STUDIES IN SCARLET FEVER

I. The Amount of Scarlatinal Toxin in the Blood of Patients with Scarlet Fever[1]

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INTRODUCTION

In an earlier paper by Trask and Blake (1), it was shown by studies in a small series of cases of scarlet fever, that a specific toxin is sometimes present in the blood during the acute stage of the disease. The presence of the toxin was demonstrated by its capacity to cause a local reaction in the skin of persons in whose serum there was no demonstrable scarlet fever antitoxin. The specificity of the reaction was shown by negative control tests in persons in whose serum scarlet fever antitoxin was present. The amount of toxin present was roughly estimated as +++, ++, + or − as judged by the size, intensity and duration of the local reaction resulting from the intracutaneous injection of 0.3 cc. of patient's serum into susceptible persons. At the time the study was made no standard unit of scarlet fever toxin with which the toxin in the blood might be compared was available.

In 1925 Dick and Dick (2) described a unit for the toxin prepared from culture filtrates of *Streptococcus scarlatinae*. This unit is called a skin test dose and is defined by them as that amount of toxin which will give a positive skin reaction in those individuals who are susceptible to scarlet fever and a negative reaction in those who are not susceptible. An area of reddening, no matter how faint the color may be, that measures one centimeter or more in any diameter twenty-four hours after the intracutaneous injection of 0.1 cc. of toxin constitutes a positive reaction.

[1] This work was done with the aid of the Goodhart Scarlet Fever Fund.

Since immunity and susceptibility to scarlet fever are relative terms it is clear that no fixed amount of toxin will satisfy the definition, even were skin reactivity to the toxin the sole factor in determining susceptibility to scarlet fever. To make the definition more accurate it must be understood that the standard unit will give a barely positive reaction in the least susceptible of the presumably non-immune group, and negative reaction in the least immune of the presumably immune group. However, the skin test dose is at present the unit of toxin in general use and the strength of other toxins may be measured against this standard unit with some degree of accuracy.

It has seemed desirable, therefore, to determine how many units or skin test doses of toxin are present in the circulating blood of patients with scarlet fever in cases of varying degree of severity. This should give more precise knowledge concerning the degree of toxemia that may occur, than was obtained by the crude estimations in the previous study. The number of skin test doses of toxin present per cubic centimeter of serum has therefore been determined in twenty-five cases of scarlet fever and in each case the estimated clinical severity has been compared with the actual amount of toxin found.

EXPERIMENTAL METHODS

Serums from scarlet fever patients which had previously been shown to contain scarlet fever toxin were used. Four of these sera had produced a +++ reaction, ten a ++ reaction, and eleven a + reaction in susceptible test subjects.

The amount of toxin in the blood was determined by finding the smallest amount of serum which would give a positive reaction on intracutaneous injection in highly susceptible individuals. Then, by discovering the reactivity of the same individuals to the standard filtrate toxin, the toxin content of the blood serum could be calculated in terms of skin test dose units.

Serial dilutions of the serums to be titrated were made in 0.9 per cent saline. One-tenth cubic centimeter of each dilution was injected intracutaneously into human volunteers, susceptible and non-susceptible in each case. The former were two individuals, the most

reactive to the toxin among twenty susceptible people found in a study of forty-five people who gave a negative history of scarlet fever. The smallest amount of serum which caused in one or both of these individuals an erythema 1 cm. in any diameter twenty-four hours after injection was taken as the end point of the reaction. These two volunteers were then tested with serial dilutions of a standard filtrate toxin,[2] 1, $\frac{1}{2}$, $\frac{1}{4}$, $\frac{1}{8}$, $\frac{1}{16}$, and $\frac{1}{32}$ skin test doses being employed. It was found that a similar end point was obtained with $\frac{1}{16}$ of a skin test dose of standard filtrates toxin. The number of skin test doses of toxin per cubic centimeter of the serum samples was calculated from this data. Thus if $\frac{1}{320}$ cc. of serum was the smallest volume to give a positive reaction, there were per cubic centimeter 320 reacting doses for this test subject, who reacted similarly to $\frac{1}{16}$ standard skin test dose. Hence in 1 cc. of the sample of blood serum there were 20 skin test doses of toxin.

The errors of this method of comparing the toxin contents of various samples and referring them to standard skin test doses are large and probably range between 100 and 400 per cent. However, the values obtained showed differences of a much greater order.

RESULTS

The results of the titrations are shown in table 1. It will be seen that the amount of toxin in the serum varied greatly in different patients, ranging from $\frac{1}{4}$ of a skin test dose to 330 skin test doses per cubic centimeter.

It is also evident that the degree of toxemia in cases 2, 10, 11, 13, 14, 15, 22, 23, and 25 did not parallel the clinical severity of these cases. That this discrepancy exists is not surprising, since the estimate of clinical severity frequently depends upon a composite of the specific toxic and septic phases of scarlet fever, and at best, can be but a very rough estimate of the degree of the specific toxemia when septic processes are present.

The estimation of the toxin content of the blood samples from the observation of the extent of the local reaction to 0.3 cc. of serum, and recorded by the scheme of +++, ++, and +, corresponds roughly

[2] The standard toxin was that supplied by the Hygienic Laboratory of the United States Public Health Service, Washington, D. C.

with the titration of skin test doses. One may say that a +++ reaction indicates a much greater toxemia than a + and generally a greater toxemia than a ++. The comparison of the ++ and +

TABLE 1

Titration of toxin in blood serum of scarlet fever patients

Case	Clinical severity	Blood serum of patients	
		Skin reaction in test subject to 0.3 cc. of serum	Skin test doses per cubic centimeter
1	Extreme	+++	330
2	Mild	+++	120
3	Severe	+++	40
4	Severe	+++	40
5	Severe	++	25
6	Severe	++	10
7	Moderate	++	5
8	Moderate	++	5
9	Moderate	++	5
10	Extreme	++	2½
11	Severe	++	1¼
12	Moderate	++	1¼
13	Extreme	++	¼
14	Extreme	++	¼
15	Mild	+	5
16	Moderate	+	2½
17	Mild	+	2¼
18	Moderate	+	¾
19	Moderate	+	¾
20	Moderate	+	¼
21	Mild	+	¼
22	Severe	+	¼
23	Extreme	+	¼
24	Moderate	+	¼
25	Severe	+	¼

+++ indicates strongly positive reaction, 50 to 70 mm. in diameter, bright red, moderately indurated and tender, of 3 to 4 days' duration followed by pigmentation and desquamation; ++, positive reaction, 30 to 50 mm. in diameter, bright red, with slight induration, of 2 to 3 days' duration, followed by moderate pigmentation and occasionally slight desquamation; +, moderately positive reaction, 20 to 35 mm. in diameter, red, no induration, of 1 to 2 days' duration, with slight pigmentation and no desquamation.

reactions with the titrated values shows that it is difficult to judge the strength of toxin in a given sample of serum from the observation of a single moderate reaction in a highly susceptible volunteer.

DISCUSSION

The titration of the amount of scarlet fever toxin in the blood serum in a small series of cases has shown that the toxin content varies through extremely wide limits which are more than a hundred times the experimental error of the methods. Occasionally, a very low toxin content has been found in the serum from a patient extremely sick. When the importance of the septic phase of scarlet fever and the probable variations in the duration of the specific toxemia are taken into consideration this is not difficult to understand. It is, however, quite surprising to find a large amount of toxin in the serum of an apparently mild case, as shown in case 2. This would lead one to suspect that the general susceptibility of individuals to the toxin may depend on more factors than the mere absence of specific antitoxin. This appears to be the case in laboratory animals, which are highly refractory to even large amounts of toxin in culture filtrates of *Streptococcus scarlatinae*, and yet in their blood serum no specific scarlet fever antitoxin is found.

The wide and often unpredictable variations in the amounts of toxin in the various samples studied, indicates that a large excess of antitoxin should be used for therapeutic purposes to obtain consistently satisfactory results.

SUMMARY AND CONCLUSIONS

1. The amount of scarlet fever toxin found in the blood of scarlet fever patients during the acute stage of the disease varies between very wide limits.

2. The size and intensity of the local reaction caused by 0.3 cc. of serum from scarlet fever patients in the skin of susceptible persons provides a rough but fairly satisfactory measure of the amount of toxin in the serum.

3. Clinical estimation of the degree of toxemia in individual patients with scarlet fever is subject to a considerable error.

4. Because of the difficulty of estimating the actual degree of toxemia by clinical observation, a generous excess of antitoxin should be used in the treatment of scarlet fever if the best results are to be obtained.

BIBLIOGRAPHY

1. Trask, J. D., and Blake, F. G.: Jour. Exp. Med., 1924, xl, 381. Observations on the Presence of a Toxic Substance in the Blood and Urine of Patients with Scarlet Fever.
2. Dick, G. H., and Dick, G. L.: Jour. Amer. Med. Assoc., 1925, lxxxiv, 1477. Results with the Skin Test for Susceptibility to Scarlet Fever.