less, proves fatal on injection. Nitrous oxid and oxygen anesthesia does not lower the resistance. Since in acute obstruction the body is continually receiving histamin and allied substances, ether is distinctly to be avoided. The resection should be performed under nitrous oxid or local anesthesia if possible. Otherwise drainage should be established with the patient under one of these forms of anesthesia, and the more elaborate operation delayed until, by these other measures, the toxemia has been reduced.

Hull and Rettger, and others have shown that the growth and action of the putrefactive bacteria is optimal in slightly alkaline mediums. The fermentative flora of the intestine, however, are distinctly favored and will displace the others in an acid medium. Replacing meat in the diet as much as possible by carbohydrates, especially lactose, which is slowly hydrolyzed and absorbed, favors the aciduric organisms, which produce acids by the fermentation of the sugars; and practically eliminates putrefaction. *Bacillus coli* does not disappear, but acts as a fermenter while these conditions are maintained. Cannon and Dragstedt have obtained favorable results with rats in this manner. The administration of lactose, besides the establishment of drainage, may, therefore, prove valuable in reducing the toxemia prior to the actual removal of the obstruction.

Hull House.

TOXIN-ANTITOXIN IMMUNIZATION AGAINST DIPHTHERIA *

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The development of antitoxin in the bodies of animals injected with diphtheria toxin is one of the best established of facts. Since von Behring and Roux announced the results of their investigations, large numbers of horses have been injected with toxin and have developed abundant antitoxin.

Unaltered diphtheria toxin has been used also as a stimulating injection in man, but it has to be used in very small and repeated doses; otherwise it would produce annoying local reactions and possibly even paralysis. It was early realized that if we ever attempted actively to immunize children, the advantage would be great if we could replace pure toxin with an altered toxin which would be equally effective and without danger.

USE OF TOXIN MODIFIED BY ANTITOXIN FOR ACTIVE IMMUNIZATION IN ANIMALS

The earliest knowledge that injections of toxin almost neutralized by antitoxin are capable of stimulating in animals the production of antitoxin came quite accidentally. As is well known, antitoxin can be detected and measured only by its characteristic of neutralizing toxin. The degree of neutralization of the toxin by the antitoxin is determined by the injection of a definite quantity of the mixture into guinea-pigs. The testing of the potency of the drawings of the serum from the various horses under treatment is likely to leave a certain proportion of the test animals alive because of their having received subcutaneously toxin with an overneutralizing amount of antitoxin.

* Read before the Section on Preventive and Industrial Medicine and Public Health at the Seventy-Third Annual Session of the American Medical Association, St. Louis, May, 1922.

The attempt to use these treated guinea-pigs several months later revealed the fact that many of the animals were immune. Investigation proved that this antitoxin immunity did not appreciably develop until the lapse of from four to six weeks.

Babes, in 1895, was the first to inject experimentally diphtheria toxin-antitoxin mixtures and to appreciate that not only slightly underneutralized diphtheria toxin, but also that which was slightly overneutralized, would bring about the development of antitoxin in animals.

A little later (1896), but independently, I made the same observations. Wernicke, in 1895, noted that guinea-pigs actively immunized by the injection of living bacilli and antitoxin gave birth to immune young, and that antitoxin was present in both the mothers and their offspring for at least eight months. In the winter of 1896, I began to use this knowledge concerning much overneutralized toxin practically, in starting the immunization of the horses which were employed for the production of diphtheria antitoxin.

I noted that the use of large amounts of overneutralized toxin was a safe and rapid method of beginning immunization. In the same year, Dreyer and Madsen made systematic investigations as to the effect of different degrees of overneutralization on the effectiveness of the toxin-antitoxin to stimulate antitoxin.

In 1903 I published results showing that an injection into a horse of 10,000 lethal doses of toxin which has been just neutralized usually causes the development of about 60 units of antitoxin per cubic centimeter of serum, while the same toxin neutralized sixfold usually causes the production of about three units.

In 1905, Theobald Smith studied the duration of immunity in guinea-pigs which had received toxin-antitoxin. He corroborated the work of Wernicke, and extended to two years the time during which guinea-pigs retain immunity.

The fact that the antitoxin would take a number of weeks to develop in those not originally possessing it made it not applicable to persons in immediate danger of infection. Therefore, in the presence of diphtheria, immunizing antitoxin injections would still be necessary in families and institutions. In the absence of any simple test for determining which individuals had natural antitoxin and which did not; we had to inject many unnecessarily, if active immunization were to be attempted. The success of the treatment would also be difficult to determine. These considerations delayed its application in man. On the other hand, we had the growing conviction that, wonderful as were the results of antitoxin, diphtheria could never be conquered by it. The combination of the ever present carrier of bacilli, and the slowness of people to recognize diphtheria when it develops, still permits the occurrence of 50 per cent. more diphtheria than we would otherwise have, and perhaps one sixth of the number of deaths. Furthermore, vital statistics revealed that diphtheria mortality and morbidity had not decreased during the last five years; for instance, in the state of New York, the mortality was 12.8 in 1917 and 16.8 in 1921.

Only one means presented itself to our minds which gave any hope of making another distinct advance. This was active immunization by means of toxin injections.

In 1913, the application by Schick of the intracutaneous neutralization test to detect antitoxin immunity

gave a simple means of testing for antitoxic immunity before and after the injections.

PRACTICAL APPLICATION OF DIPHTHERIA TOXIN-ANTITOXIN IN MAN

Von Behring, May 8, 1913, reported the injections of neutralized toxin in a small number of persons. Before giving the injections he used no Schick tests or other means of testing whether or not the subjects were already immune. He demonstrated by repeated guinea-pig tests that there was a quick development of antitoxin in many of those treated, but in others no antitoxin was detected at the time the tests were made. It is now known that the retests were made too soon to detect the development of antitoxin in those who had none at the time of the injections. The duration of the immunity was not investigated. Although von Behring referred to the toxin-antitoxin mixture as his discovery, what he used was exactly what several of us had described and used in experimental animal immunization during the last eighteen years. His real contribution was the demonstration in a few human beings of the safety of the injections.

The example of von Behring led Hahn and Summer shortly afterward to offer the toxin-antitoxin to the 4,300 children of six villages in the district of Magdeburg, where diphtheria was endemic. Of the 1,097 children injected, 633 received the full series of three injections; 255 received two injections, and 209 received one. The Schick test was not used before or after treatment, so it is impossible to know how many of the injected children possessed natural antitoxin and how many of the others developed it.

There was no difference in the development of cases of diphtheria among the treated and the untreated portion during the first two weeks following the completion of the injections; but after that time there was a lessening of the number in the treated portion. The immunization had no apparent effect on freeing carriers from infection. Until after the war, no further observations or immunizations were made in Europe.

Oct. 21, 1920, Bieber published his study of the histories of all the children mentioned above. Fortunately, he was able to trace the majority of those who were living in the district at the time of the injections. He reported that during the six years, 15 per cent. of those who had not received injections had had attacks of diphtheria; that only 4.6 per cent. of the total number inoculated, and only 3.3 per cent. of the fully treated had developed it. Because of the war, many of the diagnoses were not confirmed by cultures, and he believed that some of the cases were almost surely not diphtheria. Two of the incompletely treated children had died from diphtheria.

Bieber concluded that although the toxin-antitoxin had not given a lasting immunity to all who had received the injections, the results were satisfactory in that the percentage of persons having diphtheria was very much less in the inoculated portion than in that uninoculated. He believed that the results should stimulate more extensive trials.

PERSONAL OBSERVATIONS

Before and since the period of the war, the practical value of the toxin-antitoxin injections was subjected to continuous investigation by workers in the Bureau of Laboratories of the Department of Health of the City of New York. The results obtained and the conclusions drawn are as follows:

THE ANTITOXIN RESPONSE AND THE PERMANENCE OF THE IMMUNITY ACQUIRED

Late in 1913 we began the practical use of toxin-antitoxin injections for the immunizing of children against diphtheria, and established the facts that the procedure was harmless and that after three injections about 80 per cent. of those individuals possessing no antitoxin or insufficient antitoxin to protect from diphtheria, developed immunity. Those showing positive Schick reactions and receiving two injections, developed negative Schick reactions in about 70 per cent.; those receiving one injection, in about 50 per cent. We soon realized that the most important problem was the duration of the antitoxic immunity in those that had developed antitoxin. A satisfactory answer to this question required that immunizations be carried out in institutions where the children would be under observation for a number of years. A few suitable institutions were immediately sought for and obtained by Dr. Abraham Zingher and, later, additional ones

TABLE 1.—RECORD OF PERSONS ORIGINALLY GIVING POSITIVE SCHICK REACTIONS, NOV. 16, 1915; INDIVIDUAL RESULTS FOR FIVE AND SIX YEARS AFTER THREE TOXIN-ANTITOXIN INJECTIONS GIVEN ON NOV. 20 AND 25, AND DEC. 3, 1915

Observation Child No.	Retests					
	Jan. 29, 1916	June 29, 1916	January, 1917	January, 1919	January, 1921	January, 1922
1	—	—	—	—	—	—
2	—	—	—	—	—	—
3	—	—	—	—	—	—
4	±	—	±	—	—	—
5	—	—	—	—	—	—
6	±	—	—	—	—	—
7-12	—	—	—	—	—	—
13*	—	±	—	±*	—	—
14	—	—	—	—	—	—
15	—	—	—	—	—	†
16	—	—	—	—	—	—
17	—	—	—	—	—	—
18	±	—	—	—	—	—
19	±	—	—	—	—	—
20*	±	—	±	±*	—	—
21	±	—	—	—	—	—
22-26	—	—	—	—	—	—
27	+	—	±	—	—	—
28	—	—	—	—	—	—

* Given series of three injections.

† Fourteen of the twenty-eight present in 1921 had left.

± indicates a very faint Schick reaction; ±, a very moderate Schick reaction.

were added by Dr. M. C. Schroder. We have thus been able to keep under supervision for from three to six and one-half years about 10,000 children. From year to year, Drs. Zingher and Schroder have been reapplying the Schick test to these original children. With a few of them we are now in the seventh year of observation. We have had no serious immediate or late after-effects. In these institutions diphtheria has not developed in any child who has received three injections. Eighty per cent. of those who received three inoculations have developed sufficient antitoxin within three months to prevent the positive Schick reaction. Fifty per cent. of the remainder developed antitoxic immunity sufficient to give the negative Schick test before the end of the first year. The remainder received then or later a second series of injections, and all of these concerning whom we have information became immune. In some later investigations, we have encountered occasional children who resisted even two series of injections.

As an illustration of the methods used in retesting the children from year to year in the institutions, Table 1 is given. In it are entered the results of frequent Schick tests

of twenty-eight children who, having given positive Schick reactions, received immunizing injections and later gave negative reactions; these children remained in the institution and continued negative during five years. Of these, fourteen remained and continued negative for six years and ten continued negative for six and one-half years.

DISCUSSION OF RESULTS OF TESTS

Twenty-two became negative within two months, twenty-seven in seven months; twenty-five of these remained negative during the five years. One of the remaining became finally immune and two, Numbers 13 and 20, required a second series of injections in 1919.

In cases such as 13 and 20 it is impossible with our present knowledge to determine whether the difference in the degree of reaction is wholly due to a fluctuation in the amount of antitoxin present or whether the deviation from the negative is partly due to a variation in the strength of the toxin used in the Schick retest or to error in the placing of the supposedly intracutaneous injection.

The results in the twenty-eight children are representative of those obtained in the other institutions. With one or two exceptions among hundreds of children, all who did not respond to the first series of injections became negative to the Schick test after the second treatment. The 1916 and 1917

TABLE 2.—RESULTS OF ATTEMPTED IMMUNIZATION AS SHOWN BY SCHICK TEST THREE OR MORE MONTHS AFTER TREATMENT WITH THREE INJECTIONS OF TOXIN-ANTITOXIN; CHILDREN FROM PUBLIC SCHOOLS OF BROOKLYN; TESTS BY DR. SCHRODER

Number of School	Location	Total Number Children Retested	Positive Cases Which Became Immune	Per Cent.	Length of Period Between Treatment and Retest
158	Belmont Ave. near Warwick St.	370	254	68.7	3 mos.
156	Sutter Ave. near Barrett St.	329	292	88.8	3 mos.
173	Penn. Ave. near Liberty Ave.	163	144	88.9	4 mos.
29	Columbia and Amity Sts.	57	45	79.0	5 mos.
142	Henry and Rapelye Sts.	127	112	88.0	5 mos.
50	S. 3d St. and Driggs Ave.	82	74	90.3	6 mos.
16	Wilson Ave. near Bedford Ave.	241	216	89.7	6 mos.
72	New Lots Road	199	195	98.0	6 mos.
109	Dumont Ave. near Sackman St.	141	99	70.0	6 mos.
4	Berkeley Pl. near 5th Ave.	103	91	88.4	7 mos.
Total		1,812	1,522	83.9	

tests were made by Dr. Zingher, the latter one by Dr. Schroder.

As an example of the results following the injections in the schoolchildren, Table 2 is given.

The knowledge that about 80 per cent. of the children who possess no diphtheria antitoxin develop it after three injections of toxin-antitoxin and with very few exceptions retain it for at least six years, and that those who partially fail to respond do respond after a second series of treatments, affords us ground for the belief that we have a practical means of immunizing the child population of the country. Even though the belief that this change in the antitoxin content of these children is a permanent one should prove erroneous, it would merely mean that one would have to repeat the injections not oftener than once in six years.

PERMANENCE OF NEGATIVE SCHICK REACTION IN PERSONS WHO DEVELOP NATURAL IMMUNITY

At the Convent of St. Dominick, ninety-four of the original children who had given Schick negative reactions with Dr. Zingher's tests remained for five years. These children were retested at the two and five year periods by Dr. Schroder. In both retests ninety of these children showed negative reactions, while four showed positive reactions in one or the other retest. It is an interesting point as to whether the children who were negative originally had lost their antitoxin or whether the apparent change in reaction was due to other causes. We know from making the double Schick test (that is, one test on each arm) on several hundreds of

children, that routine tests made even by an expert are likely to show occasional errors. In this test series, about 2 per cent. of the children showing positive tests had them only on one arm. There was, therefore, no doubt that in 2 per cent. of these children, one of the two injections had been inserted too deeply so that the toxin did not remain in the skin and therefore could not produce the reaction. We

TABLE 3.—DEATHS FROM DIPHTHERIA GROUPED BY SEX AND AGES, CITY OF NEW YORK, YEAR 1917

Age	Males	Females	Total	Per Cent.
Under 1 year	73	60	133	11+
1 to 4 years inclusive	390	319	709	60+
Total under 5 years	463	379	842	72+
5 to 9 years inclusive	119	132	251	21+
10 to 14 years inclusive	9	13	22	2
15 to 19 years inclusive	6	4	10	1
20 to 24 years inclusive	2	8	10	1
25 to 60 years inclusive	9	14	23	2
Total all ages	608	550	1,158	

know also that slight differences in the strength of the toxin solution cause a borderline case to give either a negative or a positive reaction. Differences in technic and in toxin solution possibly account, therefore, for the apparent change in one or all of the four cases. On the other hand, we know that the amount of antitoxin in an individual changes somewhat from time to time, so that it is possible that one or all of the four subjects might have reacted at one time and not at another to the standard Schick toxin properly given.

Whatever the explanation of the apparent change in four cases, we have the remarkable fact that nearly 96 per cent. of the originally negative children remained negative during five years. Practically the same results have been obtained in all the other institutions.

INFLUENCE OF AGE ON SUSCEPTIBILITY AND THE RESPONSE TO IMMUNIZING INJECTIONS

It is common belief that the mortality from diphtheria is greatest at the ages of from one-half year to 4 years, inclusive; that it then drops steadily until at 10 years it is quite low and so remains during the rest of life. The figures in Table 3 give evidence that this belief is founded on fact.

The greater liability to infection during the first years of life is clearly shown in the results from the Schick test. Our findings in New York City are given in Table 4.

All reports show that under similar conditions the highest percentage of persons having antitoxin occurs among infants passively carrying their mothers' antitoxin, and among adults; between these ages there is first a decrease and then an

TABLE 4.—AVERAGE SUSCEPTIBILITY OF VARIOUS AGES TO DIPHTHERIA (AS INDICATED BY THE POSITIVE SCHICK DIPHTHERIA-TOXIN SKIN TEST), IN NEW YORK CITY*

Age	Schick + (Susceptible)
Under 3 months	15 per cent.
3 to 6 months	30 per cent.
6 months to 1 year	60 per cent.
1 to 2 years	60 per cent.
2 to 3 years	60 per cent.
3 to 5 years	40 per cent.
5 to 10 years	35 per cent.
10 to 20 years	25 per cent.
20 to 40 years	18 per cent.
Over 40 years	12 per cent.

* The percentage of positive reaction is considerably higher among those living in the country.

increase. The same reports show that similar age groups of different children reveal surprising differences in the percentages of those possessing antitoxic immunity.

Table 5 notes the very small percentage of susceptibles in an institution caring for little children gathered from the poorest and most crowded homes of the city. Table 6 exhibits the surprising difference in the results obtained from tests of pupils in different parts of Brooklyn.

A minimum, an average and a maximum result from among the larger Brooklyn public schools subjected to the Schick

test by Dr. Schroder or her assistants is given in Table 6. The ages ranged from 6 to 12 years.

The highest percentage of positive tests obtained by Dr. Schroder in any Brooklyn school was 72, and the lowest 16. These were in small schools. The average percentage of positives among 30,000 children in seventy-three Brooklyn schools was 41.5.

TABLE 5.—RESULTS OF THE SCHICK TEST IN AN INSTITUTION CARING FOR CHILDREN GATHERED FROM DENSELY POPULATED PORTIONS OF NEW YORK CITY

Age	Schick Reactions				Per Cent. Positive
	Positive		Border-land	Negative	
	+	±	±	—	
Under 5 years.....	6	2	0	35	18.5
5 to 10 years.....	21	2	8	220	9.0
10 to 15 years.....	5	2	4	79	7.7
	32	6	12	334	9.9

The sign ± indicates a trace of antitoxin.

In the Manhattan schools at the same time or a little later, Dr. Zingher among 52,000 children found that the percentage of positives was 30. The highest percentage of positives in any school was 67, and the lowest, 13.6.

The results obtained by Dr. Schroder among adults are very interesting as showing a much older age group. Among 4,396 adult inmates in an insane asylum there were 633 positive reactions, a percentage of 16. At all ages between 20 and 50 years, the percentage was about the same, but above 50 years of age the positives dropped to 10. There were a good many persisting pseudoreactions which made it extremely difficult in some instances to decide between a pseudoreaction and a combined reaction. The patients responded to the toxin-antitoxin injections as well as younger people, except that they showed more local reaction.

TABLE 6.—DIFFERENT PERCENTAGES OF CHILDREN GIVING SCHICK-POSITIVE REACTIONS IN FOUR LARGE PUBLIC SCHOOLS

No. of Brooklyn School	Total Number of Tests	Per Cent. Positive
50.....	1,433	19.60
125.....	1,064	36.84
149.....	1,056	41.19
156.....	1,148	61.84

IMMUNIZING EFFECT OF TOXIN-ANTITOXIN INJECTIONS IN INFANTS AT BIRTH AND DURING THE FIRST TWO YEARS OF LIFE

If it were possible to immunize young infants, this would be most desirable. In order to test this possibility, 2,000 infants were given full doses by Miss Denny on the third, eighth and eleventh days after birth. Most careful observations revealed absolutely no deleterious effects. At the end of a year, 100 of these infants were retested. Only 52 per cent. gave negative Schick reactions. Since untreated infants of this age give about the same result, it is evident that the combined effect of immature cells and the overneutralization of the toxin-antitoxin present (because of the passive immunity derived from the mother) prevents any appreciable response at birth to the toxin-antitoxin injections. Infants aged 6 months and over gave far better results.

Thus Dr. Blum observed the results of the injections in a number of older infants, in the Home for Hebrew Infants. His figures are given in Tables 7 and 8.

Dr. Byard also reports very favorable results among children in private homes. Many of these were not given the Schick test before receiving the immunizing injections. It is fair to assume that about 50 per cent. would have given negative Schick reactions. Of 286 such children, more than half of whom were under 1 year of age when injected, he noted that 143 (under 2 years of age when injected) when

retested after seven months showed 136 negative, five positive and two very doubtful Schick reactions. Of the whole number, seven, or 2.4 per cent., when retested at the end of eight months were definitely positive. Eighteen months after the injections, 1.8 per cent. were positive. These results are certainly very encouraging.

These results of Blum and Byard among infants aged 4 months and over are of extreme practical importance, because from 6 months to 3 years is the period when immunization is most necessary and when it creates the least disturbance.

CONSTITUTIONAL AND LOCAL REACTIONS FOLLOWING THE TOXIN-ANTITOXIN INJECTIONS

Constitutional and local reactions following the toxin-antitoxin injections are negligible in the infant; slight and infrequent in the young child; moderate or rather severe in perhaps 10 per cent. of older children, and slight, moderate or quite severe in a large percentage of adults. The effects are largely due to the protein contents of the culture fluid and are not due to the toxin as such. This is evident because the same reaction follows the injection of the toxic broth rendered atoxic by heating, or of a solution containing a minute quantity of autolyzed diphtheria bacilli. If the toxin were the cause, there would be little or no reaction in naturally immune persons. As is well known, these show

TABLE 7.—RESULTS OF TOXIN-ANTITOXIN INJECTIONS IN SCHICK-POSITIVE CHILDREN

Number of Infants	Age	Toxin-Antitoxin Injections	Lapsed Period at Time of Retest	Results of Schick Test
6	5 mos.	3	3-5 mos.	—
5	5 mos.	3	9 mos.	—
3	6 mos.	3	4 mos.	—
4	7 mos.	3	4-5 mos.	—
12	8 mos.	3	4-5 mos.	—
Total 30				

fully as much reaction as those who have no antitoxin, if not more reaction. Those individuals who give the strong pseudoreactions with the heated or unheated toxin of the Schick test are those who give the most severe reactions with the toxin-antitoxin injections. However, some who give no pseudoreaction with the Schick test give moderately severe reactions to the toxin-antitoxin injections. The horse serum is present in such a minute amount as to cause no appreciable reaction except in a few extremely susceptible individuals. It does not seem to sensitize them appreciably to later doses of horse serum.

In children of school age about 10 per cent. develop fairly sore arms and temperatures of from 99 to 103 F. About 5 per cent. feel miserable enough to stay at home from school

TABLE 8.—RESULTS OF TOXIN-ANTITOXIN INJECTIONS IN SCHICK-NEGATIVE INFANTS

Number of Infants	Age	Toxin-Antitoxin Injections	Lapsed Period at Time of Retest	Results of Schick Test
1	3 mos.	3	4 mos.	±
2	4 mos.	3	4 mos.	—
2	5 mos.	3	4 mos.	—
3	6 mos.	3	4 mos.	—
6	7 mos.	3	4 mos.	—
1	8 mos.	3	4 mos.	—
1	9 mos.	3	4 mos.	—
3	10 mos.	3	4 mos.	—
1	11 mos.	3	4 mos.	—
Total 20				

for one day, and a very few for two days. We have given about 40,000 inoculations this fall and winter without a single infection. Children that are constipated are advised to take a laxative on the day of the injection and to apply a moist dressing to the arm if swelling and soreness develop.

In adults, the reactions are not quite as severe as with the typhoid inoculations. The most severe reactions are restricted almost entirely to those who develop the marked pseudoreaction with the heated or overneutralized toxin. The fol-

lowing history gives an account of one of the most severe reactions that we have encountered:

A nurse at the Willard Parker Hospital was given toxin-antitoxin subcutaneously in the right arm, February 8. In the evening the arm in the region of the injection felt sore and looked red. The next day the soreness and tenderness were more marked. The highest temperature was 103 F. February 9, the patient was in bed. The temperature was 99. The right arm showed moderate redness of the lower two thirds, some induration and tenderness, and slight axillary tenderness. February 10, constitutional symptoms were

TABLE 9.—RESULTS OF INJECTION OF DIFFERENT PREPARATIONS OF TOXIN-ANTITOXIN IN GUINEA-PIGS

Number	Preparation Amt. in C.c.	Number Doses	Weeks Elapsed	Percentage of Neg. Schick Reactions	Number	Weeks Elapsed	Percentage of Neg. Schick Reactions	Number	Weeks Elapsed	Percentage of Neg. Schick Reactions
24	0.5	1	1	100	2	5	100	24	7	100
18	0.5	1	12	66	2	4	75	18	7	100
22	0.5	1	8	50	2	8	50	22	7	100
20	0.5	1	..	..	2	9	33	20	9	25
24A*	0.5	1	..	..	2	7	50	24A*	7	50
24	0.1	3	7	75	4	7	100			
18	0.1	3	10	50	4	9	60			
22	0.1	3	8	25	4	8	25			
20	0.1	3	8	0	4	8	40			
24A*	0.1	3	7	0	4	8	0			
10	0.1	3	8	0	4	8	0			

* Preparation 24 with an added 10 per cent. of its original amount of antitoxin.

absent. The temperature was normal. Redness and swelling persisted; induration was moderate; tenderness and pain were less marked; axillary tenderness was very slight. A Schick test and control which were made, February 9, both showed a moderate pseudoreaction, the two reactions appearing alike. An area of redness about the size of a 25 cent piece and some induration were present. A small secondary areola around the central area was of marked redness. The probability is great that the test was a pseudoreaction and not a combined reaction.

THE DEGREE OF IMMUNITY TO DIPHTHERIA INSURED BY A NEGATIVE SCHICK TEST

There is overwhelming indirect evidence which supports the view that under ordinary conditions sufficient antitoxin in the body to prevent the development of a positive Schick test will prevent the development of diphtheria. There can be no doubt that the injection of 500 units of antitoxin will give children an immunity for a period of at least twelve days and usually twenty days. (This is the period during which the Schick test remains negative when performed on such children.) The proof has been derived from its use in many outbreaks and in the exposed children of hundreds of thousands of families.

The recent statements by Havens that about 20 per cent. of diphtheria bacilli are of a different type from the one used to produce toxin for the immunization of horses, that the available monovalent antitoxin will not completely neutralize the toxin made by this other type and, therefore, that diphtheria may develop from infection with this other type in children showing negative Schick reactions to the standard toxin, have not been borne out by experience nor confirmed by us (Park and Williams) in experimental work.

The evidence that antitoxin is the only substance in the body that can prevent the toxin from acting is so conclusive that we can assume that a negative Schick test means the presence of sufficient antitoxin to neutralize it. The debatable points are: Is the minimum amount of antitoxin which is required to give a negative Schick reaction sufficient to prevent absolutely the development of diphtheria? if not, is it sufficient to prevent a toxemia? Closely bound up with the answer to these questions is the degree of certainty that the general practitioner can assume that, as ordinarily carried out, a negative Schick test proves the presence of at least this minimum amount of antitoxin.

It is undoubtedly true that a certain number of persons who have given the negative Schick reaction have developed inflammatory conditions of the throat with positive cultures and that these have been diagnosed as moderate cases of diphtheria. In discussing such cases, it is wise at present to let each person make his own deductions. It is unquestionably true that a certain percentage of Schick tests are made in a faulty way. It is essential to have toxin of approximately the right strength for the test. Toxin of the proper strength when it leaves the laboratory may deteriorate quickly. In testing outfits sent from a number of biologic plants, Zingher found marked irregularity in the contents of some of them. In one case, two out of five outfits failed to give any positive Schick reactions, even though the other outfits gave them regularly in the same children. We ourselves received by mistake a shipment of capillary tubes made of unsuitable glass. The toxin deteriorated rapidly when it was placed in these tubes.

Owing to imperfect technic or weak toxin, a certain number of persons are undoubtedly considered to have antitoxin when none is present. Such individuals are, of course, liable to diphtheria. Besides these, there are those in whom the Schick test is truly negative who have tonsillar exudate and positive cultures. These cases are comparatively few, and so far as I know are never characteristic of well developed diphtheria. It is possible, certainly, for a person to have virulent diphtheria bacilli and develop a throat inflammation from other bacteria. In such a case the positive culture shows the person to be merely a carrier. Even with a positive culture, a case can be considered as undoubted diphtheria only when the lesions are characteristic.

THE TOXIN-ANTITOXIN MIXTURE

The best mixture is one that is underneutralized and yet perfectly safe. As the mixture stands, the toxin deteriorates faster than the antitoxin, so that it gradually becomes neutralized and later overneutralized by the antitoxin. Therefore, a safe preparation is at its best when freshly prepared. As it would not be practicable to make new mixtures every day, we keep both the toxin and the antitoxin until they have become stabilized. After this has occurred, the toxin-antitoxin mixture changes very slowly. Even so, it is better not to use mixtures later than three months after their preparation unless animal tests prove them to be still slightly underneutralized.

It is noticeable that Preparation 24 gave much better immunizing than any of the others, except Preparation 18, which was a little inferior. The addition of 10 per cent. of the original amount of antitoxin to Preparation 24 lessened

TABLE 10.—IMMUNIZING EFFICIENCY OF DIFFERENT MIXTURES OF TOXIN-ANTITOXIN IN CHILDREN

School or Institution	Mixture Three Doses 1 C.c. Each	Date Injected	Date Retested	Total Number of Chil- dren	Percentage of Posi- tive Reac- tions	
					+	-
Colored Orphan Asylum.....	No. 18	12/ 5/19	3/ 1/20	70	3	67
Hebrew Sheltering and Guardian Home.....	No. 22	4/24/20	10/23/20	84	27	57
N. Y. Orphanage.....	No. 22	6/ 5/20	10/23/20	63	35	28
P. S. No. 90.....	No. 24	12/17/20	5/ 3/21	160	20	140
						87.5

greatly its value. The other preparations had stood for some time, become less toxic and lost in immunizing power.

The comparative results of animal and human inoculations with different preparations show that very considerable differences in immunizing value exist. As yet we find it extremely difficult to determine by animal tests the finer differences which decide just when the ideal degree of neutralization is obtained. Dr. Banzhaf now standardizes our preparation so that 1 c.c. causes paralysis in the majority of guinea-pigs weighing 250 gm.; in all, 5 c.c. causes paralysis which ends in death. The results obtained in children and in animals with five different preparations clearly bring out the different degrees of success which are obtained with unequally neutralized preparations (Tables 9 and 10).

SAFETY OF TOXIN-ANTITOXIN INJECTIONS

In utilizing a substance which is a combination of a poison and an antipoint, it is of extreme importance to be certain that there is no possibility of a properly neutralized mixture becoming at some later period toxic. We have tested out many mixtures and kept them at all possible temperatures, and always found that the mixtures became very slowly more and more overneutralized. The antitoxin portion of the combination is more stable than the toxin. The only objection to using products that have been kept a long time after neutralization is that they are somewhat less effective. The only accident that has occurred in the use of toxin-antitoxin mixtures, so far as is known, was due to an error through which an improperly tested product was sent out. The regulations now adopted by all biologic plants make a repetition of such an accident impossible.

PRACTICAL APPLICATION IN THE PUBLIC SCHOOLS

The health and school authorities determined to put their chief efforts for the first two years into an attempt to immunize as many schoolchildren as possible rather than to endeavor to protect the children of preschool age who needed the protection so much more. The reasons for this were many and important. It was deemed wise to acquaint as many parents and others as possible with the value of the Schick test and the toxin-antitoxin injections. No better way seemed available than to use the schools as the means of doing this. If each pupil presented his parents with a circular picturing the danger from diphtheria, describing the preventive treatment and asking for permission to administer this treatment if the family physician approved, it would mean that nearly a million adults and a million children would have the arguments for the use of the toxin-antitoxin vaccine presented to them in a favorable way. If, as we hoped, about one half of the children brought back the acceptance of the offer to give them the toxin-antitoxin, we should be able not only to immunize those shown by the Schick test to possess no antitoxin but, by preventing those children from contracting diphtheria, we should also prevent their carrying diphtheria home to the younger children in their families.

The testing of the schoolchildren would also give us the chance to determine exactly what effect the immunization had had. We could make an index of 90,000 children who had been tested and, when Schick positive, had been injected with toxin-antitoxin; a similar index of 90,000 children of the same ages who had refused the test and the injections could be used for comparison. The cases of diphtheria occurring among the children of school age could thus be looked up in either index, and observations made as to how many cases of diphtheria occurred in the two groups. We believed that after one or two years of such observations we should have had evidence of convincing value as to the protection guaranteed by a negative Schick test due either to natural antitoxic immunity or to the response to the toxin-antitoxin injections.

Now, at the end of two years, we actually have such an index completed. The 90,000 tested children and the 90,000 control children have been gathered about equally from the schools of the different boroughs; they were collected by the groups of nurses and teachers from the schools which had been tested by Dr. M. C. Schroder and Dr. Abraham Zingher. Among an equal number of untreated and treated children, there were four times as many cases among the untreated children. The majority of the cases in both groups were of slight or moderate severity. Some of them were possibly cases of nondiphtheritic tonsillitis in children who happened to be carriers of diphtheria bacilli. The methods which we have adopted in the diphtheria prevention work in the schools have already been published by Dr. Zingher (No. 96 of the Reprint Series, Department of Health, City of New York). I will describe them briefly.

A very important point is the enlistment of the interest of the principal of a school. As a rule Dr. I. H. Goldberger, of the bureau of educational hygiene of the department of education, first prepares the way by obtaining permission for us to do the work in the school. According to the borough in which the school is situated, Dr. Zingher, Dr.

Schroder or one of their representatives sees the principal and explains fully the objects we have in view. Literature is left for the teachers. Either the principal or the physician meets the teachers in a conference, gives them the necessary information, and tries to arouse their enthusiasm. The success or failure in getting a favorable response from the children or their parents depends largely on the interest which the principal, the assistant principal and the teachers take in the matter. When they give us their enthusiastic cooperation, we expect to obtain consents from three fourths of the parents; when we fail to arouse the teachers' interest, we are fortunate if this is obtained from one fourth of them.

The preparatory work being furnished and the date for the test being determined, we send to the school the circulars and consent slips to be taken by the children to their homes.

Table 11 shows the results among the 180,000 schoolchildren whom we have listed.

TABLE 11.—NUMBER OF CASES OF SUSPECTED DIPHTHERIA DEVELOPING IN 90,000 UNTREATED SCHOOLCHILDREN AND IN 90,000 TESTED BY SCHICK METHOD AND WHEN POSITIVE GIVEN TWO OR THREE INJECTIONS OF TOXIN-ANTITOXIN

	Cases Reported as Clinical Diphtheria
In Brooklyn:	
26,000 originally Schick-negative children (observation from October 1 to February 15).....	2
15,000 Schick-positive children, 3, 2 or 1 toxin-antitoxin injections.....	4*
40,000 control children of same ages.....	27
In Manhattan:	
31,000 Schick-negative children (observation from October 1 to February 15).....	3
19,000 Schick-positive children, 3, 2 or 1 injections.....	5
50,000 control children.....	29
Summary:	
57,000 Schick-negative children (observation from October 1 to February 15).....	5
33,000 Schick-positive children injected with toxin-antitoxin.....	9
Among a total of 90,000 Schick-negative or injected children.....	14
Among a total of 90,000 control children untreated....	56

* Two of these children received but one injection and had no Schick retest. The third showed a Schick + and the fourth a Schick ± reaction on the retest and refused further injections.

As may be seen, there were among the 90,000 untreated schoolchildren four times as many cases of probable diphtheria as developed in the 90,000 tested children.

SUMMARY AND CONCLUSIONS

The results of twenty-five years of experimental and practical investigation of the immunizing effect of toxin-antitoxin injections and the value of the Schick test are as follows:

Three injections, 1 c.c. each, of a suitable toxin-antitoxin mixture spaced one or two weeks apart, will cause about 85 per cent. of susceptible children or older persons to develop sufficient antitoxin to give the negative Schick reaction and produce marked, if not absolute, protection against diphtheria.

The development of the immunity is slow. An amount of antitoxin sufficient to prevent the positive Schick reaction develops in the different children in from one to six months after the receiving of the injections. Antitoxin as heretofore must continue to be used to produce immediate immunity.

The duration of the immunity in at least 90 per cent. of the children is for more than six years and probably for the remainder of life. There seems to be no difference in this respect between these, and those who develop antitoxin naturally.

Toxin-antitoxin injections should not be given within two weeks after an injection of antitoxin; otherwise the toxin is slightly overneutralized and the resulting development of antitoxin is lessened.

Mixtures made from old toxin and antitoxin are fairly stable and may be used for a period of one year. Even such preparations are at their best when first

sent out, as the mixtures slowly tend to become at first neutralized and then slightly antitoxic. This change gradually lessens the immunizing power of the toxin. The toxin-antitoxin should be kept cool and in a dark place; it is best to use the mixtures within three months after their final preparation.

A toxin-antitoxin mixture of stabilized materials which is safe when it leaves the laboratory cannot become more toxic on being kept. No serious effects have ever resulted from the injections given to the tens of thousands of the New York children since we began our work, seven years ago.

The Schick test is an extremely reliable means of separating those individuals who have antitoxic immunity from those that have none. Although a simple test, it must be carried out with extreme care. The toxin must be retained intracutaneously, and the toxin must be neither 25 per cent. more nor less than the desired amount. It is extremely important to choose glass of suitable chemical composition for the containers in which the toxin is to be placed, as otherwise rapid deterioration may take place.

The preliminary Schick test is usually omitted in children under 3 years of age. This is for two reasons: 1. Two thirds of these children require the toxin-antitoxin injections anyway. 2. We are not certain whether those that do give the negative reaction are immune because of an unusual persistence of the antitoxin given them by their mothers, or because of the active development of antitoxin in their own bodies. After this age the test is desirable, but it is often omitted.

Thus, in practical school work, the first Schick test is frequently omitted in children up to the age of 6 because it is easier to inject the children at once rather than to delay for the test. At this age the percentage of children requiring immunization is still high, and the annoyance from the injections is slight. The omission of the preliminary Schick test facilitates the introduction of the immunizing injections in the schools. Above the age of 6 years, the preliminary Schick test should be made whenever practicable.

No child should be pronounced immune from diphtheria because of having received three immunizing injections of toxin-antitoxin. A negative Schick test is absolutely necessary before one can properly make such a statement or issue a certificate.

The use of the control protein test made with the heated toxin is advisable at all ages when a careful separation of the pseudonegative reaction from the combined positive reaction is important. As with the Schick test, it is frequently omitted because of local conditions. The older the child the more likely it is to be immune and to give a confusing protein reaction. In children under 5 years of age, the protein reaction seldom confuses the picture if the Schick tests are read as late as on the fourth day; between 5 and 7 years, the control does not help greatly in more than 5 per cent. In older children and adults, not only does the control protein test help us to decide more correctly in about 10 per cent. of doubtful reactions; but when it is marked it also indicates with some probability those persons who are likely to have the marked local and constitutional reactions from the toxin-antitoxin injections.

The toxin-antitoxin injections are inadvisable before the age of 6 months. During this time most of the infants retain the antitoxin received from their mothers. Up to the age of 3 months, immunizing

injections are usually ineffective, as the infant tissues do not respond sufficiently during this period to the toxin-antitoxin to produce antitoxin. Under usual conditions, it is probably safe to wait until the infant is 9 months old and then to give the injections at the first suitable occasion. During the first three years there is almost no annoyance from the injections. As the child grows older, the danger from diphtheria gradually lessens, and the percentage of those developing annoying local and constitutional reactions slowly increases.

The immunization of schoolchildren in acting to prevent their contracting diphtheria also lessens the exposure to infection of the younger children of preschool age in their families.

There appears to be no difference in the degree of immunity between those individuals who have developed antitoxin from natural causes and those who did so because of the stimulus of the toxin-antitoxin injections.

Institutions in which the children have been given the immunizing injections have been remarkably free from diphtheria.

The schoolchildren who have been injected have had one-fourth as many cases as the untreated children, and these cases have been of less severity.

ABSTRACT OF DISCUSSION

DR. ABRAHAM ZINGHER, New York: I should like to mention one or two points in connection with the work that we are planning for this summer among children of preschool age. We have practically finished all the public schools in New York City. A great educational campaign has been conducted through these schools in teaching the people the great value of these newer preventive measures against diphtheria. More than 800,000 homes have been reached. We intend to utilize this valuable propaganda. We shall offer the people the opportunity of having their children who are from 6 months to 6 years of age protected against diphtheria. This work will be carried out in the baby health stations, in the day nurseries and in the various mothers and babies' playgrounds in the public schools. We are emphasizing the fact that every child in this age group should be inoculated against diphtheria just as it is vaccinated against smallpox. We shall give these young children the three injections of toxin-antitoxin without a preliminary Schick test; reserving, however, the issuing of a diphtheria protection certificate for the time when the children show a negative Schick reaction. These Schick tests will be made when the children are admitted to school. We feel quite strongly that no child should be pronounced immune to diphtheria until it shows a negative Schick reaction. Another point worth emphasizing is that we found great variations in the immunity response to the same mixture of toxin-antitoxin in retesting several thousand schoolchildren who had been injected with two doses, each 1.5 c.c., of toxin-antitoxin. The number of children who showed a negative Schick retest varied in different schools from 25 to 75 per cent. One of the interesting facts in connection with these results is that the percentage of successfully immunized children in a school was in inverse ratio to the percentage of children who had given a positive Schick reaction at the original test. We noticed no symptoms of anaphylactic shock in giving more than 100,000 injections of toxin-antitoxin. This was also true when repeated series of injections of toxin-antitoxin were given. We shall be glad to send the literature that we use in our work in the schools and in the baby health stations to any physician who is interested in this subject. He should write for it to the Research Laboratory of the New York City Department of Health.

DR. JOHN F. HOGAN, Baltimore: From studies made recently in Baltimore we know that more than 80 per cent. of the deaths in that city from diphtheria were from the laryngeal type. We have no reasons for thinking the rest of the country is different. It is well known by those who have worked in

infectious diseases, especially diphtheria, that a great many of the deaths between the ages of 2 and 5 are from laryngeal diphtheria. Therefore, if we are going to do any good with toxin-antitoxin we must start before the child reaches the age of 2 years. In Baltimore we are going to make a drive for toxin-antitoxin, and we are using the schoolchild as an opening wedge. We are having the schoolchild bring the mother with the baby at the time the second dose is given. In that way we shall reach the young children before they reach the most susceptible age. With the amount of knowledge that we have of the pathologic, etiologic and epidemiologic peculiarities of diphtheria, its death rate should be practically nil and, if we succeed in immunizing practically all children, then this will be accomplished.

DR. WILLIAM H. THALER, St. Louis: The School Hygiene Division in the St. Louis public schools has followed out this work by sending a letter to the home of every schoolchild in the city of St. Louis, recommending the Schick test, and the responses were very gratifying. It may be a mere coincidence, but this year we have had the lowest death rate in diphtheria that I think was ever heard of in St. Louis. We also noted a peculiar situation. There was one child in one block in one of the school districts who received toxin-antitoxin and he was the only child in the block who contracted diphtheria. This incident was reported by the district nurse and later authenticated by investigation.

DR. C. A. EARLE, Des Plaines, Ill.: Diphtheria is the most dangerous infectious disease, and more children die from it than from any other infectious disease. We have reached the end of our rope with antitoxin. Diphtheria may be more prevalent now than it was before the days of antitoxin. There is abundant evidence for believing that these mixtures do the work for which they are designed. To Theobald Smith belongs the greatest credit for the experimental work, and to Dr. Park for the practical application. In a series of more than 400 susceptible children, 85 per cent. were immune six months after the injection of three doses of toxin-antitoxin. When we study Smith's experiments it becomes evident that we cannot expect to immunize all children. He shows that some guinea-pigs may be immunized by even neutral or balanced mixtures of toxin and antitoxin, while others require mixtures of varying degrees of toxicity. It is likely that there is an unknown optimum proportion of the ingredients of the toxin-antitoxin mixture required for each individual. Because of the reliability of the Schick test, no child should be given the toxin-antitoxin mixture whose susceptibility has not been demonstrated by this test. I feel certain that if the whole proposition is explained to the parents, the vast majority would prefer to have the test made first.

DR. W. S. RANKIN, Raleigh, N. C.: Last year in North Carolina the state epidemiologist went into twenty-five counties, called together the practitioners and said, "Gentlemen, your people should be inoculated against typhoid, and your children against diphtheria. I should like to propose a plan by which you can do it and be paid for it." The physicians decided they would do it. They go to the county commissioner and say, "We want to organize with the help of the state board of health a number of public dispensaries to be held for five weeks in this county at ten or fifteen different points." The state board of health sets the time and place for the dispensary, and notifies the public to come in and be inoculated. There is just enough added about the value of inoculation to educate the public. The profession itself divides up the work. Last year we inoculated 70,000 persons against typhoid fever, and 1,000 children between 6 and 12 years of age against diphtheria. The county commissioner paid the local practitioners 25 cents for each complete inoculation and that was \$20,000 which went to the profession last year which otherwise would not have been received. The work of the medical profession with the state board of health does not stop when that \$20,000 is paid. It goes on. In the dispensaries which were conducted in Union County, N. C., with 35,000 people, the physicians vaccinated 10,000 people in a campaign of five weeks. That was \$2,500 paid to twenty physicians—only \$125 each, but think of the effect on the business of the profession in keeping up that work. It goes on. The physicians are assuming the leadership in public health work, and they come into complete harmony with the public health officers of the state.

DR. ABRAHAM ZINGHER, New York: Dr. Rankin's remarks are very suggestive. I believe that in the rural sections the only practical way to carry out this work is to immunize with toxin-antitoxin every child of school age as well as of pre-school age. The reason is that we have found that more than 85 per cent. of schoolchildren in rural sections give a positive Schick reaction. These children, however, should always be given a final Schick test, after toxin-antitoxin injection, before they are pronounced immune to diphtheria. It is important that every health officer and school physician should be acquainted with the method of diluting bulk toxin. He will then be able to test at a cost of \$1 an entire school of 2,000 or 3,000 children. Uniformity of the dilution of toxin he uses and great accuracy in the reactions he obtains will soon give the health officer confidence in the results of the Schick test. This confidence, I am sorry to say, is lacking at the present time wherever physicians use outfits supplied by many of the commercial laboratories.

THE ETIOLOGY OF EOSINOPHILIC PLEURAL EFFUSION *

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In consideration of the frequency of pleural effusion in general, it is surprising that so few cases of pleural effusion with a large number of eosinophils have been reported in the literature. It is surprising also that the tubercle bacillus as the etiologic agent in these cases has never been isolated from the exudate. Bayne-Jones¹ states that this condition occurs in about 1 to 5 per cent. of all pleural effusions, as determined by investigators applying constant methods to cases in series. Schwartz² compiled sixty-eight cases from the literature in his monograph on the subject of eosinophilia. Klein³ has reported two cases. One was a right-sided pleural effusion following an operation for hemorrhoids, the necropsy revealing septic, thrombosed hemorrhoidal veins, which were believed by the prosecutor to have been the source of the pleural infection. A second case followed stab wounds in the chest, which resulted in a right-sided hemorrhagic pleural effusion. In the same paper, Klein refers to two cases reported by Harman,⁴ in both of which were bloody pleural effusions. One case differed in that the pleural effusion eosinophilia, after rising to 39 per cent. suddenly changed to 95 per cent. mononuclears, which, however, still presented indistinct, though recognizable, eosinophilic granules. No etiologic, parasitic or bacteriologic agency was isolated in any of these cases.

Widal and Ravaut⁵ have reported three cases. One had followed typhoid fever. A second occurred in a man, recently returned from the tropics, who presented an enlarged liver and large glands in the axillae and the groin, but in whom no etiologic factor was found. The third case was a hemorrhagic pleural effusion occurring in a case diagnosed by them clinically as tuberculous. This case is identical with one reported by Auché and Carrière,⁶ but in neither case were the tubercle bacilli demonstrated. Widal and Ravaut found the fluid in their cases highly toxic to experimental animals, but most observers have not found this. In no animal were

* From the Department of Internal Medicine, University of Michigan Medical School.

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