

striking improvement in the general symptoms, but no crisis occurred.

Pane's turkey serum has been used extensively in Italy, and many physicians have reported favorable results. The temperature has been lowered by it, the pulse improved and the actual number of deaths has been lower than these same physicians were able to obtain by any previous method of treatment. Massalongo, for instance, is very positive that Pane's serum prevents the extension of the pneumonic process and assists resolution. He tried it in 7 cases and states that in alcoholic patients and those suffering from nephritis and endarteritis, the serum will save many patients who otherwise would die. Bordoni used the serum in an epidemic of pneumonia, and says he was able to obtain a lower death-rate than he previously had been able to do. He believes that the serum acts more on the general condition than on the local process. De Rienzi has injected 200 c.c. in twenty-four hours, with no ill effect; the usual dose has been 10 to 20 c.c. twice a day. In 32 cases he reports 29 recoveries and 3 deaths. In 7 the serum has been injected intravenously. Dr. Antonio Fanoni, of this city, last August reported (*N. Y. Med. Jour.*) 6 cases of pneumonia treated with Pane's serum. He obtained 5 recoveries and 1 death. The improvement noticed was in the general condition and feeling of the patients, a lowering of the temperature and an improvement of the pulse. The disease ran the usual course of six to ten days, and the temperature came down by lysis. Dr. Fanoni firmly believes in the efficacy of the serum and that the patients showed distinct improvement after its use. The patient who died recovered from her pneumonia but died of a complicating pericarditis.

Many others might be quoted in Italy, who have used the serum, but this must suffice as giving the general consensus of opinion. Those who have expressed opinions there against it seem to have done so on theoretic grounds, or have used it in only minute doses and have not given it a fair trial.

The writer's own experience with his own serum has been confined to 12 cases of pneumonia, with 9 recoveries and 3 deaths. Summarizing the impressions obtained, the serum seemed to cause a slight reduction of temperature and an improvement in the pulse. It did not cause a crisis in any case, nor seem to cut short the pneumonic processes. It did cause the disappearance of the pneumococci from the general circulation in one patient, although it did not prevent the development of an empyema, and the patient made a good recovery. Another patient with double lower pneumonia complicated with a furious delirium tremens recovered, relapsed with a double upper and right middle lobe pneumonia and recovered. The serum in this patient seemed to be of decided benefit, and the patient showed improvement after its use. In two of the patients who died, both alcoholics, the serum had absolutely no effect. The leucocytosis was not influenced by the serum except in one patient, in whom it was increased by 10,000 an hour after the injection. It had fallen again by the next day. I have not persisted in the use of the serum because I could not see that it shortened the duration of the disease nor held in check the pneumonic processes within the lungs. In one or two patients I honestly believe it did marked good; in others it was useless.

The pneumonia serum at present does not seem to shorten the duration of the disease, nor cut short the pneumonic processes in the lungs, nor bring about the desired "crisis." But it does seem, in certain cases, to

prevent a general pneumococcus septicemia, and thus in these cases it may save life.

There are problems in obtaining pneumococcus serum which at present baffle and puzzle us, and whether these can be solved can not be answered yet. This is no cause for discouragement, but simply one for continued work. Until we can obtain a serum which will distinctly cut short the disease processes, the antipneumococcus will be limited in its use and its usefulness.

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## USE OF DIPHTHERIA ANTITOXIN IN THE TREATMENT AND PREVENTION OF DIPHTHERIA.\*

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The final test of the value of diphtheria antitoxin in diphtheria is the results derived from its use. The difficulty, however, of knowing what would have been the course of a case, if antitoxin had not been used or had been used, is so great that it is well to gather proofs from other possible sources, as well as from personal experience. Therefore, I will consider certain facts derived from laboratory experience and from statistics.

Is the diphtheria bacillus capable of growing in the human throat and there producing poisons, which when absorbed and brought in contact with the cells of the body excite processes which we call diphtheria? The truth of this is established. Personally I know of three instances in which the virulent bacillus we use in our laboratory was sucked into the mouth by mistake. In two severe diphtheria developed within sixty hours, and in the third no harm resulted.

Almost countless investigations have shown that in undoubted cases of what we would call real diphtheria, the diphtheria bacilli are present in the local lesions and can be detected there when properly sought. I believe that all who know about this subject agree with this.

Are there any diseases which simulate diphtheria in which other micro-organisms than the diphtheria bacilli are the exciting factors? Certainly there are diseases due to other bacteria, whose local lesions or general symptoms closely resemble those of certain types of true diphtheria. By this I do not mean that these other diseases even have all the characteristics of well-developed, true diphtheria, nor that one who is experienced can not tell in most instances clinically whether a well-developed case is or is not due to the diphtheria bacillus, but I mean there are cases of "croup" or "tonsillitis" in the exudate of which no man can say, from merely looking at it, what bacteria are growing and producing their poisons. This is true of the diseases of other regions. Very often it is impossible for a physician to say whether a pneumonia is due to the pneumococcus or to the influenza bacillus. Or again, there are drug and serum rashes which can not be differentiated from atypical cases of scarlet fever. No one would say that a serum rash and a scarlatina rash were due to the same infection, or that the after-effects or the danger of communication were in both equal.

Perhaps some are thinking: "What difference does it make, anyway, so far as treatment goes, what bacteria are the exciting factor?" It makes every difference, for we are here dealing with bacteriologic remedies, and the different antitoxins act only, or at least chiefly, on one bacterial poison. Thus diphtheria antitoxin completely

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neutralizes the poisons produced by diphtheria bacilli, and so far as we know those only.

Let us dwell a moment on the action of diphtheria antitoxin on the diphtheria toxins. When a minute quantity of diphtheria antitoxin is mixed with a large amount of toxin, it neutralizes the poison completely in about twenty minutes, so that the mixture, when injected in an animal, is an inert substance. Recent investigation seems to prove that the antitoxin acts in the body also on the diphtheria poison. We see, therefore, why we have to inject the antitoxin early in the disease, for its action is to render harmless the toxin circulation in the blood, but not to cure nor even help the injuries already suffered by the cells.

One other bacteriologic fact must be noted before considering the practical results of the use of antitoxin. The body at the same time may be invaded by more than one micro-organism. Clinically, we all recognize that we may have a scarlet fever and a diphtheria together. Less clearly, probably, we recognize that an otitis media, a pneumonia or a septicemia occurring in the course of diphtheria is usually really just as much, as in the example just given, the addition of one or more diseases to one already existing, i. e., in bacteriologic language, an invasion of the body by more than one variety of bacteria at the same time. Now, against the poisons of these other micro-organisms the diphtheria antitoxin is helpless. This is another reason for using it early, as these secondary pneumonias and septicemias come as a rule only when the diphtheria poisons have paved the way by their cell injuries. Of those who feel that the advocates of the diphtheria antitoxin treatment mislead themselves by their desires, I would ask why it should be that we believe so strongly in the value of diphtheria antitoxin and yet at the same time believe that no other protective serum has shown great value? Is it not because the evidence of years in diphtheria is for the serum treatment, while in other diseases the evidence is for the serum being of either little or no appreciable value. In diphtheria everything is favorable, for we have a strong antitoxin and we can diagnose the disease before constitutional poisoning has developed. In tetanus we have an equally strong antitoxin, though we can not make our diagnosis on the appearance of the wound, but only after development of general symptoms due to the cell poisoning.

Let us now turn to a few statistics, which I shall give as fairly as I can:

TOTAL NUMBER OF DEATHS FROM DIPHTHERIA FOR THE PAST 20 YEARS IN NEW YORK CITY (MANHATTAN AND BRONX BOROUGHS).

A study of diphtheria statistics in New York will show that the actual number of deaths from diphtheria before 1895 did not vary much for a number of years. The influence of the increase in population was counteracted by our better knowledge of how to handle the disease. About every sixth year the deaths would mount to 3000, and then diminish gradually to about 2000. Thus for the fifteen years previous to the introduction of the use of antitoxin, the average number of deaths per year from diphtheria and croup was 2373; highest number 3287 (1881), lowest 1653 (1883). In the year previous to the beginning of the use of antitoxin (1894) the deaths were 2870. In the past four years, during which antitoxin has been quite generally used, the deaths have averaged 1341 a year, more than 1000 less than the average of the previous fifteen years. During the past two years the average deaths number 1005, or 600 less than the smallest number in any year since 1880.

In Boston, Dr. McCullum has informed me, previous

to 1894 there died yearly, from diphtheria, from 15 to 18 persons in every 10,000 inhabitants. In the past four years the average number has been 7, and in the past two years less than 4 (3.6).

The great reduction in the number of deaths from diphtheria in almost every place in the world since the general introduction of the antitoxin treatment may not be entirely due to the effects of the diphtheria antitoxin, but certainly the fact is so striking that it rightly tends to make us believe that a large portion at least of this saving of life is due to its use.

Let us turn a moment now to consider the results in cases actually treated with antitoxin. We will first take up cases of diphtheria among the poor of New York, injected with free antitoxin by department of health inspectors and by physicians, from Jan. 1, 1898, to Jan. 1, 1900. The total number amounted to 2528, of which 302 died, a mortality of 11.9 per cent. All of these had diphtheria (clinically) and all showed diphtheria bacilli in the cultures made. Considering the nature of the cases I believe that without antitoxin the mortality would have been at least doubled. Of these 2528 cases, there were 802 in which the larynx was affected; 185 died, a mortality of 23 per cent.; 191 were intubated and 69 of these died, a mortality of 36.1 per cent., certainly not a bad result when you consider the conditions; 70 per cent. of the 2528 patients were under 5 years of age.

One word as to the important point of the day of disease on which treatment was begun: Of 319 injected on the first day, 13 died, a mortality of 4 per cent.; 850 were injected on the second day, and 57 died, a mortality of 6.7 per cent.; 573 were injected on the third day, with a mortality of 12 per cent. The value of the early injection is apparent. These figures, as before stated, include all cases injected; some died within a few hours of being seen, the antitoxin only being administered because the physicians desired it. Many had complicating diseases, e. g., 25 had scarlet fever.

IMMUNIZATION WITH DIPHTHERIA ANTITOXIN.

The department of health inspectors immunized, from Jan. 1, 1895, to Jan. 1, 1900, 6506 cases, of which 28 developed evidences of diphtheria within twenty-four hours; all recovered. After twenty-four hours and within thirty days, 27 cases of uncomplicated diphtheria developed, and all these recovered. The only one of these patients dying within one month was one with scarlet fever and diphtheria, who died on the second day of illness. We have, therefore, among 6506 persons, mostly children and mostly exposed directly to diphtheria, no fatal cases of diphtheria developing within thirty days, with the exception of the one having scarlet fever.

About 3 per cent. of the persons injected showed rashes, and about .5 of 1 per cent. more or less febrile disturbance. In several the symptoms were quite distressing for from twenty-four to seventy-two hours, but in no case, however, did any permanent injury, so far as we could detect, result. For the use of the above statistics I wish to thank Drs. Biggs and Billings.

The high mortality at the Willard Parker Hospital is due to the condition of the children sent there. A great many come there late in the disease, when septic or exhausted from prolonged obstruction to their breathing. These are unsuitable for any treatment, especially for that of antitoxin, which must be given early to exert its beneficial effects.

In Boston, where the hospital is centrally situated, instead of regarding it as a last resort the people endeavor to gain entrance to it, so that last year more than one-

half of all the cases were treated there. For the past two years their mortality percentage in the hospital has only been 12.5 per cent., nearly as good as that obtained among the poor in their homes by our own inspectors.

STATISTICS OF DIPHTHERIA WARDS OF WILLARD PARKER HOSPITAL.

Year.	ALL CASES ADMITTED.			INTUBATION CASES ONLY.		
	Number.	Died.	Mortality.	Number.	Died.	Mortality, Per cent.
ANTITOXIN NOT USED.						
1898 . . . . .	343	108	31.48			
1894 . . . . .	699	204	29.33	47	40	85
ANTITOXIN USED.						
1895 . . . . .	778	190	24.42	154	114	74
1896 . . . . .	823	205	24.91	143	101	71
1897 . . . . .	844	214	25.36	130	92	70
1898 . . . . .	593	109	18.38	115	48	40
1899 . . . . .	758	192	24.24	150	90	60
1900, Jan. and Feb.				45	25	55

Average mortality before use of antitoxin, 30.41 per cent.

Average mortality since use of antitoxin, 28.46 per cent.

Mortality six months previous to use of antitoxin in intubation, 85 per cent.; for last two years, 52 per cent.

A very interesting test of the value of antitoxin in diphtheria, even under the conditions met with at the Willard Parker Hospital, was tried a year ago last summer. For six weeks only every alternate case received antitoxin. Dr. Winters looked after the treatment of those not receiving it, and Dr. Berg, I believe, those receiving it. I carefully watched both series of cases, and the difference was very marked in favor of the antitoxin series. Even Dr. Winters did not ask to have the test prolonged. Before 1892 no culture examinations were made and all suspected cases were admitted. In 1892 culture examinations were made after admission to the hospital, but all cases were kept. Thus, in 1892, 492 were admitted, and 113 died, a mortality of only 23 per cent. Of those containing diphtheria bacilli the mortality was, however, 34 per cent., the others having a mortality of only 3 per cent. In 1891 the mortality in all cases of suspected diphtheria was 26.32 per cent.

ADMINISTRATION OF ANTITOXIN IN DIPHTHERIA.

The serum should be clean looking and sterile and not over six months old. It may or may not have in it a small percentage of trikresol or carbolic acid. Our own has no antiseptic added. Diphtheria antitoxin is measured in units, not grains. A unit is the amount of antitoxin which protects a guinea-pig from 100 fatal doses of toxin; all the physician needs to remember is the number of units to employ.

Antitoxin is put up in different grades, the lower grade having 100-300 units in each c.c. of serum, the higher having 400-600 units. Other things being equal, the higher grades are better and more convenient than the lower ones. In the laboratories of the New York Health Department we have, until recently, striven for a serum which had the greatest possible amount of antitoxin in each c.c. In the future our effort will be to get the highest grades of serum which will not produce rashes, for we find that the serum extracted from the blood from different horses, and even from the blood of the same horse, at different times, varies not only in the amount of antitoxin it contains, but also in the amount of substances which cause rashes, fever, etc. A serum should therefore first be chosen because it has proved not to be irritating, and then only because of its grade. Samples of all bleedings will be used first in a few mild cases and then only those serums which pass this test without giving rashes will be used. In the course of a few months we hope that we will have no serum at the stations, or in

use by our inspectors, which will produce rashes or other deleterious results in any except a very few extremely susceptible persons, and even in these that no serious effect will be noticed.

AMOUNT OF ANTITOXIN TO BE ADMINISTERED AND THE NUMBER OF INJECTIONS IN A SINGLE CASE.

There is still some difference of opinion among competent observers as to this. Our practice is the following: Patients seen early, in whom the onset is mild, 1000 units; those seen early in whom the onset is severe, either as shown by local signs such as swelling, hyperemia or, extent of exudate or by constitutional symptoms, 2000-4000 units, according to severity; those seen after the disease has progressed so far that its local extent can be guessed, mild cases, 1000-2000 units according to size, moderate ones 2000-3000 units. Severe, showing necrosis, swollen glands, laryngeal stenosis, receive 3000-4000 units.

The effects to be expected are that the local disease should not extend, that the swelling and hyperemia should lessen and the constitutional symptoms abate. If these changes have not begun to clearly manifest themselves twelve hours after the injection it should be repeated. If in twelve hours more no decided improvement occurs, which rarely happens excepting in cases already very severe when first injected, still a third dose should be given; some even advise a fourth. The extent of the disease rather than the size of the patient guides the dosage; still, size should be considered somewhat, and I should not advise, in a child under 1 year, more than 3000 units at a single injection, and under 6 months, not over 2000. If the cases are severe, injections should be repeated just as in larger children. In adults attacked with malignant diphtheria, the largest doses mentioned should be used and fearlessly repeated. With the serums as now used, both ours and those of other manufacturers, these large doses have produced, in a small percentage, very disagreeable, but in so far as I know no dangerous, results, namely, rashes, fever and, in a few, joint inflammation. In the hospital, in some of the severe laryngeal cases the course of the disease has undoubtedly been unfavorably influenced by the development of rashes, fever, desquamation, etc. Most of these, the majority seeing the cases, believe to have been a complicating scarlet fever. They looked in every way like it. Others believe that it was antitoxin.

Whether some samples of serum may or may not cause, along with their beneficial effects, really serious deleterious effects is a question; still, we know that many samples of serum produce practically no disagreeable results. I have seen 60 patients treated with but one rash resulting. I have also seen twenty treated with ten rashes developing. To select good serum and throw away the irritating is only a matter of expense. At present I see no other way of eliminating rashes and other deleterious effects from substances in some sera.

In closing let me simply say that from my own almost constant observation of diphtheria during the past eight years, that is both before and since the introduction of antitoxin, I believe that the early use of antitoxin does great good in diphtheria, and that it should be used immediately in all patients where the onset is active without waiting for cultures. In mild cases already fully developed or on the mend when first seen the use of antitoxin is a matter of minor importance, as they will do well anyway. Let me also recommend its use in all suitable cases for immunization. It gives us a guarantee of at least two weeks of safety, and this period can be lengthened at will by repeating the dose.