

THE ANOMALOUS FEATURES OF THE DICK REACTION.

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MORE than ten years have now elapsed since G. F. and G. H. Dick (1923) established evidence that a haemolytic streptococcus is the primary invader in scarlet fever. Although specific treatment and specific prophylaxis have followed their pioneer studies, the latter have been subjected to a growing volume of criticism. To-day there are certain workers who maintain that our present conception of scarlet fever is fundamentally unsound. They believe that the test of susceptibility introduced by the Dicks is fallacious in theory and of little value in actual practice.

The paradoxical behaviour of the Dick test has always given rise to a degree of criticism. During recent years the wealth of anomalous findings reported in the literature has so accumulated, and attempts to explain these anomalies have proved in some respects so unsatisfactory, that there has arisen a tendency to discredit the Dicks's work.

It has been pointed out that Dick "toxin" presents some unusual features, which separate it from other toxins such as diphtheria toxin. It exhibits remarkable stability for a primary toxic substance, resisting a temperature of 100° C. for a considerable time; laboratory animals have a high natural immunity even to large intravenous doses of "toxin," although no antitoxin can be demonstrated in their blood; the skin of young persons shows a remarkable resistance; further, the Dick reaction differs from the Schick reaction in its time of appearance, in its duration and in the ease with which a positive reaction may become negative. Brockman and Mayzner (1927) have shown that the reaction may change its character after the onset of illness, after the injection of scarlet-fever toxin or even of milk, or when used in combination with a weak solution of adrenalin.

These rather curious features presented by Dick-filtrate and its apparently paradoxical behaviour in the disease itself, have forced certain investigators to conclude that Dick "toxin" is not a true toxin, and that scarlet fever should be regarded as a manifestation of allergy. This view, which has been widely propounded by von Gröer (1927) and other continental workers, has found a measure of support in America. Cooke (1927, 1928), in an interesting series of papers on this subject, maintains that scarlet fever is an anaphylactic response in persons susceptible to a specific antigen, streptococcus protein. In one of her papers ((1928), p. 784) she claims to have produced this hyper-sensitive state in a non-susceptible person.

To the writer it would appear that this claim is scarcely justified and that,

in fact, none of the results obtained by this worker necessarily clash with the conception of scarlet fever as a specific toxæmia as originally suggested by Mair (1923) and apparently confirmed by the publication of the Dicks's work a few months later. It is not possible to discuss fully here the merits or demerits of the allergic conception of scarlet fever. It is intended, rather, to record a recent experience of the Dick test in a series of scarlet fever cases, and to discuss briefly the anomalous features which have been encountered.

METHODS.

Until four or more readings were obtained, 160 patients suffering from scarlet fever were skin-tested in each week of the disease. A control test was performed on admission in every case, but, if no trace of a pseudo-reaction was obtained, it was not repeated in the subsequent weeks. All readings recorded were made at the end of 24 hours.

The material used was the ordinary commercial product of "Dick Toxin" and "Dick Control" supplied by Messrs Burroughs, Wellcome and Co. The diluent used in this preparation is an isotonic buffered solution of borax, boric acid and saline in the proportions suggested by Glenny, Pope and Waddington (1928). This has been shown to give more satisfactory results than normal saline (O'Brien, Okell and Parish, 1928). The control fluid is heated to 96° C. for 2 hours.

0.2 c.c. of toxin or control was introduced intracutaneously in the anterior aspect of the forearm at each test, using an ordinary 1 c.c. "Record" syringe fitted with a fine-bore needle.

Apart from the exclusion of two cases with pseudo-reactions, there is only one respect in which the clinical material must be regarded as selected. All were moderate or mild attacks, as the routine administration of antitoxic serum to all sharp cases rendered these unavailable for inclusion in the present series.

RESULTS.

Table I. *Showing summary of results in each week of the disease.*

Week of test	No. of cases	Negative		Positive	
		No.	%	No.	%
1st	160	42	26.0	118	74.0
2nd	160	100	62.5	60	37.5
3rd	160	128	80.0	32	20.0
4th	160	145	90.6	15	9.4

In ten of the forty-two cases recorded as negative on admission the rash was so intense that a positive reaction may well have been obscured. This conclusion is supported by the fact that in the second week three of these doubtful negative cases were clearly positive. It would probably, therefore, be more accurate to regard at least seven of these ten doubtful cases as positive or, alternatively, to exclude them from the series. Whichever method

of correction be adopted the amended figure would become between 78 and 79 per cent. instead of the 74 per cent. recorded above.

All the above cases were admitted during the first 7 days of their illness, 147 out of the total 160 being admitted between the second and fourth day of disease. Six cases admitted on the first day all gave positive reactions, but it has not been possible to demonstrate any diminution in positives from day to day, the groups of cases on each day being too small to give significant results and an accurate history being often impossible to obtain.

The percentage of positive reactors decreases in each week, the fall being sharpest between the first and second weeks, so that by the end of the first 10 days of the illness only about one-third of the cases give positive reactions.

Neglecting negative cases, of the 118 cases definitely positive in the first week, 105 have become negative in the fourth week; *i.e.* 89 per cent. of cases showed the change from positive to negative, held to be characteristic of the disease.

All the reactions were carefully measured, and in the majority of cases the size of the reaction was seen to become progressively smaller each week. More striking than this, however, was the characteristic decrease in the intensity of the reaction from week to week. This is obviously of more significance than a variation in size, which, if of minor degree, may be due to mechanical error in spite of the most careful technique.

Unexpected fluctuations either in size or in intensity were notably few. In some cases the reaction appeared to be stronger in the second week than during the acute phase of the illness and such reactions tended to remain positive in the subsequent weeks.

One case appeared to become faintly positive again in the third week, only to become negative once more in the fourth, fifth and sixth weeks. Such a variation in the reaction has been described by Lichtenstein (1926), but as this was the only example in 160 cases, it seems more probable that a faintly positive reaction in the second week was overlooked.

In two cases the reaction became positive again just prior to leaving hospital. One of these cases is of special interest in that the scarlet fever developed in hospital following an attack of diphtheria. When Dick-tested on admission to the diphtheria ward the reaction had been recorded as a "good positive." When re-tested on the second day of scarlet fever (a mild attack with a poorly developed rash) the reaction had changed to a feeble erythema measuring 10 mm. in diameter. There was no reappearance of the previous test, such as has been recorded by several workers (Toomey, Brown, Moriwaki); nor was there any area of pallor as described by Zingher (1924). In the second week the reaction was quite negative and remained so until the fifth week, when a positive reaction measuring 15 mm. in each diameter reappeared. In 1924 Zingher recorded that three children had become Dick-positive again in the fifth week of the disease.

In the fourth week there was 9.4 per cent. of positive reactions (fifteen

cases): four of these children were giving decreasing reactions each week, and two, who remained in hospital till the following week, were then negative: on the other hand eleven cases were showing no sign of losing their positive reaction, and nine were discharged Dick-positive. Two of these nine have been re-tested 12 months later; both are still giving strong positive Dick reactions, the test in the control arm being quite negative.

The other two cases both relapsed in the fifth week.

No relapses occurred in the other 149 cases.

Table II. *Showing the effect of age on the reaction.*

		52 cases (1-5 years)	68 cases (6-10 years)	40 cases (11-40 years)
1st week.	Positives	43 (83 %)	46 (68 %)	29 (72.5 %)
	Negatives	9	22	11
2nd week.	Positives	25 (48 %)	23 (34 %)	12 (30 %)
	Negatives	27	45	28
3rd week.	Positives	13 (25 %)	13 (19 %)	6 (15 %)
	Negatives	39	55	34
4th week.	Positives	6 (11.5 %)	6 (8.8 %)	3 (7.5 %)
	Negatives	46	62	37

It can be seen from Table II that the change from positive to negative has usually taken place by the second week at all ages, but the change is most clearly marked in the oldest age group. In each week of the disease the percentage of positives is highest in the youngest age group.

This suggests that the change from a positive to a negative reaction would appear to occur less readily in young children. This lag in the development of immunity is also evident if the first two age groups are carefully compared.

In the first week the predominance of positives is clearly shown in the first age group. In the second group it is less marked.

In the second week the positives and negatives about balance each other in the first age group, but in the second group there is already a clear predominance of negatives.

In the third and fourth weeks the numbers of positive cases in the two groups are exactly the same, despite the disparity in the size of the groups.

Pseudo-reactions. The frequency of pseudo-reactions in health appears to vary with the age of the subjects tested. Benson and Simpson (1927) found that no less than 15.5 per cent. occurred in healthy nurses, whereas O'Brien and Okell (1926) obtained only 5.2 per cent. in 673 tests made at various ages. In scarlet fever they are apparently very uncommon (Rosen and Korobicina, 1925).

Only two such reactions occurred in the present series, and they are worthy of description.

Case Agnes R. aged 12 years, mild scarlet fever, admitted on third day, clinical picture typical.

	Dick test	Control test
3rd day	20 × 15 mm. fading at 24 hr.	25 × 22 mm. increasing at 24 hr.
4th day	20 × 15 mm. "	35 × 18 mm. "
3rd week	21 × 14 mm. "	25 × 18 mm. "
4th week	23 × 17 mm. very faint	27 × 15 mm. "
7th week	Nil	22 × 18 mm. "

Case Minnie L. aged 6 years, mild scarlet fever, admitted on fourth day. Throat and tongue typical. Rash; punctiform element rather coarse, erythema patchy, blanched by scarlet anti-toxin 1/10.

	Dick test	Control test
1st week	15 × 15 mm. mod. bright	15 × 15 mm. faint
2nd week	20 × 15 mm. bright	12 × 10 mm. „
3rd week	20 × 10 mm. „	10 × 10 mm. very faint
4th week	28 × 14 mm. „	Nil
15 months later	30 × 25 mm. „	Nil

The first case appeared to be pseudo-negative on admission, but the subsequent fading of the test from week to week suggested that the child was Dick-positive from the commencement, this state being masked by a pseudo-reaction, which was for some reason disproportionately bright.

The second child was Dick-positive, and the case illustrates how the reaction may tend to be diminished in the early stage of the illness. Apparently no immunity was acquired during the course of the disease, and subsequently the reaction tended to increase again to what was presumably its previous strength. The case is described rather to show the change from positive to negative in the control test. This child gave first a combined-positive and later a straight-positive reaction.

DISCUSSION.

These results do not in themselves call for any lengthy discussion. The figure of 74 per cent. of early positives tallies fairly closely with the 75 per cent. recorded by Lichtenstein (1926) and the 76 per cent. recorded by Toyoda, Moriwaki and Futagi (1930). These workers conducted their observations over a large series of cases. On the other hand, one finds in the literature a most remarkable variation in the figures obtained by other observers, ranging from the 100 per cent. of Zingher (1924) and the 95 per cent. of Joe (1925) down to the 49 per cent. recorded by Peters and Allison (1928). On the continent still lower figures have been obtained. These variations are not so surprising when one considers the numerous factors involved.

Uniformity in strength of toxin is obviously of primary importance, whether the tests are being made in healthy persons or in the disease itself.

In the actual reading of the reaction there are many sources of discrepancy. Most workers have adopted an erythema of 10 mm. in both diameters as a minimal standard for a positive reaction, but different observers have had different standards. The time at which the reaction is read may also be of considerable importance. The usual practice is to read the reaction at the end of 24 hours, but in scarlet fever it is by that time fading. One has seen a reaction, positive at the end of 16 hours, fade completely in the course of the next 8 hours. An earlier reading would probably give a higher percentage of positives.

One would like also to stress the care which is necessary in the reading of the reaction. Zingher (1924) said that a really strong positive reaction in the acute stage of the illness spoke strongly against the diagnosis of scarlet

fever, and, in the opinion of the writer, this conclusion has been amply justified. The strong reaction appears to lose its brilliance in the earliest stage of the disease, while the recognition of a weak reaction in the midst of the generalised erythema may present great difficulty. A casual glance at the patient's arm is not enough in scarlet fever. A little gentle friction will often bring a positive reaction into view, whereas the very slightest traction or pressure on the skin may completely obscure the reaction. The importance of the personal factor is therefore obvious, and any initial prejudice must inevitably influence the results obtained.

Errors in diagnosis are also liable to occur, and the difficult, doubtful case should be excluded. In this connection one might mention the Dick-negative child with the local infection admitted to hospital along with a Dick-positive brother or sister, both cases being dubbed and sometimes erroneously accepted as scarlet fever. The mistake is very liable to occur when the Dick-negative child is alleged to have had a fleeting rash. This is often due to sweating, or it may be of septic origin. It is obviously fallacious to call such a case "scarlet fever" and then, when the Dick reaction is found to be negative, criticise the test. It seems to the writer that "*Scarlatina sine eruptione*" is an expression which should no longer be retained.

Lastly, there is the variation in the type of case tested. In the present series of cases no clinical features could be found to account for variations in the reaction, but as all the cases were mild in character, variations in the clinical picture were not prominent. The inclusion of the septic or toxic type of case might have markedly influenced the results. Here is another reason why the results of different workers in different parts of the world in different years can never be expected to coincide.

As for the paradoxical behaviour of the reaction, it appears to the writer that this has been exaggerated. That the reaction is, for practical purposes, a reliable indication of immunity seems to be usually accepted, and numerous examples of its reliability might be quoted. Occasionally a Dick-negative person, often a nurse in a fever hospital, develops scarlet fever, but that is to be expected, if the multiple factors involved in the establishment of any infection are considered.

Much stress has also been laid on the early negatives. The rash, which varies so widely in intensity from case to case, depends on the potency of what Okell (1932) has called the "erythrogenic" toxin, the antitoxin content of the patient's blood and a local factor. The nature of this local resistance is not understood, but local and general resistance do not necessarily run parallel. The rash, which is the summation effect of these three factors, is in reality a generalised Dick reaction to a toxin of variable potency. It is not surprising that the response to the intracutaneous injection of a little additional toxin may be so feeble as to be imperceptible. The relatively insusceptible person has a poorly developed rash and a very feeble Dick reaction, while the highly susceptible person has an intense rash and the test may be

obscured. The relatively good positive and the "dead negative" may be partly dependent on a disproportion between the potency of the erythrogenic toxin absorbed from the site of infection and the test toxin introduced at the site of injection. The importance of the local factor is difficult to assess, and the nature of the resistance difficult to understand. This resistance is not necessarily specific in character.

At the other end of the illness one has to consider the cases which fail to become Dick-negative. Relatively few of these relapse, and second attacks are uncommon. Some of these, moreover, are stated to give a positive blanching (Schultz-Charlton) test. A proportion of these late Dick-positives may be explained eventually by the demonstration of multiple toxins.

It has been suggested by Ando (1930) and also by Toyoda, Moriwaki and Futagi (1930) that they may be due to the development of an allergy to an endotoxin (nucleoprotein) factor contained in Dick-filtrate. One has been able to show that the development of this allergic state occurs in a high percentage of scarlet fever cases when an extract freed from exotoxin is used (Gibson and McGibbon, 1932), but this type of reaction does not develop when a commercial preparation of Dick-filtrate widely used in this country is employed. One of the late Dick-positives in the present series was found to give a negative blanching test. It was found, further, that while the Dick reaction could be completely inhibited by the addition of antitoxin, the skin reaction to the exotoxin-free extract remained strongly positive when neutralisation was attempted. A year later both reactions are strongly positive. The two reactions are evidently based on an entirely dissimilar active principle and on the basis of this case, at least, it would not appear possible to ascribe these late Dick-positive reactions to any contained "endotoxin" factor.

The two cases with pseudo-reactions illustrate the difficulty in the interpretation of this type of reaction and show that, if tests be performed once only, there is a great possibility of error arising. The first case suggests that Zingher's original contention that for the purpose of the test the proteins are unaffected by heat will have to be reconsidered. The use of a heated fluid may apparently cause such vivid reactions in certain individuals as to render this method of control unreliable. The second case is of interest because it shows that the reaction to the control fluid may be inconstant and may fluctuate from time to time in the same person. Von Gröer (1927) believes that a control test has no value, and he has dispensed with its use entirely. This may represent an extreme view, but to the writer it would certainly appear that the real nature of the pseudo-reaction is as yet imperfectly understood, and that with the limited extent of our present knowledge it is not possible to assess its true value.

SUMMARY.

About one-fourth of the cases in a series of 160 patients suffering from scarlet fever appeared to be Dick-negative in the acute stage of the disease.

Throughout the illness there was a progressive decrease in the number of

positives and in the intensity of the reactions, till in the second week two-thirds and in the fourth week nine-tenths of the total cases were negative. Almost 90 per cent. of the original positives showed this characteristic loss of the Dick-positive state. It would appear that this change occurs less readily in young children. Fluctuations in the reaction during the course of the illness are very uncommon, if indeed they occur at all.

Of eleven cases which failed to show the above change two relapsed. In the other 149 cases no relapses occurred.

Pseudo-reactions are uncommon. Two examples have been described. It is suggested that the use of heated filtrate may be unsatisfactory and that the mechanism of these reactions requires further study.

Some of the anomalous features of the Dick reaction have been briefly discussed. In the opinion of the writer these difficulties have been exaggerated, and they do not in themselves form sufficient grounds for concluding that the test is fallacious.

On the evidence at present available one must continue to regard scarlet fever as a specific toxæmia. The allergic conception of the disease is less convincing.

I am indebted to Dr W. T. Benson, Medical Superintendent of the Edinburgh City Hospital, for kindly giving me the opportunity of making these observations.

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(MS. received for publication 13. x. 1933.—Ed.)