

Wherever industrial conditions have obtained for several generations, the death rate has been declining. In England, where the decline has been more pronounced than in any other country, the decline began to take place in 1833 and has continued ever since.⁹ The beginning of the nineteenth century was the period of England's industrial development, and here the decrease in the death rate from phthisis has been contemporaneous with the adaptation of a people to urban life.

There are so many factors entering into this complex problem, which still remain obscure, it is difficult to arrive at satisfactory conclusions. It would seem that recent improvements in the social and hygienic conditions of the working classes, who constitute the majority of the candidates for the disease, must be a factor in future, if not in present tuberculosis morbidity and mortality. But the adaptation of people to city life and to the tubercle bacillus, is perhaps of greater importance than all other factors taken together, in bringing about the mortality reduction which has occurred.

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THE SCHICK TEST AND IMMUNIZATION WITH DIPHTHERIA TOXIN-ANTITOXIN

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THE prevention of diphtheria, and even its eradication among the permanent population of the Commonwealth of Massachusetts, is possible of accomplishment. We now have at our disposal, in addition to the established antitoxin treatment, not only a reliable method for determining the susceptibility of human beings to diphtheria, but also a simple and safe procedure for rendering susceptible individuals immune to this disease.

Diphtheria, in 1919, was responsible for 14.9 deaths per 100,000 population, or a total of 591 deaths out of 7,928 reported cases in this

State. It is reasonable to assume that all cases were not reported. In addition to the toll of 591 lives we suffer great economic loss, anxiety, and time entailed in the sickness and treatment of 8,000 persons. Moreover, diphtheria is essentially a disease of childhood, and the State is yearly deprived not only of approximately 600 prospective citizens, but also of their possible contribution as potential parents.

We still have an incidence of about 8,000 cases and a mortality of approximately 8 per cent. of all reported cases in spite of the complete efficacy of antitoxin treatment when promptly and properly applied. Antitoxin, when given in sufficient amounts on the first day of the disease, in cases without serious complications, effects 100 per cent. of recoveries. With the possession of such an efficient means of treatment, it would be difficult to understand why we continue to have deaths from diphtheria were it not for the astonishing facts revealed in Carey's investigation of the circumstances attending 1,000 deaths from this disease. He found that "31.5 per cent. of these deaths occurred in individuals who had been sick one week or more without medical attention; 11.8 per cent. occurred in individuals who were moribund at the doctor's first visit; 7.6 per cent. occurred in individuals in whom the condition was unrecognized until it was too late for the antitoxin to be efficacious, and 65 per cent. of these deaths occurred in children who were 5 years or under."

The causes for the prevalence of diphtheria with its stationary death rate are:

1. The presence of susceptible individuals in every community and failure to detect and immunize them.
2. The existence of healthy human carriers of virulent diphtheria bacilli.
3. The neglect of parents or other temporary or permanent guardians to procure medical attention for children in the early stages of the disease.
4. The failure to report some cases of diphtheria.
5. The failure to diagnose diphtheria in its early stages.
6. The failure of some physicians (a) to administer antitoxin in suspicious cases before making a definite diagnosis; (b) to avail themselves of the diagnostic facilities offered by the

State and various cities; and (c) to administer antitoxin early enough or in sufficient amount, or (d) to administer antitoxin intravenously in late or severe cases.

It must be apparent that by detecting all susceptible persons in every community and rendering them immune to diphtheria the other causes for the present continued morbidity and mortality from this disease would eventually cease to operate.

I. THE PRESENCE AND DETECTION OF PERSONS SUSCEPTIBLE TO DIPHTHERIA INFECTION.

As a result of the work of Schick, we know that individuals who possess less than one-thirtieth unit of diphtheria antitoxin in one cubic centimeter of their blood may, and frequently do, contract diphtheria if exposed, while those possessing this or a larger amount of antitoxin rarely, if ever, develop clinical diphtheria. The earlier methods for determining the antitoxin content of the blood were far too intricate to permit of their clinical application. In 1913, however, Schick described a simple test for this determination. Following the introduction of this method, Park, Zingher, and others carried out investigations on the susceptibility or immunity of various age groups, and the figures recently published by Park may be taken as indicating the percentage of individuals liable to contract diphtheria.

SUSCEPTIBILITY OF VARIOUS AGES TO DIPHTHERIA.

AGE	SUSCEPTIBLE
Under 3 months	15%
3 to 6 months	30%
6 months to 1 year	60%
1 to 2 years	70%
2 to 3 years	60%
3 to 5 years	40%
5 to 10 years	30%
10 to 20 years	20%
Over 20 years	12%

From this table it is apparent that the majority (85 per cent.) of infants under three months of age are immune to diphtheria and that the percentage is practically the same as in adults. This may be explained by the theory that babies are born with a passive immunity acquired from the mother through the placental circulation. But this immunity disappears to a considerable extent with the succeeding months, resulting in the susceptibility of about 70 per cent. of all children between one year and two years of age. The age of greatest susceptibility is from six months to

five years, which corresponds closely to the age groups in which the most dangerous laryngeal forms of diphtheria and complicating bronchopneumonias occur. As the age increases, the proportion of susceptibles decreases, which also squares with the lower incidence of diphtheria in the higher age groups.

1. *Theory of the Schick Test.* Diphtheria toxin causes an inflammatory action when injected into susceptible tissues. This reaction does not occur if the toxin is neutralized with its antitoxin before injection, or if an adequate amount of antitoxin is already present in the blood of the individual. Schick found that an antitoxic content of one-thirtieth unit per cubic centimeter of blood is ample, not only to render one immune to infection, but also to neutralize and prevent the inflammatory action of a small amount of toxin injected into the skin. Upon this phenomenon is based the Schick test. A positive reaction means susceptibility, a negative reaction shows immunity. Those who show a positive reaction may and do contract the disease; those who show a negative reaction may become carriers of virulent diphtheria bacilli, but do not develop clinical diphtheria.

2. *Technic of the Schick Test.* The test is carried out by injecting intracutaneously one-fiftieth of a minimum lethal dose (M. L. D.) for a guinea pig weighing 250 grams. The State Department of Public Health supplies free an outfit, which contains sufficient titrated diphtheria toxin with the proper amount of sterile salt solution for fifty tests. The toxin is contained in a capillary tube, and when it is desired to perform the test the contents of the tube are expelled into the bottle containing the salt solution. One-tenth of a cubic centimeter of this mixture represents the dose to be injected into the skin and contains one-fiftieth M. L. D. of toxin. This diluted toxin must be used within a few hours after mixing, because it rapidly loses its potency when exposed to light and room temperature. The skin on the flexor surface of the arm, preferably above the elbow, is cleansed with alcohol, acetone or ether, and one-tenth cubic centimeter of the diluted toxin is injected into the epidermal layers of the skin. This is best accomplished by means of a short but sharp-pointed No. 26 or 27 gauge hypodermic needle. The 1 c.c. "Record," or other tuberculin syringe, is well adapted for the purpose. If the

point of the needle has been properly inserted with the lumen uppermost and visible through the skin, the injection should produce a small, slightly raised, white area, or wheal, which should move with the skin and disappear in about one-half hour. The injection should never be made *under* the skin. The technic of the test is easily acquired. The injection causes little or no pain, it is never followed by constitutional symptoms, and the site of injection requires no subsequent care.

3. *The Positive Reaction.* A positive reaction begins to appear in 24 to 36 hours and is characterized by a circumscribed area of redness and slight infiltration which measures one to two centimeters in diameter. It develops gradually, reaches its greatest intensity on or about the fourth day, then fades very slowly, leaving a scaly, brownish pigmented spot. The positive result of the test represents the true irritant action of diphtheria toxin, and signifies that the individual possesses little or no antitoxin in the blood, and therefore may contract the disease.

4. *The Negative Reaction.* The native diphtheria antitoxin in the tissues of an immune person neutralizes the injected diphtheria toxin, and on the day following the injection no signs are present except the slight and fleeting mark incident to the insertion of the needle.

5. *The Pseudo-Reaction.* In some individuals, particularly in adults, a reaction develops which may be confused with a positive reaction. Owing to the hypersensitiveness of some persons to the protein of the diphtheria bacillus present in the toxin, a local reaction may appear at the point of injection. The pseudo-reaction is distinguished from the positive reaction by its more rapid development. "It appears usually within twelve to eighteen hours, and fades in about three to four days, leaving only an irregular area of brownish pigmentation and generally shows no scaling. In appearance the moderate pseudoreactions, at the end of twenty-four hours, resemble very much the fully developed positive reactions, while the marked pseudoreactions show a considerable amount of infiltration with a central darker reddish area, surrounded by a fainter areola, which shades off into the surrounding skin" (Zingher). In order to exclude pseudoreactions, repeated observations over a period of five or more days should be made and the appearance

carefully noted. "By this time the pseudoreaction will have faded and can be recognized by a blotchy area of pigmentation, while the true positive reaction will be at its height. The positive reaction will show at this time a definite circumscribed area of scaling redness, which gradually develops a brownish pigmentation. Those tests, however, which show only an area of bluish discoloration, or faded irregular areas of brownish pigmentation which do not scale, are generally the remains of pseudoreactions" (Zingher).

A control test should be performed on the other arm, injecting one-tenth cubic centimeter of a similar dilution of toxin which has been heated to 75° C. for five minutes. "By heating the toxin broth at this temperature the soluble toxin is destroyed, while the autolyzed protein of the diphtheria bacillus, which causes the pseudoreactions, is not appreciably affected. The control test with the heated toxin will reveal the pseudoreaction and combined reactions. Observations must be made at the end of seventy-two or ninety-six hours. The twenty-four-hour reading will give fairly accurate results in about 95 per cent. of the tests, when the control test with heated toxin has also been made. If negative, both the test and control will be normal. If a pseudoreaction is present, both the test and the control will show areas of redness and infiltration, which are similar in size and appearance; both reactions will fade at the end of seventy-two hours and leave only a small, irregular area of pigmentation, and generally no scaling. The pseudoreaction varies in intensity in different individuals from an area of circumscribed redness without infiltration to a reaction which shows a considerable degree of redness and infiltration, and a more or less characteristic clinical appearance."

6. *The Combined Reaction.* "If a combined reaction is present, the redness and infiltration at the site of the Schick test will be more marked at the end of twenty-four hours than in the control test. At seventy-two hours, the positive reaction will be quite distinct, while the control test will show only a blotchy area of pigmentation representing the pseudoreaction elements of the test. If the test is positive, the reaction at the end of twenty-four and seventy-two hours will be positive only at the site of the Schick test. The negative and the pseudo-

reactions indicate immunity, the positive and the combined reactions, susceptibility of diphtheria" (Zingher). The appearance of pseudo-reactions presents no especial difficulties. A short experience in reading the reactions will suffice to enable one to make a correct interpretation of the results.

7. *Importance of the Schick Test.* The importance of this test cannot be too strongly emphasized. The information which it yields as to the susceptibility of an individual enables us to apply a method for transforming susceptibility into immunity, thus protecting that person against a possible attack of diphtheria.

The immunity possessed by persons giving a negative Schick reaction obviates the necessity of administering antitoxin to them even though they are exposed to infection. Park states, "It seems safe to rely on the belief that a person with a sufficient amount of antitoxin to give a negative Schick test is incapable of developing constitutional toxæmia, or a severe infection from diphtheria bacilli. There is a doubt as to whether very slight infections of the superficial mucous membrane may occur in such persons. My own opinion is that cases supposed to be of this character are instances of streptococcus infection, the diphtheria bacilli being present as in a carrier. Those that show a faintly positive Schick test are probably liable to moderate local infection."

The reliability of a negative test as a true indicator of the immunity possessed is convincingly attested by the observation of Park that in spite of the fact that 24 per cent. of all children showing a negative Schick reaction were found to be carriers of virulent diphtheria bacilli, none developed diphtheria, and, furthermore, he has never seen a case of clinical diphtheria develop in a person reacting negatively to the Schick test.

The saving of time and inconvenience and of the expense for antitoxin effected by omitting the prophylactic injection of antitoxin in immune persons is a matter of no small moment among the general population as well as in institutional practice.

II. ACTIVE IMMUNIZATION AGAINST DIPHTHERIA.

In many communicable diseases the greatest and most lasting immunity is that conferred by an attack of the disease, while a transient passive immunity is that produced by antitoxic and

other immune serums. When exposure to infection is recent, immediate, or likely to occur within a few days, the prophylactic injection of diphtheria antitoxin is by far the most efficient means for warding off an attack of the disease. It should be borne in mind, however, that the protection afforded by an immunizing dose of antitoxin can be depended upon for a period of only two to four weeks. In the past decade there has been developed a method of producing active immunity in human beings, which is far more lasting, although it requires a considerably longer time to develop, than that produced by antitoxin. The injection of diphtheria toxin partially neutralized with its antitoxin—and, therefore, harmless—stimulates the production of sufficient native antitoxin in the body to cause persons previously reacting positively to the Schick test to react negatively, and to render them immune to an attack of diphtheria.

The development of active immunization by means of toxin-antitoxin mixtures constitutes one of the most notable contributions of medical science to the welfare of mankind. The possibilities of its universal adoption and application must be apparent when it is realized that by such a means it would be possible to immunize all susceptible persons to diphtheria, thereby preventing the clinical disease. The complete harmlessness of the procedure, and the efficacy of the protection it affords for a period of at least four and a half years have been firmly established by the results of Park's experience in 15,000 immunizations.

1. *The Toxin-Antitoxin Mixture.* The rationale of immunization with diphtheria toxin-antitoxin consists in the production of an active immunity by the injection of small amounts of diphtheria toxin so neutralized with its antitoxin as to be devoid of any harmful or undesirable action. Potent diphtheria toxin is aged until its strength becomes constant, its potency is then accurately determined, and to 86-100 per cent. of the L+ dose (L+ dose equals the amount of toxin required to kill a 250 gram guinea pig in four days, when mixed with one unit of antitoxin) is added one unit of antitoxin. The mixture is so prepared that the dose used, usually one cubic centimeter, contains three L+ doses of toxin with three to three and one-half units of antitoxin. The mixture is subjected to the most rigid bacteri-

ological tests for sterility, and its harmlessness for human beings is determined by animal tests. Guinea pigs receive one and five human doses, respectively and must survive five weeks before the mixture is finally released for distribution.

2. *Dosage.* The toxin-antitoxin mixture as supplied by the State Department of Public Health is prepared in strict accordance with the requirements of the United States Public Health Service. The course of immunization consists of three injections of 1 c.c., each given at intervals of seven to ten days. The injections of the undiluted mixture are made subcutaneously, preferably over the insertion of the deltoid. For children under six months of age, the dose is 0.5 c.c., and three injections are given at seven-day intervals.

3. *Reactions.* A local inflammatory reaction characterized by moderate swelling and some redness and tenderness, may develop at the site of the injection in adults, but this rapidly subsides and causes no inconvenience. At times, in adults, a slight constitutional reaction consisting of slight fever and some malaise may be caused by the injection. This reaction may be due to hypersensitiveness to protein of the diphtheria bacillus, or it may possibly be caused by pepton in the toxin. This allergic condition exists in many adults, but is rarely found in young children. In the latter, accordingly, reactions seldom occur. Park reports that in his large number of immunizations no serious effects have appeared.

4. *Appearance of Immunity.* The immunity produced in response to this method of immunization develops slowly, it may require a period of eight to twelve weeks for a sufficient amount of antitoxin to develop to inhibit the Schick test. Each individual so immunized should be given a Schick test three months after the last injection. The failure of a person to react to the Schick test shows that sufficient antitoxin is present in the body to render that person immune to diphtheria.

5. *Duration.* The use of toxin-antitoxin mixtures is of such comparatively recent introduction that it is impossible at present to determine the full duration of the protection which it confers. From Park's observations it is definitely established that the immunity persists for four and a half years at least, which is the period over which his studies have con-

tinued. It is likely that it exists for life; but, be that as it may, the fact that complete protection continues for over four years, makes it possible by applying this procedure to infants to insure children against infection during what would otherwise be the most susceptible period of their lives.

6. *Influence on Reactivity to Schick Test.* When the full course of three injections is given it will be found that within three months after the last injection over 90 per cent. of all individuals previously giving a positive Schick test will give a negative reaction, and that this number will have acquired an active immunity to diphtheria. The remainder should be immunized by repeating the course of injections.

7. *Influence of Antitoxin Injections on Production of Immunity by Toxin-Antitoxin Injections.* It has been found by Zingher that recent administration of diphtheria antitoxin interferes with and retards the development of immunity following the injection of diphtheria toxin-antitoxin mixtures. Whenever, therefore, the course of injections is given to an individual who has recently received diphtheria antitoxin, retests with the Schick reaction should be performed at the end of ten or twelve weeks after the last injection of toxin-antitoxin.

Under no circumstances should the mere fact that a person has received the usual course of diphtheria toxin-antitoxin be relied upon as proof that complete protection against diphtheria has been produced. All immunizations should be controlled by subsequent Schick tests, and all persons reacting positively to the test should be given a second course of injections of toxin-antitoxin.

III. GENERAL CONSIDERATIONS AND RECOMMENDATIONS.

1. All persons over 18 months of age in the entire community should have their susceptibility to diphtheria determined by means of the Schick test, and the reaction which they show should be noted either in institutional records or in the records of the family physician.

2. In infants below 18 months of age the Schick test is not necessary because a negative reaction may give rise to a false sense of security. Very young infants may exhibit a negative Schick test owing to the immunity passively acquired from the mother, but, inasmuch as this type of immunity is transient, it is safer to as-

sume that no child under 18 months possesses permanent immunity.

3. All infants below 18 months of age accordingly should be actively immunized with three doses of 1.0 c.c. of diphtheria toxin-antitoxin mixture, irrespective of the reaction to the Schick test which the infants might show at the time of immunization. The doses should be 0.5 c.c. for babies under six months of age and 1 c.c. for all others.

4. All persons over 18 months of age who give a positive Schick test should be immunized by receiving three subcutaneous injections of 1 c.c. each of toxin-antitoxin at intervals of seven days.

5. All persons immunized by this method should be retested three months after the last injection, and re-immunized if they should by any chance still give a positive Schick reaction.

The medical profession now possesses in the Schick test a simple and reliable means for ascertaining the susceptibility or immunity of an individual to diphtheria; in diphtheria toxin-antitoxin, a safe and sure method for rendering all susceptibles immune; and in diphtheria antitoxin, an effective means for treating the disease. The State, through the Department of Public Health, offers to the physicians of the Commonwealth the biologic agents required both for the Schick test and for active immunization; every facility for the rapid diagnosis of suspected cases; the service of epidemiologists and district health officers to discover foci and to trace the course of infection; and offers a free and abundant supply of potent diphtheria antitoxin. It would seem, therefore, that with these facilities at our disposal, and with the active coöperation and participation of the medical profession in their use and application, children could be permanently spared from this scourge. The only cases of diphtheria occurring in the Commonwealth would be among those individuals who came from without the boundaries of the State, or those who have failed to receive or avail themselves of the means of protection freely offered to them.

HONOR FOR DR. JELLIFFE.—Dr. Smith Ely Jelliffe of New York has been made an honorary member of the Société de Médecine Mentale de Belgique at its recent reunion.

INTERNAL DRAINAGE OF ACUTE EARS, AND ABORTION OF ACUTE MASTOIDITIS BY THE USE OF SIR A. E. WRIGHT'S SOLUTION.*

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DRAINAGE of the middle ear is furnished by Nature through the Eustachian tube. This tube is not an open pipe, but merely a slit in the side of the naso-pharynx leading up to the bony isthmus, the posterior and superior walls of which are formed by cartilage, and inferior and anterior by soft fibrous (fascia) tissue. In hardened specimens at the top there appears to be a small opening which may be the lumen of a very small part of the structure which, in normal conditions may be more or less open. In very early life, the direction of the Eustachian tube is nearly horizontal, assuming a more and more oblique downward direction as life advances. Now the tube is not simply a pipe to allow the passage of fluids either way, but is lined with mucous membrane whose surface cells are ciliated, the direction of whose constant motion is towards the pharynx.

Moreover, the position of the tube and the downward moving ciliae are not the only factors which assist drainage from the middle ear. The tensor palati, which might be called the dilator of the tube as it is continuous with Rudinger's dilator tubae has its attachment to the anterior lip of the Eustachian cartilage and the fascia of the anterior wall, and by its action pulls the whole anterior wall of the tube forward; and the levator palati is attached inferiorly to a part of the lateral plate and to the membranous part of the floor of the tube. By their contractions, these muscles exert a pumping action on the pharyngeal end of the tube with every movement of the velum, as in talking, swallowing, etc. This is very prettily shown by the late Dr. Holmes' naso-pharyngoscope. Through this little instrument may be seen the forward pull of the anterior wall of the Eustachian tube and also a bulge under the mouth, so as to wedge it open. This swelling is described (Quain) as the belly of the levator of the palate. At all events, this pumping action is very well seen to open the tube by the tensor palati and the bulging belly of the levator to push the anterior wall forward and the posterior harder wall somewhat backward. And it may also be seen that if the inner part of

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