Why type streptococci? The epidemiology of group A streptococci in Oxfordshire 1976–1980

BY R. T. MAYON-WHITE AND ELIZABETH M. PERKS

*Public Health Laboratory and Department of Bacteriology,
John Radcliffe Hospital, Oxford*

(Received 5 October 1981; accepted 22 October 1981)

SUMMARY

The results of typing all group A streptococci isolated in one laboratory in 5 years were reviewed to see if the collected information showed epidemiological patterns. The great majority of the 5858 streptococci typed came from patients seen in general practice: 72 % from throat swabs and 11 % from skin lesions. Eight types, M types 1, 2, 3, 4, 6, 12, 22 and type 28R accounted for 65 % of strains. These eight types had different patterns: types 2 and 6 caused small circumscribed outbreaks and were uncommon between epidemics; types 3, 4 and 12 caused larger, wider epidemics, whereas types 1, 22 and 28R had a more stable pattern. Type 4 was more commonly resistant to tetracycline than most other types, a finding which affected the apparent incidence of tetracycline resistance in group A streptococci. Streptococci from superficial sites were more likely to have serum opacity factor and to lack a detectable M-antigen than strains isolated from the throat. Routine typing of streptococci helped to detect outbreaks of infection in special groups. It is concluded that regular streptococcal typing should be continued in some places.

INTRODUCTION

Group A streptococcal infections are common, are sometimes severe, and have important, if rare, sequelae. Therefore these infections merit surveillance. Most laboratories test beta-haemolytic streptococci for group A polysaccharide antigen, or employ a marker like bacitracin sensitivity, and assess antibiotic resistance. A few laboratories extend the identification of group A streptococci to typing T- and M-antigens. Although this detailed typing has obvious value in the investigation of an outbreak, the advantages of regularly typing all or most isolates of group A streptococci have not been established. In this paper we examine the results of typing all group A streptococci isolated in one laboratory in a five year period. We hope to show that there are epidemiological patterns justifying the labour involved in this detailed surveillance at some centres.

There are two complementary systems of typing group A streptococci, based on the T- and M-antigen in the bacterial cell walls. The T-antigens are detected by

agglutination of a trypsinised suspension of the streptococci with specific rabbit antisera (Griffith, 1934), and the M-antigens by precipitation of acid extracts by other specific rabbit sera (Lancefield, 1928). The two typing systems are related and it is usual practice to find the pattern of T types first and from this, test for the related M types. The M type is the more specific of the two systems, as each strain has only one M-antigen but may share several T-antigens. In this paper we shall refer to organisms by their M types, without the prefix M. However some strains did not have a known M-antigen, and these will be referred to as T types. The R protein antigen of the type 28 is detected by precipitation, like an M type antigen; we have given the type 28 R the same status as M types.

MATERIALS AND METHODS

Our laboratory serves an acute general hospital and about 60 general practices within a radius of 25 miles. The practices have been grouped by local authority districts for the analysis of geographical distribution. Although the workload of the laboratory has increased since 1976, the number and source of group A streptococci has remained fairly constant.

The streptococci were cultured from clinical specimens on blood agar (Oxoid blood agar base plus 5% horse blood) incubated aerobically and anaerobically. Beta-haemolytic streptococci, usually picked from the anaerobic culture, were grouped by precipitation of acid extracts. T typing was performed on suspensions of group A streptococci grown overnight at 30 °C in 5 ml Todd-Hewitt broth (Difco) enriched with 2% neopeptone [Difco] and containing 0.3 ml of saturated trypsin solution. The trypsinized bacterial suspensions were tested against agglutinating sera (Streptococcus Reference Laboratory, Colindale) for T types 1-6, 8, 9, 11-15, 17, 19, 22, 23, 25, 27, 28, 44, 47, B3264 and Imp 19. For M typing, the streptococci were grown in 40 ml of Todd-Hewitt broth enriched with 2% neopeptone at 37 °C overnight. The M protein was extracted by N/5 hydrochloric acid at 100 °C for 10 min. The neutralized extract was tested by double-gel diffusion in 0.9% agarose, against appropriate M type antisera (Rotta *et al.* 1971). Antisera against types 1, 2, 3M, 3R, 4, 5, 6, 9, 11, 12, 14, 15, 17-19, 22-26, 28R, 29-31, 33, 36, 37, 39, 41, 43, and 46-62 were available. The reactions to type 3R antiserum are closely associated with reactions to type 3M antiserum, and we have recorded these together as M type 3.

The streptococci were tested for resistance to 10 µg tetracycline discs on blood agar. The zone diameters were compared to that given by the Oxford *Staphylococcus aureus* (NCTC 6571). The presence of opacity factor was determined by placing a spot of acid extract (from M typing) onto 50% pig serum in 0.9% agarose. The plate was incubated at 37 °C overnight, and a visible increase in the opacity of the agar was scored as a positive reaction.

The first isolate in each illness was recorded, and repeated isolates of the same type from the patient were excluded from the analysis. Information about the type of specimen, streptococcal type, its tetracycline sensitivity and the practice where the patient was seen was entered into a desk-top computer (Hewlett-Packard

9825 A) in monthly batches. In order to see whether a type clustered in time or space, the number of isolates of that type in a practice was compared to an 'expected' number. Clusters were defined as practice-areas where the number of one type in a month was more than three standard deviations above the expected number. The expected number was calculated as:

$$\frac{\text{no. of isolates of that type}}{\text{total no. of isolates}} \times \frac{\text{no. of isolates from practice area}}{\text{no. of months recorded}}$$

As the number of types from each practice area in any month was small, a Poisson distribution was assumed, so that the standard deviation equalled the square root of the expected number.

The main part of our report is on the streptococci isolated between January 1976 and December 1980. We had two additional sources of data: firstly the typing results and tetracycline sensitivity for the streptococci isolated from mid 1970 to 1975. These earlier records were used to examine long term trends in the commonest eight types. Because T types 2, 4 and 6 are known to be closely related to their respective M types, and as M type 4 serum was not available before 1975, these T types have been counted with the respective M types in the 10½ year analysis. Secondly, in 1980, selected strains for which we could not detect M types were examined by the Streptococcus Reference Laboratory. This permitted us to assess the impact of the recently discovered M types which were not included in our basic set.

RESULTS

General observations

There were 5858 strains of *Streptococcus pyogenes* isolated and typed in the 5 years 1975–80; 5030 (86 %) came from patients seen in general practice, 448 (8 %) from hospital in-patients, 286 (5 %) from out-patients including accident department patients, and the remaining 94 (1 %) came from hospital staff. Eighty percent of the strains from general practice and staff were isolated from throat swabs, (Table 1). The majority (74 %) of the isolates from hospital out-patients were from superficial sites (skin, wounds, eyes, ears, vulvae). In hospital inpatients 15 % of isolates came from 'deep' sites (high vaginal swabs, sputum, blood and urine), and the remainder came equally from throats and superficial sites. The great majority of specimens came from people with clinical infection, as there was little screening of symptomless people practised at the time.

Seven M types (types 1, 2, 3, 4, 6, 12, 22) and type 28 R predominated over the 5 years studied in both throat and skin infections. Together they accounted for 3790 (95 %) of the 4010 strains for which an M type was found, and for 65 % of all isolates. The other M types found are shown in Table 2. The next most common M type was type 49 (82 isolates) and differed from most others by having more isolates from superficial sites (50 strains) than from the throat (30 strains). This difference is due in part to an outbreak of type 49 skin infection in meat workers in 1980. The proportion (29 %) of non-M typable isolates from superficial sites was

Table 1. *Numbers (and percentages) of isolates from different sites of infection by place of consultation*

	Throat	Superficial	Deep	Total
General practice	4201 (72 %)	636 (11 %)	193 (3 %)	5030 (86 %)
Hospital outpatients	51 (1 %)	212 (4 %)	23 (< 1 %)	286 (5 %)
Hospital inpatients	189 (3 %)	192 (3 %)	67 (1 %)	448 (8 %)
Hospital staff	76 (1 %)	17 (< 1 %)	1 (< 1 %)	94 (1 %)
Total	4517 (77 %)	1057 (18 %)	284 (5 %)	5858 (100 %)

Table 2. *M types found in Oxfordshire 1976-80*

M type	Number	% of all isolates	M type	Number	% of all isolates
1	475	8	28R	166	3
2	399	7	30	1	—
3	573	9	31	5	—
4	366	6	33	7	—
5	30	1	41	7	—
6	286	5	48	1	—
9	8	—	49	82	1
11	18	—	52	4	—
12	777	13	53	5	—
14	5	—	55	6	—
18	1	—	57	1	—
19	11	—	58	13	—
22	748	13	60	6	—
25	4	—	61	2	—
26	1	—	62	2	—

(— = less than 1 % of all isolates).

significantly greater than the proportion (13 %) of M typable strains (Table 3). If the M typable strains are divided into those that usually produce opacity factor and those that do not, the proportion of opacity factor positive types (types 2, 4, 9, 11, 22, 25, 48, 49 and 58-62) isolated from superficial sites is greater than the proportion of opacity factor negative types from the same sites (Table 4*a*). The same association between superficial infection and opacity factor was observed in the non-M typable strains in 1980, when the opacity factor was recorded for all isolates (Table 4*b*). No association was found between particular types and deep infections.

Six hundred and thirty-two (10.8 %) strains were resistant to tetracycline. The proportion of resistant strains from superficial sites (201/1057, 19 %) was significantly higher than the proportions from the throat (404/4517, 9 %) and deep sites (27/284, 10 %) ($\chi^2_2 = 90.79$, $P < 0.001$). This difference is related to the association of two types, M types 4 and 49 with skin infections and tetracycline resistance (Table 5). The proportions of tetracycline resistant strains in each year were: 1971, 33 %; 1972, 29 %; 1973, 32 %; 1974, 30 %; 1975, 24 %; 1976, 11 %; 1977,

Table 3. *M* typable and non-*M* typable strains by site of infection

	Throat	Superficial	Deep	Total
<i>M</i> typable	3305	525	180	4010
Non- <i>M</i> typable	1212	532	104	1848
Total	4517	1057	284	5858

$$\chi^2 = 222.59; \quad P < 0.001.$$

Table 4. (a) *Opacity factor and site of infection, M typable strains, 1976-80*;
(b) *Opacity factor and site of infection, non-M typable strains, 1980*

	Throat	Superficial	Deep	Total
(a) 1976-80				
OF + <i>M</i> types	1419	304	92	1815
OF - <i>M</i> types	1886	221	88	2195
Total	3305	525	180	4010
(b) non- <i>M</i> typable Types, 1980				
OF +	78	99	9	186
OF -	125	56	4	185
Total	203	155	13	371

$$\text{OF} = \text{Opacity Factor} \quad (a) \chi^2 = 43.58, P < 0.001 \quad (b) \chi^2 = 24.73, P < 0.001.$$

Table 5. *Number (and percentage) of tetracycline resistant strains of certain types of group A streptococci*

	Throat	Superficial	Deep	Total
Type 4	96 (32 %)	13 (29 %)	4 (22 %)	113 (31 %)
Type 49	22 (73 %)	41 (82 %)	2 (100 %)	65 (79 %)
Types 1-62 (excluding types 4 and 49)	85 (3 %)	31 (7 %)	5 (3 %)	121 (3 %)
Non- <i>M</i> typables excluding type 81	201 (17 %)	89 (17 %)	16 (15 %)	306 (16 %)
Type 81	0	27 (84 %)	0	27 (84 %)

8 %; 1979, 11 %; 1980, 15 % (Fig. 1). The fall in 1976 coincides with the end of an epidemic of type 4 and the figure of 15 % in 1980 is partly the consequence of an epidemic of tetracycline resistant strains in meat workers that year. There was little difference between the proportions of hospital and general practice strains with tetracycline resistance.

There was seasonal variation in the number of pharyngeal isolates from general practice (Fig. 2), with the lowest number in August. The 1980 data show that this variation was partly due to a smaller number of throat swabs submitted, and partly due to a lower proportion of swabs growing group A streptococci in the summer months. This seasonal pattern was not observed in throat swabs from hospital nor in the isolates from superficial and deep sites.

Fig. 1. Tetracycline resistance 1970-1980. □, Tetracycline sensitive; ▨, Tetracycline resistant.

Fig. 2. Monthly variation in group A streptococci from general practice. Top section shows group A streptococci by month, 1976-80. Bottom section shows all throat swabs (□) and group A streptococci (▨) in 1980. %, Percentage of swabs positive for group A streptococci.

Observations on specific types 1975-80

While each of the eight commonest types had an individual epidemiological pattern, the patterns fell into three classes. The first class contained types 2 and 6 (Fig. 3). These caused short sharp localized epidemics. The second class was formed by types 3, 4 and 12 (Fig. 4), with large long epidemic waves. The third

Fig. 3. Small epidemics of group A streptococci. Number of isolates per quarter on vertical axis.

Fig. 4. Large epidemics of group A streptococci. Number of isolates per quarter on vertical axis.

class included types 1,22 and 28R (Fig. 5). These types were endemic throughout Oxfordshire, but there were small clusters in villages and small towns.

(1) *Small epidemics* (types 2 and 6)

The pattern for this class is illustrated by type 6 (Fig. 6). This type caused two peaks in successive winters, 1975-6 and 1976-7, apparently as part of one epidemic. Two of the four practices with clusters in the first winter also had clusters

Fig. 5. Endemic patterns of group A streptococci. Number of isolates per quarter on vertical axis.

in the next. The practices were widely dispersed, but the outbreak in the city followed outbreaks elsewhere. Type 6 was the only common type to cause a significant cluster in Cherwell district.

Apart from a small peak in late 1973 produced by adding T type 2 isolates to M type 2 strains, type 2 was infrequently isolated from 1970 to 1978. In 1978, an increase affected the whole area, appearing as clusters in practices in three districts within three months of each other. If these are regarded as parts of a single epidemic, this epidemic lasted three years. There is no evidence that one practice acted as a focus from which infection spread to others, although the city was involved with small numbers of isolates at an early stage. One practice, in South Oxfordshire, had a small outbreak in 1980, eighteen months after outbreaks in nearby practices.

(2) *Large epidemics* (types 3, 4 and 12)

Type 3 caused a large epidemic affecting most districts from 1974 to 1977, with three winter peaks (Fig. 7). In the first half of 1976, the numbers were greatest in two practices in South Oxfordshire. In the next winter, 1976–77, the epidemic reached practices in the Vale of the White Horse, the City and later in West Oxfordshire. One West Oxfordshire town practice was not part of this large epidemic, but had an outbreak on its own in the winter 1979–80. Between these peaks type 3 was relatively uncommon.

Combining T typing results with M type 4 showed that an apparently sudden increase in numbers in 1975 was part of a longer epidemic extending over 4 years.

Fig. 6. Cluster of type 6, 1976–80 by practice area. The clusters are numbered 1–5 on the graph, and plotted on the map (*).

Fig. 7. Clusters of type 3, numbered 1–6.

Most of this epidemic was over by the beginning of the detailed study period 1976–80, but the tail of the epidemic affected four districts. In one district, the Vale of White Horse, significant clusters continued to appear at annual or biennial intervals.

Type 12 was common throughout the study period, with two large epidemics

Fig. 8. Clusters of type 1, numbered 1-12.

1972-4 and 1979-80. The increase in numbers in the whole area and the peaks in individual practices occurred in all quarters of the year. There was no pattern of an epidemic wave spreading from practice to adjacent practice, except that peaks in the winter of 1979-80 in practices in the Vale of White Horse and South Oxfordshire followed each other at monthly intervals.

(3) *Endemic patterns* (types 1,22 and 28R)

M type 1 appears to have been endemic in Oxfordshire since mid 1970, with slight increases in most winters to 25-30 isolates per quarter. Within this overall pattern there were distinct clusters in different districts occurring at different times. Thus, three widely spaced practices were affected by M type 1 early in 1976, and two practices had outbreaks in the winter 1976-77 (Fig. 8). A similar pattern was observed in the next three winters, with a coincidence of outbreaks in three practices in the first half of 1980 producing a higher peak in total numbers than earlier years. The outbreaks in individual practices were small, with a maximum of seven isolates in a month. Two practices had three clusters in five years. There was no relation in the timing of clusters in neighbouring practices, even in Oxford City.

Type 22 was another common type, with one to ten isolates in most months in most districts. Apart from an outbreak in West Oxfordshire early in 1976 the main clusters occurred in South Oxfordshire.

Type 28R had an unimpressive epidemiological pattern in the whole area, but cluster analysis showed three unrelated outbreaks in different districts. Once again, these peaks came in winter months.

Other types

Type 49 caused two outbreaks during the 5 years 1976–80. The first produced throat infections in one practice in South Oxfordshire in the first three months of 1977. The second was associated with skin infections in meat workers in the autumn of 1980. In this latter outbreak, abattoir workers in West Oxfordshire and butchers in three districts were affected.

After testing the 1341 strains isolated in 1980 against the range of M type antisera 1–62, 371 strains remained not M typed. Of those selected for further testing, 103 gave a specific type reaction, either with established M type antisera 63 to 81 or to provisional types tested by specific opacity factor inhibition. Twenty were M type 80, selected because they were T type 14 (an infrequent T type). Ten of the type 80 isolates occurred in a cluster in central Oxford in the summer of 1980.

Thirty-two tetracycline resistant strains of T type 3/13/B3264 were found to be M type 81. These were discovered to be part of an outbreak of skin infection amongst abattoir workers in South Oxfordshire and adjacent parts of Buckinghamshire and butchers scattered throughout the county.

Provisional type 80/4931 was isolated from a detention centre in Cherwell district. This new type, which is T type 3/13/B3264, appeared late in 1979, and caused 26 throat infections in the centre in one year. It has also been isolated from skin lesions of vagrants and prisoners in the City of Oxford.

We found no distinct clusters in the T types, apart from T types 2 and 4 mentioned above with their respective M types.

There were no large outbreaks in hospital; the types found in hospital patients reflected the patterns in the community. The high proportion of skin infection amongst hospital out-patients was due to sporadic wound infections seen in the Accident and Emergency Department. The number of 'deep' infections was small and there were no significant clusters.

DISCUSSION

The main purpose of this study was to determine whether epidemiological information could be derived from the results of routine typing of all group A streptococci isolated in one laboratory. In doing so, we have made the assumption that the specimens received in the laboratory represent clinical infection in the community. Of course, an unknown proportion of people with clinical pharyngitis are seen by their doctors, and only some of these patients will have swabs taken. We realize that some practices investigate a greater proportion of their patients than others, and that differences of age and social factors between practices make direct comparison invalid. The numbers of specimens submitted by individual practices have changed relatively little during the study period. Therefore we think that it is reasonable to make comparisons of the results from one year to the next.

It is difficult to see how the selection of specimens that lead to our results could have produced the patterns observed for different types. Our main finding is that

the commoner types of group A streptococci have one of three main patterns as described, at least in Oxfordshire in the years 1970–80. It is accepted that types differ in their propensity to cause skin infection and to cause nephritis (Wannamaker, 1970). Some types have been particularly associated with outbreaks in special groups, for example type 5 in schools and military recruits (Lancet, 1981) and newer types in the meat industry (Fraser *et al.* 1977). Therefore it is not surprising that we find variation in epidemic patterns. As far as we know, this variation has not been previously defined. Perhaps this is because a large number of isolates and a long term analysis are required to see the patterns.

We do not know why types vary in their epidemic patterns. If observations in other places fitted our classification of the patterns of the eight commonest types, we would deduce that the M types have differences in ability to spread and cause clinical infection. We think that the host population and the environment have remained constant during the survey. It is possible that types causing the 'small' epidemics are more easily transmitted, more readily cause symptoms or produce more type-specific immunity, with the result that the outbreaks are short and sharp. Continuing the argument, the 'endemic' types are less easily transmitted but are carried for longer, and the so-called 'large epidemic' types are intermediate. We do not see how herd immunity to individual types could, by itself, account for these differences. There was no association between opacity factor and the epidemiological pattern observed. Despite these large-scale differences between types, all the eight common types and some of the less common types are clearly able to cause localized outbreaks. A cyclical pattern with a frequency of 5–7 years is suggested by the graphs of types 4 and 12, but further observations are needed to confirm this.

The eight commonest types observed in Oxfordshire are also amongst the commoner types in other series (Bergner-Rabinowitz & Ferne, 1978; Kohler, 1974; Parker, 1967; Public Health Laboratory Service, 1954). However comparisons with these other series are difficult, because of differences in the proportions of strains M typed, and different selection of strains for analysis. In a study in a general practice in Gloucestershire, M types 1, 2, 6 and 12, R type 28 and T type 4 were common (Hope-Simpson, 1981). In this study types 2 and 6 were found to cause, small well-defined outbreaks; type 1 was endemic for half of the study period; types 4 and 12 had two epidemic waves. These findings are similar to our own.

The decline in tetracycline resistant streptococci in the last decade has been observed elsewhere in Britain (Robertson, 1973). Other authors (Ad hoc Study Group, 1977) have shown the difference in tetracycline resistance between isolates from skin and throat infections, and stressed the variation in time and place. It appears to us from our observations on types 4, 49 and 81 that these differences are at least partly due to the epidemiology of these particular types which are more commonly resistant than others. The association between opacity factor, M type and skin infection amongst strains sent to a reference laboratory has been recorded (Maxted & Widdowson, 1972); our results confirm this association for a less selected series of strains.

The observation that a relatively small number of M types account for 65% of infections has practical implications, for surveillance and typing. Because the M

types outside the commonest ten are so relatively uncommon, and because many T types are shared, it might be worth testing for only a limited range of M types as a first step. Further typing with T type and other M type antisera could be kept for isolates of clinical or epidemiological interest. The test for opacity factor would have immediate relevance to such a modified typing system because each strain would then only have to be tested for about half the commonest eight or ten M types.

This leads the discussion to the question of the reasons for typing streptococci. There are different circumstances in which it may be useful to carry the identification of micro-organisms beyond the immediate requirements for clinical diagnosis and treatment. When an epidemic is suspected, typing streptococci may show links between cases or, more formally, may test the hypothesis that the epidemic is caused by the spread of a single strain. We extend this application to the surveillance of unusual infections, including wounds and deep sites in hospital patients. Typing will also help to find whether recurrent infections in an individual patient are relapses with one organism or re-infections by different strains. If there is no significant difference between the isolates, it is conventional to accept the probability that the organisms are the same. In our study we have assumed that differences were insignificant if they occurred within the common T type complexes T 3/13/B3264, T 8/25/ Imp 19 and T 5/27/44, or were between T 4 non-M typable and T 4 M type 4 strains. On the other hand, we have treated differences in M type and other differences in the T types of M untypable strains as distinctive.

Another situation is where the existence of an epidemic is established, with sufficient detail to offer new knowledge on the pathogenesis and epidemiology of the disease. There are links between the type antigen and the disease process (Maxted, 1980). For example nephritis is associated with the M types 12, 49, 55, 57 and 60, which were found in Oxfordshire during the study. The absence of a noticeable increase in nephritis at the time of the epidemics of type 12 and 49 reflects the low incidence of post streptococcal nephritis in this area. An epidemic is said to occur when there is more illness than expected in a population. The regular typing of streptococci, in at least some places, provides some measure of the expected frequency of individual types. The occurrence of several isolates of an unusual type may be the first sign of an epidemic. This application is illustrated by the type 81 outbreak in meat workers in 1980 and the provisional type 80/4931 outbreak in 1979 and 1980. On the other hand, the coincidence of several infections by a common type, which occurred in our hospital patients, is not necessarily an unusual event (implying outbreak). Therefore streptococcal typing must be continued between outbreaks for apparently non-epidemic strains, with the advantage that this practice maintains and develops expertise. The determination of the frequency of different types would be relevant if ever there were a potential vaccine.

When a disease is commonplace, there is a tendency to regard it as part of the normal human condition. Detailed microbiological diagnosis may reveal unexpected variations. We think that one apparently endemic disease, streptococcal infection seen in clinical practice in Oxfordshire, is made up by a series of epidemics. Some in this series are large and slow, and others are smaller and shorter. Even the types

that we termed 'endemic' were not constantly present in all parts of the population. Although there is no immediate prospect of modifying the natural history of streptococcal infection, the epidemic pattern implies a potential for change, in the host, micro-organisms or both. Therefore we conclude that it is worthwhile to continue to type streptococci and to record the epidemiological patterns in a few centres.

We gratefully acknowledge the work of Mr F. C. Saunders who has supervised the identification and typing of group A streptococci in our laboratory. The staff of the Streptococcus Reference Laboratory, Division of Hospital Infection, Colindale, London, generously provided the typing sera and helped with typing. We thank these and Dr R. E. Hope-Simpson, Dr W. R. Maxted and Dr Mary P. E. Slack for their advice and encouragement.

REFERENCES

- AD HOC STUDY GROUP (1977). Tetracycline resistance in pneumococci and group A streptococci. *British Medical Journal* **1**, 131-133.
- BERGNER-RABINOWITZ, S. & FERNE, M. (1978). Type distribution of B-haemolytic Streptococci in Israel: A 10-Year Study. *The Journal of Infectious Diseases* **138**, 152-159.
- FRASER, C. A. M., BALL, L. C., MORRIS, C. A. & NOAH, N. D. (1977). Serological characterization of group A streptococci associated with skin sepsis in meat workers. *Journal of Hygiene (Cambridge)*, **78**, 283-296.
- GRIFFITH, F. (1934). The serological classification of *Streptococcus pyogenes*. *Journal of Hygiene (London)* **34**, 542-584.
- HOPE-SIMPSON, R. E. (1981). *Streptococcus pyogenes* in the throat: a study in a small population, (1962-75). *Journal of Hygiene (Cambridge)* **87**, 109-129.
- KOHLER, W. (1974). Results of the second international *Streptococcus pyogenes* type distribution survey. *Streptococcal Diseases and the Community* (ed. M. J. Haverkorn), pp. 10-13. Amsterdam: Excerpta Medica.
- LANCEFIELD, R. C. (1928). The antigenic complex of *Streptococcus haemolyticus* - Demonstration of type-specific substance in extracts of *S. haemolyticus*. *Journal of Experimental Medicine* **47**, 91-103.
- LANCET EDITORIAL (1981). Streptococci in Institutions **1**, 311-312.
- MAXTED, W. R. & WIDDOWSON, J. P. (1972). The protein antigens of group A streptococci. In *Streptococci and Streptococcal Diseases* (ed. L. W. Wannamaker and J. M. Matsen), pp. 251-266. New York: Academic Press.
- MAXTED, W. R. (1980). Disease Association and geographical distribution of the M types of group A streptococci. In *Streptococcal Diseases and the Immune Response* (ed. J. B. Zabriskie and S. E. Read), pp. 763-777. New York: Academic Press.
- PARKER, M. T. (1967). International survey of the distribution of serotypes of *Streptococcus pyogenes* (group A streptococci). *Bulletin of the World Health Organization* **37**, 513-527.
- PUBLIC HEALTH LABORATORY SERVICE (1954). Serotypes of *Streptococcus pyogenes*. Their relative prevalence in England, Wales and Northern Ireland, 1952-1953. *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service* **13**, 171-174.
- ROBERTSON, M. H. (1973). Tetracycline resistant beta-haemolytic Streptococci in south-west Essex: Decline and Fall. *British Medical Journal* **4**, 84-85.
- ROTTA, J., KRAUSE, R. M., LANCEFIELD, R. C., EVERLEY, W. & LACKLAND, H. (1971). New approaches to the laboratory recognition of M types of group A streptococci. *Journal of Experimental Medicine* **134**, 1298-1315.
- WANNAMAKER, L. W. (1970). Differences between streptococcal infections of the throat and of the skin. *New England Journal of Medicine* **282**, 23-30 and 78-85.