and in all cases is above the normal, the more rapid the cure the higher the amount, apparently. 2, this hypersecretion of urea is only to be attributed to sero-therapy, since it is not due to thermic influences or to any modification of diet. 3, it only lasts for the twenty-four hours following the injection, after which the amount of urea decreases until the normal is again reached. 4, the inversion of the formula of phosphates and chlorides seems to be a consequence of the diphtheritic infection. 5, the injections of serum destroy this inversion and bring the phosphates and chlorides back to the physiologic figure.

Concerning the Action of the Diphtheria Antitoxine on the Kidneys and on the Heart.—C. V. Kahlden (*Centralbl. für Allg. Path. u. Path. Anat.* Band vi, Nos. 3 and 4) made the following experiments in order to determine whether or not the diphtheria antitoxine has any special effect upon the heart or upon the kidneys. He injected guinea-pigs and rabbits with very large quantities of serum as compared with the body weight of the animals and then after one or more injections the animals were killed and the kidneys and the heart muscle examined microscopically, after fixing and hardening according to the most approved methods. There were no changes of any kind to be found, either in the kidneys or in the heart muscle V. Kahlden is not prepared to say from the results of these experiments that the serum might not aggravate the morbid process often present in the kidneys of human diphtheritic patients as the result of the elimination of the toxic products of the diphtheria bacillus, but direct anatomic evidence of such an effect is still lacking.

Kolisko, who has made over 1,000 autopsies upon children dying of diphtheria, before the days of antitoxine, 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 antitoxine. 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.—*Editorial Amer. Med.-Surg. Bulletin, April 1,* 1895.

THE VALUE OF THE ANTITOXINE TREATMENT ILLUSTRATED BY TWO CASES OF DIPHTHERIA.

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On January 12, 1895, I was called to see two of the children of A. S. They were respectively a boy of seven years and a girl of two years and eight months. They had both been previously in good health, although I had treated the boy for scarlatina some years ago. On examination I found the boy had tonsillar diphtheria, and in the girl the diphtheritic deposits could be seen on both tonsils, the arches of the fauces, and the uvula.

With an improvised sterilized mop I detached some of the deposit from each of the two and inoculated two culture-tubes that had been prepared at the Bacteriological Laboratory of the German Hospital. Microscopic examination, in twenty-four hours, of the stained culture showed Klebs-Löffler bacilli in great profusion.

The boy, who was able to do so, was ordered to gargle with a diluted solution of liquor sodæ chloratæ 1:60, alternately with a spray of hydrogen dioxid, every hour, together with calomel internally, 3 centigrams, every three hours. Milk and whisky were also ordered.

The girl, who could not gargle, was treated locally with the hydrogen dioxid spray alone and centigram-doses of calomel. Through the courtesy of the German Hospital authorities I was able to procure one bottle of Behring's antitoxine No. 1, which had been personally brought to this country by Mr. Charles Meyer, Imperial German Consul in this city. This was injected in one dose into the little girl, and the calomel treatment was stopped. The same day laryngeal stenosis developed in her case, and with the aid of my friend, Dr. Rosenthal, intubation was performed. The visible deposits in the throat seemed to have diminished the following day, and had entirely disappeared three days subsequently. The tube was removed after forty-eight hours, and the little child made an uninterrupted recovery.

The boy's case seemed to have progressed favorably for the first two or three days, when reinfection occurred, and spreading of the deposit all over the arches and uvula was noticed. Not being able to obtain any more antitoxine at the time, the original treatment in his case was adhered to, stimulants were vigorously pushed and strychnine was added, but in spite of our efforts the child died from general toxemia on the tenth day.

I publish these cases as an illustration of the value of the antitoxine. The younger child was the more seriously affected from the start, and recovered. It might readily be inferred that the older and stronger of the two, with a milder infection, would have survived could the antitoxine have been used in his case also.—*Medical News.*