STUDIES IN SCARLET FEVER

II. The Relation of the Specific Toxemia of Scarlet Fever to the Course of the Disease[1]

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INTRODUCTION

It has been shown in previous papers that a specific toxin is present in the blood of patients with scarlet fever during the early acute stage of the disease (1) and that the amount of toxin present varies within wide limits in different patients (2). The present communication deals with a further study of the specific toxemia of scarlet fever made in an effort to correlate the degree and course of the toxemia with the clinical course of the disease. It is based on the data obtained from the study of 132 of the 254 cases of scarlet fever admitted to the Medical and Pediatric Services of the New Haven Hospital from January, 1924, to June, 1925.

The conception of a disease formed on the basis of the compilation of single observations on many cases is less satisfactory than one resulting from the more detailed study of selected cases. However, this latter method was not open to us because all the patients more than moderately sick, and almost all those seen early in the disease were treated with scarlet fever antitoxin. Since efficient treatment promptly neutralizes the toxin in the blood (3) (4) (5), there was available for the study of the toxin in the great majority of the cases, only the blood taken immediately before treatment. In all, one hundred and forty-three serum samples were obtained from one hundred and thirty-two patients. From four untreated cases there were repeated bleedings and from three cases repeated bleedings

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before treatment. The presence or absence of demonstrable scarlet fever toxin in the blood samples was determined and the amount of toxin present was roughly estimated. These observations were then analyzed with reference to the day of the disease on which the sample was obtained, the estimated clinical severity of the case, the presence of rash, and finally the presence of septic complications. Thus a composite picture was constructed, based, for the most part, on single observations in as many patients as could be studied.

EXPERIMENTAL

Methods. The serum from the blood samples was stored in the ice-chest without preservative. The toxin in the serum was demonstrated by injecting 0.3 cc. intracutaneously into known susceptible and non-susceptible human volunteers, in whose blood the presence or absence of scarlet fever antitoxin had previously been determined. The usual site of inoculation was the flexor surface of the upper and fore arms. Readings were taken at twenty-four-hour intervals. The test was considered negative if there was no definite local erythema noted in the susceptible volunteer. The test was considered positive when there was in the susceptible volunteer a local erythema 1.5 cm. or more in any diameter, at twenty-four hours. The positive reactions varied considerably in size and intensity and consequently were divided arbitrarily into +, ++ and +++ reactions as follows: + reactions indicate a moderate erythema at twenty-four hours, 1.5 to 3.5 cm. in diameter, which was frequently followed by slight pigmentation; ++ reactions consisted of a marked erythema 3.5 to 5.0 cm. in diameter which generally persisted two to three days, was associated with slight induration and tenderness, and was followed by moderate pigmentation and occasionally slight desquamation; +++ reactions indicate an intense erythema 5.0 to 9.0 cm. in diameter, of three to four days duration, moderate induration and tenderness, followed by pigmentation and desquamation.[2]

[2] With the serums causing a +++ reaction, the non-susceptible volunteers frequently gave a + reaction. In all other cases the non-susceptible controls remained negative. It was noted that among the susceptible volunteers there was considerable variation in reaction, but that this variation followed a regular order in that those who gave the strongest reaction to any sample, also reacted most to

Scarlet fever antitoxin was demonstrated by means of the Schultz-Charlton phenomenon (6). Of the serum to be tested 0.5 cc. was inoculated intracutaneously in a scarlet fever patient. A site was chosen where the rash was bright red and diffuse. Readings were taken eighteen hours after inoculation and at twenty-four hour intervals thereafter. If definite local blanching of the rash was noted at any reading the test was considered to show the presence of scarlet fever antitoxin. If no blanching was seen at any time and there were satisfactory positive controls the test was considered negative. The test for antitoxin was made with sera from all the human volunteer test subjects, with samples of serum from all the late cases, and with sera from many of the early cases of scarlet fever. All the tests, whether for toxin or antitoxin, were made on samples of serum taken before the administration of scarlet fever antitoxin for therapeutic purposes.

An estimate of the clinical severity of the disease was made for each patient and recorded as in one of four groups; extreme, severe, moderate, and mild. The extreme group comprised those patients in whom the immediate prognosis as to recovery was doubtful. They all showed the appearance of profound intoxication, and also suffered from some more or less severe septic process. In the severe group were placed those who appeared very sick and usually suffered from some septic process, generally less severe than the septic process occurring in the former group. The moderate cases appeared moderately sick. Septic processes were generally less frequent and less severe than in the preceding groups. The mild cases varied from those showing scarcely any evidence of disease except fever, sore throat and rash to those who seemed less than moderately sick. In some of the cases of this group, however, considerable purulent rhinopharyngitis was present. The fever corresponded roughly to the estimated

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all samples, and frequently gave + reactions with serums to which the less reactive remained negative. At least one highly susceptible person was used in each test, and it was the reaction of this individual which determined the final reading for the specimen. Certain serums in either or both the test and control volunteers gave an immediate wheal and erythema reaction similar to the allergic skin reactions seen in hay fever and asthma. This reaction had no relation to the presence of scarlet fever toxin.

clinical severity. The rash was studied and recorded as bright, fading or faded, or absent. A special note was made in each instance as to the presence and character of septic processes or complications. The first day of the disease was considered as that on which the initial symptoms of the onset appeared. The days were reckoned

TABLE 1

Incidence and degree of specific toxemia in 121 cases of scarlet fever with rash present

Clinical severity	Cutaneous reaction of susceptible volunteers to toxin in blood of patients	Day of disease								Totals		
		1	2	3	4	5	6	7	8	In groups	Positive	Negative
Extreme	+++			2				1		3	11	
	++		3		1		1	1		6		
	+		1						1	2		
	−					1				1		1
Severe	+++		1	1		1				3	20	
	++		4	3	2					9		
	+		2	2	3	1				8		
	−	1		2						3		3
Moderate	+++									0	31	
	++		1	4	3	1	1	1		11		
	+		9	4	2	3	1	1		20		
	−	2	3	2						7		7
Mild	+++			1		1				2	28	
	++		3	1		2	1			7		
	+	1	3	9	5	1				19		
	−	4	6	11	7	3				31		31
Totals	+++		1	4		2		1		8	90	
	++		11	8	6	3	3	2		33		
	+	1	15	15	10	5	1	1	1	49		
	−	7	9	15	7	4				42		42
Per cent positive		13	75	64	70	77	100	100	100			

as periods of twenty-four hours from hour of onset in all those patients admitted up to the fifth day. For those admitted on the fifth day or later, time was reckoned as calendar days.

Results. In table 1 are listed the results of tests for toxin in 132 samples of blood serum from 121 scarlet fever patients. These

represent all the samples collected from patients who still seemed sick up to the ninth day of the disease, and in whom the rash was still present. The cases are grouped according to the day of disease on which the sample of blood was obtained and according to the estimated clinical severity. The toxin is recorded as not demonstrable (−) or, if demonstrable, as +, ++, or +++, depending upon the size, intensity, and duration of the cutaneous reaction of the sus-

TABLE 2

Eleven cases of scarlet fever with fading or faded rash

Case	Clinical severity	Rash	Complications	Blood			
				Day	Toxin*	Antitoxin	Culture
P. H.	Moderate	Fading	Jaundice. Septic tonsillitis	7	+	−	−
F. S.	Mild	Fading	Cervical adenitis	7	+	−	−
S. S.	Mild	Faded	Cervical adenitis	8	+	−	−
C. S.	Severe	Faded	Otitis media. Mastoiditis. Cervical adenitis	9	+	−	−
A. S.	Mild	Faded	Purulent rhinitis. Cervical adenitis	10	+	−	−
M. N.	Severe	Faded	Purulent rhinitis. Otitis media. Cervical adenitis	13	+	−	−
E. D.	Extreme	Faded	Septicemia. Purulent arthritis	14	−	+	+†
G. G.	Extreme	Faded	Otitis media. Broncho pneumonia	14	−	+	−
R. H.	Mild	Faded	Seventeenth day cervical adenitis	19	−	+	0
H.	Mild	Faded	Nineteenth day cervical adenitis	21	−	−	0
V. H.	Mild	Faded	Twentieth day cervical adenitis	21	−	−	0

* No reaction for toxin in this group was stronger than +.

† Pure culture *Streptococcus hemolyticus.*

ceptible volunteer. The numbers in the columns represent the total numbers of samples in each group.

In table 2 are shown all cases studied in whom the rash was fading or had faded and who still seemed sick. In these the presence of septic complications is noted. The results of the tests for the presence of toxin and antitoxin in the serum samples is recorded, and also the results of blood cultures when these were made.

Analysis of the data in table 1 shows that there is a striking increase

in the incidence of demonstrable specific toxemia during the first two days of the disease, then a slight decrease on the third day, which is followed by a gradual increase to reach 100 per cent on the sixth day. The cases on the first and second days represent a relatively homogeneous group of patients who for the most part had not as yet reached the peak of the disease. Those of later days represent a less homogeneous group of patients, some of whom had begun to recover, some of whom were stationary and some of whom were becoming sicker. It seems probable, therefore, that the decreased incidence of the third and fourth days is due to the inclusion in the group of some patients who were beginning to recover and in whom the specific toxemia was abating.

The high incidence on the later days of the first week does not mean that the course of the specific toxemia is usually so extended, but is undoubtedly due to the fact that only those who were still sick were included in the study. That this is so is illustrated by the course of the toxemia in N. G., a moderate case of scarlet fever without complications, in whom the temperature reached normal on the sixth day. Repeated bleedings were made with the following results: Second day +, third day ++, fifth day +, sixth day −.

The duration of the specific toxemia in patients remaining sick after the first week has been studied in only ten cases, nine of which are shown in table 2, the tenth being included in table 1 because the rash was still present. From so small a number it is wise merely to say that the latest record of demonstrable specific toxemia was on the thirteenth day and that the earliest record of the natural appearance of demonstrable antitoxin in cases that remained sick was the fourteenth day. In the cases in which the rash was still present the relation of the degree of clinical severity to the incidence of demonstrable toxemia and to the amount of toxin in the blood was close. This is shown in the last column of table 1. This relation did not hold in the cases in which the rash was fading or had faded, as is shown in table 2. In none of these cases did the test for toxin show a stronger reaction than +, while in the two extreme cases there was no toxin at all.

RELATION OF SPECIFIC TOXEMIA TO SEPSIS

In the data presented above all the cases have been grouped primarily as to whether they were in the exanthematous or post-exanthematous stage, secondarily according to the day of the disease and total clinical severity, irrespective of the presence or absence of septic complications. Since it is well recognized that as the disease progresses septic processes play an increasingly important rôle as regards the total clinical severity, it has seemed desirable to study the relation of sepsis to the incidence and degree of specific toxemia.

Sepsis is used here to mean the local or distant invasion of the tissues of the host by *Streptococcus scarlatinae.* In the cases studied the majority of the septic complications were apparently due to the direct spread of the primary infection to the mucous membrane of adjacent structures, such as nose, sinuses and pharynx. Not infrequently the infection extended to the middle ear, less frequently to the mastoid cells, and in one case to the meninges. There was also in some cases invasion of the deeper tissues and lymph nodes. In these places suppuration occasionally followed. There was one case of postpartum scarlet fever with parametritis and general peritonitis. The presence of a positive blood culture was an uncommon finding, occurring in but one of the fifty-two cases in which blood cultures were taken. It is recorded under case E. D., table 2. The most frequent single complication observed was a purulent rhinopharyngitis. The mere presence of a slight amount of exudate on the tonsils was not considered as evidence of invasion of the body tissues. When there was definite ulceration of the tonsils, however, the case was included in the septic group.

Based on ordinary clinical examination an attempt was made to evaluate the importance of any septic process which was present at the time the blood samples were obtained. The presence of one or more of the following conditions was considered to constitute an extreme degree of sepsis and classified as +++ sepsis; septicemia, septic arthritis, meningitis, acute purulent mastoiditis, ulcerative stomatitis, suppurative cervical adenitis, and parametritis. The presence of one or more of the following conditions was considered to constitute a moderate degree of sepsis and was classified as ++

sepsis: severe purulent rhinopharyngitis with or without sinusitis, purulent otitis media, ulcerative tonsillitis, severe non-suppurative cervical adenitis and peri-tonsillar abscess. The presence of one or more of the following was considered to constitute a mild degree of sepsis and was classified as + sepsis: moderate or mild purulent rhinopharyngitis, with or without sinusitis, and moderate non-

TABLE 3

Specific toxemia of scarlet fever in respect to degree of sepsis and day of disease in 121 cases with rash present

Degree of sepsis	Cutaneous reaction of susceptible volunteers to toxin in blood of patients	Day of disease								Totals		
		1	2	3	4	5	6	7	8	In groups	Positive	Negative
+++	+++			1				1		2	3	
	++						1			1		
	+									0		
	−									0		0
++	+++		1	2		1				4	22	
	++		5	2	2		1	1		11		
	+		1	1	2	1		1	1	7		
	−					1				1		1
+	+++			1		1				2	33	
	++		2	2	4	2	1			11		
	+		6	5	6	2	1			20		
	−	2	5	4	3					14		14
−	+++									0	32	
	++		4	4		1		1		10		
	+	1	8	9	2	2				22		
	−	5	4	11	4	3				27		27

suppurative cervical adenitis. Such a scheme is subject to much error but was as satisfactory as the conditions permitted, and was probably not any more inaccurate than the method used to judge the degree of specific toxemia.

The relations between the septic and toxic factors in the disease are presented in table 3 and figure 1.

Table 3 records observations on the same group of cases as those

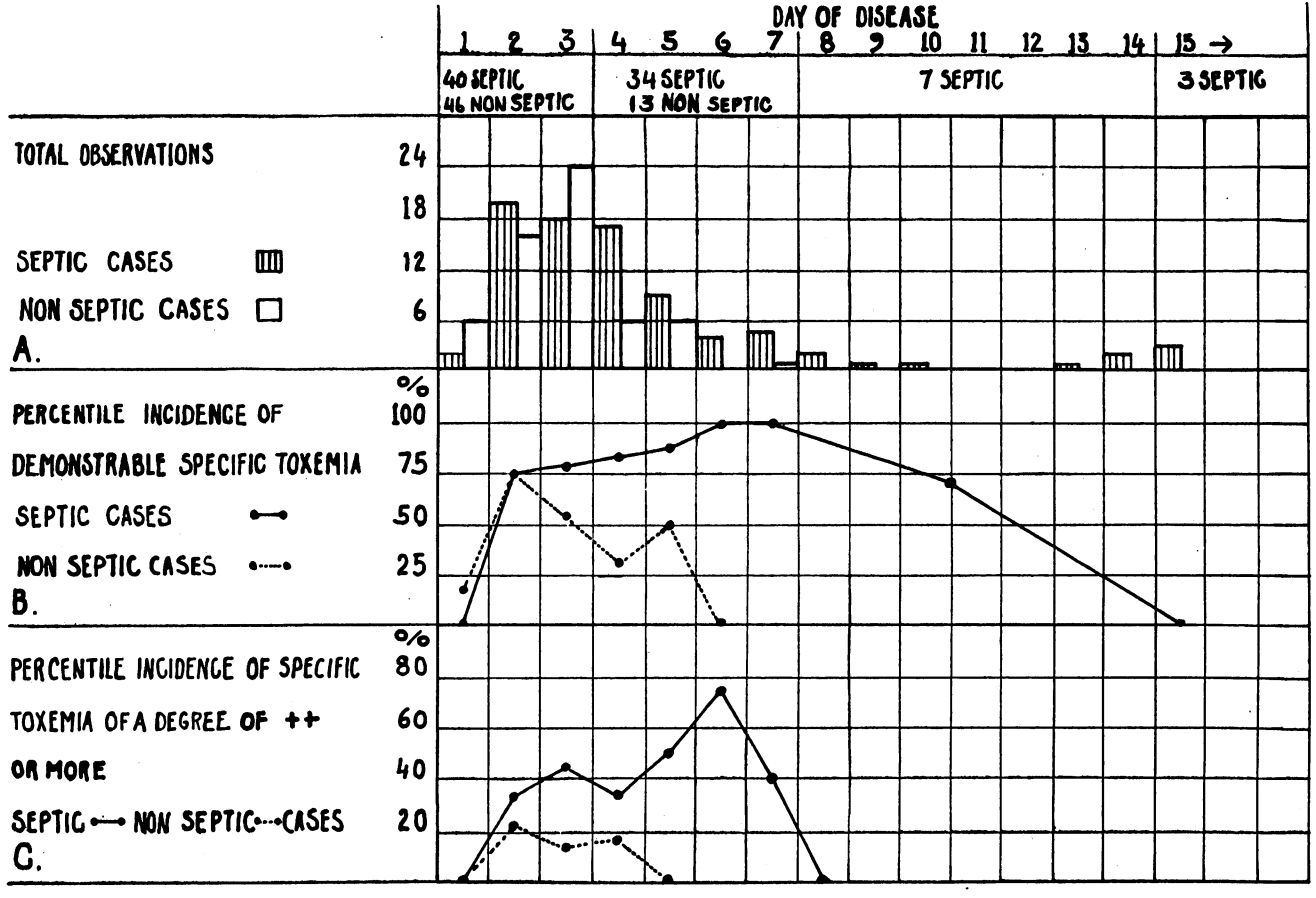
DAY OF DISEASE
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 →
40 SEPTIC 46 NON SEPTIC
34 SEPTIC 13 NON SEPTIC
7 SEPTIC
3 SEPTIC
TOTAL OBSERVATIONS
24
18
SEPTIC CASES
12
NON SEPTIC CASES
6
A.
%
PERCENTILE INCIDENCE OF
100
DEMONSTRABLE SPECIFIC TOXEMIA
75
SEPTIC CASES
50
NON SEPTIC CASES
25
B.
%
PERCENTILE INCIDENCE OF SPECIFIC
80
TOXEMIA OF A DEGREE OF ++
60
OR MORE
40
SEPTIC NON SEPTIC CASES
20
C.

FIG. 1

in table 1, i.e., all cases in which the rash was still present at the time the blood was collected for the determination of the presence of toxin.

Comparison of the columns of totals on the right side of tables 1 and 3 shows that while the incidence and degree of specific toxemia agree quite closely both with the estimation of total clinical severity and with the severity of the sepsis, the degree of specific toxemia agrees more closely with the estimated severity of sepsis than with the estimated total clinical severity. That this relationship does not hold after the rash has faded or, in terms of duration, after the first week of the disease, has already been pointed out in connection with the group of cases shown in table 2.

The relationship throughout the course of the disease, irrespective of the presence or absence of the rash is shown graphically in figure 1 in which all cases in the study are included.

In figure 1 (a) it will be seen that the ratio of septic to non-septic cases increases rapidly after the third day of the disease among patients who remain sick. In this particular group of patients the ratio was 40:46 for the first three days, 34:13 for the fourth to seventh days, and 10:0 after the first week. All the cases in the first week, with two exceptions on the seventh day, had a bright rash. In all cases after the first week, with one exception on the eighth day, the rash had faded.

From figure 1 (b) it will be seen that the percentile incidence of demonstrable specific toxemia rises abruptly to 75 per cent on the second day of the disease in both the septic and non-septic groups but that after this point there is a marked divergence. The incidence for the septic group continues upward gradually to reach 100 per cent on the sixth day, and maintains the level to the thirteenth day. On the fourteenth day it falls abruptly to zero. This is not shown by the chart, however, since, as there were but seven cases in the second week, they were all grouped together and plotted on one point at the middle of this period. The incidence for the non-septic group falls after the second day and reaches zero on the sixth day. On the seventh day occurred the last non-septic case and in this instance specific toxemia was demonstrated. But this case has been omitted in plotting the curve as it would give an undue weight to a single exceptional finding.

This apparent exception emphasizes the fact that the relations between the various features of the disease depend on more variable factors than have been considered. In this case it was impossible to fix the date of onset accurately as the onset was gradual during the course of common head cold. If the date of onset was reckoned as early as possible the serum was obtained on the seventh day. However this would put the appearance of the rash on the fourth day, which is two days later than usual. Therefore it seems likely that onset was dated too early.

It is desirable to know the changes in the degree of specific toxemia during the disease. If table 1 is analyzed for the incidence of+++ reactions, and if the cases are taken in periods of two days to obtain larger groups one finds the per cent of cases showing +++ reactions to be as follows: for the first and second day 2; for the third and fourth 6; for the fifth and sixth 11; and for the seventh and eighth 20. After this time no reactions stronger than + were found.

To establish a curve for degree of toxemia on the basis of more cases, and to correlate this with the presence or absence of septic complications, figure 1 (c) was constructed. This shows the percentile incidence, for each day, of cases with a ++ or +++ specific toxemia in the septic and non-septic groups. The non-septic case on the seventh day which was omitted from figure 1 (b) had a ++ reaction and is also omitted from figure 1 (c) for the reason given above. The difference between the two groups is obvious. The specific toxemia is greater throughout in the septic cases. The peak for the non-septic cases is on the second day, but for the septic cases is on the sixth day. The figure also shows that the rather high incidence for the septic group during the second week is associated with a low degree of specific toxemia. This emphasizes that only while the rash is present does the intensity of the toxemia vary with the incidence of septic complications.

DISCUSSION

This study has been concerned with the most common types of scarlet fever, namely, those of various grades of clinical severity, with and without septic complications. In an attempt to relate the demonstrable specific toxemia to the clinical features of the dis-

ease a composite picture has been constructed from all observations. This procedure probably has obscured some information which might be brought to light in a detailed investigation of cases untreated with antitoxin.

Determinations of the presence of scarlet fever toxin in the blood serum of patients and rough estimations of the toxin content have been made and the results have been discussed in relation to certain clinical features of scarlet fever. These features are the duration of the disease, the presence or absence of the rash, the estimated total clinical severity and the presence and apparent severity of septic complications.

The present conception of scarlet fever holds that the characteristics of the disease by which it is differentiated from other hemolytic streptococcus infections depend in large part on the presence of scarlet fever toxin in the blood stream of the patient and its action on the body. Accordingly one would expect that the rash, which is the most striking sign of scarlet fever, would in some way run parallel with the specific toxemia. The results given above suggest that the duration of the specific toxemia is measured by the duration of the rash. In severe septic cases remaining sick into the second week of the disease, the rash is usually pigmented and consequently it is often difficult to decide whether it is fading or faded. In this group the specific toxemia was found to be of low degree. In the later septic cases when the rash was completely faded there was found, even in two extremely sick patients, not only no toxin but an actual excess of autogenous scarlet fever antitoxin.

The data accumulated in this study provide definite indications with respect to the therapeutic use of scarlet fever antitoxin. In the first place it is clear that antitoxin should be administered as early as possible in the disease in order to check the toxemia during its period of increase. In the second place it is obvious that patients with incipient septic processes early in the disease are potentially much sicker than those without septic processes. Consequently these patients should receive more antitoxin, even though they may not appear more severely ill at the moment. In the third place it is evident the largest amounts of antitoxin are required in those cases with severe septic processes in whom the rash is still bright. Finally

it is apparent that in late cases with faded rash little or no benefit may reasonably be expected from antitoxin therapy.

The observations indicate that *Streptococcus scarlatinae* may have at least two quite different methods of attack, and that the defensive mechanisms of the host against these may be dissociated. Variable combinations of these factors result in different clinical pictures of the disease.

SUMMARY AND CONCLUSIONS

1. The specific toxemia of scarlet fever is a self-limited phase of the disease.

2. The duration of the specific toxemia of scarlet fever parallels the duration of the rash.

3. The degree of specific toxemia of scarlet fever, while the rash is present, depends largely on the presence and severity of septic complications.

4. When the rash has faded the specific toxemia of scarlet fever is of low degree or has terminated, even though severe septic complications continue.

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