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THE ROLE OF ANIMAL EXPERIMENTATION IN THE DISCOVERIES LEADING TO OUR PRESENT KNOWLEDGE OF THE ETIOLOGY, PREVENTION AND CURE OF DIPHTHERIA*

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The disease which is now called diphtheria is believed to have been prevalent in Europe for a long time. We have reason to think that it occurred at first chiefly in epidemics. The great increase of population and travel during the past one hundred years with its necessary mingling of infected and non-infected persons has aided its dissemination, so that it is endemic in many countries.

THE IDENTITY OF "CROUP" AND LARYNGEAL DIPHTHERIA

It is very important when studying deaths from diphtheria to remember that physicians did not formerly recognize, as we now do, that various forms of ulcerated throat and croup are forms of a single disease. In fact they did not realize this until Bretonneau in 1826 appreciated the fact and gave the disease, however manifested, the name of diphtheria. Bretonneau's statements were soon accepted by many in France, but were not so quickly adopted in the rest of Europe and in America. As late as 1855, he was compelled to reassert his reasons for his conviction, that membranous croup and membranous pharyngitis were both forms of diphtheria, and that either form was capable of communicating the other. He adduced in proof of these statements the details of small epidemics in which in the same family, or group of families, different persons presented every form of the disease. He also showed how nurses caring for cases of "croup" frequently contracted the pharyngeal form of the disease. Bretonneau and those who agreed with him gradually convinced the majority of physicians and so we find such names as inflammation of the throat, sprue, etc., gradually disappearing as they were recognized as forms of diphtheria. The designation "croup" has remained much longer because it designated briefly a form of diphtheria which because of its location in the larynx had special symptoms and required special treatment. This gradual inclusion of all forms of the disease under the name diphtheria has led to confusion among some who do not believe in the value of antitoxin for, failing to note the change in the reporting, they have believed that deaths from diphtheria instead of being greatly diminished have remained nearly constant.

The following extracts from the mortality tables of the Department of Health of the City of New York show interestingly how the name diphtheria has supplanted other names for special varieties of the disease.

GRADUAL SUBSTITUTION IN DEATH CERTIFICATES BY PHYSICIANS OF NEW YORK CITY OF THE NAME DIPHTHERIA FOR EARLIER SPECIAL DESIGNATIONS

Year	Inflammation of Throat	Sprue	Angina	Croup	Diphtheria
1856	50	49	14	550	....
1858	70	56	11	478	5*
1860	132	15	37	599	422
1862	68	27	2	685	594
1864	18	4	37	754	781
1865	..	4	5	449	534
1875	..	..	..	758	2,329
1895	..	..	..	342	1,634

* First use of name diphtheria.

As already stated, laryngeal diphtheria has continued to be reported by some as croup, but, as the years have passed, more and more have designated the disease rather than its location, so that the proportion of cases reported as diphtheria has grown ever greater.

Thus in 1860 there were reported in New York City 599 deaths from croup and 422 from diphtheria or an approximate ratio of 1.4 : 1; in 1875 there were reported 758 cases of croup and 2,329 of diphtheria, or a ratio of 0.3 : 1; in 1895 there were reported 342 cases of croup and 1,634 of diphtheria or a ratio of 0.2 : 1.

Exactly the same changes have been taking place in nomenclature everywhere; thus the registrar general's report for England and Wales, 1898, says, "With regard to the changes which have taken place from time to time in the nomenclature of diphtheria, it is important to bear in mind the following points:

> Diphtheria as a distinct affection had scarcely been recognized in England previous to 1855, in which year this disease was first separated from scarlet fever in the national records of the causes of death. As to the unity of diphtheria and croup it states: "The diphtheria epidemic of 1863 was accompanied by parallel movements in the mortality ascribed to croup." After giving more reasons the report continues: "These facts taken in conjunction certainly warrant the assumption that by far the greater number of deaths hitherto attributed to croup have been caused by laryngeal diphtheria."

This gradual recognition of the true nature of croup came about with the clearer understanding of the disease. With our present knowledge we now know that when Francis Home gave the name croup to a certain disease which attacked the larynx and altered the voice, he described by that name true laryngeal diphtheria. Home's accounts of his autopsies make this very clear.

The correctness of the view stated by the registrar general's report, that fatal croup is laryngeal diphtheria,

* This paper is one of the series prepared for and reprinted by the Bureau on Defense of Medical Research of the Council on Health and Public Instruction of the American Medical Association for circulation among the public. Twenty-two of these pamphlets are now ready, taking up the relation of animal experimentation to ethics, diagnosis, cancer, vaccination, the live stock industry, tuberculosis, typhoid, dysentery, plague, rabies, surgery, internal secretions, circulation of the blood, tropical diseases, syphilis, obstetrics, etc. A price-list will be sent on application.

seems so evident that it is difficult to believe that those who affirm they are different diseases, are really sincere.

It would only be necessary for persons having such a belief to look up the cases reported as deaths from diphtheria and they would find that more than 75 per cent. of all such deaths were due to laryngeal diphtheria and that they presented the identical symptoms described by Home in his work published in 1765, entitled "An Enquiry into the Nature, Cause and Cure of Croup." At least, if they believe that croup is not diphtheria, they should eliminate all deaths from diphtheria statistics which are due to croup.

The importance of realizing that the vast majority of cases of croup are diphtheria is, in the first place, that they may be treated as such, and in the second place, that we may rightly judge the benefit derived from antitoxin treatment as shown in the lessened mortality in cases of croup. It would be as reasonable to assert that cases previously designated meningitis had ceased to exist, because with better knowledge we were able to place them under inflammations due to the tubercle bacillus or to the meningococcus, as to state that croup seldom occurred because it was now usually reported as laryngeal diphtheria.

THE MEANS BY WHICH WE OBTAINED OUR PRESENT COMPREHENSIVE KNOWLEDGE CONCERNING THE NATURE AND PREVENTION OF DIPHTHERIA

The careful clinical observations of cases and the study of the spread of the disease, without resort to animal experiments, yielded many facts which justified the conclusion that diphtheria was a contagious disease producing definite lesions in the pharynx and larynx. There remained numerous cases, however, the nature of which continued doubtful. There seemed indeed no way to differentiate between these cases, unless possibly a specific microorganism could be discovered. Many attacked the investigation of this problem. Laycock published a paper in Edinburgh in 1859 declaring that diphtheria was due to the *Oidium albicans*. One after another discovered different organisms which they tried to connect with the disease. Klebs demonstrated in 1881, that there were no microorganisms in the internal organs of the majority of diphtheria patients. Two years later he demonstrated that in sections there were near the surface of the membrane, little rod-shaped bacteria. In the same year, Heubner showed that pyogenic cocci were regularly present, but that these, while pathogenic for animals, still did not produce lesions like those of human diphtheria. He came to the conclusion that the organism was yet to be discovered. Koch at that time laid down his three postulates which required as proof that any of the numerous varieties of microorganisms, shown to be present in the throat in cases of diphtheria, was the exciting factor, the finding of the organism in the affected part, its isolation in pure culture and its reproduction of the disease when inoculated in pure culture.

The investigations due to Koch's suggestions led to the discovery of the diphtheria bacillus and of its antidote. The following pages will again and again have to record the fact that these results would have been impossible without animal experimentation.

THE DISCOVERY OF DIPHTHERIA BACILLUS BY LOEFFLER

As already stated, the results published prior to the investigations of Loeffler were so inconclusive that many different kinds of bacteria were under consideration as the possible cause of the disease. Loeffler in 1884 reported the results of a very careful series of studies. He examined sections stained by a special alkaline solution of methylene blue, of the locally affected parts and also of the organs of patients who had died of diphtheria. These investigations showed that the lesions were not always uniform in character, but could be arranged in various groups. The first group was characterized by loss of substance and the presence of greyish-yellow necrotic material, false membranes being absent. All the cases of post-scarlatinal diphtheria belonged to this group. Micrococci, arranged in chains, were found pushing their way in wedge-like masses into the tissues and leaving necrotic areas behind them. Masses of micrococci were also frequently found in the organs of fatal cases. In the second group, thick false membranes occurred on the deeply congested mucous membranes of the throat, larynx or bronchi. Masses of bacteria of various kinds were found covering the surface of the false membranes in disorderly confusion, and more deeply, small rods were found arranged in groups and stained most intensely with methylene blue.

Anatomic and cultural investigations indicated that either streptococci or the bacilli now known to be the diphtheria bacilli were the exciting organisms, but gave no conclusive proofs of the specific significance of either. As other means failed, it was necessary to discover whether either of them was capable of producing in animals a disease analogous to human diphtheria. Experiments were made with pure cultures of the streptococci and other micrococci in a number of animals, mice, guinea-pigs, rabbits and monkeys, partly by feeding, and partly by subcutaneous, intratracheal and intravenous inoculations. Certain animals, especially mice, died from septicemia, with numerous chains of cocci in the blood, but in no case was a disease produced which resembled diphtheria. Since these organisms were only discovered alone in a limited number of cases simulating human diphtheria, and since they have been found similarly arranged in the organs in other infective diseases which are associated with lesions of the mucous membrane, Loeffler came to the conclusion that, in diphtheria also, the chain-forming micrococci were merely of secondary importance, occasionally invading the body under favorable conditions and giving rise to slight or grave local and general complications. Loeffler also regarded it as possible that the chain-forming micrococci might set up a disease resembling diphtheria by attacking the mucous membranes of the throat and multiplying in the lymph spaces.

With the pure cultures of the suspected bacilli obtained from a number of cases experiments were made on several species of animals. Mice were not affected by inoculations, but guinea-pigs died with characteristic lesions, greyish-white, pseudo-membranous masses at the seat of the inoculation, hemorrhagic edema, effusion into the pleural cavities, lobular consolidation of the lungs and catarrhal inflammation of the kidneys. The bacilli were found usually in small numbers only at the seat of inoculation, but were never observed in the organs. These facts "clearly indicated that a poison produced at the seat of inoculation must have circulated in the blood." Characteristic and striking results were obtained by the inoculation of rabbits. After inoculation of the conjunctiva was performed, the parts became much swollen and covered with whitish tough membranes. Inoculations into the opened trachea produced tracheitis, leading in the majority of cases to the formation of more or less extensive false membranes, which occasionally extended into the bronchi. The operation

wounds frequently became covered with fibrinous deposits accompanied by hemorrhagic edema of the neck. Extension of the process from the trachea into the pharynx was never observed. In the false membranes, the bacilli were only found in small numbers and were only observed in those parts of the mucous membrane which were injured during inoculation and which appeared to be totally absent from the internal organs. Since the animals died, in spite of the scarcity of bacilli, Loeffler considered that this confirmed his idea that death was due to the absorption of a chemical poison produced by the bacilli at the site of inoculation.

These results of animal tests established for all time the rôle of the diphtheria bacillus as the sole essential exciting factor in producing diphtheria. The streptococci and other pathogenic bacteria were proved to be an associated and engrafted infection, which at times probably became as dangerous as the diphtheria bacilli, as in the case of a complicating pneumonia or septicemia. The idea of Loeffler that the lesions distant from the original site of the disease were caused by soluble poisons was proved correct by the work of Roux and Yersin. The injection of the filtrate from cultures produced the same histologic lesions in guinea-pigs as infection with the culture. Without animal tests it would have been impossible to determine this, for the chemical composition of diphtheria toxin is still unknown to us.

The etiologic importance of the bacillus isolated by Loeffler being established, it was possible to establish the nature of doubtful cases. Numerous tests by means of animal inoculations in cases of croup occurring in many parts of Europe and America showed that the opinion of Bretonneau, that fatal croup was almost invariably laryngeal diphtheria, was absolutely correct. Other discoveries were made, such as the fact that there were many mild cases of diphtheria which had not been recognized and had thus been fruitful sources of contagion. It was also disclosed that convalescent cases carried virulent bacilli for weeks or months after recovery and that healthy persons who were brought into contact with diphtheria were occasionally infected and thus might become carriers of diphtheria bacilli, infecting others though escaping themselves.

In all these discoveries it was necessary to use guinea-pigs because it was found that there were harmless bacteria in the throat which so closely resembled the diphtheria bacilli in every respect, except that of poison production, that the two could only be separated and identified through the injection of guinea-pigs.

The information thus obtained proved to be very useful and it was hoped that the intelligent separation, through practical cultures, of suspected cases into those that were diphtheria and those that were not, would make it possible to isolate the one and liberate the other. It was also believed that examination of persons exposed to diphtheria would make it possible to detect the diphtheria bacillus carriers and so prevent their disseminating the germs of the disease. Experience showed that while we could act much more intelligently than before, yet the doubtful cases and the bacillus carriers were so numerous that the problem was too difficult to handle. While the culture test was reliable in cases with exudate, it proved unreliable in convalescent cases and in bacillus carriers because the bacilli might at the moment be so few at the time of making the culture as to be missed, and the case passed as free from contagion, when, in fact, diphtheria bacilli were present in some recess ready to multiply at any moment. We found that in New York City, during the winter months, nearly 1 per cent. of the children are diphtheria bacillus carriers. These conditions, together with the influence of increasing congestion of the population, brought it about that the deaths from diphtheria (which had diminished for a time after the promulgation of Loeffler's discovery), began again to increase. Fortunately, the discovery by Behring, of the antitoxic power of the blood of animals which have recovered from slight poisoning with the toxin produced by the diphtheria bacillus, gave us a new and potent preventive which also could be used as a cure. This discovery would have been absolutely impossible without animal experimentation, for diphtheria antitoxin is only known by the fact that it acts to neutralize the poisonous action of the toxin. Furthermore, every lot of antitoxin which is sent out must be produced by animals and must be tested in animals.

THE RÔLE OF ANIMAL EXPERIMENTATION IN THE DISCOVERY AND PRACTICAL PRODUCTION OF DIPHTHERIA ANTITOXIN

Behring discovered that not only was an animal, after recovery from a less than fatal dose of diphtheria toxin, immune to an otherwise fatal dose of a diphtheria culture, but also, the far more important point, that the blood-serum contained the protective substance and that this injected into another animal conferred immunity. By testing a number of animals it was found that the horse produced the largest amount of this protective substance. By judicious treatment with repeated inoculations of toxins the antitoxin accumulated in the blood, since it was so slowly eliminated, and the newly formed antitoxin after each injection was added to the major part of that formed in response to the previous injections. It was found that when an animal is injected with the antitoxin produced by one of its own kind, its immunity lasts from four to six months, but when injected with antitoxin produced in another species, immunity lasts only two or three weeks. This difference in the retention of the antitoxin is of both practical and theoretical interest. As human beings always receive antitoxin produced by the horse, the duration of immunity is limited to about two weeks. With each repetition of the injection there is a restoration of the immunity. The duration of immunity as estimated in animal tests has been also proved in man by the exposure of persons during epidemics. The long retention of antitoxin in the bodies of animals of the same species as the one producing it, proves it to be a true cell product.

THE VALUE OF ANTITOXIN IN THE PREVENTION AND TREATMENT OF DIPHTHERIA

I shall first consider the results with which I have been personally familiar. The experience that we have had in New York in the immunization of persons subjected to danger of infection has been very extensive.

The health department inspectors immunized fourteen thousand six hundred persons last year. These were all exposed to contact with diphtheria. In the last three years over thirty-five thousand cases have been treated without a single serious accident. Very few of these contracted diphtheria and not a single one died of the disease. In over 100,000 persons immunized since the introduction of antitoxin there has been but one known fatality due to the serum injection. This child suffered from status lymphaticus and died shortly after an injection of 1,000 units. This was four years ago and followed an injection of serum which had not been refined. The sister of the child received 5,000 units

from the same vial and suffered no deleterious after-effects.

Two occasions in which the immunizing value of the antitoxin was strikingly manifested are the following: The first was in an epidemic that was raging in a large institution for children. It broke out in the fall of 1894, a few weeks before we obtained our first antitoxin. Every endeavor was made to isolate not only the sick, but also those from whom diphtheria bacilli were obtained. These measures proved to be insufficient and three or four new cases developed daily. The danger to the children was so great that we decided to use the greater part of a small consignment of antitoxin which we at that time obtained from Germany. All the children were given a moderate injection (300 units). The epidemic ceased at once and no new case developed after the day of the injections for a full ten days when one mild case developed. This summer an epidemic started in a large insane asylum near New York City. Within six days of the discovery of the first case, many developed. These were not only among patients, but also among the doctors and nurses. As rapidly as possible over two thousand persons were given 1,000 units of antitoxin. No immunized person was attacked and the epidemic was stopped within less than a week. Similar experiences to those we have had in New York City have been met with wherever antitoxin has been used.

TREATMENT

The value of antitoxin in the treatment of disease is not so readily determined as in the prevention. Our experimental tests in animals show that as soon as antitoxin enters the blood-stream it neutralizes any toxin present, but that it only slowly passes through the capillaries to reach any toxin which has passed out previously or is still retained in the mucous membranes at the site of the disease. When antitoxin is subcutaneously injected it is absorbed quickly enough to render the blood-current feebly antitoxic within a few minutes, but strongly so only after several hours, for the antitoxin is apparently chemically allied to the globulins and, like them, is slowly absorbed. Animal tests have demonstrated that by injecting antitoxin into the vein of a patient, we immediately stop further passage of toxin from the blood-stream, and, within a short time, we neutralize any toxin in the tissue fluids and so prevent further injury of cells whether situated at the point of disease or at distant parts. Animal experiments give us no reason to believe that cellular injury already accomplished can be remedied. Antitoxin is really therefore a preventive of further poisoning and cannot restore to health those who have suffered irreparable injury, any more than rescuing from the fire can save one from death who has been burned to an extent incompatible with continued life. Animal experiments give us reason to expect that in cases of diphtheria treated early, the lesions will not advance. In early cases the patients will recover and in the more advanced cases they will improve at least locally, but in many cases they will die from paralysis due to the progress of degeneration from previous injury or complications such as pneumonia, due to bacteria, the toxins of which are not neutralized by diphtheria antitoxin.

RESULTS OF ANTITOXIN TREATMENT

It is now sixteen years since the antitoxin treatment of diphtheria began to be used. At first only a small percentage of the patients received the treatment, but steadily year by year a greater proportion of patients were injected with serum until now probably 90 per cent. of all cases are treated with antitoxin. The cases treated in one year in the United States equal at least one hundred thousand and those treated in Europe must total nearly one quarter of a million more. If antitoxin is of real value, we shall find as it becomes more used, a lessened number of deaths, and an increasing consensus of medical opinion in its favor.

THE ABSOLUTE MORTALITIES DURING A LONG SERIES OF YEARS IN LARGE CITIES AS AN INDEX OF THE VALUE OF ANTITOXIN TREATMENT

Of all methods at present available, perhaps the least open to error is a comparison of the absolute number of deaths per 100,000 before and after the introduction of antitoxin.

To be of value, statistics of this kind must cover a long period of years. While this, of course, is true for all kinds of statistics it is particularly important in diphtheria in which mortality figures move up and down in irregular waves. These irregularities, however, become apparent only when a considerable number of years are taken into account. For example, in the six years ending 1882, the average of deaths per 100,000 from diphtheria and croup was always above 140 in Baltimore, and reached 200 or over in three of these years. In the seven years following, the mortality fell sharply and continuously until it reached its lowest point in 1889, when it was 52 per 100,000; yet no difference in treatment occurred in 1882.

Care must therefore be taken to secure readings which do not constitute merely a part of an epidemic, unless due allowance be made for this fact. In order to distinguish epidemics, it is necessary to know the average number of deaths for many years. Lack of this knowledge was the weak point in a number of earlier statistic studies and was made use of by the opponents of serum therapy. Further, statistics of this kind ought to be taken mainly from the large cities, for reports of deaths are usually indifferently kept in the rural districts. It must also be remembered that, at first, antitoxin was used in only a minority of the cases and often at too late a stage of the disease.

In compiling the following statistics, therefore, we have taken only cities having over 125,000 inhabitants, in which the registration of deaths has long been efficient. Apart from these two points the cities were taken at random, some from the United States, some from Great Britain, and the remainder from the continent of Europe. The figures are in all cases from the official records and are, with the exception of Paris, the combined "diphtheria" and "croup" figures. In order to overcome the fluctuations commonly seen in diphtheria mortalities, we have gone back to 1878, i. e., fifteen years prior to the introduction of antitoxin, and have carried our figures up to December 31, 1905, i. e., ten years after the use of antitoxin. We believe that the evidence thus obtained of the great value of diphtheria antitoxin is overwhelming. The figures obtained by us of the deaths in a number of the cities up to the present year show a continuous lessening in the deaths.

Before giving the combined figures of many cities, we shall give those for New York City since 1860 and some for England and Wales and London. The English figures are especially interesting as there has been much discussion of the results in England. The conditions there were somewhat peculiar.[1] The antitoxin treat-

1. Thirty-Ninth Annual Report of the Local Government Board for 1909-10, Appendix A, No. 1, pp. 6 and 7.

ment was slower in being adopted than in continental Europe and America. Then again, diphtheria had been increasing for a couple of years and this epidemic influence continued until 1899. The fact that during the earlier years membranous croup was not reported as diphtheria and later was included with it, made it possible to mislead by quoting only those reported as diphtheria. This subject has already been fully considered.

STATISTICS FROM NEW YORK CITY

Year	Deaths from Diphtheria and Croup in the Old City of New York	Deaths Per 100,000
1878	1,506	132
1879	1,193	101
1880	2,300	190
1881	3,287	264
1882	2,254	184
1883	1,653	125
1884	1,838	136
1885	2,180	158
1886	2,695	188
1887	3,056	206
1888	2,553	167
1889	2,291	146
1890	1,783	110
1891	1,970	118
1892	2,105	123
1893	2,558	145
1894	2,870*	158*
1895*	1,976*	105*
1896	1,763	91
1897	1,590	81
1898	923	46
1899	1,085	53
1900	1,276	62
1901	1,227	58
1902	1,142	53
1903	1,270	56
1904	1,270	57
1905	860	38
1906	983	39
1907	1,015	40
1908	1,097	41
1909	1,065	39
1910	1,034	37
1911†	787	28

* The Antitoxin Laboratory established in the autumn of 1894. Free distribution to the poor begun early in 1895.
† Estimated for last four months.

The deaths during the first eight months of 1911 are 24 per cent. less than during the same period of 1910. If this improvement continues the death-rate will be 28, or about one-fifth of the average before the introduction of antitoxin. In the whole city of New York, there were reported from January 1 to April 1, 1911, 4,198 cases, and 411 deaths as against 4,957 cases and 597 deaths in 1910. The case fatality was thus only 9.8 per cent. as compared with 12 per cent.

DIPHTHERIA IN LONDON

Year	London: Rates per 1,000 Persons Living — Notifications	London: Rates per 1,000 Persons Living — Deaths *	Hospitals of Metropolitan's Asylum's Board. Mortality Percentage in Diphtheria Cases Treated in Hospital *
1892	1.96	.44	29.3
1893	3.18	.74	30.4
1894	2.58	.61	29.3
1895**	2.57	.52	22.8
1896	3.07	.59	21.2
1897	2.97	.50	17.7
1898	2.66	.39	15.4
1899	3.05	.43	13.9
1900	2.66	.34	12.3
1901	2.68	.29	11.1
1902	2.31	.25	11.0
1903	1.68	.16	9.7
1909	1.39	.126	9.8

This table is from page 7 of Appendix A of thirty-ninth annual report of the local government board.
* These figures include those dying from "membranous croup."
** Introduction of antitoxin treatment.

From the last registrar general's report we find that there were in England and Wales 8,609 deaths in 1889, 10,516 deaths in 1894, 10,301 deaths in 1899 and 5,889 deaths in 1908 from diphtheria and membranous croup. The death-rate in 1889 was 30.3; in 1894, 34.7; in 1899, 32.4, and in 1908, 16.6 per 100,000.

Combined statistics of deaths and death-rates from diphtheria and croup in New York, Brooklyn, Boston, Pittsburgh, Baltimore, Philadelphia, Berlin, Cologne, Breslau, Dresden, Hamburg, Königsberg, Munich, Vienna, London, Glasgow, Liverpool, Paris, Frankfort.

Year	Population	Deaths from Diphtheria and Croup	Deaths Per 100,000
1890	16,526,135	11,059	66.9
1891	17,689,146	12,389	70.0
1892	18,330,737	14,200	77.5
1893	18,467,970	15,726	80.4
1894	19,033,902	15,125	79.9
1895*	19,143,188	10,657	55.6
1896	19,489,682	9,651	49.5
1897	19,800,629	8,942	45.2
1898	20,037,918	7,170	35.7
1899	20,358,857	7,256	35.6
1900	20,764,614	6,791	32.7
1901	20,874,572	6,104	29.2
1902	21,552,398	5,630	26.1
1903	21,865,299	5,117	23.4
1904	22,532,848	4,917	21.8
1905	22,790,000	4,323	19.0

* Introduction of antitoxin treatment.

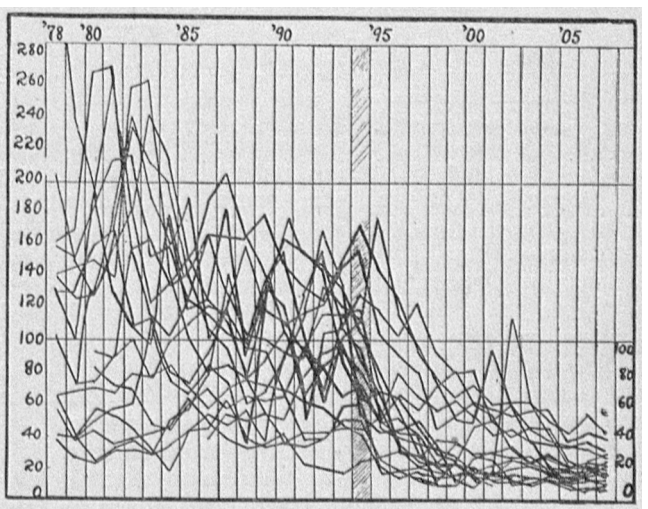

Chart showing deaths from diphtheria (including membranous croup) per 100,000 in nineteen large cities, 1878-1908. The death-rate of each of the nineteen cities is represented by a line. The marked lowering of the death-rates is clear in spite of temporary variations in certain cities.

We see from these figures that although there were marked fluctuations in the absolute mortality per 100,000 in the pre-antitoxin years, in no period did all of the cities show a decrease. Thus in 1884 about half of the cities show a decline and the other half an increase in mortality; the same is true for 1888. Not until we come to the critical year, 1894, do we find almost all the cities showing a like behavior, a drop in the mortality per 100,000. This drop, moreover, has continued until the present time. The difference between 79.9 per cent. in 1894 and 17 per cent. in 1907 is so great and the time of the beginning of the decrease so coincident with the introduction of the antitoxin treatment that it is difficult to attribute any other explanation than that the saving of life was due to antitoxin.

THE RESULTS OBTAINED IN HOSPITALS AND ELSEWHERE IN THE YEARS BEFORE AND AFTER THE INTRODUCTION OF ANTITOXIN

The figures from the London hospitals have already been given. They show that a mortality of 29 per cent. has been reduced to about 10 per cent.

The Boston City Hospital[2] has had a similar experience. Before the use of antitoxin about 70 per cent. of the patients presenting intubation cases died; now only about 35 per cent. die.

At the Hospital for Contagious Diseases in New York City very few patients having membranous croup die

2. See article by Park and Bolduan, quoting from McCollom's 1905 report.

unless they develop pneumonia. We have little fear of the outcome in any uncomplicated case of diphtheria which receives the antitoxin early.

Similar results have been obtained by physicians in Europe and America both in hospitals and private practice. The results are much the best in cases of patients treated early in the disease. Royer[3] has analyzed 3,894 cases of diphtheria in which the patient received antitoxin treatment as to the results according to the day on which treatment was begun.

DEATH-RATE ACCORDING TO DAY OF INJECTION

	Death-Rate
218 cases treated on first day	.....
1,153 cases treated on second day	4.59
880 cases treated on third day	12.50
598 cases treated on fourth day	16.40
351 cases treated on fifth day	14.24
694 cases treated after fifth day.....	14.15
Total, 3,894 cases.....	10.57

THE SIMULTANEOUS OBSERVATION OF CASES OF DIPHTHERIA RECEIVING AND NOT RECEIVING THE ANTITOXIN TREATMENT

Fibinger[4] observed during a period of time a series of cases of alternate patients treated with and without antitoxin.

Among 238 patients treated with antitoxin, 8 died (mortality 3 per cent.).

Among 245 patients treated without antitoxin, 30 died (mortality 12 per cent.).

This method, however, for obvious reasons cannot be extensively used. We made in 1895 a similar test at the Willard Parker Hospital, but the difference in the behavior of the patients appeared to us to be so greatly in favor of those treated with antitoxin that the test after six weeks was stopped and all patients since that time have received antitoxin.

A POSSIBLE DECLINE IN THE VIRULENCE OF THE DISEASE

The observation of the cases of patients who come to us without having had antitoxin treatment, indicates that there has been no marked change in the average virulence of the disease.[5]

THE EXTENT TO WHICH ANTITOXIN IS USED

The observations made under the direction of the Department of Health show that in New York City almost every physician uses antitoxin. There are a good many patients among the poorest classes who do not receive antitoxin early, but this is because a physician has not been called to see the child.

The health authorities of all the northern states have arrangements for making antitoxin available either for the poor or for all classes. So far as I can determine there is no hospital for the care of diphtheria patients in any part of the world in which diphtheria antitoxin is not used.

AFTER-EFFECTS OF SERUM INJECTION

Serum carrying the antitoxin is apt to produce after-effects of varying intensity. These effects are due chiefly or altogether to the serum and not to the antitoxin or other antibody which it carries, which is proved by the fact that serum containing no antibodies gives the same symptoms. This fact is of importance, and has led to the elimination of much of the useless serum elements.

3. Modern Treatment, Hare, p. 815.
4. Reported by Faber, 1904.
5. See chapter on Mortality in Bacteriology of Diphtheria, Nuttall and Graham Smith, p. 594.

FIRST INJECTION

Von Pirquet and Schick have given the name "serum sickness" to the symptoms caused by an injection of serum. After an incubation period which usually covers from five to twelve days, local redness and itching or swelling surrounded by urticarial wheals develop. This is followed by swelling of the lymph nodes, fever, a rash which may spread over the body, edema and swelling of the joints. These symptoms all develop only in severe cases, various combinations occur, and one or another symptom may be most prominent. In the great majority of cases, the rash is the most prominent symptom and is best likened to an attack of "hives" and is of no more seriousness.

Only about 20 per cent. of those injected with serum develop a rash and in many cases only a local reaction occurs.

In a few cases, the reaction occurs more quickly. An immediate general reaction is very rare. This immediate general reaction may be severe and alarming; in a very few instances it has been fatal.

Not all the cases described as fatalities due to the serum will stand close investigation. Some are clearly due to heart paralysis caused by the diphtheria toxemia, and in some the cause is doubtful. These serious accidents have been mostly in adults and many of the cases were asthmatics. How rarely this occurs is seen from our own experience in New York City, already referred to, where only two fatalities occurred since the introduction of antitoxin. If we refer to the number of deaths from diphtheria in nineteen cities for 1894 and 1904 we find there is a reduction of over 10,000. On this basis, one is safe in estimating that the daily saving of life by antitoxin is greater than the total number of fatalities due to its use during the entire sixteen years since its introduction. Further, the danger from immediate general reactions is fortunately almost *nil* in young children. It is in them that the disease causes the greatest loss of life, and antitoxin must be used most freely.

SECOND INJECTION

Arthus, in 1903 at the instigation of Lichet, investigated the results of repeated injections of horse serum into rabbits. Rosenau and Anderson, Otto and others observed the results in guinea-pigs. They found that serum itself gave no toxic effects on the first injection, but if a certain time was allowed to elapse the succeeding injections were toxic. Von Pirquet also found that when a second injection in man gave symptoms, these came on much more quickly, at times immediately, instead of occurring after an incubation period of some days. An interval of about ten days must elapse between two injections for this change in reaction to become evident.

With this interval coming between, the second injection in man is apt to be followed by a local reaction in a few hours and a general reaction within twenty-four hours. In some cases the reaction comes on in a few minutes. These reactions may in some cases be much more violent than reactions following the first injection; in some instances they have been alarming. The most important point, however, is the change in the time of reaction.

THE FREQUENCY OF SERUM REACTIONS

The frequency of serum reactions increases somewhat with the size of the dose; thus Weaver[6] reports that 11 per cent. of those receiving less than 10 c.c. of serum

6. Arch. Int. Med., 1909, III, 485.

showed reactions, while 27 per cent. developed symptoms when between 10 and 20 c.c were given. The serum of some horses is more apt to cause a rash than that of others; further, some people react more readily than others.

ERADICATION OF AFTER-EFFECTS

The first method that would occur to anyone would be to give as much antitoxin as possible with a minimum of serum. One way to do this is to have very high potency serum so that little need be used. If we could separate the antitoxin from the serum elements this would be the ideal way. A long step in this direction has been taken. The antitoxin is bound up with a portion of the globulins. These are separated from the other constituents, giving a refined and concentrated antitoxin. In this way a large number of units can be given in a small bulk, and naturally less foreign proteid than if the same number of units had been given in the original serum.

This globulin solution containing antitoxin can be injected with much less tendency to produce serum after-effects.

After-effects do still occur, and in rare instances are serious, but compared with the benefits of antitoxin, viz., in the prevention of diphtheria and the saving of thousands of lives yearly, they are very small indeed. There is every possibility that with further experimental work, based on animal tests, the antitoxin will be obtained in a practically pure state, and that even these few untoward effects will be wholly eliminated.

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ELEMENTS OF ERROR IN STATISTICS OF BREAST AMPUTATION FOR CANCER

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I have long held the belief that the statistics of recoveries after operations for neoplasms of the female breast, diagnosed as cancer, were unreliable as a basis of scientific knowledge.

It is not my purpose in presenting this paper to arraign a settled professional judgment, or to impeach the accuracy of eminent observers. My object is to emphasize the fact that tumors of the breast diagnosed as malignant, do not, in a certain considerable percentage of cases, undergo malignant degeneration, and that the histologic arrangement of a tumor does not necessarily determine its future life history or development; that certain tumors removed for malignancy would, if unmolested, eventually disappear. This announcement may be regarded as rank heresy, although easily demonstrable; and if proved, render, *pro tanto*, the records of recoveries for long periods of time after amputation of the breast for cancer, unreliable. Opinions based on the macroscopic appearances of breast tumors are no longer regarded as of much diagnostic value. The topography, mobility, density, contour, duration, absence of adhesions, trauma, pain, sensations, family history, etc., are contributory evidences. The final decision as to diagnosis rests on morbid histology. But there is obviously something more required than microscopic arrangement of cells in order to predict malignant activity in a given tumor; essential factors in the chemistry, biology and physiology of malignant and benign neoplasms that have thus far eluded our cognition. Dr. H. Gideon Wells,[1] in an interesting paper on "The Resistance of the Body to Cancer," refers to the abundant available evidence that the human body has some means of natural defense against cancer, and that this property of resistance applies more or less to all tumors. Among the natural means of defense he cites the following:

1. Spontaneous local inhibition or temporary retardation of growth.
2. Retardation of recurrence after removal.
3. Retrogression of secondary growths after removal of the primary tumor.
4. Disappearance of portions of tumor tissue left after an incomplete operation.
5. Spontaneous healing of a primary tumor without any operative intervention whatever.

Actual spontaneous disappearance of tumors, microscopically determined to be malignant, is attested by numerous eminent observers; e. g., Martin of Greifswald reports spontaneous disappearance of scirrhus of the cervix and vaginal vault, microscopically determined, with no recurrence after twenty-two years; Jacobsthal, carcinoma of the temple; Saar, a small carcinoma of the breast, and the spontaneous healing of chorion tumors observed by Gaylor and Clows and the spontaneous disappearance of superficial carcinoma observed by Mohr and others. The processes of natural defense in these cases are variously ascribed to calcification and the ensnaring and invasion of the cancer cell-nests by fibrous tissue and the strangulation of cancer tissue by fibrous overgrowth. This body resistance to active malignant proliferation is abundantly attested and proves the presence of at least one constant element of error in the surgical statistics of cancer cure after amputation of the breast.

In view of these facts, it is interesting to inquire what would become of the 40 per cent. of reported recoveries after amputation of the breast by skilled operators, and the 10 to 20 per cent. of this 40 per cent., free from recurrence after three years, could we have eliminated from the records the cases that were non-malignant, those that would not have taken on malignant activity, and the smaller percentage that might have spontaneously disappeared by the natural process of body resistance? An unbiased consideration of these elements of error in our scientific data, at present indeterminate, and possibly indeterminable, leads to the pessimistic conclusion that tumors of the breast, having once taken on malignant degenerative action, are never, or rarely cured by any operation whatsoever.

Here permit me a word regarding the classical three-year period, after which, there being no return, patients are considered cured. As such they swell statistics as operative triumphs in cancer cure. The professional world has, I believe, quite generally adopted Professor Volkmann's teaching, that patients three years after operation with no return, are to be regarded as cured. Now as we are considering statistics of cancer after operation with reference to accuracy as a basis of final judgment and scientific knowledge, it behooves us to define accurately our meaning of "cure." If by cure, we mean a definite eradication of a disease, leaving the organism in a healthy state, we clearly misuse and strangely pervert its meaning. It is sheer sophistry or juggling to apply the term "cure" to the mere arrest, or temporary disappearance of a morbid process, and unlimited audacity to consider the results of the operation as *post hoc*—a necessary anatomic sequence. It is known that the surgical records are replete with numberless examples of recurrence of cancer in the bones,

1. Wells, H. Gideon: The Resistance of the Body to Cancer, THE JOURNAL A. M. A., May 29, 1909, p. 1731.