

THE SCHICK TEST IN DIPHTHERIA AND TOXIN ANTI-TOXIN IMMUNIZATION.

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More is known to-day of the cause, manifestations and cure of diphtheria than perhaps any other disease.

Science knows but one remedy for the cure of an attack of diphtheria, viz. large doses of diphtheritic antitoxin given early in the disease. This remedy has reduced the mortality 50%, yet diphtheria is still the most fatal of the infectious diseases of children, and its prevalence is absolutely undiminished. 700 to 800 children die of diphtheria in Chicago every year. Too often the child is overpowered by the diphtheritic poison before antitoxin is given, and disaster is unobstructed. It is believed that with our present methods of prevention and cure the mortality and incidence of this disease can not be further lessened.

The modus operandi of an attack of diphtheria is as follows: Virulent diphtheria bacilli by personal contact with a case of diphtheria or with a carrier are implanted upon the mucous membrane of a child's throat. They begin to grow in the throat like the mold on a contaminated glass of jelly. These germs do not enter the child's tissues or blood. They start at once to manufacture one of the most deadly poisons known, viz., diphtheritic toxin. This diphtheritic toxin enters the blood stream and if unneutralized by antitoxin produces its characteristic destructive and paralyzing effects.

If, however, the child shortly before contact had received a sufficient amount of antitoxin, or if the child is naturally immune to diphtheria, or if active immunity had been induced by the injection of T. A. mixtures to which I shall refer presently, this deadly toxin is neutralized and diphtheria does not result. The germs themselves prowl around the child's throat, get discouraged, and in course of time varying from one week to several months leave for more fertile fields or disintegrate.

It is interesting to know that approximately only 50% of children of school age are susceptible to diphtheria. In other words, about one-half of the children are naturally immune to this disease. They would not get the disease even upon the closest contact with a case of diphtheria. This is due to the fact that there exists in the blood of such children at least $1/30$ of a unit of diphtheritic antitoxin to each cc. of blood. The amount of antitoxin in a child's blood can be as accurately determined as the composition of the rocks or the interplanetary distances. This natural immunity is technically called active immunity and is believed to be permanent; that is, if after the first year of life the child is immune, he will always be immune. Carefully distinguish between this active immunity and what is called passive immunity, because I shall use these terms later. Passive immunity is the immunity occasioned by the transitory presence in the blood of sufficient antitoxin to prevent or cure diphtheria. This condition of immunity may be brought about by the direct injection of diphtheritic antitoxin into the child's blood or tissues. In practice, 1000 or 1500 units of antitoxin are injected into a child who has been exposed to diphtheria to prevent his getting it. The immunity so conferred is passive immunity. It is short lived, lasting about four weeks, after which the child is as susceptible as ever and perhaps more susceptible.

It will be conceded readily that it is important to determine if possible by some safe simple test a child's status with reference to diphtheria. If he is permanently immune, he will not get diphtheria nor will he need the immunizing dose of antitoxin if exposed to diphtheria. Sore throat of some kind is one of the most frequent diseases of childhood; comparatively few cases are true diphtheria but every case is potentially diphtheria, hence thousands of bottles of diphtheritic antitoxin are needlessly given every year in this state.

Until nine years ago the only way to determine whether a child was susceptible or not was by a tedious process of blood examination. In 1913, an Austrian physician by the name of Schick devised a simple skin

test that is almost infallible. It consists in injecting into the skin of the arm or any where a few drops of a high dilution of diphtheritic toxin. If in 3 or 4 days a small area of redness develops which gradually disappears, leaving a discolored scaly spot, the child is susceptible. If nothing results from this intra cutaneous injection, the child is naturally immune and probably for life. I have given nearly 8000 of these tests. It is almost painless and absolutely devoid of any danger whatever. Having determined by the Schick test that about one-half of the school children might get diphtheria if exposed to it, no vivid imagination is required to understand the desirability of immunizing, if possible, those that are susceptible. To me, how a great discovery is made is as interesting as the discovery itself. In this instance, as often happens, chance is entitled to almost as much credit as science in elaborating this most wonderful discovery. Again and again opportunity knocked at the Laboratory door of science, and offered a way and means of preventing this dreadful disease. As I shall presently indicate, the solution of this problem of active immunization in diphtheria was going on right under the eyes of every antitoxin laboratory worker in Christendom long before they knew it. I have thought sometimes that research workers, elated with their victory over laboratory diphtheria, have been slow to realize the importance of discovering some way of permanently immunizing the oncoming hoards of susceptible children. Behring himself sooner or later saw the necessity of active immunization because the protection afforded by immunizing doses of antitoxin was short lived. This often necessitated repeated doses of antitoxin which sometimes resulted in serious anaphylactic reaction. It is 14 years since Smith suggested, but 9 years since Behring, Park and others first used TA mixtures to actively immunize children. Of course this time is too short for us to be dogmatic, but the results thus far attained justify us in asking for the widest possible use of such mixtures if we are to limit further the ravages of this disease. Time will, I believe, demonstrate that few discoveries in medical science have been made which offer greater po-

tential possibilities for the prevention of a serious disease than the elaboration of the toxin-antitoxin mixtures for the prevention of diphtheria.

While Behring christened the mixtures which he used with the name TA and was the first to employ them for immunization in humankind, he was in no wise the first to suggest their use. Apparently Behring's TA mixtures were born with teeth and fully armed to fight diphtheria, for nowhere does he state how and when he conceived the idea nor does he give the relative proportions of the toxin and antitoxin in his mixtures. The evolution of a great discovery is usually a tortuous record of blunders, stumbling, infinite patience and industry, keen observation, half-baked conclusions and fearlessness in breaking away from traditional lines of thought. This is the history as I see it of the development of the TA mixture. Of those who contributed to the solution of the mystery of active immunization in diphtheria, one name so far outdistances all others that what I shall say is taken largely from his reports. That name is Theobald Smith.

The first step toward active immunization against diphtheria was made in 1895, when Wernicke reported that the offspring of the guinea pigs which had previously been treated with toxin and antitoxin possessed increased resistance to diphtheria toxin. He also showed that the male parent guinea pig in no way influenced the immunity of the young. These important observations passed unnoticed for a number of years. In 1902, Park immunized horses, goats and guinea pigs by mixtures of diphtheria toxin and antitoxin. As a matter of fact, he and others had actively immunized horses long before this, because in the treatment of horses to be bled for furnishing diphtheria antitoxin they had almost from the first learned that by injecting antitoxin with initial dose of toxin, stronger doses of toxin could be used, resulting in a greater and more rapid formation of antitoxin in the animal's blood.

None at this time seemed to realize the possibilities of all they were doing. They were interested only in the commercial production of a potent antitoxin.

Three years later, in 1905, Theobald Smith reported an interesting observation. Guinea pigs have always been used to test and standardize diphtheria toxin and antitoxin. Bearing this in mind, it can be understood readily how vital it is that the susceptibility of the animals used in these tests should vary as little as possible. Smith noticed that guinea pigs bought in the open market were less resistant to toxin than those he raised in his laboratory. He also noticed that the resistance of his own animals varied. He at first attributed these variations to individual susceptibility or to differences in food and environment. For the time being he ruled out any preliminary treatment of the animals as a cause of variations in their immunity. Continued irregularities in his tests seemed to have disturbed Smith's mind, for he studied more intensely and carefully the effect of preliminary treatment of the female parent with reference to the antitoxin content of the blood of the offspring. Two years later, in 1907, he reported that preliminary treatment of female guinea pigs with TA mixtures not only immunized them, but the offspring of these treated mothers were passively immunized. In addition he demonstrated conclusively that this passive immunity of the offspring is a correct measure of the active immunity of the mother guinea pig. This discovery was exceedingly important, for by testing the successive litters of guinea pigs he was enabled to watch the persistence of the active immunity in the parent guinea pig. Behring had maintained that the immunity of the animal parents had absolutely no influence on the susceptibility of their offspring. This fiat of Behring undoubtedly adversely influenced research workers the world over.

Smith found that this active immunity lasted for several years. He also showed in this paper of 1907 that there is apparently no relation between the severity of the reactions produced by the immunizing agents used and amount of active immunity resulting. Animals that were just able to survive a most powerful dose of toxin did not thereby possess any immunity, while the injection of a single dose of a mixture of toxin and antitoxin that caused no local or general disturbance did confer a

high degree of lasting immunity. It was in this paper that he made that memorable suggestion that human kind might thus be actively immunized by neutral mixtures of toxin and antitoxin.

This idea was so revolutionary and contrary to accepted theories that it attracted no attention. Two years later, in 1909, this medical Leverrier, with the courage of his convictions, again pointed the way to human immunization. Three years more followed and still no one arose to follow Smith's prophetic finger. It was not until 1912 and 1913 that Behring himself, who had evidently experienced a change of heart, without mentioning Smith's name, reported successful active immunization with TA mixtures. The fear of the known effects of diphtheria toxin on the nerves and heart, together with Behring's dictum mentioned before in this paper, undoubtedly deterred research workers and clinicians from the earlier use of TA mixtures. It seems to me no one can read Smith's reports and not be convinced that TA mixtures do produce a lasting immunity in these animals.

Experimentation has abundantly proved that the tests, manifestations of the disease, immunity and susceptibility observed in the guinea pig are exactly the same in human kind. TA mixture, as the name indicates, is a simple mixture of the diphtheria toxin with antitoxin in which the toxin is not quite neutralized. It is given subcutaneously in three doses of 1 cc. each at intervals of seven days. Immunity develops slowly, often not reaching its maximum until five or six months have elapsed. Experience shows that about ninety percent of the children receiving the three doses have been rendered immune during the whole period of observation, namely three to seven years. You will hear undoubtedly of the danger of giving these TA mixtures. In fact several deaths resulted in Dallas, Tex., because a mistake was made in the laboratory in the preparation of the mixture. I have given about 3500 injections in children without an unpleasant result. Park and Zingher in New York have given thousands and thousands of these injections without a death or loss of an arm. I had one

unpleasant result from an injection I gave a nurse. Recovery was not complete for four or five months.

SUMMARY

1. Experimental evidence is unimpeachable that TA mixtures do produce lasting immunity to diphtheria in lower animals. Clinical results are accumulating which show that similar active immunization can be produced in human kind. In my own experience the persistent use of such mixture has immunized 98 to 99 percent for a period up to three and one-half years.

2. The Schick test made with a potent toxin carefully performed and properly interpreted is almost an infallible indication of susceptibility or immunity to diphtheria.

3. All children above one year of age should be given a Schick test to determine their status with reference to diphtheria and also whether they are to be given subsequently TA or not, just as a person should know his history with reference to other infectious diseases.

4. All school children should be required to present to the school authorities a certificate showing at least the results of a Schick test and if possible active immunization with the TA mixture.

5. On account of the severe reaction following the use of TA mixtures in adults and because of the relative immunity of adults, only nurses and doctors given strong Schick reactions should be given TA.