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STUDIES IN SCARLET FEVER

III. INFECTIONS WITH STREPTOCOCCUS SCARLATINAE IN PERSONS WITH SCARLATINAL ANTITOXIC IMMUNITY¹

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INTRODUCTION

For a number of years writers have noted that cases of sore throat without a rash may occur among persons who have been exposed to scarlet fever. Hebra (1866) speaks of the "Scarlatina sine exanthemate." He says the use of this expression can be justified only in such cases as the following,—“several persons residing in the same locality and exposed to similar epidemic influences, fall ill at the same time; some of them present, in a well marked form, all the symptoms of scarlatine; others suffer merely from fever and an affection of the throat, there being in these patients no efflorescence, nor, at a later period, any desquamation.”

Thomas (1875) mentions cases of irregular scarlet fever in which the chief symptoms are angina, slight fever, malaise lasting but a few days. He designates these cases as “angina scarlatinosa” and “febris scarlatinosa sine exanthemate sive sine scarlatina.” He says “every throat affection during a scarlet fever epidemic is suspicious.”

Leichtenstern (1882) in describing the scarlet fever epidemic in Köln mentions cases of scarlet fever without a rash which later developed severe nephritis.

Waring (1921) gives a report of an epidemic of septic sore throat which occurred in an army hospital. When the epidemic was at its

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height an outbreak of scarlet fever suddenly appeared in the hospital. There was not a single case of scarlet fever within a radius of one hundred miles. Ward A 2 stood at the head of the list of wards in the number of cases of septic sore throat and also of cases of scarlet fever. An effort was made to discharge patients with septic sore throat due to hemolytic streptococci when the throats were free from these organisms. The scarlet fever outbreak then subsided.

During the last few years a number of writers have cultivated from from the throats of persons without scarlet fever streptococci having the same characteristics as those of *Streptococcus scarlatinae*. Bliss (1920) found that three of seventeen strains of *Streptococcus hemolyticus* of non-scarlatinal origin were specifically agglutinated by antiserums prepared by immunizing animals with scarlatinal streptococci. He points out that all three strains were obtained from persons who had been in contact with scarlet fever.

Williams (1925) found that two strains from sources other than scarlet fever fell in the group of scarlatinal strains. One was from a wound and the other from a case of endocarditis. Two other strains, one from a case osteomyelitis and one from a case of bronchitis produced toxic filtrates neutralizable by convalescent scarlet fever serum. She also found that of fifty-six excised tonsils fourteen contained hemolytic streptococci, six of which produced toxic filtrates neutralized by convalescent scarlet fever serum.

Stevens (1926a, b) quotes the history of six cases of acute throat infections caused by *Streptococcus scarlatinae*. All these cases had been in contact with scarlet fever and they were apparently the source of infection for other cases of scarlet fever.

Rosenow (1926) reported five cases of scarlatinal infection, with positive precipitin reaction but with no rash. Two of the cases had previously had scarlet fever. In all five cases the Dick test was negative.

Stevens and Dochez (1926) found that five of seventeen strains of *Streptococcus hemolyticus* which they obtained from cases of acute pharyngitis during an epidemic of scarlet fever and angina, showed the agglutination and the toxin producing properties of *Streptococcus scarlatinae*. They also found that these cases of pharyngitis occurred in individuals with a negative Dick reaction. They point out that

the Dick test is not a reliable index of immunity to throat infections with *Streptococcus scarlatinae*.

The earlier clinical observations cited above suggest the probability that infections with *Streptococcus scarlatinae* may occur not infrequently without the infected person developing those signs and symptoms upon which the clinical diagnosis of scarlet fever depends. The more recent bacteriological studies, especially those of Bliss, Stevens, and Stevens and Dochez, demonstrate that these infections actually do occur. It has become, therefore, a matter of considerable epidemiological importance to determine the frequency of occurrence of pyogenic infections with *Streptococcus scarlatinae* in individuals without scarlet fever. It is equally important for the elucidation of the pathology and immunology of infections with *Streptococcus scarlatinae* to discover, if possible, under what circumstances scarlatinal streptococcus infection may occur without the infection causing the specific clinical features of scarlet fever.

The present study was, undertaken therefore, in order to determine (1) how frequently pyogenic infections with *Streptococcus scarlatinae* occur without the characteristic rash of scarlet fever accompanying the infection; (2) whether there is any relation between the occurrence of these infections and known exposure to cases of scarlet fever; (3) whether the persons so infected are protected against the development of the specific toxic phase of scarlet fever by already possessing an antitoxic immunity; and (4) whether the possession of an antitoxic immunity to scarlet fever also provides an immunity to pyogenic tissue infections with *Streptococcus scarlatinae*.

SOURCE OF MATERIAL

Twenty-one strains of *Streptococcus hemolyticus* were obtained in cultures from twenty-one patients suffering from various acute infections. The cases were not chosen from a selected group. All cultures coming to the laboratory which showed *Streptococcus hemolyticus*, and were not from scarlet fever patients, were studied. The majority of the strains were isolated from throat cultures from patients with tonsillitis, pharyngitis or sinusitis. There were four exceptions—one was obtained from the sputum from a case of pneumonia, one from the blood from a case of septicemia, one from a pleural exudate and the fourth from a discharging ear.

METHODS

The method used for the identification of *Streptococcus scarlatinae* was that described by Dick and Dick (1925) with some necessary modifications. The organisms were isolated in pure culture on blood agar plates and a tube of broth containing 1 per cent of defibrinated rabbit's blood was inoculated from a single colony. The blood broth culture was incubated for four days. It was then filtered through a Berkefeld filter and the sterility of the filtrate was determined. The filtrate was then diluted 1:100, 1:500, and 1:1000 with sterile salt solution. One-tenth of a cubic centimeter of each of these three dilutions was inoculated intracutaneously into the arm of an individual having a positive Dick test. The tests were read twenty-four hours after injection. A resulting area of erythema was tentatively considered to indicate that toxin was present in the filtrate. A positive reaction having a diameter of approximately one centimeter was recorded as a + reaction, between one and two centimeters as a ++ reaction, and over two centimeters as a +++ reaction. Faint reactions under one centimeter were recorded as a ± reaction of doubtful significance. One-tenth of a cubic centimeter of the dilution giving a ++ reaction was selected as a suitable skin test dose for subsequent tests. These consisted of control tests in Dick negative individuals and neutralization tests with blanching and non-blanching human serums.

Neutralization tests were performed as follows: a dilution of the filtrate as made up so that 0.5 cc. contained 10 skin test doses of toxin. This was mixed with equal part of blanching and non-blanching human serums, five blanching and five non-blanching serums being used with each filtrate. A control of the activity of the filtrate was made by mixing 0.5 cc. of the same dilution of filtrate with an equal part of sterile saline. All tubes were incubated for one hour at 37°C. One-tenth of a cubic centimeter of each mixture was then inoculated intracutaneously into the arm of an individual having a positive Dick test. Neutralization of the toxic action by the blanching serums, provided the non-blanching serums failed to neutralize, was considered satisfactory evidence that the strain of hemolytic streptococcus from which the filtrate was prepared was *Streptococcus scarlatinae*.

EXPERIMENTAL

Experiment 1. Diluted filtrates from twenty-one strains of *Streptococcus hemolyticus* were injected intracutaneously in a subject susceptible to scarlatinal toxin as previously determined by a Dick

TABLE 1
Determination of the presence of soluble toxin in the filtrates from 21 cultures of Streptococcus hemolyticus

Filtrate number	Skin reactions in Dick positive subjects			Reactions to 1 skin test dose of filtrates	
	Dilution of filtrate			Dick-positive subject	Dick-negative subject
	1:100	1:500	1:1000		
1	++	+	±	+*	-
2	++	+	±	+	-
3	++	++	+	+	-
4	+++	++	+	+	-
5	++	+	±	+	-
6		+++	++	+	-
7	+++	++	+	+	-
8	+++	++	+	+	-
9	++	+	±	+	-
10		+++	++	+	-
11	++	+	±	+	-
12	++	+	±	+	-
13	+++	++	+	+	-
14	++	+	+	+	-
15	+++	++	+	+	-
16	++	±	-	+	-
17	++	+	±	+	-
18	++	+	±	+	-
19	++	±	-	+	-
20	++	+	±	+	-
21	++	+	±	+	-

+++ = local erythema more than 2 cm. in diameter. ++ = local erythema between 1 and 2 cm. in diameter. + = local erythema approximately 1 cm. in diameter. ± = faint reaction less than 1 cm. in all diameters. - = no reaction. Readings were made 24 hours after injection.

* In this column all positive reactions are indicated by +.

test. The volume of the inoculum was 0.1 cc. The dilution used and the results obtained are shown in table 1.

It will be seen from table 1 that all filtrates contained a toxic substance which induced a local erythema. The strength of the filtrates

varied considerably. Only two gave ++ reaction with the 1:1000 dilution, six more gave a ++ reaction at a dilution of 1:500, the remaining thirteen gave ++ reactions only with the 1:100 dilution. One-tenth cubic centimeter of the highest dilution giving a ++ reaction was employed as a skin test dose in subsequent experiments.

Experiment 2. One skin test dose of each filtrate was injected intracutaneously in Dick positive and Dick negative subjects. All the filtrates gave positive reactions in the Dick positive subjects, negative reactions in the Dick negative subjects (table 1).

From the result of the foregoing experiment it appears that the soluble toxic substance present in all the filtrates, though it causes a local erythema in the skin of individuals who give a positive Dick test, nevertheless fails to do so in persons who give a negative Dick test, when one skin test dose of the filtrate as defined above is employed. While this might seem to indicate that the strains of streptococci from which the filtrates were prepared were *Streptococcus scarlatinae*, neutralization, tests described below will show that such a conclusion is not warranted.

Experiment 3. Each of the twenty-one filtrates was subjected to a neutralization test with known blanching and non-blanching human serums according to the method described above. The results are shown in table 2, the filtrates being grouped according to the results of the neutralization tests.

It will be seen from table 2 that the toxic action of filtrates 1 to 10 was completely neutralized by the blanching serums with a few exceptions in the case of serums IV and V, but that it was not neutralized in any instance by the non-blanching serums. In contrast with this there was no neutralization of filtrates 11 to 21 by either the blanching or non-blanching serums. The failure of complete neutralization by serums IV and V was suspected to be due to a low antitoxin content of these serums. They were consequently tested for their capacity to neutralize standard scarlet fever toxin. Five-tenths of a cubic centimeter failed to neutralize completely ten skin test doses, indicating that the foregoing supposition was correct.

It may be concluded from this experiment that 10 of the 21 strains of *Streptococcus hemolyticus* studied produced toxic filtrates capable of being specifically neutralized by scarlet fever antitoxin. These

ten strains are, therefore, considered to be strains of *Streptococcus scarlatinae*.

As noted above it was found that the filtrates from all strains of *Streptococcus hemolyticus*, whether *Streptococcus scarlatinae* or not,

TABLE 2

Neutralization tests with blanching serum containing scarlet fever antitoxin and non-blanching serum containing no antitoxin

Filtrates	Skin reactions										Filtrates plus 0.85 per cent saline
	Filtrates plus blanching serums					Filtrates plus non-blanching serums					
	I	II	III	IV	V	I	II	III	IV	V	
1	-	-	-	-	-	+	+	+	+	+	+
2	-	-	-	-	±	+	+	+	+	+	+
3	-	-	-	-	±	+	+	+	+	+	+
4	-	-	-	-	0	+	+	+	+	+	+
5	-	-	-	-	±	+	+	+	+	+	+
6	-	-	-	-	-	+	+	+	+	+	+
7	-	-	-	+	0	+	+	+	+	+	+
8	-	-	-	+	0	+	+	+	+	+	+
9	-	-	-	+	0	+	+	+	+	+	+
10	-	-	-	-	-	+	+	+	+	+	+
11	+	+	+	+	+	+	+	+	+	+	+
12	+	+	+	+	+	+	+	+	+	+	+
13	+	+	+	+	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+	+	+	+	+
15	+	+	+	+	+	+	+	+	+	+	+
16	+	+	+	+	+	+	+	+	+	+	+
17	+	+	+	+	+	+	+	+	+	+	+
18	+	+	+	+	+	+	+	+	+	+	+
19	+	+	+	+	+	+	+	+	+	+	+
20	+	+	+	+	0	+	+	+	+	0	+
21	+	+	+	+	0	+	+	+	+	0	+

- = no reaction, complete neutralization. ± = slight reaction, partial neutralization. + = positive reaction, no neutralization. 0 = test not done.

gave a positive reaction when one skin test dose was inoculated intracutaneously in individuals with a positive Dick test but no reaction in individuals with a negative Dick test. In view of this result it would seem probable that persons possessing an immunity to

scarlatinal toxin have some immunity to toxins derived from non-scarlatinal strains of *Streptococcus hemolyticus*, or at least have a lower degree of skin reactivity to these toxins than have persons who are susceptible to scarlatinal toxin. In order to test out this assumption the following experiment was done.

Experiment 4. Eight non-scarlatinal filtrates from cases 11 to 18 were injected in amounts of one, two and five skin test doses in test subject M, who gave a negative reaction to five skin test doses of

TABLE 3
Skin reactivity of Dick negative persons to culture filtrates of non-scarlatinal hemolytic streptococci

Filtrate number	Toxin tests				Neutralization test	
	Skin reactions				Skin reactions in Dick-positive subject	
	In Dick-positive subject 1 S.T.D.*	In Dick-negative subject M			Filtrate and blanching serum from subject M	Filtrate and non-blanching serum
		1 S.T.D.	2 S.T.D.	5 S.T.D.		
11	+	-	±	+	+	+
12	+	-	-	-	+	+
13	+	-	+	+	+	+
14	+	-	-	+	+	+
15	+	-	-	+	±	+
16	+	-	-	+	+	+
17	+	-	+	+	+	+
18	+	-	-	+	±	+
Control with scarlet fever toxin.....	+	-	-	-	-	+

* Skin test dose. + = positive reaction 1 cm. or more in diameter. ± = faint reaction less than 1 cm. in diameter. - = no reaction.

standard scarlet fever toxin. The blanching serum from this same subject was used for neutralization tests with these eight filtrates, together with a control non-blanching serum. The results are presented in table 3. This experiment was repeated with some of the filtrates in two other Dick negative subjects with the same result.

From the table it will be seen that 3 of the 8 non-scarlatinal filtrates gave positive reactions in test subject M when two skin test doses were used, 7 of the 8 when five skin test doses were used. It

is furthermore clear from the neutralization tests that the serum from test subject M, though containing a considerable amount of scarlatinal antitoxin, failed to neutralize the toxic action of the non-scarlatinal filtrates. From this result it may be concluded that at least some individuals who are immune to scarlatinal toxin as determined by the Dick test, exhibit less skin reactivity to the toxic filtrates from non-scarlatinal hemolytic streptococci than do individuals who are susceptible to scarlatinal toxin. The result, furthermore, emphasizes the necessity for a neutralization test before it can be concluded that a toxin producing strain of hemolytic streptococcus is *Streptococcus scarlatinae*.

DISCUSSION

In table 4 are summarized the results of the foregoing experiments together with the data concerning the patients from whom the twenty-one strains of hemolytic streptococci were obtained. The cases are arranged in two groups, group 1 (cases 1 to 10) consisting of those patients in whom it had been found that the infection was due to *Streptococcus scarlatinae*, group 2 (cases 11 to 21) consisting of those patients in whom the infection was due to some other variety of hemolytic streptococcus.

That ten of twenty-one unselected cases of acute streptococcus infection should prove to be infected with *Streptococcus scarlatinae* without any one of these patients developing clinical scarlet fever might seem surprising. It is believed, however, that the explanation for this is found in the data concerning contact with scarlet fever and susceptibility to scarlatinal toxin as determined by the Dick test. It will be seen by reference to Table 4 that nine of these ten patients had a history of direct and fairly intimate contact with scarlet fever. Cases 3 and 10 had children with scarlet fever. Case 5 was nursing two children with scarlet fever. Case 7 had slept with a relative who developed scarlet fever. Case 6 was an interne who developed a severe sore throat one week after serving on a scarlet fever ward. The remaining cases were nurses who had been caring for patients with scarlet fever. In striking contrast with this is the fact that only one of the patients in group 2 had had any known contact with scarlet fever. The source of infection in the patients of group 1, then,

would appear to be satisfactorily explained by their direct exposure to scarlet fever.

In explanation of the fact that none of these ten patients developed clinical scarlet fever, it is to be noted that nine of them, in whom the

TABLE 4
Occurrence of scarlatinal and non-scarlatinal streptococcus infections in persons without clinical scarlet fever

Case	Data on patients			Data on streptococci isolated from patients			
	Clinical diagnosis	Contact with scarlet fever	Dick test	Test for toxin production		Neutralization of toxin by	
				Dick-positive subject	Dick-negative subject	Blanching serum	Non-blanching serum
1	Peritonsillar abscess	+	-	+	-	-*	+*
2	Tonsillitis	+	-	+	-	-	+
3	Pharyngitis	+	0	+	-	-	+
4	Pharyngitis	?	-	+	-	-	+
5	Tonsillitis	+	-	+	-	-	+
6	Tonsillitis	+	-	+	-	-	+
7	Pharyngitis	+	-	+	-	-	+
8	Tonsillitis	+	-	+	-	-	+
9	Tonsillitis	+	-	+	-	-	+
10	Bronchopneumonia	+	-	+	-	-	+
11	Tonsillitis	-	-	+	-	+	+
12	Septicemia	+	0	+	-	+	+
13	Pharyngitis	-	-	+	-	+	+
14	Sinusitis	-	-	+	-	+	+
15	Tonsillitis	-	-	+	-	+	+
16	Tonsillitis	-	0	+	-	+	+
17	Pharyngitis	-	-	+	-	+	+
18	Pharyngitis	-	-	+	-	+	+
19	Pleurisy	-	-	+	-	+	+
20	Otitis media	-	-	+	-	+	+
21	Pharyngitis	-	0	+	-	+	+

* - = no reaction, complete neutralization. + = positive reaction, no neutralization. 0 = test not done.

Dick test was done either before or shortly after the onset of their infection, showed a negative test indicative of an existing immunity to scarlet fever toxin. It seems reasonable to suppose, therefore, that the failure of these patients to develop the clinical picture of

scarlet fever was due to this existing antitoxic immunity. The toxin elaborated at the site of the local tissue infection in the throat or elsewhere would presumably be neutralized locally by the patient's antitoxin. Under these circumstances the specific toxic phase of scarlet fever, which is clinically represented by the early toxemia and the exanthem, would not occur.

Of great interest in relation to the problems of immunity to infection in general and to scarlet fever in particular is the apparent fact that an existing immunity to the soluble toxin of *Streptococcus scarlatinae* does not necessarily prevent the development of even severe local pyogenic infections with this organism in persons in intimate contact with scarlet fever. The epidemiologic and public health problems arising from this fact are obvious and need not be discussed in detail. In brief, it would appear highly probable that the frequency of pyogenic infections by *Streptococcus scarlatinae* is greater than generally supposed, that persons so infected may serve as foci for the spread of scarlet fever, and that a negative Dick test is little or no indication that a person exposed to scarlet fever is not liable to serious pyogenic infections with *Streptococcus scarlatinae*.

SUMMARY

Of 21 strains of *Streptococcus hemolyticus* isolated from 21 unselected patients with acute streptococcus infections, 10 were found to be *Streptococcus scarlatinae*. Of the 10 patients in whom the infection was due to *Streptococcus scarlatinae* 5 had acute follicular tonsillitis, 3 had acute pharyngitis, 1 had peritonsillar abscess, and 1 had bronchopneumonia. None developed clinical scarlet fever. Nine of these patients had been intimately exposed to scarlet fever. No information on this point was obtained in the tenth. Nine of them gave a negative Dick test either before or shortly after the onset of the infection. No test was made in the tenth. Of the 11 patients with acute hemolytic streptococcus infections due to non-scarlatinal streptococci only one had knowledge of exposure to scarlet fever. None developed scarlet fever. Eight in whom the test was done gave a negative Dick test.

CONCLUSIONS

1. *Streptococcus scarlatinae* infections without clinical scarlet fever occur with considerable frequency among persons exposed to scarlet fever.

2. The failure of persons infected with *Streptococcus scarlatinae* to develop clinical scarlet fever is probably dependent upon the possession of immunity to scarlet fever toxin prior to the onset of the infection.

3. Immunity to the toxin of *Streptococcus scarlatinae* as determined by the Dick test, does not necessarily provide the immunity to local pyogenic infections with *Streptococcus scarlatinae*.

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