

## BACTERIOLOGICAL AND CLINICAL STUDY OF ONE HUNDRED CASES OF SCARLET FEVER.

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### CONTENTS.

	PAGE
Introduction . . . . .	250
Bacteriological Technique . . . . .	251
Results of the Bacteriological Examination of One Hundred Cases of Scarlet Fever	252
Data regarding the Numbers of Streptococcal colonies derived from Swabs . . . . .	255
Persistence of the Primary Infecting Type of Haemolytic Streptococcus . . . . .	256
Correlation of Clinical History with Serological Type . . . . .	256
1. Temperature . . . . .	257
2. Pulse-rate . . . . .	257
3. Incidence of faucial angina, vomiting and early adenitis . . . . .	257
4. Complications . . . . .	258
5. Desquamation and stay in hospital . . . . .	259
Schultz-Charlton Reaction in Relation to Serological Type . . . . .	259
Dick Reaction in Relation to Serological Type . . . . .	260
Dick Test and Relapses or Secondary Rashes . . . . .	261
Discussion . . . . .	262
Summary . . . . .	266
References . . . . .	266

### INTRODUCTION.

THE conception of scarlet fever as an infection with haemolytic streptococci which produce locally a diffusible specific toxin has gained considerable ground as a result of recent research, notably that of Dick and Dick in 1924. Their results gave a fresh stimulus to the study of the whole group of haemolytic streptococci, especially of the question whether streptococci from the throats of scarlet fever patients can be differentiated from similar organisms occurring in puerperal fever, erysipelas and pyaemic conditions.

We do not propose to enter into this question in the present study, but to confine ourselves to the different serological varieties of haemolytic streptococci of scarlatinal origin, and their association with some of the clinical features of scarlet fever. It has seemed to us that before one can hope to solve the problem of the inter-relationship of streptococci causing different diseases, linked as it is with the question of toxin production, one must first ascertain

to what extent scarlatinal streptococci differ in regard to the amount and quality of the toxin they form.

An essential step in such research was the immunological classification of the scarlatinal streptococci which have been shown (Griffith, 1927) to comprise four chief serological types and a heterogeneous group. An attempt has already been made to correlate the bacteriological findings with the clinical manifestations of scarlatina, and it has been shown in a preliminary communication by one of us (Gunn, 1927), that there is apparently a fairly definite and constant relation between serological type of streptococcus and severity of disease. For instance, there was definite evidence that infections with Type 2 scarlatinal streptococcus were more severe and more frequently followed by complications than those caused by Type 4. The only relapse in the series occurred in a Type 4 case in the 5th week of the disease when the Dick reaction was still positive. Unfortunately, no bacteriological examination was made after the relapse.

Following on these observations, we decided in this second series of 100 cases to make periodical tests during the whole time that the patients were in hospital. On admission, before removal to the wards, swabs were taken from the throat and nose, and these were repeated at weekly intervals until discharge. In addition, a bacteriological examination was made of any secondary lesions, such as abscesses, discharging ears, or other infective foci, which occurred during the course of the disease.

The Schultz-Charlton test was performed on all scarlatinal patients suitable for observation.

The Dick test was done on admission and afterwards at weekly intervals until the patient was discharged from hospital.

Careful clinical notes were made on the character and severity of the disease, on the occurrence of complications, and on the appearance of accidental or secondary rashes.

We may remark that the diagnosis, care, and discharge of the scarlet fever patients in the series were carried out without reference to the bacteriological findings in order to avoid the possibility of unconscious bias in the making of the records, and similarly the bacteriological examination was conducted without any knowledge of the source of the swabs examined.

#### BACTERIOLOGICAL TECHNIQUE.

The swabs were received at the Laboratory within a few hours of being taken, and cultures were made on plates of nutrient agar containing 3 to 5 per cent. fresh oxalated horse blood. The plates were incubated at 37° C. for 24 hours, after which period the colonies of haemolytic streptococci were readily recognised. Whenever the numbers were sufficient, three colonies at least from each plate were picked off and subcultivated.

The test of serological type was made as soon as possible after isolation, generally on the second or third subculture. The cultures for this purpose were

made on three different media, viz. (a) trypsinised meat-broth, (b) trypsinised meat-broth containing 5 per cent. horse serum, (c) nutrient agar slopes. Sometimes one medium and sometimes another gave a more suitable suspension. If the growth, as was often the case, took place at the bottom of the fluid media, the supernatant broth was pipetted off without disturbing the deposit. The latter, re-suspended in a very small amount of the broth, generally made a much better suspension for the test than the deposit after centrifugation.

The agglutination tests were carried out in the manner previously described (Griffith, 1927), viz. small drops of a thick suspension were mixed on a slide with a tiny loopful of neat serum of each of the four types and the rapid formation of clumps was observed under a low-power objective. As a rule, the serological classification could be made without difficulty, one type serum causing rapid coarse clumping. Where no reaction occurred with any of the four type sera the strain was placed in the heterogeneous group. In a doubtful test fresh cultures were sown until a clearly defined reaction was obtained; it was rarely necessary to resort to the agglutinin absorption test. Sometimes it was difficult to obtain a clear-cut result with Type 1 strains. Although the homologous serum gave the most marked reaction, there was also a persistent agglutination with the other three type sera. The difficulty was overcome by treating the sera beforehand with a culture of one of the heterogeneous group; the specific Type 1 agglutinin was unaffected but the non-specific agglutinins of the other sera were more or less completely removed.

#### RESULTS OF THE BACTERIOLOGICAL EXAMINATION OF ONE HUNDRED CASES OF SCARLET FEVER.

The types of haemolytic streptococci obtained from the throat or nose at the time of admission of the patient to hospital were distributed in the proportions shown in Table I. For comparison, the incidence of the types in the previous investigation in 1926 is also shown.

Table I.

	Type 1	Type 2	Type 3	Type 4	Heterogeneous group	Totals
1927	8	14	26	12	31	91
1926	2	34	17	23	17	93

In the present investigation haemolytic streptococci were not found on the first examination either in the throat or nose of 9 patients, though they were obtained subsequently at the end of the 1st and 2nd week after admission to hospital. From these 9 patients the first positive swab yielded Type 1 in 2 cases, Type 2 in 4 cases, Type 3 in 1 case, and unclassified strains in 2 cases. They are not included in the statistical table since, as will appear later, one cannot be sure that the type of streptococcus found after the patient has been for some time in the hospital ward is the same as that which infected the patient on admission.

It will be noted that the number of strains in the heterogeneous group was much larger than in the previous investigation. The attempt to classify them serologically has not so far met with success, and it appears very probable that this group is composed of individualistic strains.

In 50 out of the 100 cases one and the same serological type was found during the period of hospital treatment (averaging 7 weeks), and in 20 of these it was still present either in throat or nose, when the patient was discharged. These observations are in favour of the stability of the type characters.

In the remaining 50 cases there was an apparent change of type during the course of the disease. These cases are given in Table II, which shows the results of the examinations of throat and nose week by week until the patient was discharged. Sometimes the swabs from both throat and nose were positive; at other times haemolytic streptococci were found only in one situation. In order to limit the size of the table, the throat and nose results are not given separately, and, when a strain was derived from the ear, an asterisk is put against the numeral in the table.

An analysis of Table II shows that in addition to the primary infecting type, a second type appeared in 38 cases, a third in 10, and a fourth in 2. One case, No. 38, which on the first test yielded a mixture of Types 2 and 4, differed from the rest in having been for some time in the ward before examination, thus being exposed to risk of cross-infection.

There are three possible explanations of the changes in type observed in a single case.

(1) They might indicate that the serological characters of haemolytic streptococci are too unstable to admit of a reliable classification by the method employed. Against this suggestion is the previously mentioned observation that in 50 per cent. of the cases examined there was no alteration of type during the attack and convalescence. Moreover, one may point to the regularity of the results in those cases where different types were found.

(2) The streptococcal type characters may be stable under the ordinary conditions of growth outside the body, but under the influence of antibodies formed in successful resistance to the infection a change of type may be induced.

(3) Reinfection may occur through the close association of patients harbouring different types.

While the possibility of modification of type cannot be excluded, the following points are in favour of the third explanation, viz. reinfection:

(a) Among the 50 cases, the fresh type of haemolytic streptococcus appeared in 5 instances during the 2nd week and in 8 instances during the 3rd week, that is to say, in 13 instances during the period when the patients were confined to bed. On the other hand, during the subsequent 4 weeks when the patients got up and were allowed to associate closely with each other, in no less than 37 instances a fresh type was obtained from the throat or nose.

(b) Four patients in the series were isolated strictly on account of the

Table II. *Types found at weekly examination of swabs (throat or nose).*

Case No.	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	
3	3	3	2	2	0	0	H	—	—	—	—	—	
4	3	3	3	2	0	0	—	—	—	—	—	—	
5	4	4	4	4	4*	2*	0	2	2	1	1	H	H
6	H	H	2	2	2	0	3	3	—	—	—	—	
8	H	0	0	H	H, 2, 4	2	H, 2	—	—	—	—	—	
9	3	0	3	0	3*	3	0	0	0	1	0	1	
11	H	H	H	2*	0	0	0	0	0	—	—	—	
16	3	3	2	0	0	0	—	—	—	—	—	—	
17	4	4	0	0	1, 2	1, 2	2*	1, 2	1	—	—	—	
18	2	0	2	2	0	H, 2	0	0	—	—	—	—	
28	4	0	0	0	2	0	2	0	—	—	—	—	
30	H	H	2	2	2	0	—	—	—	—	—	—	
32	H	H	0	0	0	3	—	—	—	—	—	—	
33	1	0	1	0	1	1, H	0	0	1	—	—	—	
37	1	2	2	2	2	H	0	—	—	—	—	—	
38	4, 2	2	2	2	2	—	—	—	—	—	—	—	
39	H	H	H	2	2	0	—	—	—	—	—	—	
42	4	4	2	2	2	1	1	1	1	—	—	—	
43	3	0	0	0	0	0	2	0	0	—	—	—	
44	4	4	4	4	4	0	3	3	3	1	1	—	
46	2	2	2	2	4	4	4	4	—	—	—	—	
51	2	2	0	0	4	0	—	—	—	—	—	—	
52	4	4	0	4	4, H	4, H	4, H	H	H	—	—	—	
57	4	4	0	4	4	H	—	—	—	—	—	—	
58	H	4	H	3	3	2	2	2	—	—	—	—	
59	1	1	1	0	H	—	—	—	—	—	—	—	
61	2	2	2	3	3	0	—	—	—	—	—	—	
63	H	H	2	H	2	0	—	—	—	—	—	—	
64	H	4	H	0	H	3	3	3	—	—	—	—	
66	0	0	1	0	0	0	3	3	—	—	—	—	
67	2	0	2	2	0	0	1	—	—	—	—	—	
68	3	H	H	H	H	—	—	—	—	—	—	—	
70	4	4	4	4	4	4	4, 3	—	—	—	—	—	
72	H	H	H	H	H	H	4	4	4	—	—	—	
73	H	H	H	H	H	3	3	3, 4	—	—	—	—	
77	3	0	0	0	0	0	4	4	—	—	—	—	
78	3	3	H	H	H	H	0	H	—	—	—	—	
80	1	0	1	1	1	H	H	H	H	—	—	—	
81	3	0	H	H	3, 4	H	H	H	—	—	—	—	
82	2	0	0	0	3	3	—	—	—	—	—	—	
86	3	2	2	2	2	—	—	—	—	—	—	—	
88	0	H*	H*	H*	1, H	H	H	H	—	—	—	—	
90	H	0	0	0	0	3	—	—	—	—	—	—	
91	H	H	0	H	0	4	—	—	—	—	—	—	
94	3	0	3	0	4	0	4	—	—	—	—	—	
97	3	3	3	3	3	0	H	0	—	—	—	—	
102	3	3	3	0	0	H	—	—	—	—	—	—	
111	1	1	1	3	3	3	0	—	—	—	—	—	
112	2	2	2	0	0	H	0	—	—	—	—	—	
113	H	0	0	0	4	4	4	—	—	—	—	—	

H = strain of heterogeneous group.  
 \* against the type figure indicates that the source of the culture was the ear.

concurrency of other infectious diseases; in each instance the primary infecting type remained unchanged throughout.

(c) The majority of the patients who yielded more than one type were very young children, the average age being  $3\frac{1}{4}$  years. The intimate association of young children at play with free exchange of toys, etc. renders them particularly liable to the risk of secondary infection. On the other hand, the average age of the 50 patients in whom no change of type was found was  $7\frac{1}{2}$  years.

(d) There were two instances where the source of the new infection could be traced with some degree of probability. Three children, whose ages ranged from 2 to 5 years, occupied adjacent beds in a ward. The first child had a Type 1 infection, the second a Type 2, and the third a Type 4, the streptococci being obtained in each case from the throat. Child No. 1 developed otitis media, and for 2 days there was a purulent discharge from which haemolytic streptococci were not grown. About the same time, child No. 2 developed a sore throat which was followed a few days later by suppurative otitis media; from both the throat and the ear Type 1 streptococci were obtained. Child No. 3 also contracted tonsillitis together with bilateral otitis media, and from both throat and ears Types 1 and 2 streptococci were obtained on several examinations, but the Type 4 strain, with which the child was originally infected, never reappeared. The inference is that the Type 1 streptococcus passed from the first child to the other two.

In the second instance, 2 patients were being nursed together and isolated from other cases. One carried a Type 4 streptococcus in the throat, and the other a heterogeneous strain. Shortly after they were brought together the first mentioned patient developed a sore throat which was followed by adenitis and suppurative otitis media; a heterogeneous strain was then obtained from the throat and the ear. It is probable that the heterogeneous strain was derived from the second patient, though this could not be confirmed by serological tests owing to lack of the appropriate agglutinating serum.

(e) In 3 patients in whom immunity was not established, as shown by the persistence of a positive Dick reaction, the discovery of the new type coincided with a relapse, or fresh attack of clinical scarlatina (see p. 261).

#### DATA REGARDING THE NUMBERS OF STREPTOCOCCAL COLONIES DERIVED FROM SWABS.

The colonies of haemolytic streptococci obtained from the throat swabs on the first examination were generally numerous. In the majority of those cases where no fresh type appeared the colonies on subsequent examination became fewer in number until finally the swab was negative. When haemolytic streptococci still persisted in the throat of the patient on discharge from hospital, the colonies obtained were generally sparse.

On ten occasions the first swab yielded numerous colonies, and all subsequent swabs were negative.

Only in 8 out of the 100 cases were numerous or moderately numerous colonies of haemolytic streptococci obtained from the first nose swab.

The conditions under which new type strains made their appearance varied. There were some particularly striking instances, where, after a period of negative swabs, one yielded numerous haemolytic colonies of a type different from the primary infection. In 18 out of the 50 cases where a new type appeared, the plate on which it was first found showed numerous haemolytic colonies. As generally only three colonies were examined one cannot assume

that all were of the new type, though there is a strong possibility that such was the case where in subsequent swabs only this new type was found. Two types were actually found on the same plate on six occasions, and on four occasions one type was found in the throat and another in the nose or ear. In the remainder of the 50 cases, the new type appeared when the haemolytic colonies derived from the swab were sparse, and not infrequently, even when limited to one or two.

#### PERSISTENCE OF THE PRIMARY INFECTING TYPE OF HAEMOLYTIC STREPTOCOCCUS.

Observations on the rate of disappearance of scarlatinal streptococci from throat and nose or other foci are confined to the group of cases in which no change of type was found. Of the 50 patients comprising this group, 20 carried the infecting agent in the throat until discharge from hospital, when it was no longer practicable to take swabs. The average stay of these 20 patients was  $6\frac{1}{4}$  weeks—the extreme limits being  $4\frac{1}{2}$  and  $8\frac{1}{2}$  weeks. In the remaining 30 patients of this group, the average time of disappearance of the organism from the throat was  $3\frac{1}{4}$  weeks, the limits being 1 week and  $7\frac{1}{2}$  weeks respectively. The average time of disappearance of the streptococci from the nose was  $2\frac{1}{4}$  weeks, and from the ear 3 weeks. These latter findings are somewhat at variance with the opinion of most clinicians who have regarded discharges from nose or ear as specially liable to remain infective for long periods.

Swabs were taken from each patient immediately before discharge from hospital with a view to correlating the bacteriological findings with the occurrence of "return cases." The throat swabs of 49 patients, taken prior to discharge, were found to contain haemolytic streptococci; 4 plates showed numerous colonies, 3 yielded a moderate number, 27 showed only a few colonies, while on 15 plates only one haemolytic colony was found. From 9 of these 49 patients the nose swab was also positive and from an additional 6 patients haemolytic streptococci were obtained from the nose only, giving a total of 14 "nasal carriers" against 49 "throat carriers." The numbers of colonies on the plates from the nasal swabs were as follows: on 2, colonies were numerous, on 6 they were found in moderate numbers, in 3 they were sparse, and in 3 only one colony was noted.

As far as could be ascertained none of these 55 patients gave rise to any "return cases."

#### CORRELATION OF CLINICAL HISTORY WITH SEROLOGICAL TYPE.

After the 100 cases were discharged from hospital, the completed clinical histories were collected and the records analysed. The usual criteria of mildness or severity in a given case, viz. degree of pyrexia, amount of faucial angina, incidence of complications, etc., were recorded, and the details are given briefly in the following tables.

1. *Temperature.*

The degree of pyrexia, by itself, is of little value in estimating the character of the disease; the duration of the initial pyrexia is a more reliable index of severity. In Table III the average admission-temperature and the average duration of initial pyrexia are detailed for each group in the series. Type 2 shows the highest figures and Type 4 the lowest.

Table III.

Type	1	2	3	4	H	All cases
Average admission temp.	100.2° F.	101.1° F.	100.5° F.	100.0° F.	100.4° F.	100.5° F.
Av. duration of pyrexia	5½ days	6 days	5¼ days	3¼ days	4½ days	4¾ days

2. *Pulse-rate.*

In scarlet fever great importance has always been attached to the degree of the tachycardia both in diagnosis and prognosis, but in a series of cases where the ages range from 6 months to 30 years many discrepancies appear. Variations in the pulse-rate depend more upon the age of the patient than upon the severity of the disease, making strict comparison impracticable; for this reason records upon the pulse-rate are not included.

3. *Incidence of faucial angina, vomiting and early adenitis.*

In most cases of scarlet fever some faucial angina is present, but in a certain proportion it is appreciable, with a varying amount of exudate, and usually indicates a severe infection. The expression "appreciable" must necessarily be somewhat arbitrary, but the findings of the same observer may reasonably be used for comparison. Records of the incidence of vomiting and early adenitis are much less open to error and assist in forming an estimate of the type of the disease. In Table IV the number of cases and percentage incidence of these early clinical features are detailed under each type.

Table IV.

Type	1	2	3	4	H	All cases
Faucial exudate	3 (37.5 %)	6 (42.8 %)	9 (34.6 %)	1 (8.3 %)	11 (35.5 %)	— 33 %
Vomiting	6 (75.0 %)	10 (71.4 %)	10 (38.4 %)	4 (33.3 %)	13 (42.6 %)	— 47 %
Early adenitis	6 (75.0 %)	12 (85.7 %)	16 (61.5 %)	5 (41.6 %)	18 (58.4 %)	— 62 %

These figures would appear to indicate that the more severe forms of scarlet fever are associated with Types 1 and 2; Type 3 causes a moderate attack, while Type 4 produces the mildest form of the disease. The heterogeneous group on the whole approximates fairly closely to Type 3 in point of severity, but examination of individual case records of the former revealed wide variations in the clinical type; some cases were exceptionally severe, while others were so mild that a satisfactory diagnosis based solely upon the clinical findings was occasionally not possible. The percentage incidence of

these early features corresponds very closely to the findings in 100 cases of scarlet fever similarly analysed in 1927, though the incidence of faucial angina was somewhat higher in the present series.

#### 4. Complications.

In general the most serious menace of scarlet fever is the liability of the patient to develop complications and sequelae, the number and nature of which are a more definite index of severity of the attack than the early clinical data detailed above. The type of streptococcus responsible for the complication, *e.g.* otitis media, must be determined by direct examination, since, as will be seen later, it may not be the same as that which caused the primary infection.

Table V gives under each type the case and percentage incidence of the most important and typical scarlatinal complications in the series.

Table V.

Type	1	2	3	4	H	All groups
Otitis media	3 (37.5 %)	2 (14.3 %)	2 (7.7 %)	1 (9.1 %)	3 (9.7 %)	— 12 %
Mastoiditis	1 (12.5 %)	—	—	—	—	— 1 %
Rhinorrhoea	3 (37.5 %)	4 (28.6 %)	3 (11.5 %)	3 (25.0 %)	10 (32.2 %)	— 25 %
Adenitis (late)	3 (37.5 %)	4 (28.6 %)	4 (15.4 %)	2 (16.6 %)	7 (22.6 %)	— 22 %
Adenitis (suppur.)	—	—	—	—	1 (3.2 %)	— 1 %
Nephritis	—	2 (14.3 %)	—	—	—	— 2 %
Rheumatism	—	3 (21.4 %)	2 (7.7 %)	—	2 (6.4 %)	— 7 %
Endocarditis	—	2 (14.3 %)	—	—	—	— 2 %
Jaundice	—	—	—	—	1 (3.2 %)	— 1 %
Relapse	—	—	—	2 (16.6 %)	1 (3.2 %)	— 3 %
Death	—	—	—	—	—	—

Examination of Table V shows that the types of haemolytic streptococci which are associated with greater severity of attack in the early stages cause the highest incidence of complications. Type 1 appears to be the type most frequently found in those complications which are the result of direct extension from the local lesion in the throat, *viz.* otitis media, mastoiditis and adenitis. Type 2, on the other hand, appears to produce distal lesions through the general circulation; thus, all the cases of nephritis and endocarditis in the series belong to this group. The only serious complication under the Type 4 group was a case of otitis media; the otitis pus, however, yielded Types 1 and 2 haemolytic streptococci on culture, indicating that the lesion was due to reinfection and not to the primary infecting type. The heterogeneous group

and the Type 3 group appear somewhat similar in the number and kind of complications which they cause.

#### 5. *Desquamation and stay in hospital.*

As a rule, the more intense the rash and the more severe the disease, the greater is the likelihood of the typical desquamation of scarlatina ensuing. The term "desquamation" is taken to mean definite peeling of the palms and soles. Prolonged duration of stay in hospital is not necessarily an indication of the character of the disease, since quite frequently conditions unrelated to the attack of scarlet fever are responsible for detention of a patient. As far as possible, the figures in Table VI are corrected in such special cases.

Table VI.

Type	1	2	3	4	H	All groups
Desquamation	5 (62.5 %)	10 (71.5 %)	18 (69.2 %)	3 (25.0 %)	19 (61.3 %)	— 60 %
Stay in hospital	7 $\frac{3}{4}$ wks.	7 $\frac{1}{2}$ wks.	6 $\frac{1}{2}$ wks.	6 $\frac{1}{4}$ wks.	6 $\frac{3}{4}$ wks.	6 $\frac{3}{4}$ wks.

While the above data do not show very marked differences between the various groups, they are not inconsistent with the inferences drawn from the preceding tables.

#### SCHULTZ-CHARLTON REACTION IN RELATION TO SEROLOGICAL TYPE.

The same sample of scarlatinal antitoxic serum was employed throughout to elicit the Schultz-Charlton phenomenon. This serum, concentrated by accepted methods, was obtained from the horse after graduated injections of scarlatinal toxin prepared from the "Dochez" scarlatinal streptococcus. (Agglutination tests show that this strain belongs to the heterogeneous group.) The serum was proved, by means of the various tests for potency, to possess a high antitoxin content, and in a 1-10 dilution produced satisfactory blanching of suitable rashes. On admission, each patient tested was injected intracutaneously with 0.2 c.c. of this 1 in 10 dilution of the serum into the brightest part of the rash (usually on the upper abdomen), and an equal quantity of normal horse serum, similarly concentrated and diluted, was injected as control. As the intensity and age of the rash have an important bearing on the result of the reaction, the findings are subject to a certain degree of error, for the cases were injected at periods varying from the first to the third day after the eruption appeared. Moreover, some rashes remain vivid for 5 or even 6 days, while others are relatively transient, occasionally lasting only for a few hours. In view of these variations, the average duration of the rash for each group is given in Table VII together with the results of the Schultz-Charlton reactions.

Table VII.

Type	1	2	3	4	H	All groups
Av. duration of rash	3 $\frac{1}{4}$ days	4 days	3 $\frac{3}{4}$ days	2 $\frac{1}{4}$ days	3 days	3 $\frac{1}{2}$ days
Positive Schultz-Charlton reactions	3 (37.5 %)	6 (42.5 %)	21 (80.8 %)	3 (25.0 %)	20 (64.5 %)	— 58 %

The most striking feature of Table VII is the relatively large number of positive reactions in the Type 3 group. If one attempts to explain this high proportion on the ground that these rashes remain bright for relatively long periods— $3\frac{3}{4}$  days, one is faced with the difficulty that the rash of the Type 2 group lasts even longer, while the percentage of positive reactions is little more than half. In the heterogeneous group the rash lasts on an average for 3 days and returns 64.5 per cent. positive reactions, against 37.5 per cent. for the Type 1 group with an average duration of  $3\frac{1}{4}$  days. The low figures for the Type 4 group are probably due mainly to the fleeting nature of the rash.

It is difficult to find an explanation which will satisfactorily cover all these anomalies. The large number of brilliant rashes in the Type 2 group which did not blanch with the serum, even under the most favourable conditions, suggests strongly the possibility of the existence of qualitative differences in the toxins producing the eruptions. Thus the antitoxin produced with the Dochez strain may not be homologous with Type 2 toxin. On the other hand one cannot exclude the possibility that these variations depend on the nature of the rash. In support of this suggestion one may record that brick-red and dusky rashes which were noted very commonly in Type 2 patients tend in general to resist the blanching action of the antitoxin. (These varieties of rashes are not to be confused with the "fixed" rash which is only found late, third to fifth day, in the evolution of a brilliant rash.) Whatever view one takes of the failure to react, these observations point to serious limitations to the reaction, which is usually regarded as specific. While a positive reaction supported by the clinical evidence justifies the diagnosis of scarlet fever, a negative reaction is inconclusive. The latter may mean (1) that the rash is not scarlatinal, (2) that the serum employed is inactive, (3) that the serum is not sufficiently specific for the given rash, or (4) that the nature of the rash inhibits the typical blanching phenomenon, whatever serum be used. At present no definite conclusion is permissible, but evidence is accumulating that (3) is responsible for most doubtful or negative reactions in true scarlatina.

#### DICK REACTION IN RELATION TO SEROLOGICAL TYPE.

It was hoped in this inquiry to discover the relation, if any, of serological type of streptococcus to the development of immunity. With this object all the patients in the series were tested by the Dick method on admission and at weekly intervals until discharge from hospital. Scarlatinal toxin prepared from the Dochez strain and diluted to the standard strength according to the recommendations of Dick and Dick was used at first, but for the last 70 patients a toxin from a Type 2 strain occurring in the series, similarly standardised for potency, was substituted.

In Table VIII the Dick reactions on admission and discharge and the average periods during which the reaction changed from positive to negative are recorded under each serological type.

The number of positive reactions (95 per cent.) in the first 5 days in this

Table VIII.

Type	1	2	3	4	H	All groups
Positive Dick reactions on admission	7 (87.5 %)	12 (85.7 %)	25 (96.2 %)	12 (100.0 %)	29 (93.6 %)	— 95 %
Positive Dick reactions on discharge	1 (12.5 %)	0	3 (11.5 %)	7 (58.3 %)	5 (16.1 %)	— 16 %
Average period of change of reaction	4½ wks.	2 wks.	3½ wks.	5½ wks.	3½ wks.	3¾ wks.

series agrees fairly closely with the findings of other observers, *e.g.* Zingher (1924), 98 per cent.; Rosen and Korobicina (1925), 82.5 per cent.; Smith and Taylor (1926), 86.3 per cent.; the differences between the figures are probably due chiefly to the difficulty of standardising accurately a given sample of toxin. In the various groups in the present series, the proportion of positive reactions does not differ greatly, the widest divergence being 85.7 per cent. for the Type 2 group against 100 per cent. for the Type 4 group; this latter high proportion may indicate that only very susceptible subjects can acquire scarlatina by infection with Type 4. On the other hand, there is an obvious difference between the immunity production of the various types when one examines the figures denoting the state of the reaction on the discharge of the patient (average 6¾ weeks). All the patients in the Type 2 group were Dick negative reactors and were presumably immunised by the attack for the rest of their lives, while more than one half of the cases in the Type 4 group gave a positive reaction, and, if no subsequent change occurred, were therefore liable to another attack of scarlet fever. As regards the remaining three groups, the figures approximate fairly closely to each other. The results show that the relatively severe Type 2 infections give rise to a more complete immunity than the milder Type 4 infections, while the other types occupy an intermediate position. As the severity of the scarlatinal attack is probably proportionate to the amount of toxin absorbed into the blood stream, one may infer that Type 2 is a more active producer of toxin than Type 4 and, in consequence, provokes a more energetic immunity response.

The possibility, however, of qualitative differences between the toxins of different serological types is again raised. It may be that the antitoxin formed during recovery from a Type 4 infection does not neutralise the Type 2 toxin (used in 70 per cent. of the Dick tests) so effectively as the antitoxin developed in a Type 2 infection.

#### DICK TEST AND RELAPSES OR SECONDARY RASHES.

Three instances of "relapse" or "secondary rash" were observed among the 100 cases.

The first patient on admission appeared to have a mild but fairly typical attack of scarlet fever, but did not desquamate; Type 4 haemolytic streptococci were isolated from the throat for four successive weeks, the Dick reaction remaining positive. During the 5th week the typical symptoms and rash of

scarlet fever appeared and Type 3 haemolytic streptococcus was isolated from the throat; this latter type persisted for the four following weeks. The Dick reaction became negative during the 7th week after the primary attack.

The second case also had a Type 4 attack; the same type was isolated from the throat on each occasion for 5 weeks but the patient remained a Dick-positive reactor. In the 5th week a second attack of typical scarlatina supervened, the Dick reaction becoming negative in the course of the following week. Type 2 haemolytic streptococci were obtained from the throat on the next swab and were found on three consecutive occasions subsequently.

The third instance belonged to the heterogeneous group; peeling was observed in the 4th week but the Dick reaction did not change. In the 5th week a relapse occurred and a heterogeneous streptococcus was isolated from the throat for the next 3 weeks. An agglutinating serum of high titre prepared with the first strain obtained failed to agglutinate any of the three strains isolated after the relapse. In addition, toxin was prepared from the strain first obtained from the throat and from that isolated immediately after the relapse, and it was found that the latter was five times more potent than the former. These results show that the heterogeneous strain obtained after the relapse was a different variety from that causing the primary attack.

#### DISCUSSION.

Every specific disease exhibits different grades of severity but probably none is characterised by so wide a range of variation as scarlet fever. While giving full credit to the influence on the clinical features of the disease of differences in individual resistance one is, nevertheless, forced to the conclusion that the causal agent of scarlatina, now widely accepted as the haemolytic streptococcus, is unequal in its disease-producing potentiality.

That all haemolytic streptococci of scarlatinal origin have not the same capacity to form a soluble toxin, to which the scarlatinal symptoms are undoubtedly due, is now well known. In addition, it has been established that scarlatinal streptococci are not identical in agglutination reactions but that the majority of strains—roughly 60 per cent.—in this country and during two years, at least, fall into four well-defined serological types.

The relation between serological type and capacity to form toxin is being studied by one of us (Gunn) and will form the subject of a future communication. It may be mentioned here, since our results point to a similar conclusion, that there are strong indications of a correlation between serological type and both the quantitative and qualitative conditions of toxin production. That certain types are consistently weaker than others in their power to form toxin seems fairly clear but there is also a suggestion of qualitative differences between these toxins.

The observations which we give in this article on the relation of serological type of streptococcus to the clinical course of scarlatina support those made by Gunn in 1927. The cases so far dealt with are, we admit, too few in number

to justify deductions as to the disease-producing capacity of each individual type, but the differences in the severity of the attack caused by the Type 4, on the one hand, and the Types 1 and 2, on the other, are too consistent to be merely accidental. If we confine the comparison to Types 2 and 4, as the cases due to Type 1 are few in number, the greater severity of the Type 2 cases is evident, standing out, as they do, among the relatively mild cases of scarlet fever characteristic of the present day. Type 4, on the other hand, causes mild scarlet fever with infrequent complications; immunity, as is shown by the persistence of a positive Dick reaction, is slowly produced and in two cases, no doubt in consequence, typical second attacks of scarlet fever occurred. In Type 2 infections there is a much higher incidence of complications, including those which depend on circulating toxin, and the Dick reaction is quickly abolished, showing active production of antibody.

Without further consideration one might be content to ascribe the apparent differences in the immunity response in the two infections to the probable superiority of Type 2 over Type 4 in the amount of toxin it produces. On the other hand, there are two circumstances which might be taken to suggest the existence of qualitative differences between toxins.

1. The Dick tests were made with two varieties of toxin, one from the Dochez strain and the other from a Type 2 strain, the latter being employed for 70 per cent. of the cases. The fact that the Dick reaction invariably became negative at an early date in the Type 2 infections suggests that the toxin produced by Type 2 excites the formation of an antitoxin more suitable for neutralising the Dick toxin (either Dochez or Type 2) than that produced in a Type 4 infection. We use the expression "more suitable" since it is not suggested that the streptococcal toxin-antitoxin specificity in relation to serological type is so pronounced as is the case, for example, with the protective antibodies of the pneumococcal types.

2. Relapse was recorded in two patients who were recovering from Type 4 infections but were still Dick positive. These relapses were in reality second attacks of scarlet fever due to reinfection with a fresh type in patients in whom such antitoxic immunity as was present was ineffective against the toxins of the secondary strains. Reinfection with a fresh type does not commonly set up scarlatina owing to the presence of antitoxin, though it may be followed by complications, since antitoxic immunity confers little, if any, protection against local streptococcal infections.

These indications which are supported by the numerous observations of the failure of the Dochez antitoxin to blanch the rash in the Schultz-Charlton reaction suggest that the combining properties of the toxins of different streptococcal strains are not identical. Our observations, however, do not provide evidence that such failures can be correlated with serological type, but the hypothesis will be tested directly when antitoxins prepared with various streptococcal types are available.

At the present stage of the inquiry into the relation of type characters to

pathogenicity it would be premature to discuss the rôle of each type but there are some features of interest which are worthy of further study.

In the first place, one may recall, as possibly showing the influence of serological type on the character of the disease, the frequency with which Type 1 produces complications that are the result of direct extension from the mucous membrane of the throat, such as otitis media and mastoiditis, though these lesions are by no means confined to this group.

Again, one may ask why there should be a heterogeneous group in which the strains are highly individualistic in serological character, *i.e.* are rarely found in the disease, but to judge from the severity of the attack may produce a powerful toxin, whereas Type 4 which is of common occurrence in the disease (12 per cent. of our cases) and therefore presumably a more effective producer of scarlet fever can secrete only a mild form of toxin. It seems that the antigenic structure of the streptococcus has an influence on its capacity to pass from person to person irrespective of its disease-producing power once it is established.

The plan which we adopted in this inquiry of making weekly examinations of swabs from individual cases of scarlatina has elicited some facts bearing on this question of the infectivity of scarlatinal streptococci.

The occurrence of reinfection with a different serological type of streptococcus from that which originated the attack in no less than 50 of the 100 patients shows the remarkable facility with which these organisms implant themselves on the mucous membrane. It is evident that a patient treated in a hospital ward may incur a risk not present in home treatment. He may, for instance, as a result of reinfection develop a second typical scarlatinal attack, or, if his antitoxic immunity is sufficiently high to inhibit the rash, he may become the victim of a complication such as otitis media.

The fact established by our work that complications are not infrequently due to a different type from that of the primary infection indicates that the greatest possible care should be taken to avoid cross-infections in the scarlatina ward. It may even be found practicable and desirable to keep together the infections of similar type, and especially to prevent cases of Type 4 running any risk of infection with other types.

When change of type has occurred during the course of the scarlatinal attack we have rejected, at least in the majority of instances, the alternative hypothesis of modification of type, pointing in justification to the regularity of the results and also to the fact that in 50 cases the type of infecting organism remained the same throughout the period of stay in hospital.

Stevens and Dochez (1924) found occasionally in the throat at the end of convalescence, as well as in the complications, strains differing in agglutination from those causing the primary scarlatinal attack. They concluded that in a certain percentage of cases of scarlet fever a mixture of scarlatinal and non-scarlatinal streptococci occurred. They did not, however, recognise the existence of types among scarlatinal streptococci, and it is possible that they might, by

the use of type-specific sera, have been able to identify their so-called secondary pyogenic streptococci with strains capable of producing scarlatina.

It must be recalled that in order to satisfy ourselves that the agglutination test was reliable each successive swab in an individual case was given a different serial number and it was only late in the investigation that the results were tabulated under each case. The method had certain disadvantages. For instance, if the information as to the previous result in a case had been available it would have been possible to make a closer scrutiny of the colonies for the presence of different types on a plate from a particular swab. In 9 cases, moreover, the results of the first tests were negative and it was only after the patient had been in the ward for a week or more, with opportunities for reinfection that another swab was taken and the positive result was obtained. It was thus impossible to be certain that the type found was the same as that with which the patient was admitted.

There is considerable variation in the persistence of scarlatinal streptococci in the throat; the type responsible for the primary infection may disappear during the 1st week of the attack or may still be present at the time of the patient's discharge after 6-7 weeks in hospital.

Although 55 patients were discharged still carrying in the throat or nose haemolytic streptococci, many of which were of the chief scarlatinal types, so far as could be ascertained none was responsible for a return case. This is difficult to understand in view of the above observations on the readiness with which these streptococci infect the mucous membrane. No doubt the fact that their numbers were sparse in the majority of such cases is in part responsible; the change to home conditions, too, may have exercised a favourable influence so as to abolish the carrier condition.

Among the instances of correlation of type with clinical disease in other bacterial groups the most striking is in the *Salmonella* group in which the *B. paratyphosus* B. produces a specific fever and the *B. aertrycke* an acute gastro-enteritis.

In the case of the pneumococci, Cecil, Baldwin and Larsen (1927), from an analysis of a large group of cases of pneumonia, showed that pneumococcal type has an influence on certain clinical features of the disease. For example, serious complications were almost twice as common in Type I pneumonia as in other types, and Types II and III pneumonia were almost twice as fatal as Type I or Type IV.

Tulloch (1919) in his work on tetanus suggests two explanations of his facts: "A, either that Type I (tetanus) bacilli are, on the whole, less virulent or less toxigenic in character than are those of Types II and III; B, or that the serum prophylaxis in use until recently afforded more adequate protection against Type I infections than it did against infections due to Types II or III."

While these observations on the correlation of serological type of streptococcus with the clinical course of scarlet fever cannot be regarded as justifying any final or conclusive statement, we think that we have sufficiently indicated the desirability of further investigation of this subject.

## SUMMARY.

1. The bacteriological examination of the throat or nose in 100 cases of scarlet fever on admission to hospital showed the following incidence of the different serological types of streptococci. Of 91 cases yielding positive results on the first examination, haemolytic streptococci of Type 1 were found in 8, Type 2 in 14, Type 3 in 26 and Type 4 in 12; the remaining 31 fell into the heterogeneous group. In the 9 patients who gave a negative swab on admission a later test showed Type 1 in 2 cases, Type 2 in 4 cases, Type 3 in 1 case and heterogeneous strains in 2 cases.

2. The heterogeneous group comprised individualistic strains, none of which occurred with sufficient frequency to form a fifth type.

3. In 50 out of the 100 cases examined at weekly intervals the type of streptococcus remained the same throughout the attack.

4. In 50 cases there was a change of type during the course of the disease; a second type appeared in 38, a third in 10 and a fourth in 2.

5. The change of type was considered to be a reinfection since it appeared most often in the youngest children and after the 3rd week of treatment; the source of reinfection was traced in two instances.

6. In 3 patients, in whom the Dick reaction remained positive, the appearance of the new type coincided with a second attack of clinical scarlatina.

7. Of the 50 patients in whom no change of type was demonstrated 20 still carried the haemolytic streptococci on discharge after periods in hospital ranging from 4 to 8 weeks.

8. Of the total 100 cases there were on discharge 49 throat carriers of haemolytic streptococci and 6 nose carriers. None of the 55, so far as was ascertained, gave rise to "return cases" of scarlet fever.

9. There was evidence of correlation between serological type of streptococcus on the one hand and severity of scarlatinal attack and occurrence of complications on the other. The importance of this in hospital practice is emphasised.

10. The Dick test and Schultz-Charlton reaction were carried out on all cases in the series; the results indicated that the four serological types have different immunological values.

11. The evidence in favour of qualitative as opposed to quantitative differences in toxin production by the different types is discussed.

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