Diphtheria : problems in connection with the Schick test and active immunization / by R.A. O'Brien.

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Diphtheria : Problems in Connection with the Schick Test and Active Immunisation, by R. A. O'Brien, C.B.E., M.D., D.P.H., Wellcome Physiological Research Laboratories.

I KNOW that at a meeting such as this, where we all are interested in public health, and well acquainted with all the latest achievements in this field of work, it is not to-day necessary for me to take up your time by presenting arguments in favour of the fundamental two propositions on which the more recent measures for combating diphtheria are based. These two propositions are : (1) that it is possible by means of the Schick test to discover those who are susceptible to diphtheria, and (2) when we have discovered them, it is possible by means of immunisation with preparations made from diphtheria toxin, to give these susceptible people prolonged protection against the disease. We may refresh our memories with a few charts setting forth the basal theory and practice of the measures we are to discuss. (Charts shown.)

No serious observer who studies the results of the work that has been done by Park in New York, and his co-workers in other American States, by many workers in England, Austria, France, Germany, Holland, and in almost every civilised country in the world, has any longer any doubt of the general truth of the two propositions above-mentioned. From them it follows that any community has it in its power, if it decides that the work and expense are worth while, to reduce the incidence of diphtheria as completely as we can prevent or stamp out smallpox in an adequately vaccinated population.

Two small tables may here be of interest ; our own small figures, and the results obtained by Park and colleagues.

Table I.—*Results obtained by Dr. Park and colleagues in New York.*

Year.	Total Cases.	Total Deaths.	Deaths per 100,000 Population.
1919 ...	14,000 ...	1,239 ...	22
1920 ...	14,100 ...	1,045 ...	21
1921 ...	15,000 ...	891 ...	16
1922 ...	10,000 ...	876 ...	15
1923 ...	8,050 ...	547 ...	9·5

Table II.—*Results obtained by Dr. O'Brien and colleagues in England.*

Schick Tests and Immunisation.		Number Immunised and Retested.	
Total	3,903	Total	992
Number negative	2,695	Per cent. negative after :	
Per cent. negative.. ...	71	8 weeks	90.2
Number positive... ...	1,208	12 weeks	98
		20 weeks	99·1

From our experience we conclude that we can rapidly test a population of children—for it is amongst children that most diphtheria occurs, and where

the need for protection is greatest—and confer a considerable degree of immunity on the greater part of the children within a fortnight, and upon almost all of them within six weeks.

Park's results obtained from the testing of several hundred thousand children have demonstrated over a period of some years that these measures of testing and immunisation are well worth while.

Probably the best use I can make of my time is to deal with the difficulties and interesting problems that arise in this work. The ultimate value and success of the modern campaign depends on the truth of the statement that "A person who gives a Schick negative reaction, whether at the first test or after immunisation, will not suffer from diphtheria." Having made this assertion, we must consider where we are open to attack.

We must have a clear idea of what we understand by " immunity " in relation to this work. It is probable that there is no such thing as absolute immunity against a toxin or infecting agent such that no dose, however large, of the agent will break through the immunity possessed by an animal and cause toxaemia or infection. It is possible to produce diphtheritic paralysis in a horse whose blood contains a considerable amount of diphtheria antitoxin, and this sequence is occasionally seen in any institution where diphtheria antitoxin is produced. A horse receives a series of doses of toxin which from previous experience of that particular horse, and from general experience of many hundreds of horses, one would imagine is a safe series, yet the horse, although possessing some antitoxin in its blood, develops paralysis and either dies or is killed. When we say that a population is immune against a certain disease, we understand it to mean that the members of the population will either remain entirely unaffected by the disease or at the worst a very small percentage will become affected.

We know from the work of Guthrie and colleagues at Baltimore, that a person giving a negative response to the Schick test will not develop diphtheria, even if a swab containing a culture of virulent diphtheria organisms is rubbed on his throat. In that experiment, every one of the volunteers who was a Schick negative reactor, showed no symptoms following the swabbing, while all those who were positive reactors developed typical clinical diphtheria.

We know, too, that if a person who has given a Schick reaction does later on suffer from a sore throat and virulent diphtheria bacilli are found in the throat, he will suffer from no more than what Dr. Harries calls " a transient tonsillitis associated with the presence of morphological diphtheria bacilli or a frankly " carrier " state." Such instances are very rate. We have found in three years work, three instances in which a slight degree of pharyngitis occurred, and virulent diphtheria bacilli were found in throat swabs made from people who had at an earlier date given a negative response to the Schick test.

It is, I think, worth our while to consider instances in which definite diphtheria is said to have occurred in people who have been "Schick negative reactors." Here the familar facts concerning inoculation against typhoid fever and vaccination against smallpox will help us. We know that an *adequately* vaccinated hospital staff can go through an epidemic of virulent smallpox without a single infection. We also know that a hospital staff thoroughly vaccinated against typhoid fever can, with impunity, treat and nurse cases of typhoid fever.

From time to time public health investigators have met with instances in which protection apparently broke down—in which people vaccinated with calf lymph have later developed severe smallpox, and again where people recently injected with typhoid vaccine have suffered from a disease diagnosed as typhoid fever.

The so-called failure of vaccination above described, mostly occurring in the tropics, has been found to be due to the use of improperly prepared inert calf lymph, or of calf lymph stored in the tropics under conditions that cause rapid deterioration of the lymph. The efficiency of lymph can be tested in the laboratory, and should always be so controlled. We find as the result of much enquiry that we can say " a patient properly vaccinated with efficient calf lymph is immune to smallpox."

In the instances where vaccination against typhoid fever had apparently failed, enquiry showed that the typhoid vaccine used was of proper quality and efficiency. Careful clinical study of the cases and laboratory investigation soon showed that many patients recently and efficiently vaccinated against typhoid fever who were supposed to be infested with typhoid fever, were really suffering from a closely allied disease or diseases caused by bacilli of paratyphoid A and B fevers. Against these, typhoid vaccine gives little or no protection. When this was discovered, the logical change was made and the well-known combined vaccine, the familiar T. A. B. of army days conferring protection against all three fevers, was used. We are justified, on the evidence available, in saying that a person properly vaccinated with typhoid vaccine is immune against typhoid fever.

I have digressed from our study of diphtheria for an important reason. These recent anti-diphtheria measures are not in universal use mainly because of the apathy of public health authorities, whose attitude probably is that these measures are all interesting purely as scientific experiments in small institutions, but that it is not practicable to apply them on a large scale. I do not propose to spend further time meeting this contention, but I should like to call attention to another argument, *i.e.*, that these measures have been used, and they have failed. It is not one frequently heard, but a public health authority must always be prepared for this objection.

We have in our past three or four years' work, met with a number of instances in which a person stated to have given a negative response to the Schick test has later suffered from a disease said to be diphtheria ; such instances, if confirmed, would represent " failures " of the modern anti-diphtheria measures. Several enquiries must immediately be made. Experience with vaccine against smallpox and typhoid fever leads us to expect that we shall possibly here also find that in cases thought to be failures in the procedure, improper material was used, or the diagnosis needed reconsideration.

Was the patient really a negative reactor ? Was the toxin used potent ? Was the experience of the worker sufficient to enable one to assume that the toxin was properly injected *into* and not *under* the skin, and that the reaction on the arm was properly read ? We can answer at once that we have met instances in which, owing to oversight or misunderstanding, diluted Schick toxin was used for many weeks after it had so deteriorated as to be incapable of giving a satisfactory reaction. In connection with reading of the reactions, in our early work, we often met with a number of reactions which we could not with certainty state were positive or negative, and we still find that we must, in rare cases, repeat the test or examine a small sample of the blood before we can be quite certain of the reading ; we hope, therefore, we may be forgiven if we say that medical men engaged in public health work can read the great majority of Schick reactions accurately, but there are very few men who could, without considerable experience, make an accurate reading in the odd 5 per cent. of patients who give anomalous or " difficult " reactions. We know that here lies the explanation on some of the instances regarded as " failures " of the artificial protection against diphtheria.

But by far the greater number of " failures " were erroneously so regarded ; they really represented errors in diagnosis. I may conclude this section by stating that recently, we had the opportunity of studying a series of about 500 successive admissions to a fever hospital, of patients certified as cases of " diphtheria." The final diagnosis, after the cases had been studied, rested with the clinician who had a vast experience and knowledge of diphtheria. We found that 59 per cent. of the 500 patients were suffering from indubitable or probable clinical diphtheria when admitted, but that in 41 per cent. the diagnosis of diphtheria made by the general practitioner could not be confirmed or accepted.

Table III. recalls what one finds in cases of frank clinical diphtheria ; Table IV. records some instances we have encountered where diphtheria has been erroneously diagnosed.

TABLE III.

Frank Clinical Diphtheria.
Schick positive
No antitoxin in blood
Clinical picture typical
Overnight culture—smear usually shows profuse typical K. L. B.
K. L. B. are Virulent.

TABLE IV.—*Diphtheria wrongly diagnosed in Schick Negative Reactors.*

Clinical picture.	Bacteriology, etc.
A.—Not typical	Hofmann.
B.—Not typical	Other diphtheroids.
C.—Not typical	A virulent K. L. B.
D.—Not typical	Streptococci.
E.—Membrane not typical ...	Profuse Vincent's organisms.
F.—Membrane not typical ...	Profuse Vincent's and few K. L. B. Avirulent.
G.—Membrane not typical...	Profuse Vincent's and few K. L. B. Virulent.
H.—Chronic Rhinitis and Sore Throat	K. L. B. Virulent (Chronic Carrier).
I.—Cyanosis, recession ...	Papilloma of Larynx, Foreign Bodies, *e.g.*, button. (Laryngitis and Laryngismus).

I earnestly hope that the position taken up in this communication will be clear. I would wish to distinguish sharply between what we may, for want of better terms, call the temporary diagnosis and the final scientific diagnosis of diphtheria. I emphatically agree with all the great teachers of the past and present who say that the clinician faced with an ill patient showing signs of disease sufficiently definite to warrant sending a swab to the laboratory for diagnosis, must at once give antitoxin without waiting for the laboratory diagnosis. In other words, where the treatment of an ill person is concerned, the whole responsibility for diagnosis and treatment must remain with the clinician and the laboratory must have no influence on the treatment to be followed. Delay in commencing treatment while waiting for the laboratory verdict may deprive the patient of his only chance.

But the point I wish to make is that for anything beyond the temporary clinical diagnosis, the clinician will fall into many errors unless he has full bacteriological and immunological data. I would say that the physician is not justified in giving a final scientific diagnosis unless he has the full immunological data.

It may be of interest to consider possible improvements in the Schick test and in immunisation. One of the urgent improvements most desired is

the preparation of a toxin for the Schick test which will not cause the production of a " pseudo " reaction. At present, it is necessary to inject into each patient not only the Schick toxin, but a control in the other arm. If we could prepare a toxin free from the " pseudo " constituent we should give only one injection. We should also save much time in reading the results, for if the pseudo constituent were not present it would be easy to decide almost at a glance whether the person under observation were positive or negative.

Unfortunately, notwithstanding a great amount of work all over the world, no one has yet succeeded in preparing toxin free from a " pseudo " constituent.

My colleague, Dr. Watson, has concentrated toxin so that the combining power per milligram of nitrogen has been considerably increased, and yet a small dose of this toxin produced, in my colleagues at the laboratory, as definite a " pseudo " reaction as the ordinary crude toxin in common use. No method of precipitation, filtration or dialysis that has yet been tried has effected the desired separation. The " toxin " must adhere very closely to the " pseudo " constituent unless indeed, it is part of the same molecule.

The other improvement which one eagerly desires is such a concentration of the immunising efficiency of the prophylactic that one injection may produce immunity within a few weeks. A large amount of work is being done in an attempt to achieve this result. We know much more of the immunising efficiency of various mixtures to-day than we did several years ago. Park and colleagues have made a very large number of valuable observations on groups of school children. The " immunity index " test devised by my colleague, Mr. Glenny, has enabled us with reasonable accuracy to measure in the laboratory the immunising efficiency of various mixtures.

One injects into a guineapig a dose which may be 1 c.c. or a fraction thereof, and a week or two later, one Schick tests the guineapig. If the result is positive one repeats the test each week until the result is negative. If the guineapig has received no prophylactic he may give a positive response to the Schick test every week, for a year or more, but a guineapig which has received 1 c.c. of the ordinary prophylactic, will give a negative response in about five weeks. We have recently prepared a concentrated toxin, almost entirely free of toxicity but of such immunising power that an injection of 1 c.c. causes a guineapig to become negative to the Schick test within twelve to 14 days. This is a great improvement. Unfortunately, opportunities for testing such immunising preparation mixtures in England are few, even though we are sure from our own personal experience that such a mixture causes no ill effects. Park in New York, has recently used a diphtheria " toxoid " made by the methods elaborated by my colleagues, Mr. Glenny and Miss Hopkins, and has in various schools found that 80-90 per cent. of the children rapidly became negative to the Schick test after a course of this toxoid. This has been used in England on a very small scale, and we are much encouraged by the results.

The first object we have in view is to prepare an antigen which will, by one injection, produce an immunity sufficient to yield a negative response to the Schick test within a few weeks.

If one could reduce the present three injections to one, one would go far to reduce correspondingly the administrative difficulties in connection with immunisation of the public on a large scale.

We also hope that, during the processes used in an attempt to make more efficient prophylactic, we may be able to free the immunising mixture from the constituent which causes definite local and general reactions in some sensitive adults.

It is reasonable to say that the success of the present methods of Schick testing and immunisation are to-day so firmly established that it is the duty of public health authorities to see that full facilities for the performance of this test and immunisation are available to the public. It is a reproach to a hospital whenever a nurse on the staff suffers from diphtheria, for a nurse should not be in contact with cases of diphtheria unless she is immune against diphtheria. Similarly, a community should not be obliged to suffer from diphtheria unless it has deliberately neglected measures recommended by the public health authority.

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