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Changes in the pattern of infection caused by *Streptococcus pyogenes*

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SUMMARY

The distribution of T- and M-protein antigens was determined in 12469 cultures of *Streptococcus pyogenes* sent to a reference laboratory. Of these 7232 (58%) were isolates from hospital patients, 249 (2%) from hospital staff and 4988 (40%) from the community. The survey extended from January 1980 to June 1987. During this time the numbers of isolates of M-types 6, 49 and 81 rose then fell, being replaced by types 1, 3 and 28. The proportion of isolates of M-types 4 and 12 remained constant. Few strains were received from cases of nephritis or rheumatic fever but there has been an increase in the number of strains from serious infections and deaths. Forty-four of the 55 (80%) strains received since 1985 from fatal infections have belonged to M-type 1. All other strains, bar two, received from fatal infections in those years belonged to M-type 3. Representatives of M-type 1 were also associated with erysipelas. Types 3 and 4 predominated among the isolates from scarlet fever, types 1, 4, 12 and 49 from nephritis, types 49 and 81 from skin infections in meat workers and type 28 in cases of puerperal sepsis. The M-typability rate was 97% but new M antigens await definition among strains causing pyoderma.

INTRODUCTION

Since typing of group A streptococci became available, there have been few surveys to investigate changes in the relative prevalence of different serological types.

Some 35 years ago the Public Health Laboratory Service instituted regular studies of *Streptococcus pyogenes* by sampling all strains isolated by its constituent laboratories in England and Wales during one week periods, twice a year, from 1952 to 1956 (Anon., 1954, 1957). No further large studies were undertaken until 1964 when an attempt was made using different sampling methods, to carry out an international survey of the distribution of *S. pyogenes* serotypes. Two such studies were instigated: in 1964–5 (Parker, 1967), and 1968–9 (Köhler, 1974). The aim was to study 300–500 isolates in each country during one year. The cultures were to consist of an equal number of cases of scarlet fever, acute pharyngitis and others streptococcal diseases. In both studies the list of participating laboratories and the range of sera available were similar. The only other surveys that have been

published involved studying streptococcal infections in a single city (Mitchell, 1962; Lütticken *et al.* 1977; Duben *et al.* 1978) or in a district centred on an acute general hospital and involving some 60 general practices (Mayon-White & Perks, 1982).

It became clear several years ago that representatives of several serotypes hitherto rare were becoming more numerous and a study of patterns of isolation was essential.

MATERIALS AND METHODS

The survey was based on the study of all adequately documented strains of *S. pyogenes* referred here from laboratories within the UK between 1 January 1980 and 30 June 1987. Cultures sent from abroad and those investigated by T-typing only were excluded, as were repeat isolates from the same patient. On receipt, the cultures were checked for haemolysis and bacitracin-sensitivity. A combined T- and M-typing scheme was used (Williams & Maxted, 1953) supplemented with detection of opacity factor (OF) (Top & Wannamaker, 1968).

All typing sera were prepared by the Streptococcus Reference Unit. Rabbits were injected intravenously with whole-cell vaccines . Washed bacterial cells that had been exposed to trypsin were used for the preparation of T-typing sera (Williams, 1958). M-typing sera for OF-negative serotypes were prepared with saline vaccines (Williams, 1958) but for OF-positive strains the animals were given priming doses of saline vaccines followed by vaccines composed of phenol-extracted cells (Pranitis, Murray & Kornfeld, 1973). Packed cell suspensions of the strain NCTC 8709, a glossy variant, were used to remove group A antibodies from the rabbit antisera. Suspension of strains of heterologous serotypes were used, when necessary, to remove cross-reactions.

T types were determined by the agglutination of trypsinized cell suspensions (Efstratiou, 1980). M antigens were detected in Lancefield acid extracts by double diffusion tests in agarose gels. Lines of identity were confirmed using extracts of stock strains. Broth supernates were tested for the presence of OF and, when necessary, the M-type of particular strains was confirmed by the inhibition of this activity with specific antisera (Maxted *et al.*, 1974).

The current set of M sera available at the Streptococcus Reference Unit is composed of sera against M-types 1, 3 M, 3 R, 5, 6, 12, 14, 15, 17, 18, 19, 23 ,24, 26, 29, 30, 31, 33, 36, 37, 39, 41, 43, 46, 47, 51, 52, 53, 54, 55, 56, 57, 64, 72, 74, 80, provisional types 5757, 2631 (OF negative types) also 2, 4, 9, 11, 22, 25, 48, 49, 58, 59, 60, 61, 62, 63, 66, 68, 73, 75, 76, 77, 79, 81, provisional types 180, TRIN 179, 1658, TRIN 2233, TRIN 2612, TRIN 2407, 2841, 3875, 4245, 4931 and Potter C (OF positive types) and R 28 sera. Opacity factor sera prepared in guinea-pigs (Fraser, 1982), were available against types 2, 4, 9, 11, 22, 25, 28, 48, 49, 58, 59, 60, 61, 62, 63, 66, 68, 73, 75, 76, 77, 78, 79, 81 and provisional types 180, TRIN 179, 1658, TRIN 2233, TRIN 2612, TRIN 2407,2841, 3875, 4245, 4931 and Potter C.

Laboratory records of age and sex of patient, site of infection and source of isolate relied on information provided by the sending laboratories. This was sometimes inadequate. Testing of sensitivity to antibiotics was not done routinely.

RESULTS

In all 12469 cultures were examined between January 1981 and June 1987. This included 7232 (58%) isolates from hospital in and out patients, 249 (2%) from hospital staff and 4988 (40%) community isolates. The overwhelming proportion of strains came from patients showing signs of clinical infection. Screening of symptomless carriers occurred only in a few large hospital outbreaks where symptomless staff, patients and environmental sites were swabbed routinely until the conclusion of the outbreak.

The number of cultures submitted by individual laboratories has varied between 1391 and 2016 per year with the general trend being an increase in the number of isolates. Sending laboratories are spread evenly across the country and it seems fair to assume that this sample is representative of current trends in the UK. There was also a reasonably constant pattern of referral. Of the 143 laboratories referring cultures in the years 1985 to 1987, for instance, 71 did so in all three years, 37 did so in two of three years and 13, 7 and 15 did so only in the years 1985, 1986 and 1987 respectively.

Typability rates

Using the current set of antisera to M and T antigens and repeated testing of refractory strains it was possible to type 99% of isolates by T agglutination and 97% by M precipitation. Without exception, all non-typable strains were isolated from superficial sites and wounds. One or other of the M antigens named above could be detected in all isolates from the throat. During the course of the survey, M sera were raised against four new provisional types (PT), PT 4245, PT 4854, PT 2110 and PT 4931 (Fraser & Colman, 1985).

Representatives of ten M-types, namely 1, 3, 4, 6, 12, 22, 28, 49, 73 and 81, predominated during the survey. They comprised 61% of all isolates but their relative prevalence changed during the period of study. A decrease in the isolation of previously common types such as types 6, 49 and 81 (Fig. 1) has coincided with increased isolation rates of type 3 and in particular, a marked increase in the isolation of types 1 and 28 (Fig. 2). At the same time, the prevalence of other types such as 4 and 12 has remained relatively constant (Fig. 3). The increase in the number of isolations of type 1 in the last two years appears to be slowing down, but the actual isolation rate remains at about 30% of all UK isolates. Types 1, 3 and 28 now account for over 50% of all UK isolates.

Associations between serotype and sources

The distribution, by source, of all the isolates included in the survey is summarized in Table 1. One half (50%) of all isolates were from throat swabs but many strains were recovered from wounds (22%) and other superficial sites (17%). There were 466 (4%) isolates from blood cultures but few (< 1%) were cultured from CSF.

Analysis of isolation sites of the most common serotypes shows that the once popular distinction between 'throat' and 'skin' strains is no longer clear cut (Table 2). Some strains such as types 3 and 6, do seem to occur predominantly in the throat with 77% (type 3) and 83% (type 6) of all isolates being from throat

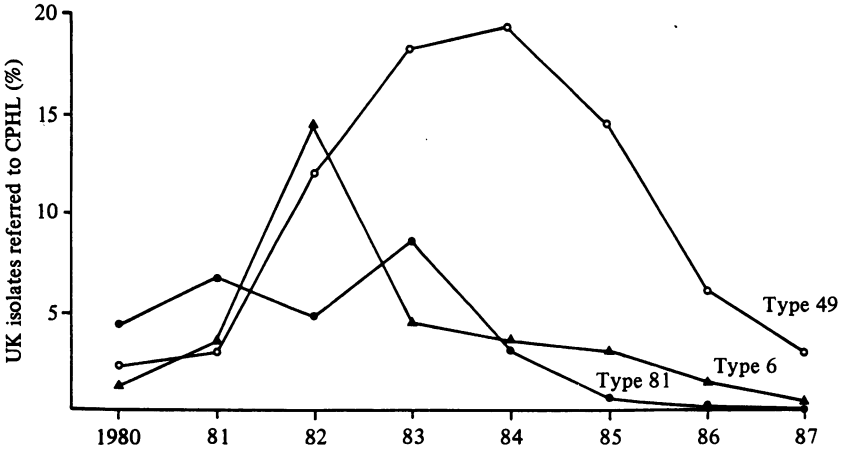

Fig. 1. The changing prevalence of M types 6, 49 and 81 (1980–7). Data for 1987 is for the period 1 January to 30 June.

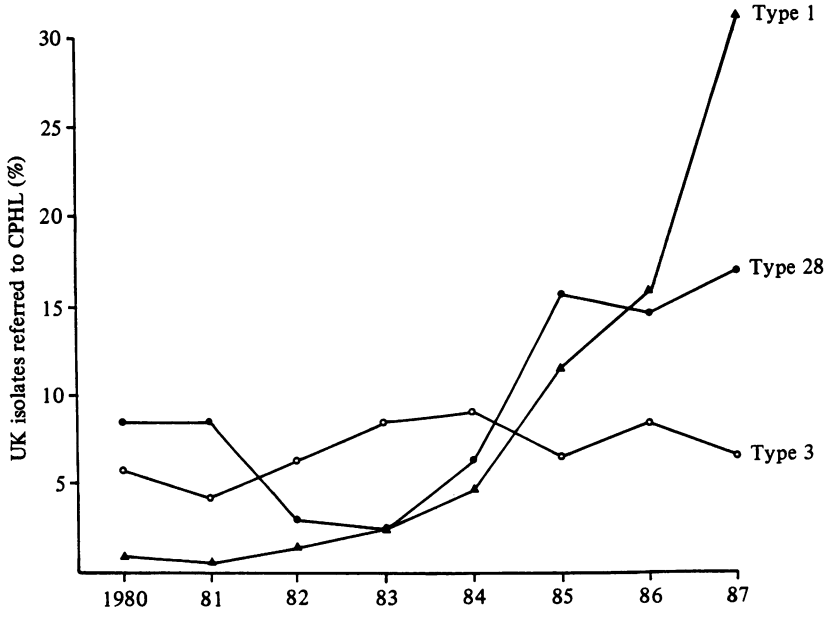

Fig. 2. The changing prevalence of M types 1, 3 and 28 (1980–7). Data for 1987 is for the period 1 January to 30 June.

swabs. Others such as type 81 are isolated mainly from wounds and superficial sites with only 19% being recovered from throat swabs. Many serotypes, for instance 28 and 49, appear to be able to colonize or infect diverse sites.

It emerged from this analysis (Table 2) that of the 487 cultures isolated from blood or CSF, 159 (33%) belonged to M-type 1 and 65 (13%) to type 3. These represented 12·9% and 6·9% respectively, of all isolates of these serotypes. With the exception of type 12 (4·4%) and type 22 (4·0%) the proportion of strains of

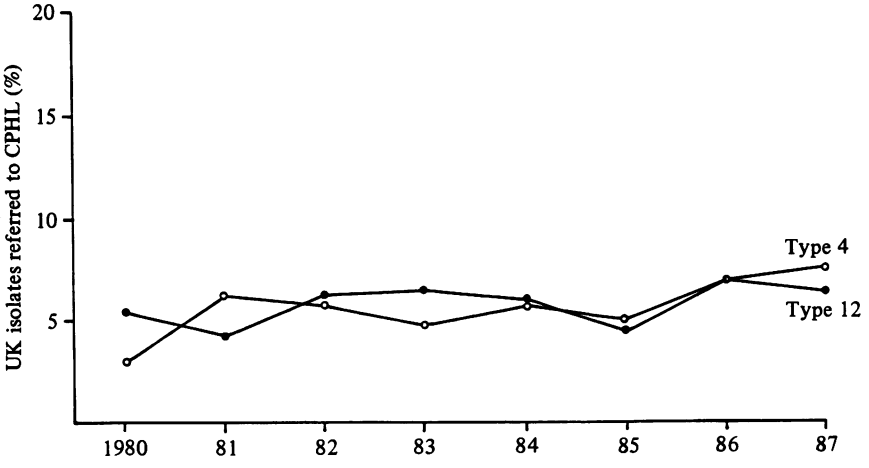

Fig. 3. The prevalence of M types 4 and 12 (1980–7). Data for 1987 is for the period 1 January to 30 June.

Table 1. *Group A streptococcal infections – number of isolates received*

Source of isolates	Year								Total	%
	1980	1981	1982	1983	1984	1985	1986	1987*		
Throat	744	720	1051	834	745	964	817	386	6261	50
Nose	47	9	19	45	56	25	47	23	271	2
Ear	21	3	7	5	8	15	43	31	133	1
Skin	193	592	339	313	337	180	97	54	2105	17
Wound	822	54	194	303	133	241	643	300	2690	22
Blood	52	35	47	32	71	62	88	79	466	4
CSF	2	1	1	4	4	4	0	5	21	< 1
HVS	37	14	33	13	28	59	123	118	425	3
Other	16	6	12	13	8	23	7	12	97	1
								Total	12 469	

* Data for the period 1 January to 30 June.

other serotypes isolated from blood was lower. This is evidence of an association of type 1 in particular with invasive disease (Table 3). The number of strains of type 1 as a proportion of all isolates from blood or CSF has risen from 11–14% in 1981–3 to 64% in the first 6 months of 1987.

Septicaemic deaths

At the same time, there have been more isolates from fatal infections received by this laboratory: 5–10 per year between 1980 and 1984, 14 in 1985, 19 in 1986, increasing to 22 deaths in the first 6 months of 1987. Since 1984, depending upon the year, between 71–95% of all fatal infections have been caused by serotype 1 (Table 4). Many (> 73%) of these deaths occurred in patients with no serious underlying medical condition, as was noted also by Cruickshank and his colleagues (1981). Information on predisposing causes was, however, neither routinely sought nor given but the calamitous nature of the infection was often described.

Table 2. *Group A streptococcal infections: sources of the ten most common M types expressed as percentages of the type at each site*

	Source of isolates (%)							
M type	Throat	Nose	Ear	Wound	Skin	HVS	Blood + CSF*	Total no. of isolates
1	59·2	3·0	2·7	11·8	5·5	4·9	12·9	1208
3	77·0	1·5	1·4	7·5	3·9	1·8	6·9	941
4	65·6	1·6	1·9	12·1	9·1	6·4	3·3	672
6	82·7	1·6	1·6	6·0	4·1	1·8	2·3	515
12	70·4	3·8	0·8	12·2	6·3	2·1	4·4	712
22	59·5	1·9	1·1	17·7	12·2	3·5	4·0	622
28	54·1	1·2	1·4	24·6	6·0	9·7	3·1	850
49	42·6	3·6	0·5	16·6	34·0	0·9	1·8	1208
73	52·6	2·6	0·7	24·2	14·5	2·6	2·8	462
81	19·1	4·3	0·7	31·1	41·5	0·7	2·7	441

* During the period of this study, fewer than five isolates each year were received from CSF.

Table 3. *Group A streptococci received from serious invasive diseases*

	Total no. of isolates from blood or CSF	No. of isolates of M type	
		1	3
1980	54	11 (20)*	11 (20)
1981	36	5 (14)	2 (6)
1982	48	6 (13)	4 (8)
1983	36	4 (11)	5 (14)
1984	75	12 (16)	7 (10)
1985	66	24 (36)	11 (16)
1986	88	35 (40)	15 (17)
1987†	84	54 (64)	7 (8)

* Percentage.
† Data for the period 1 January to 30 June.

Table 4. *Number of strains received from fatal group A streptococcal infections*
(These organisms are included also in Table 3.)

	M type 1	M type 3	Other types
1980	3	4	1
1981	0	0	5
1982	6	2	2
1983	3	4	2
1984	5	2	0
1985	13	1	0
1986	13	4	2
1987*	18	4	0

* Data for the period 1 January to 30 June.

Erysipelas

There was no evidence among the 12469 strains of an association between a single serotype and a particular disease state, except for erysipelas. Erysipelas is now a rare disease in the UK but is apparently more common in Sweden (Jorup-Rönström, 1986). All of the 17 isolates examined during this study were of type 1. This association was noted by Dowsett and her colleagues (1975) in a hospital outbreak. The few strains received from patients with erysipelas could be attributed in part to the well-known difficulty of isolating group A streptococci from within the lesion (Leppard *et al.* 1985).

Scarlet fever

Scarlet fever in the UK currently has a mild course and this may be due to the failure of strains to produce the pyrogenic exotoxin A (Hallas, 1985). Notifications of the disease in England and Wales have also fallen and for part of the period covered by this survey fell from 11118 in 1980 to 6327 in 1984 (Anon. 1986). Isolates from 154 diagnosed cases and 9 probable cases were received and the distribution of serotypes is shown in Table 5. As was noted in an earlier survey (Parker, 1967) there is an association between types 3 and 4 and scarlet fever. The numbers of cultures identified as types 1 and 6 are inflated by the inclusion of 8 isolates of type 1 from a single outbreak in 1981 and 6 of type 6 from one incident in the following year.

Rheumatic fever

Few strains are received in this laboratory from patients with rheumatic fever. There were seven strains from diagnosed cases and four from probable cases with never more than one strain in each category in any one year. The distribution of M types is given in Table 6 and of these, types 1, 3 and 5 have in the past been associated, among others, with outbreaks of this condition (Bisno, 1980). The absence of M-type 18 is noteworthy because representatives of this serotype have been associated with a recent resurgence of this disease in the USA (Veasy *et al.* 1987). Type 18 is a rare serotype in the UK and apart from 28 strains received early in 1987 from a single outbreak of sore throat, never more than one strain was received in any year of the survey. The virulence factor responsible for rheumatic fever is unknown but one of the properties of strains causing outbreaks of rheumatic fever is that they often form mucoid colonies. This property was noted among the serotypes isolated in the recent American outbreak (Veasy *et al.*1987) and our strains of serotypes 5 and 18.

Acute glomerulonephritis

As with rheumatic fever, representatives of many serotypes have in the past been associated with sporadic cases of acute glomerulonephritis but a more restricted distribution is to be seen among strains causing outbreaks. All of the strains included in Table 7 were from sporadic cases. Of the 49 isolates from diagnosed cases, and 15 where there was some doubt, one half belonged to one or other of the serotypes 1, 4, 12 or 49. Representatives of these serotypes have in the

Table 5. *Distribution of M-serotypes among strains isolated from patients with scarlet fever*

	M type												
	1	2	3	4	5	6	12	22	28	73	75	77	Total
No. of strains associated with													
Definite diagnosis	16	9	76	39	1	7	2	2	0	1	0	1	154
Probable case	1	0	0	0	0	1	2	1	1	0	3	0	9

Table 6. *Serotypes recovered from patients with rheumatic fever*

	M type							
	1	3	4	5	22	58	77	Total
No. of strains associated with								
Definite diagnosis	2	1	1	2	0	0	1	7
Probable diagnosis	1	0	1	0	1	1	0	4

Table 7. *Serotypes of* S. pyogenes *associated with acute glomerulonephritis*

	M types											
	1	2	3	4	5	6	9	12	22	49	55	58
No. of strains associated with												
Definite diagnosis	8	0	3	4	1	1	2	11	2	7	1	0
Probable diagnosis	1	2	0	2	0	1	0	1	1	0	0	1

	73	78	81	PT 2841	T3/M−/OF+	T8/25/M−OF+	Total
Definite diagnosis	1	4	2	0	0	2	49
Probable diagnosis	2	1	1	1	1	0	15

past caused outbreaks of streptococcal sore throat that were followed by glomerulonephritis (Ferrieri, 1975).

Infections in meat workers

In November 1977 the Public Health Laboratory Service set up a Working Group on Streptococcal Infection in Meat Handlers (Morris *et al.* 1982) and its work had been completed by the end of 1984. Almost all of the strains that compose Table 8 were referred as a result of surveys conducted by members of the Group and the results of typing some of the strains have been reported by others (Barnham & Kerby, 1984). Clusters of strains in Table 8 indicate outbreaks which occurred either within one geographical area, as with M-type 41 or T3/M− /OF-, or involved abattoirs in several parts of the country as with M-types 49, 80 and 81 and also strains with the pattern T8/M−/OF+. An M antigen was detected in 435 of the 592 strains isolated from meat workers giving a typability rate of 73%. It is likely that the 157 that could not be typed with the current set of antisera represent at least five new serotypes. For instance, a new provisional type antiserum, PT 4854, was prepared against one of the strains isolated in the

Table 8. *Results of typing 592 strains isolated from skin lesions on meat workers*

Typing result M antigen identified	No. of strains referred in year								
	1980	1981	1982	1983	1984	1985	1986	1987*	Total
6	2	—	—	—	—	—	—	—	2
9	—	—	—	7	—	—	—	—	7
11	1	—	1	—	1	—	—	—	3
12	1	—	—	—	—	—	—	—	1
22	—	—	3	2	3	1	—	—	9
28	—	—	—	—	—	1	—	—	1
33	8	5	—	—	—	—	—	—	13
41	33	—	—	—	—	—	—	—	33
49	1	7	1	13	31	4	20	—	77
58	1	—	—	1	—	—	—	—	2
59	—	—	—	9	—	—	—	—	9
60	—	2	—	—	—	—	—	—	2
64	—	—	—	—	2	1	—	—	3
66	—	5	3	6	3	—	—	—	17
73	—	—	—	1	—	—	—	—	1
75	—	—	—	1	—	—	1	—	2
76	1	5	—	1	1	7	—	1	16
78	—	—	—	3	1	—	—	—	4
80	2	—	—	70	1	—	—	—	73
81	19	30	3	44	5	—	—	—	101
PT 180†	—	2	—	1	1	—	—	—	4
PT 2841	—	—	—	—	1	—	4	—	5
PT 3875	—	—	—	15	5	—	—	—	20
PT 4245	—	2	—	—	—	—	—	—	2
PT 5757	—	10	—	—	—	1	12	2	25
Potter C	—	—	—	3	—	—	—	—	3
M antigen not detected									
T3/M−/OF+	—	—	1	—	—	—	—	—	1
T3/M−/OF−‡	5	70	9	—	—	—	—	—	84
T8/M−/OF+	—	1	4	17	46	—	—	—	68
T8/M−/OF−	—	—	—	—	1	—	—	—	1
T5/M−/OF+	—	—	1	—	—	—	—	—	1
T5/M−/OF−	—	2	—	—	—	—	—	—	2
Total	74	141	26	194	100	16	38	3	592

* To 30 June 1987.
† Provisional type numbers.
‡ An unknown proportion of these cultures belong to serotype PT 4854 – see text.

outbreak caused by strains listed in Table 8 as T3/M−/OF−. This serum was prepared after the outbreak had been brought under control and as not all isolates could be tested for the presence of this antigen, they are all classed as non-typable.

Puerperal sepsis

The 90 strains brought together to form Table 9 are those isolates described as being from patients with puerperal sepsis together with those present *post partum* in both blood cultures and high vaginal swabs. About one half of the strains, 41

Table 9. *Type distribution of strains isolated from cases of puerperal sepsis*

	M types															
	1	2	3	4	9	12	22	28	58	60	73	75	77	81	PT 2841	Total
No. of cases	3	2	6	3	14	3	5	37	1	1	6	1	1	6	1	90

of 90 isolates, were from incidents in which one mother only had become infected. The remainder, strains of M-types 9 and 73 and R 28, were isolated from eight outbreaks – each in a different hospital. Five of these outbreaks were caused by isolates carrying the R 28 antigen.

Since mid-1985 more isolates from high vaginal swabs have been referred for typing (Table 1). These cultures are not known to be associated with infection. Type 28 is the commonest single serotype among these commensals and this may be the explanation for its association with puerperal sepsis.

DISCUSSION

Earlier studies in England and Wales (Anon. 1954, 1957; Mayon-White & Perks, 1982) have shown that some serotypes of *S. pyogenes* are present constantly in the community but there are fluctuations in the isolation rates of others. There remained a need to look again for associations between particular serotypes and disease states particularly among hospital patients. The first step in this investigation was to prepare antisera for hitherto undefined serotypes (Fraser & Colman, 1985). The typability rate for M proteins was increased to 97% but still more M antigens await definition among the strains isolated from skin sepsis (Table 8). The set of typing sera employed would be less useful for strains islated at other places or different times. For example, extracts of only one third of the strains received from West Africa or South East Asia during the survey yielded M antigens that could be identified with the current set of antisera (results not presented). Or, strains carrying the M antigens 79 (formerly PT 2015) or PT 1658 were rare in this survey although they had caused outbreaks a few years earlier (Fraser *et al.* 1977; Efstratiou *et al.* 1982).

In previous longitudinal studies of outbreaks involving more than one strain a waxing and waning of the different organisms has been observed with isolates of one serotype predominating and then being replaced by another (Ferrieri *et al.* 1972; Efstratiou *et al.* 1982). Such a change was observed in this study on a national scale with type 49 being replaced by type 1. No adequate explanation can be offered for this succession. We doubt that this is due to the acquisition of circulating antibodies. There has been no large scale survey of the prevalence of antibodies to the various M proteins. The presence of these antibodies, however, does not protect against pharyngeal acquisition of strains of the homologous serotype (Guirguis *et al.* 1982) and our own experience with the indirect bactericidal test (Maxted, 1956) suggests that few individuals have circulating opsonic antibodies to more than one or two serotypes.

The relative frequency of strains carrying the R 28 antigen as a cause of

puerperal sepsis can be explained, most simply, by its prevalence in high vaginal swabs taken from normal women.

The attack rate of acute nephritis following infection of the skin or throat with strains of type 49 was much lower in this study than among outbreaks in North America. Before 1980 few isolations of M-type 49 strains were made in the UK and when they were detected some family association with the Western Hemisphere could usually be found on enquiry. Of the 1208 isolates of type 49 handled, 515 were from throat swabs and 411 from skin lesions (Table 2). The skin lesions were of all grades of severity from a small area of impetigo to surgical wounds or to burns involving much of the body surface. Yet only seven of the strains were from patients who had developed nephritis (Table 7). A much greater proportion of American Indian children who had been in contact with a strain of type 49 developed acute nephritis or unexplained haematuria (Anthony *et al.* 1969). In that study, 10 of 42 (24%) of those with pyoderma, 2 of 44 (5%) of those with sore throats and 3 of 16 (19%) infected at both sites developed one or other condition. Some of the strains of type 49 isolated in the UK in 1980 were subtyped by a bacteriophage method (Skjold & Wannamaker, 1976) and they could be distinguished from strains of type 49 that had caused epidemics of nephritis in Minnesota and Trinidad (Skjold *et al.* 1983). A likely explanation of the difference in virulence could be that, perhaps, the UK isolates do not produce the streptokinase found in nephritis strains (Johnston & Zabriskie, 1986).

It seems clear that the strain, or strains, of M-type 1 that is currently being isolated is particularly virulent. In the past an understanding was sought of the reasons why strains causing skin sepsis did not become invasive (Pinney, 1974) or produced an unexpected antibody response (Kaplan *et al.* 1970). The need is now reversed. It has been suggested that toxaemia can be an important determinant of the outcome of streptococcal infection (Cone *et al.* 1987). Given the variety of toxins produced by *S. pyogenes* (Wannamaker, 1983) much remains to be learnt.

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