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

WILLIAM H. PARK, M.D.

NEW YORK

This communication was suggested by reading an article on an outbreak of tonsillitis suspected to be diphtheritic by Dr. S. A. Blauner.¹ Through the courtesy of Dr. Blauner, I was enabled to study the outbreak described. I saw the last three cases in the acute shape, and made cultures from the sick and convalescent children and from many of the healthy children distributed in the different parts of the institution. The laboratory and clinical material considered together lead me to somewhat different conclusions from those drawn by Dr. Blauner. Although the results of all the laboratory examinations were sent to him, he either failed to remember them or did not interpret them as I do.

Before considering this special outbreak, it seems desirable to state the evidence which supports the view that sufficient antitoxin in the body to prevent the development of a positive Schick test under ordinary conditions 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. The proof of this is derived from its use in many outbreaks and in the exposed children of hundreds of thousands of families. The recent statement by Haven's 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, and that the available monovalent antitoxin will not completely neutralize the toxin made by this other type, and that, therefore, diphtheria may develop from infection with this other type in children showing a negative Schick test to the standard toxin, has not been borne out by experience nor confirmed by us in experimental work. The evidence that antitoxin is the only substance in the body that can prevent the toxin acting is also so conclusive that we can assume that a negative Schick test means the

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presence of sufficient antitoxin to neutralize it. The debatable points are: is the minimum amount of antitoxin required to prevent the Schick test sufficient to prevent the development of diphtheria and, 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 will be wise to dispose of the last query first.

A Schick test requires the injection intracutaneously of one-fiftieth of a lethal dose for a 250 gm. guinea-pig in 0.1 c.c. or an equivalent amount of toxin in a different amount of fluid. We recommend one-fourtieth M. L. D. in 0.2 c.c. because we find the larger amount of fluid easier to give and, therefore, safer for the inexpert. Reports sent us some time ago of several series of cases with no positive Schick reactions caused us to obtain outfits from various manufacturers. Dr. Zingher found in a considerable number of instances that the available quantity of toxin in some of the outfits was much less than the required amounts. The children tested with these solutions gave negative Schick reactions when control tests made with standardized toxins gave positive ones. More recent tests of outfits from these firms have given uniformly good results.

Not only must the toxin be measured accurately, but the toxin must be delivered wholly intracutaneously. If injected a little too deep it will not be retained in the skin and will not exert the desired effect. If the small white area does not appear at the point of injection the Schick test cannot be relied on. Careful investigation leads us to believe that from 2 to 4 per cent. of the persons giving negative Schick tests do so because of error in technic. When great care has been taken to have the toxin strength correct and the injection given strictly intracutaneously, we have not discovered any errors. Too strong a toxin will give a larger percentage of positives than will the standard amount. The endeavor of Schick was to choose the amount that would as nearly as possible divide the susceptible from the immune.

During the past seven years my colleagues in the laboratory have made over 150,000 Schick tests, and have immunized about forty thousand of those giving a positive reaction. We have also tested from year to year about fifteen thousand children who are inmates in institutions so as to note any changes. There has been an average difference of about 2 per cent. in the annual readings. This we have considered as partly due to borderline cases and partly to errors in technic. The major part of this work has been directly carried out or has been supervised by Dr. A. Zingher and Dr. M. C. Schroder. We have during these years earnestly sought to discover all cases of

suspected diphtheria which occurred among those who had given negative Schick reactions, either before or after the toxin-antitoxin injections.

During this time we have learned of and investigated eighteen cases of suspected diphtheria in those who had given a negative Schick reaction. Two of these were in an institution in Brooklyn, two in an institution in New York, eight in Dr. Blauner's institution and six in their homes. In none of these cases has death occurred. Undoubtedly, there have been other cases concerning which information has not reached us. We are now cataloging 100,000 New York City school children who have given negative Schick tests, and 100,000 untested children from the same schools.

During the next year we are going to look up every case reported as diphtheria and determine the difference between the incidence of diphtheria in the two groups of children. In as far as possible, we will inquire into each case so as to have both the physician's original report and the results of the inspector's investigation. We hope by this method that within a year we may get a decision as to the degree of immunity from diphtheria insured to children giving a negative Schick reaction.

It is very difficult to decide whether any of the sixteen cases with positive cultures which had patches of pseudomembrane either confined to the tonsils or spreading to the pharyngeal borders were cases in which a faulty Schick test had been done, or whether they must be considered as moderate cases of diphtheria developing in spite of an amount of antitoxin sufficient to prevent a positive Schick test or whether they were due to other microbes, the diphtheria bacilli being present by accident and taking no active part. An important fact to remember is that whatever the final decision is as to the etiology of these cases that they are extremely rare.

A detailed discussion of the outbreak that occurred in Dr. Blauner's service will show the complexity of the factors involved. We will combine a consideration of the clinical observations supplied by Dr. Blauner and the laboratory findings of Miss Mann who carried out extensive investigations under the general direction of Dr. A. W. Williams and myself.

The clinical facts can be stated briefly as follows: In a ward of about twenty children ranging from 2 to 5 years of age, all but one of whom had given a negative Schick reaction, three cases of croupous tonsillitis developed December 23, one on the twenty-sixth, two on the twenty-eighth, one on the twenty-ninth and two on the thirty-first. Eight of these showed grayish patches on the tonsils. In five, the patches spread from the tonsils to the edges of the pharynx. One of the two cases developing on the thirty-first was mild and had no

exudate. The temperatures of the cases ranged from 102 to 104 F. on the first day, and dropped rapidly by lysis.

Dr. Blauner states in his article that at first he had no suspicion that the earliest three cases had diphtheria because of the previous negative Schick reactions, but when the positive laboratory reports came in he became convinced that they were cases of true diphtheria. The three cases I saw would have been considered by me as probably, but not at all certainly, diphtheria. The cultures from all the cases, except the ninth, which was very mild, contained virulent diphtheria bacilli. The mild case contained no diphtheria bacilli.

Four of the eight moderately severe cases had given negative Schick reactions on their entrance into the institution; three had become negative after injections, and one, though injected, had remained positive. The first seven² of the children received antitoxin and recovered promptly; the last two received no antitoxin and recovered equally rapidly. The possibilities seemed to be (1), that the amount of antitoxin as shown by the negative Schick reaction had been in these cases insufficient to prevent moderate diphtheria; (2) that some other infection had caused the croupous tonsillitis, and that the diphtheria bacilli were accidentally present in carriers, and (3) that the sore throat started by the pyogenic organisms had paved the way for the local action of the accompanying diphtheria bacilli. To test out these possibilities we omitted giving antitoxin in the last two cases which had just developed and one of which was very mild. These two cases progressed favorably as I felt certain they would and the children recovered as promptly as did those that had received antitoxin. This result suggested that whether or not the diphtheria bacilli had taken part in the formation of the exudate, the recovery was probably not due to the additional antitoxin injected.

A week later, January 7, cultures were made from twenty-seven of the children in the room in which the infected cases occurred, and from eleven of them virulent diphtheria bacilli were obtained. As these children had been given an immunizing injection of antitoxin, Dr. Blauner thought that the cessation of the cases, in spite of the presence of so many carriers, was a strong point in favor of the former amount of antitoxin having been insufficient to protect. This led me to make cultures from nineteen children taken at random from other parts of the building where no antitoxin immunization had been given. To our surprise, we found the carriers even more abundant here than in the ward from which the cases came. Miss Mann isolated diphtheria bacilli from the cultures made from ten of nineteen children (See accompanying table). All strains were tested and found to be toxin

2. There is some confusion as to whether it was the eighth case or an additional case that received no antitoxin. There is no doubt that there was a case with tonsillar exudate similar to the eighth case.

producers. The children in the general building were, therefore, apparently protected by the amount of antitoxin which had given a negative Schick reaction. With these results before us, we see that if the tonsillitis in the ward had been caused by some other infection than diphtheria, the throats, if not already infected, would almost necessarily have become carriers of the bacilli. Dr. Blauner's complete dependence on the culture results to solve the nature of the infection is not surprising, since health departments have so emphasized the value of the bacterial reports in suspected cases of diphtheria that many physicians believe that a positive report from a suspected case proves that the case is one of diphtheria.

RESULTS OF THE CULTURE EXAMINATION OF NINETEEN HEALTHY CHILDREN
FROM WARDS IN WHICH NO DIPHTHERIA HAD OCCURRED

Name	Result	Name	Result
A. R.	Negative	L. E.	Diphtheria bacilli
A. M.	Diphtheria bacilli	L. M.	Diphtheria bacilli
B. F.	Diphtheria bacilli	M. L.	Diphtheria bacilli
B. A.	Diphtheria bacilli	R. L.	Negative
B. W.	Negative	S. L.	Negative
D. M.	Diphtheria bacilli	S. S.	Diphtheria bacilli
G. I.	Negative	W. S.	Negative
H. M.	Negative	W. J.	Diphtheria bacilli
H. D.	Diphtheria bacilli	Z. J.	Negative
H. M.	Negative		

The absence of bacilli in a culture properly made is fairly good proof that no bacilli are in the throat and, that, therefore, the case is not one of diphtheria. If bacilli are present, the probability of diphtheria being present is greater or less according to the more or less characteristic appearance of the lesions. The laboratory indicates the presence or absence of the bacilli and the danger of the case spreading infection; the clinical examination determines the probability or certainty of the presence of diphtheria. It would be more helpful if the laboratory could make the diagnosis, but, unfortunately, it cannot. If we apply the above facts to Dr. Blauner's cases, we see that as certainly half of the children in the institution were carrying virulent diphtheria bacilli in their throats during the month of January, that whatever nasal or throat infection took place diphtheria bacilli would probably be associated with it. With 50 per cent. of the normal cases carrying bacilli, practically every diseased child would almost immediately become a carrier.

CONCLUSIONS

A negative Schick test in cases which have an active immunity, either natural or acquired, when the toxin used and technic employed have been suitable, gives an almost complete security from diphtheritic disease, not only for the immediate time but for the future.

Those that have natural antitoxin and those who acquire it through toxin-antitoxin injections may harbor diphtheria bacilli, and if they later suffer from tonsillitis, due to other microbes, throat cultures will contain diphtheria bacilli. The positive culture alone suggests but does not establish that the suspected case is one of diphtheria.

Under unusual conditions it is possible that when diphtheria bacilli are present in a throat which becomes the seat of some other infection they may develop their toxin and cause superficial lesions in the mucous membrane even though the cases have sufficient antitoxin to give a negative Schick reaction. Cases which present this possibility are rare, and when met with by us have done well without additional injection of antitoxin.

In the outbreak discussed in this communication, the fact that while an extraordinarily large percentage of all the children in the institution were carriers of virulent bacilli, only one group developed cases of tonsillitis with pseudomembranous patches makes it uncertain that the cases were diphtheria.