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Streptococcus pyogenes in the throat: a study in a small population, 1962–1975

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SUMMARY

A general practice population of around 6700 was kept under clinical and laboratory surveillance from 1962 to 1975. Illnesses totalled 18703 in three morbidity classes: sore throat (Throats) 4451, acute febrile respiratory diseases (FRD) 4934, acute non-febrile respiratory diseases (Non-FRD) 9318. Specimens were examined for *beta*-haemolytic streptococci (BHS) from 37·1% of these illnesses: from Throats 33·3%, from FRD 67·8%, from Non-FRD 22·6%, and 515 specimens were collected from a miscellaneous ('Other') class consisting of healthy persons and ailments that could not have had a streptococcal component.

Strains of BHS were isolated from 7448 specimens as follows: group A (*Streptococcus pyogenes*) 353, group C 36, group G 15, other groups 274.

Group A strains were isolated from specimens at the following rates: Throats 16·7%, FRD 2·4%, Non-FRD 0·9%, Other 1·4%. The last two classes reflect the carrier rate in the general community, which must be deducted to obtain the streptococcal morbidity in the other classes. Carriers thus accounted for 6% of the strains isolated from the Throats class and for 42% of those from FRD illnesses.

No consistent seasonal trend of prevalence was detected. Long-term fluctuations in prevalence over several years affected all groups and most group A serotypes.

Serotyping was performed on 304 strains from 1963 to 1975. The commonest types found were T-types 4 and 12 and M-type 12.

Immunity against re-infection by identical strains appeared to be fairly strong and also against heterotypic strains that shared a T-antigen, but little protection was conferred against re-infection by group A strains with no shared M- or T-antigen. R-28 antigen is considered here as a marker epidemiologically equivalent to an M-antigen.

Epidemicity, as measured by a simple estimate of aggregation, appeared to be low and there were differences between and within serotypes.

The infecting organism appeared to linger in the pharynx, sometimes for several months, after a streptococcal illness.

INTRODUCTION

This paper describes the strains of group A *beta*-haemolytic streptococcus (*Streptococcus pyogenes*) isolated from the throats of patients of a small general

practice during fourteen years of continuous clinical and laboratory surveillance. Most of the strains isolated after 1962 were serotyped.

The attempt made to interpret the epidemiological significance of the findings is beset with difficulties. Some are technical: the number of streptococci isolated varies according to the technique used to isolate them; persons harbouring few organisms will therefore be missed by some techniques and found by others. Streptococcal sore throat is characterized by the presence of the organism in prodigious abundance, and the sufferers are unlikely to be missed by even the less sensitive techniques; carriers, however, who may be of epidemiological importance, are less heavily infected, and the apparent carrier rate may vary widely according to the isolation technique employed.

In the surveillance described here the same technique of streptococcal isolation was used throughout, so variations in isolation rates are likely to reflect changes in streptococcal prevalence rather than technical variations. Many specimens from healthy persons and from patients with non-streptococcal ailments were being similarly examined contemporaneously with those from patients whose illnesses might have been streptococcal. The prevalent carrier rate can therefore be taken into account when considering the pathogenicity of the streptococcal strains isolated in the different morbidity classes.

Another difficulty is the inherent variability of the carrier rate itself, which alters in a complex manner because persons harbour streptococci for different periods. The organism lingers in the throat after recovery from the illness; the carrier rate will therefore vary directly with the amount of steptococcal pharyngitis recently affecting the community.

A further difficulty lies in the multiplicity of group A streptococcal serotypes and the complexity of their antigenic relationships. An attempt has been made to examine the immunological specificity of individual serotypes in the natural situation by looking at the patterns of homotypic and heterotypic re-infection of individuals and households.

One important aspect of the epidemicity of an organism is indicated by the degree to which cases of the disease it is causing are aggregated in time. A simple method of quantifying such secular aggregation, described in the Appendix, has been used to determine the aggregation (A)-values of the strains of *Streptococcus pyogenes*, and to compare them with the A-values of strains belonging to individual serotypes and with those of other common pathogens isolated during the surveillance.

The study is on too small a scale to do more than indicate certain trends in the natural behaviour of these streptococci, and to give an account of the relative frequency of the visits of some of the serotypes to this community during one fairly long period.

MATERIALS AND METHODS

Population. The general practice population, served by the author and his partner, numbered 3511 on 1 January 1962 and increased to 3919 on 1 January 1974. Table 1, summarizing a census taken near the middle of the survey period, shows the composition by age and sex. The increase in population during the survey period did not seriously alter the age and sex composition. The population was

Table 1. *Summary of census of general practice population at* 31 *December* 1968

Age group (years)	Male	Female	Percentage male	Total	Distribution (%)
0–9	264	277	48·8	541	14·9
10–19	223	260	46·2	483	13·3
20–9	216	235	47·9	451	12·4
30–9	211	195	52·0	406	11·2
40–9	244	225	52·0	469	12·9
50–9	253	229	52·5	482	13·3
60–9	207	211	49·5	418	11·5
70–9	101	144	41·2	245	6·8
80–9	43	68	38·7	111	3·1
90+	4	10	28·6	14	0·4
Age not known	3	0	—	3	0·1
Total	1769	1854	48·8	3623	99·9

fairly evenly divided between the market town of Cirencester and the surrounding villages and farms.

Morbidity. The illnesses to which most attention was directed were classified in three classes: sore throat (Throats), acute febrile respiratory diseases (FRD) and acute non-febrile respiratory diseases (Non-FRD). Morbidity figures for illnesses in these three classes are available for the 13 years 1962 to 1974.

No overall morbidity figures are available for a fourth miscellaneous class (Other) from which specimens were collected. It contains specimens from healthy persons and from persons suffering from a wide variety of ailments – non-acute illness, accidents, gastro-intestinal diseases, mumps, etc.

Specimens. The doctor carried with him at all times a supply of glass test-tubes each containing three sterilized cotton-wool swabs on wooden sticks, and a supply of bijou bottles containing sterilized transport medium for the specimens for virus examination. One of the three swabs was used for the nostrils and broken into the transport medium. The other two swabs were used jointly for swabbing tonsils and pharynx, one of them being then broken into the same bottle of transport medium, the other returned to the dry test-tube for streptococcal examination. A record was made in the Cirencester Research Unit and the specimens transported rapidly to the Public Health Laboratory (in the same building as the general practice) where the bijou bottles were examined virologically, and the dry swab was plated onto blood agar, incubated aerobically for 24 h and examined for *beta*-haemolytic streptococci (BHS). BHS colonies were grouped by Lancefield's precipitin test and reported as of group A, C, G or 'other groups', strains belonging to groups A, C and G being at that time considered to be those potentially pathogenic for man.

The present paper is concerned with group A strains because too few were found belonging to groups C and G to merit detailed analysis. Strains of groups C and G and those belonging to 'Other groups' are, however, included in some tables in order to place group A strains into numerical perspective.

Serotyping by agglutination (T) and precipitation (M) was performed at the Streptococcus Reference Laboratory, Colindale, on most of the group A strains isolated from 1963 to 1975.

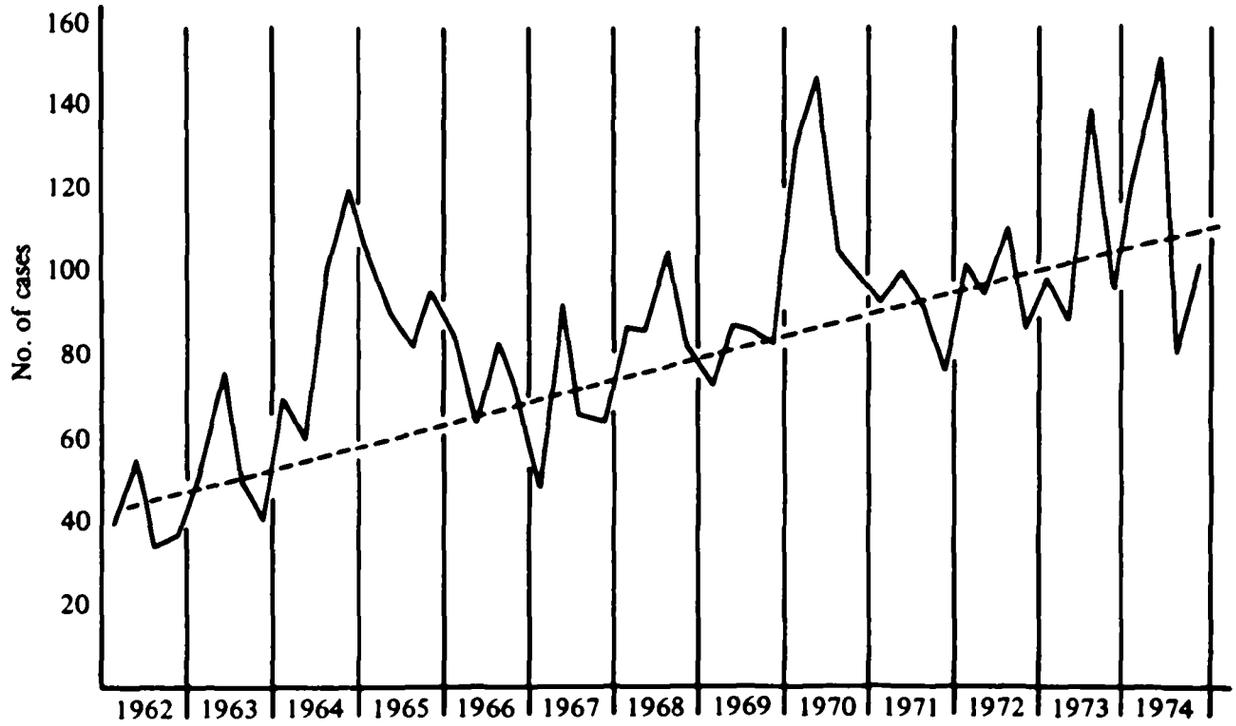

Fig. 1. Quarterly morbidity in Throats class to show short-term fluctuations and long-term trend (broken line).

Table 2. *Seasonal distribution of morbidity by class (percentages)*

Quarter of year	Throats	FRD	Non-FRD
First	24·7	51·6	34·2
Second	26·7	14·2	19·6
Third	25·3	7·5	13·6
Fourth	23·3	26·7	32·6
Total	100·0	100·0	100·0

RESULTS

Morbidity. Illnesses in the three main morbidity classes totalled 18703, of which 4451 (23·8%) were sore throats, 4934 (26·4%) were FRD and 9318 (49·8%) were Non-FRD. In all three classes the annual morbidity varied from around 3% to around 11% of the total for the class, but peak morbidity for Throats (1970, 1973, 1974) did not coincide with peaks of FRD (1966 and 1969) or of Non-FRD (1966). Years of lowest morbidity also differed – Throats in 1962, FRD in 1967, Non-FRD in 1974.

In Fig. 1 the broken line indicates the slope of a gradual increase in sore throats by about 22 cases annually through the 13 years, more than double that anticipated from the increase in population.

The regular annual seasonal swing in morbidity from FRD and Non-FRD illnesses is not found in illnesses in the Throats class (Fig. 2, Table 2).

Specimens. The total of 7448 specimens examined came from the morbidity classes as follows: 515 from the miscellaneous class 'Other' and 6933 from 37·1% of the 18703 illnesses in the three major morbidity classes. Throats accounted for

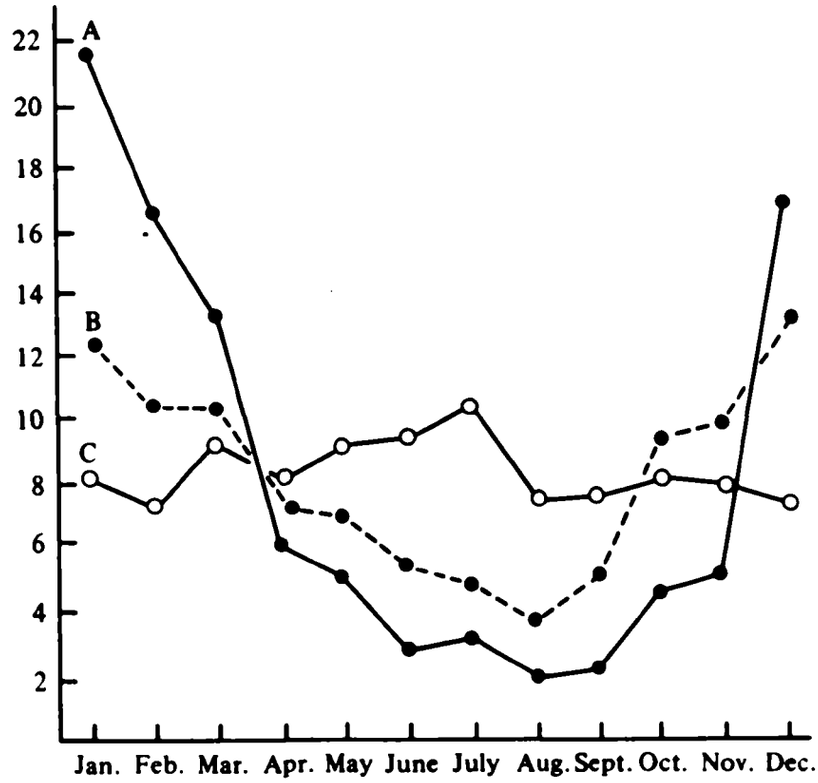

Fig. 2. Seasonal distribution of illnesses in the morbidity classes (A) FRD, (B) Non-FRD, (C) Throats. Illnesses in each class have been totalled from 1962–1974, and percentage of total falling in each cumulated calendar month is shown.

Table 3. *Percentage of morbidity class examined for streptococci by season*

Quarter	Throats	FRD	Non-FRD	Total
First	34·2	63·6	22·0	39·5
Second	30·6	72·6	20·7	33·6
Third	38·3	77·4	27·0	38·3
Fourth	30·2	70·7	22·4	35·7

1484 specimens from 4451 illnesses (33·3 %), FRD for 3346 from 4934 (67·8 %) and Non-FRD for 2103 from 9318 (22·6 %).

Table 3 shows that throughout the different seasons of the year a consistent proportion of specimens was collected from each morbidity class. Despite the lower sampling rate from the Non-FRD illnesses, the class was so large that more specimens were collected from it than from sore throats.

Isolations of BHS. Figures for specimens and isolations are available for the full 14 years but can be related to the background morbidities for only the first 13 years (Table 4).

Group A strains isolated from the 7448 specimens numbered 353 (4·7 %), group C strains 36 (0·5 %), group G strains 15 (0·2 %) and strains belonging to 'other groups' 274 (3·7 %). These figures suggest an average annual rate in the practice population of 19·3/1000 for group A strains, 2·1/1000 for group C strains, 0·8/1000 for group G strains and 15·2/1000 for 'other groups'.

The isolation rates of group A strains from specimens from the different morbidity classes were: Throats 16·7 %, FRD 2·4 %, Non-FRD 0·9 %, 'Other' 1·4 %.

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Table 4. Beta-*haemolytic streptococci isolated by group and year*

Year	No. sick	Specimens	Group A	Group C	Group G	Group Others	Total isolations
1962	1216	460	14	3	0	25	42
1963	1369	622	37	3	0	53	93
1964	1474	592	53	2	2	50	107
1965	1488	536	56	1	2	37	96
1966	1726	509	23	1	1	18	43
1967	1171	369	6	1	1	3	11
1968	1475	495	13	2	1	7	23
1969	1548	720	7	2	0	13	22
1970	1464	424	19	4	2	13	38
1971	1378	534	31	4	0	21	56
1972	1427	801	27	2	1	20	50
1973	1478	564	27	6	2	7	42
1974	1489	550	30	4	2	4	40
1975	Not known	272	10	1	1	3	15
Total	18703	7448	353	36	15	274	678

The rates in Non-FRD and 'Other' approximate to that found by the same isolation technique in healthy persons (Hope-Simpson & Higgins, 1969).

The group A strains and the strains not belonging to groups A, C or G were distributed similarly throughout the survey period, most abundant in 1963–5, then becoming scarce, but from 1971 again becoming more abundant. The group C and group G strains were widely scattered throughout the 14 years.

Carriers of group A strains. The overall carrier rate by the isolation technique used was around 1 % of the population, as shown by isolations from healthy persons and from those clearly not suffering from streptococcal illness. It is therefore reasonable to suppose that most isolations in the large Non-FRD class, with a rate of 0·9 %, also came from carriers. The variation in carrier rate can be seen in Table 5 to be linked to the amount of streptococcal illness by comparing the annual isolations in the Non-FRD class with those in the Throats class.

In order to determine the streptococcal morbidity, the current carrier rate must be deducted from the current total isolation rate. The class 'Other' is too small to permit annual assessments of a value of the order of 1 %, and it has therefore been combined with Non-FRD findings to determine the annual carrier rates (Tables 5 and 6).

Pathogenicity. Streptococcus pyogenes was isolated most frequently from illnesses in the Throats class. Allowing for carriers, group A strains were causing around 16 % of such illnesses, an average annual rate of 15 per 1000 of the population, varying from four per 1000 in 1969 to 29 per 1000 in 1964. They were responsible for much less illness in the FRD class, around 1·5 %, or one case per 1000 of population annually, varying from none in some years to nearly seven per 1000 in 1965. Despite the tenfold difference in incidence, periods of high and low prevalence corresponded fairly closely in these two morbidity classes. No pathogenicity can be ascribed to *Streptococcus pyogenes* in the illnesses in the Non-FRD class (Tables 5 and 6).

Table 5. *Infections by* Streptococcus pyogenes *by year and morbidity class*

Year...	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	Total
Population...	3511	3573	3631	3665	3636	3617	3634	3623	3701	3753	3868	3891	3919	48022
Throats														
(1) Morbidity	165	215	350	373	289	260	360	329	479	360	393	422	456	4451
(2) Specimens	57	96	143	150	87	45	77	96	121	118	168	137	142	1437
(3) Isolations	11	18	45	38	19	5	8	5	19	20	18	17	19	242
(4) (3) as percentage of 2	19·3	18·8	31·5	25·3	21·8	11·1	10·4	5·2	15·7	16·9	10·7	12·4	13·4	16·8
(5) Carriers deducted	19·3	17·5	30·1	21·7	21·8	10·6	9·8	4·7	15·7	15·3	10·7	12·4	13·4	15·9
(6) Rate/1000 of population	9·1	10·5	29·0	17·2	17·3	7·6	9·7	4·3	20·3	14·7	10·9	13·4	15·6	14·7
FRD														
(1) Morbidity	398	417	401	322	534	170	449	569	244	326	381	402	321	4934
(2) Specimens	142	201	191	138	185	108	250	425	174	270	458	278	340	3160
(3) Isolation	3	14	5	10	4	0	3	1	0	8	9	7	11	75
(4) (3) as percentage of 2	2·1	7·0	2·6	7·3	2·2	—	2·8	0·2	—	3·0	2·0	2·5	3·2	2·4
(5) Carriers deducted	2·1	5·7	1·2	3·7	2·2	−0·5	2·2	−0·3	0	1·4	2·0	2·5	3·2	1·5
(6) Rate/1000 of population	2·3	6·7	1·3	3·2	3·3	—	2·7	—	-	1·2	2·1	2·6	2·6	1·5
Non-FRD														
(1) Morbidity	653	737	723	793	903	741	666	650	741	692	653	654	712	9318
(2) Specimens	159	228	219	222	187	186	158	191	117	126	153	93	45	2084
(3) Isolations	0	3	3	8	0	1	1	1	0	2	0	0	0	19
(4) (3) as percentage of 2	—	1·3	1·4	3·6	—	0·5	0·6	0·5	—	1·6	—	—	—	0·9
Other (excluded from total)														
(2) Specimens	102	97	39	26	50	30	10	8	12	20	22	56	23	515
(3) Isolations	0	2	0	0	0	0	1	0	0	1	0	3	0	7
(4) (3) as percentage of 2	—	2·1	—	—	—	—	10·0	—	—	5·0	—	5·4	—	1·36
Total														
(1) Morbidity	1216	1369	1474	1488	1726	1171	1475	1548	1464	1378	1427	1478	1489	18703
(2) Specimens	358	525	553	510	459	339	485	712	412	514	779	508	527	6681
(3) Isolations	14	35	53	56	23	6	12	7	9	19	30	27	24	336
(4) (3) as percentage of 2	3·9	6·7	9·6	11·0	5·0	1·8	2·5	1·0	4·6	5·8	3·5	4·7	5·7	5·0
(5) Carriers deducted	3·9	5·4	8·2	9·6	5·0	1·2	2·0	1·0	4·6	4·2	3·5	4·7	5·7	4·1
(6) Rate/1000 of population	11·7	20·7	33·3	39·0	23·7	3·9	8·1	4·3	18·1	15·4	12·9	17·7	21·7	16·0

Note: (1) Carrier rates have been estimated from isolation rates in Non-FRD and 'Other' classes. (2) 272 specimens and 10 group A isolations have been omitted because 1975 morbidity figures were unobtainable. (3) The annual rate per 1000 of population was estimated by isolation rate (corrected for carriers) × (morbidity ÷ 100) ÷ (population ÷ 1000).

Table 6. *Estimate of* Streptococcus pyogenes *illness per* 10000 *population per annum by morbidity class by season* (*quarter-year*)

	Morbidity class															
	Throats								FRD							
Quarter	M	Sp.	gpA	R1	R2	R3	P	P[1]	M	Sp.	gpA	R1	R2	R3	P	P[1]
1	1101	377	56	14·8	0·3	14·5	160	33 × 4	2548	1621	37	2·3	0·3	2·0	51	11 × 4
2	1188	364	54	14·8	1·2	13·6	162	34 × 4	700	508	13	2·6	1·2	1·4	10	2 × 4
3	1124	430	53	12·3	0·8	11·5	131	27 × 4	371	287	7	2·4	0·8	1·6	6	1 × 4
4	1038	313	85	27·2	1·4	25·8	268	56 × 4	1315	930	22	2·4	1·4	1·0	13	3 × 4
Total	4451	1484	248	16·7	1·0	15·7	699	146	4934	3346	79	2·4	1·0	1·4	69	15

Notes: M = morbidity in class; Sp. = number of specimens; gpA = number of strains of *Str. pyogenes* isolated; R1 = isolation rate per 100 specimens from morbidity class; R2 = isolation rate per 100 specimens from non-streptococcal ailments and healthy persons ('carrier rate'); R3 = R1 − R2; P = R3 × M ÷ 100, estimate of number of persons with illness caused by *Str. pyogenes*; P[1] = P per 10000 of population per annum = P ÷ 4·8, because there were 48000 person-years of surveillance.

Table 7. *Number of strains of* Streptococcus pyogenes *isolated by months and years*

Year	J	F	M	A	M	J	J	A	S	O	N	D	Total
1962	—	—	2	1	1	1	2	—	2	1	—	4	14
1963	5	4	3	5	5	4	1	—	1	6	1	2	37
1964	—	1	5	4	1	1	1	3	—	3	19	16	53
1965	11	10	4	1	5	1	3	1	5	4	5	6	56
1966	4	2	2	1	1	2	7	1	1	—	2	—	23
1967	1	—	—	1	4	—	—	—	—	—	—	—	6
1968	1	—	2	—	1	—	—	2	1	5	1	—	13
1969	—	1	—	—	1	—	—	—	—	1	2	2	7
1970	2	1	—	4	1	—	1	—	—	5	5	—	19
1971	3	1	—	—	2	4	3	—	4	3	3	8	31
1972	6	3	2	1	4	3	2	1	1	1	2	1	27
1973	6	3	—	3	—	1	3	6	3	—	—	2	27
1974	6	3	1	1	—	6	3	2	2	1	4	1	30
1975	2	1	—	—	1	—	3	—	—	—	1	1	10
Total	47	30	21	23	27	23	31	13	20	30	45	43	353

The carrier rate will probably have been the same in each morbidity class and therefore the lower the number of isolations, the higher will be the proportion isolated from carriers. Thus some 42% of the strains isolated from illnesses in the FRD class probably came from carriers, whereas carriers in the Throats class probably accounted for only 6% of the group A strains isolated (Table 6).

Seasonal distribution. The monthly isolations (Table 7) show no consistent seasonal pattern over the fourteen years. The cumulated figures for each calendar month show a remarkably low cumulated total for the 14 months of August, which is not caused by inadequate sampling and is not reflected in the morbidity figures. The high cumulated figures for Novembers, Decembers and Januarys are not caused by a regularly high prevalence in these months but by the timing of the two largest concentrations of streptococcal illness. Table 6 shows the cumulated quarterly totals of isolations in Throats and FRD classes, with estimates of the numbers of persons suffering illness caused by *Strep. pyogenes* in each class each quarter, and of the rate of such seasonal streptococcal illness per 10000 of the population per annum. Sore throats caused by these streptococci were nearly twenty times more frequent than FRD illnesses except in the first quarter of the year when they were only three times as common.

Serotypes. Table 8 and Fig. 3. Typing by agglutination (T), precipitation (M) or by both tests was undertaken from the beginning of 1963. The antigenic signature of the strains isolated is written T/T//M, so that 4/28//24 indicates that the strain was found to have antigens T4, T28 and M24. A dash indicates a test that failed to detect any antigen, whereas ND indicates that the test was omitted.

Of the 339 group A strains isolated from 1963 to 1978, 303 were typed as follows: 1963 to 1969, 195/195; 1970, 18/19; 1971, 31/31; 1972, 21/27; 1973, 19/27; 1974, 17/30; 1975, 2/10.

The M-type is specific but the M-antigen is not always detectable. The detection of an M-antigen should be looked upon as a more definite finding than the detection of T-antigen, because (1) with some exceptions, strains have only one M-antigen and (2) the M-antigen is both an important virulence factor and also determines

Table 8. *The serotypes of the strains of* Streptococcus pyogenes *isolated*

Serotype	Strain signatures (with number isolated in brackets)	Total
M 1	1//1 (13), 1//– (2) See Note 1	15
M 2	2//2 (8), 2//– (1) See Note 1	9
M 3	3//3 (5)	5
M 5	5/27//5 (7), 27/44//5 (1)	8
M 6	6//6 (2), –//6 (1), 6//– (11) See Note 1	14
M 12	12//12 (43) See Note 2	43
M 22	12//22 (2), 13//22 (1), 22//22 (2)	5
M 24	4/28//24 (3)	3
M 25	25//25 (2)	2
R 28	4/28//R 28 (21), 28//R 28 (2)	23
M 41	13//41 (2)	2
M 47	17/23//47 (1)	1
M 52	3/12/B 3264//52 (1)	1
Total M-typed strains		131
T 3/13/B 3264 complex	3//–(14), 3/13//– (3), 3/13/B 3264//– (1), 3/B 3264//– (2), 13//– (11), 13/B 3264//– (1)	32
T 'odd' unclassifiable	3/11//– (1), 3/12//– (1)	2
T 4	4//ND (39) (no M 4 type sera then available)	39
T 4/28 complex	4/28//– (8), 28//– (11)	19
T 5/27/44 complex	5//– (1), 5/27//– (1)	2
T 11	11//– (1)	1
T 12	12//– (46) See Note 2	46
T 14	14//– (3)	3
T 17/18/23 complex	18//– (1)	1
T 22	22//– (8)	8
T 8/25/Imp. 19 complex	8/Imp. 19//– (2), 8/25/Imp. 19//– (2), Imp. 19//– (5), 25/Imp. 19//– (2), 25//ND (1), 25//– (7)	19
Total T-typed strains		172
Total typed strains		303

Notes: (1) T 1, 2 and 6 antigens are almost always found either alone or with the corresponding M-antigen, and therefore strains of 1//–, 2//– and 6//– are included under the M-type of the same numbering. (2) Many T 12 strains probably belong with M-type 12 strains but some may belong with M-type 22 strains, and so all have been separately typed as T-type 12.

type-specific immunity. T-antigens may be present singly or in multiple patterns, and serve to 'label' strains that have M-antigens for which no serum is available. However, strains with the same or a similar T-pattern in many cases include members of a number of different M-types. Thus, groups of strains defined by T-pattern that do not react with available M-antisera are generally heterogeneous in respect of M-antigens.

No serum for testing for M 28 antigen was available. However, serum was available for testing for another precipitating antigen, R 28, which though not a virulence factor is a good epidemiological marker. Strains with R 28 are here classed among the M-types.

In Great Britain, strains possessing T-antigens 1, 2 or 6 are, with rare exceptions, found either to have no other antigen or to have the corresponding M-antigen, and they have therefore been included in Table 8 under the appropriate M-serotype.

Thirteen M-types, thus classified, totalled 131 strains.

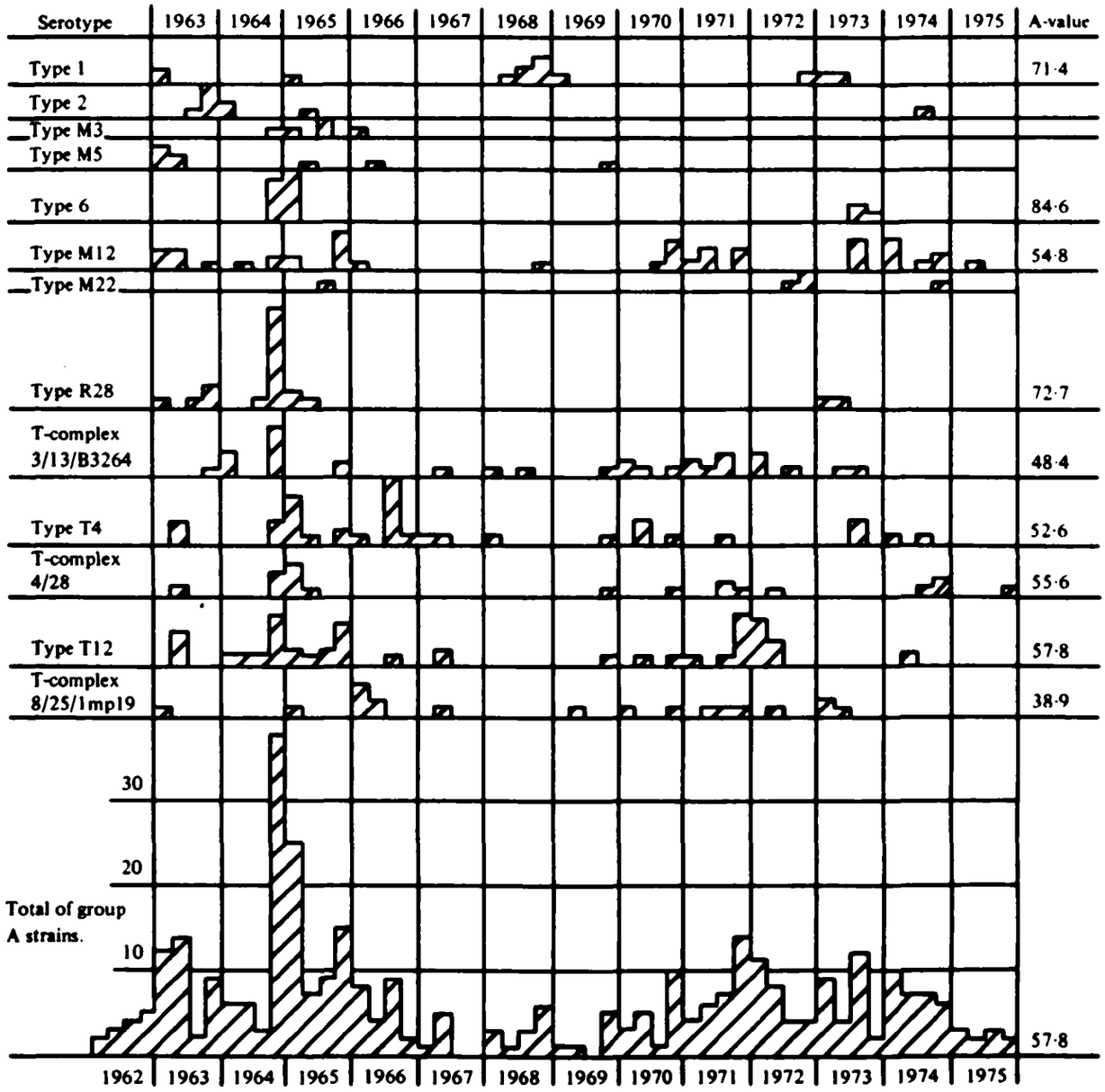

Fig. 3. Secular distribution of *Streptococcus pyogenes* and some serotypes. Quarterly isolations. A-values are shown for comparison with the pictorial distributions.

A single strain often carries two or more T-antigens, and certain T-antigens are epidemiologically associated whether they appear singly in different strains or associated together in the same strain. Such a natural grouping is considered to constitute a single T-complex. The T-typing adopted in Table 8 is guided by 'The International Survey of the Distribution of Serotypes of *Streptococcus pyogenes*' (Parker, 1967). Eleven T-types accounted for 172 of the strains.

Most serotypes were uncommon, only eight of them averaging more than one strain per annum, namely: Types 1, M12, M28, 3/13/B3264 T-complex, T4 (M4 typing serum was not then available), 4/28 T-complex, T12, and 8/25/Imp. 19 T-complex. These commoner types contributed 236 strains, 77·9% of the total typed strains. Strains of most of the scarcer types did not appear in clusters, but were sparsely distributed throughout the survey period. Types 2 and 6 however each appeared (Fig. 3) in a small but well-defined outbreak.

The most abundant types were T4, M12 and T12, and these were distributed

Table 9. *Intervals between isolations of group A strains from the same person*
(Percentages are cumulated)

	(A) Identical		(B) Shared T-antigen		(C) Dissimilar		Total	
Interval	No.	%	No.	%	No.	%	No.	%
Months								
0–	7	63·6	0	0	2	6·1	9	17·0
1–	1	72·7	0	0	1	9·1	2	20·8
2–	0	72·7	0	0	1	12·1	1	22·6
3–	0	72·7	0	0	2	18·2	2	26·4
4–	0	72·7	0	0	2	24·2	2	30·2
5–	0	72·7	0	0	0	24·2	0	30·2
6–	0	72·7	0	0	2	30·3	2	34·0
7–	0	72·7	0	0	1	33·3	1	35·8
8–	0	72·7	0	0	1	36·4	1	37·7
9–	0	72·7	1	11·1	0	36·4	1	39·6
10–	0	72·7	0	11·1	2	42·4	2	43·4
11–	0	72·7	0	11·1	1	45·5	1	45·3
Years								
0–	8	72·7	1	11·1	15	45·5	24	45·3
1–	2	90·9	5	66·7	8	69·7	15	73·6
2–	0	90·9	0	66·7	4	81·8	4	81·1
3–	1	100·0	0	66·7	2	87·9	3	86·8
4–	0		1	77·8	1	90·9	2	90·6
5–	0		0	77·8	3	100·0	3	96·2
6–	0		0	77·8	0		0	96·2
7–	0		0	77·8	0		0	96·2
8–	0		1	88·9	0		1	98·1
9–	0		0	88·9	0		0	98·1
10+	0		1	100·0	0		1	100·0
Total	11		9		33		53	

Note: (A) Homotypic strains of identical signature. (B) Heterotypic strains possessing T-antigen(s) in common. (C) Heterotypic strains with no shared antigen.

in a broadly bimodal pattern through the 13 years, their larger numbers determining the overall secular distribution of *Streptococcus pyogenes*. By contrast with them, strains of types R28 and T4/28 complex were all found in the first three years. Type 1 strains appeared in a desultory fashion in six of the years, but in 1968, at the nadir of general streptococcal prevalence, eight of the total 15 strains were isolated, four of them between 14 and 25 October.

Successive infection of the same person by Streptococcus pyogenes (*Table 9, Fig. 4*)

Fifty persons are recorded to have had more than one strain of *Streptococcus pyogenes* isolated during the survey period, 40 of whom had only a second isolation; 6 had three and 5 had four. Not all the strains were serotyped.

Table 9, column A, shows the intervals between successive infections by strains of the same serotypes and identical antigenic signature. Eight intervals were of less than two months and the other three were long intervals. Table 9, column C, shows that subsequent infections with heterotypic strains with no shared antigens occurred at any interval from simultaneity to several years, about 50% of the

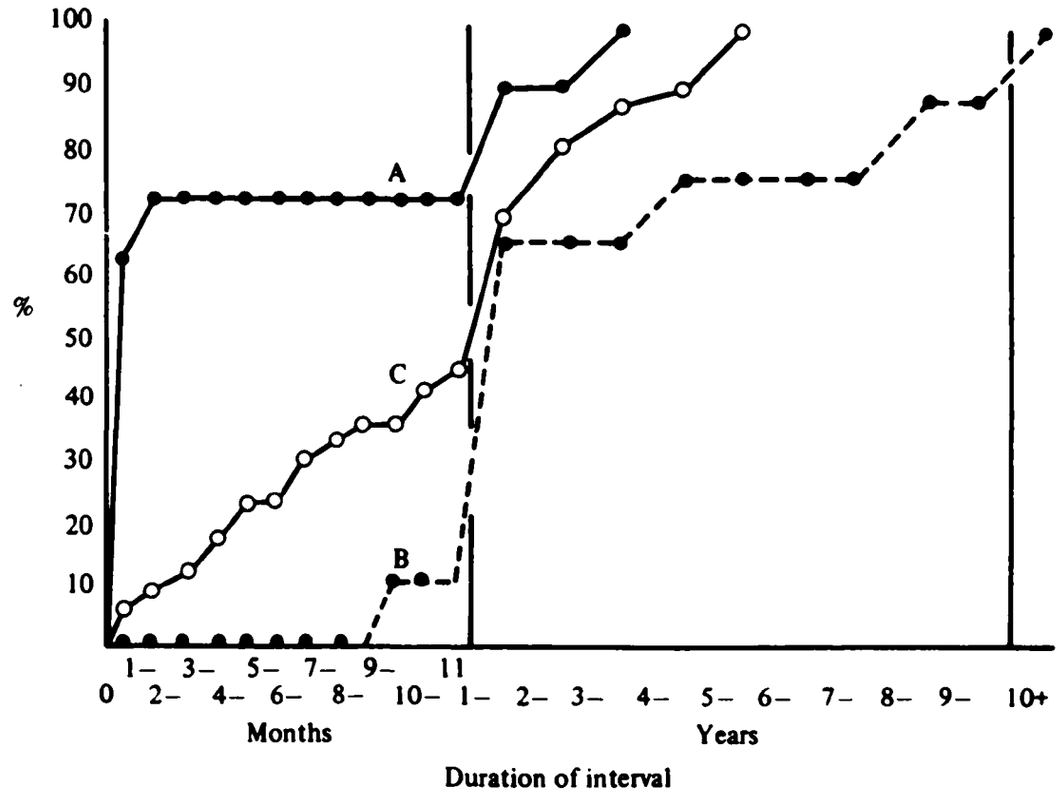

Fig. 4. Intervals between successive isolations of *Streptococcus pyogenes* from the same person. Each graph shows cumulating percentages of the total as in Table 9. Intervals are between (A) homotypic strains of identical signature, (B) heterotypic strains possessing T-antigen(s) in common, (C) heterotypic strains with no antigen in common. Note the shorter intervals in (A) (harbourage of the intial strain for a few months) followed after a long interval by true second infections by another strain of identical signature. (B) shows a similar long interval before reinfection with a heterotypic strain sharing T-antigen(s) with its predecessor in contrast to the random distribution of intervals in (C) when the second strain shared no T- or M-antigen with the first strain.

intervals being of less than a year and the proportion diminishing rapidly as the intervals lengthened. Table 9, column B, shows the intervals between successive infections by a heterotypic strain that possessed at least one T-antigen in common with the previous strain. No interval of less than nine months is recorded.

Successive infections in households (Table 10, Fig. 5)

Ninety-six intervals were recorded between successive infections in the same household. Not all strains were typed. Intervals between identical strains (Table 10, column A) showed a distribution resembling that of intervals between recurrent homotypic infections in the same person (Table 9, column A), 70% of them being of less than one month and 90% of less than one year. By contrast heterotypic strains with no shared antigens showed a more random distribution of intervals with a fairly steady decline in frequency with increasing interval lengths (Table 10, column C). The distribution of intervals between heterotypic infections with a shared antigen was intermediate though approximating to that of intervals between identical strains (Table 1, column B).

Aggregation (see appendix for method of estimation). Secular aggregation is an important aspect of epidemicity. Table 11 gives the aggregation (A-) values of strains of serotypes of which a sufficiency of strains was isolated, and compares

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Table 10. *Intervals between group A strains from different members of household*
(Percentages are cumulated)

	(A) Identical		(B) Shared T-antigen		(C) Dissimilar		Total	
Interval	No.	%	No.	%	No.	%	No.	%
Months								
0–	19	73·1	8	42·1	4	8·3	31	33·3
1–	1	76·9	3	57·9	1	10·4	5	38·7
2–	2	84·6	1	63·2	2	14·6	5	44·1
3–	1	88·3	0	63·2	2	18·8	3	47·3
4–	0	88·3	0	63·2	4	27·1	4	51·6
5–	0	88·3	0	63·2	1	29·2	1	52·7
6–	0	88·3	0	63·2	1	31·3	1	53·8
7–	0	88·3	0	63·2	0	31·3	0	53·8
8–	0	88·3	0	63·2	1	33·3	1	54·8
9–	0	88·3	1	68·4	1	35·4	2	57·0
10–	0	88·3	0	68·4	0	35·4	0	57·0
11–	1	92·3	0	68·4	0	35·4	1	58·1
Years								
0–	24	92·3	13	68·4	17	35·4	54	58·1
1–	0	92·3	2	78·9	10	56·3	12	71·0
2–	0	92·3	0	78·9	5	66·7	5	76·3
3–	0	92·3	0	78·9	4	75·0	4	80·6
4–	0	92·3	1	84·2	5	85·4	6	87·1
5–	2	100·0	1	89·5	2	89·5	5	92·5
6–	0		0	89·5	0	89·5	0	92·5
7–	0		0	89·5	3	95·8	3	95·7
8–	0		2	100·0	1	97·9	3	98·9
9–	0		0		0	97·9	0	98·9
10+	0		0		1	100·0	1	100·0
Total	26		19		48		93	

Note: (A) Homotypic strains of identical signature. (B) Heterotypic strains possessing T-antigen(s) in common. (C) Heterotypic strains with no shared antigen.

them with the A-values of other agents isolated from the same population during the surveillance. Most serotypes gave moderate or low A-values. Only type 6 strains and M-type 22 strains gave high A-values. Strains with signature 4/28//– gave much higher values than other strains belonging to the 4/28 T-complex. Similarly strains with signature 4/28//R28 were much more aggregated than other R-type 28 strains, and 25//– strains were more highly aggregated than other strains of the 8/25/Imp. 19 T-complex.

Where numbers allow, single year A-values have been estimated for comparison with the 13-year A-value. Fig. 3 shows the 13-year A-values for comparison with the picture of the secular distributions during the survey period.

Age distribution. Infection by *Streptococcus pyogenes* occurred at all ages from babies a few months old to septuagenarians. The average age of persons infected, 15·9 years, is much later than the mode, which is at about six years of age (see Fig. 6).

Sex distribution. Of the 353 group A strains, 142 came from males (40·2%) and 211 (59·8%) from females, an unexpected female preponderance that occurred in

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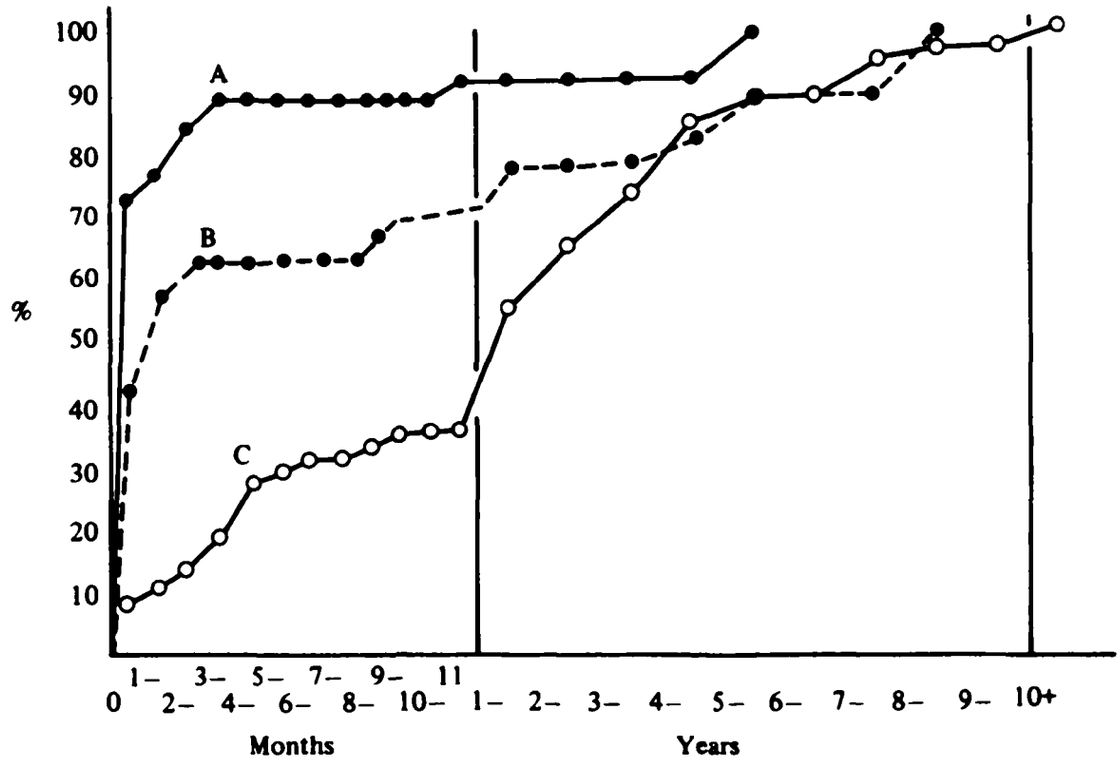

Fig. 5. Intervals between successive isolations of *Streptococcus pyogenes* from different persons in the same household. (A), (B) and (C) as in Fig. 4. Note the short intervals or very long intervals in (A) and (B) in contrast to the random intervals in (C). Percentages cumulated as in Fig. 4 and Table 10.

all but three of the 14 years of surveillance. The year of lowest prevalence, 1967, showed equal numbers of males and females infected, and 1966 and 1972 showed more males.

DISCUSSION

Secular trend of streptococcal prevalence

The number of strains of *beta*-haemolytic streptococci of all groups (BHS) increased from 1962 to 1965, waned to a very low level until 1970 and then again increased. The illnesses in the various classes did not parallel these long-term secular changes in prevalence. Sore throats continued to be seen frequently when BHS had almost disappeared in 1967, 1968 and 1969. Streptococci were not alone in becoming scarce at that time. Parainfluenza viruses and respiratory syncytial virus, whose presence had been recorded frequently in the previous five years, were almost totally absent from the specimens collected between 1966 and 1970. No fault in field or laboratory technique could be found to explain the phenomenon, and other common agents, e.g. rhinoviruses, showed no decline or were isolated more frequently during these lean years for BHS.

Strains of BHS not belonging to groups A, C or G, and the group A strains both exhibited these long-term changes in prevalence, and some of the individual group A serotypes shared the overall pattern. The period of scarcity affected all except type 1 group A strains, of which the only concentration occurred when general streptococcal prevalence was at its lowest.

The fluctuations in the prevalence of *Streptococcus pyogenes* were relatively slow,

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Fig. 6. Age distribution of persons infected with *Streptococcus pyogenes*. Annual average rate per 1000 of the population in each age-group. (A) Single-year age-groups under the age of 20 years. (B) Five-year age-groups of whole practice population.

long-term affairs, totally different from the brief intense epidemics that characterize the visits of, for example, measles or influenza virus to this small population. The epidemic mechanisms by which these streptococci are surviving must accordingly differ from those of the viruses mentioned. The suggestion that a close succession of more intense epidemics by individual group A serotypes was concealing their individual epidemicities is belied by their secular distribution shown in Fig. 3. Strains belonging to most serotypes, even the scarcer ones, were distributed widely throughout the survey period and participated in the long-term fluctuations with only occasional concentrations, and even these clusters were small and slow as compared with the behaviour of other common epidemic agents.

Table 11. *Aggregation (A) values of* Streptococcus pyogenes *serotypes and contemporaneous agents*

Agent	Number *N*	Time *T*-days	A-value
Streptococcus pyogenes, all strains 1962–75	353	5113	57·8
T-type 1 and M-type 1, all strains 1963–75	15	4748	71·4
T-type 1 and M-type 1, 1968 strains	8	366	57·1
T-3/13/B3264 complex, all strains 1963–75	32	4748	48·4
T-3/13/B3264 complex, 3//– strains only	14	4748	69·2
T-3/13/B3264 complex, 3// 1964 strains	9	366	75·0
T-type 6 and M-type 6, all strains 1963–75	14	4748	84·6
M-type 12, all strains 1963–75	43	4748	54·8
T-type 12, all strains 1963–75	46	4748	57·8
T-type 12, 1964 strains	9	366	50·0
T-type 12, 1965 strains	10	365	55·6
T-type 12, 1971 strains	8	365	57·1
T-type 12, 1972 strains	8	366	71·4
Signature 13//–, all strains 1963–75	11	4748	60·0
T-type 4 (no M-serum), all strains 1963–75	39	4748	52·6
T-type 4 (no M-serum), 1965 strains	9	365	75·0
T-type 4 (no M-serum), 1966 strains	10	365	66·7
T–4/28 complex, all strains 1963–75	19	4748	55·6
T–4/28 complex, 28//– strains only	11	4748	50·6
T–4/28 complex, 4/28//– strains only	8	4748	82·8
R-type 28, all strains 1963–75	23	4748	72·7
R-type 28, 4/28//R28 strains only	21	4748	85·0
T-type 22, all strains 1962–75	8	4748	82·8
T–8/25/Imp. 19 complex, all strains 1963–75	19	4748	38·9
T–8/25/Imp. 19 complex, 25//– strains only	8	4748	82·8
T–8/25/Imp. 19 complex, strains with T. Imp. 19	11	4748	60·0
Group C beta-H.S., all strains 1963–75	36	5113	48·6
Group G beta-H.S., all strains 1963–75	15	5113	35·7
Myxovirus influenzae type A, 1963/64 strains	27	366	84·6
Myxovirus influenzae type A, 1969/70 strains	112	365	91·9
Myxovirus influenzae type B, 1975/76 strains	16	366	86·7
Herpes virus hominis, average of 10 annual A-values			44·2

Streptococcus pyogenes *and morbidity*

The analyses suggest that *Streptococcus pyogenes* was present as a pathogen in only two of the three morbidity classes examined causing some 16 per cent of the sore throats and contributing to perhaps 1·5 per cent of the acute febrile respiratory illnesses. The annual isolation rate from specimens from sore throat sufferers varied from 30·1 per cent in 1964 to 4·7 per cent in 1969. The highest isolation rate from sore throats occurred in the months of November and December in 1964 when more than 60 per cent of specimens yielded *Streptococcus pyogenes*.

The proportion of strains isolated from specimens from the large class of Non-FRD illnesses was similar to that from non-streptococcal ailments and healthy persons, indicating a carrier rate of around 1 per cent of the population as detected by the isolation techniques employed, but varying with the amount of recent streptococcal illness.

No analysis of the clinical impact of different serotypes has yet been undertaken,

but it was recorded that most of the streptococcal illnesses with a scarlatiniform rash were caused by T-type 4 strains.

Seasonal distribution of Streptococcus pyogenes *infections*

The group A strains showed no regular seasonal preference. The month of August recorded a very low average number of isolations, a trend reflected neither in the number of specimens taken nor in the morbidity figures. Yet in 1973 August shared with January the most isolations of any month. The high average figures for isolations in Novembers, Decembers and Januarys are caused largely by the contribution of one period of high prevalence in 1964–5, and do not indicate a seasonal trend (see Table 7).

Homotypic and heterotypic immunity

Survival, for the streptococcus, must depend to some extent on the specific immunity that it provokes in the host, and the mechanisms that it has evolved for evading the consequences. Of the three types of antigen used here for serotype classification, only the M-antigen is thought to be concerned in pathogenicity. An attempt was made in the present study to examine the protection that a streptococcal infection confers against subsequent re-infection by homotypic identical strains, by heterotypic strains sharing at least one T-antigen in common with the initial strain and by heterotypic strains of totally unrelated signature. The results in Table 9 and Fig. 4 suggest that an infection by *Streptococcus pyogenes* confers little or no protection against subsequent infection by a heterotypic strain with which it shares no T-antigen, but that it confers good protection against homotypic strains and, temporarily, against heterotypic strains with a shared T-antigen. Table 9 column A also suggests that the infecting strain may be carried for four months after it has caused an illness.

These conclusions find some support from the examination of successive *Streptococcus pyogenes* infections in the same household. Table 10 and Fig. 5 show homotypic infections recurring in the household either within a few months or at much longer intervals, whereas heterotypic infections might occur at any interval unless the streptococcus shared a T-antigen with the initial strain, in which case it behaved more like a second homotypic infection.

Household outbreaks were not very common, and usually few members were affected. Although two or more cases sometimes occurred simultaneously or within a few days, more often weeks would elapse between cases. For example, in 1968, when six of the eight type 1 strains came from the same housing estate, only two came from the same household, the first on 28 August and the second on 25 November. Such desultory behaviour within households frequently occurred and formed a striking contrast to the behaviour of many of the other common pathogens within households.

Clustering

Table 11 and Fig. 3 attempt to quantify the degree to which the infections are aggregated in time. The results suggest that the different serotypes differ in epidemic potential. The types with the most abundant strains, M-type 12 and T-type 12, gave consistently low A-values, 40–57, both overall and for individual years.

Two rather scarce types, type 6 and T-type 22, gave high A-values (84·6 and 82·8). Table 11 supports the indications from Tables 9 and 10 that T-antigens may have epidemiological importance in addition to their identification value. For example, T-type 4 strains and R-type 28 strains have moderate A-values but strains with signature 4/28//R28 have a high A-value (85·0). Similarly strains of the 4/28 T-complex have an A-value of 55·6. Strains of this T-complex with signature 28//– gave an A-value of 50·0 whereas those strains with signature 4/28//– gave a high A-value, 82·8, as if the combination of T4 and T28 antigens had potentiated the epidemicity of both. Another example can be found in strains belonging to 8/25/Imp. 19 T-complex. These had a very low overall A-value of 38·9, yet strains with the signature 25//– were highly aggregated (82·8).

CONCLUSIONS

The conclusions drawn from the findings of this survey must be tentative because of the small numbers involved. The findings suggest that the epidemic behaviour of *Streptococcus pyogenes* is best interpreted as that of an organism usually of low epidemic potential which confers strong homotypic but poor heterotypic immunity, and which tends to linger in the pharynx for up to four months after causing an infection. The epidemiological importance of the agglutination (T) antigens merits further study.

This study has led the author into the unfamiliar and perilous territory of the group A streptococcal serotypes. He is deeply indebted to Dr T. M. Parker and Dr R. Mayon-White for their patience and guidance and for much help and criticism.

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APPENDIX 1. METHOD FOR QUANTIFYING SECULAR AGGREGATION

Principle

No aggregation of events in time occurs if they come with perfect regularity as, for example, the sounds from a regularly ticking clock. This is the minimal situation from which any departure from regularity causes aggregation of the events. Maximal aggregation is simultaneity of the events as, for example, in relation to the expulsion of each pellet in a single shot fired from a shotgun.

Method

The degree of aggregation A is expressed on a scale from nil (absolute regularity) to 100 (simultaneity) by

$$A = \frac{100\,(N-n^+)}{N-1},$$

where N is number of events in total period of observation T time units;

$t = T/N$, the time (in the same units) in which with regularity one event and no more would be expected: $Nt = T$

n^+ is number of t in which one or more events were observed to occur.

Examples

Example 1. Twenty-one group A streptococcal strains of signature 4/28//R28 were isolated in thirteen years of observation. Time units: months.

$$N = 21 \text{ strains},$$

$$T = 156 \text{ months},$$

$$t = \frac{T}{N} = \frac{156}{21} = 7{\cdot}43 \text{ months}.$$

The total observation period T is then divided into 21 sub-periods (t) each approximating 7·43 months. All 21 strains were found to have been isolated in four of the sub-periods:

$$n^+ = 4$$

$$A = \frac{100\,(N-n^+)}{N-1}$$

$$= \frac{100\,(21-4)}{21-1}$$

$$= \frac{1700}{20}$$

$$= 85{\cdot}0.$$

The method gives an estimate of the epidemic potential of the agent, but no information of when and how the aggregation has occurred, e.g. in a single cluster or in several clusters during the period of observation. Moreover the A-value may vary according to the period selected for observation, and epidemiological understanding may be obtained by comparing A-values determined in different periods. For instance an organism showing high aggregation on a scale of years might show little aggregation on a scale of weeks or days during its periods of high prevalence. A-values can also be used for comparing the epidemicity of one organism with that of another, or of the same organism in different epidemics.

Example 2. In 1964 twelve of the strains of signature 4/28//R28 were isolated. Time units: days.

$$N = 12 \text{ strains},$$

$$T = 366 \text{ days},$$

$$t = \frac{366}{12} = 30{\cdot}5 \text{ days.}$$

The strains were all isolated in three of the sub-periods

$$n^+ = 3$$

$$A = \frac{100(12-3)}{12-1} = 81{\cdot}82.$$

Evidently in the examples chosen strains of signature 4/28//R28 showed high epidemic potential both over the whole period of observation of 13 years and in the more detailed situation of a single year of high prevalence.

A-values of various organisms are given in Table 4.

Caution. For the method to provide reliable information about epidemicity the material should have been collected continuously with reasonable uniformity and sufficient events should have been observed. Choice of a suitable observation period T is determined by such factors as natural repetitive cycles, e.g. a year, and choice of time unit (day, week, month, year) by the number of events N in relation to total time T.

If N is a small number of events in relation to the observation period T, high A-values are more likely to occur by chance, and low A-values are good evidence of low epidemicity. Similarly in the converse situation where N is numerous, high A-values are good evidence of high epidemicity.

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