THE DICK TEST: ITS RELATION TO SCARLET FEVER AND ITS VALUE IN DIAGNOSIS.

T H E S I S

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by

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C O N T E N T S.

INTRODUCTION.

Great and growing ever is the debt of Medicine to the allied science of Bacteriology. There is, however, a contra-account as the former provides many of the problems and at the bedside tests the solutions offered by the latter. Though this debt cannot be computed accurately, individual items may be submitted to a scrutiny and the item chosen here is the Dick test.

To the epidemiologist, the bacteriologist, and to the clinician, Scarlet Fever presents many problems. Towards the solution of these a great advance was made when, in 1923, G.H. and G.F.Dick of Chicago produced experimental Scarlet Fever in a human volunteer by swabbing his throat with a culture of haemolytic streptococci. Later they showed that these streptococci produce a soluble toxin. Working on the analogy of the test for susceptibility to Diphtheria introduced in 1913 by Schick of Vienna, they used this toxin for a test for susceptibility to Scarlet Fever and, in 1924, published their first communication on this aspect of the work. The test consists of the injection into the skin of a minute quantity of a dilution of the streptococcal toxin and a positive reaction is manifested by the development, within twenty-four hours, of an area of erythema round the site of injection. This skin test is now known generally as the Dick test.

Following these discoveries many workers have tried

to fill the gaps in our knowledge of Scarlet Fever and the progress made has raised the hope that this disease will provide the key to many of the problems associated with the infectious diseases in general. Thus Scarlet Fever, which, compared with other infections, is apparently decreasing in significance as a disease, is becoming more and more prominent in the field of research.

This thesis embodies the results of the Dick test in patients suffering from Scarlet Fever and other diseases and an attempt is made to assess the present value of this test. The investigation was carried out at Monsall Fever Hospital, Manchester, during the greater part of the years 1928 and 1929. I am much indebted to Dr.D.Sage Sutherland, Medical Superintendent, for his encouragement and for the facilities provided.

THE RELATIONSHIP OF THE STREPTOCOCCI TO SCARLET FEVER.

In 1884 Loeffler noted that haemolytic streptococci were present almost invariably in the throats of patients suffering from an acute attack of Scarlet Fever. Crooke, in 1885, demonstrated the presence of streptococci in the bodies of patients who had died of Scarlet Fever. In 1887, Klein, after investigating milk-borne epidemics, stated that streptococci had an etiological relationship to Scarlet Fever. Marmorek, in 1895, and Moser, in 1902, produced antistreptococcal sera to strains isolated from Scarlet Fever patients and reported the favourable influence of these sera on the course of the disease. These results were confirmed by Rossiwall and Schick in 1905. In 1903, Moser and von Pirquet stated that the blood of Scarlet Fever patients frequently agglutinated streptococci. They stated also that the streptococci isolated from the blood of these patients could be agglutinated specifically by immune sera produced with such streptococci while streptococci from other sourses seldom were agglutinated. Savchenko, in 1905, showed that scarlatinal streptococci produce an exotoxin and, in 1906, Gabritschewsky immunised children with a vaccine of these streptococci. Tunnicliff, in 1920, found specific increase of opsonins for haemolytic streptococci in the blood of Scarlet Fever patients, and that streptococci from these patients fall into homologous groups by agglutination tests. However the relationship of the streptococci to Scarlet Fever

was not placed on a sound basis till the work of the Dicks in 1923 and later.

THE WORK OF THE DICKS.

The original paper of the Dicks may be summarised as follows.

> A nurse developed Scarlet Fever. She had a septic finger two days previously. A little pus was obtained from the finger on the second day of disease. Stained smears showed polymorphonuclear leucocytes, Gram positive cocci and Gram positive diphtheroid bacilli. Cultures on sheep's blood agar plates produced colonies of haemolytic streptococci and isolated colonies of diphtheroids. Pure cultures of the streptococci were obtained by plating out single colonies. The throats of five human volunteers were smeared with cultures of these streptococci. Three showed no reaction, one had fever and sore throat without a rash, and one volunteer, smeared with a three weeks old culture, developed typical Scarlet Fever of a mild type. Further cultures in bouillon were passed through a Berkefeld filter. The filtrate was sterile and produced no effect when swabbed on the throats of other volunteers. The culture was then swabbed on the throats of those who had shown no reaction to the filtrate. Two showed no reaction, two had sore throat and one developed Scarlet Fever.

The Dicks' conclusions were (1) Scarlet Fever in two volunteers was caused by Streptococcus haemolyticus or by an unrecognised organism associated with the streptococcus and (2) if any unrecognised organism was present it did not pass through a Berkefeld filter. Later work by the same observers showed (a)that the filtrate mentioned above contained a toxic substance and that this filtrate in suitable dilution could be used for a skin test, (b)that serum from a convalescent Scarlet Fever patient neutralised the toxicity of the filtrate, (c)that the injection of this filtrate into persons showing a positive skin test produced symptoms of

Scarlet Fever and that the skin test later became negative and (d) that an antitoxic serum can be produced by immunising a horse against this filtrate and that the serum so produced can be concentrated by the usual methods. The Dicks regard this toxic substance in the filtrate as a true toxin though it differs from other bacterial exotoxins in being non-toxic to animals and very thermostable.

CONFIRMATORY WORK.

The human inoculation experiments of the Dicks have been confirmed by Nicolle, Conseil and Durand (1926) but Ciuca and Gheorghiu(1927) failed to produce Scarlet Fever in Dick positive volunteers either with the Dick strain of streptococcus or other strains obtained from the throats of patients.

Trask and Blake (1924) demonstrated, in the serum of Scarlet Fever patients, a toxic substance which caused the typical erythematous reaction when injected intracutaneously into persons who had not had Scarlet Fever and whose serum did not produce the Schultz-Charlton blanching phenomenon. This toxic substance was neutralised by the serum of horses immunised against haemolytic streptococci.

Since 1925 streptococcal toxin has been used successfully to produce active immunity to Scarlet Fever in persons yielding a positive Dick test. After a varying number of injections the Dick test becomes negative. In this country such immunising has been confined almost wholly to the nursing staffs of isolation hospitals. During

immunising by this method I have confirmed, on several occasions, the observation that Dick toxin, on injection, can produce malaise, vomiting, fever and a scarlatiniform rash.

Numerous observers, both here and abroad, have recorded the beneficial effect of scarlatinal antitoxin on the clinical course of Scarlet Fever and on the incidence of complications. Also, this serum has been used successfully to produce passive immunity to Scarlet Fever.

IDENTIFICATION AND CLASSIFICATION OF SCARLATINAL STREPTOCOCCI.

Many investigators have studied the identification and classification of scarlatinal streptococci. The work has centred round the agglutination reactions of the organisms and their toxigenic properties.

I have referred to the specific agglutination of scarlatinal streptococci obtained by Moser and von Pirquet (1903), Neufeld (1903) and Aronson (1903) were unable to differentiate between types of haemolytic streptococci by agglutination tests. Rossiwall and Schick (1905) confirmed the work of Moser and von Pirquet. Gordon (1905) found that the types of streptococci obtained from the throat in Scarlet Fever corresponded with those met with in normal conditions. Bliss (1922) found that twenty of twenty-five strains of haemolytic streptococci isolated from Scarlet Fever patients were agglutinated at equal titre by a serum obtained from a rabbit which had been immunised against a

single strain. None of these twenty strains were agglutinated by sera obtained against streptococci from other sources. Gordon (1921) found nineteen strains of scarlatinal streptococci to be identical in their agglutination and agglutinin-absorption reactions. Tunnicliff (1922) obtained similar results from seventy-two strains isolated from seventy-five Scarlet Fever patients. Stevens and Dochez (1924) came to the conclusion that the strains of haemolytic streptococci found in Scarlet Fever were closely related and probably belonged to one group. By agglutination tests Eagles (1924) found that nineteen strains of scarlatinal streptococci fell into one group. The Dicks found no cross-agglutination between the two strains of streptococci with which they produced Scarlet Fever though these strains differed in their sugar reactions.

This serological classification of the scarlatinal streptococci into one group has not been confirmed by later investigations. Williams (1925) tested seventy strains. She found 30% of these to fall into one group but was unable to classify 63% of the remainder. Smith (1926) obtained haemolytic streptococci from the throats of 92% of two hundred and ten Scarlet Fever patients and was able to divide the strains into two main serological groups. He made the interesting observation that the strains obtained from members of the same family were usually in the same serological group and that those obtained from patients in small isolated

outbreaks were also of the same group. Griffith (1926) obtained similar results. James (1926) found that 56% of scarlatinal streptococci fell into three main serological groups but was unable to classify the remainder. Further work by Smith (1927), Griffith (1927) and McLachlan and Mackie (1928) showed that the scarlatinal streptococci could be divided into an agglutinable and a non-agglutinable group. The proportion classed as non-agglutinable varied from 30% to 50%. Griffith sub-divided the agglutinable group into four types.

Gunn and Griffith (1928) examined on admission to hospital, the throats of one hundred patients suffering from Scarlet Fever. Haemolytic streptococci were found in ninety-one. They were identified as follows ;- eight Type I, fourteen Type II, twenty-six Type III, and twelve Type IV, but the remaining thirty-one strains could not be classified. Of the nine patients who gave negative results on admission two later yielded Type I, four Type II, one Type III, and two gave serologically heterogeneous strains. Weekly examinations of the throat were made in all of these patients. In fifty the type remained the same throughout and in fifty there was a change of type during the course of the disease. A second type was obtained in the thirty-eight, a third type in ten, and a fourth type in two patients. In three patients in whom the Dick test remained positive the appearance of a new type of streptococcus coincided with a

second attack of clinical scarlatina. Comparable results were obtained by Burton and Balmain (1929).

The Dicks emphasise the importance of toxin production in the identification of scarlatinal streptococci. The findings on this aspect of the subject show much variation. Reichenmiller (1926) found haemolytic streptococci in 9% of four hundred and thirteen healthy persons and in 26% of one hundred cases of inflammatory lesions of the throat and nose; several of the strains isolated from each group produced a toxin presenting the same features as the Dick toxin. Williams (1924) Kirkbride and Wheeler (1925) and Rosenow (1925) examined the soluble toxins produced by various strains of scarlatinal streptococci and concluded that all strains produced the same toxin. Paraf (1925) and Eagles (1926) working with filtrates from scarlatinal and non-scarlatinal strains found differences of a quantitative but not of a qualitative nature. The work of Birkhaug (1927) suggested that both qualitative and quantitative differences exist. Most of these conclusions were based on the results of skin reactions.

Using various antitoxic sera for neutralisation tests others have investigated these toxins. Park and Spiegel (1925) found that the serum from a Scarlet Fever patient would neutralise the toxin in some individuals but not in others. Birkhaug (1925) obtained a toxin from a strain of Streptococcus erysipelatis and this toxin was not neutralised

by anti-scarlatinal serum. Kirkbride and Wheeler (1926,1927) examined the filtrates obtained from over one hundred strains each of streptococci from scarlatinal and non-scarlatinal sources and found 90% of the scarlatinal and 68% of the non-scarlatinal filtrates to be toxic. Having obtained an antitoxic serum from a goat immunised against the Dochez strain of streptococcous they used this for neutralisation tests on goats and almost 68% of the filtrates from both sources were neutralised. McLachlan (1927) found that horse antitoxic scarlatinal serum neutralised the majority of toxins obtained from scarlatinal and non-scarlatinal streptococci.

Smith (1927) by skin and neutralisation tests, and Okell and Parish (1928), by protection experiments on rabbits, found that the toxins of all strains of streptococci were identical qualitatively. From skin and neutralisation tests the Dicks (1929) found that the soluble toxins produced by streptococci from Scarlet Fever and from Erysipelas were immunologically specific and distinct. Friedemann, Deicher and Abraham (1927) showed that haemolytic streptococci may lose temporarily their toxigenic properties. Lancefield (1928) isolated, by chemical methods, three different antigenic fractions from haemolytic streptococci while Ando (1929) has shown that Dick toxin contains both thermostable and thermolabile fractions.

SCARLATINAL STREPTOCOCCI FROM OTHER SOURCES.

Several observers have reported the finding of haemolytic streptococci, indistinguishable from the scarlatinal strains, in situations other than the throats of Scarlet Fever patients. It is to be recalled that the Dicks obtained them from the finger of a nurse suffering from Scarlet Fever. Tunnicliff found them in the discharges of convalescent patients. Stevens and Doches (1926) found them in the throats of Dick negative patients suffering from Tonsillitis. Kinloch, Smith and Taylor (1927) state that the serological types of streptococci characteristic of Scarlet Fever may be isolated from cases of Tonsillitis, Erysipelas, Puerperal Fever and Bronchopneumonia. The Dicks (1927) remark that, in more highly immune persons, scarlatinal streptococci may cause sore throat only. Stevens (1926) recorded six cases of atypical infection with scarlatinal streptococci: three of the six gave rise to secondary cases of Scarlet Fever and apparently one of the six was infected from a case of that disease. Smith (1927) found streptococci serologically similar to the scarlatinal type in fourteen persons who were not suffering from Scarlet Fever: eight of these persons gave a negative Dick test and six a slight positive reaction. Tunnicliff and Crooks (1929) found a healthy carrier of scarlatinal streptococci who gave rise to five secondary cases of the disease. Smith (1929)

concluded that it is not possible to distinguish with certainty between haemolytic streptococci of human and of animal origin.

OTHER VIEWS.

The causal relationship of the streptococci to Scarlet Fever is not accepted by some observers. Caronia and Sindoni (1923) believe that Scarlet Fever is due to an anaerobic diplococcus while Cantacuzène and Bonciu (1925) think it due to a filterable virus. Toyoda, Satake and Takeda (1925) suggest that, in addition to the haemolytic streptococci, other factors are involved in causing Scarlet Fever. They obtained a staphylococcus from the throat of a Scarlet Fever patient and from this they produced a toxin which gave positive positive skin tests in 13% of one hundred and seventy-eight persons and which, on intra-muscular injection, produced in one person nausea, vomiting, fever and a scarlatiniform rash. O'Brien (1926) pointed out that experimentally produced Scarlet Fever has not been shown to be infectious and cites the observations of Borsett that, although Bacillus suipestifer can produce the clinical and post-mortem characteristics of Swine Fever, the disease so produced is not infectious. Zlatogoroff, Koudriavtzeva and Palante (1927) do not deny the presence of haemolytic streptococci but state that a virus is also necessary to produce Scarlet Fever. However, Rachkowska (1928) has shown that some strains of haemolytic streptococci

are filterable. Smirnowa-Zamkowa (1927) states that an organism belonging to the protozoa is the causal organism.

CONCLUSION.

The evidence is overwhelming in favour of the haemolytic streptococci being the cause of Scarlet Fever. Authorities differ as to whether or not the scarlatinal streptococci form a separate group, which can be distinguished definitely from other haemolytic streptococci. This difference of opinion is reflected in the two views prevailing on the etiology of this disease. The American view is that Scarlet Fever is caused by a specific type of haemolytic streptococcus and Dochez (1925) states that the evidence is "as strong as that in many diseases whose etiology is now accepted without discussion." The prevailing opinion in this country is that Scarlet Fever is a particular phase only of streptococcal infection and the problem of immunity to the disease has been summed up by Smith (1927) thus "That at least two immunity substances are required to give complete protection against streptococcal infection namely anti-toxic and anti-bacterial properties and that the anti-bacterial properties are probably more type-specific than the anti-toxic. Further, that the clinical manifestationsof streptococcal infection vary not according to the serological type of haemolytic streptococcus causing the infection but in

relation to the biological activity of the type, in relation to the site of inoculation, in relation to the antibody content of the patient's tissues, and finally in relation to the response of the patient's immunity mechanism to the infection".

The Medical Research Council's System of Bacteriology states "if any difference exists between scarlatina and non-scarlatina strains (of streptococci) it must depend on the more highly specialised toxigenic properties of the former; this, associated with a particular grade of invasiveness, may confer on strains an almost specific property of reproducing uniformly in passage among susceptible persons the scarlatinoid syndrome, so long regarded as almost a specific disease."

Not only has all this work thrown interesting light on the etiology and epidemiology of Scarlet Fever and on immunity to that disease but it has increased our knowledge of the biological relations between man and the streptococci and given a foundation and stimulus for further research.

THE DICK TEST.

The Dicks showed that the filtrate of a broth culture of the streptococcus causing experimental Scarlet Fever could be used, in suitable dilution, for a skin test. The filtrate was diluted 1 in 1,000 in sterile salt solution and 0.1 c.c. of this dilution was injected into the skin on the anterior aspect of the forearm. The presence of a positive reaction was shown by the subsequent development of an area of redness around the site of injection. Positive reactions began to appear about four to six hours after the injection. The erythematous area gradually increased in size and intensity and reached its maximum in from twenty-four to thirty-six hours. Following this the reaction rapidly subsided and even the most strongly positive had faded at the end of forty-eight hours. They classified their results as negative and positive and the positive reactions were sub-divided according to the degree, size, time of appearance and duration of the erythema. The details of their classification of reactions read at the end of twenty-four hours were as follows.

Negative - no reaction.

Slightly positive - a faint red area less than 2 cm. in diameter and not accompanied by swelling or tenderness.

Positive - a red area 1-5 to 3 c.m. in diameter with some swelling and tenderness.

TYPE OF PATIENT.	NUMBER OF PATIENTS.	NEGATIVE	SLIGHTLY POSITIVE.	POSITIVE.	STRONGLY POSITIVE.
Convalescent Scarlet Fever Patients.	65	62	3	-	-
Patients with a history of Scarlet Fever.	16	15	-	-	1[x]
Patients with no history of Scarlet Fever.	72	35	7	17	13

[x] History of previous Scarlet Fever very doubtful.

TABLE 1. The Dick test in 153 patients — Dick and Dick.

Strongly positive - a red area more than 3 cm. in diameter accompanied by swelling and tenderness. They carried out a series of tests on convalescent Scarlet Fever patients, on patients with a history of previous Scarlet Fever and on patients with no history of the disease and their results are given in Table I.

On the positive reactors they carried out tests with undiluted fluid from sterile culture medium. The results were negative showing that the reactions were not due to the foreign proteins of the medium. Some of the negative reactors gave positive Schick tests therefore the negative reactions were not due to inability of the skin to react. The positive reactors were submitted to further tests with the following fluids; A. a mixture of equal volumes of the filtrate and of serum from a convalescent Scarlet Fever patient and B. a mixture of the filtrate and salt solution. In each case the mixture was heated for thirty minutes before use. Mixture A gave negative and Mixture B positive results. Thus the filtrate was neutralised by serum from a canvalescent. Later two of the positive reactors developed Scarlet Fever and in each case the reaction was found to be negative in convalescence. The Dicks concluded that the skin test described bore a specific relation to immunity to Scarlet Fever.

In 1924, Dochez and Sherman reported that, following experiments with haemolytic streptococci on the lower animals, they had produced a serum which had the capacity,

when injected intradermally, of locally blanching the rash in Scarlet Fever and which, when used therapeutically, caused a marked amelioration of all symptoms. Though they obtained no conclusive evidence of the production of a soluble toxin they advanced the hypothesis that Scarlet Fever resembles Diphtheria in being a local infection of the throat and that the rash and general symptoms are due to absorption of toxin. Mair (1923), after investigating the Schultz-Charlton phenomenon, suggested a similar view of Scarlet Fever. In 1924 the Dicks published observations on the production of immunity by the injection of the toxic filtrate and came to the conclusion that the immunity was for a true toxin and not for a filterable virus.

Branch and Edwards (1924) introduced the use of a control in this test. Their control was the toxic filtrate heated to 90°-100° C. for one hour. Zingher (1924) used a similar control and the great majority of subsequent workers have done so. The terminology has been brought into line with that used in the Schick test, namely

Negative - no reaction.

Pseudo and negative - little or no reaction from the toxin but definite reaction from the control.

Positive - a reaction from the toxin but none from the control.

Pseudo and positive - a reaction shown by toxin and control but the toxin reaction greater.

In August 1924 Zingher published the results of Dick tests on acute and convalescent Scarlet Fever patients. In this country the first contribution on this subject was by Ker and McCartney of Edinburgh along with McGarrity of Cardiff (1925). Since then many observers have recorded the results obtained from the use of this test and I will have occasion to refer to these contributions later.

The Dicks and other workers believe the test to be a true tissue response to a true bacterial toxin and therefore of a similar nature to the Schick test. Recently some observers have doubted this explanation. Sherwood and Baumgartner (1926) investigated, in persons who had not suffered from Scarlet Fever, the relationship between the result of the Dick test and the presence in the blood of agglutinins for scarlatinal streptococci. Agglutinins were found in 11.3% of the Dick positive and in 26.1% of the Dick negative reactors. Tezner and Ungar (1927) state that the sensitiveness of the skin to the Dick toxin is readily affected by non-specific processes such as vaccination and doubt if the change in the Dick reaction during the course of Scarlet Fever is due to the presence of antitoxin in the blood. Zoeller, Ribadeau-Dumas and Chabrun (1929) found seven Dick negative infants whose serum contained no antitoxin, did not neutralise streptococcal toxin and did not produce the extinction sign.

Meyer (1927) suggested that Scarlet Fever is an

anaphylactic phenomenon in response to streptococcal infection and that the Dick test is not a true expression of susceptibility or immunity. Von Groër and Redlich (1928) consider the Dick test to be essentially an allergic reaction and Progulski and Redlich (1928) state that the test, in the same person, is liable to spontaneous alteration from time to time. Cooke and Ermatinger (1928) consider that the rash in Scarlet Fever and consequently the Dick reaction are not toxic phenomena but due to bacterial anaphylactic hyper-sensitivity. Grunke (1929) showed that Dick toxin has a characteristic feature of an allergic substance in that hypersensitiveness to it can be conveyed passively to an otherwise insusceptible person. He succeeded in showing this in four only out of forty-seven experiments.

Copeman (1926) showed that the result of the Dick test varied according to the dilution of the toxin and Lorenz and Nobel (1927) found a marked variation in the results obtained with toxins from various sources. These workers and others have pointed out the need for a uniform standard for the toxin. The difficulty lies in the fact that laboratory animals are not susceptible to this toxin and therefore, as O'Brien and O'Dell have shown, the dosage or dilution of the test toxin cannot be determined accurately. Neutralisation by scarlatinal antitoxin and skin tests in known susceptibles are the chief methods available. Recent work by Hartley (1928)

and Pulvertaft (1928) on the production of concentrated toxin suggests that in future more accurate standardisation will be possible.

The exact nature of streptococcocal toxin is still in doubt. Lancefield (1928) has isolated three antigenic fractions of a nucleoprotein, a polysaccharide and a protein nature while Ando (1929) has demonstrated the presence of heat-labile and heat-stable toxins. The investigations of Toyoda, Moriwaki and Futagi (1930) suggest that skin tests with heat-labile toxin give a true indication of susceptibility or immunity to Scarlet Fever and that the response of the skin to heat-stable toxin is allergic in nature. Further research on this aspect of the subject is necessary.

MATERIALS AND TECHNIQUE USED AT MONSALL HOSPITAL.

The materials used for the Dick test were Dick Test Toxin (Scarlet Fever Toxin) and Dick Control (Heated Scarlet Fever Toxin) supplied by Burroughs Wellcome and Company. The test toxin is a dilution of the filtrate obtained from a broth culture of "Streptococcus scarlatinae". The control is toxin heated to destroy its specific toxicity. These were obtained in small quantities at a time and were kept in an ice-chest till required.

The test consists of the injection of 0.2 c.c. of the test toxin INTO the skin in one situation and of 0.2 c.c. of the control INTO the skin in another situation. The anterior aspects of the forearms were the situations chosen; the left arm being used for the toxin and the right arm for the control. Accuracy is essential and care must be taken that the injection is wholly intradermal. A finely graduated syringe and a sharp closely fitting needle are required. The criteria of a successful performance are a feeling of resistance as the injection takes place and the simultaneous appearance of a well-defined white wheal at the site of injection. Sometimes the puncture of a venule causes slight haemorrhage: if this occurs the injection should be repeated into another portion of skin. The same syringe and needle were used for the toxin and the control but the control injection was always given first.

Some of the patients were given anti-scarlatinal serum. The serum used was Concentrated Scarlet Fever Antitoxin = Globulins supplied by Burroughs Wellcome and Company. It was administered always by the intramuscular route.

SUMMARY OF THE WORK.

Since 1926 all patients admitted to Monsall Hospital with a diagnosis of Scarlet Fever have been submitted, on admission, to the Dick test, and where a positive result was obtained, the test has been repeated on the twenty-first day of disease. All patients with a diagnosis of Diphtheria have been Dick tested on admission. Every member of the nursing staff has been submitted to the Dick test. This routine work has been done by the Resident Medical Officers. Apart from this I have performed the Dick test at other times on various patients and the results of these tests have been incorporated into this thesis.

This investigation covers a period of three years; from June 1926 to June 1929. It was greatly facilitated by the full and accurate clinical notes found in the hospital records. The Dick test was investigated in the following groups of persons.

1. FOUR THOUSAND, SEVEN HUNDRED AND THIRTEEN patients suffering from Scarlet Fever. This includes two hundred and ninety-one patients to whom 10 c.c. of anti-scarlatinal serum were given on admission.
2. THREE THOUSAND, ONE HUNDRED AND NINETEEN persons among the nursing staff and patients admitted as suffering from Diphtheria.

3. SEVENTY persons who had been submitted to the Dick test previous to developing Scarlet Fever.

4. TWO HUNDRED AND THIRTY persons who were reputed to have suffered from Scarlet Fever.

5. ONE HUNDRED AND TWENTY-TWO patients in whom the original diagnosis of Scarlet Fever remained doubtful.

6, TWO HUNDRED AND NINETY-TWO patients in whom the original diagnosis of Scarlet Fever was not confirmed.

These include almost all the patients with a diagnosis of Scarlet Fever or Diphtheria admitted during the three years covered by this study, and the total number of persons dealt with is EIGHT THOUSAND, FOUR HUNDRED AND EIGHTY-NINE.

In the following sub-sections the Dick test is considered in relation to certain stages and to certain features of Scarlet Fever and one sub-section is devoted to those patients to whom anti-scarlatinal serum was given on admission.

A. Dick Tests on Admission.

In Scarlet Fever the rash is an early and important feature of the disease and varies greatly in different patients. It may be absent, faint and transient or bright and lasting. A positive Dick test may be regarded as a local infection with streptococcal toxin and so the possibility of the rash interfering with the Dick reaction must be borne in mind. If the skin has already made the maximum response to the toxin circulating in the blood, the injection of toxin into the skin, as in the Dick test, will produce no appreciable result. Sutherland has drawn attention to this obscuring of the Dick test in patients with a bright rash and I have confirmed this. In others with a bright rash a positive reaction is shown by a local increase in the intensity of the rash round the site of injection of the toxin.

Four thousand, four hundred and twenty-two Scarlet Fever patients were submitted to the Dick test on admission. The day of disease on admission varied but the

DAY OF DISEASE.	No. OF PATIENTS.	NUMBER POSITIVE.	No. PSEUDO-POSITIVE.	NUMBER NEGATIVE.	NUMBER OBSCURED.	PER CENT. POSITIVE.
1st.	242	122	14	93	13	59·4
2nd.	1181	653	89	389	50	65·6
3rd.	1439	816	105	447	71	67·3
4th.	757	413	67	273	4	63·7
5th.	293	148	22	123	-	58·0
6th.	143	63	10	70	-	51·0
7th.-14th.	239	78	10	151	-	36·8
14th onwards.	128	33	12	83	-	35·1

TABLE II. The Dick test on admission in 4422 Scarlet Fever patients.

majority of patients were admitted during the first week of illness. The results of these tests are given in Table II. The pseudo and positive and the obscured reactions are given separately but in calculating percentages the obscured reactions have been omitted and the pseudo and positive have been included among the positive reactions. Negative and pseudo and negative results have been grouped together.

Thus the majority of patients give a positive Dick test during the first six days of the disease but after the sixth day there is a marked decline in the percentage of positive reactors. It is of interest to note that the highest percentage of positives is recorded, not on the first but on the third day of disease. This remains so even when the obscured reactions are included among the positives. Zingher found positive reactions on the first day of disease in all his patients and in 98% during the first five days. Rosen and Korobicina in one hundred and twenty-three patients found that 82.5% gave positive reactions on the second and third days, 74.1% on the fourth day, 50% on the fifth day and 44.9% from the fifth to the tenth day. Ker and his co-workers obtained positive reactions in 73.9% during the first three days and in 68.6% from the third to the sixth day of disease. Ker noted the disparity between his results and those of Zingher; he attributed this to various causes but chiefly to the greater

AGE IN YEARS.	No. POSITIVE OR PSEUDO-POSITIVE.	NUMBER NEGATIVE.
0-1	1	1
1-2	3	3
2-3	13	4
3-4	21	7
4-5	22	18
5-6	9	12
6-7	12	11
7-8	9	8
8-9	11	6
9-10	7	7
10-15	19	10
15-20	4	2
20-30	2	3
30-40	2	1
40-50	1	-
over 50	-	-
TOTAL.	136	93

TABLE III

TABLE III. Age and Dick test results in 229 Scarlet Fever patients admitted on the first day of disease.

dilution of toxin which he himself used. Smith and Taylor in one hundred and seventy patients found 86.3% to be Dick positive on the first two days, 70% on the third day and 60% on the fourth day of disease. Satake found 83.2% of two hundred and sixty-six patients to be positive early in the disease and Jacobowitz 57.1% of one hundred and seventy-nine patients during the first five days. In two hundred and seventy-three patients tested on admission, Brown recorded positive Dick tests in 60% on the first day, 73.5% on the second day, 72.7% on the third day and 68% on the fourth day of disease. Although there are differences in the actual figures recorded by these observers, the findings are comparable and in conjunction with Table II show a general agreement. My figures, however, show a lower percentage of positive reactions throughout. Ker has pointed out that the history of the onset of disease is not reliable always. Though this, in part, may account for some of the differences recorded, it is to be remembered that the toxins used by these workers were not all from the same source.

I find 59.4% only to be Dick positive on the first day of disease; this is in marked contrast to the 100% recorded by Zingher. For this I can find no satisfactory explanation. Table III shows that it is not due to a difference in the age distribution of the positive and negative reactors. Lees has shown that, even under the strictest conditions, a certain

CONDITION OF SKIN	Vivid Rash	Bright Rash	Faint Rash	Fading Rash	Staining	No Rash	Desquamation
NUMBER OF PATIENTS	137	2017	964	459	401	151	293
NUMBER POSITIVE	54	1217	648	300	235	87	101
NUMBER NEGATIVE	36	709	316	159	166	64	192
NUMBER OBSCURED	47	91	-	-	-	-	-
PER CENT. POSITIVE	60·0	63·2	67·2	65·3	58·6	57·6	34·4

TABLE IV. The Dick test on admission and in relation to the rash in 4422 Scarlet Fever patients.

proportion of patients give a negative Dick test on the first day of Scarlet Fever. Therefore in a doubtful case, a negative Dick test, early in the disease, does not exclude a diagnosis of Scarlet Fever.

The possible influence of the rash on the Dick test has been mentioned and in Table IV the cases have been arranged according to the condition of the skin on admission. Although this classification of the cases is open to objection the results do, to some extent, confirm the findings in Table II. The larger percentage of positive reactions among those with faint rashes is probably due to the greater ease with which a positive reaction is manifested. If the obscured reactions are included among the positives the highest percentage is recorded among those with a vivid rash, but there is too great a disparity between the number of patients in each group to permit of strict comparison.

In 3.1% of the total patients the rash so obscured the Dick test that a satisfactory reading could not be obtained. This occurred in 34.3% of the patients with a vivid rash and in 4.5% of those with a bright rash. This obscuring was of little clinical significance as in none of these cases was the diagnosis in doubt.

B. Dick Tests on the 21st day of disease and later.

Two thousand, two hundred and eighty-three patients who were Dick positive on admission were re-tested on the twenty-first day of disease. To none of these patients

DAY OF DISEASE	NUMBER OF PATIENTS	NUMBER POSITIVE	NUMBER NEGATIVE
28th.	43	8	35
35th.	84	26	58
42nd.	23	6	17
49th.	20	7	13
56th.	12	5	7

TABLE V. Further Dick tests on 182 Scarlet Fever patients who were Dick positive on 21st day of disease.

had anti-scarlatinal serum been administered. Seventeen hundred and thirty-six or 76.1% were found to be negative while five hundred and forty-seven or 23.9% remained positive. Thus the majority had become Dick negative during the course of the disease.

Of those who remained positive one hundred and eighty-two were re-tested later and the results of these tests are shown in Table V. This table does not refer to systematic re-tests at weekly intervals but to haphazard re-testing at varying intervals after the twenty-first day and each patient was re-tested once only. Though this detracts from the value of the table the figures show that some patients remain Dick positive as late as the fifty-sixth day of disease.

Other observers have reported positive Dick tests in Scarlet Fever convalescents. The Dicks in their original paper noted three cases. Ker found 7.3%, Rosen and Korobicina 17.2%, Satake 5.6% and Peters and Allison 31% to be positive during convalescence. Murray found 10% of four hundred patients to be positive on the twenty-first day of disease and Smith and Taylor 14% of one hundred and fifty-eight in the fourth week. Zingher in his series of one hundred and seventy patients had twelve persistent Dick positive reactors. He suggested as an explanation that there may be occasional strains of the haemolytic streptococci causing Scarlet Fever which produce different toxins.

A further twenty patients who were Dick positive on the

NUMBER OF PATIENTS.	21st. DAY	28th. DAY	35th. DAY	42nd. DAY	49th. DAY	56th. DAY
8	Pos.	Neg.	—	—	—	—
7	Pos.	Pos.	Neg.	—	—	—
3	Pos.	Pos.	Pos.	Pos.	Neg.	—
2	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.

TABLE VI. Weekly Dick tests after the 21st. day in 20 Scarlet Fever patients who were Dick positive on admission.

twenty-first day of disease were submitted to weekly re-tests till a negative result was obtained or till they were discharged from hospital. The results are given in Table VI.

The number of observations here recorded is too small to be conclusive but the general inference is that, using the Dick test as an indicator, there is a steady increase in immunity and that the rate of increase varies in different patients. In some patients the development of immunity, if it does occur, is considerably delayed. Brown carried out a series of weekly Dick tests on eighty-seven patients and found a steady decrease in the number giving positive reactions.

On the twenty-first day of disease 80.5% of the patients with a vivid rash and who were Dick positive on admission were found to be negative while of those with a faint rash 70.9% were found to be negative. This suggests that there is an association between the intensity of the rash and the rate of development of immunity but the number of patients with a vivid rash is too small to permit of any conclusion.

Of one hundred and twelve patients in whom the Dick test on admission was obscured, 15.2% gave positive reactions on the twenty-first day of disease. This suggests that, but for the rash, many of these patients would have manifested a positive Dick test on admission.

Lindsay and his co-workers have shown that the amount of antitoxin in the blood of convalescent Scarlet Fever

patients varies greatly in different individuals while Henry and Lewis found the amount of anti-toxin in the blood of patients to be considerably greater than that found in normal "resistant" controls. Abramson has recorded seven and Brown thirteen patients in whom, during the course of Scarlet Fever, the Dick test was sometimes positive and sometimes negative.

Thus the Dick test throws light on the development of immunity to Scarlet Fever but further work is required to explain the mechanism of immunity production and the relationship between the antitoxin content of the blood and the sensitiveness of the skin to streptococcal toxin.

C. <u>The Dick test in relation to the incidence of complications and the number of days in hospital.</u>

By deducting from the four thousand, four hundred and twenty-two patients who were Dick tested on admission, eighty-three to whom anti-scarlatinal serum was administered later and one hundred and thirty-eight in whom the test was obscured I was left with four thousand, two hundred and one patients. Of these two thousand, six hundred and five were Dick positive and fifteen hundred and ninety-six Dick negative on admission. In each of these groups the incidence of Rhinitis, Adenitis, Otitis Media, Albuminuria, Nephritis and Rheumatism was investigated and the results are shown in Figure I.

These complications were defined as follows and only

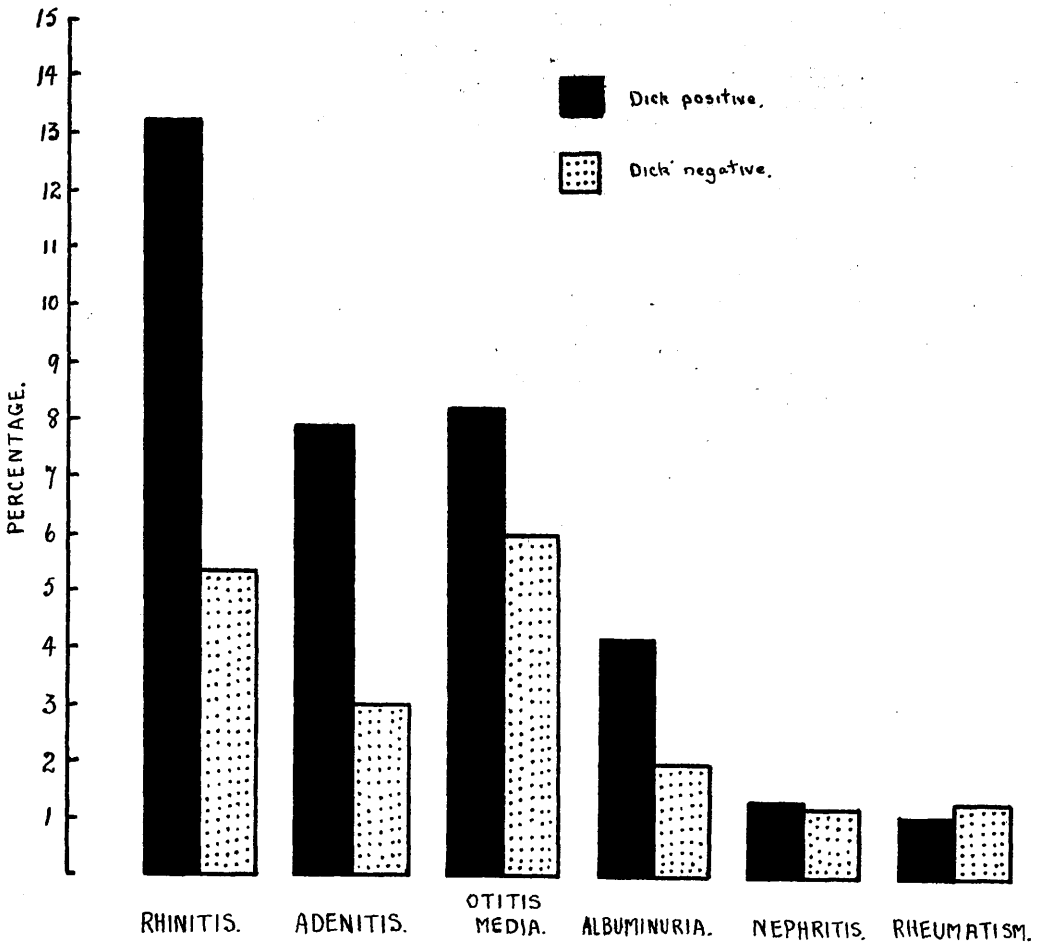

FIGURE 1. The percentage incidence of complications in 2605 Dick positive and 1596 Dick negative Scarlet Fever patients.

[Dick tests on admission.]

those fulfilling these requirements are incorporated.

Rhinitis means nasal discharge persisting later than or arising after the twenty-first day of disease.

Adenitis means late adenitis and includes all stages from simple enlargement to suppuration.

Otitis Media does not include the lighting up of pre-existing middle ear disease.

Albuminuria means albuminuria occurring after defervescence, persisting for at least four days and not associated with febrile conditions such as adenitis.

Nephritis does not include any similar pre-existing condition.

Rheumatism means swelling, pain and tenderness in the joints whether or not accompanied by fever.

This analysis clearly demonstrates that, viewing each group as a whole, complications were more frequent in Dick positive than in Dick negative patients and suggests that in the latter the disease was less severe. It is interesting to note that Rheumatism was a little more prevalent in the Dick negative patients. This was not due to the patients who developed Rheumatism having been admitted at a later stage of the disease than the average.

From the above findings it is reasonable to assume that complications would be less frequent in those patients, originally Dick positive, who were found to be Dick negative on the twenty-first day of disease than in those who

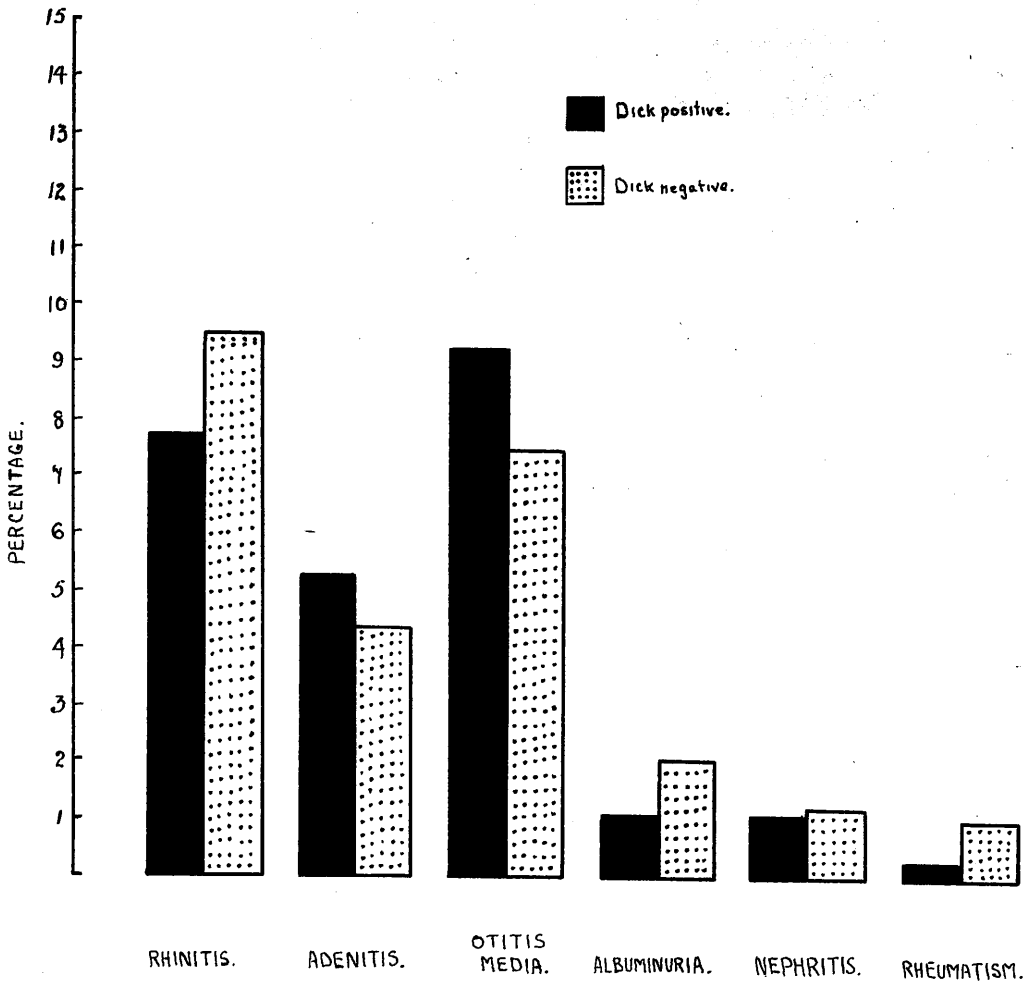

FIGURE II. The percentage incidence of complications in 547 Dick positive and 1936 Dick negative Scarlet Fever patients all of whom were Dick positive on admission.

[Dick tests on 21st day of disease.]

remained Dick positive. Figure II shows that with the exceptions of Adenitis and Otitis Media the reverse was found to be the case.

The complications of Scarlet Fever are due to the invasion of various tissues by micro-organisms as a result of the lowering of the patient's general resistance. Haemolytic streptococci are the invading micro-organisms in many cases but in what proportion this is so cannot be stated. My findings favour Smith's view that, in addition to the anti-toxic factor, some other factor is concerned in immunity to Scarlet Fever. Further local conditions in the nose and throat such as enlarged tonsils, adenoids or a deflected septum must have an influence on the occurrance of Rhinitis, Adenitis and Otitis Media. Apparently there is little relation between the antitoxin content of the blood revealed by the Dick test and the incidence of complications.

The classification of Scarlet Fever into severe, moderate and mild cases is an arbitrary one in which the dividing lines are indistinct and into which the personal bias of the observer must enter. However the criteria on which a patient is considered fit for discharge are practically uniform in this country and I submit that, where a sufficiently large number of cases can be investigated, the duration of stay in hospital will give some indication of the type of disease. Omitting those who

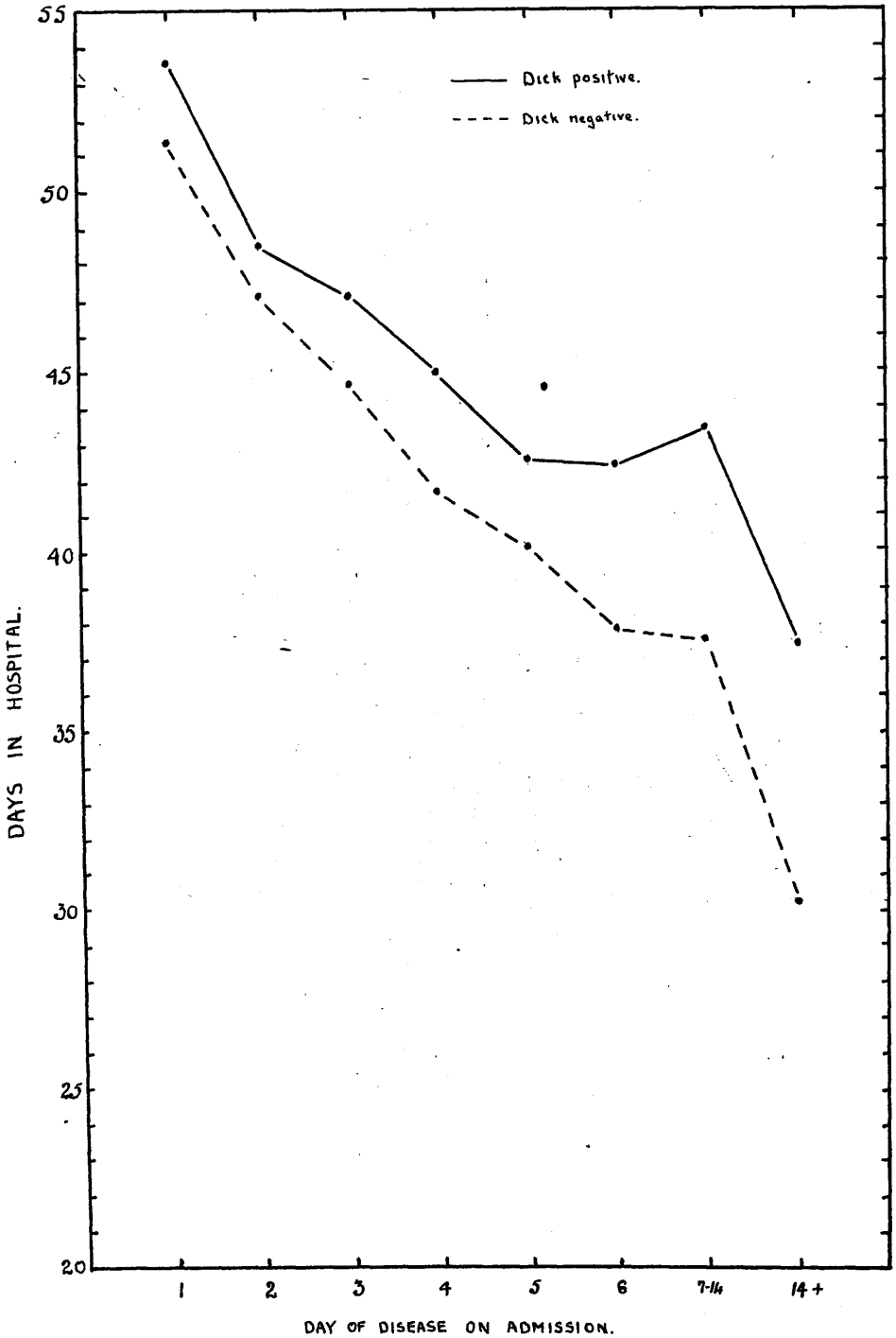

FIGURE III. Average number of days in hospital in 2450 Dick positive and 1501 Dick negative Scarlet Fever patients.

[Dick tests on admission.]

died, those in whom the Dick test was obscured, those treated by serum and those who developed Chicken Pox, Measles or other disease not directly attributable to Scarlet Fever, three thousand, nine hundred and fifty-one cases were found to be suitable for this investigation. Two thousand, four hundred and fifty were Dick positive on admission and their average stay in hospital was 44.9 days. Fifteen hundred and one were Dick negative on admission and in them the average number of days in hospital was 41.3 days. No Scarlet Fever patient was discharged from Monsall Hospital before the fourth week of disease and the majority were detained till the thirty-fifth day. A comparison of these two groups according to the day of disease on admission is shown in Figure III.

Whatever the day of disease on admission the Dick negative patients were detained, on the average, for a shorter period than those who were Dick positive. This again suggests that Scarlet Fever is a milder disease in Dick negative patients but the difference is not sufficiently marked to warrant a definite statement to that effect.

Of thirty-three fatal cases sixteen were Dick positive, fifteen Dick negative and in two the Dick test on admission was obscured. The Dick positive and those in whom the test was obscured were all admitted on the second, third or fourth day of disease. As five of the Dick negative were admitted later than the sixth day of disease it

is possible that some of them were Dick positive at the onset of disease. No conclusions can be drawn from this small number of fatal cases.

D. The Dick test in relation to secondary attacks.

Secondary attacks occurred in thirty-five or 0.8% of four thousand, three hundred and thirty nine patients who were not treated by anti-scarlatinal serum. Here, a secondary attack is defined as the occurrence, after defervescence and the fading of the primary rash and at least eight days after admission to hospital, of sore throat, peeling tongue, fever and a scarlatiniform rash.

Of these thirty-five patients, one was admitted on the first day of disease, eight on the second day, fifteen on the third day, five on the fourth day, one on the fifth day, three on the sixth day, one on the eighteenth day and one on the twentieth day. Thirty-three were Dick positive and two were Dick negative on admission. Previous to the secondary attack twenty-nine of those who were Dick positive on admission were re-tested on the twenty-first day of disease; nineteen were positive and ten were negative. The following case is the only one which remained Dick positive after a secondary attack.

> A boy, aged 11 years, was admitted on the 3rd day of disease with all the typical features of Scarlet Fever. Pin-hole desquamation followed. On the 18th day of disease he developed cervical adenitis which proceeded to suppuration. On the 40th day, fever, sore throat, peeling tongue and a punctate erythema were noted. Further desquamation followed in due course. The Dick test was positive on admission, on the 21st and on the 60th day of disease.

The majority of these secondary attacks occurred between the twenty-eighth day and the forty-second day of disease: the earliest appeared on the twelfth day and the latest on the seventy-seventh day. In almost every case the patient was no longer confined to bed when the secondary attack developed. The minimum time which elapsed between admission to hospital and the secondary attack was eleven days and the maximum seventy-three days. In Monsall Hospital cases of all degrees of severity are nursed in the same ward.

The theory of auto-inoculation has been advanced as an explanation of the occurrence of secondary attacks but Burton and Balmain have recorded two thousand and eighty three Scarlet Fever patients who were nursed at home and in whom no secondary attacks developed. The other view is that the secondary attack is due to superimposed infection derived from a new admission or from another patient in the ward. Some support for this view is given by the work of Gunn and Griffith who, in three patients with persistent positive Dick tests, found that the appearance in the throat of a second type of streptococcus coincided with a secondary attack of clinical scarlatina.

The Dick test throws little light on this problem. Abramson records a case where after a secondary attack the Dick test became temporarily negative and then definitely positive. Burton and Balmain have obtained positive Dick

DAY OF DISEASE.	NUMBER OF PATIENTS.	NUMBER POSITIVE	No. PSEUDO-POSITIVE.	NUMBER NEGATIVE.	NUMBER OBSCURED.	PER CENT. POSITIVE.
1st.	15	1	3	10	1	26·6
2nd.	103	20	11	70	2	29·8
3rd.	109	18	3	88	-	19·2
4th.	47	11	2	34	-	27·6
5th.	13	-	2	11	-	15·3
6th.	3	-	-	3	-	Nil.
7th - 14th.	1	-	-	1	-	Nil.
14th onwards	-	-	-	-	-	Nil.

TABLE VII. Dick tests on admission in 291 Scarlet Fever patients to whom 10 c.c. serum were given on admission.

tests after secondary attacks. It has been seen that the majority of Scarlet Fever patients are Dick positive on admission and that, of the Dick positive, twenty-three per cent. are still so on the twenty-first day of disease yet secondary attacks occur in only one per cent. of all cases. Here apparently, some factor which has no definite relation to the Dick test is involved.

In two patients who were Dick positive on the twenty-first day and in whom secondary attacks appeared on the twenty-third and twenty-fourth days respectively, a blanching of the rash at the site of the recent injection of toxin was noted. This "toxi-extinction" phenomenon was described first by Zoeller

E. The Dick test in patients treated by serum.

In connection with another investigation two hundred and ninety-one Scarlet Fever patients were given on admission and intramuscularly 10 c.c. of anti-scarlatinal serum. At the same time a Dick test was carried out on each case and the results are shown in Table VII.

In comparison with Table II there is a marked reduction in the percentage of positive reactions. Though the number of observations recorded here is small, this reduction can be attributed only to the action of the serum. Variation in the rate of absorption of the serum no doubt permitted the manifestation of positive reactions but even allowing for this the percentage seems to be high. Most

of the patients showed a rapid fading of the rash and amelioration of the symptoms. The obscured reactions show that in some cases the rash was "fixed".

Sixty-nine of the positive reactors were re-tested on the twenty-first day and nine or 13% were positive. Seventy-nine of the Dick negative patients were re-tested at the same stage of the disease and six or 7.6% were found to be positive. Apparently in these patients the passive immunity, if any, conferred by the serum was of less than twenty-one days duration and active immunity had not been sufficiently established by that time to yield a negative Dick reaction. Banks and Mackenzie, in one hundred patients to whom serum was administered intravenously, found twelve to be Dick positive fifteen to twenty days after the onset of disease. Brown carried out weekly Dick tests on patients treated by serum and came to the conclusion that "the administration of serum delays the process of natural antitoxin formation."

Here, my observations are not sufficient to warrant definite conclusions but they appear to favour Brown's view. Further, anti-scarlatinal serum is to some extent " an unknown quantity" as O'Brien, Okell and Parish have shown that there is no satisfactory method of titration available as yet. Craig found that anti-scarlatinal sera had, as indicated by the Dick test, widely varying protective powers; he considered these variations to be due more to

the sera than to the individuals.

Many have recorded the production of passive immunity in susceptible persons by the administration of serum. The proof of immunity was either the production of a negative Dick test or a failure to contract Scarlet Fever on exposure. Others have recorded the duration of this immunity as ascertained by the Dick test. The findings vary in regard to the quantity of serum required and to the duration of the protection. In this connection the following case is of interest.

> A male aged 16 years was admitted with a diagnosis of Scarlet Fever. After examination there was much doubt as to the diagnosis but finally the condition was considered to be atypical Scarlet Fever. A Dick test was performed, 10 c.c. anti-scarlatinal serum were given, and he was admitted to a Scarlet Fever Ward. Next day the Dick test was positive, the rash fading, the temperature fallen and the patient felt much better. At the end of forty-eight hours the rash had gone but the tongue showed no signs of peeling.
> Five days after admission he vomited, complained of sore throat and his temperature rose to 100° F. Another Dick test was immediately carried out. Next day he presented the typical picture of acute Scarlet Fever with early cervical adenitis. The Dick test was negative. Despite the administration of a further 50 c.c. of serum he was acutely ill for seven days. Typical desquamation followed and the Dick test was negative on the 21st day.

I think the original diagnosis of Scarlet Fever was wrong. The positive result of the first Dick test roused no suspicion as this had been found in other patients (see TableVII). In this case the serum ultimately rendered the Dick test negative but did not protect against Scarlet Fever. Despite the massive exposure to infection such a failure to protect on the part of anti-scarlatinal serum must be rare.

AGE IN YEARS.	NUMBER TESTED.	PERCENTAGE POSITIVE.
0-1	73	46·6
1-2	165	73·9
2-3	218	81·7
3-4	224	72·3
4-5	284	75·4
5-6	375	71·7
6-7	316	69·6
7-8	241	61·8
8-9	158	54·4
9-10	132	60·6
10-15	396	44·4
15-20	236	34·3
20 + over.	301	28·9

TABLE VIII. The Dick test in 3119 persons.

AGE IN YEARS.	NUMBER TESTED.	PERCENTAGE POSITIVE.
under 4	15	93
4	104	79
5	547	68
6	882	63
7	813	58
8	719	52
9	665	49
10	654	46
11	524	49
12	417	41
13	302	42
14	205	42
15	115	33
16	48	27
17	26	31
18	12	17
Adults	265	42
No age given.	136	52

TABLE IX. The Dick test in 6452 persons
[Smythe and Nesbit]

AGE IN YEARS.	NUMBER TESTED.	PERCENTAGE POSITIVE.
0-½	29	44·8
½-1	52	65·3
1-2	233	71·6
2-3	204	64·2
3-4	241	60·5
4-5	264	48·4
5-10	1955	33·6
10-15	2965	22·8
15-20	981	16·8
20 + over.	776	14·4

TABLE X. The Dick test in 7700 persons.
[Zingher.]

AGE IN YEARS.	NUMBER TESTED.	PERCENTAGE POSITIVE.
0-5	63	96·4
5-10	602	81·2
10-15	664	65·5
15-20	119	60·8
20-25	44	52·4
25 + over	8	27·7

TABLE XI. The Dick test in 1500* persons.
[Kinloch.]

* including 121 with a history of Scarlet Fever.

THE DICK TEST IN THE NURSING STAFF AND OTHER PATIENTS.

Every member of the nursing staff and all patients admitted with a diagnosis of Diphtheria were submitted to the Dick test on admission. The results of these tests are shown in Table VIII. No person reputed to have suffered previously from Scarlet Fever is included. These patients and staff cannot be considered as "normal" individuals but I think they may be taken as representative of the general population.

Zingher investigated the Dick test in over seven thousand normal individuals in New York. A similar investigation, on fifteen hundred persons selected at random, was carried out by Kinloch and his co-workers in Aberdeen while Smythe and Nesbit have recorded the results of the Dick test on over six thousand persons in Indiana. The results of these workers are shown in Tables IX, X, and XI.

These four tables all show differences, which may be due to a variety of causes. They may be due to the employment of different toxins, to differences in the dosage or standardisation of the toxin, to real differences of herd immunity in the populations tested or to a combination of these factors.

The results of these four investigations are compared in Figure IV. My findings correspond fairly closely with those of Smythe and Nesbit and occupy an intermediate position

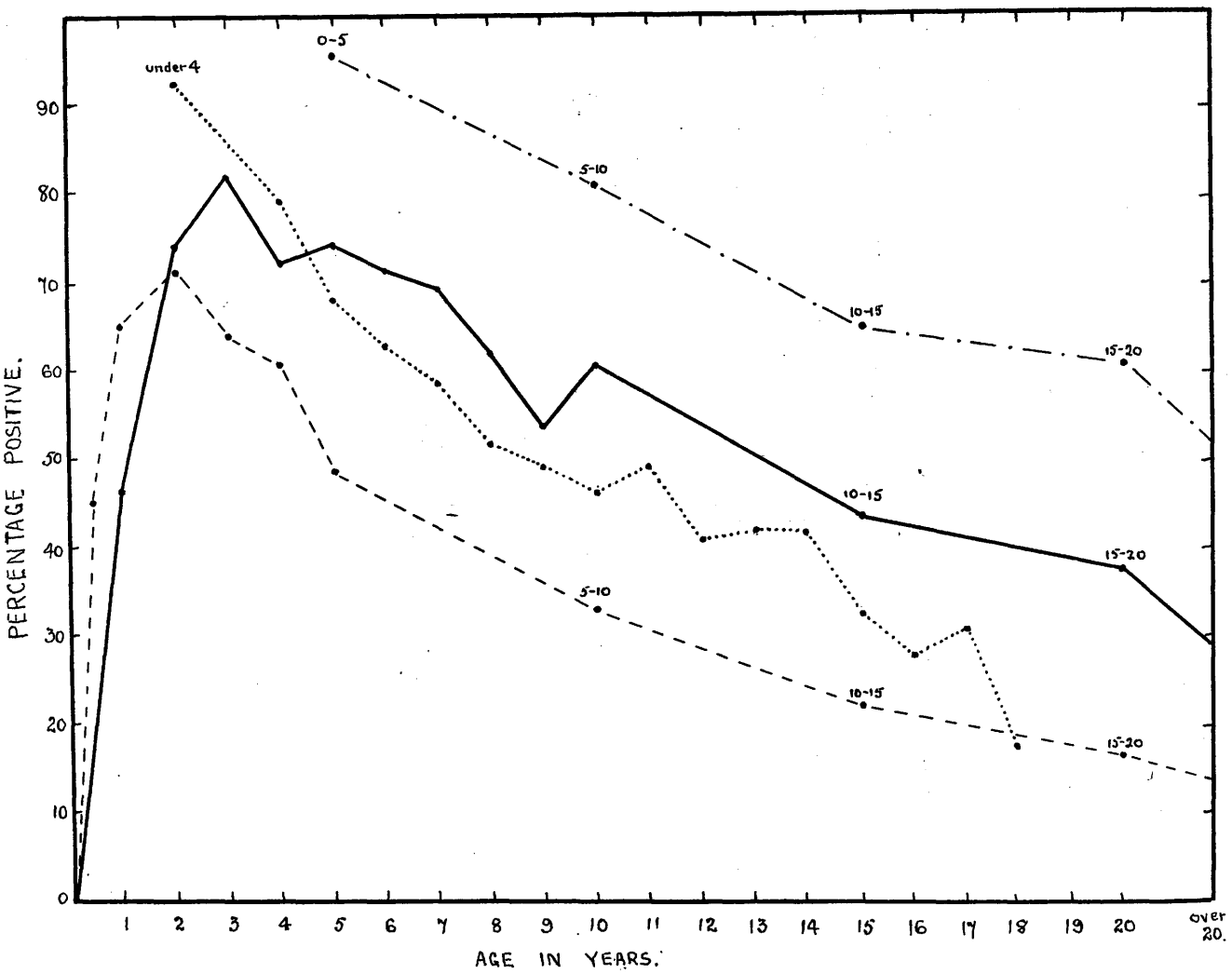

FIGURE IV. Percentage of Dick positive reactors according to age.

—·— Kinloch.
——— Myself.
····· Smythe and Nesbit.
– – – – Zingher.

between those of Kinloch and those of Zingher. All agree in showing that susceptibility to Scarlet Fever is greatest during the first five years of life and that susceptibility diminishes in each succeeding quinquennial period. Statistics show that the second quinquennial period furnishes the largest number of cases, then the first five years and after that the remaining five-year periods in order of succession. The discrepancy between the susceptibility and the incidence in the first two quinquennial periods is due to the increased exposure to infection resulting from attendance at school during the second of these periods.

Thus the Dick test, when used as an indicator of susceptibility to Scarlet Fever and when applied to the population in general, yields results which do not differ from those previously established by clinical and statistical observations.

THE DICK TEST IN PERSONS WHO LATER CONTRACTED SCARLET FEVER.

During the three years covered by this investigation sixty-eight Diphtheria patients, one patient suffering from Tonsillitis and one nurse developed Scarlet Fever. The nurse, Dick positive and not yet immunised, had been placed on duty, in error, in a Scarlet Fever ward, and the patient with Tonsillitis was cross-infected in the bed-isolation ward. The majority of these cases occurred sporadically and the largest number in one outbreak was four.

All had been submitted to the Dick test on admission to hospital and therefore previous to developing Scarlet Fever; sixty-three were positive and seven were negative. Three of the negative reactors were submitted to the Schultz-Charlton test and in each case a positive result was obtained. Lees, Brown and other writers have noted the occurrence of Scarlet Fever in persons giving a negative Dick test but Kinloch reports that "in a series of 6,807 Dick reactions observed during the past two years, Scarlet Fever has been found to occur only in individuals giving a marked Dick reaction". These statements are difficult to reconcile but from the evidence of competent observers it must be accepted that Scarlet Fever may occur among negative Dick reactors.

In twenty-eight of the Dick positive patients a re-test was carried out on the twenty-first day of disease

and in twenty-four or 86% the re-test was negative. This confirms my previous observation that the majority of Dick positive reactors become negative reactors during the course of Scarlet Fever.

Zoeller's toxi-extinction sign was noted in one of the positive reactors in whom the rash appeared four days after the performance of the Dick test. The "reappearance phenomenon" described by Zingher was not recorded in any of these patients.

Five of the Dick negative reactors were under my care. In four the attack of Scarlet Fever was mild but in one it was moderately severe, The latter patient developed double Otitis Media and late Adenitis occurred in one of the mild cases.

THE DICK TEST IN PERSONS GIVING A HISTORY OF SCARLET FEVER.

One hundred and eighty-eight patients notified as suffering from Diphtheria and forty-two members of the nursing staff were reported to have suffered previously from Scarlet Fever. All were submitted to the Dick test and fifty-five or 24% were found to be positive.

Where the diagnosis of Scarlet Fever is not confirmed, the patients or their relations are not informed always of this fact and thus a false history will be given later. In other cases the history is so vague and indefinite that no reliance can be placed on it. I do not think that these two groups would account for 24% of the total.

Among persons with a history of Scarlet Fever Ker and his co-workers found positive Dick tests in 17.7%, Kinloch and his co-workers in 10%, the Dicks in 9.3%, Rosen and Korobicina in 23.4% and Brown W.A. in 6.6% . In none of these groups was the history verified and the figures show great variation.

In another group of fourteen persons Rosen and Korobicina verified the history but found two to be Dick positive. Brown found no positive reactions in eighty-three persons who undoubtedly had suffered from Scarlet Fever five years previously. In eight of my cases I was abole to verify the history; seven were negative and one

was Dick positive. The history of the positive reactor is as follows:-

> A nurse, aged 17 years, was found to be Dick positive when she joined the staff on 4.3.27. She was immunised against Scarlet Fever by the Dick method. The injections were given at four-day intervals and in all 18,000 skin test doses of toxin were administered. The Dick test was negative on 12.4.27. She developed Scarlet Fever on 21.6.27 but the Dick test performed on that date was obscured by the rash. Though the rash was marked the attack was mild. Typical desquamation followed and the Dick test was negative on the 21st day of disease. On 18.6.29 I carried out another Dick test and obtained a positive reaction.

Thus during the two years which had elapsed between the attack and the final Dick test this nurse had again become susceptible despite her repeated exposure to infection.

Apparently where the history of previous Scarlet Fever can be verified few positive Dick reactions are obtained and this is in agreement with the known rarity of second attacks.

Positive Schick tests have been found in persons who have suffered from Diphtheria. Dudley suggests that in these cases the clinical Diphtheria has acted as the "primary stimulus" but has not produced sufficient antitoxin to give a negative Schick test and that later exposure to diphtheria infection may act as the "secondary stimulus" and quickly produce antitoxin to protect against a second attack. I do not think the rarity of second attacks of Scarlet Fever, despite the persistence of positive Dick reactions in those who have suffered from the disease, can

be explained on this basis as the serum of a Dick positive reactor may produce a positive Schultz-Charlton test. Further Kondo has reported eighty patients in whom a change in the Dick reaction from negative to positive was observed during Scarlet Fever and yet the serum of all these patients produced positive Schultz-Charlton blanching.

The work of Ando and of Toyoda and his co-workers on the thermolabile and thermostable fractions of Dick toxin suggests that the persistence of positive Dick tests after Scarlet Fever is due to the development of allergy to the thermostable fraction.

THE DICK TEST WHERE THE DIAGNOSIS OF SCARLET FEVER REMAINED DOUBTFUL.

As far back as 1829 Trousseau noted that all the typical manifestations of the disease were not present in every case of Scarlet Fever. His findings have been confirmed universally and to-day the diagnosis of Scarlet Fever presents many difficulties. The rash may be fleeting or absent and may not be followed by desquamation; obvious sore throat may be missing and even the changes in the tongue may be ill-defined and incomplete. It is impossible to differentiate Scarlet Fever from some types of Puerperal Fever on bacteriological or epidemiological grounds and the clinical distinctions are far from clear. When considering relapses the possibility of one variety being engrafted on another has been mentioned. Again the incubation period is variable and variations from twenty-four hours to six days have been reported by competent observers. Varying types of haemolytic streptococci have been isolated from Scarlet Fever patients but as yet no true correspondence between the type of streptococcus and the type of disease has been demonstrated. The diagnosis of Scarlet Fever is based on clinical observations and the clinical conception of what is to be regarded as Scarlet Fever will vary with different observers.

In some patients admitted to Monsall Hospital with a diagnosis of Scarlet Fever the clinical findings were so

indefinite that these patients were classified on discharge as "doubtful Scarlet Fever". In this group were placed one hundred and twenty-two or 2.4% of the total cases admitted. These patients were nursed in the bed-isolation ward, desquamation was absent in each and the minimum period of detention was twenty-one days. No return cases occurred.

On admission eighty-seven or 71.3% were found to be Dick positive. In seventy-seven of these re-tests on the twenty-first day of disease showed that twenty-six or 33.8% had become Dick negative. This is in marked contrast to true Scarlet Fever where 76% of the positive reactors were found to be negative on the twenty-first day.

These Dick tests suggest that the majority of these patients did not suffer from Scarlet Fever though, on clinical grounds, one hesitated to be so dogmatic.

DIAGNOSIS	NUMBER OF PATIENTS	NUMBER POSITIVE	NUMBER NEGATIVE
Tonsillitis	128	76	52
Erythema	81	42	39
Rubella	15	11	4
Pneumonia	13	6	7
Urticaria	11	3	8
Bronchitis	9	6	3
Dermatitis	6	3	3
Diphtheria	5	2	3
Otitis Media	4	4	-
Coryza	4	2	2
Drug Rash	3	1	2
Rheumatism	2	1	1
Abscess	2	-	2
Enteritis	2	1	1
Jaundice	1	1	-
Purpura	1	-	1
Mumps	1	1	-
Chicken Pox	1	1	-
Smallpox	1	-	1
Psoriasis	1	-	1
Measles	1	1	-
TOTAL	292	162	130

TABLE XII. The Dick test and Disease in 292 patients in whom the original diagnosis of Scarlet Fever was not confirmed.

THE DICK TEST WHERE THE DIAGNOSIS OF SCARLET FEVER WAS NOT CONFIRMED.

In two hundred and ninety-two or 5.7% of the total patients admitted as suffering from Scarlet Fever, that diagnosis was not confirmed. The final diagnosis and the results of the Dick tests on admission are shown in Table XII. These patients were nursed in the isolation or bed-isolation wards.

One hundered and twelve of the positive reactors were re-tested twenty-one days after admission: one hundred and one were positive and eleven were negative. In these eleven patients the diagnosis was Tonsillitis and short notes on each are given in Appendix I.

How are Scarlet Fever without a rash and Tonsillitis to be differentiated with any degree of certainty ? The faucial condition is not distinctive and vomiting may or may not occur in each; the changes in the tongue, so characteristic of Scarlet Fever may be ill-defined or absent and in Tonsillitis the tongue may be red, raw and papillated. The occurrence of Nephritis would favour a diagnosis of Scarlet Fever but otherwise the usual complications are common to both conditions. A history of previous exposure to infection, although of value, is not conclusive. In these patients no detailed enquiries were made regarding previous exposure to infection or the occurrence of further cases in the same household.

Does a change in the Dick reaction occur in cases of

Tonsillitis in whom there has been no suspicion of Scarlet Fever ? I re-tested, twenty-one days after admission, thirteen patients who had yielded positive Dick reactions on admission and in whom the original diagnosis of Diphtheria was changed to Tonsillitis; a negative result was obtained in four. All these patients were suffering from what is usually called Septic Tonsillitis and short notes on the four in whom the Dick reaction changed are given in Appendix II. In these four cases careful enquiries elicited no evidence of exposure to Scarlet Fever and no other person in any of the households was infected. Rhoads found haemolytic streptococci in the throats of twenty-seven out of one hundred Diphtheria patients and 55.2% of these streptococci were considered to be scarlatinal strains.

Nobel and Schonbauer have reported two cases of Erysipelas in whom the Dick reaction changed from positive to negative during the course of the illness. I found a similar though much delayed change in the following case of Acute Rheumatism.

> A girl, aged 14 years, was admitted on the third day of illness with a diagnosis of Scarlet Fever. She gave a history of vomiting and sore throat but no rash had been seen. No evidence of Scarlet Fever was found but the tonsils were acutely inflamed. She was admitted to the bed-isolation ward.
> The fever continued and three days later double otorrhoea was noticed. The temperature remained high and the patient seemed more acutely ill than the aural condition warranted. A further examination four days after admission revealed acute endocarditis. Her condition became grave and six weeks elapsed before the temperature subsided. At the end of six months

her heart was sufficiently improved to permit of her being transferred by ambulance to her home.
No desquamation was noted.
The Dick test was positive on admission and again one month later but was found to be negative four and five months after admission.

Thus a change in the Dick reaction from positive to negative has been reported in two cases of Erysipelas and I have found a similar change in fifteen cases of Tonsillitis and in one case of Acute Rheumatism. The researches of Burt-White, Colebrook and their co-workers suggest that women with positive Dick reactions show an increased susceptibility to Puerperal Fever but I have been unable to find any record of an alteration in the Dick reaction during the course of that disease. It is known that haemolytic streptococci produce diseases other than Scarlet Fever but bacteriologically these streptococci are not of the same species though some, isolated from conditions other than Scarlet Fever, give all the reactions of the Dick strain. My findings support this and suggest that Scarlet Fever is not a specific disease.

Epidemiologically the association of Scarlet Fever with Tonsillitis is known. Halliday, after investigating outbreaks of Scarlet Fever in Schools in Glasgow, came to the conclusion that "a series of sore throats may act as the connecting link between two apparently sporadic cases of Scarlet Fever". Scammon reported a milk-borne epidemic of sore throat which was traced to the dairyman and his family where all had Scarlet Fever except the mother who had a septic finger.

Clinically there are different types of Scarlet Fever and apparently one type can become engrafted upon another. Again, new admissions to Scarlet Fever wards reinfect convalescents and cause epidemics of complications. Between the type of disease and the type of streptococcus no correspondence has been established. These facts favour the view that Scarlet Fever is not a specific disease but against this is the knowledge that Scarlet Fever protects against itself and tends to breed true.

SUMMARY AND CONCLUSIONS.

The association of streptococci with Scarlet Fever has been recognised for many years but, until the work of the Dicks, no convincing evidence that streptococci cause this disease had been forthcoming. This etiological relationship is now accepted generally but no certain method of differentiating these streptococci from other haemolytic streptococci has been discovered. At the present the evidence available suggests strongly that Scarlet Fever is not a specific disease but rather one manifestation of streptococcal infection.

The discovery by the Dicks of a soluble streptococcal toxin capable of producing clinical Scarlet Fever has advanced greatly our knowledge of the disease. The production of an antitoxic serum followed close on this discovery. As man alone is susceptible to this toxin an accurate method of titrating the toxin or the antitoxin is not yet available.

The use of this toxin, in soluble dilution,as a skin test for susceptibility to Scarlet Fever was introduced by the Dicks. The material in this thesis includes almost all the Dick tests performed at Monsall Fever Hospital from June 1926 to June 1929. The investigation was concerned with the results of the Dick test in (a) patients suffering from Scarlet Fever (b) patients in whom the diagnosis of Scarlet Fever remained doubtful or was not confirmed (c) patients with a history of Scarlet Fever,(d) patients who, subsequent to testing,developed

Scarlet Fever and (e) in patients notified as suffering from Diphtheria and (f) in the nursing staff.

The results of the Dick test in the early and late stages of Scarlet Fever have confirmed in general those obtained by other observers. The majority of patients give positive tests early in the disease and the greater proportion of these become negative reactors during the course of the disease. In general complications are less frequent and the duration of stay in hospital is shorter in those patients who give a negative reaction early in the disease but this does not apply to individual cases. Secondary attacks are more frequent in patients giving a positive reaction in the early stages but do not appear to be influenced to any extent by the rate of development of natural immunity as shown by Dick tests on the twenty-first day of disease. In patients treated by anti-scarlatinal serum my results are inconclusive but here neither the serum nor the toxin can be accurately assessed.

A positive Dick test indicates susceptibility to Scarlet Fever but a negative result does not indicate complete immunity in every case. The test has been shown to be suitable for application to the community and the occasional occurrence of Scarlet Fever in a negative reactor does not detract to any extent from the value of the test in this respect.

In persons reputed to have suffered from Scarlet

Fever a considerable number give positive reactions but where this history is verified positive reactions are infrequent. This is in agreement with the fact that second attacks of the disease are rare.

In general the relation between the Dick test and Scarlet Fever is very close but in particular it is not sufficiently constant to warrant complete acceptance in diagnosis. Many patients give negative tests on the first day of disease, others remain positive in the late stages and in patients suffering from other diseases a change from positive to negative in the result of the test has been observed. A change from negative to positive during the course of Scarlet Fever has been recorded by some observers and the serum of a positive reactor may produce Schultz-Charlton blanching. Clinically Scarlet Fever in a positive reactor cannot be distinguished from the same disease in a negative reactor. A bright rash may obscure the reaction but this is of little import as in such cases the diagnosis is not usually in doubt.

Though, on bacteriological grounds, Scarlet Fever can no longer be looked upon as a specific disease, it is, for clinical and administrative purposes, still regarded as a definite entity. Where its manifestations are typical the Dick test is not required for diagnosis and the test, in doubtful cases, is of little or no value.

The fault seems to be more with the toxin than with

the test and recent work suggests that in the future a standardised and more specific toxin will be available and so greatly enhance the value of the test.

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A P P E N D I X I.

This contains short notes on eleven patients in whom the original diagnosis of Scarlet Fever was altered to Tonsillitis and in whom the Dick reaction changed from positive to negative during the course of the illness.

1. A male, aged 2 years, was admitted on the 3rd day of illness. The faucies were deeply injected but no rash or peeling of the tongue was observed. Neither pyrexia nor desquamation was recorded.

2. A female, aged 6 years, was admitted on the 2nd day of illness. The tonsils were enlarged and inflamed but no rash or stripping of the tongue was noted. The temperature was raised for 24 hours after admission. Desquamation did not occur.

3. A female, aged 7 years, was admitted on the 1st day of disease. She had vomited, the face was flushed and she complained of sore throat. No rash, fever or desquamation was noted.

4. A female, aged 6 years, and giving a history of sore throat, was admitted on the 8th day of illness. No staining was seen and the tongue was neither congested nor peeled. Slight cervical adenitis was present. No desquamation occurred.

5. A female, aged 4 years, was admitted on the 2nd day of disease. No rash was seen nor was the tongue typical but the tonsils were inflamed and partly covered by loose exudate. The temperature was raised for 36 hours. Desquamation did not occur.

6. A male, aged 7 years, was admitted on the 6th day of illness. A history was obtained of vomiting and sore throat but not of rash. Flaky desquamation was present on the forehead. No fever or further desquamation was observed.

7. A female, aged 8 years, was admitted on the 3rd day of illness. There was a history of sore throat and flushing of the face. No rash was seen but the fauces were acutely inflamed. Fever persisted for three days, the tongue did not peel and no desquamation was seen.

8. A male, aged 3 years, was admitted on the 6th day of illness. A rash was said to have been present on the face. No staining was seen, the tongue was not typical and there was no fever. Slight cervical adenitis was noted. No desquamation occurred.

9. A female, aged 4 years, was admitted on the 4th day of disease. No erythema was present but the skin showed numerous flea bites. The tonguewas thickly coated and the tonsils were swollen and inflamed. Fever was present for 48 hours, the tongue did not strip and no desquamation was seen.

10. A female, aged 6 years, was admitted with a history of sore throat starting on the previous day. The face was flushed but no rash was present. Apart from slight faucial injection no lesion was found and desquamation was absent.

11. A male, aged 6 years, and giving a history of sore throat and vomiting, was admitted on the 2nd day of illness. No rash was present but the face was flushed. The tonsils were greatly enlarged. Fever lasted for 3 days, the tongue did not peel and no desquamation occurred.

Patient 4 was detained for 50 days owing to rhinitis and excoriation of the nostrils but in the other ten patients the average stay in hospital was 22.3 days. No return cases occurred.

A P P E N D I X II.

This contains notes on four patients in whom the diagnosis of Diphtheria was changed to Tonsillitis and in whom an alteration from positive to negative in the result of the Dick test was noted during the course of the illness.

1. A male, aged 1 year, was admitted on the 2nd day of illness. A small patch of exudate was present on one tonsil. Cultures failed to reveal diphtheria bacilli. He was nursed in a Diphtheria ward. At no time was any evidence of Scarlet Fever found and no Scarlet Fever occurred in the ward.

2. A male, aged 5 years, was admitted on the 3rd day of disease. Septic exudate was present on the tonsils, but all cultures were negative. Fever persisted for 2 days. He was nursed in a Diphtheria ward for two days and then transferred to the bed-isolation ward. No evidence of Scarlet Fever was seen and no cases arose in the ward.

3. A male, aged 1 year, was admitted on the 1st day of illness. The tonsils were swollen and inflamed and a patchy exudate was present. All cultures were negative. The temperature was raised for three days. He was nursed in the bed-isolation ward and no signs of Scarlet Fever were seen.

4. A female, aged 6 years, and giving a history of vomiting and sore throat, was admitted on the 3rd day of illness. Septic exudate was present on the tonsils which were acutely inflamed. No culture showed diphtheria bacilli. Fever was present for two days. She was barrier nursed in a diphtheria ward and no evidence of Scarlet Fever was seen.

A P P E N D I X III.

Age and sex of 4,422 Scarlet Fever patients.

Age in years.	Number of Males.	Number of Females.	TOTAL.
0 - 1	6	6	12
1 - 2	25	30	55
2 - 3	107	98	205
3 - 4	172	177	349
4 - 5	197	192	389
5 - 6	239	272	511
6 - 7	256	247	503
7 - 8	178	229	407
8 - 9	133	168	301
9-10	115	127	242
10 -15	379	418	797
15 -20	147	165	312
20 -30	105	131	236
30 -40	26	46	72
40 -50	11	16	27
Over 50	2	2	4
TOTAL	2098	2324	4422

A P P E N D I X IV.

Age and sex of 291 Scarlet Fever patients to whom 10 c.c. antiscarlatinal serum were given on admission.

Age in years.	Number of Males.	Number of Females.	TOTAL.
0 - 1	-	-	-
1 - 2	1	-	1
2 - 3	8	5	13
3 - 4	6	7	13
4 - 5	12	11	23
5 - 6	12	15	27
6 - 7	10	13	23
7 - 8	14	19	33
8 - 9	9	11	20
9 - 10	8	11	19
10 - 15	28	40	68
15 - 20	10	15	25
20 - 30	8	11	19
30 - 40	1	5	6
40 - 50	-	1	1
Over 50	-	-	-
TOTAL	127	164	291

A P P E N D I X V.

Age and sex of 122 patients in whom the diagnosis of Scarlet Fever remained doubtful.

Age in years.	Number of Males.	Number of Females.	TOTAL.
0 - 1	1	-	1
1 - 2	1	6	7
2 - 3	8	6	14
3 - 4	4	6	10
4 - 5	6	9	15
5 - 6	4	11	15
6 - 7	4	9	13
7 - 8	7	4	11
8 - 9	5	-	5
9 - 10	4	1	5
10 - 15	8	10	18
15 - 20	2	4	6
20 - 30	1	-	1
30 - 40	-	-	-
40 - 50	-	1	1
Over 50	-	-	-
TOTAL	55	67	122

A P P E N D I X VI.

Age and sex of 292 patients in whom the diagnosis of Scarlet Fever was not confirmed.

Age in years.	Number of Males.	Number of Females.	TOTAL.
0 - 1	7	6	13
1 - 2	12	11	23
2 - 3	13	11	24
3 - 4	10	10	20
4 - 5	9	12	21
5 - 6	14	16	30
6 - 7	12	14	26
7 - 8	8	10	18
8 - 9	2	13	15
9 - 10	7	9	16
10 - 15	22	24	46
15 - 20	10	12	22
20 - 30	5	8	13
30 - 40	1	4	5
40 - 50	-	-	-
Over 50	-	-	-
TOTAL	132	160	292