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Changes in Occurrence of Capsular Serotypes of *Streptococcus pneumoniae* at Boston City Hospital During Selected Years Between 1935 and 1974

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The number of patients with pneumococcal bacteremia, empyema, and meningitis at Boston City Hospital during selected years between 1935 and 1974 is reported. The distribution of specific types in the bacteremic patients during each of the selected years and in the various focal infections in all the years is also detailed. The numbers and rates per 1,000 admissions of bacteremic pneumococcal infections and the numbers of cases of pneumococcal meningitis and empyema varied independently over these years and differed from those previously reported for 1929 to 1936. The types most frequent in pneumococcal bacteremias varied over the years, and the distribution of types among them differed markedly from that among the patients with focal infections. Variations in the distribution of pneumococcal types at different times in the same place, in different places, and in various sites of infection may be important in selecting types to include in pneumococcal vaccines for different populations.

Prior to the advent of modern antibacterial therapy, essentially the only successful agents for the treatment or control of serious bacterial infections depended on the development of highly active immunological agents, i.e., specific antisera and vaccines. Just before the sulfonamides became available, some progress in developing potent antisera effective against pneumonias caused by some of the more common types of pneumococci (*Streptococcus pneumoniae, Diplococcus pneumoniae*) was being achieved, and effective type-specific capsular polysaccharide vaccines were also being developed. Successful utilization of the specific antipneumococcal sera depended on the availability of a simple and rapid method of determining the specific type of the causative *Pneumococcus*.

When it became evident that the sulfonamides, and later penicillin and other antibiotics, were equally active against pneumococci of all serotypes, there was no longer any need for typing of pneumococci for selection of therapy. As a result, this procedure, which was coming into use in increasing numbers of hospitals and public health laboratories, was essentially abandoned in all but a very few clinical laboratories.

In more recent years, there has been a revival of interest in extending the range of serious bacterial infections that might be successfully controlled or prevented by specific vaccines, including those against meningococci and *Haemophilus influenzae* type B and also against the types of pneumococci responsible for the great majority of cases of serious pneumococcal disease (9). However, results obtained in a few places where typing of pneumococci had been carried out over long periods indicated that the incidence of many types may vary at different times in the same hospital, community, or country and also at the same time in different places (23, 24).

At Boston City Hospital, pneumococci from all infected sources had been subjected to specific typing for many years through the early 1940s. After that, "routine" typing of pneumococci from sources in the respiratory tract was discontinued. However, the typing of pneumococci isolated from blood cultures and from the purulent exudate of focal infections was continued, although in some years such typing was not carried beyond identification with one of the "pooled" typing sera. The occurrence of various specific types of pneumococci at this hospital during the 7-year period from July 1929 through June 1936 was previously reported (7). In this paper we present data on the occurrence of specific capsular types of pneumococci for selected years between 1935 and 1974, including those years during which all or nearly all the strains from any given site or body fluid were

identified with the use of sera against all available specific serotypes.

MATERIALS AND METHODS

The data to be presented are part of a broader study of the changing etiology of serious bacterial infections that developed after the successive introduction and extensive use of modern effective chemotherapeutic and antibiotic agents at Boston City Hospital (10, 26). The data reported here are essentially limited to the specific serotypes and sources of pneumococci isolated during the years between 1935 and 1974 that were originally selected to reflect the impact of the various new antibacterial agents or their continued use. The pneumococci were identified first by their morphology in Gram-stained smears and by the distinctive colonial morphology on sheep blood agar and confirmed by the optochin test and bile solubility in some instances; however, principal reliance was placed on the Neufeld test, which is the specific capsular swelling (Quellung) of the pneumococci with pooled typing sera and the further identification of the specific type with individual sera that constituted the positive-reacting pool. The test was usually applied directly to suspect cultures from blood or purulent foci and also to characteristic pneumonic sputum and tracheal aspirates. Mouse inoculation, which had been carried out routinely in earlier studies (7, 31), was done only occasionally during the years covered in the present report. Multiple isolates of the same type from any one source in the same patient are counted as a single strain. Isolates of cultures from the respiratory tract secretions (sputum, nasal or pharyngeal swabs or both, or tracheal aspirates) were included only if collected from the patients from whom type-specific pneumococci had been obtained from blood or from a purulent focus. Complete typing of pneumococci was carried out in cultures from autopsies in only 3 of the years included in this study.

RESULTS

Distribution of types before modern chemotherapy. The relative frequency of isolation of the six most frequent types in the 7 years from July 1929 through June 1936 is represented in Fig. 1 and 2. These are shown for comparisons with the more recent findings in the same hospital. On the left of Fig. 1 and 2 are shown the percentage of strains of each type isolated from all sources in each of the 7 years and the average for the 7 years. To the right are shown the proportions of each type isolated from different clinical categories of cases in all 7 years. The designation "bronchopneumonia" represents cases in adults with clinical and X-ray findings of pneumonia that were not those chracteristic of lobar pneumonia and were previously termed "atypical pneumonias." "Pediatric pneumonias" include all cases with pneumonia or empyema or both in infants and children less than 13 years old. The 69 cases listed in the early

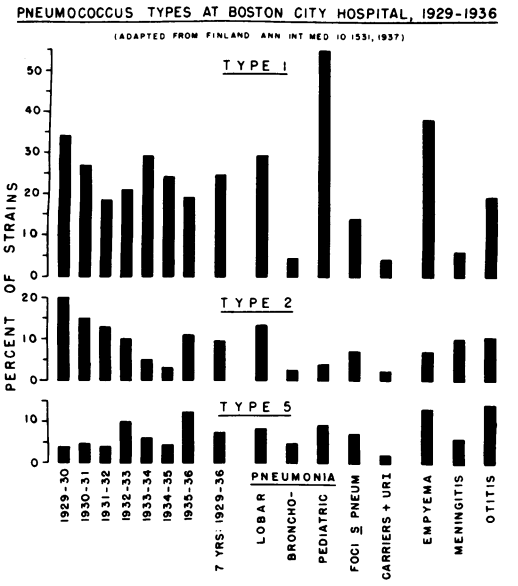

FIG. 1. *Distribution of Pneumococcus types 1, 2, and 5 in successive years and from different sources at Boston City Hospital between 1929 and 1936. (Adapted from Finland [7].)*

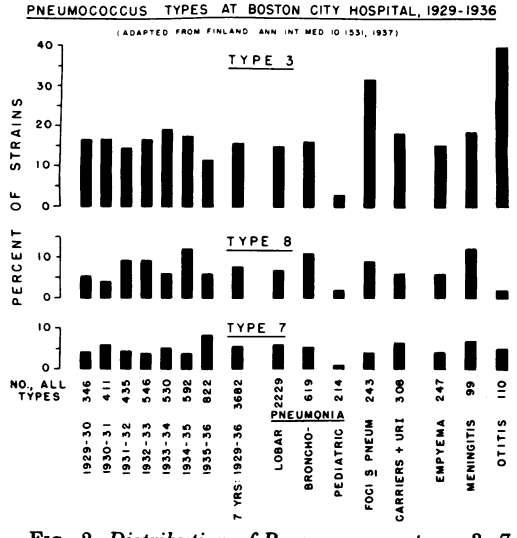

FIG. 2. *Distribution of Pneumococcus types 3, 7, and 8 in successive years and from different sources at Boston City Hospital between 1929 and 1936. (Adapted from Finland [7].)*

report as "adults with empyema on admission" are included with the other empyemas. The total number of cases in each category is shown below the columns in Fig. 2.

Figure 1 shows the relative frequency of types 1, 2, and 5. Each type presented a different pattern of change in distribution of the

types and distinct differences in the frequency of the types in the various clinical categories over this 7-year period. Noteworthy is the steady decline in the proportion of type 2 strains over the first 6 years, with a rise in the last years. Also, for each of these three types the proportion of strains from the cases of (atypical) bronchopneumonias was much smaller than among the lobar pneumonias and comparable to the percentage of the corresponding type in healthy carriers or in patients with acute upper respiratory infections without pneumonia. The very high proportion of type 1 strains in the pediatric pneumonias (and empyemas) is also striking. The percentage of types 1 and 5 among the strains from pleural empyemas was higher than the percentage of the corresponding types in cases of lobar pneumonia, whereas the reverse was true for type 2 (which is antigenically related to type 5). The relative proportions of each type from cases of otitis and meningitis were also different.

The corresponding data for types 3, 7, and 8 (Fig. 2) also demonstrate distinctive relationships that differ from one another and also from those seen with types 1, 2, and 5. Of interest are the independent annual fluctuations in the proportion of the antigenically closely related types 3 and 8. Also, in contrast to types 1, 2, and 5, the proportions of types 3 and 8 among atypical pneumonias were the same or higher than among the corresponding cases of lobar pneumonia. Particularly distinctive is the very high proportion of type 3 strains among those isolated from all focal infections in patients without pneumonia, especially among those isolated from otitic exudates. Noteworthy are the small proportions of each of these three types among the pediatric pneumonias. In addition, type 3 was the most frequent of all types among strains isolated from normal carriers and from patients with upper respiratory tract infections without pneumonia.

The six types shown in Fig. 1 and 2 accounted for 69% of all pneumococci isolated from all sources during the earlier 7 years. The relative frequency of the types isolated from the blood of patients with pneumococcal pneumonia before 1936 was reported separately (33). The same six serotypes accounted for 84.5% of the 582 strains from bacteremic pneumonias included in that report, which covered the period from November 1929 through May 1935. For types 1, 2, and 3, the proportions of strains from bacteremic pneumonias in that report were appreciably higher than that for the corresponding type among strains from all sources in the 7 years; for type 5 the proportion was considerably lower, and for types 7 and 8 it was essentially the same.

Types of pneumococci during selected years between 1935–1974. (i) Types isolated from blood cultures. (Twelve years between 1935 and 1972 were originally selected to document the changing ecology of bacterial infections in relation to the successive introduction and extensive use of antimicrobial drugs [26]. Three of those years were excluded in the present study because complete typing of pneumococci was not carried out in those years. However, in the years 1968 through 1974 [which include 2 of the 12 years], such typing was done on pneumococci isolated from blood and focal purulent infections; these data permit a better comparison of data from pre-antibiotic years [1928–1936] with those from the most recent years and are, therefore, included.) Table 1 lists the number of strains of the specific types of pneumococci identified in blood cultures during each of the 15 selected years (from 1935 through 1974). The last column lists the number of years (among the 15 that were selected) during which each type was isolated, and the bottom line shows the number of specific types identified in each of those years. The number of strains serotyped each year ranged from 77 to 140 and averaged 105. Only 22 of the 1,572 strains (1.4%) could not be identified with the available pools and individual serotypes, and 7 strains were identified only with one or another of the pools containing several types.

Only seven types (types 1, 3, 4, 7, 8, 14, and 18) were found in every one of the 15 selected years; total numbers ranged from 165 (for type 1) to 96 (for type 18). Together, these seven types accounted for 60% of the 1,543 strains identified by specific type. Seven additional types (types 6, 9, 12, 19, 20, 23, and 33) were found in blood cultures from 60 to 23 patients during 12 or 13 of the 15 years, accounting for another 19.4% of all the typed strains. From 16 to 28 (average, 22) types were found among the strains specifically identified in the different years.

Noteworthy features of the data shown in Table 1 are the variations and fluctuations in the number of strains of each type from year to year. This is best illustrated in Fig. 3 through 5 for 11 or the most frequent types; the corresponding data for 1929 through 1936 for 6 of those types are shown in Fig. 1 and 2. The different and distinctive fluctuations in the number of strains of each type isolated in the different years of the study are clearly evident. Some of the findings are particularly worth noting.

The proportion of strains of type 1 (Fig. 3, bottom tier) continued to exhibit fluctuations as seen in the early years when it was the most frequent type each year (Fig. 1, top tier) and in

TABLE 1. *Specific types of pneumococci identified in blood cultures at Boston City Hospital During 15 selected years between 1935 and 1974*

Pneumococci	No. of strains																
	1935	1941	1951	1953	1955	1957	1965	1967	1968	1969	1970	1971	1972	1973	1974	Total	No. of yr[a]
Type																	
1	38	32	11	14	18	5	9	14	5	5	5	3	2	2	2	165	15
2	9	15	19	9		2	2	1								57	7
3	22	17	16	15	5	8	10	12	9	11	5	5	4	4	7	150	15
4	4	5	4	5	5	6	17	13	9	12	5	11	10	10	5	121	15
5	9	8	7	6	5	2	8	6								51	8
6		3		3	1	5	7	3	3	3	2	6	6	11	7	60	13
7	4	16	8	11	8	7	16	10	10	10	4	7	5	3	4	123	15
8	5	12	13	8	6	5	10	16	5	14	7	7	13	11	13	145	15
9	1			2	1	1	2	3	3	6	3	1	2	4	3	32	13
10						3		1	1	1		3				9	5
11	2						2	3	1		2			1	2	13	7
12	2			3	4	5	4	6	5	7	2	2	3	2	3	48	13
13			1	1		1	1	1	1	1			1			8	8
14	4	10	7	4	8	10	11	12	3	9	6	18	28	12	17	159	15
15			1		2		2	1	1			1	1	1	1	11	9
16		1		2		1	2		1	1	4	1	3			16	9
17			2		1			4	2	1	3			2	1	12	7
18	1	6	2	6	2	1	6	4	7	9	10	13	12	11	6	96	15
19		2		4	1	5	3	2	5	2	3	7	9	6	5	56	13
20		1	1	1	2	3		2	2		3	1	1	5	1	23	12
21								1			2		1		1	5	4
22	1		1	2		1		2	3	1	2	1		2	4	20	11
23	1	2	2	1		1	3	3	8	2	4	5		6	6	44	13
24		2					2	2	1	4	1		1			13	7
25	1	1		3			1	2	2			3	5	1	3	22	10
28	1	1					1				1	1			2	5	4
29			1		1		2					1	1			6	5
31		1			1		1	2	1	1	2			1		10	8
33		3	2	2	2	3		3	1	8	3		3	5	2	37	12
34					1					1	1	1		2		6	5
35								1				1	1	1		4	4
Others	1[b]	2[c]	3[d]	2[e]	2[f]	1[g]	1[h]	1[i]			2[j]	1[k]				16	10
Grouped[l]		1		2	1	2	1									7	5
NT[m]			3	2		7	2	1	3		2	1			1	22	9
Total	105	140	104	108	77	85	126	130	92	109	84	101	112	102	96	1,572	
Types (no)[n]	16	20	20	21	21	21	24	28	24	21	25	23	20	22	21	40	81[o]

[a] Number of years in which the designated type was identified.
[b-k] The specific types were: 27; 18A and 32; 18A, 36, 40A; 10A (two strains); 10A and 18A; 32; 27; 37; 36 and 39; 42, respectively.
[l] Identified only with one of the available "pooled" antisera.
[m] NT, Not typable.
[n] Includes only those identified with single "specific" typing sera.
[o] Mean number of years for the 40 specific types.

the last few years when it dropped to very low levels.

Types 2 and 5 are of particular interest. These antigenically related types fluctuated independently in frequency over the earlier years and through 1967, but neither of these types was identified in any blood cultures at this hospital in the selected years after 1967.

The antigenically related types 3 and 8 (Fig. 2 and 4) continued to show independent fluctuations in occurrence in different years, with proportions of the type 3 strains fluctuating over lower levels after 1953. Type 4 was infrequently found in blood cultures before 1936, but ranked sixth in total number of strains isolated during the 15 selected years. Figure 5 (bottom tier) shows the high peaks of occurrence of type 7 in 1941 and 1965, but the numbers of strains of this type were present over lower levels after that year. Type 6 (Fig. 4, second tier from top) occurred infrequently and irregularly in blood cultures before 1957 but increased in relative frequency during the last few years.

Types of pneumococci in infected foci and body fluids. In Table 2 are listed the number of strains of each of the *Pneumococcus* types isolated in the selected years from foci of infection other than pneumonia. These include cerebrospinal fluid in 198 cases of meningitis, pleural exudate from 196 cases of empyema (Fig. 6), purulent exudate from the ears of 195 cases of acute otitis media, swabs of exudate from 101 cases of conjunctivitis and other ocular infections (Fig. 7), and 152 cultures of exudate from

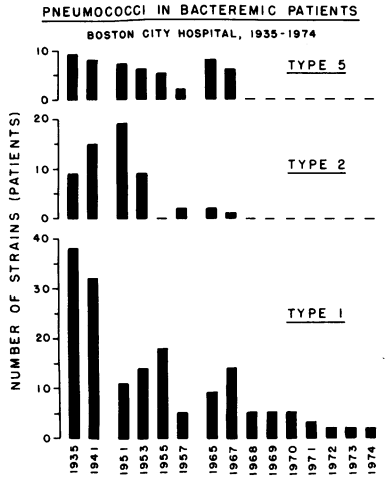

FIG. 3. *Occurrence of S. pneumoniae types 1, 2, and 5 in bacteremic patients at Boston City Hospital during 15 selected years between 1935 and 1974.*

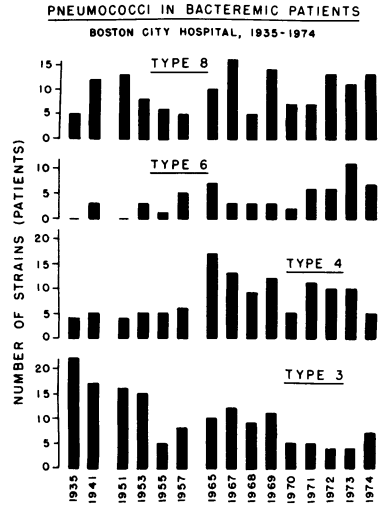

FIG. 4. *Occurrence of S. pneumoniae types 3, 4, 6, and 8 in bacteremic patients at Boston City Hospital in 15 selected years between 1935 and 1974.*

patients with various other purulent foci except from the lower respiratory tract.

These other foci are enumerated in Table 3. Some 45 different foci are represented, but the most frequent were: peritoneal exudate (32 strains of 16 types); infected or draining wounds (31 strains of 19 types); subcutaneous abscesses (18 strains of 15 types); infected urine (17 strains of 10 types); and synovial fluid (16 strains of 11 types).

From 25 to 34 different specific types were identified in the materials from each of the categories listed in Table 2. However, no single

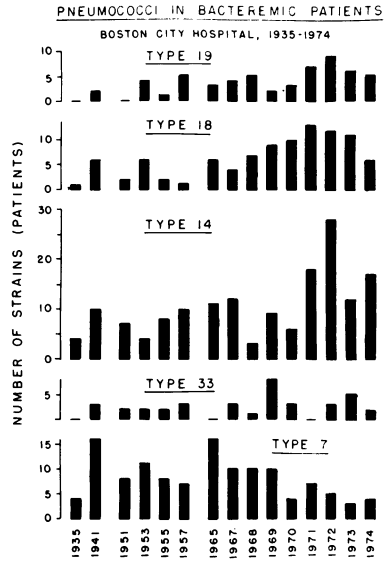

FIG. 5. *Occurrence of pneumococci of types 7, 14, 18, 19, and 33 in bacteremic patients at Boston City Hospital in 15 selected years between 1935 and 1974.*

type was isolated from any one of these foci during all of the selected years. Only a few types were isolated from 10 or more cases of infection of one or more foci; types 3, 4, 6, 8, and 12 were obtained from the cerebrospinal fluid of 17, 15, 14, 16, and 12 cases, respectively; types 1, 3, and 8 were cultured from the pleural exudate of 47, 28, and 13 patients, respectively (43 of the 47 type 1 strains were isolated in 1935 and 1941); types 3, 6, 14, and 19 were obtained from swabs or pus from draining ears of 49, 15, 16, and 38 patients, respectively; and types 3 and 19 were grown from various other foci in 37 and 11 cases, respectively.

The most frequent types among all 842 strains of typed pneumococci isolated from focal infections outside of the respiratory tract were: type 3 (140 cases), type 19 (61 cases), type 1 (59 cases), type 6 (53 cases), type 14 (38 cases), types 4 and 8 (33 cases each), and type 18 (30 cases). Together these eight types accounted for 447 (53%) of all the typed extrapulmonary foci of pneumococcal infections. Of the 842 strains, 73 (8.7%) were identified only with one of the pooled sera, and 45 (5.3%) did not react with sera of any of the available pools or individual serotypes.

Types of pneumococci in the respiratory tract. Identification of specific types from sputum or from nasal or pharyngeal swabs of patients with pneumonia was not done routinely during the years after 1935 that were selected for this study. However, pneumococci recognized in such materials from patients with focal infections were frequently identified by type

TABLE 2. *Pneumococcus types identified in cultures of 842 infected foci and body fluids[a] during selected years between 1935 and 1974*

Pneumococcus	CSF[b]		Pleural fluid				Otitic fluid		Eye		Others[c]	
	16-yr period[d]	No. of yr[e]	1935	1941	16-yr period	No. of yr[f]	16-yr period	No. of yr	16-yr period	No. of yr	16-yr period	No. of yr
Type												
1	2	2	36	7	4	4	8	6	1	1	1	1
2	8	4[g]	1	1	2	2[g]					2	2[h]
3	17	8	2	7	19	13	49	11	9	4	37	12
4	15	7	1		4	4	3	3	2	2	5	5
5	4	3[h]	2	2	4	4[i]	1	1				
6	14	11		1	3	3	15	8	12	7	8	6
7	8	6		3	3	2	2	2			4	3
8	16	11	1	2	10	8	2	2	1	1	3	3
9	9	8			2	2	2	1	3	3	7	6
10	4	4		1	1	1	1	1	1	1	4	4
11	3	3		1			2	1	1	1	2	2
12	12	7	1		3	3	1	1			3	3
13	6	6					2	2			3	3
14	7	6	1		3	2	16	6	6	5	5	4
15	4	3			1	1	5	4	2	2	2	2
16	1	1		1			1	1	1	1		
17	3	1			2	2			2	2	2	1
18	9	7	1		1	1	7	6	4	3	8	6
19	7	7	1		2	2	30	8[j]	10	7	11	8
20	2	2	1		3	3	1	1	1	1	5	5
21							4	4	2	1	2	2
22	6	6			4	3	2	2	2	2	3	3
23	6	4			4	4	6	3	6	5	7	5
24	5	3									1	1
25	6	5			1	1	1	1			1	1
27	1	1		1								
28	1	1					1	1			1	1
29	1	1			1	1					1	1
31	1	1			1	1					3	3
32				1								
33	7	4		1	2	2	2	1	3	3		
34	4	3			2	2			1	1	1	1
35	1	1					1	1			1	1
36	2	2										
41											1	1
10A	3	3										
40A	1	1										
Grouped[k]					32	7	17	7	9	5	15	10
NT[l]	2	2			5	3	13	6	22	7	3	3
Total	198	16	48	29	119[m]	16[m]	195	16	101	12	152	16
Types no.[n]	34		11	13	24[o]		25		28		29	

[a] Excluding those isolated from blood cultures (Table 1), or from the respiratory tract, and at autopsy (Table 4). The number in the columns under the dated years represents the number of strains (patients).

[b] CFS, Cerebrospinal fluid.

[c] Sources and sites are listed in Table 3.

[d] The 16-year period included the years between 1935 and 1974. For cultures taken from pleural fluid, the 16-year period included the years between 1947 and 1974.

[e] The number of years during which the indicated type was isolated.

[f] Excluding 1935 and 1941.

[g] The last one was isolated in 1951.

[h] The last one was isolated in 1965.

[i] The last one was isolated in 1967.

[j] Eight, five, and nine strains were isolated in 1970, 1971, and 1974, respectively.

[k] Reacted with one or another of the "pooled" sera but "specific" type was not further identified.

[l] NT, Not typable with available antisera.

[m] Excluding 1935 and 1941.

[n] Includes only "specific" types.

[o] Twenty-seven types, including three that were identified in 1941 and not in any other year.

TABLE 3. *Occurrence of specific types of pneumococci in 152 "other" infected foci and body fluids[a] at Boston City Hospital during selected years betwen 1935 and 1974*

Infected site	No. of strains	Specific types[b] (no. of strains)
Brain abscess	2	*3,4*
Atrioventricular shunt	1	*22*
Mastoid	3	*3*(2),*19*
Ethmoid sinus	2	*2,3*
Lacrimal duct	2	*4,P*
Alveolar abscess	1	*3*
Tonsillar abscess	1	*3*
Esophagus	1	*3*
Peritoneum	32	*3*(4),*4,6*(2),*7*(3),*8,9*(2), *10*(3),*12,13,14* + *18,18* (2),*19,22*(2),*25,P*(5),*U*
Gall bladder	2	*3*(2)
Perirectal abscess	1	*3*
Feces	2	*3,19*
Urine	17	*3*(5)*6,8*(2),*9*(2),*18,19*,20(2), *23,28,P*
Prostatic fluid	1	*34*
Vagina	5	*3,6,9,19,23*
Bartholin's gland	1	*11*
Uterus	1	*6*
Placenta	1	*14*
Vernix caseosa	1	*6*
Bone marrow	1	*21*
Subcutaneous abscess	18	*2,*[c]*3*(3),*4,6,12,14,17*(2),*19, 20,23,31,41,P*(2),*U*
Infected or draining wound	31	*3*(7),*6,9,11,13*(2),*14,14* + *18,15*(2),*19,20,21,23*(4), *24,29,31,35,P*(2)
Breast abscess	1	*3*
Abscess of hand	2	*3,U*
Abscess or ulcer of foot	4	*3*,19(2),31
Synovial fluid	16	*1,3*(2),*4,7,9,10,12,18, 19*(2),*20,P*(4)
"Cyst"	1	*3*
Source (?)	1	*18*

[a] As listed in last two columns of Table 2.

[b] The specific types are italicized. The number of strains (if more than one) per type is given in parentheses. *P*, strains identified with one of the pooled sera but not further identified with specific serotypes. *U*, untypable; strain failed to react with any of the available pooled typing sera.

[c] Isolated in 1965.

during several years. The distribution of types of these respiratory strains for 4 years between 1941 and 1965 and for the 8 years between 1967 and 1974 is given in Table 4. In the latter period, the bacteriologists were interested in verifying their skill in recognizing types 3 and 8 pneumococci from their colonial morphology on blood agar; this accounts for the inordinate numbers of strains of these two types during those years. However, this does not apply to tracheal secretions obtained by aspiration; pneumococci thus obtained in 1965 and subsequently were regularly and completely typed.

The most frequent types in sputum and nasal or pharyngeal cultures during the four selected years from 1941 through 1965 were (in the order of decreasing numbers): types 3, 1, 2, 8, 7, 14, 4, and 5, with types 2 and 8 of equal rank. Each of these eight types was identified in 11 to 54 strains, and together they accounted for 199 (72%) of the 276 strains from these sources. Ten of the strains (2.6%) failed to react with any of our available antisera.

During the last 8 years, the most frequent types (excluding types 3 and 8) were (in descending order of occurrence): types 14, 4, 19, 6, 18, 7, and 9. These seven types were found in 192 (50.6%) of the 379 cases other than those in whose cultures types 3 and 8 were identified. Eleven of the 379 strains (2.9%) were not typable. Pneumococci from 137 tracheal aspirates were typed with all available types of antiserum from 1965 through 1974. Seven of them (5.1%) did not react with any of the typing sera, and the other 130 yielded 21 different types. The most frequent types in these tracheal aspirates were types 3, 8, 7, and 6, which were identified in 71, 14, 7, and 6 cases, respectively. Two types were identified in each of 4 of these aspirates, in 3 of the other respiratory cultures in the earlier 4 years, and in 75 of the cases in the last 8 years. Type 3 was one of the two types in 45 of the 75 cases.

Types of pneumococci cultured at autopsy. The earlier report (7) included the distribution of specific types among 764 strains of pneumococci isolated from various sources at autopsy between the years 1929 and 1936. The anatomical and bacteriological findings in infections with specific types of pneumococci, including types 1 to 32, during those years were also reported (11). The six most frequent types were types 3, 1, 5, 2, 8, and 7; they accounted for 532 (69.6%) of the 764 strains of pneumococci identified from the cultures made at autopsy.

Typing was carried out in a large proportion of strains of pneumococci from autopsies during only three of the selected years included in the present report (namely, 1935, 1941, and 1965). The distribution of types identified during those 3 years is shown in the last three columns of Table 4. Type 3 was the most frequent type during each of these 3 years, and type 1 ranked second in 1935. There were more than five strains each of types 2, 4, 8 and 10 in 1935, but only types 7 and 17 were represented by more than five each in 1941. Totals of 26 and 30 types were identified among the 136 and 116 strains, respectively, during these 2 years, and 13 types were noted among the 38 strains in 1965.

DISCUSSION

We previously reported on the changes in the etiology of serious bacterial infections at Boston

TABLE 4. *Distribution of types of pneumococci isolated from cultures of the respiratory tract during life and at autopsy in selected patients[a] at Boston City Hospital during selected years between 1935 and 1974*

Type	Cultures from sputum, nasal and/or pharyngeal swabs, and (tracheal aspirates)[b]		Cultured from any source at autopsy		
	4 yr (1941-1965)	8 yr (1967-1974)	1935	1941	1965
1	25	12 (1)	21	3	
2	23	3[c]	8	3	
3	54 (7)	1,252 (64)[d]	32	25	9
4	20	34 (7)	8	4	1
5	11	4[e]	5	3	
6	9 (1)	26 (2)	5	3	4
7	22	24 (3)	3	11	1
8	23	277 (14)[d]	7	4	2
9	3	20 (2)		3	2
10	1	6 (1)	9	3	
11	2	11	3	4	
12	3	7	1		
13		7 (1)	1	5	
14	21 (1)	38 (6)	4	3	3
15	2	16	2		
16	5 (1)	10 (2)	1	3	
17	2	9 (1)		6	
18	7	25 (1)	2	2	1
19	4	30 (2)	3	3	3
20	4	12 (2)	3	3	
21		3	5	2	1
22	2 (1)	13 (1)	3	2	
23	2 (1)	15 (3)	3	2	
24	(1)	1 (1)	2	2	
25	3	5 (1)	1	1	1
27			1		
28	0	6 (1)	1	2	
29	2	6	2	3	4
31	1	9		4	
32	1			1	
33	1	6		1	
34	1	6		1	
35		1			
36		1			
37		1			
41		2			
10A				1	
18A	1			2	1
NT[f]	10	11 (7)		1	5
Total	276 (13)	1,908 (124)	136	116	38
Types (no.)	29 (7)	34 (21)	26	30	3
>2 Types	3	75[g] (4)	5[h]	4[i]	

[a] Includes only patients from whom pneumococci were grown from blood (Table 1) or from infected foci or body fluids (Table 2).

[b] The number of strains obtained from tracheal aspirates are listed separately (in parentheses). A few were from patients in whom the same type was grown from either nasal or pharyngeal swabs or both.

[c] The last one was isolated in 1969.

[d] The spuriously large numbers of types 3 and 8 are due to the special interest of the bacteriologists to verify the identity of these types as selected by colony morphology of materials cultured directly on sheep's blood agar.

[e] None identified after 1967.

[f] NT, Not typable with any of the available pooled typing sera.

[g] Type 3 was one of the pair of types in 45 of these 75 cases.

[h] Two of the five included type 3.

[i] Type 3 in three of the four pairs.

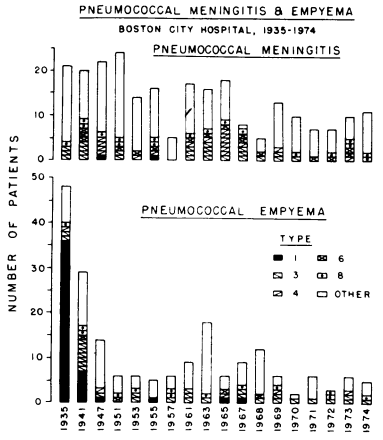

FIG. 6. *Occurrence of types 1, 3, 4, 6, and 8 and of all other types in patients with pneumococcal meningitis and empyema at Boston City Hospital during 18 selected years between 1935 and 1974.*

City Hospital during years between 1935 and 1957 to reflect the effects of the introduction and the widespread and continued use of modern effective antibacterial agents (10). The observations were subsequently extended to include bacteremic infections during 5 additional years through 1972 (26). Over that period, the number of patients admitted to the hospital each year declined steadily; but the decline was most rapid after 1965. Nevertheless, the number of patients with bacteremic infections and the rate of these infections per 1,000 hospital admissions as well as the number of deaths and rates per 1,000 deaths from such infections increased steadily through 1965. After that year these numbers and rates all declined.

In 1935, *S. pneumoniae* (pneumococci) and *Streptococcus pyogenes* (plus some non-group D beta-hemolytic streptococci) accounted for one-half of all bacteremic infections and 62.6% of all deaths from such infections. The proportion of bacteremic infections due to hemolytic streptococci declined sharply to less than 1% of all bacteremias during the successive years that were selected; there were no deaths by 1955, and cases due to pneumococci dropped from 32.5 to 12.5% of all cases, and from 41.7 to 9.0% of deaths from all bacteremic infections by 1955. After 1955, the number and proportions of cases and deaths due to beta-hemolytic streptococcal bacteremia rose steadily to about 6%, and the corresponding proportions for pneumococcal bacteremia fluctuated to slightly higher levels (13 to 15.5% of cases and 7 to 12% of deaths) over the subsequent years of the study. These changes occurred in spite of the marked, and essentially unchanged, effectiveness of the available antibacterial agents against the strains of both species (12, 13). Some strains of pneumococci resistant to tetracycline and isolated strains resistant to other antibiotics have been reported (25). The early decline in the proportions of bacteremic infections due to these two species was accompanied by an upsurge in the numbers and rates of cases due to *Staphylococcus aureus* and gram-negative rods. The cases of *S. aureus* bacteremia continued to increase through the 1950s but declined steadily after that, whereas gram-negative rod bacteremias continued to increase through 1972.

The present paper deals primarily with the changes in occurrence of specific types of pneumococci. For orientation, Fig. 8 shows the changes in the number of patients with serious infections caused by pneumococci of all types during 18 selected years from 1935 through 1974. The total number of patients with pneumococcal bacteremia fluctuated considerably over that period, with a marked downward trend from 1941 through 1955, a rise to 1963, and another downward trend after that. However, the rates of cases of pneumococcal bacteremia per 1,000 patients admitted to the hospital in the successive years of observation shows a moderate and irregular downward trend to 1955 with a more or less steady increase in rate in the 1960s and early 1970s. Figure 8 also shows

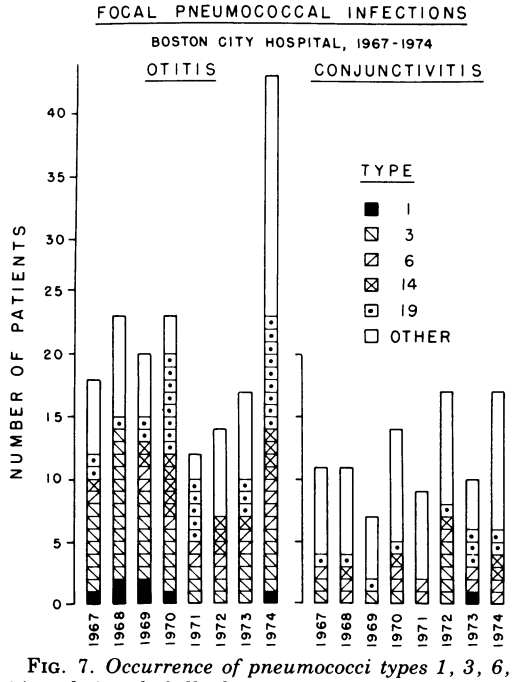

FIG. 7. *Occurrence of pneumococci types 1, 3, 6, 14, and 19 and of all other types in patients with otitis and conjunctivitis at Boston City Hospital between 1967 and 1974.*

the number of cases of pneumococcal meningitis and empyema over the same period; these varied independently from each other and from those of bacteremia and will be referred to later.

Within the overall changes in the occurrence of cases of pneumococcal bacteremia, it was shown that fluctuations occurred in the relative frequency of infections due to each of the most frequent, specific pneumococcal capsular types

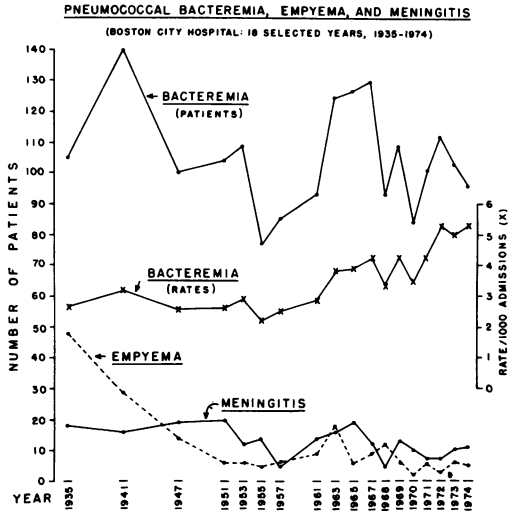

FIG. 8. *Number of patients with pneumococcal bacteremia, empyema, and meningitis, and number of bacteremic patients per 1,000 hospital admissions at Boston City Hospital during 18 selected years between 1935 and 1974.*

and that these variations appeared to be distinctive and independent of one another, even with respect to the antigenically related types 2 and 5 and types 3 and 8. It was also shown (Fig. 1 and 2) that these independent fluctuations in the relative frequency of occurrence of the most frequent types had already manifested during the several years preceding the period covered in this report. Of particular interest is the failure to identify type 2 or type 5 pneumococci in bacteremic pneumococcal infections that occurred in this hospital after 1967. Similar observations were made by Austrian (1). Mufson and co-workers (29) did not identify any cases of bacteremic pneumococcal infections that were caused by type 2 during the period of September 1967 through February 1970 at Cook County Hospital in Chicago, but they reported an outbreak of type 5 infections during an A_2 influenza epidemic in Chicago during the winter of 1969. Griffith (15) had earlier called attention to a marked change in the incidence of type 2 infections with declines from 32.6 to 21.6% and then to 7.4% in successive periods between April 1920 and March 1927. Lund (24) noted the decline of type 1 infections in Denmark after 1955 and of type 2 infections as early as 1937. She also pointed out the change in rank order of the top seven types during the period of 1955 to 1970 as compared with those during the period of 1930 to 1947.

The changes in predominance of various *Pneumococcus* types in bacteremic infection over the period of this report are shown in Table 5, which lists the top ranking eight types

TABLE 5. *Changes in rank order of occurrence of Pneumococcus types at Boston City Hospital during 15 selected years between 1935 and 1974*

Yr	Rank of types								% of total no. of strains from ranks
	1	2	3	4	5	6	7	8	1-8
1935	1	3	2	5[a]	8	4	7[a]	14[a]	83
1941	1	3	7	2	8	14	5	18[a]	73
1951	2	3	8	1	7	5	14[a]	4	66
1953	3	1	7	2	8	5	18[a]	4	58
1955	1	7	14[a]	8	3	4[a]	5[a]	12	65
1957	14	3	7	4	1	6[a]	12[a]	19[a]	60
1965	4	7	14	3	8[a]	1	5	6	58
1967	8	1	4	3	14[a]	7	5	12[a]	59
1968	7	3	4	23	18	1	8[a]	12[a,b]	52
1969	8	4	3	7	14	18[a]	33	12	60
1970	18	8	14	1	3[a]	4[a]	7	16[a,c]	45
1971	14	18	4	7	8[a]	19[a]	6	3[c]	62
1972	14	8	18	4	19	6	7	25[a]	70
1973	14	6	8[a]	18[a]	4	19	23[a]	20[d]	59
1974	14	5	3	6[a]	18	23[a]	4	19[a]	58

[a] Same number of strains as preceding type.
[b] Also type 19.
[c] Also type 23.
[d] Also type 33.

in order of descending frequency of their occurrence during the 15 years for which the pneumococci were identified by their specific types. The shifts in order of predominance in the different years are clearly evidenced. In Table 6, these data are summarized according to type; 16 different types appeared among the eight top ranking types during one or more of the 15 years, but not one of them appeared among the eight top ranking types during all 15 years. Type 4 occurred in 14 years, and types 3, 7, 8, and 14 were among the top 8 in 13 years, but 7 of the 16 types "made" the top eight in only 1 to 5 years. Noteworthy is the fact that type 1, which was by far the most frequent of the types during each year in the earlier study and during the first two selected years in this study (as shown in Fig. 1 and 3), is missing from the eight top ranking types in 1969 and in each of the last 4 years (1971–1974). The absence of type 2 in 1955 and of types 2 and 5 each year after 1967 has already been noted. Type 2 was not found among 315 strains of typed pneumococci in Cologne, Germany, from October 1970 to January 1972 (25).

In the earlier studies of the significance of *Pneumococcus* types in disease at this hospital (7, 11), it was shown that the distribution of types in typical cases of lobar pneumonia differed considerably from that in cases of atypical pneumonia or bronchopneumonias. The types in the latter more closely resembled those identified in healthy carriers and in acute upper respiratory infections (without pneumonia). The distribution in focal infections other than in pleural empyema was generally intermediate among those in carriers and those with lobar pneumonia. The distribution of types in pediatric cases of pneumococcal pneumonia and in bacteremias in infants and children differed from those in adults. Some of these differences are shown in Fig. 1 and 2. Similar differences were reported for the preantibiotic years from other large municipal hospitals and public health laboratories (8, 17, 18). Differences in type distribution in focal lesions and in bacteremias during more recent years were reported by Lund (23, 24). Differences in the distribution of types of pneumococci in acute otitis media were reported for Turku, Finland, in 1953 (22) and 1964 (16), and the latter differed in several respects from that reported for Stockholm in 1970 (21).

TABLE 6. *Types of pneumococci among the eight top ranking types at Boston City Hospital during the 15 selected years between 1935 and 1974*

Type	No. of yr in "Top 8"	First yr	Last yr	Yr not in "Top 8"
1	10	1935	1971	
2	4	1935	1953	
3	13	1935	1974	1973 or 1974
4	14	1935	1974	1941
5	7	1935	1967	
6	6	1957	1974	
7	13	1935	1972	1973, 1974
8	13	1935	1972	1957, 1974
12	5	1955	1969	
14	13	1935	1974	1953, 1968
16	1	1970		
18	9	1941	1974	
19	5	1957	1974	
20	1	1973		
23	2	1973	1974	
25	1	1972		

The changes in the numbers of cases of pneumococcal empyema and meningitis during the years studied in this report as compared with those of pneumococcal bacteremias are shown in Fig. 8. The different distribution of types among these and other focal infections is shown in Table 2 and in Fig. 3 through 5. Only in the empyemas does there appear to be some association of the predominant type, namely, with that in bacteremias; that was during 1935 and 1941. However, the number of cases of these and other focal infections in subsequent years are too few to permit any correlations. One outstanding feature of these data, as in those from most other reports, is the prominence, and generally the predominance, of type 3 *Pneumococcus* in all types of focal pneumococcal infection other than empyema in most of the years, as shown in Tables 2 and 3.

Although the marked drop in the incidence of pneumococcal infections during the early years covered in this report may be ascribable to the marked effectiveness of the new antibacterial agents against the pneumococci, the more recent increases are more difficult to explain. The latter may be part of the general and continued increase in serious bacterial infections (26). This, in turn, may be related to the occurrence of such infections in patients whose immunity or resistance is depressed by genetic factors, old age, certain systemic diseases including neoplastic diseases of antibody-forming cells and organs, and exposure to drugs, particularly immunosuppressive agents. Many such patients may be repeatedly cured of infections caused by the common pathogens and infections often caused by unusual or ordinarily nonpathogenic, endogenous, or exogenous organisms by treatment with effective antibiotics, but they returned with new infections and steadily increased the pool of these susceptible patients. In this respect, the *Pneumococcus* (and beta-hemolytic *Streptococcus*) may be participating in this general trend.

The cyclic fluctuations in the occurrence of infections of the many varied etiologies has long been recognized, and pneumococcal infections also show such fluctuations. However, at any given time, or in any particular population, local factors may contribute to the changes. For example, there may be special interest or enthusiasm for specific diagnostic procedures. At Boston City Hospital there was a marked increase in the number of blood cultures done in febrile infants and children after the publication of the report by Burke et al. (5), who focused on cases of pneumococcal bacteremia having an undetermined focus. This led to prospective studies of the occurrence of bacteremia in febrile infants and children in the "walk-in" pediatric clinic which showed that *S. pneumoniae* was by far the most frequent species isolated from blood cultures taken routinely from febrile children (27, 32). However, this could account for only a small part of the recent increase in all pneumococcal bacteremias and in the relative incidence of certain types during these years. The special interest of our bacteriologists in identifying types 3 and 8 pneumococci was previously mentioned to account for the extraordinarily high proportion of these types in specimens from respiratory tract during recent years.

There are certain known facts about the *Pneumococcus* types that could be invoked as possible implications in the variations in their occurrence. Lund (24) mentioned the transformation of types in vitro and under special experimental conditions in mice, but this has not been shown to occur in vivo under natural conditions. Among other features that could be noted are: the decapsulation and loss of virulence of type-specific pneumococci grown in homologous type-specific antiserum; the development of type-specific antibodies in otherwise normal carriers who acquire the pneumococci from contact with infected patients; the decomposition of various *Pneumococcus* capsular polysaccharides by specific enzymes from natural sources; and the occurrence of shared antigens of specific types of pneumococci and various species of bacteria, yeasts, and other biological substances. However, since none of these has been demonstrated to affect the occurrence or changes of *Pneumococcus* types in normal or diseased individuals, these do not need to be documented or discussed here.

From a practical point of view, the changing incidence of different *Pneumococcus* types is of special interest in relation to the possible application of pneumococcal polysaccharide vaccines (1, 3). In the past, the application of such vaccines has been successful in halting an outbreak of infection in a closed population (30) and in reducing the occurrence of pneumonia due to the types contained in the vaccines in large populations of predominantly adolescents and young adults (6, 28). The vaccines would be most useful in closed or well-defined populations or in patients with certain congenital or acquired conditions in which pneumococcal infections are particularly endemic or of high virulence. Among the former could be included military or educational institutions, nursing homes, hospitals for mental or other chronic diseases, penal institutions, etc., and they would be of particular value if given before or during epidemics of influenza. Among the special disease entities with possibly increased susceptibility to pneumococcal infection might be included Hodgkin's disease, multiple myeloma, sickle cell anemia, chronic bronchitis and obstructive pulmonary disease, and asplenia (or postsplenectomy).

To be successful, however, such vaccines must contain antigens against the specific *Pneumococcus* types that are occurring or can be expected to occur in such groups or diseases (2, 20). In view of the changing incidence of types, this would require a certain amount of continuous or intermittent monitoring of the occurrence of *Pneumococcus* types in the infections within such populations. The considerable mortality that still accompanies pneumococcal infections in these populations would justify such monitoring if the apparently successful application of these vaccines is sustained.

In view of the continuing high prevalence of infections with type 3 *Pneumococcus* and the significant fatality rate from such infections in spite of the seemingly adequate therapy with potent antibiotics (4, 29), it will be particularly interesting to observe the efficacy of vaccines against infections of this type. Studies reported in 1935 showed that the type 3 polysaccharide then available was a poor antigen (14).

Type 19 was noted as being one of the most frequent types in recent years. This type has long been known to be epizootic in guinea pigs among breeding colonies and in clinical and research laboratories (19). It may be of interest, therefore, to see whether this type could be eradicated by the appropriate application of the type 19 capsular polysaccharide.

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