THE DICK TEST AND IMMUNITY TO SCARLET FEVER.

BY ROBERT CRUICKSHANK, M.D.ABERD.,
Belvidere Hospital for Infectious Diseases, Glasgow.

RECENT researches into the etiology of scarlet fever seem to have established the causal relationship of a hæmolytic streptococcus to the disease (Dick and Dick). The infection resembles diphtheria in that the organism itself remains localised to the throat and the general manifestations (fever, punctate erythema, &c.) follow the elaboration and diffusion in the blood-stream of its "exotoxin." Although earlier work supported the view that there is a specific streptococcus scarlatinæ, recent investigations have shown the difficulties in distinguishing the S. scarlatinæ either culturally or serologically from other strains of hæmolytic streptococci. Further, streptococci isolated from such infections as erysipelas, tonsillitis, and puerperal septicæmia may produce toxins similar to the scarlatinal streptococcic toxin. It is known that a test of susceptibility to scarlet fever—the Dick test—depends on the local reaction of the skin to the intradermal injection of a small quantity of this toxin. If a localised erythema results within 24 hours, the individual is said to be susceptible to scarlet fever: if there is no reaction, he is immune. The test is also used diagnostically: theoretically every case of scarlet fever should give a positive reaction at the onset of infection since presumably he is then in the susceptible stage; during the following weeks he should become "Dick negative," that is, he has developed his immunity. Numerous workers have found that such a sequence of events does not always happen, and have therefore questioned the diagnostic value of the test.

Most toxins are inactivated by heating at 60° C. for half an hour. The diffusible principle—or "exotoxin"—of S. scarlatinæ is characterised by its great thermostability, for it requires heating—often for three to four hours—at 100° C. before it is destroyed. Moreover, it is non-toxic when injected into laboratory animals such as the mouse, rat or guinea-pig.

These facts have led to the theory that the product of S. scarlatinæ acts not as a true toxin but as a foreign protein which in specially sensitised individuals produces the scarlatinal skin-eruption, a rash closely simulated by the scarlatiniform rash of " serum-disease."

For the present, however, we may assume that scarlet fever is a true toxæmia and that the Dick-reaction is reasonably reliable in indicating susceptibility or immunity to the infection. In the following pages a description is given of the uses to which the test has been put in Belvidere Hospital, Glasgow. Its value lies not so much in diagnosis as in determining when immunity develops and how long it lasts (*a*) in individuals infected with scarlet fever, (*b*) in those actively immunised with scarlatinal streptococcic toxin, and (*c*) in those passively protected with antiscarlatinal serum.

Susceptibility to Scarlet Fever.

Scarlet fever is a rare infection among children under 1 year and practically never affects infants under the age of six months. During 1926, of 1,320 scarlet fever admissions to Belvidere Hospital only 12 were less than a year old (ages varying from 6—12 months). This neo-natal immunity is probably transmitted by the placenta from mother to child, as has been proved to occur in diphtheria. It is gradually lost, so that with each succeeding year up to 3 or 4 years of age, the susceptibility of the child to scarlet fever increases. This increased susceptibility is well shown epidemiologically by an analysis of the admissions to hospital—

Age.	Belvidere, 1926. Number.	Grove Hospital (Rolleston), 1922. Number.
Under 1 year, . . .	12	11
1—2 years, ...	60	47
2—3 years, ...	120	85
3—4 years, ...	161	81
4—5 years, ...	171	76
*5—6 years, ...	233	110
6—7 years, ...	216	136
7—8 years, ...	130	120

* The sudden increase in numbers during the years 5—7 is probably due to the greater exposure to infection when the child goes to school.

The Dick test affords a ready means of corroborating the above figures. In a large series (4,570) of normal children who were Dick-tested, Zingher found that the percentage of positive reactors was :—

0—1 year.	1—2 years.	2—3 years.	3—4 years.	4—5 years.	5—10 years.
56 per cent.	71 per cent.	68 per cent.	59 per cent.	46 per cent.	35 per cent.

i.e., susceptibility to the infection appeared to be at its maximum during the age period 1—4 years. Other workers (Branch and Edwards, Dick and Dick, Smith and Taylor, &c.) have recorded results which correspond more or less to Zingher's figures, although Okell and Parish found 70 positive reactors among 95 medical students. The strength of toxin used and the social status of the community being tested are factors which influence the percentage of positive reactors. For example, in a private school 83·7 per cent of the pupils reacted positively to the Dick test, whereas in a public school in a poor class district only 22 per cent gave positive reactions (Zingher).

An analysis of the Dick test performed on 85 patients (Belvidere) who had not had scarlet fever—they were selected from diphtheria, whooping-cough, and chicken-pox wards—showed a high incidence of susceptibles (69 per cent), but about two-thirds of these were under 5 years of age.

DICK-TEST AT DIFFERENT AGE-GROUPS.

Age.	Number.	Positive.	Negative.	Percentage Positive.	Zingher. Percentage Positive.
1— 2,	10	5	5	50	71
2— 3,	9	6	3	66	68
3— 4,	21	18	3	85	59
4— 5,	16	12	4	80	45
5—10,	22	15	7	68	35
10—20,	7	3	4	43	...
	85	59	26	69	

It seems that a small proportion of susceptible individuals may react negatively to the test. Lees has reported an epidemic of scarlet fever among agricultural students, 15 (31 per cent) of whom were Dick-negative when they developed the infection, while other workers have had experience of cases who although

Dick-negative subsequently developed scarlet fever. What is the explanation of this phenomenon? Lees showed that the *strength* of toxin did not materially matter, as his cases still reacted negatively when tested with 10 skin test doses of toxin. The *nature* of the toxin or the strain of streptococcus from which the toxin is derived may be the important factor, since recent work (James, Smith, &c.) has shown that there are numerous serological strains of scarlatinal streptococci. The possibility, too, of variability in the resistance of the individual must not be disregarded as affording an explanation of why a Dick-negative individual may succumb to an attack of the streptococcus scarlatinæ.

Development of Immunity to Scarlet Fever.

It is generally accepted that most cases of scarlet fever are Dick-positive at the onset of the attack, and in the course of 2—3 weeks become Dick-negative, that is, they have acquired immunity to the disease. Zingher found that the majority of cases were Dick-negative in 6—10 days from the onset of infection, while 90 per cent of Sutherland's cases (Monsall Hospital) gave negative reactions by the 9—15th day of illness. The results obtained in Belvidere showed that most of the patients reacted negatively by the 10th day, thus coinciding closely with Zingher's figures. For example, of 50 patients tested within 4 days of admission to Hospital, 37 (74 per cent) were Dick-positive, while only 2 out of 25 cases tested at regular intervals reacted positively after the 9th day of infection. One case only gave a weak positive reaction after the 15th day of illness.

25 Cases of Scarlet Fever Dick-Tested at Weekly Intervals.

	Positive.	Negative.	Percentage Positive.
1st week (2nd—7th day), .	14	11	56
2nd week (8th—14th day), .	6	19	24
3rd week (15th—21st day), .	1	24	4
4th week (22nd—29th day), .	1	24	4

Sutherland has advocated the Dick-testing of all scarlet fever

patients on the 21st day of the disease. Those still Dick-positive—of whom he found 10 per cent—should be given 300 skin test doses of scarlatinal toxin, an amount sufficient as a rule to render them Dick-negative and so protect them from re-infection. Second attacks undoubtedly occur in a small percentage of cases in hospital—usually in the 4th or 5th week of residence—so that the procedure recommended by Sutherland is both reasonable and easy of performance.

The therapeutic use of scarlatinal antitoxin has introduced a fresh problem in the development of immunity. Since the antitoxin given at the onset of the fever presumably acts beneficially by neutralising the circulating toxin, the natural stimulus (that is, the toxin) to the production of an active immunity is in great part removed. It might therefore be expected that patients so treated will again become susceptible after the passive immunity, conferred by the serum, has passed off. The recent work of Davies does seem to indicate a less complete immunity in individuals treated with antitoxin compared with non-serum treated cases, and experience will presently show whether the therapeutic use of scarlatinal antitoxin is likely to increase the incidence of second attacks of scarlet fever. So far, although in the past three years over 300 patients in Belvidere Hospital have received anti-scarlatinal serum, there has not been an instance of re-infection in any case of proved scarlet fever after serum-therapy. The systematic Dick-testing of these cases, not only during residence in hospital but also at regular intervals of time after dismissal, will help to decide whether or not they have acquired a lasting immunity.

ACTIVE IMMUNISATION.

The active immunisation with the scarlatinal streptococcic toxin of individuals susceptible to scarlet fever is still in the experimental stage and the reported results of immunisation are neither uniform nor altogether satisfactory. The standardisation and dosage of toxin is the stumbling-block. Uniformity in the standardisation of toxin has not yet been attained owing to the comparative insusceptibility of experimental animals such as the rabbit and guinea-pig to scarlatinal streptococcic toxin, although recent work by Okell and Parish is hopeful in this direction. For active

immunisation, therefore, the dosage may best be estimated by testing the effect of increasing doses of toxin on susceptible individuals (Benson and Simpson). It has been shown (Dick and Dick) that 500 skin test doses is the largest initial dose of toxin which may safely be given without causing a generalised reaction—headache, sore throat, fever and scarlatinal erythema—and even that amount of toxin may produce the scarlatinoid syndrome in an individual with a minimal amount of " natural " antitoxin. Such individuals are discovered by the large size and brilliant intensity of the skin-reaction when they are Dick-tested.

In active immunisation increasing doses of toxin are used, and the American Scarlet Fever Committee has recommended five injections of toxin, commencing with 500 skin test doses, followed at weekly intervals by 1,500, 5,000, 15,000 and 30,000 skin test doses of toxin. To obviate the necessity of giving five injections, Young and Orr, after trying varying doses at varying intervals, found that immunisation at two-weekly intervals with three injections of 500, 5,000 and 30,000 skin test doses reduced the incidence and severity of reactions after injection. Similarly, Benson and Simpson (Edinburgh) reported more satisfactory results with a course of three injections (200, 1,000 and 2,000 skin test doses of a toxin apparently much more potent than that used in America) given at 14-day periods than with four injections (200, 400, 800 and 1,000 skin test doses) at 5-day intervals. Kinloch (Aberdeen), using three injections of 500, 1,000 and 3,000 skin test doses at weekly intervals, found that immunity had developed two weeks after the last immunising dose. Larson and his colleagues have recommended the use of sodium ricinoleate as an effective agent in detoxifying scarlatinal streptococcic toxin. By using such a detoxicated mixture they state that a sufficient amount of toxin (3,000-4,000 skin test doses) may be given in one dose to produce in seven days an immunity lasting for several months. The advantages claimed are that one injection only is necessary, that immunity develops in a week's time so that this method is suitable for preventing the epidemic spread of scarlet fever, and that there is no reaction from the injection nor any danger of sensitising the patient since the detoxifying agent is non-antigenic.

It is yet too early to say whether these various methods

of immunisation confer a lasting immunity to scarlet fever. If the Dick test be taken as a criterion of susceptibility then the immunity appears not to persist for any prolonged period : for example, Benson found that of nine nurses re-tested 11 months after becoming Dick-negative, five were Dick-positive, while two out of five tested 8 months after immunisation gave positive reactions. Nevertheless, an attack of scarlet fever in a person artificially immunised seems to be extremely uncommon, and Kinloch claims to have eliminated the incidence of scarlet fever among his nursing staff by this method of active immunisation. On the other hand, he and other workers have noted an increase in the occurrence of streptococcal tonsillitis, acute pharyingitis, &c., among the immunised community, and it seems probable that while these individuals are protected against the *toxin* of the streptococcus scarlatinæ, they are not immune to *local* attacks by the organism itself.

PASSIVE IMMUNISATION.

When an individual develops scarlet fever in a house or in a ward where there are other susceptible children, the likelihood of secondary cases occurring is considerable. Immediate though only temporary protection of these susceptible persons against infection from the primary case may be afforded by the use of artificially prepared scarlatinal antitoxin. Proof of its efficiency has been furnished by McClean (Great Ormond Street Children's Hospital), who Dick-tested all the children in wards where a case of scarlet fever had occurred : on the following day he injected 5 c.c. of scarlatinal antitoxin into positive reactors and was able to prevent the occurrence of secondary cases in 25 wards, each containing 20-30 children all under the age of 12 years. In Belvidere since January, 1927, passive immunisation of susceptible contacts in wards where scarlet fever has occurred (*e.g.*, in diphtheria and chicken-pox wards) has been so far successful that no subsequent case of scarlet fever has followed the primary case during the quarantine period. As an example, in a diphtheria ward of 21 patients, a child aged 5 years developed scarlet fever : none of the patients were given antiscarlatinal serum ; six days later two other cases in the ward were infected. Fourteen susceptible contacts were then given 5 c.c. each of

the scarlatinal antitoxin and there were no further cases of scarlet fever during the following week.

The obvious advantage of this method of passive immunisation is that in addition to protecting susceptible contacts the ward need not be put in quarantine and beds otherwise not available can be utilised.

An attempt was made to discover what dose of antitoxin is required to afford immunity and how long varying doses of the serum may be expected to protect against infection. Concentrated antiscarlatinal sera prepared by two different firms were used and compared. The doses of serum used were 2·5 c.c., 5 c.c., and in a few cases 10 c.c. injected intramuscularly. For comparison of the two antisera children of practically the same age were chosen. These children, who had already given definite Dick-positive reactions, were again tested at varying intervals (24 hours, 5 days, 8 days, 13 days, &c.) after the antiserum was given. There was a lack of uniformity in the results obtained, a fact which may be attributed to the variable quantity of natural antitoxin already present in the blood of different individuals. For instance, an addition of 5 c.c. of antitoxin will render one individual Dick-negative for a fortnight, while a similar amount will protect another with a smaller quantity of natural antitoxin for a week only.

The following tables briefly summarise the results obtained :—

Duration of Immunity with (*a*) 2·5 c.c. and (*b*) 5 c.c. Antitoxin.

1. Antitoxin A 4501.

(*a*) 2·5 c.c.				(*b*) 5 c.c.			
No. of Cases.	Days after Injection.	Dick Positive.	Dick Negative.	No. of Cases.	Days after Injection.	Dick Positive.	Dick Negative.
16	24 hours.	1	15	8	24 hours.	0	8
	5 days.	2	14		5 days.	0	8
	8 ,,	11	5		9 ,,	3	5
	12 ,,	16	0		13 ,,	6	2
					17 ,,	7	1

2. Antitoxin A 4462E.

(*a*) 2·5 c.c.				(*b*) 5 c.c.			
No. of Cases.	Days after Injection.	Dick Positive.	Dick Negative.	No. of Cases.	Days after Injection.	Dick Positive.	Dick Negative.
16	24 hours.	0	16	14	24 hours.	0	14
	5 days.	4	12		5 days.	0	14
	8 ,,	14	2		9 ,,	4	10
	12 ,,	16	0		13 ,,	11	3
					17 ,,	14	0

The injection of 10 c.c. antiscarlatinal serum generally protected from 2-3 weeks, as the histories of the following patients show :—

1. F., aged 25 years, admitted 15/1/27 to scarlet fever ward as (?) mild scarlatina; history and physical signs atypical. 15/1/27, 10 c.c. antiscarlatinal serum injected intramuscularly. 2/2/27 (18 days after antitoxin), temperature 100·2° F., sore throat, generalised scarlatinal rash, peeling tongue, and later typical desquamation.

2. M., aged 12 years, admitted 10/11/26 to scarlet fever ward. Feet desquamating; both ears discharging profusely; history of sore throat 11 days previously. 11/11/26, Dick-test positive (+ +); 10 c.c. antiscarlatinal serum given. 29/11/26, both ears dry. 4/12/26 (23 days after antitoxin), temperature 101·4° to 103°, typical attack of scarlatina with cervical adenitis and both ears again discharging. 9/12/26, Dick-test negative.

3. F., aged 3 years, admitted 4/12/26 to scarlet fever ward. Temperature, 102° to 104°; diagnosis on 5th December, lobar pneumonia; isolated in convalescent ward. 6/12/26, 10 c.c. antiscarlatinal serum given. 25/12/26 (19 days after serum), temperature 102° to 104°. Sharp attack of scarlet fever and second dose of antitoxin given.

4.* F., aged 8 years, admitted 15/4/27 with faucial diphtheria + cervical adenitis and purulent nasal discharge. 16/4/27, Dick-test positive; 10 c.c. antiscarlatinal serum given. Dick-test negative on 7th and 14th days after antitoxin. Faint Dick-positive on 21st day. Developed a mild but typical attack of scarlet fever 23 *days* after antitoxin injection.

It is evident, then, from these figures and illustrative cases that a transient passive immunity *is* conferred by the injection of anti-scarlatinal serum and that, broadly speaking, the duration of that immunity is proportionate to the dose of serum : 2·5 c.c. may be expected to protect a susceptible person for 3-6 days, 5 c.c. for 7-10 days, and 10 c.c. for 2-3 weeks. It is advisable, therefore, to give a 5 c.c. dose of concentrated anti-scarlatinal serum to Dick-positive reactors exposed to scarlet fever in order to render them immune to the infection during the quarantine period of 7 days. By so doing, the risk of secondary cases occurring, whether in a ward or in a private

* This last case was not directly exposed to scarlet fever, and the question arises as to whether individuals become more susceptible to the infection, that is, have a " negative phase " after passive immunity has worn off.

house, is reduced to a minimum, so that both from a medical and an economic view-point the procedure is a rational one.

SUMMARY.

1. Diagnostically the value of the Dick-test is limited, since a proportion of scarlet fever patients are Dick-negative at the onset of the infection while others fail to become Dick-negative during convalescence. Theoretically, all cases should be Dick-positive during the first few days of illness and become Dick-negative in ten to fourteen days' time.

2. The Dick-test has considerable value in indicating when immunity has developed and how long it persists in (*a*) patients affected with scarlet fever, (*b*) individuals who have been actively immunised with scarlatinal streptococcic toxin and (*c*) in those passively immunised with antiscarlatinal serum.

3. Methods of artificial immunisation (active and passive) against scarlet fever have been described and their value and limitations indicated.

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