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Orrhotherapy in Diphtheria.

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CHICAGO.

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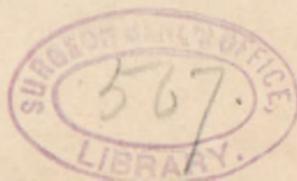


## ORRHOTHERAPY IN DIPHTHERIA.

BY E. FLETCHER INGALS, A.M., M.D.

[NOTE.—The statistics for the following paper were collected for me by Dr. Wm. R. Parkes, who had taken everything that could be found in my own journals and in the extensive files at the Newberry Library. It should be kept in mind by the reader that all statistics whether favorable or unfavorable to the use of antitoxin in diphtheria had been used and I have attempted to present an impartial statement. If I have failed to give the credit to antitoxin that many of my readers think is due, it is only because such credit is not borne out by the statistics and I beg the reader to make a careful analysis of the table. It should be specially observed that in nearly all statistics the comparison of the death rate in diphtheria has been made for the latter part of 1894 or for 1895 where antitoxin was used, with *previous* years when antitoxin was not used. As shown in observation 8 of the table Behring's statistics for Berlin prove that the death rate for diphtheria in 1895, whether antitoxin was used or not, was very much less than in previous years, it being only 14 per cent. in 4,479 cases treated in Berlin without antitoxin. If, therefore, statistics of all the patients treated with antitoxin in the latter part of 1894 or in 1895 could have been compared with those treated without antitoxin in the same period, it would appear from these statistics that the death in the latter would have been less than in the former.]

As a result of the work of Pasteur and the numerous investigations which have followed in the same line, it is now generally believed by bacteriologists that many diseases, especially those which seldom affect individuals more than once, are self-limited by the formation within the blood of a product capable of destroying the toxic material that excites the disease, hence called antitoxin. In such diseases if life be prolonged until a sufficient quantity of the antitoxin has been developed the toxic agent is destroyed and recovery follows if no serious complications have arisen.



In diseases that can be communicated from man to animals and vice versa, such for example as rabies, anthrax and diphtheria, advantage has been taken of this fact by inoculating animals with the attenuated toxic principle in small but steadily increasing quantities until an antitoxin is developed in the blood in sufficient quantity to render the animal immune to the further pernicious effects of the contagium.

Behring enunciated the law that blood serum which had in this manner been rendered immune might be transferred to another individual with the effect of rendering the latter also immune, no matter how susceptible he might be to the disease. Further investigations by Kitasato, Aronson, Roux and Behring have determined what animals have blood serum that produces the least ill effects when introduced into the human system, and how to render a small quantity of blood capable of producing immunity in a second individual. They have also discovered methods of preserving the serum and of measuring its strength and purity.

Diphtheritic poison has been introduced into animals, preferably into the horse, until immunity to its further effects has been obtained. The animal has then been bled, the blood allowed to separate and the serum preserved under the name of antitoxin.

Until recently the serum prepared by Aronson, Behring and the New York Health Department was of strength known as from 60 to 150 antitoxin units to the cubic centimeter, the different preparations being numbered 1, 2 and 3. Stronger preparations are now made; No. 4 representing 200 antitoxin units; No. 5, 300 units, and No. 6, 400 units to the cubic centimeter. These are obtained, not by concentration of weaker solutions, but directly from the animal that has been inoculated. The stronger preparations are considered quite as safe and are preferable on account of their smaller bulk which obviates to a considerable degree the pain caused by the large injections.

One thousand antitoxin units is considered the ordi-

nary curative dose, but in severe cases or those not treated until the third day, 1,500 to 2,000 units are often employed, and sometimes these are repeated until altogether from 4,000 to 6,000 units are administered in a single case. The dose considered necessary for immunizing a healthy individual is about one-fourth the curative dose. The serum is administered by hypodermic injections, preferably in some part of the body where there is an abundance of loose cellular tissue, as at the lower angle of the scapula, in the gluteal region, and upon the abdominal or chest walls. Dr. Chantemesse (*New York Medical Record*, 1896) reports that he has had quite as good results when administering the antitoxin per rectum as by hypodermic injections.

It is generally believed that the earlier the injection is made the better the result; still the classification of cases by days to determine the prognosis and the size of the dose is at fault for there is much difference in individuals in the rapidity with which absorption of toxins takes place and in their resisting power to the poison; therefore, in some, injections made the fourth or fifth day might be quite as advantageous as those in others made on the first day, though the earlier the remedy is used the better the result that would commonly be expected. The rapidity of the accession, the general condition and the age of the patient are of more importance in determining the use of the serum, its dose, and the prognosis to be given than is the number of days since the onset of the disease.

Very little interest was manifested in the antitoxin treatment of diphtheria until 1894, after Roux had presented the subject to the International Congress of Hygiene at Buda-Pesth with the report of five hundred cases treated by this method. Since then many physicians and the health departments of cities and of national governments have employed the serum extensively in the treatment of this disease. Although no crucial experiments have been made to determine the

value of diphtheria antitoxin yet the statistics obtained from many sources *seem* to prove that it is capable of greatly diminishing the mortality of this disease. In studying the literature of this subject I find the majority of reports have been from many physicians who have recorded only one or two cases. From a perusal of these one can not help suspecting that in many instances only the favorable cases have been recorded. The statistics of hospitals are probably more complete and accurate, but the statistics of Health Boards although more extensive are likely to be very inaccurate for many reasons.

In Dr. Foster's report, No. 7, of the accompanying various hospital reports and published records which I have obtained (see Table I), it was noted that all of the cases treated on the first day recovered; of those treated on the second day 9.3 per cent. died; of those treated on the third day 20 per cent. died; of those treated on the fourth day 33 per cent. died.

The following points were noted in the report from the London Hospitals (No. 12): First, that there was a great reduction in mortality in cases treated on the first and second days by antitoxin, second a lowering in mortality in all ages to a point below that of any preceding year, and third a lowering of the mortality of laryngeal cases over the preceding year.

In a personal letter (report No. 13) received from Dr. Wm. M. Welch of Philadelphia regarding the statistics from the Municipal Hospital of that city, I find that the use of antitoxin was mainly limited to cases considered favorable that were admitted in the early stage of the disease, that is, somewhere from the first to the fourth day. In cases that were far advanced, many of which were in a hopeless condition or showed great malignancy when they were admitted to the hospital, the antitoxin was not employed and a large number of the cases which received the antitoxin in the early stages were not severe. Of 302 cases receiving antitoxin 51 or 16.8 per cent. were intubation cases; of the 404 cases which did not receive antitoxin

TABLE I.

| No. | Place of observation.  | Treated by Antitoxin. |                      |   |                      | Not treated by Antitoxin. |   |  |  | References. |
|-----|--|-----------------------|----------------------|---|----------------------|---------------------------|---|--|--|-------------|
|     |  | Date of Observation.  | Number of cases.     | Per cent. of Mortality.                       | Date of Observation. | Number of Cases.          | Per cent. of Mortality.   |  |  |             |
| 1   | Kaiserlin Friedrich Hospital. . . . .                                      | 1894                  | 303                  | 13.2  | 1894                 | 230                       | 47.   | New York Med. Record, 1895.<br>"<br>"<br>"<br>"<br>"<br>"<br>" |  |             |
| 2   | Trousseau Hospital. . . . .  | 1894                  | 230                  | 14.7  | 1890 to 1894         | 520                       | 51.11   |  |  |             |
| 3   | Willard Parker Hospital. . . . .   | 1894 to Apr. 1895     | 164                  | 27.   |                      |                           |   |  |  |             |
| 4   | Hospital for Children, Paris. . . . .                                      | 1894                  | ?                    | 24.23   | 1894                 | 60.7                      |   |  |  |             |
| 5   | Trousseau Pavillon. . . . .  |                       |                      |   |                      |                           |   |  |  |             |
| 6   | Germany—Hospitals and Private Practice, reported by Dr. Enlenberg. . . . . | 1894 and 1895.        | 10,240               | under 2yrs. 21. 2 to 10, 8.8 over 10 yrs. 4.7 | Previous to 1894     | 39. 15. 8.8               | JOURNAL AMER. MED. ASS'N.   |  |  |             |
| 7   | Collected from journals by Dr. Foster of Washington. . . . .               | To February 1895.     | 2,740                | 18.5  | Same period, 1895    | 47.36                     | P HILA. Medical News, 1895.   |  |  |             |
| 8   | Berlin observations by Professor Behring. . . . .                          | 1895                  | 5,800                | 9.6   | 1895                 | 14.                       | JOURNAL AMER. MED. ASS'N.   |  |  |             |
| 9   | Russia—Dr. Zabalathni. . . . .   | 1895                  | 109                  | 12.8  | Previous records.    | 48.                       |   |  |  |             |
| 10  | New York—Dr. Louis Fisher. . . . .   | 1895                  | 200                  | 15.   | 1894                 | Laryngeal cases, 466      | 62.   |  |  |             |
| 11  | New York Board of Health. . . . .  | 1895                  | 225                  | 15.   |                      |                           |   |  |  |             |
| 12  | Chicago Board of Health. . . . .   | 1895                  | 629                  | 6.12  |                      |                           |   |  |  |             |
| 13  | Hospitals of London, Joint Report. . . . .                                 | 1895                  | Laryngeal cases, 491 | 42.   | 1894                 | 62.                       | JOURNAL AMER. MED. ASS'N and private letter, Jour. Laryngology, Apr., 1896. |  |  |             |
| 14  | Municipal Hospital, Philadelphia, reported by Dr. Wm. M. Welch. . . . .    | 1895                  | 302                  | 28.14   | 1895                 | 25.99                     |   |  |  |             |
| 15  | Professor Von Ranke. . . . .   |                       | 103                  | 18.   | Previous 8 years.    | 35.                       |   |  |  |             |
|     | Mr. Lennox Browne, Northwestern Fever Hospital, London. . . . .            | 1894                  | 100                  | 27.   |                      | 27.                       | "   |  |  |             |

71 or 17.57 per cent. were intubation cases. Of the 51 intubation cases which received antitoxin 27 or 52.94 per cent. died, while of the 71 cases in which it was not received 40 or 56.33 per cent. died. The difference, therefore, in favor of antitoxin in intubation cases amounted to only 3.39 per cent. notwithstanding the greater malignancy of the disease in some of these. In this series of cases the antitoxin was given to those in which it is claimed to be most beneficial, and was not given to the worst cases. Had the antitoxin been given in alternate cases of this group half of the more serious cases that died without the serum would probably have died with it, or at least they would not have been counted against other methods and this series would therefore have shown a record for antitoxin considerably more unfavorable than it does now.

An analysis of these reports shows that Nos. 1, 2, 3, 4, 5, 6, 7, 9 and 14 are very favorable to the use of antitoxin, but the cases reported in No. 7 were made up from journals and as already stated many of the reports so obtained were open to the suspicion of not having been accompanied by the unfavorable reports which should have been published at the same time. The observations Nos. 10 and 11 are from the Boards of Health of large cities and are very unreliable for the reason that many physicians do not report cases of diphtheria at all until they fear the patient is going to die, whereas physicians who obtain antitoxin from the Board of Health would necessarily report nearly all cases where it is to be employed. It is therefore not at all improbable that the percentage of mortality as given for cases in which antitoxin was not used is two or three times larger than it should be. There are other reasons, well known to the profession, why statistics obtained from this source are peculiarly unreliable.

In observations Nos. 4, 5, 6 and 9 the mortality among patients treated by antitoxin is compared with that of patients not treated by antitoxin in previous years, and as has already been stated the mortality varies so greatly in different years, whatever

the treatment, that very little information can be derived from such statistics. Observation No. 12 is favorable to the antitoxin treatment on its face but it will be observed that the cases treated by antitoxin were in 1895 and those not treated were in 1894. Behring's statistics, Observation No. 8, show that in Berlin diphtheria was very much less fatal in 1895 than in the previous years even when antitoxin was not employed, the ratio apparently being about 14 to 40 or 50. If a similar ratio were maintained in London for the two years of observation, No. 12 instead of being favorable to the antitoxin treatment is decidedly unfavorable; the same remark would apply to some of the other observations, where the comparison has been between different years. No. 15 can hardly be considered favorable.

As an immunizing agent it is claimed that one-fourth the curative dose is efficient and that the larger the dose given the longer the immunity, but that repeated small doses are even more effectual. The immunity is said to last from one week to thirty days. Out of ten thousand cases thus treated at Berlin only one contracted diphtheria. As reported in the Annual of the Universal Medical Sciences for 1892 Grancher of Paris stated that in a diphtheritic ward in Paris among 1,741 patients admitted there were 153 children that did not have diphtheria at the time, yet not one of these contracted the disease. This was before the days of antitoxin, and when it is remembered that the children were surrounded in the same ward by diphtheria these facts detract much from the credit given diphtheritic antitoxin as a prophylactic agent.

Several cases have been reported in which this treatment seems to have proven deleterious to the patient and some fatalities have already occurred. In the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION April 4, 1896, a fatal case is recorded in which a healthy child died within five minutes after the injection had been given to protect it from contagion. Another case with serious symptoms in which a prophylactic

dose had been given is reported in the same JOURNAL April 18, and still another fatal case has just been reported from Berlin in which Dr. Langerhans lost his little child shortly after an immunizing injection. Nevertheless considering the large number of injections which have been given and the few reports of deleterious effects it must be admitted that there is but slight danger in using the remedy as a prophylactic.

There is some reason to believe that injurious effects follow its use in remedial doses in many instances but as has been claimed by those who favor the remedy, it is possible that the deleterious effects are often observed from the fact that serious cases that would otherwise have died before the development of sequelæ are saved and that naturally in these cases the unfavorable after-effects of the disease would be more numerous. As stated by Mr. Lennox Browne in his book on "Diphtheria and its Associates," 1895, the power of the serum to do good and per contra its capacity for inflicting injury is in proportion to the duration of the disease, in other words, to the degree of toxemia. He claims that a greater number of children have been found liable to attacks of cyanosis, necessitating a demand for the freer use of nervines and stimulants, also that complete recovery is found to be delayed and that unexpected fatal results at a late period are more frequent. In the joint report of the hospitals of London already quoted 3,040 cases treated in 1894 without antitoxin are compared with 2,182 cases treated in 1895 with antitoxin. These show the following complications:

TABLE II.

|                                | Treated in 1894.<br>Without Antitoxin. |              | Treated in 1895.<br>With antitoxin. |              |
|--------------------------------|--|--------------|-------------------------------------|--------------|
|                                | Number<br>of Cases.                    | Per<br>cent. | Number<br>of Cases.                 | Per<br>cent. |
| Albuminuria. . . . .           | 603                                    | 24.0         | 1,081                               | 40.9         |
| Nephritis. . . . .             | 37                                     | 1.2          | 45                                  | 2.0          |
| Paralysis. . . . .             | 403                                    | 13.0         | 507                                 | 23.0         |
| Pneumonia, lobar. . . . .      | 11                                     | .3           | 18                                  | .8           |
| Pneumonia, lobular. . . . .    | 50                                     | 1.6          | 80                                  | 3.6          |
| Relapse of diphtheria. . . . . | 28                                     | .9           | 31                                  | 1.4          |

The above figures show a larger percentage of complications after the antitoxin treatment. The experience in these hospitals showed that by far the most frequent complication was a rash, usually urticarial, sometimes erythematous or having the appearance of scarlatina. A rash was observed in 45.9 per cent. of all cases. This was accompanied by fever in many cases, amounting to 29.6 per cent. of the patients presenting a rash. In some instances the rash persisted for many days, but usually it had run its course by the end of the third or fourth day. There were a few instances of effusion into the joints and abscesses were found at the site of injection in 2.3 per cent. of the cases.

In an abstract from the discussion at the meeting of the British Medical Association 1895, reported in the *Journal of Laryngology*, April, 1896, Dr. Goodale gave the following statistics, based on his observation: Of 105 cases of diphtheria treated with antitoxin, 29 per cent. died; of 136 cases not so treated, 33 per cent. died; albumin was found in the urine of 53.3 per cent. of the cases treated by antitoxin, but only in 49.2 per cent. of the cases not so treated. Nephritis was not noted in any of the cases; paralysis followed diphtheria in 17 per cent. of the cases treated by antitoxin, and in only 14.7 of the cases treated by other methods. Prof. Von Ranke of Munich gave statistics of 163 cases treated by antitoxin in which there was not a single case of laryngeal stenosis. Dr. A. Baginsky of Berlin gave statistics of 525 cases treated by antitoxin in which there had been no laryngeal stenosis. Dr. C. V. Kahlden (*JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION*, Oct. 19, 1895) reports that in numerous experiments on guinea pigs and rabbits that have been injected with very large doses of antitoxin for the body weight of the animal he was unable to find any evidence of nephritis in the animals that were killed after one or more injections.

The consensus of opinion of observers as to the symptoms manifested after curative doses of the anti-

toxin is that the temperature may be either reduced or rendered higher, though it appears that in the majority of cases it is rendered somewhat lower in the next twelve to twenty-four hours; the pulse is strengthened and the general condition appears to be improved in the same time; extension of the diphtheritic membrane to other parts is checked and the membrane commonly begins to loosen within twenty-four hours. The remedy, however, does not prevent suppuration of the cervical glands, does not prevent paralysis and does not favorably modify paralysis when it has once appeared.

Laboratory experiments have undoubtedly proven that antitoxin, when injected into guinea pigs that have been inoculated with large quantities of diphtheria toxin, saves their lives, and also that immunizing doses in these animals are not followed by bad results, but prevent contagion for a certain period.

The reports of clinical investigations taken as a whole are considerably in favor of the antitoxin treatment. There is still, however, much skepticism as to the efficacy of the remedy, based upon the fact that no crucial experiments have been reported. It is well known that the mortality in diphtheria varies from 10 to 75 per cent. in various epidemics or in different portions of the same epidemic, therefore accurate information can not possibly be obtained by comparing the death rate of any year with that of any preceding year, or even by comparing the death rate of one month with that of preceding or succeeding months. Until, in the large hospitals alternate cases are treated by antitoxin alone and by other methods we will have no certain information upon the subject. The report from the Municipal Hospital of Philadelphia approaches nearer a crucial test than any other that I have been able to find. It unfortunately shows a higher death rate with antitoxin than without it; even though the antitoxin was given mostly to those cases which were considered to be especially favorable for its action and in extreme conditions it was withheld. Until

more definite information is obtained conservative physicians may well be excused for declining to experiment upon their patients with this remedy. However, the wide belief that it does much good and the comparatively certain knowledge that it does but little harm suggests that our duty to our patients demands that when diphtheria exists we should administer the antitoxin if it is desired, but that at the same time we should use such other remedies as have been proven of most value in combating this disease; but we should hesitate to recommend it as a prophylactic agent.

Antitoxin certainly has not been proven a specific for diphtheria. In estimating its value it should not be forgotten that the bacteriologic diagnosis of this disease is not perfect; that in a large percentage of cases having diphtheritic membrane the Klebs-Löffler bacillus is not found and also that in a large percentage of perfectly healthy mouths a bacillus morphologically the same is present.

We believe that experimentation in the treatment of diphtheria by serum is in the right direction and we hope that the enthusiastic friends of orrhoterapy may be largely vindicated, yet we can not search far into the history of medicine to find that very many of the remedies now employed have in the beginning been lauded excessively, and that not a few of those that were formerly supposed to be extremely efficacious have been found to be practically worthless.

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