THE ECONOMIC EFFECTS OF THE NEWER TREATMENT OF DIPHTHERIA

by

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HISTORICAL

The difficulty in stating when diphtheria was first known as a specific disease can be appreciated when we remember that only in comparatively recent years were the clinical features clearly grasped and described. In the writings of Hippocrates minute and exact accounts of diseases occurring in the mouth, throat and nose are set forth, but in none is there a picture which accords with that of diphtheria. Epidemics at present are so characteristic that even the laity can diagnose them and it seems certain that if this disease had occurred in Ancient Greece, Hippocrates or men of his school would have recognized it.

The disease seems to have been well known in Egypt, Syria, and Palestine in ancient times, for there are references to it in the Babylonian Talmud, a work published in the 5th century. An Eastern origin has been indicated by the writings of a Cappodocean physician, Sallen, who lived in Rome during the latter part of the 1st century. Galen describes tonsillar ulcers which are broad, deep, dirty and covered with a white, bluish or black membrane. His treatment, the first mentioned, was clysters, cautery, embrocations, catoplasms, fomentations, and cupping of the part. Venesection and alum and honey were used in severe cases.

Hirsch in his Handbook of Geographical and Historical Pathology, 1886, says that Baronius mentions a throat pestilence in Rome in the year 856 and that Short mentions an angina plague which carried off a great number of children in England in 1389. Hirsch also mentions an account of von Ward who states that an unknown plague came to the Rhine

in 1517. In 1748 the pestilence reached England and was minutely described by Fothergill as a sore throat with ulcers. Francis Home of Edinburgh, in 1765, advised venesection, leeches, blisters, inspiration of steam and alcohol vapour and tracheotomy when the membrane became detached and lodged. No advance in therapy occurred from Galen's period, therefore, to 1748.

Our modern conception of the disease dates back to Prof. Bretonneau, who in 1826 published a classical description, giving its contagiousness, pathology and symptoms. He called the disease "diphtherie" from the Greek "diphthera" meaning leather. Trausseau, in 1828, confirmed and extended the investigations of Bretonneau but concluded that the changes in the mouth were local manifestations of a general disease. Virchow, in 1844, distinguished between the simple catarrhal membrane which could easily be stripped off and the form in which together with necrosis there was a deposition of fibrinous exudate in the mucous membrane itself. He emphasized the infectious nature of the disease by citing cases of direct inoculation. He told of the Dr. Herpin at the hospital of Tours who when cauterizing the throat of a child was struck on one of his nostrils by a membrane expelled by the child in a fit of coughing. Severe diphtheritic inflamation developed at the site and spread over the nasal cavity. Later severe paralysis developed and the doctor finally died.

In spite of the frequent instances of accidental inoculation with diphtheria material, Bretonneau, after forming false membranes by the use of chemicals, noted the dissimilarity and stated that the two

types of inflamation were by no means identical. Other men, Labodia-Lagrave, in 1873; Duchamp, in 1858; Oertel in 1871 and Hamelle in 1875 experimented with the transmissibility of diphtheria to rabbits and dogs and pigeons by inoculating them with bits of membrane, but their results were not conclusive and threw little light on the essential nature of diphtheria.

Since animal inoculation did not settle the matter it became necessary to find the etiological factor by other means. Some conception of bacteriology had been developed by the middle of the 19th century and shortly thereafter the membranes of diphtheria were studied bacteriologically. Oidium albucans and Lephothrix bucallis were found and said to be the causative agent. Oertel 1868 and von Recklinghausen 1871 found micrococci and rods which they considered the cause. Klebs, in 1883, at the Congress for Internal Medicine, gave an account of his researches in which he found "extremely short slender rods imbedded in a helly-like substance" in the membranes. He did not isolate the organism and therefore could not fulfill Koch's postulates. It remained for Loeffler in 1884 to satisfy the doctrine.

On the eve of the discovery of a specific cause for diphtheria came the first great advance in treatment. Dr. Joseph Dwyer of the New York Foundling Hospital conceived the idea of passing a tube into the throats of those having laryngeal diphtheria. It was eight years before he saved a case, however.

DEVELOPMENT OF OUR SPECIFIC THERAPY

This organism described by Klebs and isolated by Loeffler and demonstrated to be the causative agent of diphtheria is known as the Klebs-Loeffler bacillus or Coryne bacterium diphtheriae.

Loeffler noted in his animal experimentation that the bacilli were found usually in very small numbers and only at the site of inoculation. He considered the death of the animals as due to a poison produced by the bacilli. Raux and Yersin working with the knowledge that the bacilli of diphtheria does not multiply in the organs of persons or animals but is found only in the membranes set out to prove the existence of a diphtheria toxin. In a report of their work, in 1888, they tell that the bacilli free filtrate of a broth culture of diphtheria organisms has the power of producing when injected into animals the typical symptoms of diphtheria. A toxin produced by the bacilli had thus been found.At the present time the toxin has been so purified that as little as 0.0005 cc. will kill a guinea pig.

The next step in the progress toward a specific therapy was inaugurated by Behring and Kitosato, who, while working in Koch's laboratory in Berlin on toxins of diphtheria and tetanus, discovered that animals recovering from an initial dose of diphtheria poison were immune to the systemic effects of a second. Behring conceived the idea that in diphtheria an immunization might be produced artificially to simulate the immunity obtained following the convalescence of many infectious diseases. In 1891 Behring communicated his results to the 7th International Congress of Hygiene and Demography in London. He wrote:

"During the course of the last few months I have been able to demonstrate that the resistance of guinea pigs against diphtheria poison is increased with their resistance against the living bacilli, and that the blood of highly immunized guinea pigs possesses outside the body the power to destroying the diphtheria poison and further that guinea pigs can be rendered immune by interperitoneal injection of the blood of immunized animals or if infected can be cured".

Before an attempt could be made to use this newly found treatment clinically some means of standardization was necessary. Ehrlich for this purpose proceeded to investigate the subject from its biological standpoint. The absolute toxicity was accurately measured by ascertaining the exact dose required to kill a guinea pig weighing 250 gms. on the 4th or 5 th day after injection. This amount was taken as a "unit" of toxin. One thousand times the amount needed to neutralize this unit was regarded as a "unit" of antitoxin.

Not until 1894 was the immune serum produced in such quantities as to be used on a large scale in man. It was then quickly adopted throughout the world but it caused disappointment and bitter opposition. One thousand units of antitoxin was thought adequate for any case, but little did they know of the fact that unless a specific case were treated before the toxin had affixed itself in the tissues of a patient a liter of antitoxin would do not good.

TABLE I

Table Showing Effect of Early Treatment on the Mortality Rates of Diphtheria, after Faber (1904).

Commencement of serum treatment	Number of Patients	Number of Deaths	Percentage Mortality	Calculated No. deaths according to entire mortality of the group 11.5%	Difference between actual and calculated mortality.
1st Day	99	7	7.1	11	-4
2nd Day	641	48	7.5	74	-26
3rd Day	763	69	9.0	88	-19
4th Day	555	63	11.4	64	-1
5th Day	334	52	15.6	38	+14
6th Day	171	29	17.0	20	+9
7th Day	80	17	21.3	9	+8
Later than 7th	196	39	19.9	23	+16
Unknown	298	35	--	--	--

Total 3137 359 Average 11.5

In addition the variations in dosage for cases of different severity and cases in different age groups was not appreciated. Deaths fron shock and serum sickness mystified physicians. They claimed that the therapeutic serum had a bad effect upon the heart and that complications were more common. It is a thought here that perhaps more lived to show complications. Although the mortality rates were reduced, morbidity rates remained the same. Methods of prevention were sought. Passive immunity was used soon after serum was discovered, but the period of immunity was too brief. After the original mark of Romer, Bela Schick, 1913, of Vienna, introduced the skin test that made intelligent immunization possible on a large scale. This skin test in furnishing a basis for selection of persons who are susceptible and who need immuni-

zation is extremely valuable in preventing the waste of costly sera and work as well as obviating unnecessary risk of sensitizing people to horse serum.

In 1907 Theobald Smith suggested the possibility of active immunization of human beings by the use of a mixture containing both toxin and antitoxin but with a slight excess of the former in order to produce the active or longer lasting immunity. This procedure was first employed clinically by von Behring in 1913, but the methods of his procedures were not fully set forth in his earlier communications. Park and Zingher are responsible for the classification of Behring's work for clinical application in America. This form of immunization has been almost universally used. More recently Slanny and Hopkins of England, and Roman of Paris, have introduced formaldehyde treated toxin, a substance with little or no toxicity, and which gives no reactions in children, but which produces like toxin-antitoxin a long lasting active immunity.

Thus, we have through the efforts of Klebs, Loeffler, Roux and Yersin, von Behring, Schick, Theobald Smith, mainly, our newer and present day prophylactic and specific curative treatment of diphtheria. Since their time antitoxin has been markedly purified. The reaction producing fractions of the horse serums have been almost entirely removed. A careful history into previous serum therapy and allergic phenomena, a skin test and, if necessary, a desensitization will prevent serum treatment reactions.

RESULTS AND DISCUSSION OF MORTALITY RATES BEFORE AND AFTER THE INSTITUTION OF OUR NEWER TREATMENTS.

It is now about thirty eight years since antitoxin was given to the world as a specific treatment. Prior to 1895 the crude mortality rate was about 100 for each 100,000. Men who had stood helplessly by and beaten, now with the aid of this new specific were able to treat with success. Hospitals saw their mortality rates cut in two. Since 1895 the use of antitoxin in the treatment of established diphtheria has become almost universal.

An examination of the literature shows that numerous studies have been made, and that the greater number of which have shown a marked decrease in mortality as a result of the specific treatment. Nevertheless, objections have been made that such statistics are open to gross error and that granting the statistics be accurate, the fall in mortality may be similar to that of scarlet fever, for which we had no specific treatment, until 1925. In support of the view that we (do) have a definite response from our newer treatments there are the reports in the Journal of the American Medical Association of a committee studying diphtheria death rates in our principal cities for fortypne years. These are given in the following tables, Table II to Table VII, inclusive. In the studies three different eras are shown, first that from 1890 through 1894 during which we had no specific treatment, next comes the period in which the use of antitoxin as a curative treatment became widespread, 1895 to 1922. Finally we have the years from 1922 to the present time, during which both antitoxin and toxin antitoxin were used-

the first as a therapeutic agent and the second as a preventive.

TABLE II

DIPHTHERIA MORTALITY RATES

NORTHEASTERN CITIES

	1931	1930	1929	1924	1919	1914	1909	1904	1899	1894
	1925	1920	1915	1910	1905	1900	1895	1890		
Boston	4.7	2.9	8.3	20.2	26.3	20.0	26.2	53.7	83.9	112.2
New Haven	0.6	.6	1.6	7.1	14.2	14.9	22.7	15.6	54.8	74.5
Cambridge	.9	.9	3.2	8.9	12.9	23.8	26.8	46.7	71.9	58.0
Hartford	2.4	1.2	5.3	11.9	13.8	25.3	28.1	38.8	47.8	120.9
Springfield	2.6	5.3	10.3	15.4	24.9	19.1	31.3	29.6	51.3	68.2

Studying these mortality rates as a whole it is evident that the greatest decline in deaths came directly after 1894. Boston, for example, had a decrease of 28.3 for the five years following 1895, as compared with the same number of years preceding that date. Four cities in this group of twenty-five selected had increases in their death rates. The others had definite and marked drops during this period. From 1900 until 1925 the incidence of deaths took a more or less gradual trend downward, but it was not until after the first five year period between 1925 and 1929 that we began to have definitely low mortality rates.

TABLE III

CENTRAL CITIES

	1931	1930	1929	1925 1924	1920 1919	1915	1910 1909	1905 1904	1900 1899	1895	1890 1894
Rochester	0.6	1.5	7.5	16.9	12.7	22.1	32.4	32.3	45.9		96.6
Philadelphia	1.5	2.5	11.8	16.7	22.7	24.6	34.1	50.0	100		119.6
New York	2.6	2.9	10.7	14.0	21.8	28.0	40.0	58.0	85.8		134.4
Jersey City	4.1	16.1	11.5	18.4	21.0	23.2	32.6	57.9	83.4		108.6
Pittsburgh	4.1	8.8	11.5	20.1	22.3	29.3	20.4	36.9	37.9		86.4

TABLE IV

SOUTHEASTERN CITIES

	1931	1930	1929	1925 1924	1920 1919	1915	1910 1909	1905 1904	1900 1899	1895	1890 1894
Baltimore	2.8	2.5	7.6	11.4	13.5	14.2	16.1	33.0	68.1		70.0
Atlanta	3.2	1.1	7.0	13.3	10.1	12.5	14.2	11.1	10.5		8.8
Richmond	5.4	5.5	6.9	9.8	5.8	7.0	9.8	24.4	17.6		59.7
Wilmington	6.6	10.3	10.0	11.6	15.2	18.0	27.8	50.9	84.9		83.8
WAshington	7.1	3.7	7.1	10.5	11.9	6.9	11.2	23.5	50.9		77.9

TABLE V

MIDWESTERN CITIES

	1931	1930	1929	1925 1924	1920 1919	1915	1910 1909	1905 1904	1900 1899	1895	1890 1894
Cleveland	1.2	4.1	15.3	14.7	20.0	24.6	20.8	42.6	45.3		95.7
Milwaukee	1.8	3.6	8.5	11.4	19.8	27.8	26.4	22.7	51.7		116.2
Dayton	2.1	0.5	4.6	9.4	9.3	22.4	13.3	17.2	27.4		82.9
Detroit	5.8	11.0	19.7	24.3	32.2	33.3	22.6	38.5	62.9		132.9
Chicago	6.2	12.2	11.7	17.5	31.2	37.9	27.0	33.9	69.7		117.3

Statistics in order to be of value should cover a great number of years. The above tables do not given an adequate picture of the mortality rates, their fluctuations before the period of antitoxin. W. H. Park and C. Boldnan have conbined the statistics of deaths and death rates from diphtheria, and Craup in New York, Brookly, Boston,

TABLE VI

WESTERN CITIES

	1931	1930	1929	1925	1924	1920	1919	1915	1914	1910	1909	1905	1904	1900	1899	1895	1894	1890
Seattle	0.6	1.6	1.4		6.6		5.5		12.5		13.4		24.2					
San Francisco	.8	2.2	4.6		2.3		1.7		9.2		14.4		44.2		21.6		54.8	

Pittsburgh, Baltimore, Philadelphia, Berlin, Cologne, Breslau, Dresden, Hamburg, Kingsberg, Munich, Vienna, London, Glasgow, Liverpool, Paris and Frankfurt and put them into a curve covering the years between 1878 and 1905. These are shown in Figure I, following.

TABLE VII

SOUTHWESTERN SITIES

	1931	1930	1929	1925	1924	1920	1919	1915	1914	1910	1909	1905	1904	1900	1899	1895	1894	1890
New Orleans	3.8	8.5	8.5		6.5		11.6		19.6		10.2		11.5		17.1		51.3	
Oklahoma City	5.1	7.0	10.9															
Dallas	6.6	6.9	9.8		8.3		7.4		6.9		8.1		16.9		16.0		21.8	

CHART SHOWING COMBINED CURVE OF NINTEEN CITIES

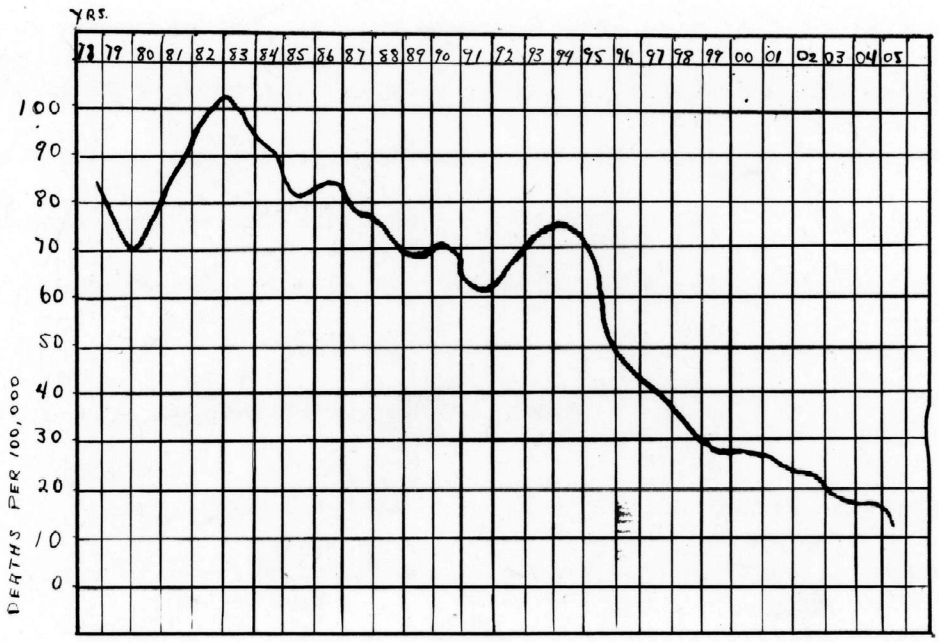


FIG. I

As was stated previously there are those opponents of serum therapy who think that apart from the use of diphtheria antitoxin death rates are falling because the disease, like scarlet fever, is becoming milder. In a paper read before the National Academy of Science, November 1926 Doering(in Massachusetts) showed that diphtheria death rates in the state of Massachusetts from 1875 to 1925 fell about on a trend line within range of chance distribution. He notes that as the curve passes through the year 1895 that there certainly was not a marked change in its direction. (See Figure II). What he found true for Massachusetts he says is also true for other countries, states and cities. He notes that the general trend for 20 years preceding 1895 is the same as that in succeeding years.

Lee in the American Journal of Public Health presented a study of curves of scarlet fever and diphtheria mortalities in England and Wales (Figure III) and remarked that there is a fall in mortality from 35 to 10 per 10,000 after 1895 but wonders whether this fall in death rate is one which we would anticipate with so specific a curative agent as diphtheria antitoxin. He says that the change does occur around 1895 but remarks also that scarlet fever, which had no specific treatment, has also fallen along a trend line practically identical to that of diphtheria. Since diseases tend to wax and wane in their prevalence Lee questions whether the decline in mortality is due to the administration of antitoxin or whether it represents a natural trend.

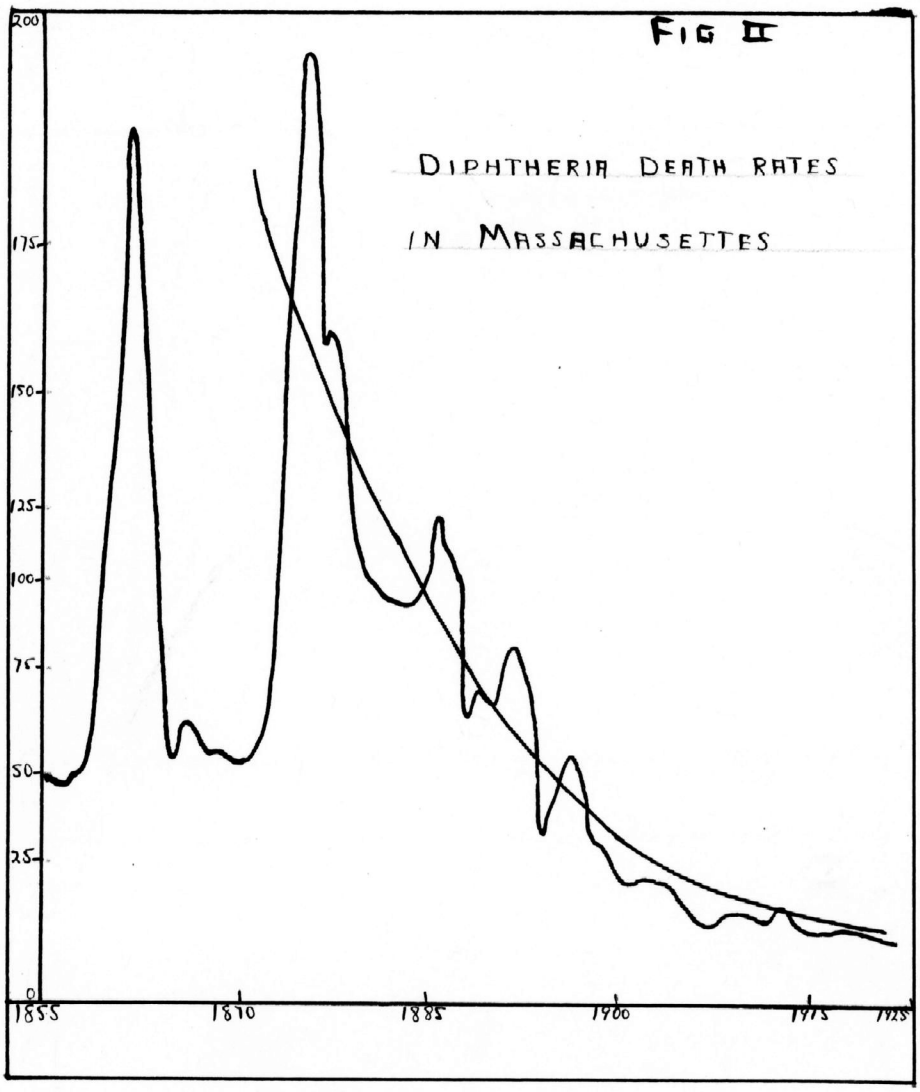
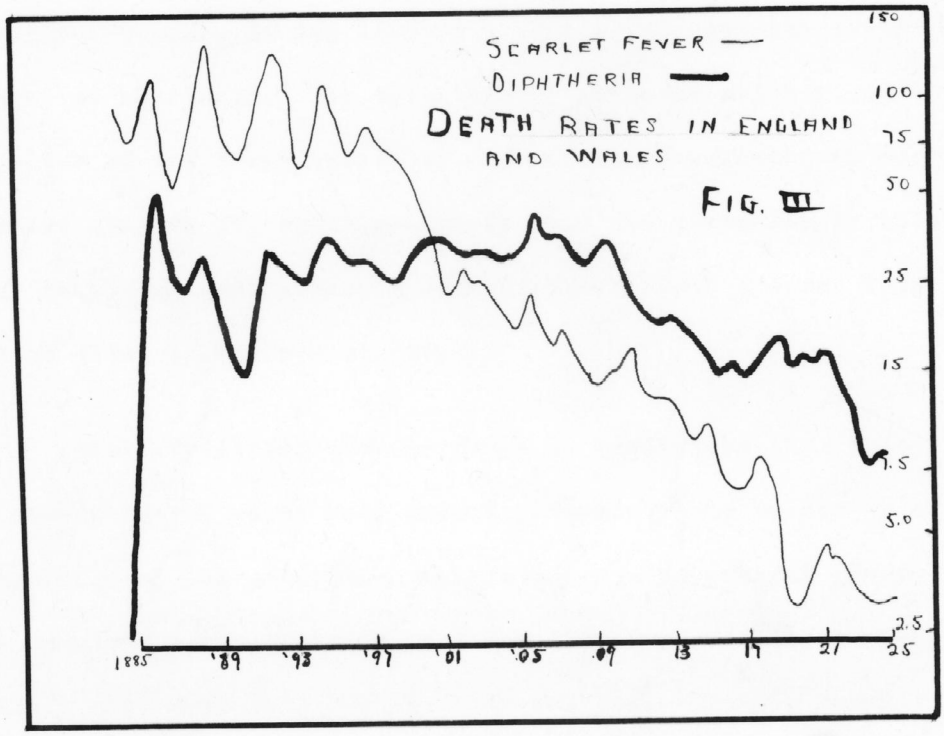


FIG II
DIPHTHERIA DEATH RATES
IN MASSACHUSETTES
200
175
150
125
100
75
50
25
0
1855
1870
1885
1900
1915
1925


SCARLET FEVER
DIPHTHERIA
DEATH RATES IN ENGLAND AND WALES
FIG. III
150
100
75
50
25
15
7.5
5.0
2.5
1885
'89
'93
'97
'01
'05
'09
13
17
21
25

On the other hand, with absolute case statistics Fibinger cited by Park gives data on the alternate treatment of cases with antitoxin. Amongst 238 cases treated with antitoxin 8 died giving a mortality of 3%. Amongst 245 cases treated without the use of antitoxin 30 died giving a mortality of 12%. Zucker in 1905 made a study of Steiermark where at the highest estimate duly two-thirds of the cases received antitoxin. The total number of cases which since the introduction of the serum treatment did not receive antitoxin was 12,000. His chart (Figure IV) shows concisely that the mortality in those cases not receiving antitoxin was roughly three times greater than in the cases to which it was administered.

With statistics such as these it would seem highly improbable that our decreased death rate from diphtheria could be due to a lessened virulence of the organism. Tabulated case reports of groups, half of which received serum treatment and the others non-specific treatment, certainly mean more than the plotting and comparison of trend lines. That a reference can be made to a cause other than specific prophylaxis and therapy for the decline in death rates from diphtheria by simple comparison with the curve of another disease seems to be an illogical assumption.

DIPHTHERIA CASE MORTALITY IN STEIRMARK

(AFTER ZUCKER)

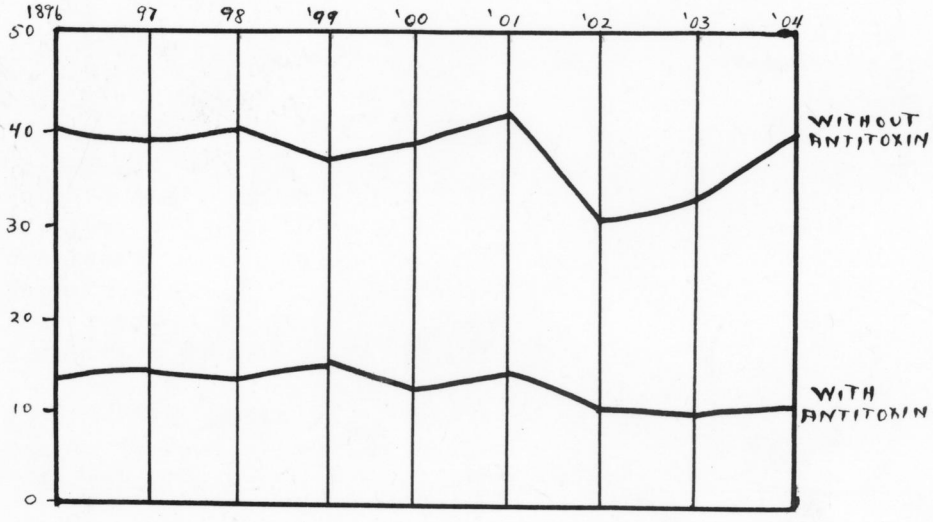


FIG. IV

During the past nine or ten years many cities have carried out extensive immunization programs. These since the greatest incidence of mortality is among children have been done for the most part in those between the ages of five and twelve.

TABLE VIII

SEX

Male 27,299
Female 26,348.

AGE	NUMBER	PERCENTAGE
Under 1 year	3,736	7
One year	8,001	15
Two years	7,990	14.5
Three years	7,207	13.5
Four years	5,989	11.
Under five years	32,923	61
Five to Nine years	14,818	27
Ten to Fourteen years	3,191	6
Unknown	87	-
Total	53,647	

A table showing the susceptibility of various ages to diphtheria is shown in Table IX. An interesting correlation between blood groups and the ability of an individual to develop an immunity is brought out by Theobald Smith. He has noted that there are variations in the degree of complete immunity an individual can produce. Some people do not have the power of producing any immunity. A mother in blood group II and a father in blood group III have a child who happens to be in group II. The mother after an immunizing procedure had only a very small titre of antitoxin in her blood, the father after the same procedure had a high

titre. The child since he is in blood group II has been observed to have, as did his mother, very little power of producing antitoxin. No matter what immunizing procedure is done they will never enjoy a good and adequate immunity. This knowledge may be of some value in our present prophylactic programs.

Toxin antitoxin has been used generally but more recently, 1924, because of the absence of reactions in its use, toxoid or antitoxin has replaced the T.A.T. New York City introduced the first mass immunization in 1918 which resulted not in a marked fall in mortality rates but only a gradual reduction. Wood, in 1928, pointed out that it is impossible to accept the New York experiment as significant in spite of the fall in mortality. If a straight line is affixed to the curve of mortality until 1917 and then exterpolated, this extended line approximates very closely to that which describes the actual experience since that date. Park, in 1922, recorded the history of 90,000 children who were Schick tested and if found Schick positive immunized, and the history of 90,000 controls who were neither tested nor immunized. During the period of observation 14 of the former contracted diphtheria as against 56 of the later. Where the risk of infection is so slight that only 56 of 90,000 controls contract the disease it is doubtful whether significant differences could be established even though they did exist. Bieber, in 1920, reported the after-history from 1913 of 1,097 immunized and 3,275 non-immunized children. Of the former 52 or 4.7% of the latter 493 or 15% contracted diphtheria.

TABLE IX

SUSCEPTIBILITY OF VARIOUS AGES TO DIPHTHERIA AS INDICATED BY THE DIPHTHERIA TOXIN TEST (SCHICK)

Under three months	15%
Three months to six months	30%
Six months to one year	60%
One to two years	70%
Two to three years	60%
Three to five years	40%
Five to ten years	30%
Ten to twenty years	20%
Over twenty years	10%

In spite of the inconclusive results noted above a few cities have had markedly striking reductions in their death rates following immunization. (Auburn, New York and Hamilton, Ontario have experienced excellent results). Auburn, having a population of 40,000, immunized in 1922 20,000 of its children. By 1925 their death rate from diphtheria was zero. Hamilton, Ontario, likewise carried out an extensive immunization of its children in 1922. Its mortality rate from diphtheria dropped from approximately 225 in 1922 to zero in 1924. Killegen, in 1932, however, has noted that non-immunized children living in a district where most children are immune show a lesser chance of surviving the infection should they contract diphtheria. This clearly is due to the fact that the non-immunized children living in an area where because of

the immune children about them, they have no chance for the light accidental subclinical infections with diphtheria organisms which would render them immune or at least more resistant to a large dose. Killigan believes that more children die in the above circumstance because immune children may harbor and disseminate an extremely virulent diphtheria bacillus without themselves being sick. This clearly is not a factor in the consideration of the disadvantages of prophylactic, but should be construed as an argument in favor of active immunization for all Schick positive children.

Anderson, in 1932, states that in the immunization of the preschool child even as early as six months after birth, we have the next step to complete eradication of diphtheria. It is a question, though, whether with the constant presence of the immune carrier and the Schick positive persons who can never be rendered immune whether we will ever have complete eradication. Perhaps the application of Darwin's survival of the fittest theory will solve this problem.

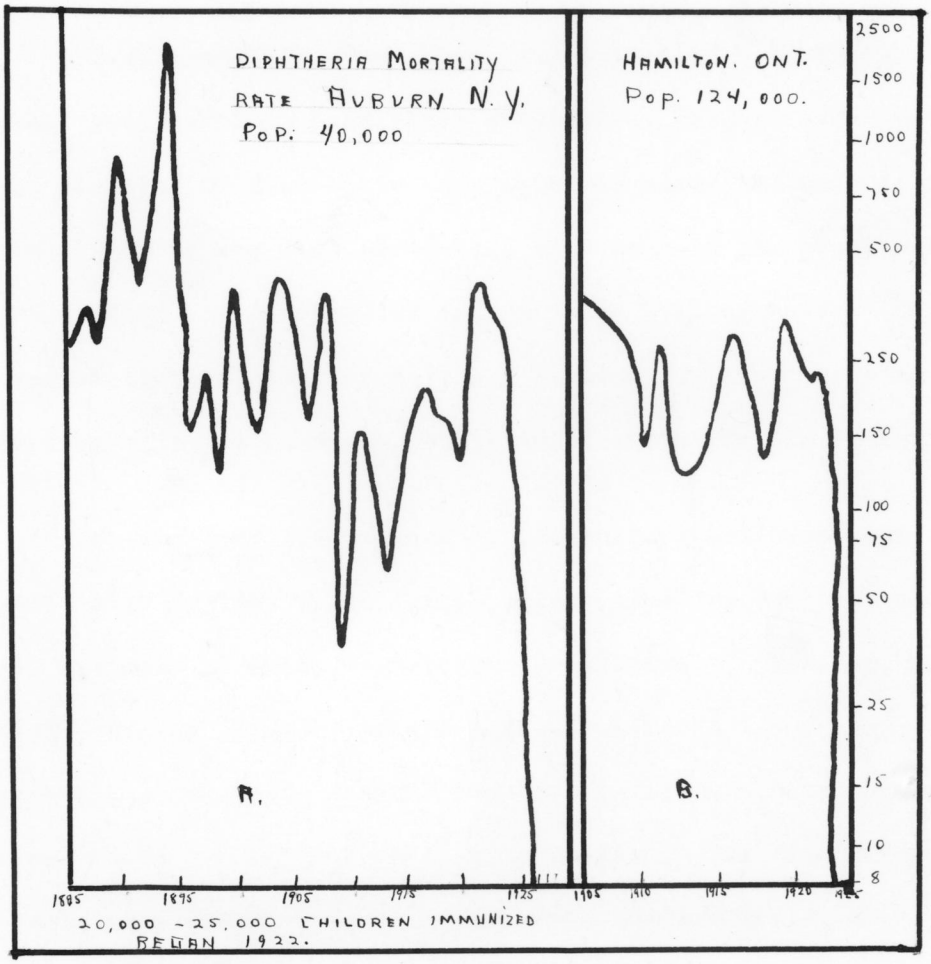

DIPHTHERIA MORTALITY
RATE AUBURN N.Y.
POP: 40,000
HAMILTON. ONT.
POP. 124,000.
2500
1500
1000
750
500
250
150
100
75
50
25
15
10
8
A.
B.
1885
1895
1905
1915
1925
1905
1910
1915
1920
20,000 - 25,000 CHILDREN IMMUNIZED
BEGAN 1922.

FIG. V

CONCLUSIONS

The problem of assessing the true value of our present day prophylactic and curative treatment of diphtheria becomes extraordinarily difficult. Several lines of approach are possible.

Case mortality rates have long been used as a basis for comparison, but our clear historical evidence of long period fluctuations in the severity of diphtheria forbids us to place too much reliance on such. It is somewhat perturbing that even in the present day there are signs that the disease can reassert its killing power. Without controlled statistical studies with and without our newer treatment it becomes impossible to estimate except in generalities the economic effects.

We are left with a mass of statistical evidence much of which suggests that antitoxin has had an effect upon lowering our mortality rates, but none of which is absolutely decisive. However, when experimental evidence is added to the above it affords in my opinion at least a perfectly sound basis for the conclusion that antitoxin is the essential weapon in the face of existing infection. The failure to establish an absolute statistical case shows merely how difficult it is to evaluate a particular remedy in human disease. Adequate countrols are never available, because immediately after obtaining sufficient evidence that a newer treatment is effective control series are discontinued.

The evidence which has accumulated with regard to the insusceptibility of Schick negative reactors is absolute proof of the value of this prophylactic measure. In spite of the meagre differences between

immunized and non-immunized in areas of low incidence there is ample evidence that epidemics by active immunization may be controlled. It is most effective in those areas where exposure to risk is high and protection especially desirable.

1. Bretanneau, 1826. Traite de ea diphtherite.

2. Behring and Kitasato. 1890. Deutche med. Wachensch. 16-113.

3. British Syst. of Bacteriology. 6-107.

4. Committee Study of Diphtheria Mortality Rates. Jour. Amer. Med. Assn. 90-1621
92-1759
94-1838
96-1768
98-1644

5. Doering. Nov. 1926. National Academy of Medical Sciences.

6. Faber. 1904. Jatrb. f. Kinderheilk. 59-620.

7. Slenny and Hopkins. Journal Hygiene. 21-142.

8. Hirsch - Handbook of Geographical and Historical Pathology. 1886.

9. Hirschfeld and Brokman. Jour. Imm. 9-571. 1924.

10. Kinnaman. Amer. J. Pub. Health 21-1013.

11. Klebs. 1883. Verhandl des Congress f. inn. Med. 2-125.

12. Lee - A Jour. Pub. Health. 18-1239.

13. Nuthal and S. Smith - Bacteriology 17. Diphtheria.

14. Park, W. H. New York Med. Jour. 68-107.

15. Park and Williams. Jour. Exp. Medicine. 1-164.

16. Park and Zingher. Am. J. Dis. of Child. 28-464. 1924.

17. Romer, P. Deutche med. Wachenschr. 27-529.

18. Roux and Yersin. 1888. Contribution a letude de la diphtheria. Ann. de l'inst.Pasteur. 2-629.

19. Rosenow - Preventive Medicine.

20. Smith, Theobald. Jour. Exp. Med. 11-24. 1909.

21. Tobley and Wilson - The Principles of Bacteriorlogy and Immun. 2-857.

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