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Contributors

Okell, C. C. 1888-1939.

Parish, H. J.

Wellcome Physiological Research Laboratories.

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THE DICK TEST IN SCARLET FEVER.

By C. C. OKELL, M.C., M.B., M.R.C.P. LOND.,

AND

H. J. PARISH, M.D., M.R.C.P. EDIN.

(From the Wellcome Physiological Research Laboratories.)

THE small number of observations on the Dick test so far published in Europe encourages us to bring forward the following results. In July last, Okell and Baxter¹ reported the results of a number of tests. Ker, McCartney and McGarrity² (1925) have reported a further series. The present communication describes a further series of tests done on scarlet fever patients and on normal individuals.

The Toxin.

The toxin used in all these tests was prepared by us from a strain of streptococcus kindly sent to us by Dr. Dochez. It consisted of a filtrate of a 16-hour-old culture of the streptococcus in Douglas's³ trypsin digest medium as modified by Hartley⁴ and subsequently by Watson and Wallace.⁵ An intradermal injection of 0.2 c.cm. of a 1/6000 dilution of the toxin was found to give a well-marked reaction 20 to 70 mm. in diameter in susceptible persons, the average positive reaction being about 20 × 30 mm. Dick toxin is much more heat stable than diphtheria toxin, and is practically unaffected by heating to 75° C. for ten minutes, a procedure which always inactivates dilutions of diphtheria toxin. The method employed for the inactivation of the toxin for the control inoculation is heating to 96° C. for 45 minutes. The constituent responsible for the pseudo reaction seems to be very little affected by this treatment. The toxin keeps for at least two weeks in the diluted state, and phenol (e.g., 0.4 per cent.) may be used as a preservative in the dilutions. Dick toxin, unlike diphtheria toxin, does not appear to produce tissue necrosis. Dick and Dick⁶ and others report that many reacting doses can be given without causing any permanent tissue damage. In the dilutions employed in the test it appears to have a vaso-dilator effect on the capillaries. We have prepared toxins not only from Dochez's strain but from strains sent us by Dr. Dick of Chicago and Dr. W. H. Park of New York, as well as from two strains isolated in London by ourselves. All these toxigenic strains appeared to fall into one

serological group by absorption tests, and produced toxins apparently identical in properties with that made from Dr. Dochez's strain. They were all neutralised by the serum of people who had recovered from scarlet fever and by the serum of Dick-negative individuals.

No animal other than man has been found to give satisfactory titrations of the toxin. The pig, guinea-pig, rat, mouse, cat, hen and rabbit are practically insusceptible. A toxin which when diluted 1/6000 and injected into susceptible human beings will give a well-marked specific reaction, fails to produce unequivocal reactions in these animals, even in the undiluted state. The monkey (*Macacus rhesus*) was also found insusceptible to the toxin. Kirkbride and Wheeler⁷ (1924) have reported that the goat is susceptible to the toxin. We have found it difficult to decide how far the reactions in goats are to be ascribed to the specific scarlet fever toxin. Control fluids such as diluted broth, diluted serum, and heated toxin give rise to quite definite reactions, while the toxin reaction can be partially but not completely neutralised by convalescent serum. The interpretation of results is therefore difficult.

Antitoxin.—We have used toxin for the immunisation of two horses, and the serum obtained was found not only to neutralise an intradermic dose of the toxin in human beings but also, even when considerably diluted, to give rise to the typical Schultz-Charlton⁸ blanching of the rash of scarlet fever patients. The therapeutic efficacy of this serum in the treatment of scarlet fever is at present being tested.

Technique of the Dick Reaction.

The technique of the injections is practically the same as that employed for the Schick test.

The skin in front of the forearms is carefully cleansed with spirit; 0.2 c.cm. of a suitably diluted toxin is injected intradermically into one arm, and 0.2 c.cm. of a similar dilution which has previously been heated to 96° C. for 45 minutes into the other.

Reading the Reactions.—Reactions are divided, as in the Schick test, into positive, pseudo-and-positive, negative, and pseudo-and-negative.

Positive Reaction.—The positive reaction develops in from six to 12 hours as a bright red flush with average dimensions of 20 by 30 mm. It has usually reached its maximum in 24 hours, and then rapidly fades away, so that it is usually almost invisible by the seventy-second hour after injection. The reaction thus develops much more quickly than the Schick reaction and fades away more quickly.

In the *pseudo-and-positive*, or "combined" reaction, there is a reaction on both arms, but that on the toxin arm is definitely greater than that on the control.

In the *negative reaction* there is no significant reaction on either arm.

In the *pseudo-and-negative reaction* the reactions, which may vary in size in different individuals, are approximately equal on both arms. The pseudo reaction, as in the Schick test, may remain for several days, and indeed may outlast the positive element of the reaction, a sequence never met with in the Schick test.

In the following series of tests we have also described a *partial positive* reaction by which we mean a small positive reaction a quarter to a half as large as the usual positive reaction, suggesting that a certain amount of the toxin has been neutralised. The significance of this type of reaction in terms of immunity is not yet clear, but as it is more common in those who have had scarlet fever than in those who have not, it possibly indicates that the patient is not susceptible to the disease.

Normal Group.

The normal group consisted of 100 medical students whom we obtained as volunteers through the kindness of Sir Frederick Andrewes. Ninety-five of these were available for reading at the end of 24 hours, the best time in our opinion for reading the tests. (Table I.) The positive rate, 74 per cent. in this group is high. The Schick-positive rate we found in a similar group of medical students was 65 per cent. Twenty of the students had a previous history of scarlet fever, and of these 65 per cent. were read as positive and 35 per cent. as negative. In several of these the history of scarlet fever appeared somewhat indefinite. Seventy-five had a negative history of

TABLE I.—*Results of Dick Tests on 95 Medical Students.*

| Reading. | Approximate percentage. | Reading. | Approximate percentage. |
|------------------------|-------------------------|------------------------|-------------------------|
| + | 64 | - | 20 |
| +* | 0 | -(?) | 1 |
| p+ | 8 | -* | 2 |
| p+* | 1 | -*(?) | 3 |
| + (?) | 1 | | |
| Percentage positive 74 | | Percentage negative 26 | |

Explanation of signs in Tables. + = Positive. +* = pseudo-and-positive. p+ = Partial positive. p+* = Pseudo-and-partial positive. - = Negative. -* = Pseudo-and-negative. (?) = A reaction difficult to interpret.

scarlet fever, and in this group there were 76 per cent. positive and 24 per cent. negative. The percentage of negative reactions is comparable to that obtained with the Schick test in similar individuals who gave no history of diphtheria.

In this series we noted the size of the reaction in relation to the history of scarlet fever. From previous observations on young children the opinion had been formed that the standard reaction with the test dose of toxin, in a completely non-immune individual, should be about 30×20 mm. Amongst the 70 students with positive reactions we found 36 in whom larger reactions developed, and in three the reactions measured upwards of 70 mm. in one axis. In all cases the area of redness rapidly disappeared. There were no definite pseudo reactions among the 36 individuals who had reactions larger than the normal. The size of the positive reaction appeared to have no relation to the history of scarlet fever. In a few cases only was the reaction greater in area at the end of 48 hours than at the end of 24 hours, and in no case did we read a reaction as definitely negative at the end of 24 hours but as positive at the end of 48 hours. In the whole series of normal individuals pseudo reactions were uncommon. Only one pseudo-and-partial-positive, and five pseudo-and-negative reactions occurred.

Convalescent Group.

The second group of individuals tested consisted of 120 cases of notified scarlet fever from the second to the twelfth week of convalescence. Table II. gives the results of the tests in relation to the period of convalescence.

TABLE II.—*Analysis of Results of Dick Tests in Relation to Period of Convalescence (120 Cases).*

| Week. | Positive group. (22 or 18 per cent.) | | | | Negative group. (98 or 82 per cent.) | | | Totals. |
|--------|---|----|----|-----|---|----|-------|---------|
| | + | +* | p+ | p+* | - | -* | - (?) | |
| 1st | .. | .. | .. | .. | .. | .. | .. | .. |
| 2nd | .. | .. | .. | .. | 1 | .. | .. | 1 |
| 3rd | 2 | .. | 2 | .. | 19 | 1 | .. | 24 |
| 4th | 4 | .. | 1 | 1 | 18 | 2 | .. | 26 |
| 5th | .. | .. | .. | .. | 9 | .. | 2 | 11 |
| 6th | 3 | 1 | 2 | 2 | 19 | .. | 1 | 28 |
| 7th | 1 | .. | 1 | .. | 14 | 1 | 1 | 18 |
| 8th | .. | .. | .. | .. | 2 | .. | 1 | 3 |
| 9th | 1 | .. | .. | .. | .. | .. | .. | 1 |
| 10th | .. | .. | .. | .. | 3 | .. | .. | 3 |
| 11th | .. | .. | .. | .. | 2 | .. | 1 | 3 |
| 12th | 1 | .. | .. | .. | 1 | .. | .. | 2 |
| Totals | 12 | 1 | 6 | 3 | 88 | 4 | 6 | 120 |

The net results of the tests on scarlet fever convalescents from the second week of convalescence onwards were as follows: Positive group 18 per cent., negative group 82 per cent., the partially positive group amounted to 7.5 per cent. Table III. gives a further analysis of the positive group.

TABLE III.—*Further Analysis of Positive Group in Table II. in Relation to Clinical Diagnosis of Scarlet Fever (22 Cases).*

| Clin. diag. of scarlet fever. | Number tested. | Result of Dick test. | Clin. diag. of scarlet fever. | Number tested. | Result of Dick test. |
|-------------------------------|----------------|----------------------|-------------------------------|----------------|----------------------|
| Definite .. | 14 | + | Doubtful | 5 | + |
| | | * 1 | | | p + |
| | | p + | Very doubtful | 3 | + |
| | | p + * 3 | | | |

Of the 22 read in the positive group 14 had a very definite clinical history of scarlet fever and the remainder were considered from their history and continuous observation during their convalescence to be of "doubtful" character. Of the 14 with a definite history of scarlet fever six only gave strongly positive reactions, one of these being a strong positive and pseudo reaction. The remaining eight gave partial positive reactions. In the case of the six strongly positive cases, the intervals after the alleged onset of the disease were 4, 5, 5, 6, 6, and 7 weeks respectively. One of the strongly positive patients with a history of a very definite attack developed a typical attack of scarlet fever the day after the test had been read. This case illustrates the possible value of the test in investigating the confused subject of relapses in scarlet fever.

As it is generally admitted that the diagnosis of scarlet fever is much more difficult in very young children, an analysis of the reactions was made in reference to age-groups. The numbers of the children under four years old were too small to enable us to draw any definite conclusion from them, but there was some indication that positive reactions were relatively more common in this group. Pseudo reactions, either positive or negative, were unexpectedly uncommon in the group of convalescents. From previous work it seemed that pseudo reactions are more common during the more acute stages of the disease.

Hospital Staff Results.—Thirteen members of the medical and nursing staffs of scarlet fever wards were also tested. All but one nurse had spent a considerable time attending scarlet fever cases, and seven had suffered from definite attacks of scarlet fever. This nurse had been in the wards only a fortnight, and was the only one to give a positive reaction. Nine days after the test she developed a typical attack of scarlet fever.

Discussion of Results.

In both groups it will be seen that an individual with a history of scarlet fever does not necessarily give a negative reaction, even though several weeks

have elapsed from the onset of the attack. The normal group with a history of scarlet fever had a Dick-positive rate of 65 per cent. and the convalescent group 18 per cent. The Dick-positive rate in the normal group with a scarlet fever history was therefore undoubtedly high. Two explanations of this unexpected finding are suggested. Either the history given by the individual himself was unreliable, or the immunity to the toxin had disappeared with the lapse of time. It seems, however, reasonably certain that the risk of scarlet fever, to those with a definite history of the disease, is small, and on these results the possibility of individuals being Dick-positive, yet insusceptible to the disease, cannot be excluded.

A similar difficulty occurs in interpreting the results in the convalescent group, where there was a Dick-positive rate of 18 per cent. Four explanations of this discrepancy appear possible: (a) That the present methods of diagnosis are not wholly satisfactory; (b) that patients who have had scarlet fever do not necessarily become immune to the toxin or become so, in some cases, very slowly; (c) that strains of scarlet fever streptococcus may produce more than one toxin; (d) that the test is not a true indication of susceptibility to scarlet fever.

With regard to (a) it is unnecessary to emphasise the difficulties in making a certain diagnosis of scarlet fever, as indeed it must be for all diseases where the specific cause is still uncertain. (b) This seems to be a very probable explanation of at least some of the discrepancies since few diseases will invariably produce immunity, or at least sufficient immunity to neutralise a dose of injected toxin. (c) Up to the present there appears to be no evidence that there is more than one scarlet fever toxin. (d) The results of the tests, both in the large series done in America and the smaller series done in this country by Ker and by ourselves, are in the main uniformly in favour of the test, and it does not appear too sanguine to consider the comparatively small percentage of discrepancies as due to the inevitable ignorance of the occasional factors governing the test.

It is possible that with the further development of knowledge the standpoint will change, and the bacteriological findings become of real value in diagnosis. For the moment the laboratory worker must accept the opinion of the experienced clinician rather than suggest any readjustment of the diagnosis by an appeal to a test which is still in the experimental stage.

Conclusions.

1. Amongst 95 medical students 74 per cent. gave positive response to the Dick test. Amongst 20,

who had a history of scarlet fever, 65 per cent. gave a positive reaction ; of 75 students who had no history of scarlet fever 24 per cent. were negative to the Dick test.

2. Amongst 120 patients entered in the hospital records as convalescent from scarlet fever, 82 per cent. gave a negative reaction ; amongst the 22 (18 per cent.) with a positive reaction there were 6 giving a strongly positive reaction, who were considered to have had a definite attack of scarlet fever.

3. On the whole, our experience of the test agrees with that of Dick, Zingher,^{9 10} and others.

Tests by Other Observers.

1. Dr. E. H. R. Harries, in conjunction with Dr. James Chalmers, made some tests at the City Hospital, Little Bromwich, Birmingham, in 1924, with toxin which we prepared from the Dochez strain. Dr. Harries has allowed us briefly to quote some of these results, which were as follows :—

Of 11 children suffering from diphtheria, without previous history of scarlet fever, eight gave a positive response to the Dick tests : one a pseudo-and-positive ; and two a pseudo-and-negative reaction.

Of nine children tested during convalescence from scarlet fever, all gave a negative response. Another child who had been notified as suffering from scarlet fever but who gave no definite evidence of the disease and was " barrier nursed " throughout, showed a positive reaction.

Some members of the nursing staff were also tested with this toxin. Of 42 nurses so tested, 16 gave a history of scarlet fever. Twenty-eight showed a negative reaction, and nine a pseudo-and-negative, whilst only four gave a positive or slightly positive response, and one a pseudo-and-positive reaction.

Two of the four positive results were obtained in nurses who stated that they had had scarlet fever. Both these attacks were said to have occurred in hospital, and it was therefore possible to investigate them. In both instances the attack was of a very doubtful nature.

It is to be noted that in all the above tests 0.1 c.cm. of the toxin and of control was employed.

Dr. Harries and Dr. Chalmers also, before deciding to use therapeutically horse serum which we had prepared by immunisation with toxin from the Dochez streptococcus, tested the serum for the production of the blanching reaction. They found that the horse sera used, either neat or diluted from 1-10 to 1-100, gave a typical Schultz-Charlton blanching of the rash in every case of scarlet fever tested, but failed to blanch an enema rash, a rash associated with encephalitis, or a toxæmic rash due to constipation. Normal horse sera used for controls failed to produce blanching in any instance.

2. Dr. F. Foord Caiger arranged for the carrying out of some Schultz-Charlton tests by Dr. Ruby

Inkster at the South-Western Hospital. Dr. Inkster has very kindly supplied us with a preliminary record of some of her work.

Serum obtained during convalescence after a typical attack of scarlet fever gave a positive Schultz-Charlton blanching when tested on the rashes of three patients suffering from scarlet fever. Various samples of normal horse sera were tested in 20 instances, but in all cases failed to blanch the rash. Serum from horses we had immunised with toxin made from a strain of the specific streptococcus was tested on the rashes of 43 patients. Serum A, when used either neat or in various dilutions up to 1 in 100, produced blanching in every instance (30 cases); serum B, tested in 13 cases, produced blanching in nine, in dilutions up to 1 in 10. Therapeutic serum which had been used in America, and which we owe to the courtesy of Dr. Dochez, gave positive blanching results in all ten cases tested, the serum being diluted 1 in 5 or 1 in 10, and some therapeutic serum which Dr. W. Park, of New York, very kindly sent us produced blanching in three out of five cases.

The figures are too small to allow of a comparison of the "blanching titre" of the various sera used, but as far as can be judged from this series of tests it would appear that the sera we have prepared possess the specific antitoxin in reasonable concentration.

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