Section of Epidemiology and State Medicine.

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The Epidemiology of Streptococcal Infections.

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I.—Dr. V. D. Allison.

The genus *Streptococcus* in relation to human disease may be divided into three species, as described by Smith and Brown [1], and Brown [2], according to their action on blood-agar plates: (*a*) *Str. hæmolyticus* giving β-hæmolysis or true hæmolysis, (*b*) *Str. viridans* showing α-hæmolysis or green coloration, and (*c*) *Str. fæcalis*, the γ-type having no action on blood. This classification enables us to limit the scope of our subject to the first species, *Str. hæmolyticus*, whose epidemiological importance is accepted. *Str. viridans* has not hitherto been found to form any soluble toxin; it is recognized as the cause of most cases of subacute bacterial endocarditis in man, and is suspect of being ætiologically connected with various forms of rheumatism, by absorption from the teeth, tonsils, gut, or other focus of infection. The causal relationship between the green-producing streptococcus, described by Tunnicliff [3, 4], and measles, has not been confirmed. *Str. fæcalis* also produces no exotoxin and is as a rule non-pathogenic, although it may, under exceptional circumstances, assume a pathogenic rôle.

THE SEROLOGICAL CLASSIFICATION AND DISTRIBUTION OF SCARLATINAL STREPTOCOCCI.

It is well known that there are serious technical difficulties associated with the classification of hæmolytic streptococci by serological methods. Much patience and modification of technique, as occasion demands, are necessary in order to obtain results and overcome inconsistencies. This is in large part due to the great tendency of the organisms to form granular growths in fluid media, and to agglutinate spontaneously in saline, and also to the fact that many strains may show antigenic variations, leading to contradictory findings.

The typing of scarlatinal streptococci.—From the mass of conflicting claims of the specificity of the agglutinative reactions of hæmolytic streptococci from various infections, we have concentrated on the work of Smith [5] and Griffith [6, 7], who described a serological classification of hæmolytic streptococci, obtained from cases of scarlet fever. Griffith described four main serological types of scarlatinal streptococci, constantly associated with cases of scarlet fever, and during the past five years I have used his methods and technique, with slight modifications, in the study with my colleague, Dr. W. Gunn, of hæmolytic streptococci from scarlet fever and other infections due to, or associated with, these organisms. The value of this method of investigating hæmolytic streptococci from scarlet fever is seen in the following instances:—

(1) The ready identification of the great majority of strains as scarlatinal.
(2) The identification of the same type (*a*) as the infecting agent when scarlet fever occurs in more than one member of the same family, (*b*) as the cause of an outbreak in a diphtheria or measles ward, or (*c*) as an epidemic in a public school as shown recently by Glover and Griffith [8].
(3) The correlation between infecting type and the clinical severity of the disease.
(4) The prevalence of a particular type, indicating the mildness or severity of an epidemic.
(5) The relation between strains found in secondary attacks to those isolated during the primary infection.
(6) The quantitative and qualitative study of the toxigenic properties of different types.

TABLE I.—THE DISTRIBUTION OF SCARLATINAL TYPES OF STREPTOCOCCI IN 700 CASES OF SCARLET FEVER, 1926-1931.

Year	No. of cases	Percentage of types					
		Type 1	Type 2	Type 3	Type 4	HET	Negative
1926	*100	2	34	17	23	17	7
1927	*100	8	14	26	12	31	9
1928	200	9	25	17	5	36	8
1929	100	18	20	22	3	36	1
1930	100	17	19	19	7	35	3
1931	100	20	16	17	10	34	3
1926-31	700	11·9	21·9	19·3	9·3	32·1	5·5

Types 1, 2, 3, 4 ... ... 62·4%
HET = Heterogeneous type ... ... 32·1%
NEG = Negative on first examination 5·5%

*Investigated by Gunn and Griffith.

The distribution of types in scarlet fever.—Table I shows the distribution of scarlatinal types of streptococci from 700 cases of scarlet fever over a period of six years. It will be seen that during this period the relative distribution of types has not varied greatly; there is a lower incidence of Type 4 strains and an increase in the incidence of Type 1 strains, while the proportion of unclassified strains has remained remarkably constant.

TABLE II.—THE SEROLOGICAL GROUPING OF 26 STRAINS OF SCARLATINAL STREPTOCOCCI.

(*From Prof. U. Friedmann, Berlin.*)

Type	Number of strains	Percentage of strains
1	8	30·8
2	—	—
3	12	46·1
4	4	15·4
Heterogeneous	2	7·7
Total	26	100

I am indebted to Professor Ulrich Friedemann, Berlin, for twenty-six strains of scarlatinal streptococci which, when typed, gave the results shown in Table II. This is noteworthy for the absence of any representatives of Type 2. Using Griffith's four type sera, Williams, and others [9], in New York City, examined a large number of strains of scarlatinal streptococci, and found that the majority could be classified, but they also failed to find a representative of Type 2 in their series. I have personally examined a number of other isolated strains from America, Germany, and Jugoslavia, and although many of them could be classified, I have been unable to assign any to the Type 2 group, which appears to be peculiar to this country.

The occurrence of primary and secondary infecting types and their significance.—In observations carried out weekly on a consecutive series of 200 cases of scarlet fever, during the whole period of detention in hospital, Dr. Gunn and I [10] found that 54% of the patients showed no change in the serological type of streptococcus present in the nose or throat; in addition to the primary type a second type was isolated in 40% of cases, and a third type in 6% of cases. In the group in which no change of type occurred, the average time of disappearance of the streptococcus from the nose and throat was 3·6 weeks, the average period of detention was 6·5 weeks, and 16% of the patients were still carrying the organism on discharge. Among those patients in whom there was an apparent change of type during the course of the disease, the average time of disappearance of the organism from the nose and throat was 5·9 weeks, the average period of detention was seven weeks, and on discharge, 62·6% of the cases were still carrying hæmolytic streptococci in the nose or throat. Among those harbouring the organism on discharge there were four times as many "throat-carriers" as "nasal-carriers," a reversal of the conditions usually found in diphtheria carriers.

Gunn and Griffith [11] have suggested three possible explanations of the change in type of organism occurring in a single case :—

(1) Instability of the serological characters of hæmolytic streptococci. Against this view are the facts that 54% of cases showed no change of type throughout, and when secondary infecting types appeared, they were, as a rule, isolated on repeated examinations.

(2) The influence of antibodies and local conditions *in vivo* may induce a change of type.

(3) Reinfection may occur from association with patients harbouring different types.

While it is impossible to exclude transmutation of type, the weight of evidence is in favour of reinfection, viz: (I) a higher proportion of reinfections occur late when the patients are convalescent and allowed to mix freely with other patients in the ward than during the first three weeks, when patients are confined to bed; (II) the occurrence of complications, such as tonsillitis, rhinitis, or otitis, is often associated with the appearance in the nose or throat of a fresh type; (III) in our experience, two cases of relapse, developing a second typical scarlatinal attack, with rash, sore throat, and temperature, showed different serological types of streptococci from those found in the primary attacks; (IV) patients, isolated by nursing in cubicles, show no change of infecting type throughout the disease.

Throat swabs from patients, taken immediately after admission to hospital, generally give a profuse growth of hæmolytic streptococci; cultures in many cases being almost pure. Cultures repeated at regular intervals usually show a gradual diminution in the proportion of hæmolytic streptococci present, until they disappear altogether, or show only a few scattered colonies on culture plates. The occurrence of reinfection with a fresh type is in some cases associated with the reappearance, following a negative culture, of large numbers of hæmolytic colonies, belonging to a type different from that causing the primary infection. As has been noted, this

group of cases has a very high discharge "carrier-rate" (62·6%), a factor which increases the probability of giving rise to "return-cases," although in our series no return-cases could be traced.

Gunn and Griffiths [11], in their series of 100 cases, found a total carrier-rate on discharge of 49%, while Gunn and I, in our series of 200 cases, found a carrier-rate of 52%. Observations made over a number of years indicate that the average rate of return-cases is 4%, and if we accept the average carrier-rate on discharge as about 50%, the question immediately arises from the small proportion of return-cases as to whether there is any change in the virulence or toxigenic powers of the hæmolytic streptococci from the onset of the attack to convalescence. We have tested the toxigenic powers of streptococci isolated from the nose and throat at various stages of the disease, and also from the desquamation scales, and no change has been found in the potency of the toxins produced. I also carried out some experiments on mice in order to ascertain whether there was any change in virulence, but the results were inconclusive, probably owing to the fact that insufficient strains were investigated, and the numbers of mice used were too small.

Many of the carriers showed only a moderate infection, and it is possible that the low return-case rate is, in some part, due to the altered environment of home conditions, leading to early abolition of the carrier state; the conditions in the ward, as may readily be understood, are conducive to persistence of the carrier state, especially when the convalescent patients are allowed to mix freely.

It is interesting to note that Gunn [12] observed a fairly definite and constant relation between the type of streptococcus and the severity of disease. This observation was fully confirmed by Gunn and Griffith [11] and later by Gunn and Allison [10] in their extensive series of cases. Dr. Gunn will deal more fully with the clinical manifestations in relation to serological type, but it may be noted that Type 1 and Type 2 organisms cause severe infections, with a tendency to complications, chiefly local in the case of the former, and mainly systemic in the latter. Type 3 infections are moderately severe and occupy an intermediate position between Types 2 and 4, the latter type being associated with extremely mild infections, free from complications.

Hæmolytic streptococci in the desquamation scales of scarlet fever.—The significance of the desquamation scales from scarlet fever as a factor in the transmission of the disease has long been a subject of discussion. Reports regarding the occurrence of hæmolytic streptococci in the scales are somewhat conflicting. Friedemann [13] examined the scales of fifty patients, and in only one case did he isolate hæmolytic streptococci, while Deicher [14] was unable to find streptococci in the scales of forty-nine patients during the seven weeks of illness. On the other hand Kanevskaya [15] in Leningrad found hæmolytic streptococci in the scales of thirty patients out of forty examined. Some time ago in collaboration with Dr. Gunn, I examined the desquamation scales of thirty-seven patients. The material was collected after the patients had had a bath, and clean sheets had been put on the beds. The specimens were removed with aseptic precautions and inoculated immediately into blood broth. Hæmolytic streptococci were isolated in ten instances (27%) and were typed as follows: Type 2, two strains; Type 3, three strains; Type 4, one strain; and heterogeneous types, four strains, indicating that the majority of the organisms, at least, were scarlatinal in type. Toxins were prepared from all ten strains, and these were found to be active, varying in strength from 2,500 to 12,500 skin test doses per c.c. when tested on suitable subjects; this indicates that all the strains were toxigenic enough to produce scarlet fever. The failure of Friedemann and Deicher to isolate the organisms in their series of cases was probably due to differences in technique and in the culture medium used.

The Toxins of Hæmolytic Streptococci.

It is generally accepted that the production of a soluble exotoxin, causing typical reactions when injected intradermally into susceptible human subjects is a characteristic of hæmolytic streptococci in general, and is not confined to scarlatinal strains. It is also agreed that the potency of the toxigenic powers of scarlatinal strains is more marked than in the case of non-scarlatinal strains.

The results of our investigations on the properties of toxins from scarlatinal streptococci agree in the main with those of other workers as regards medium for preparation, incubation time, heat resistance and keeping properties.

As already mentioned, clinical observations alone had revealed the fact that the four scarlatinal types of streptococci were associated with infections showing varying degrees of severity. The findings also suggested that the severity or mildness of the disease was tolerably constant for each serological type. We therefore investigated the toxigenic power of representative strains of the four types in order to ascertain whether there was any difference in the potency of the toxins produced.

The quantitative study of streptococcal toxins.—In our experiments we took as the unit of toxin the "skin test dose" as defined by Dyer [16]. The skin test dose was contained in 0·2 c.c. of inoculum, and controls consisted of the same solution heated for two hours at 100° C. and a skin test dose of a standard toxin. Each toxin was tested intradermally on a number of susceptible subjects, usually from 15 to 20 and not less than 10, and three or four dilutions of the toxin to be standardized were tested at the same time on the same subject. The toxins tested were prepared from 20 freshly isolated strains of scarlatinal streptococci, five strains from each of the four types. It was found that the toxins produced by the four types differed quantitatively from each other, but that the content was constant for each type. The toxin content in "skin test doses" (S.T.D.) per c.c. for the four types was as follows: Type 1—25,000 S.T.D., Type 2—12,500 S.T.D., Type 3—10,000 S.T.D., Type 4—1,500 S.T.D. per c.c. It has since been found as the result of testing a large number of toxins that strains belonging to Type 1 do not all produce an equally potent toxin; many toxins from Type 1 strains found in association with scarlet fever possess a potency of about 5,000 S.T.D. per c.c. but a few strains produced toxins containing only 1,000 S.T.D. per c.c. The respective potencies of toxins prepared from strains belonging to the other three types have been found to be remarkably constant, although the recent observations of Glover and Griffith [8] in school epidemics due to Type 2 and Type 3 suggest that these types are also subject to variations in toxigenicity.

The potency of upwards of 60 toxins from heterogeneous strains of scarlatinal streptococci has also been determined by skin tests. As was to be expected, there was no uniformity and the range of potency varied from 250 S.T.D. to 7,500 S.T.D. per c.c. Agglutinating sera were prepared for a number of these strains and those belonging to the same serological group produced toxins of equal potency. The absence of uniformity in the toxigenic powers is in keeping with the serological findings, as the great majority of these strains appear to be highly individualistic.

The conclusion may therefore be justified that the toxigenicity and serological constitution of hæmolytic streptococci, in association with scarlet fever at least, run parallel and serological typing may be regarded as a criterion of toxigenic power.

The qualitative study of streptococcal toxins.—It must be admitted at the outset that we are on less certain grounds in dealing with the qualitative differences between toxins produced by members of the hæmolytic group. Many authorities indeed, notably Parish and Okell [17, 18], deny categorically that there is any justification for assuming that qualitative differences exist. While it is difficult to adduce direct proof of qualitative differences, yet there is available a considerable

amount of evidence which, in our opinion, favours the hypothesis that such differences do exist.

In support of the unity of streptococcal toxins Parish and Okell claimed that scarlatinal and other streptococcal antitoxins could protect rabbits from the acute phase of septicæmia due to streptococci from scarlet fever, puerperal fever, erysipelas, or pyogenic infections, although the best protection in all infections was afforded by the scarlatinal antitoxin.

On the other hand, the work of Davis [19] and Pilot and Dreyer [20], on the toxins of the scarlatinal streptococcus and of the so-called *Str. epidemicus* from an outbreak of epidemic sore throat in America, affords strong evidence of the existence of qualitative differences between streptococcal toxins. They claimed that persons convalescent from scarlet fever and Dick-negative, gave positive skin reactions to the toxins of *Str. epidemicus*; similarly, subjects susceptible to both toxins became negative to scarlet fever toxin following immunization with that toxin, but still gave a positive reaction to *Str. epidemicus* toxin.

Singer and Kaplan [21] carried out cross-neutralization experiments on the toxins and antitoxins prepared from streptococci from scarlet fever and erysipelas, tested by the intradermal injection of susceptible subjects. They found a lack of absolute specificity between the toxins and antitoxins, but suggested that a relative specificity was present, with evidence of overlapping.

The observations carried out on the Schultz-Charlton reaction by Gunn and Griffith [11] and Gunn and Allison [10] suggest that the numerous failures of the Dochez antitoxin, suitably diluted, to blanch the rash of scarlet fever, may be due to differences in the combining properties of toxins from different serological types of scarlatinal streptococci. The Dochez antitoxin was observed to exert a highly specific blanching action (100%) towards Type 3 rashes (27 cases) even though the intensity and duration of the rash were shorter than found in Type 1 or Type 2 groups. The large proportion of rashes in the Type 2 group which were not blanched by the antitoxin (10 out of 23) supports the view that qualitative differences exist between the toxins producing the rashes. Convalescent serum from a patient suffering from a Type 2 infection produced pronounced blanching of rashes associated with Type 2 strains, fewer and less clear-cut reactions with Type 1 rashes, and very variable results in Type 3 and 4 groups, but unfortunately the antitoxin content of the serum was not sufficiently high for the tests to be decisive.

Observations on the Dick reaction in convalescent patients also afford evidence which suggests the existence of qualitative differences. Type 2 cases show a relatively severe infection, and the proportion of Dick-positive reactors on admission (80%) shows a rapid fall until discharge (2%), indicating active production of antitoxin. On the other hand, Type 4 infections are extremely mild, and immunity as shown by the Dick reaction is slowly produced; 100% of cases gave positive reaction on admission and 11% on discharge. It might be inferred from these figures that the greater immunity response in Type 2 infections is due to the fact that Type 2 strains are more highly toxigenic than Type 4 strains. On the other hand, the observation that the positive Dick reaction is quickly abolished in Type 2 infections suggests that the antitoxin produced is better constituted to neutralize the Dick toxin than that produced by Type 4 infections.

Further evidence of qualitative differences between the toxins of scarlatinal streptococci was afforded by a comparison of the dermal reactions to a skin test dose of each of the four type toxins in completely susceptible subjects, and in partially immune patients, convalescent from scarlet fever. Chart 1 shows graphically the dermal reactions in a completely susceptible subject to the four type toxins, the inoculum being 0·2 c.c. of a 1-1000 dilution of each toxin; Type 1 toxin is seen to be the most potent, followed by Types 2 and 3, while Type 4 toxin is very weak. Chart II shows the dermal reactions of a completely susceptible subject to

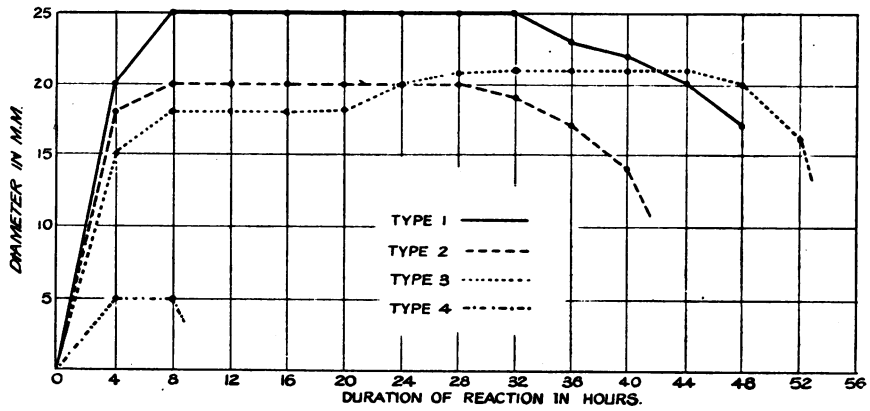

CHART I.—To compare the potencies of the four type toxins in a completely susceptible subject. (0·2 c.c. of a 1 in 1,000 dilution of each toxin given intradermally.)

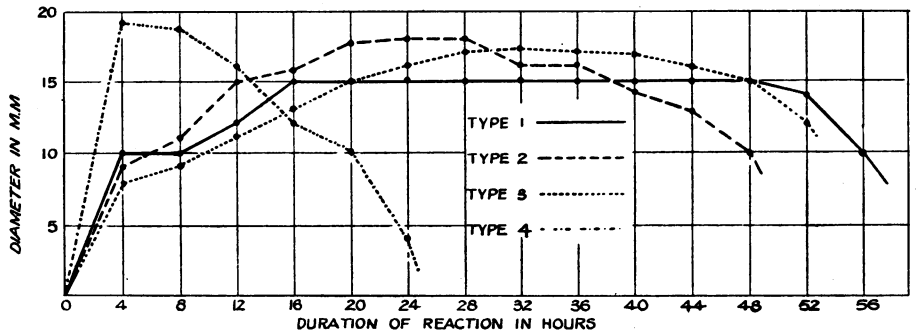

CHART II.—To show the reactions produced by *one skin test dose* of the four type toxins in a completely susceptible subject.

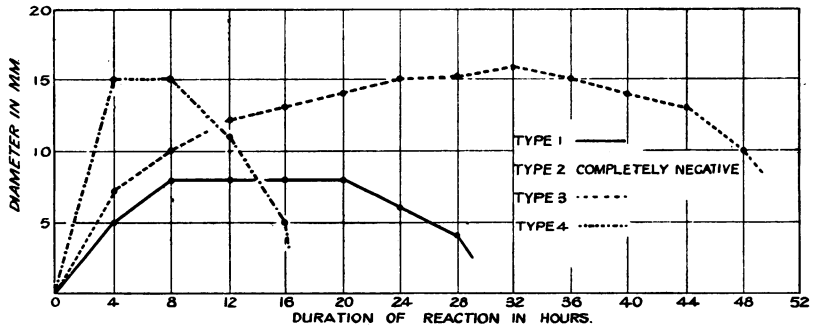

CHART III.—To show the reactions produced by *one skin test dose* of the four type toxins in a partially immune subject, infected by a Type 2 scarlatinal streptococcus.

one standardized skin test dose of each of the four type toxins; attention may be drawn to the sudden rise, short maximum and rapid disappearance of the reaction due to Type 4 toxin as compared with reactions produced by the other three Type toxins, which show a gradual rise and prolonged maximum, followed by fading. Chart III shows the dermal reactions to one standardized skin test dose of each of the four type toxins, of a partially immune subject convalescent from scarlet fever due to a Type 2 streptococcus; in this case the Type 2 toxin shows a completely negative reaction, while the other three type toxins produce well-marked positive and characteristic reactions, only slightly weaker than those found in a susceptible subject. The reactions indicate that the antitoxin produced in the patient's blood by the infecting strain (Type 2) has completely neutralized the skin test dose of Type 2 toxin, and has only slightly weakened the characteristic reactions produced by the other three type toxins. This result is very suggestive of qualitative differences between at least Type 2 toxin and the other three Type toxins, with some evidence of overlapping.

Further support of this hypothesis was afforded by a series of skin neutralization tests carried out with the toxins of the four serological types, and a standard antitoxin of known potency for the toxin-antitoxin mixtures. It was shown conclusively that Type 3 toxin was most readily neutralized by the antitoxin employed, and Type 4 least so, while Types 1 and 2 toxins occupied an intermediate position.

Similarly, using antitoxins prepared from Type 2 and Type 3 toxins, it was found that the homologous antitoxin neutralized its own toxin at higher dilutions than the other type toxins.

It seems probable that further work on the streptococcal toxins will show that while a considerable amount of overlapping occurs, qualitative differences do exist between toxins from different strains of scarlatinal streptococci, as well as between toxins from strains associated with conditions such as erysipelas, puerperal fever, and pyogenic infections. The results suggest that the toxins have a complex structure, and if further work confirms this view, the streptococcal antitoxin of the future should be a polyvalent one produced from the toxins of hæmolytic streptococci, isolated from different infections and belonging to different serological types.

Tonsillitis.

There can be little doubt that tonsillitis is one of the most important local manifestations of infection with hæmolytic streptococci. Attention has frequently been drawn to the close resemblance between acute tonsillitis and scarlet fever. If from the clinical picture of scarlet fever we omit the rash, which results from the action of toxin, the similarity is very striking. It is a not uncommon experience for an attack of scarlet fever in one member of a household to be preceded by the occurrence of tonsillitis or pharyngitis among other members of the same household, suggesting that the same organism may be associated with different clinical conditions.

The occurrence of tonsillitis in children is probably more frequent than is suspected. In the laboratory I have been struck, especially during the epidemic season for diphtheria, by the number of cultures received between the second and fifth day of illness from cases admitted to fever hospitals as diphtheria. The great majority of these cultures gives an almost pure growth of hæmolytic streptococci with absence of diphtheria bacilli, and the fact that the cultures were sent to the laboratory at this stage of the disease, suggests that the medical officers concerned did not agree with the outside diagnosis of diphtheria. Such cases would appear in the official returns as diphtheria, when in reality they were cases of acute streptococcal tonsillitis.

Griffiths [6] and Smith [22] have both isolated scarlatinal types of hæmolytic streptococci from the throat in cases of acute tonsillitis. I isolated a Type 2 strain

from my colleague, Dr. Gunn, during an acute attack of sore throat; the organism produced a potent toxin, and as Dr. Gunn was Dick-negative, it was evident that his antitoxic immunity was no protection against invasion. This factor is probably of considerable importance in the correlation of tonsillitis and scarlet fever, and in this connection the investigations of Glover and Griffith [8] into school epidemics of acute tonsillitis due to hæmolytic streptococci are of unusual interest. Their observations, with which Dr. Gunn will deal in more detail, show that epidemics of acute tonsillitis may be due to scarlatinal types of streptococci, having a very low toxigenic power, and indicate the value of serological typing as a means of identifying the causal organism in tonsillitis, and especially in epidemics, of studying the method of spread, and the varying clinical manifestations and complications associated with a particular serological type. The evidence of these workers indicates that infection of the throat by hæmolytic streptococci may range from healthy carrier through tonsillitis, febricula, and pharyngitis, to scarlet fever; the latter infection is associated with the more highly toxigenic members of the group, which however only produce scarlet fever when their toxigenic powers are sufficiently high to overcome the antitoxic immunity of the host.

Puerperal Fever.

Recent work on the bacteriology of puerperal fever has implicated the hæmolytic streptococcus as the infecting agent in the great majority of cases, and in practically all fatal cases of puerperal septicæmia. Kinloch, Smith, and Stephen [23] isolated the organism from uterine cultures in 49 out of 56 cases (87·5%) of puerperal fever, and from the blood in 28 out of 31 positive cultures from 86 patients. In a series of 36 cases of puerperal fever which I examined bacteriologically the hæmolytic streptococcus was isolated as the infecting organism from 30 (83·3%). Many workers (Fromme [24], Kanter and Pilot [25], Lockhart [26]) have examined the flora of the vagina during the puerperium and before and after labour, and their results show that during the puerperium and immediately prior to labour, the hæmolytic streptococcus is present in rather less than 1% of cases, which is in keeping with the belief that exogenous is of greater importance than endogenous infection. The history of puerperal fever can show many instances where epidemics of this infection, occurring in lying-in hospitals, have been traced to infection from without. Smith [27] has shown that in no less than 12 cases of puerperal fever and septic abortion, out of a total of 21, the infecting strains of hæmolytic streptococci originated in the throat or nose of the doctor, nurse or student in attendance. More recently, I [28] isolated a Type 1 and a Type 3 scarlatinal streptococcus as the infecting organisms from two cases of puerperal fever, and also cultured the same serological types of organisms from throat swabs of midwives in attendance upon the respective patients. In one case I have also found a Type 2 scarlatinal streptococcus as the cause of puerperal fever. These results, and those of Smith, confirm the importance of the throat as a vehicle of infection in puerperal cases, and support the recommendation of the Ministry of Health in the Interim Maternal Mortality Report (1930) that there should be a wider use of masks and more effective antiseptic precautions by persons in attendance on midwifery cases. Infection of the puerperal patients by strains of streptococci, associated with scarlet fever, from the throats of persons in attendance, probably accounts for cases of puerperal scarlet fever which sometimes occur. I have prepared toxins from several strains of hæmolytic streptococci from puerperal fever, and skin tests have shown that they were active, although the potency fell, as a rule, considerably below that of the scarlatinal toxins. Most of the toxins of puerperal streptococci, tested by Smith, had a potency of about 5,000 S.T.D. per c.c., but the highest toxin content I have found was 2,500 S.T.D. per c.c. This suggests, in view of the high mortality,

that the puerperal streptococci depend, for their pathogenic action, to a greater extent on their invasive properties than on their toxigenic power.

Erysipelas.

Erysipelas is the classical example of acute streptococcal infection, and is remarkable in that one attack confers little protection against subsequent infection. This peculiarity is also often seen in tonsillitis among streptococcal infections, and in boils and the "common cold" among non-streptococcal infections.

Tunnicliff [29] and Birkhaug [30] claimed to recognize serological groups among streptococci from erysipelas and state that they show a high degree of specificity. Much of their work remains unconfirmed, and Stevens and Dochez [31] in a careful study conclude that while hæmolytic streptococci from erysipelas form a closely related group, and scarlatinal streptococci also form an equally compact group, the two groups are related antigenically. Smith [22] found a Type 1 scarlatinal streptococcus as a cause of erysipelas on one occasion, but I was unable to recognize any scarlatinal types among a series of twelve erysipelas strains examined. Smith also pointed out from an examination of the case-rates of scarlet fever, erysipelas and puerperal fever in England and Wales, and in Scotland, between the years 1911-24, that there is a marked increase in the incidence of erysipelas when scarlet fever is epidemic, while the case-rate for puerperal fever shows no such fluctuations.

It is worthy of note that erysipelas is an extremely rare complication of scarlet fever, despite the fact that the latter disease is not infrequently complicated by conditions such as streptococcal rhinitis with excoriations and ulceration of the nares, impetigo contagiosa, and streptococcal onychia. It would appear therefore that the erysipelas group of streptococci possess a high degree of specificity in the nature of the infection they produce, and that antitoxic immunity is not effective against invasion of the skin by these strains.

Hæmolytic Streptococci as Secondary Invaders.

Hæmolytic streptococci may occur as secondary invaders in almost any infective disease, and under such conditions may be of considerable epidemiological importance. Recently I examined, in collaboration with Dr. Gunn, nasal and throat swabs from 100 consecutive cases of diphtheria for the presence of hæmolytic streptococci. The swabs were taken on admission to hospital and hæmolytic streptococci were isolated from the nose or throat in sixty-two cases. A similar series of swabs from 100 cases of measles yielded hæmolytic streptococci on thirty-two occasions. None of the ninety-four strains isolated were found to belong to any of the four main types of scarlatinal streptococci. Apart from these two series of cases, I have on one occasion isolated a Type 2 scarlatinal strain from an empyema following measles and a Type 2 strain has also been found as a secondary invader in the throat in a case of diphtheria. It is probable that such strains are associated with outbreaks of scarlet fever in diphtheria and measles wards.

Hæmolytic streptococci are also important as secondary invaders in many of the acute respiratory infections. Williams, Nevins, and Gurley [32] studied the nasopharyngeal flora in persons suffering from the common cold and from influenza, as compared with the organisms present in normal subjects. Normal persons harboured the hæmolytic streptococcus in 6% of cases, persons suffering from colds in 16% of cases, and influenza patients in 27% of cases. In secondary broncho-pneumonia following influenza, Dwinell [33] found, in sixty-nine autopsies on fatal cases, the hæmolytic streptococcus present in 59% of cases, Pfeiffer's bacillus being second in order of frequency with 49%. There is little doubt

that a considerable proportion of complications and fatal terminations to these infections is due to the implantation of a virulent strain of hæmolytic streptococcus on the primary infection; the local conditions are probably so altered by the action of the primary invader as to favour infection by this organism. The frequency with which the hæmolytic streptococcus occurs as the cause of complications in influenza, measles, and, occasionally, diphtheria, may be associated with the increase in the carrier-rate and spread of the organism seen especially during epidemics.

REFERENCES.

[1] SMITH, T., and BROWN, J. H., *Journ. Med. Res.*, 1915, xxxi, 455. [2] BROWN, J. H., *Mono. Rock. Inst. Med. Res.*, 1919, No. 9. [3] TUNNICLIFF, R., *Journ. Amer. Med. Assoc.*, 1917, lxviii, 1028. [4] Id., *Journ. Infec. Dis.*, 1918, xxii, 462. [5] SMITH, J., *Journ. Hyg.*, 1926, xxv, 165. [6] GRIFFITH, F., *ibid.*, 1926, xxv, 385. [7] Id., *ibid.*, 1927, xxvi, 363. [8] GLOVER, J. A., and GRIFFITH, F., *Brit. Med. Journ.*, 1931 (ii), 521. [9] WILLIAMS, A. W., GURLEY, C. R., and others., *Arch. Path. and Lab. Med.*, 1927, iv, 481. [10] ALLISON, V. D., and GUNN, W., *Ann. Rep. Met. Asylums Board*, 1928-29, 262. [11] GUNN, W., and GRIFFITH, F., *Journ. Hyg.*, 1928, xxviii, 250. [12] GUNN, W., *Ann. Rep. Met. Asylums Board*, 1926-27, p. 177. [13] FRIEDEMANN, Professor U, *Deutsch. med. Wochenschr.*, 1926, lii, 2147. [14] DEICHER, H., *Zeitschr. f. Hyg. u. Infkr.*, 1927, cviii, 167. [15] KANEVSKAYA, M. I., *Centralbl. f. Bakt.*, Ref., 1927, lxxxviii, 18. [16] DYER, R. E., *Pub. Health Rep.*, Washington, 1928, xliii, 1659. [17] PARISH, H. J., and OKELL, C. C., *Lancet*, 1928 (i), 746 [18] OKELL, C. C., and PARISH, H. J., *ibid.*, 1928 (i), 748. [19] DAVIS, D. J., *Journ. Amer. Med. Assoc.*, 1929, xciii, 978. [20] PILOT, I. E., and DREYER, I., *Journ. Infec. Dis.*, 1931, xlix, 135. [21] SINGER, H. A., and KAPLAN, B., *Journ. Amer. Med. Assoc.*, 1926, lxxxvii, 2141. [22] SMITH, J., *Journ. Hyg.*, 1927, xxvi, 420. [23] KINLOCH, J. P., SMITH, J., and STEPHEN, J., *Maternal Mortality*, 1928, Scottish Board of Health, H.M. Stationery Office. [24] FROMME, F., *Arch. Gynäk.*, 1908, lxxxv, 154. [25] KANTER, A. E., and PILOT, I., *Surg. Gyn. and Obst.*, 1924, xxxviii, 96. [26] LOCKHART, L. P., *Journ. Obst. Gyn. Brit. Emp.*, 1925, xxxii, 49. [27] SMITH, J., *Causation and Source of Infection in Puerperal Fever*, 1931, Dept. of Health for Scotland, H.M. Stationery Office. [28] ALLISON, V. D., *Lancet*, 1931 (ii), 844. [29] TUNNICLIFF, R., *Journ. Amer. Med. Assoc.*, 1920, lxxiv, 1886; *ibid.*, 1920, lxxv, 1339; *Journ. Infec. Dis.*, 1921, xxix, 91. [30] BIRKHAUG, K. E., *Bull. Johns Hop. Hosp.*, 1925, xxxvi, 248; *Brit. Med. Journ.*, 1926, ii, 518. [31] STEVENS, F. A., and DOCHEZ, A. R., *Journ. Exper. Med.*, 1926, xliii, 379. [32] WILLIAMS, A. W., NEVINS, M., and GURLEY, C. R., *Journ. Immun.*, 1921, vi, 5. [33] DWINELL, W. G., *Amer. Journ. Med. Sci.*, 1919, clviii, 216.

II.—Dr. William Gunn.

Although a vast amount of research and a flood of literature have been focussed on the streptococcal infections in recent years, we feel that no apology is needed for bringing this subject up for discussion before the Section, for the streptococcus admittedly occupies a high place, possibly chief place, in the production of human disease. Each fresh study only serves to widen the apparent range of its activities both in acute and chronic conditions, and, even now, our knowledge is still nebulous in many directions, especially in respect of the milder grades of streptococcic invasions. While we propose to direct our survey chiefly to infections which tend characteristically to attain epidemic proportions and in which the streptococcus is accepted as the causative organism, we cannot ignore a large number of infective conditions in which the streptococcus is only probably the primary agent, in which it is merely a secondary invader, or in which the tendency to epidemicity is not always apparent.

Dr. Allison has already described the cultural, biological and serological characteristics of the hæmolytic streptococcus; he has explained why the discussion is being restricted to it, to the exclusion of viridans and fæcalis strains, so that it is unnecessary for me to deal with the strictly bacteriological aspect of our subject, except to examine the bearing of special properties of the streptococcus in the causation of diverse clinical conditions.

In common with other pathogenic micro-organisms, the streptococcus must needs possess certain definite properties before it can successfully invade a population and cause manifest disease therein. Two serious difficulties are encountered at the

outset in identifying the streptococcus as the causative organism in any disease. In the first place, it is an almost constant inhabitant of the human nose, throat or nasopharynx, and its distribution is world-wide; to assess its pathogenic importance in a given case may therefore be difficult, at times even impossible. In the second place, for its identification and proof of pathogenicity, complicated and laborious tests involving the human subject are necessary, as laboratory animals are practically all immune to the toxins of the organism. Recent work on the toxigenicity and virulence of streptococci has widened our knowledge of these properties in certain well-defined diseases, but it can hardly be held to simplify matters. Indeed, the reverse would seem to be true, and the " streptococcus problem " appears to increase in complexity the further we advance.

It is therefore imperative that we should be clear and exact in our use of terms, especially when discussing those problems which equally concern the bacteriologist, on the one hand, and the clinician and epidemiologist on the other. For instance, the term virulence, to the bacteriologist, means the power to invade, and multiply in, the tissues of the host, including the blood-stream, while, by the clinician, the term is usually employed to include all the pathogenic properties of the organism, and is associated intimately in his mind with severity of disease. It will possibly be worth while discussing at this juncture the modes of transmission of infective disease and the mechanism of infection and immunization, in order to meet our problems openly, if we cannot hope to solve them outright.

The natural habitat of the streptococcus is the nose, nasopharynx, and mouth of the human subject; here it finds a suitable pabulum, for a time at least, multiplying and provoking certain local reactions which are frequently on the boundary line between the physiological and the pathological. After a brief period, from seven to ten days or so, the organisms tend to diminish in numbers, and gradually die out in three to five weeks. By the use of highly selective media, however, it has been shown recently that hæmolytic streptococci in sparse numbers can usually be obtained in most individuals for long periods, and that not merely during times of unusual prevalence of scarlet fever or tonsillitis. The human subject is the great reservoir of the organism and no method of diminishing the incidence of streptococcal infections can succeed unless this fact is taken into account. In the past undue attention was paid to the part played by inanimate carriers, or fomites as they were called, in the propagation and dissemination of human disease. We know now that such foci are relatively ineffective; multiplication rarely, if ever, occurs, except in a few special vehicles such as milk, and exposure to sunlight and drying rapidly diminishes their numbers and probably tends to attenuate their virulence. The human subject spreads infection by coughing, sneezing and spluttering, whereby mucus charged with organisms is projected in the form of droplets. Being in a particulate state and heavier than air, these tend to sink to the ground under the influence of gravity but may be carried a considerable distance in a highly infective state, especially when air currents are present. In this manner may be explained the great risk of infection in overcrowded workrooms, places of entertainment and dormitories; this risk is probably increased by a free current of air, even of fresh air. Dormitories were first implicated as forming a suitable environment for the spread of streptococcal infections in a positive manner by Bloomfield and Felty in 1923, when they found that tonsillitis broke out afresh when the sleeping accommodation of nurses was rearranged so that they came into contact with a new set of room-mates. It was shown that the close contact of a sleeping room was necessary to bring about infection, whereas the ordinary casual contact of the wards and day-rooms was not enough. Just recently Glover and Griffith (1931) have stressed in convincing fashion the paramount importance of such intimate contact in spreading infection. The difficult problems of dosage and effective contact have been studied in detail by Dudley (1923). He has shown that a certain minimal dose, the critical

dose, of a virus is necessary to cause manifest disease. A smaller dose is probably a frequent event but it is rapidly eliminated or destroyed by the defence mechanism of the body—the healthy mucous membrane and the intact skin, in the first place. If the subject receives a succession of sub-minimal doses, which added together is greater than the minimal infecting dose, the balance between rate of infection with these fractional doses and the rapidity of destruction or elimination of the virus must determine whether or not the subject develops the disease. Successful invasion merely implies implantation of organisms on and between the body cells; to secure infection there must follow multiplication of the organisms and penetration of the tissues by them, with production of manifest disease. Where infection has taken place without the accompaniment of recognizable disease the term sub-infection or latent infection is commonly applied. In the streptococcal infections this latent infection and subsequent immunization, or, it may be, increased susceptibility, are characteristic features and explain the apparent vagaries of attack and escape in a given population. As the streptococcus is ubiquitous, we are all frequently invaded, but infection only supervenes when there is temporary lowering of our defences, local or general.

While the mechanism of infection has been studied in detail and the theories underlying it have been placed on a sound scientific basis, we are on less sure ground when we face the problems of identification of strains of the invading organisms and possible variations in their pathogenicity. Landmarks in the work of identifying the hæmolytic streptococcus were made by Baginsky and Sommerfeld in 1900, by Dochez and Bliss in 1920, and by Griffith, Smith and James in 1926. The first named workers introduced the method of classification of scarlatinal strains of hæmolytic streptococci by serological methods but they were only partially successful and further attempts were abandoned for some time. Dochez and Bliss claimed to have been able to assign all streptococci from scarlet fever cases into a single serological group. The advantage of this would be enormous but, unfortunately, subsequent investigations proved their claims to be invalid. By the discoveries of the Dicks a fresh impetus was given to the study of the hæmolytic streptococci all over the world. Griffith, Smith and James, working independently, although they exchanged cultures and sera, found that they were able to assign nearly two-thirds of the strains associated with scarlet fever in this country into four well-defined and sharply demarcated serological groups, named by Griffiths, Types 1, 2, 3 and 4, respectively, while there remained a number of strains, roughly one-third, which they failed to classify, either because they were highly individualistic in antigenic structure or because they possessed but little capacity to infect. It was assumed, although positive proof was not available at the time, that by these methods a large proportion of scarlatinal strains, or at least, of strains potentially capable of producing scarlet fever, could be identified with certainty.

Nearly a year after their investigations were published I collected the clinical data regarding the patients from whom Dr. Griffith's swabs were taken and, on analysis, found that Type 2 infections were the most severe and included nearly all the cases of nephritis, rheumatism and endocarditis; Type 1 cases displayed considerable variability in degree of rash and severity of initial attack, but a high incidence of local complications such as adenitis, otitis and mastoiditis; Type 3 infections were of moderate severity and represented fairly closely the moderate or mild type of scarlet fever prevalent within recent years, while Type 4 infections were invariably mild, never causing any complications, local or constitutional. When complications did occur in association with Type 4 infections, evidence of reinfection by a more highly toxigenic strain was found in every case in the throat or nose and in the local lesion, e.g., otitis. Considerable diversity was observed, as might be expected, in the unclassified group, both in respect of the character of the initial attack and of the occurrence of complications, but, as a rule, those strains

were associated with mild clinical forms of the disease. The same close relation between serological type and severity of associated infection was observed in three separate series of scarlet fever cases examined during the period of seasonal prevalence in three successive years and fully confirmed the previous findings (Gunn and Griffith, 1928; Allison and Gunn, 1928-29).

The toxin-producing power of representative strains of the four main serological types was determined by the usual methods of assay; the results were found to be in agreement with the clinical findings, even in respect of the toxigenic differences shown by certain Type 1 strains with which some difficulty in serological classification was encountered. In other words, the strains elaborated *in vitro* an amount of toxin which was compatible with the clinical manifestation of infection in the human subject produced by the same organisms. Not only did the four types produce different amounts of toxin which were constant for each type, but all the evidence, clinical and experimental, favoured the view that important qualitative differences existed between these toxins which were responsible for the different clinical types of disease and for the inconstant therapeutic effect of a monovalent serum. As all the serological types we examined were derived from scarlet fever cases, or from infections in which a scarlatinal source could not be definitely excluded, and as all the strains returned a constant toxin value for each group, we concluded that all members of each serological group were capable of causing scarlet fever under suitable conditions. A grave defect of our investigations was our inability to classify and identify strains of hæmolytic streptococci from extra-scarlatinal sources, e.g., measles, diphtheria, and influenza, although these organisms were probably quite as infectious as the scarlatinal or classifiable types. Moreover, the existence of overlapping of antigenic constituents in certain typed strains and the possibility of intermediate strains between the four main groups presented such serious difficulties to many workers, notably McLachlan and Mackie (1928), that they are inclined to doubt the value or validity of serological typing.

Such was the state of the streptococcus problem from the serological viewpoint, when an important paper appeared on the incidence of tonsillitis and allied infections in certain public schools in this country. This work, I venture to predict, will, at no distant date, be regarded as an epoch-making one in the history of streptococcus research. Drs. Glover and Griffith (1931) investigated several epidemics of tonsillitis, scarlet fever, and rheumatic fever, and correlated the clinical data with the strains of hæmolytic streptococci associated with each outbreak, using agglutination methods for their identification and classification. Several of the outbreaks of tonsillitis were caused by classified strains belonging to Types 1 and 2, but in some instances new types emerged, as invasive, as infectious, and even as highly toxigenic in some instances, as representatives of the main serological groups. The manner of spread of infection caused by a single strain, sometimes over long periods, was followed in several outbreaks, and it was conclusively shown that it was determined principally by the close spacing of beds in dormitories. Important—and, as it appeared to the observers at the time, conflicting—observations were made on the varying reactions of different individuals to the same infecting agent. In one subject the result was frank scarlet fever, in another, tonsillitis, in a third, influenza or febricula, and in a fourth, a symptomless infection. These diverse clinical conditions, and especially the low incidence of scarlet fever in many of the outbreaks associated with classified strains, were attributed at first to the high antitoxic immunity of the population attacked. While this explanation would account for many apparent inconsistencies, it was regarded as highly improbable, for it is well known that the antitoxic immunity of the well-to-do classes is usually low, and the results of Dick-testing the boys in two of the schools fully confirmed this. They were therefore forced to the hypothesis that many of the classifiable strains they examined had partially or completely lost their toxigenicity, but when their paper was published they had not had an opportunity

of determining the toxin-producing powers of these strains. I have since then investigated the toxigenicity of all the strains in question, and the results have furnished a complete explanation of the apparent discrepancies between serological type and the clinical condition associated therewith. It was ascertained that certain strains belonging to the four main groups (only Types 1 and 2 were encountered in these outbreaks) had lost their Dick toxin-producing power but apparently retained unaltered their invasive and infective properties, so that the incidence of otitis, mastoiditis, &c., was high in many instances. We have had no evidence, so far, to show whether these atoxigenic strains of the serological group represent the natural or primary state of the species, or whether they have undergone degradation of toxigenicity by the natural process of dilution, by separation from their host, or by contact with an immune host.

These investigations have opened up new fields of inquiry into the nature of the poison elaborated by the hæmolytic streptococcus. Since the discovery of Dick toxin, interest was focussed mainly on the erythrogenic fraction, but it would now appear that this is only a small, and probably relatively unimportant, part of the streptococcus toxin. Its existence in a given strain, so far from constituting a danger, actually is a boon, for it provides a friendly warning of the presence of a deadly enemy, which can only be combated by timely medical and nursing care. The insidious atoxigenic strains appear capable of producing all the complications we usually associated with frank scarlet fever, with the possible exception of nephritis. The series investigated is too small to warrant any conclusions on this latter point.

A broader conception of the pathogenic activities of the hæmolytic streptococcus is needed, as each fresh investigation produces further evidence of its manifold variations. A convenient clinical classification of streptococcal infections has been made by Glover and Griffith, viz. : (1) Symptomless infection or the healthy carrier state. (2) Febricula, feverish catarrh or pharyngitis, without noticeable sore throat or tonsillar involvement. (3) Tonsillitis of varying degrees of severity. (4) Scarlet fever.

The clinical condition encountered in a given epidemic is determined by the invasiveness and toxigenicity of the invading streptococcus and the state of immunity or otherwise of the population attacked. If the proportion of Dick negative reactors is high, then scarlet fever will be infrequent or absent, however high the toxigenicity of the strain, but, on the other hand, an atoxigenic strain cannot produce scarlet fever, however susceptible the population, unless exaltation of toxigenicity occur by repeated passages. So far, we have not observed this phenomenon. On the other hand, there appear to be grounds for believing that increase in invasiveness does occur, but in the absence of a specific test of susceptibility to invasion no conclusion is warranted. In collaboration with Dr. Griffith, I have carried out some experiments with emulsions of bacterial protoplasm prepared from highly invasive but atoxigenic strains of hæmolytic streptococcus isolated during these outbreaks, and the results of intracutaneous injection are suggestive of some connection between sensitivity to the "endotoxin" and liability to invasion. Most children, even those who give a strongly positive Dick reaction, are quite insensitive to endotoxin, while adults, particularly if prone to tonsillitis, tend to be highly sensitive, irrespective of their response to Dick toxin. Endotoxin differs from Dick toxin in being relatively heat-stable and unneutralizable by antitoxin. It remains to be seen whether the endotoxin reaction is simply an allergic phenomenon, indicating sensitization to bacterial protein, or whether it is a reliable test of immunity or otherwise to invasion. Collins (1931) has recently investigated the action of a similar endotoxin prepared from strains of hæmolytic streptococci found in association with rheumatic fever. He has shown that rheumatic patients are much more sensitive to the product than a series of

controls, and he has adduced evidence to suggest that acute rheumatism probably represents an allergic state, following streptococcal tonsillitis at an interval of from ten to twenty-one days—the so-called "silent period."

This brief survey of the properties of the hæmolytic streptococcus and the possible reactions of the human body to its activities may enable us to appreciate how apparently the same organism may cause such widely diverse clinical conditions as puerperal fever, wound and burn—scarlet fever, cellulitis, erysipelas, impetigo contagiosa, and the nasopharyngeal and respiratory complications of measles, influenza, diphtheria and whooping-cough—to mention but a few. The reservoir of infection is the nose, nasopharynx and throat of the human subject and the different clinical states it produces depend upon: (1) the specific properties of the organism, which differ for each strain; (2) the site of implantation and invasion, and (3) the resistance, local and general, of the host. Should a highly toxigenic strain invade a Dick-positive reactor, whether the site be skin, uterus, or throat, a general rash results; to this rash-producing toxin the body cells prepare an antitoxic immunity which usually lasts during life. On the other hand, the human body produces little antibody in response to invasion locally; if such is evoked, it appears to be transient, and is frequently succeeded by a period of lowered resistance. The immediate task before us is to seek out the means whereby resistance may be raised in anticipation of invasion, or succour may be provided at the height of the battle, by the administration of an efficent anti-bacterial serum.

REFERENCES.

ALLISON, V. D., and GUNN, W., *Ann. Rep. Met. Asylums Board for 1928-29*, p. 268. BAGINSKY, A., and SOMMERFELD, P., *Berlin. klin. Wochenschr.*, 1900, xxxvii, 588. BLOOMFIELD, A. L., and FELTY, A. R., *Johns Hopkins Hosp. Bull.*, 1923, p. 393. COLLIS, W. R. F., *Lancet*, 1931 (i), 1341. DOCHEZ, A. R., and BLISS, W. P., *T. Amer. Med. Assoc.*, 1900, L. xxiv, 1600. GLOVER, J. A., and GRIFFITH, F., *Brit. Med. Journ.*, 1931 (ii), 521. GRIFFITH, F., *J. Hyg.*, 1926, xxv, 358. GUNN, W., and GRIFFITH, F., *J. Hyg.*, 1928, xxviii, 250. GUNN, W., *Ann. Rep. Met. Asylums Board for 1926-27*, p. 177. JAMES, G. R., *J. Hyg.*, 1926, xxv, 415. MCLACHLAN, D. G. S., and MACKIE, T. J., *J. Hyg.*, 1928, xxvii, 225. SMITH, T., *J. Hyg.*, 1926, xxv, 165.

Discussion.—Dr. J. E. MCCARTNEY said that a considerable amount of work had been done in connection with the paper and many hundreds of strains of hæmolytic streptococci had been examined. The results of the investigation showed quite definitely that quantitative and qualitative differences in the toxins did occur, and these might account for diversity in the clinical picture. The epidemiological value of typing the strains was great. The technique of typing gave a clear-cut result and the agglutination between the streptococci and type sera is just as pronounced and clear as the agglutination of the red blood-cells for blood grouping. The value of typing was that it enabled a strain of hæmolytic streptococci to be traced from person to person in an epidemic. [Dr. McCartney cited a recent instance in his own work.] A noteworthy point was the absence of Type 2 infections in the United States and on the Continent. This was similar to the findings in pneumococcal types, of which the prevalent types in New York were quite different from those responsible for pneumonia on the Rand. Similarly, Type 2 strain, although an epidemic strain here, was rare or absent abroad. Some of the heterogeneous strains in this country would belong to epidemic types in others. An important fact to bear in mind when correlating bacteriological and clinical results, was that the toxigenic power, i.e., ability to produce an exotoxin, bore no definite relationship to virulence, i.e., power of invading and causing disease. If a recently isolated hæmolytic streptococcus were tested, it would be found to produce a powerful toxin as tested in man, and be capable of killing a mouse in high dilutions when injected into that animal. When the organism was successively cultured in artificial media it still produced a powerful exotoxin, but quickly became progressively weaker in its power of affecting the mouse until finally very large doses of the organism might not suffice to kill the animal. It should be realized that the toxigenic power was tested on humans who were susceptible, whereas the virulence tests were carried out on animals (rabbits and mice), for toxigenic capacity and

virulence could only be compared by tests on the same species. The differences in toxigenicity and virulence would help to explain why the hæmolytic streptococcus gave rise to a diversity of clinical conditions, e.g., scarlatina, tonsillitis, erysipelas and puerperal fever, and why each disease, when passed from one human to another, bred true.

Dr. E. W. GOODALL said that while listening to this interesting and suggestive paper a suspicion had crept into his mind that perhaps, after all, we had not got hold of the real cause of these diseases, and especially of scarlet fever. As Dr. Gunn had admitted, there were sceptics to be met with. He (the speaker) remembered Proteus X 19, which though not the cause of typhus, was yet agglutinated by typhus serum. Therefore was not the idea held by most clinicians till recently, right after all—namely, that the true cause of scarlet fever was not known and that the cocci were only secondary invaders? On the other hand, we had to admit that a toxin had been obtained which produced fever and the characteristic rash of scarlet fever in the human subject. That experiment, and others which derived from it, seemed to place the streptococcus as the true cause of the disease.

Dr. Gunn had said that definitions were necessary, a statement with which he (Dr. Goodall) quite agreed. He would therefore ask Dr. Gunn to define more exactly what he meant by the word "mild" and "severe" as applied to scarlet fever, as they evidently differed widely from his, the speaker's, use of them. He preferred the old classical and clinical words "benign" (or "mild"), "anginous" (or "septic"), and "malignant" (or "toxic"); and he suggested that in any future observations on the connection between the form of the attack and the type of coccus, those terms be used. Had Dr. Allison and Dr. Gunn had the opportunity of investigating a case of malignant scarlet fever? The investigation of such a case ought to yield valuable results. He would also like to have an exact definition of the terms "virulent" and "power of attack or invasion." He was surprised to hear that the virulence of a micro-organism had nothing to do with its toxicity.

The rash of scarlet fever was produced by the toxin of certain cocci. But it was to be remembered that there were other sorts of rashes, due, apparently, to these organisms. They had been observed, especially, in some of the severe outbreaks of milk-borne origin, of acute faucial inflammation in which streptococci were said to be the offending organisms. They had also been described as secondary rashes in scarlet fever. Were they due to a special toxin or to a protein such as had been mentioned by Dr. Gunn?

Turning to the epidemiological side of the paper, we knew that scarlet fever had been recognized as a distinct disease since Sydenham's days. Since then it had undergone various changes in severity. About seventy years ago it began to grow less severe and that decline had been going on ever since, till at the present day the disease was perhaps milder than it ever had been. According to the views advanced that evening it was clear that in past times a very toxic type of coccus must have been in the ascendant which now had disappeared. But as scarlet fever was still as prevalent as ever it was, the toxic type must either have been changed into—or been replaced by—a mild one. The discussion of the cause of that alteration raised the question whether the changes took place in the seed or in the soil. Of recent years opinion seemed to have been gaining ground that changes in external conditions, such, for instance, as those imposed by the weather, affected the soil, i.e., the human being, rather than the seed, i.e., the micro-organism. The observations related that evening showed that alterations took place in the seed by whatever means those alterations were brought about. In a series of cases occurring during the years 1905-14, analysed by Professor Greenwood and Mr. Russell, the data having been provided by himself (Dr. Goodall), it was found that the septic variety of the disease had a different seasonal prevalence from that of the mild. That fact seemed to show that changes in the seed were responsible for some of the changes in the epidemiological behaviour of the disease, but while he was inclined to attribute some importance to changes in the seed, yet equal, if not more, importance was to be attached to the influence of the environment upon the soil, considered individually and in the mass.

Dr. V. D. ALLISON (in reply) said it was important to realize that the Dick test was an index of susceptibility or immunity to the exotoxin of hæmolytic streptococci, and that the toxin was only one factor in the production of the clinical picture. Another, and in many cases more important, factor was the invasive power of the infecting strain, and a test of susceptibility or immunity to this action would be of considerable value. In this connection the recent work of Collis was very interesting; he gave intradermal injections of ground-up streptococci or "endotoxin" to children, who had had a recrudescence of

rheumatic symptoms in a hospital ward, following an epidemic of tonsillitis due to the hæmolytic streptococcus, and he found a remarkably high percentage of positive reactors, as compared with a series of control cases.

In reply to Dr. Goodall: he had not been successful in isolating hæmolytic streptococci from the blood during life, in a series of about twenty cases of scarlet fever, mainly severe in type, although he had isolated the organism on several occasions, after death, from the heart blood.