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SOME PROBLEMS CONNECTED WITH THE DICK TEST

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We know from the results of recent work in England, which broadly agree with those obtained in America, that the Dick toxin with which we are working is specifically related to the scarlet fever prevalent here. In the first few days of the disease a suitable dilution of the toxin will give a high percentage of positive reactions; these same patients will during convalescence change their reaction from positive to negative; the toxin is neutralised by the serum of patients convalescent from scarlet fever, and the toxin, if given in sufficiently large doses to volunteers, will produce what is in some essential characteristics (temperature, vomiting, and rash) a miniature attack of scarlet fever. We know also that the serum of horses immunised with this toxin contains an antitoxin giving the specific Schultz-Charlton reaction. We may go further and say that the accumulating evidence leaves little doubt that, at least in certain severely toxic cases of the disease, the antitoxin has a definite therapeutic effect. There are, however, a great many points still unexplained, and it is by the close study of these that progress will be made.

It is necessary to avoid changes in toxin while doing experimental work; one must, therefore, have a large volume of liquid toxin available. Scarlet fever toxin is strikingly resistant to heat, and of a much higher order of stability than other well-known bacterial toxins. It is not known at present whether dried toxin, or toxin precipitated by one of the well recognised methods of precipitation, would be more stable than the liquid toxin. Presumably it would be.

The Question of Dilution.

We know fairly closely what are the most suitable dilutions of toxins for use. The question is an interesting one. As Park has pointed out: "If a toxin is a little too strong there will be too many positives; if it is too weak there is a possibility of having people who are susceptible pronounced as immune."

We commenced working with a dilution of 1/6000 of our large bulk of toxin, for with this dilution several of the laboratory staff gave clear positive reactions. Several physicians in fever hospitals have kindly compared the two dilutions 1/6000 and 1/1000. One worker found in the first week of scarlet fever 12 per cent. of positive reactions with dilution 1/6000,

while a 1/1000 dilution gave 60 per cent. of positive reactions; for the second week the figures were 6 per cent. and 12 per cent. It is therefore evident that 1/1000 is the better strength to use when testing patients considered to be suffering from scarlet fever. It may, of course, not be the optimum.

Percentage of Positive Reactions.

Different observers, when testing patients admitted in the first two days of the disease, have obtained different percentages of positive reactions. Most workers give a percentage of from 66 to 100, while two clinicians, working with small groups of patients, obtained percentages as low as 22 and 42. Probably a close study of these differences would give information of value. The change from a positive to a negative response to a 1/1000 dilution of the toxin during the disease appears to occur in the average case about the fifth to the eighth day. One point of some interest is that amongst 673 reactions there were but 10 (1·5 per cent.) "pseudo and positive," and 25 (3·7 per cent.) "pseudo and negative." This low percentage we probably owe to the fact that Okell and Watson chose for the growth of the streptococcus ordinary digest medium containing no blood, and, from a study of the growth and metabolism curves, harvested the toxin at 18 hours.

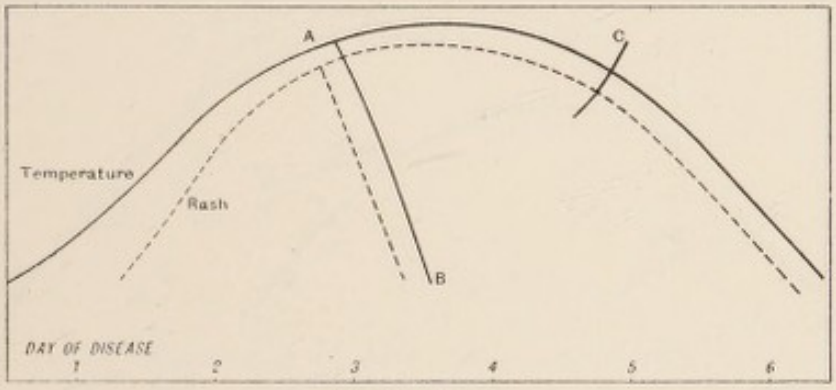
With a 1/1000 dilution of toxin the percentage of positive reactors in different ward staffs varied from 7·5 in a large hospital (106 nurses) to 10 amongst 31 nurses and probationers. Evidently the great majority of nurses of long experience in scarlet fever wards are negative to the Dick test and non-susceptible to the disease. We do not know accurately what percentage of nurses in such wards would give a history of having contracted scarlet fever during their hospital life. It is probably fairly large, but many have no such history. Evidently, as in diphtheria, nurses (and others) may become immune through minute unrecognised infections with the scarlet fever organism. Nurses with positive reactions are generally newcomers. Two nurses in fever hospitals who gave a positive response to the test developed scarlet fever later. We would not be surprised to find that practically every nurse who has been several years in scarlet fever wards has either suffered from an attack of the disease during her hospital career or has already become immune from unrecognised infections either during or prior to life in the wards.

Significance of a Negative Response.

We know broadly that a negative response to the Dick test indicates a high degree of non-susceptibility,

but we are not convinced that a positive, and particularly a "partial positive," reactor may not possess some immunity. It will be of great interest to ascertain how high the immunity represented by a negative reaction is. We have already reported that in one hospital, during a certain period, eight patients wrongly diagnosed as suffering from scarlet fever who gave a negative Dick reaction were admitted to the scarlet fever ward, but none developed the disease from ward infection, whereas of six positive reactors similarly admitted four developed the disease within a short period of admission to the ward. In another hospital a case of scarlet fever made its appearance amongst a group of 50 convalescents who were closely associated; 37 of these were "Dick-negative," none developed the disease,

FIG. 1.



Scarlet fever.

while of 13 who were "Dick-positive," six developed scarlet fever. On the other hand, we have notes of two instances in which patients were apparently negative to the Dick test when 1/1000 dilution of toxin was used, yet shortly afterwards developed an attack of what was considered to be typical scarlet fever. Such instances do not materially affect the main thesis; for the moment we simply place them on record.

With regard to the application of the Dick test to diagnosis in the disease, it will be necessary to get a clear idea of the immunity curves of the disease. This will not be completely and satisfactorily done until one can as easily measure the toxin and antitoxin of scarlet fever in the laboratory as those of diphtheria. We have constructed a hypothetical curve which may well record what happens during an attack of scarlet fever.

In Curve 1 the heavy line diagrammatically records the temperature and toxæmia in an ordinary attack

that there might easily be an overlapping of antigens between the so-called true scarlet fever streptococcus and other streptococci, at least other hæmolytic streptococci. Recently a hæmolytic streptococcus, isolated by Sir Frederick Andrewes from a spreading lymphangitis of the arm, has yielded, when grown on the same media as the Dick and Dochez coccus, a filtrate which gives a typical positive Dick reaction in a known Dick-positive reactor, and a negative in a known Dick-negative reactor. We do not know yet if the toxin is neutralisable by true scarlet fever antitoxin. As yet the relationships between the various streptococci and their toxins have not been sufficiently investigated. This field is rich in interest.

Dr. C. Rundle has had the idea that there may be two or more types of scarlet fever, and has worked particularly by the Schultz-Charlton method. Furthermore, Dr. Park has in a recent paper suggested that there may be a wide antigenic overlap between the different streptococci, that—e.g., while the ordinary scarlet fever toxin contains antigenic or toxin components *a*, *b*, *c*, *d*, others may exist which contain *a*, *b*, *c*, *e*, and so forth.

It is stated that during convalescence after what seems to be typical scarlet fever a certain number of patients continue to give a positive Dick reaction. The point needs further investigation. If such patients exist, have they cured themselves of their fever by producing antitoxin which is still locked up intracellularly, and are the cells slow to excrete the antitoxin into the blood-stream? Will they become later negative to the Dick test? Have they responded to the primary stimulus of the toxæmia and, if injected with, e.g., 500 skin doses of toxin during convalescence, will they rapidly produce sufficient antitoxin to make them negative to the Dick test? These and many other interesting points can be worked out only by those having the opportunities of making clinical observations. In the laboratory, until a satisfactory test is discovered, we can do but little.

We may here mention an interesting question for investigation. How stable are the dilutions of toxin? We have considerable evidence that they are stable for at least two weeks. This is a small practical point, but one it is important to know in order to avoid fallacies in making a series of observations. It is obvious that the old and the new dilutions must be tested on the same subject.

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